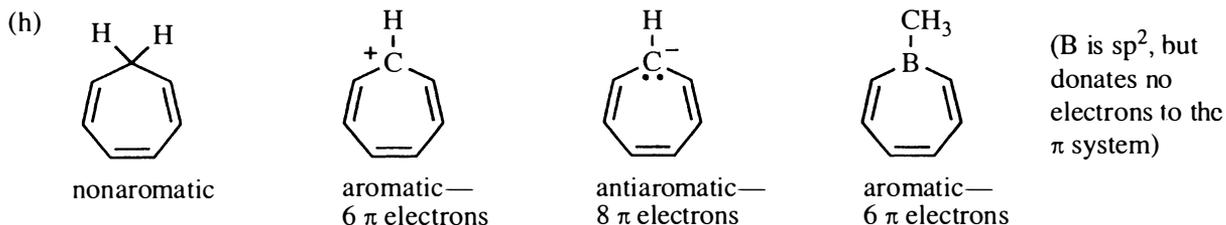
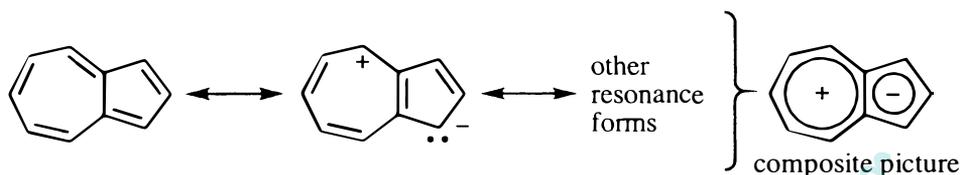


16-32 continued

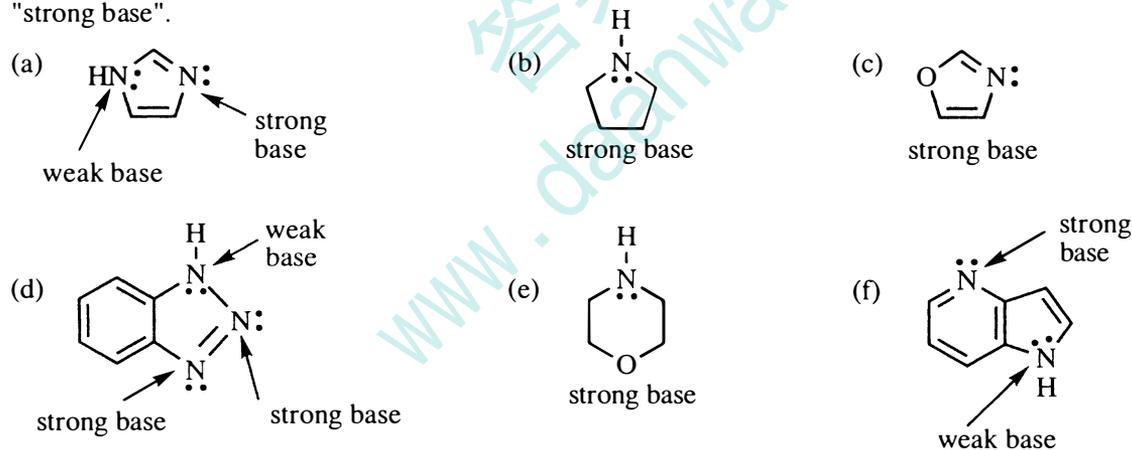


16-33 The clue to azulene is recognition of the five- and seven-membered rings. To attain aromaticity, a seven-membered carbon ring must have a positive charge; a five-membered carbon ring must have a negative charge. Drawing a resonance form of azulene shows this:

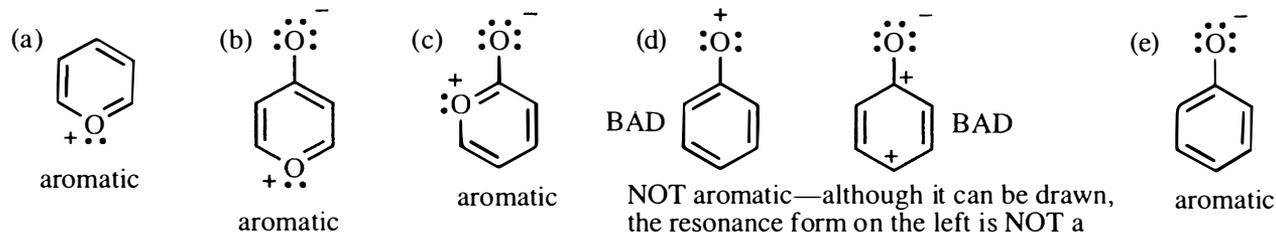


The composite picture shows that the negative charge is concentrated in the five-membered ring, giving rise to the dipole.

16-34 Whether a nitrogen is strongly basic or weakly basic depends on the location of its electron pair. If the electron pair is needed for an aromatic π system, the nitrogen will not be basic (shown here as "weak base"). If the electron pair is in either an sp^2 or sp^3 orbital, it is available for bonding, and the nitrogen is a "strong base".



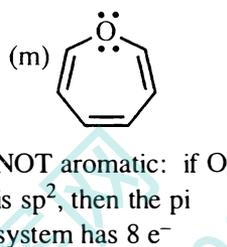
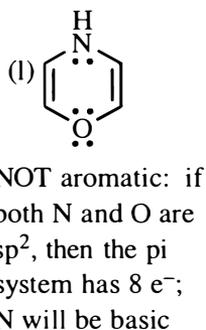
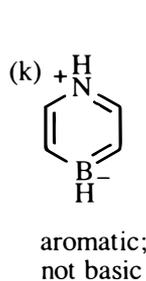
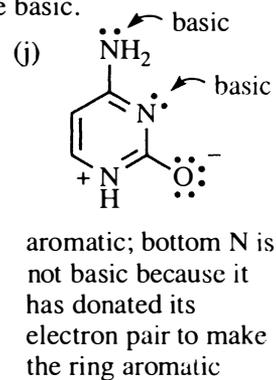
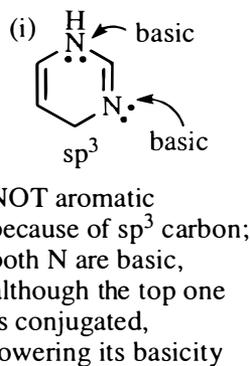
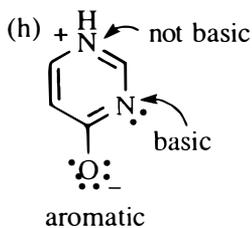
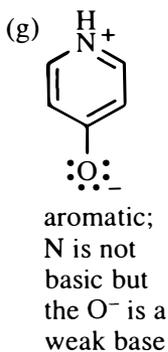
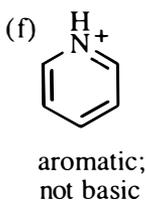
16-35 Where a resonance form demonstrates aromaticity, the resonance form is shown.



NOT aromatic—although it can be drawn, the resonance form on the left is NOT a significant contributor because the oxygen does not have a full octet; the form on the right shows the correct polarization of the carbonyl, but it's still not aromatic because of only 4 π electrons

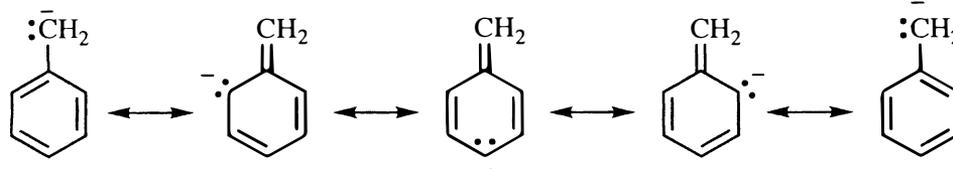
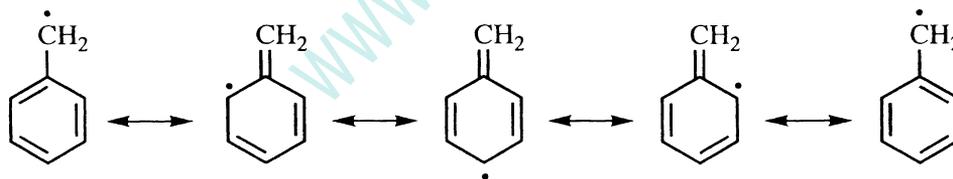
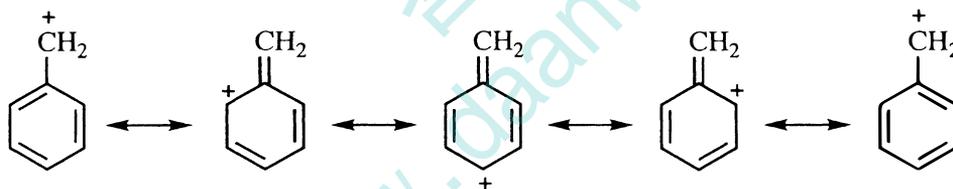
16-35 continued

Nitrogens whose electrons are needed to complete the aromatic π system will not be basic.

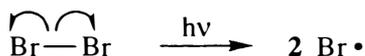


16-36

(a)

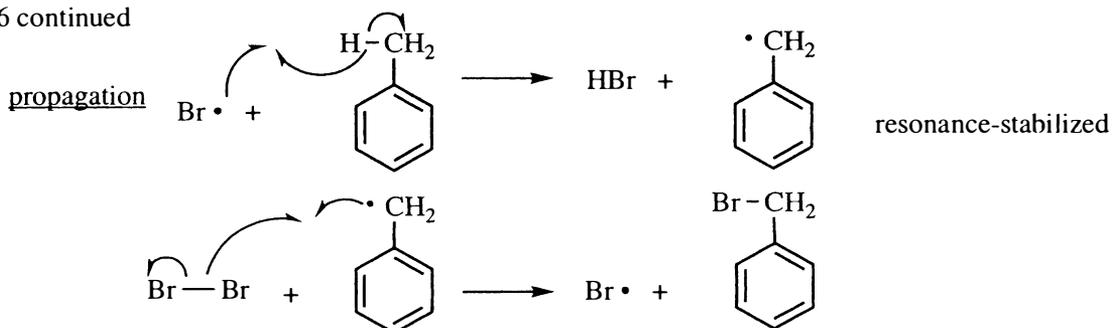


(b) initiation

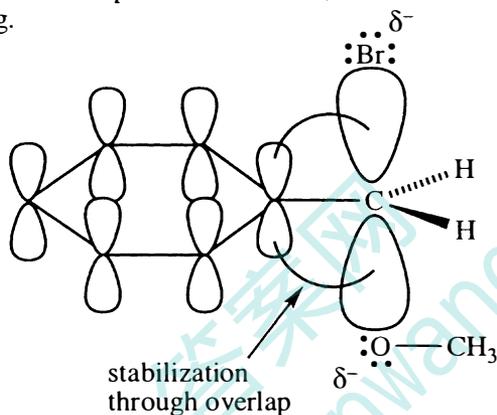


propagation steps on the next page

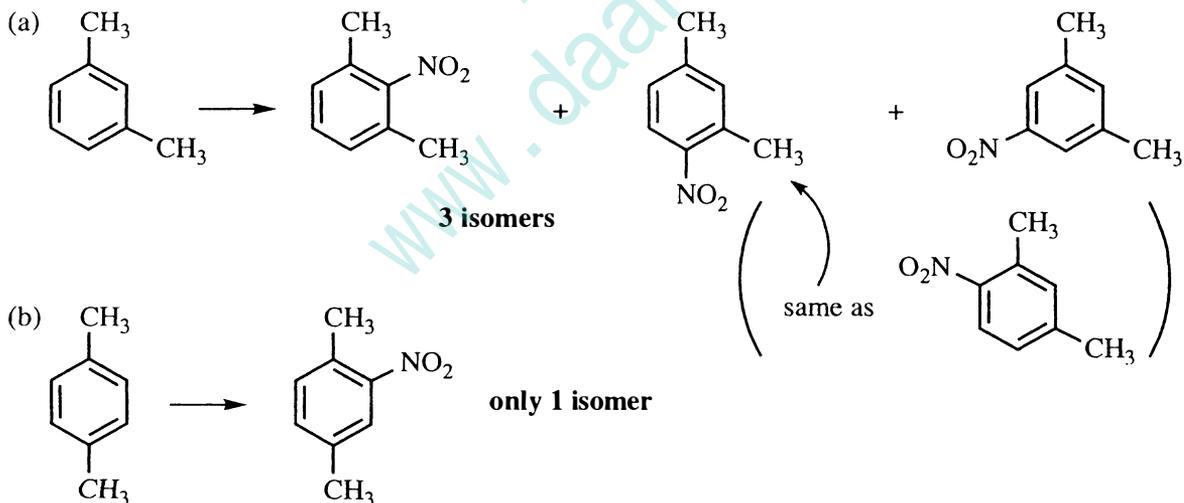
16-36 continued



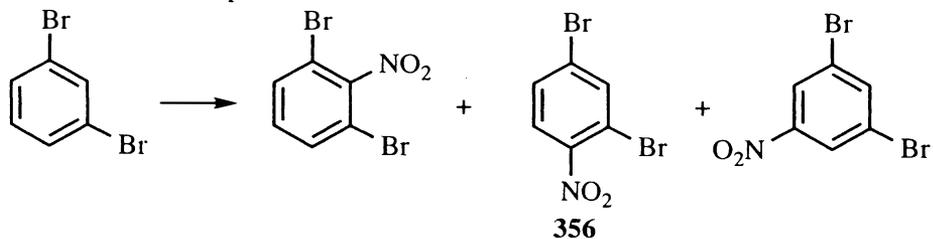
(c) Both reactions are S_N2 on primary carbons, but the one at the benzylic carbon occurs faster. In the transition state of S_N2 , as the nucleophile is approaching the carbon and the leaving group is departing, the electron density resembles that of a p orbital. As such, it can be stabilized through overlap with the π system of the benzene ring.



16-37

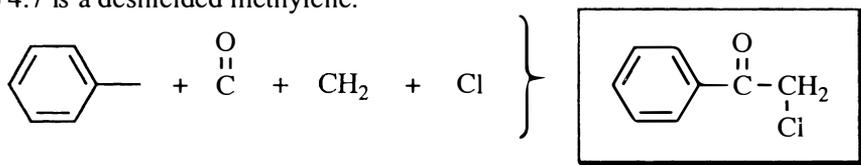


(c) The original compound had to have been *meta*-dibromobenzene as this is the only dibromo isomer that gives three mononitrated products.

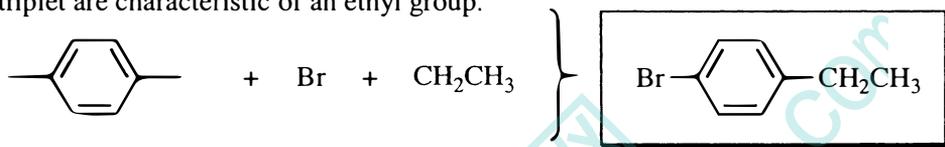


16-38

(a) The formula C_8H_7OCl has five elements of unsaturation, probably a benzene ring (4) plus either a double bond or a ring. The IR suggests a conjugated carbonyl at 1690 cm^{-1} and an aromatic ring at 1602 cm^{-1} . The NMR shows a total of five aromatic protons, indicating a monosubstituted benzene. A 2H singlet at $\delta\ 4.7$ is a deshielded methylene.

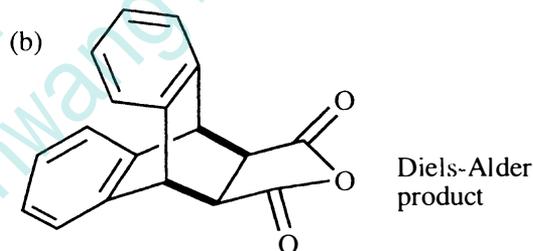
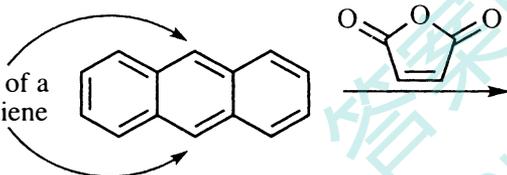


(b) The mass spectral evidence of molecular ion peaks of 1 : 1 intensity at 184 and 186 shows the presence of a bromine atom. The m/z 184 minus 79 for bromine gives a mass of 105 for the rest of the molecule, which is about a benzene ring plus two carbons and a few hydrogens. The NMR shows four aromatic hydrogens in a typical *para* pattern (two doublets), indicating a *para*-disubstituted benzene. The 2H quartet and 3H triplet are characteristic of an ethyl group.



16-39

(a) like the ends of a conjugated diene



new sigma bonds shown in bold

16-40

- (a) No, biphenyl is not fused. The rings must share two atoms to be labeled "fused".
 (b) There are 12 π electrons in biphenyl compared with 10 for naphthalene.
 (c) Biphenyl has 6 "double bonds". An isolated alkene releases 120 kJ/mole upon hydrogenation.

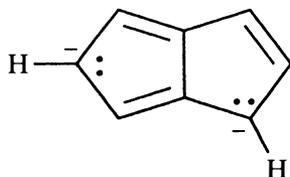
predicted: $6 \times 120\text{ kJ/mole}$ (28.6 kcal/mole) $\approx 720\text{ kJ/mole}$ (172 kcal/mole)

observed: 418 kJ/mole (100 kcal/mole)

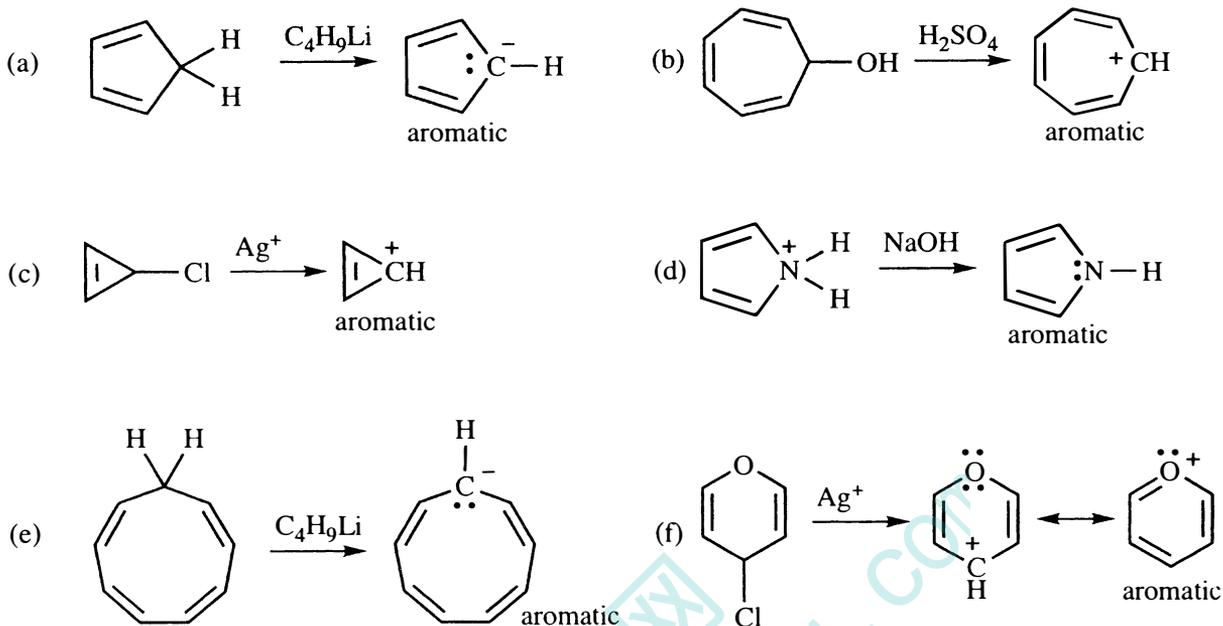
resonance energy: 302 kJ/mole (72 kcal/mole)

(d) On a "per ring" basis, biphenyl is $302 \div 2 = 151\text{ kJ/mole}$, the same as the value for benzene. Naphthalene's resonance energy is 252 kJ/mole (60 kcal/mole); on a "per ring" basis, naphthalene has only 126 kJ/mole of stabilization per ring. This is consistent with the greater reactivity of naphthalene compared with benzene. In fact, the more fused rings, the lower the resonance energy per ring, and the more reactive the compound. (Refer to Problem 16-20.)

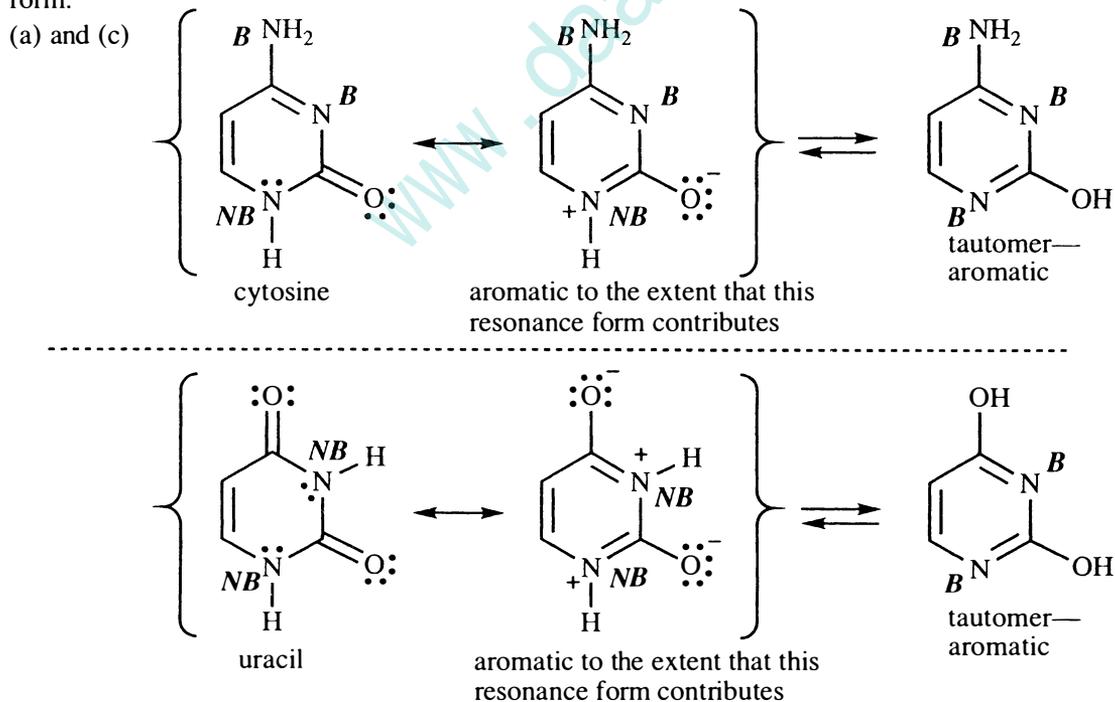
16-41 Two protons are removed from sp^3 carbons to make sp^2 carbons and to generate a π system with 10 π electrons.



16-42

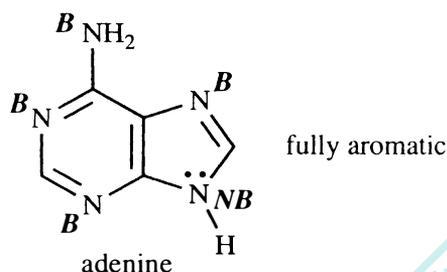
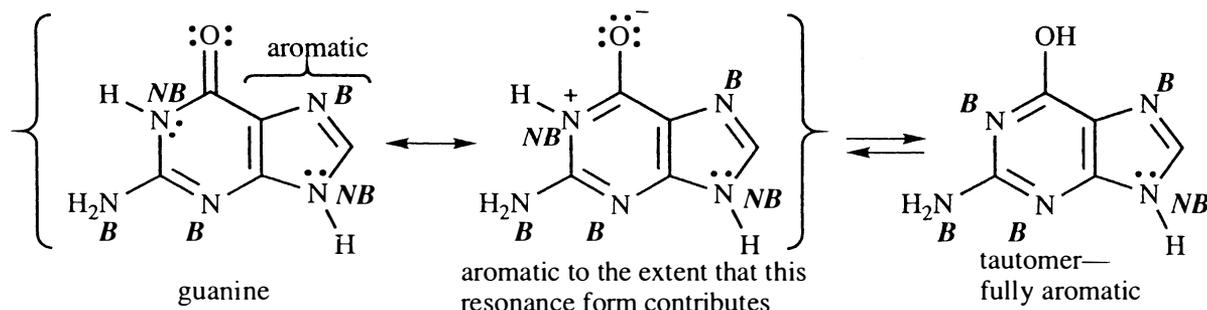


16-43 These four bases can be aromatic, partially aromatic, or aromatic in a tautomeric form. In other words, aromaticity plays an important role in the chemistry of all four structures. (Only electron pairs involved in the important resonance are shown.) For part (b), nitrogens that are basic are denoted by *B*. Those that are not basic are shown as *NB*. Note that some nitrogens change depending on the tautomeric form.



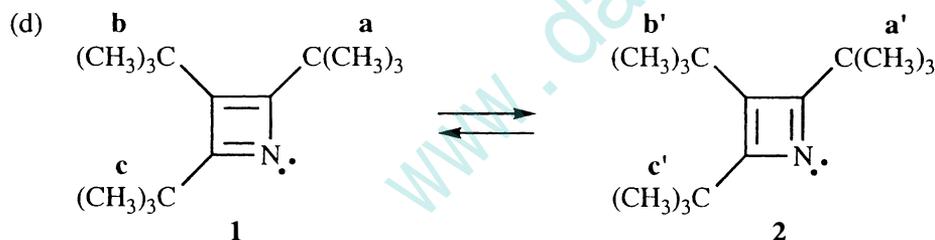
continued on the next page

16-43 continued



16-44

- (a) Antiaromatic—only 4 π electrons.
- (b) This molecule is electronically equivalent to cyclobutadiene. Cyclobutadiene is unstable and undergoes a Diels-Alder reaction with another molecule of itself. The *t*-butyl groups prevent dimerization by blocking approach of any other molecule.
- (c) Yes, the nitrogen should be basic. The pair of electrons on the nitrogen is in an sp^2 orbital and is not part of the π system.



Analysis of structure **1** shows the three *t*-butyl groups in unique environments in relation to the nitrogen. We would expect three different signals in the NMR, as is observed at -110°C . Why do signals coalesce as the temperature is increased? Two of the *t*-butyl groups become equivalent—which two? Most likely, they are **a** and **c** that become equivalent as they are symmetric around the nitrogen. But they are *not* equivalent in structure **1**—what is happening here?

What must happen is an equilibration between structures **1** and **2**, very slow at -110°C , but very fast at room temperature, faster than the NMR can differentiate. So the signal which has coalesced is an average of **a** and **a'** and **c** and **c'**. (This type of low temperature NMR experiment is also used to differentiate axial and equatorial hydrogens on a cyclohexane.)

The NMR data prove that **1** is not aromatic, and that **1** and **2** are isomers, not resonance forms. If **1** were aromatic, then **a** and **c** would have identical NMR signals at all temperatures.

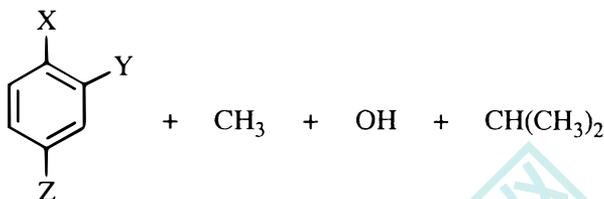
16-45

Mass spectrum: Molecular ion at 150; base peak at 135, $M - 15$, is loss of methyl.

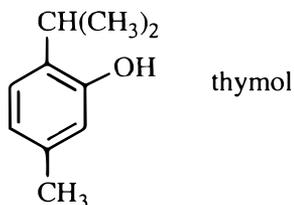
Infrared spectrum: The broad peak at 3500 cm^{-1} is OH; thymol must be an alcohol. The peak at 1620 cm^{-1} suggests an aromatic compound.

NMR spectrum: The singlet at $\delta 4.8$ is OH; it disappears upon shaking with D_2O . The 6H doublet at $\delta 1.2$ and the 1H multiplet at $\delta 3.2$ are an isopropyl group, apparently on the benzene ring. A 3H singlet at $\delta 2.3$ is a methyl group, also on the benzene ring.

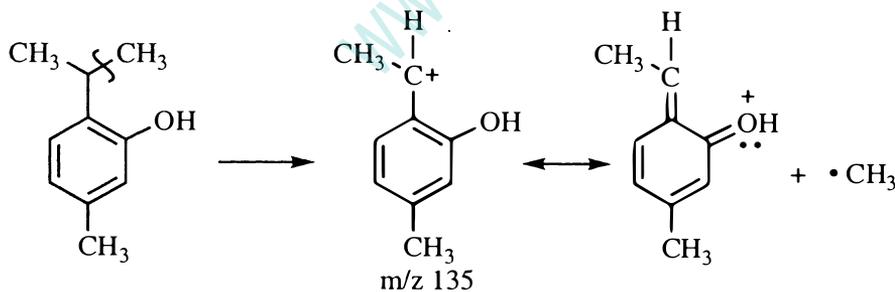
Analysis of the aromatic protons suggests the substitution pattern. The three aromatic hydrogens confirm that there are three substituents. The singlet at $\delta 6.5$ is a proton between two substituents (no neighboring H's). The doublets at $\delta 6.75$ and $\delta 7.1$ are ortho hydrogens, splitting each other.



Several isomeric combinations are consistent with the spectra (although the single H giving $\delta 6.5$ suggests that either Y or Z is the OH group—an OH on a benzene ring shields hydrogens ortho to it, moving them upfield). The structure of thymol is:



The final question is how the molecule fragments in the mass spectrometer:



resonance stabilization of this benzylic cation includes forms with positive charge on three ring carbons and on oxygen (shown)

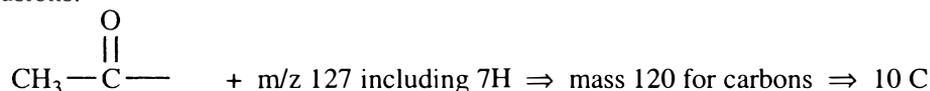
16-46

Mass spectrum: Molecular ion at 170; two prominent peaks are $M - 15$ (loss of methyl) and $M - 43$ (as we shall see, most likely the loss of acetyl, CH_3CO).

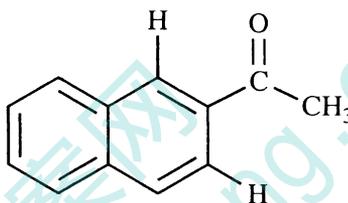
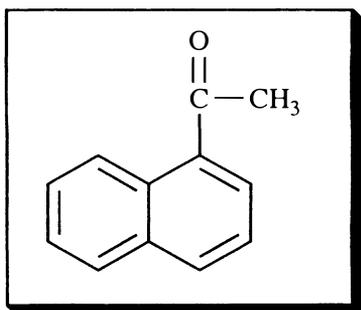
Infrared spectrum: The two most significant peaks are at 1680 cm^{-1} (conjugated carbonyl) and 1600 cm^{-1} (aromatic $\text{C}=\text{C}$).

NMR spectrum: A 3H singlet at $\delta 2.7$ is methyl next to a carbonyl, shifted slightly downfield by an aromatic ring. The other signals are seven aromatic protons. The 1H at d 8.7 is a deshielded proton next to a carbonyl. Since there is only one, the carbonyl can have only one neighboring hydrogen.

Conclusions:



The fragment C_{10}H_7 is almost certainly a naphthalene. The correct isomer (box) is indicated by the NMR.

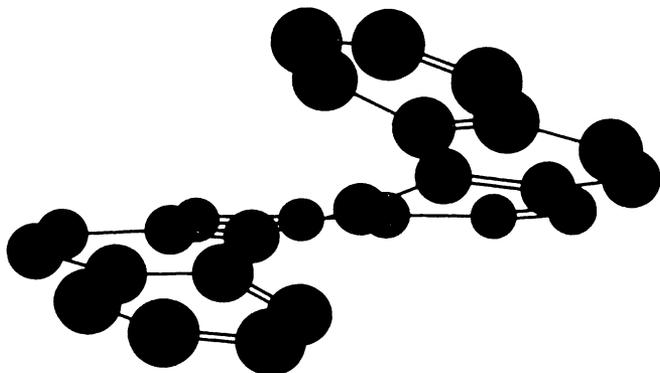


This isomer would have two deshielded protons in the NMR.

16-47

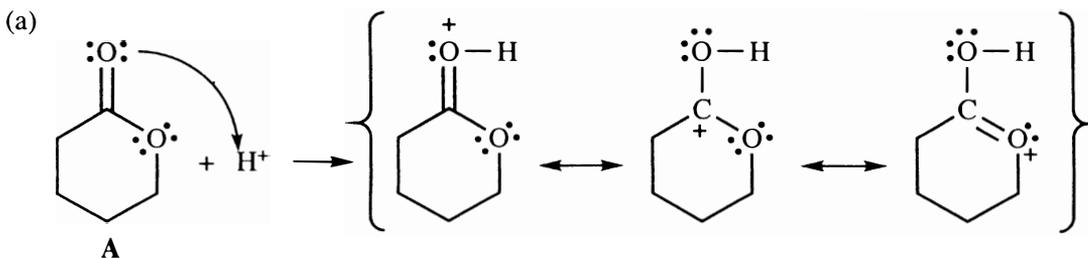
Although all carbons in hexahelicene are sp^2 , the molecule is not flat. Because of the curvature of the ring system, one end of the molecule has to sit on top of the other end—the carbons and the hydrogens would bump into each other if they tried to occupy the same plane. In other words, the molecule is the beginning of a spiral. An "upward" spiral is the nonsuperimposable mirror image of a "downward" spiral, so the molecule is chiral and therefore optically active.

The magnitude of the optical rotation is extraordinary: it is one of the largest rotations ever recorded. In general, alkanes have small rotations and aromatic compounds have large rotations, so it is reasonable to expect that it is the interaction of plane-polarized light (electromagnetic radiation) with the electrons in the twisted pi system (which can also be considered as having wave properties) that causes this enormous rotation.

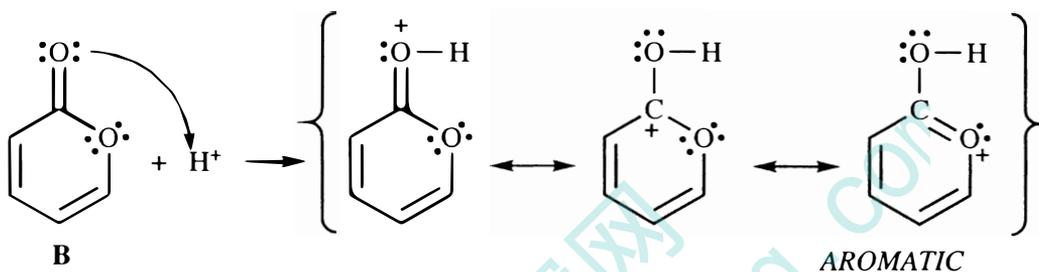


three-dimensional picture of hexahelicene showing the twist in the system of six rings

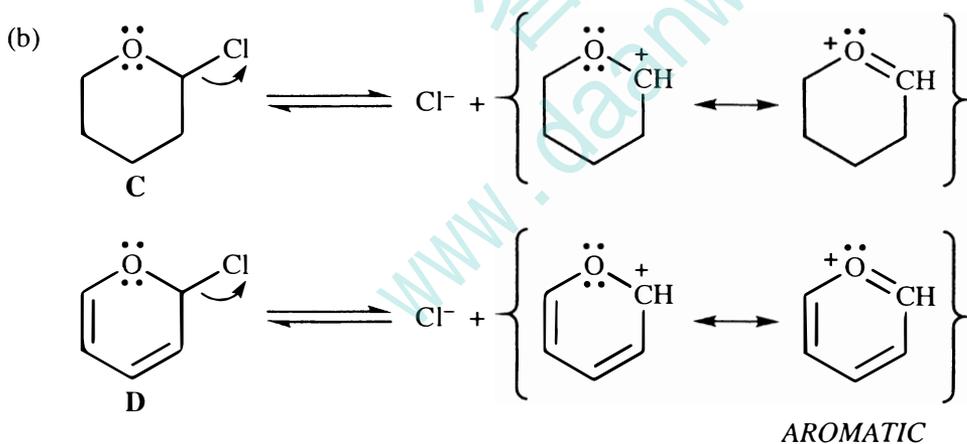
16-48 The key concept in parts (a)-(c) is that an aromatic product is created.



The protonated carbonyl gives a resonance-stabilized cation. Protonation of the singly bonded oxygen does not generate a resonance-stabilized product.



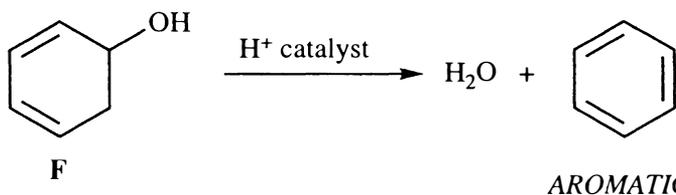
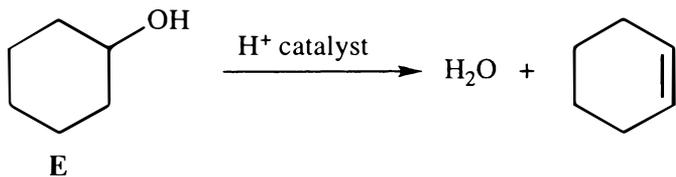
The last resonance form shows that the cation produced is aromatic and therefore more stable than the corresponding nonaromatic ion. In this second reaction, the products are more favored than in the first reaction which is interpreted as the reactant **B** being more basic than **A**.



The product from ionization of **C** is stabilized by resonance. The ionization product of **D** is not only resonance-stabilized but is also aromatic and therefore more stable. A reaction that produces a more stable product will usually happen faster under milder conditions because the transition state leading to that product will be stabilized, leading to a lower activation energy.

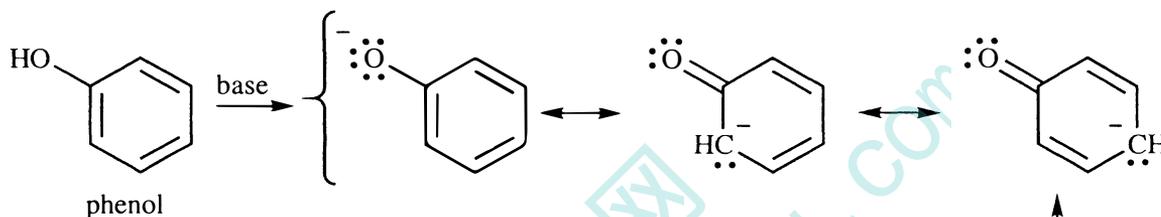
16-48 continued

(c)

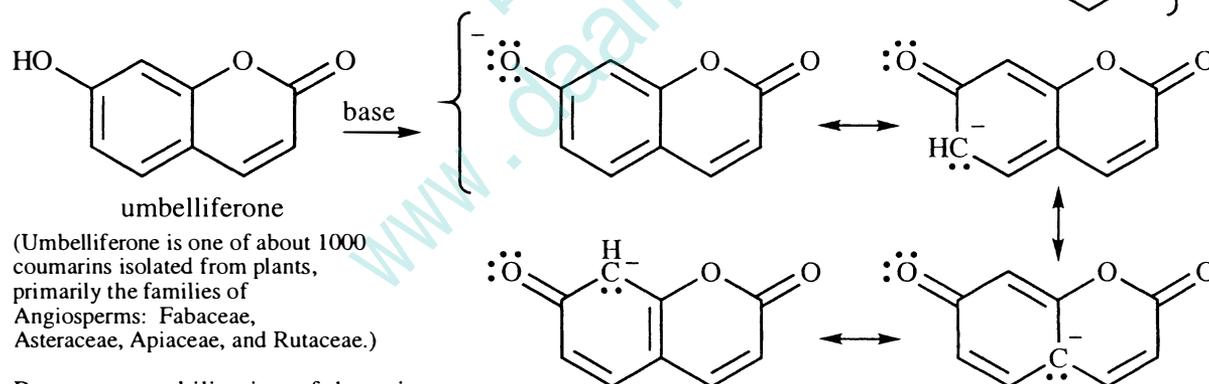


Dehydration of **F** produces an aromatic product that is more stable than the product from **E**. A reaction that produces a more stable product will usually happen faster under milder conditions because the transition state leading to that product will be stabilized, leading to a lower activation energy.

(d)



Resonance stabilization of the phenoxide anion shows the negative charge distributed over the one para and two ortho carbons.

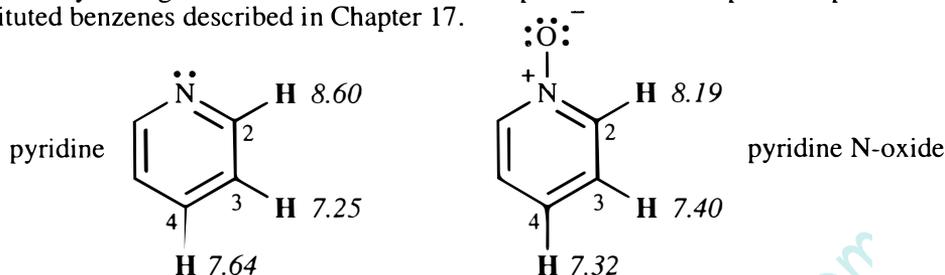


(Umbelliferone is one of about 1000 coumarins isolated from plants, primarily the families of Angiosperms: Fabaceae, Asteraceae, Apiaceae, and Rutaceae.)

Resonance stabilization of the anion of umbelliferone gives not only the same three forms as the phenoxide anion, but in addition, gives an extra resonance form with (-) charge on a carbon, and the most significant resonance contributor, another form with the (-) charge on the other carbonyl oxygen. This anion is much more stable than phenoxide which we interpret as enhanced acidity of the starting material, umbelliferone. In fact, the pKa of umbelliferone is 7.7 while phenol is about 10.

16-49 Humulon (sometimes spelled humulone), even though highly resonance stabilized, cannot be aromatic because the carbon shown at the bottom of the ring is tetrahedral and must be sp^3 hybridized. A ring is aromatic only when all of the atoms in the ring have a p orbital which the sp^3 carbon does not.

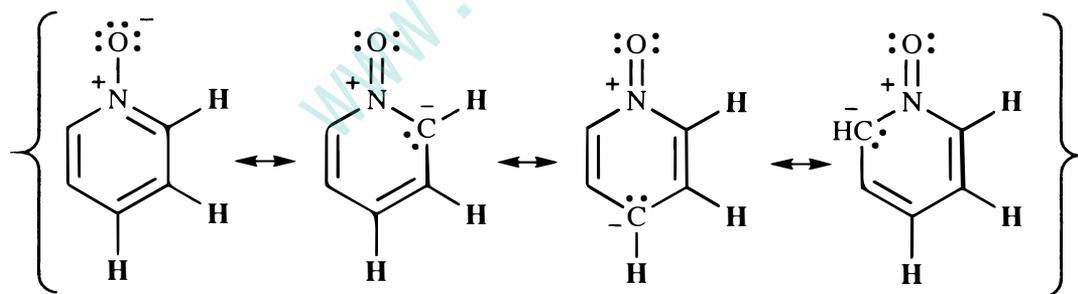
16-50 Are you familiar with the concept "tough love", that is, sometimes you have to be stern with someone you love for their own good? The concept is that sometimes to demonstrate one emotion, the behavior has to appear exactly the opposite. Granted, this is a stretch to apply it to atoms, but the point is that sometimes atoms like oxygen and nitrogen can have conflicting effects: they can withdraw electron density by their strong electronegativity (an inductive effect) but at the same time, they can donate electron density through their resonance effect. This phenomenon will prove important in the reactivity of substituted benzenes described in Chapter 17.



Nitrogen is electronegative, so it exerts a deshielding effect on H-2 in pyridine. The effect diminishes with distance as expected with an inductive effect, although it is harder to explain why H-4 is deshielded more than H-3.

In pyridine N-oxide, with an even more electronegative oxygen attached to the N, it would be reasonable to expect that the hydrogens would be deshielded. This is the case with H-3; we can infer that the effect on H-3 is purely an inductive effect.

Even more interesting is the *shielding* effect on H-2 and H-4; these chemical shifts are shifted *upfield*. This must reflect the other side of oxygen's personality, the donation of electron density through a resonance effect. Drawing the resonance forms clearly shows that the electron density at H-2 and H-4 (and presumably H-6) increases through this donation by resonance, in perfect agreement with the NMR results. As we will see in Chapter 17, in most cases, resonance effect trumps inductive effect.



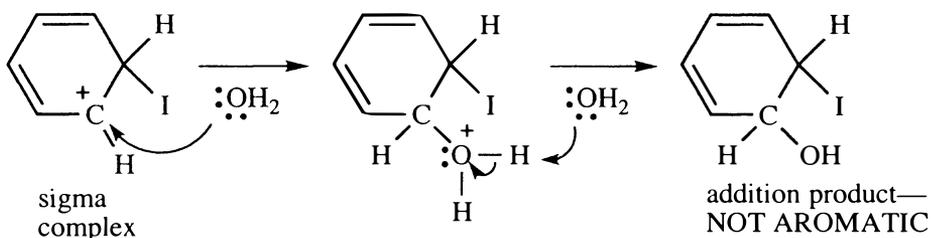
Note: The practice of applying human emotions to inanimate objects is called "anthropomorphizing". For example, we say that an atom is "happy" when it has a full octet of electrons. In casual conversation, this gets a point across, but it is not appropriate in rigorous scientific terms, for example, on exams. Under more formal conditions, we are expected to use the specific terms of science because they are well defined and do not permit sloppy or fuzzy concepts.

As our equipment technician says: "Don't anthropomorphize computers. They hate that."

CHAPTER 17—REACTIONS OF AROMATIC COMPOUNDS

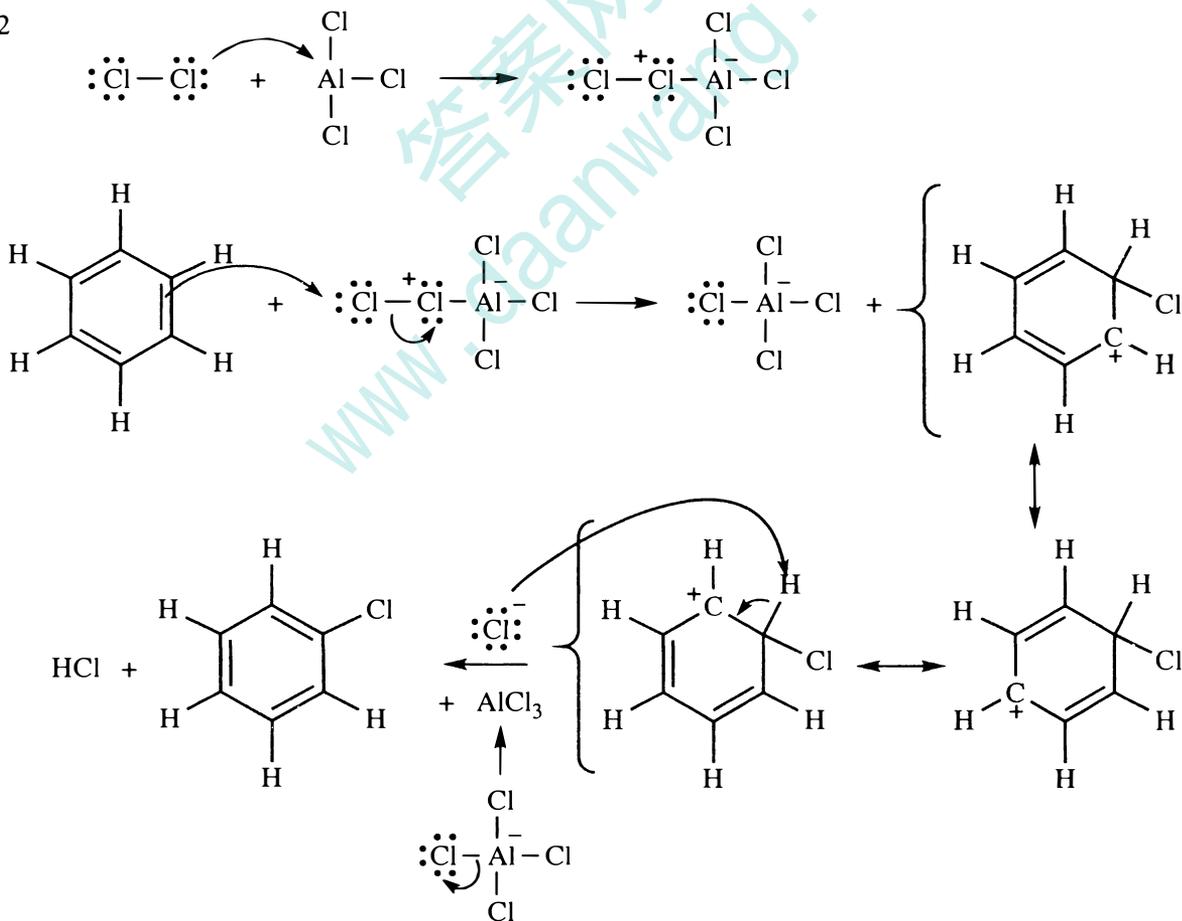
The representation of benzene with a circle to represent the π system is fine for questions of nomenclature, properties, isomers, and reactions. For questions of mechanism or reactivity, however, the representation with three alternating double bonds (the Kekulé picture) is more informative. For clarity and consistency, this Solutions Manual will use the Kekulé form exclusively.

17-1

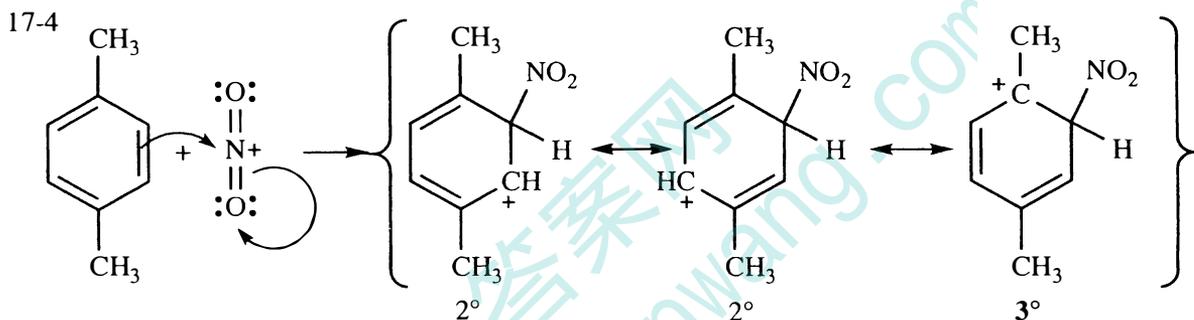
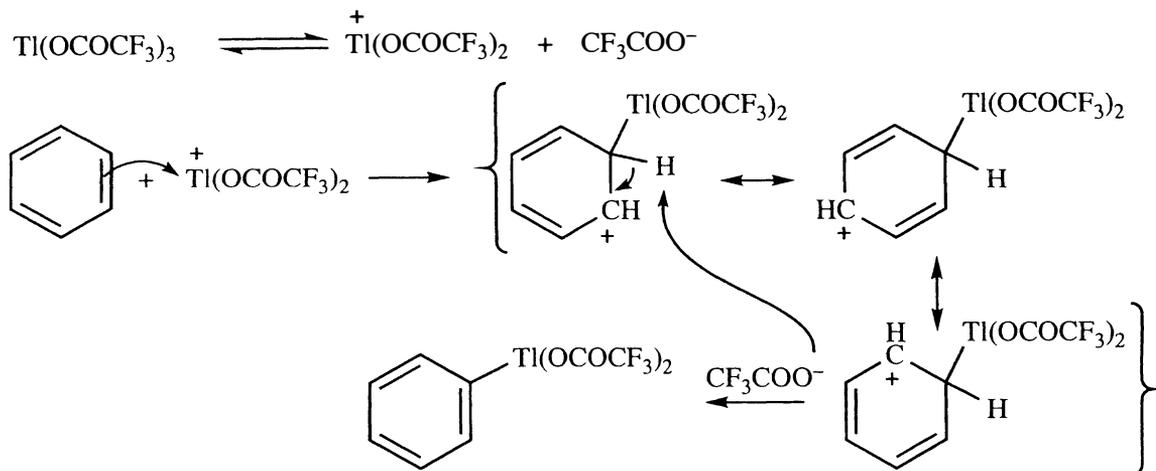


While the addition of water to the sigma complex can be shown in a reasonable mechanism, the product is not aromatic. Thus, it has lost the 152 kJ/mol (36 kcal/mole) of resonance stabilization energy. The addition reaction is not favorable energetically, and substitution prevails.

17-2

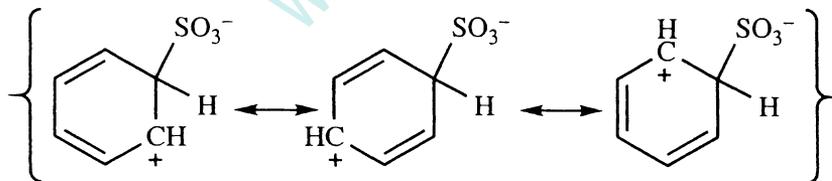


17-3 Like most heavy metals, thallium is highly toxic and should not be used on breakfast cereal.

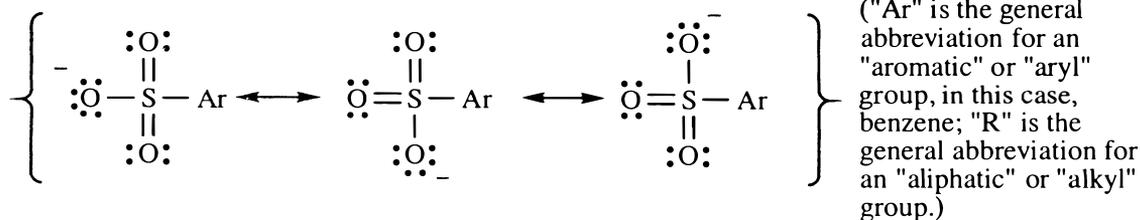


Benzene's sigma complex has positive charge on three 2° carbons. The sigma complex above shows positive charge in one resonance form on a 3° carbon, lending greater stabilization to this sigma complex. The more stable the intermediate, the lower the activation energy required to reach it, and the faster the reaction will be.

17-5 delocalization of the positive charge on the ring

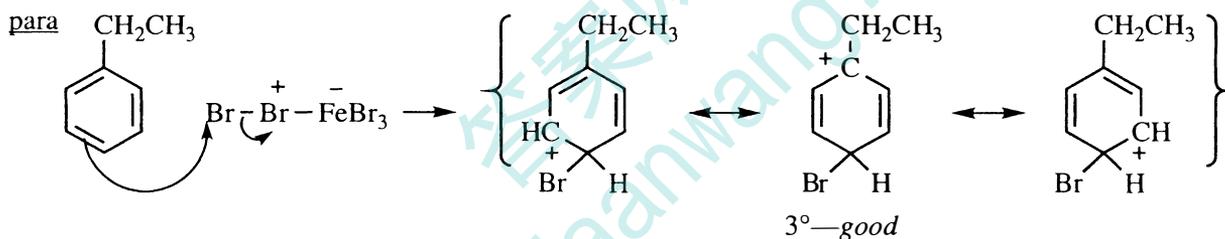
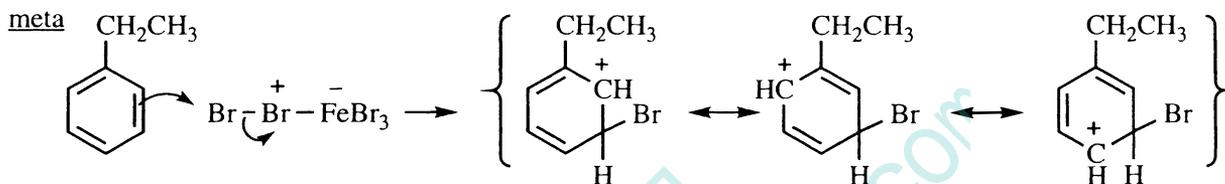
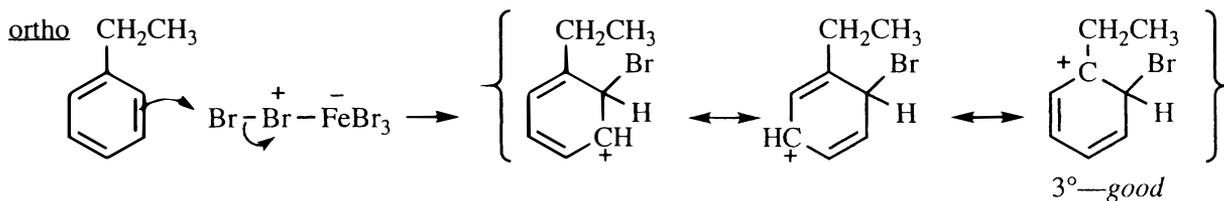


delocalization of the negative charge on the sulfonate group



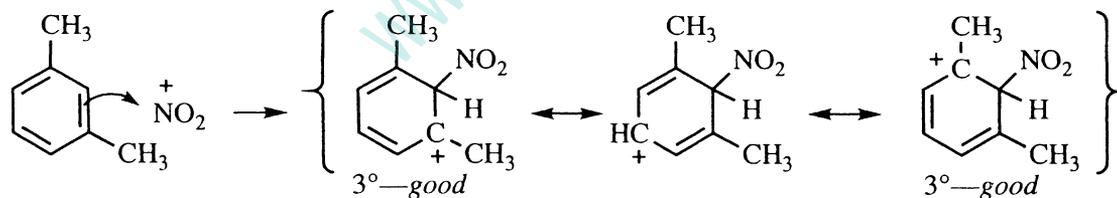
17-6

(a) The key to electrophilic aromatic substitution lies in the stability of the sigma complex. When the electrophile bonds at ortho or para positions of ethylbenzene, the positive charge is shared by the 3° carbon with the ethyl group. Bonding of the electrophile at the meta position lends no particular advantage because the positive charge in the sigma complex is never adjacent to, and therefore never stabilized by, the ethyl group.

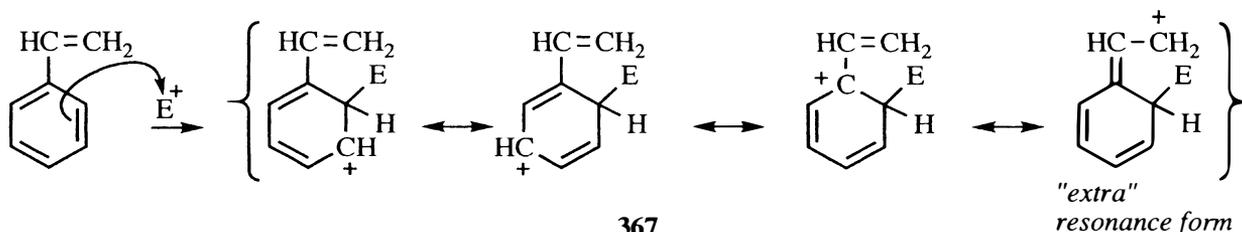


(b) Electrophilic attack on *p*-xylene gives an intermediate in which only one of the three resonance forms is stabilized by a substituent (see the solution to Problem 17-4). *m*-Xylene, however, is stabilized in two of its three resonance forms. A more stable intermediate gives a faster reaction.

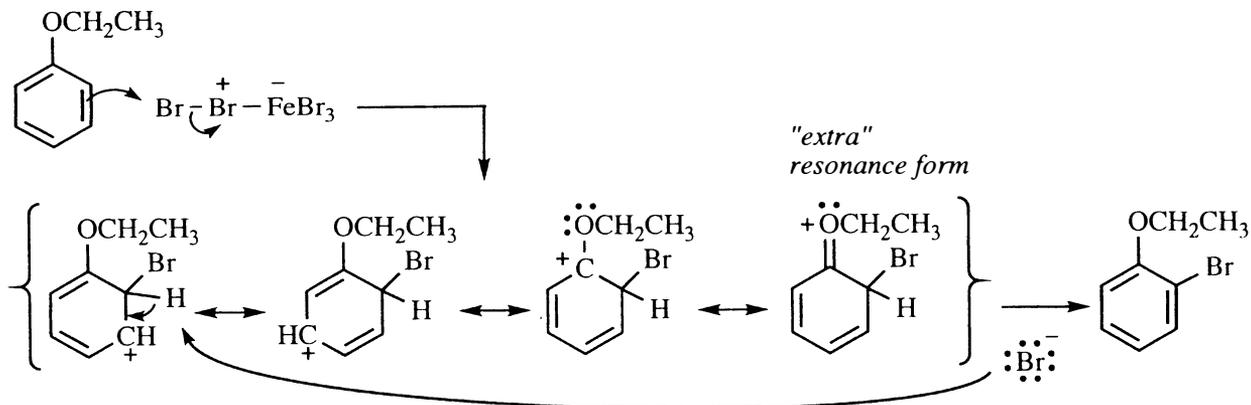
m-xylene



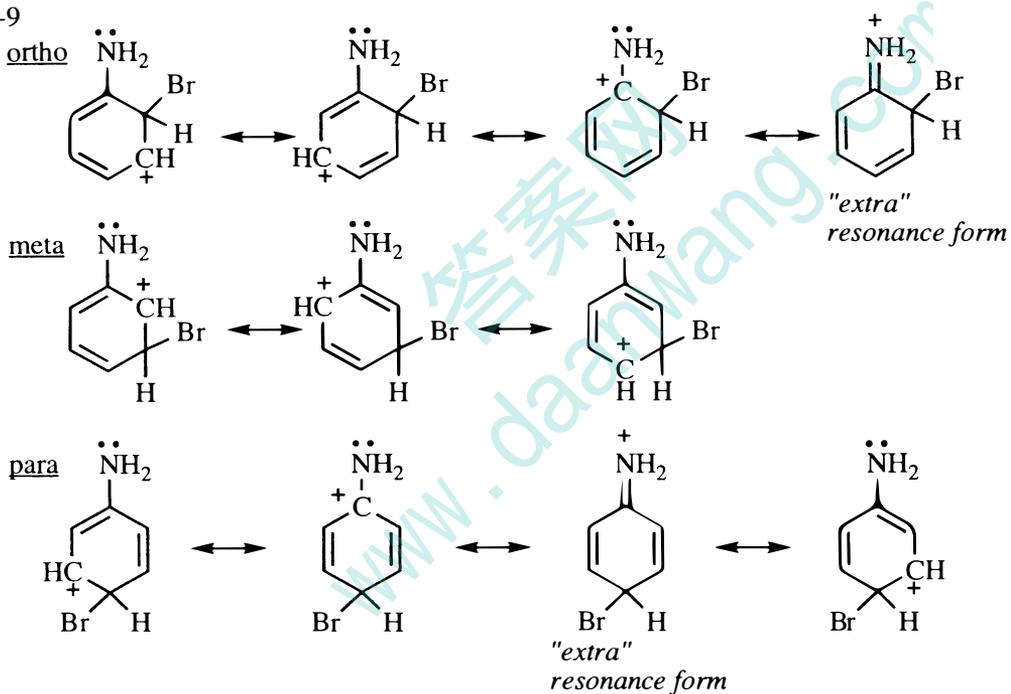
17-7 For ortho and para attack, the positive charge in the sigma complex can be shared by resonance with the vinyl group. This cannot happen with meta attack because the positive charge is never adjacent to the vinyl group. (Ortho attack is shown; para attack gives an intermediate with positive charge on the same carbons.)



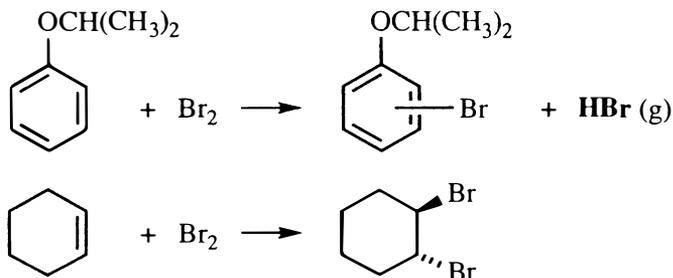
17-8 Attack at only ortho and para positions (not meta) places the positive charge on the carbon with the ethoxy group, where the ethoxy group can stabilize the positive charge by resonance donation of a lone pair of electrons. (Ortho attack is shown; para attack gives a similar intermediate.)



17-9



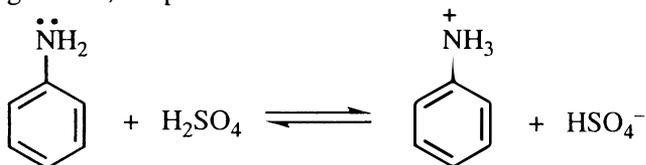
17-10



Substitution generates HBr whereas the addition does not. If the reaction is performed in an organic solvent, bubbles of HBr can be observed, and HBr gas escaping into moist air will generate a cloud. If the reaction is performed in water, then adding moist litmus paper to test for acid will differentiate the results of the two compounds.

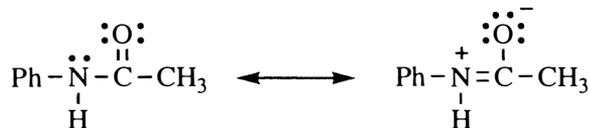
17-11

(a) Nitration is performed with nitric acid and a sulfuric acid catalyst. In strong acid, amines in general, including aniline, are protonated.



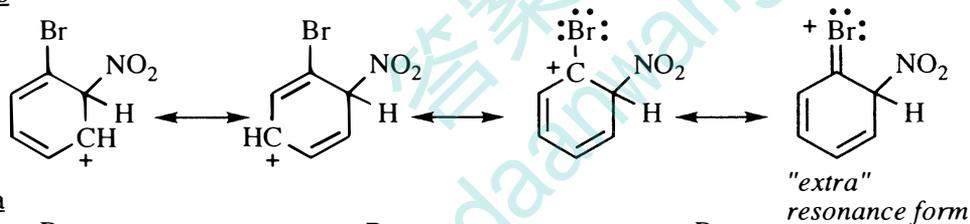
(b) The NH_2 group is a strongly activating ortho,para-director. In acid, however, it exists as the protonated ammonium ion—a strongly **deactivating meta-director**. The strongly acidic nitrating mixture itself forces the reaction to be slower.

(c) The acetyl group removes some of the electron density from the nitrogen, making it much less basic; the nitrogen of this amide is not protonated under the reaction conditions. The N retains enough electron density to share with the benzene ring, so the NHCOCH_3 group is still an activating ortho,para-director, though weaker than NH_2 .

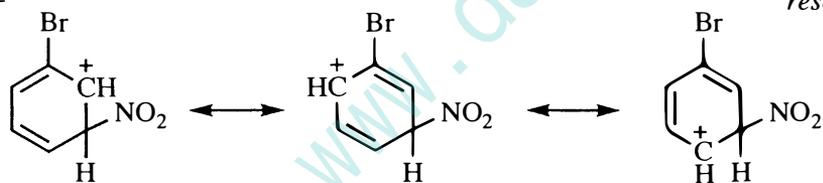


17-12 Nitronium ion attack at the ortho and para positions places positive charge on the carbon adjacent to the bromine, allowing resonance stabilization by an unshared electron pair from the bromine. Meta attack does not give a stabilized intermediate.

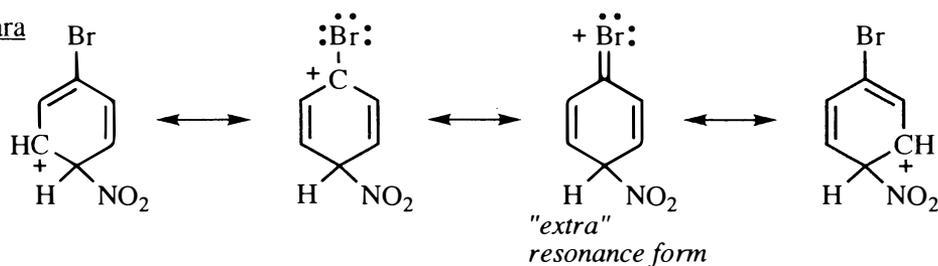
ortho



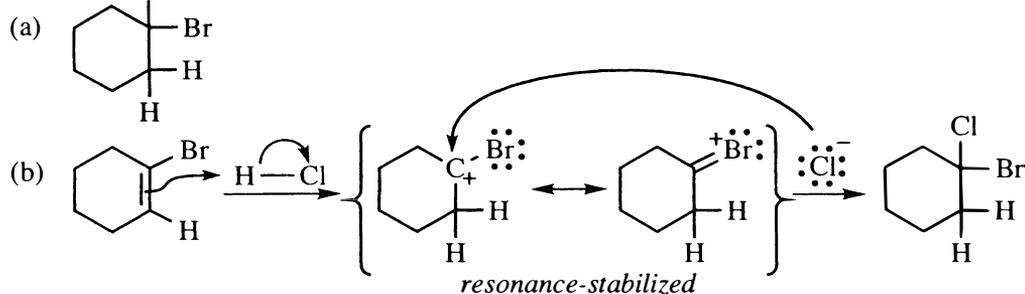
meta



para

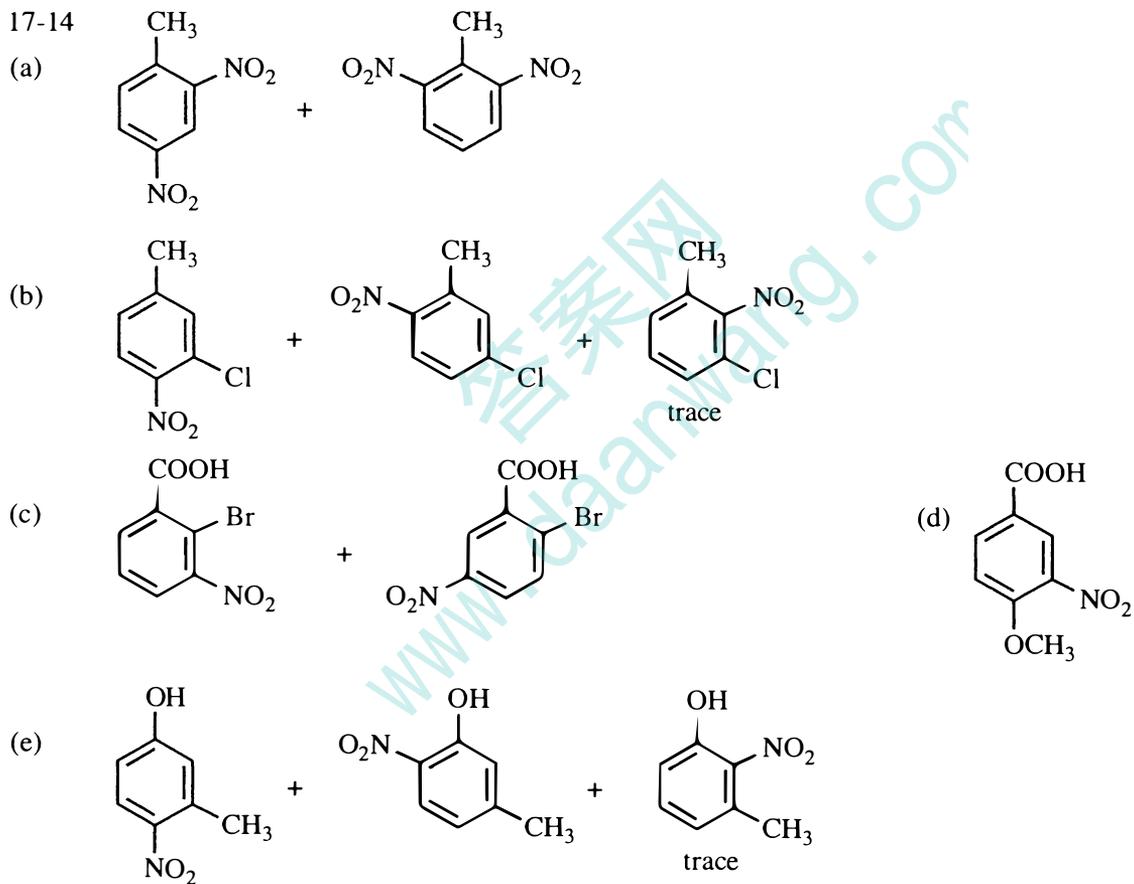


17-13

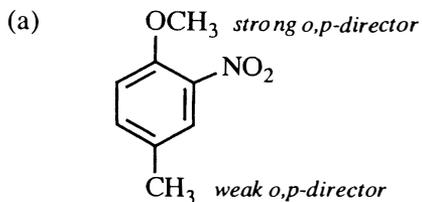


(c) A bromine atom can stabilize positive charge by sharing a pair of electrons. Bromine can do this in any cationic species, whether from electrophilic addition or electrophilic aromatic substitution.

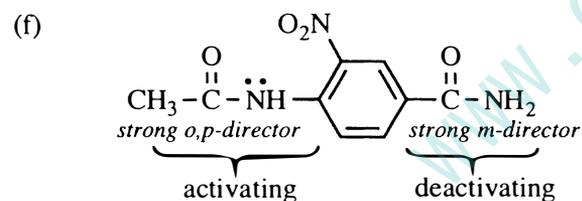
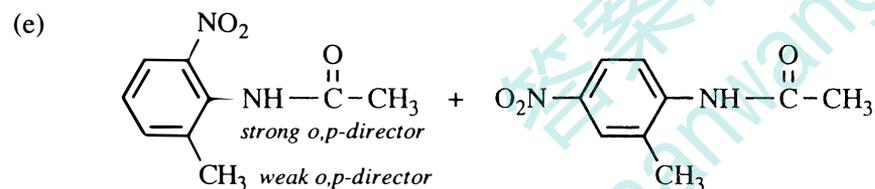
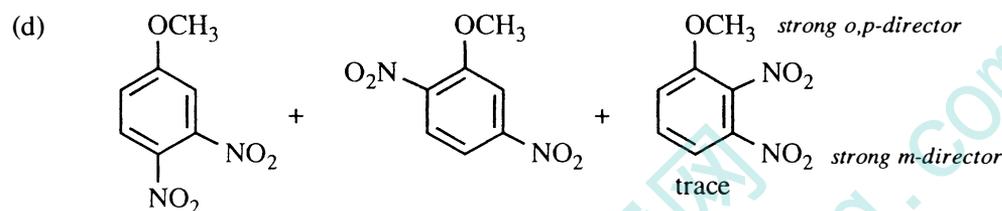
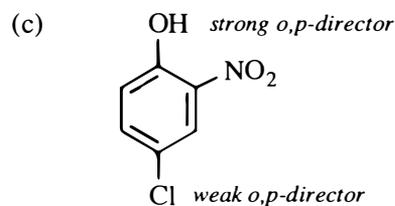
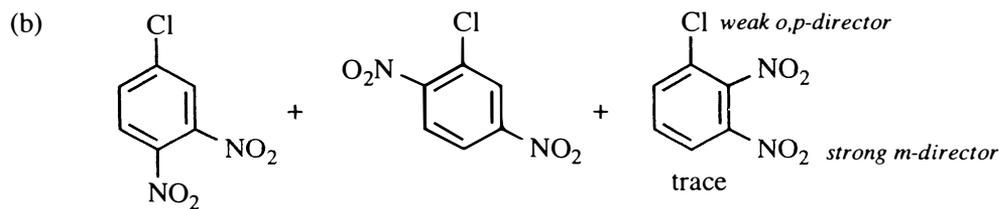
17-14



17-15

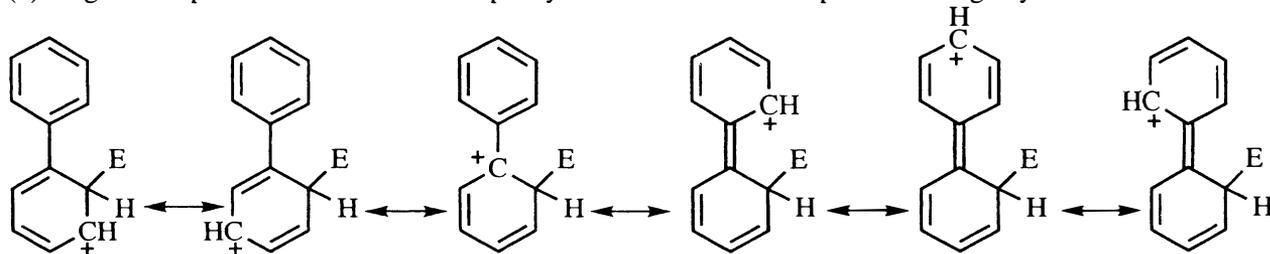


17-15 continued



17-16

(a) Sigma complex of ortho attack—the phenyl substituent stabilizes positive charge by resonance:

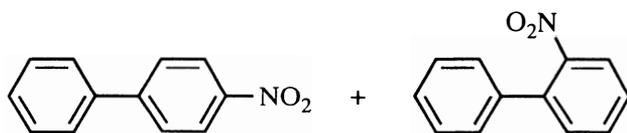


Para attack gives similar stabilization. Meta attack does not permit delocalization of the positive charge on the phenyl substituent.

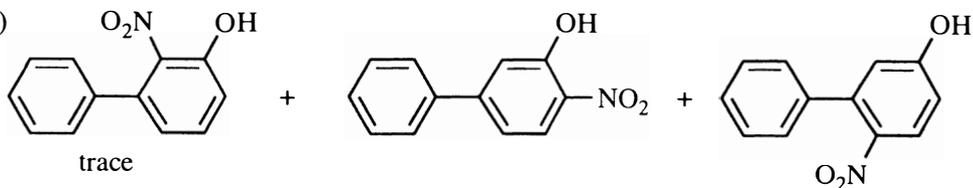
17-16 continued

(b)

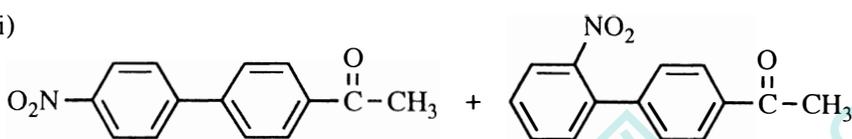
(i)



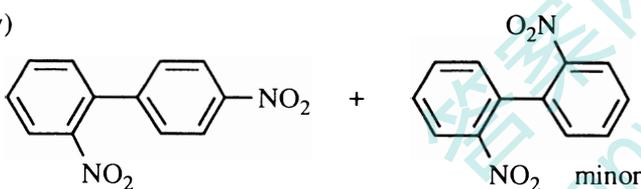
(ii)



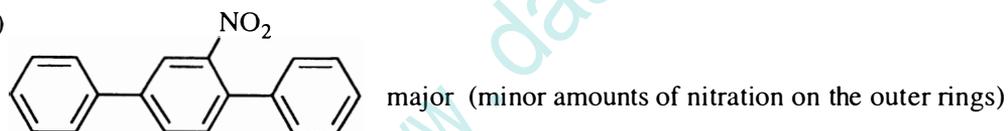
(iii)



(iv)

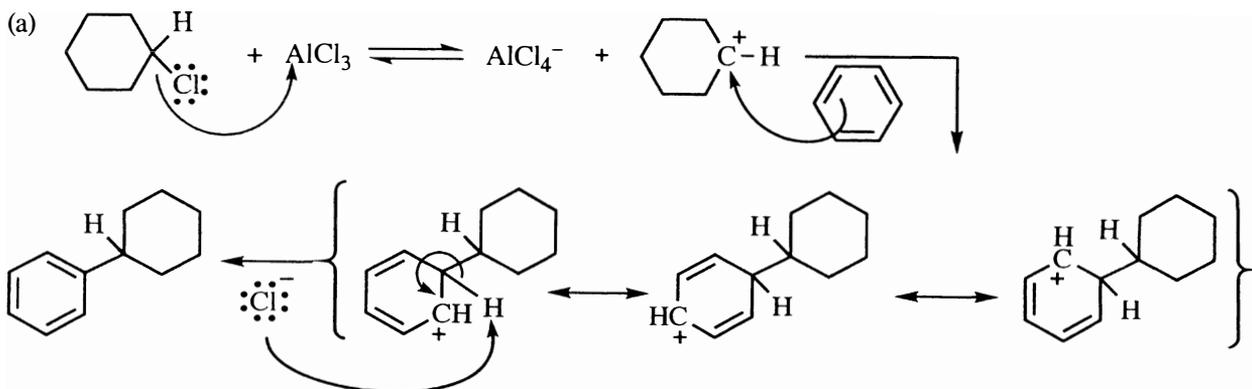


(v)

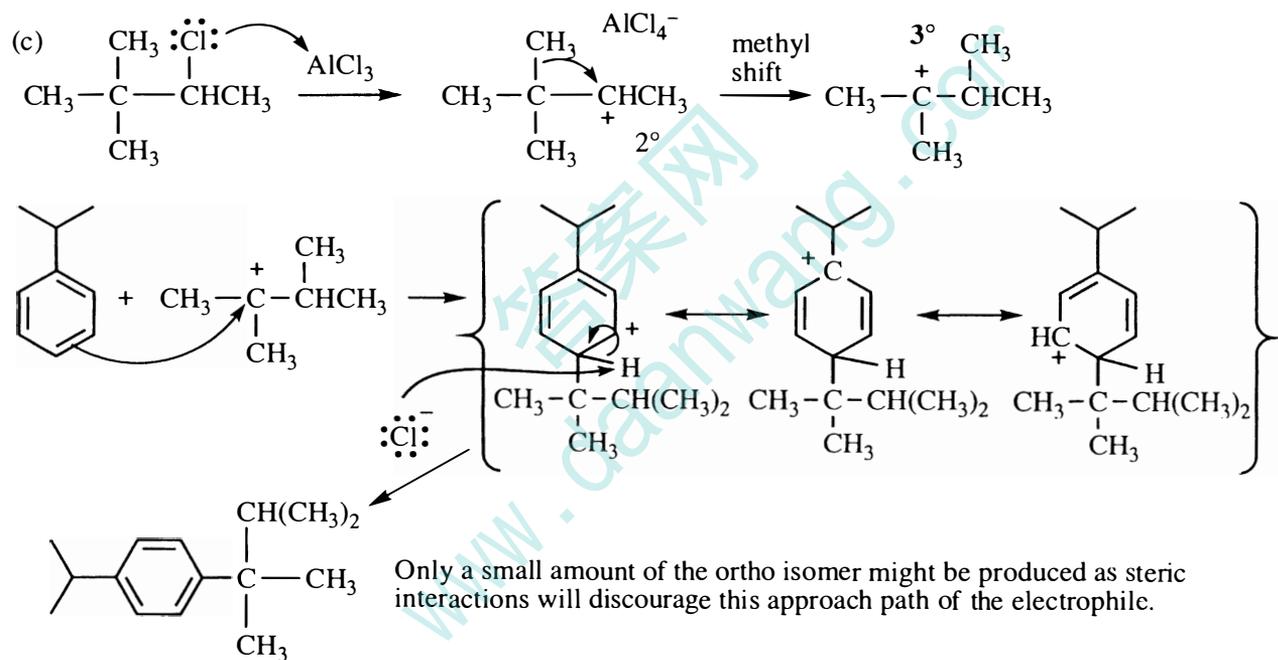
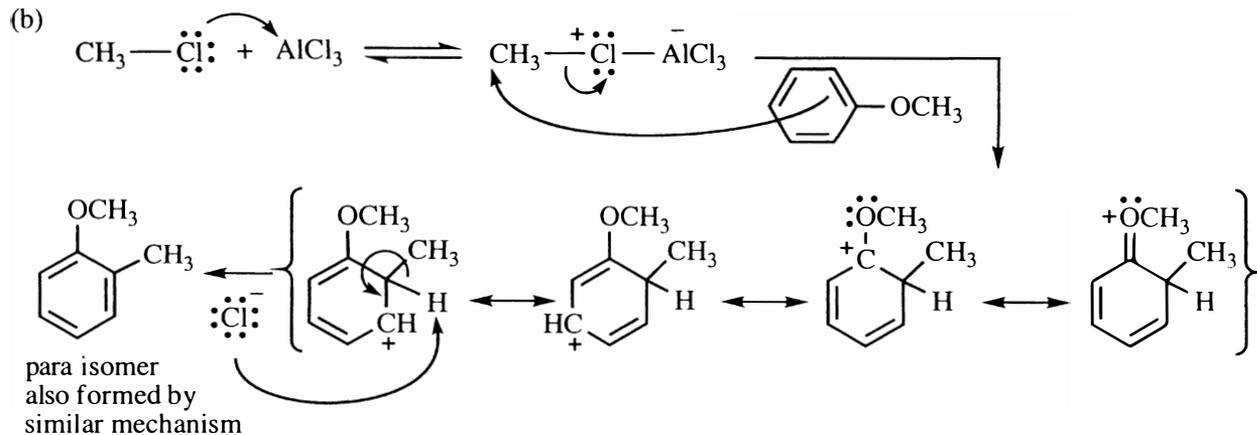


17-17

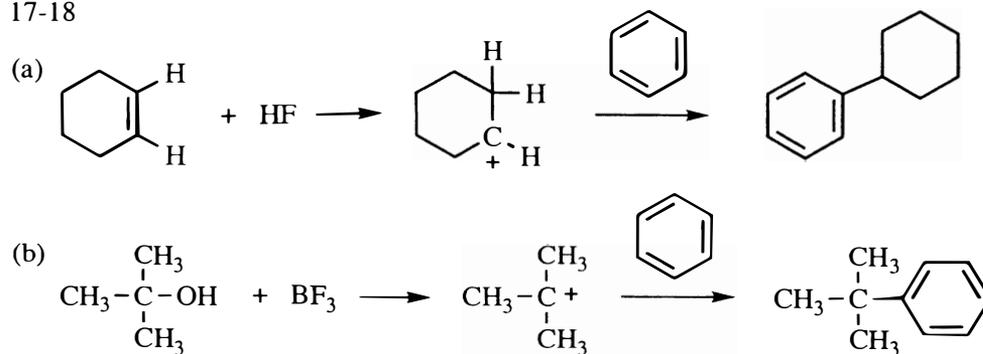
(a)



17-17 continued

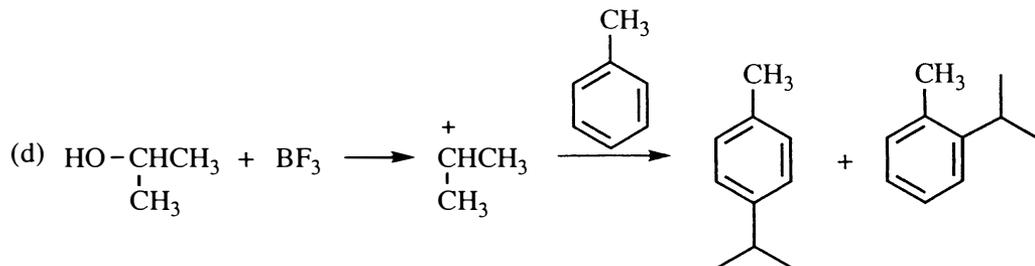
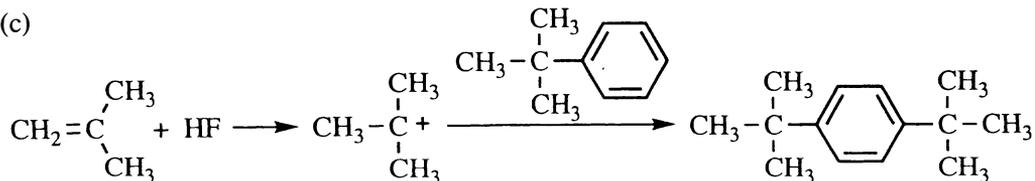


17-18

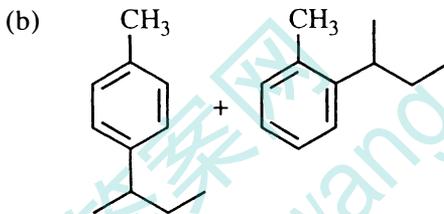
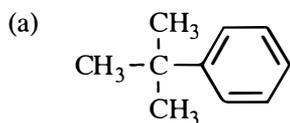


17-18 continued

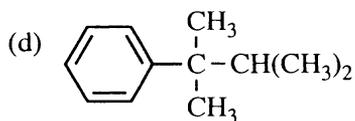
(c)



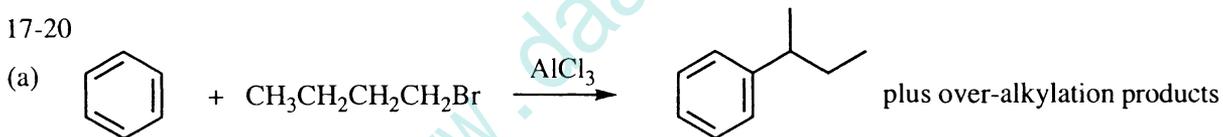
17-19 In (a), (b), and (d), the electrophile has rearranged.



(c) No reaction: nitrobenzene is too deactivated for the Friedel-Crafts reaction to succeed.



17-20



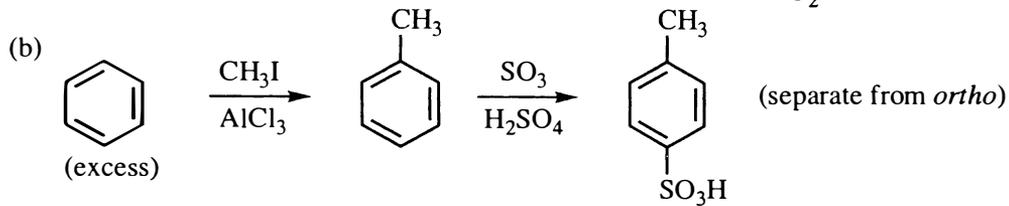
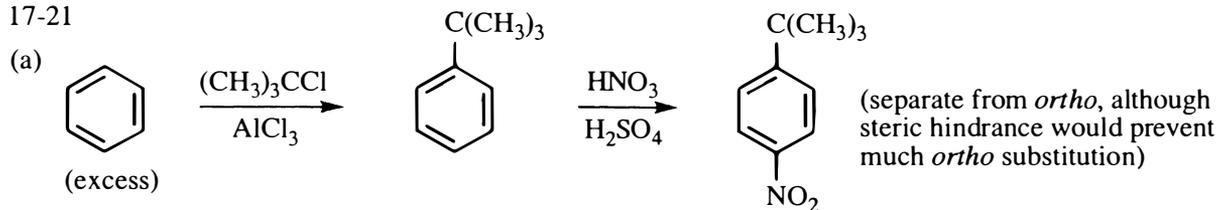
(b) gives desired product

(c) gives desired product, plus ortho isomer; use excess bromobenzene to avoid overalkylation

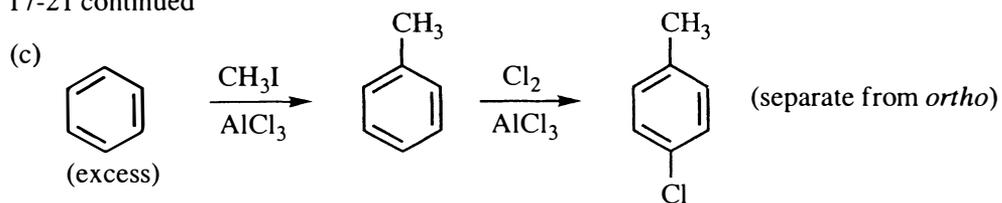
(d) gives desired product, plus ortho isomer

(e) gives desired product

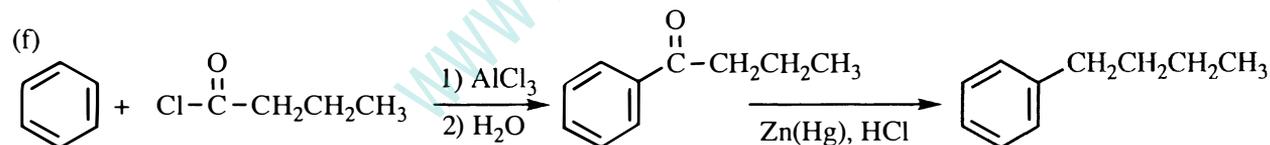
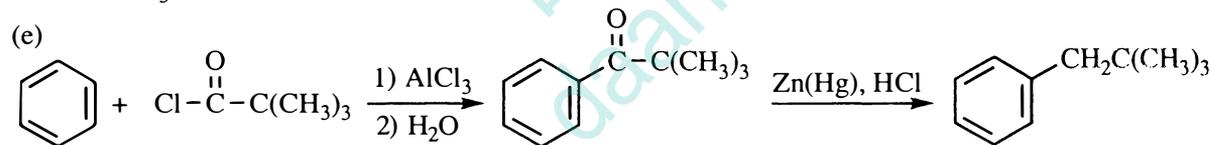
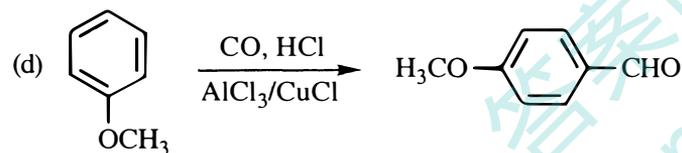
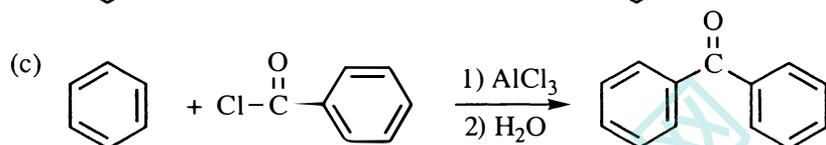
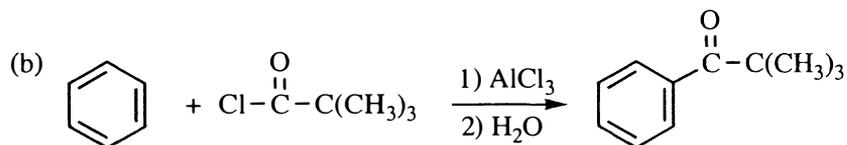
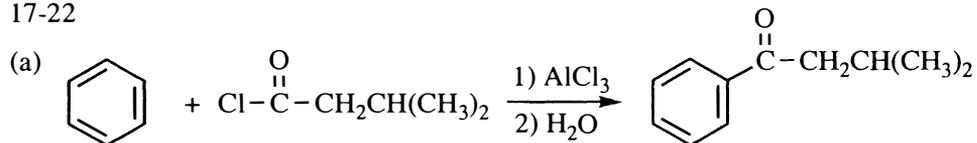
17-21



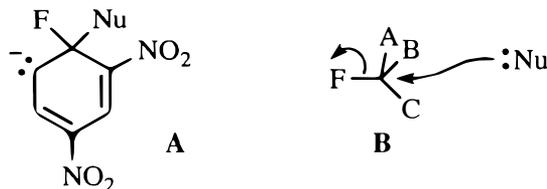
17-21 continued



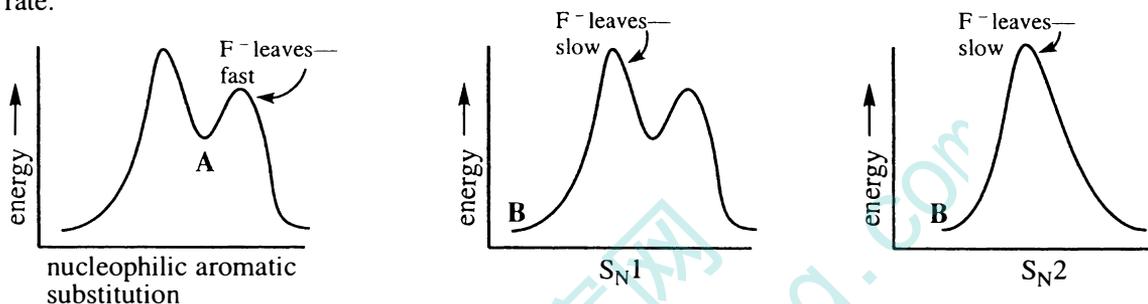
17-22



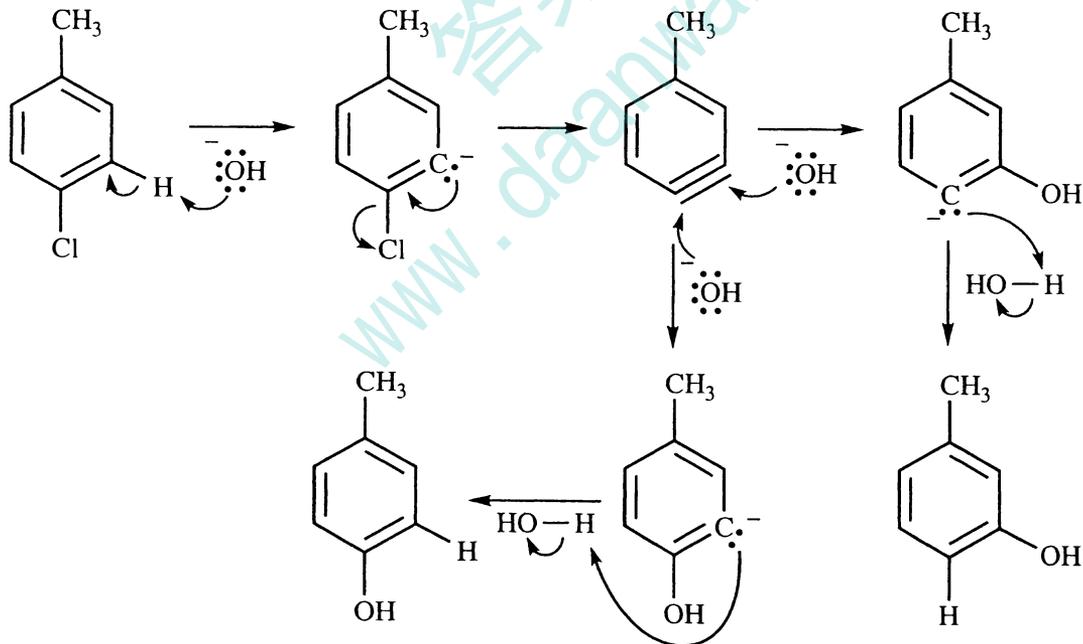
17-23 Another way of asking this question is this: Why is fluoride ion a good leaving group from **A** but not from **B** (either by S_N1 or S_N2)?



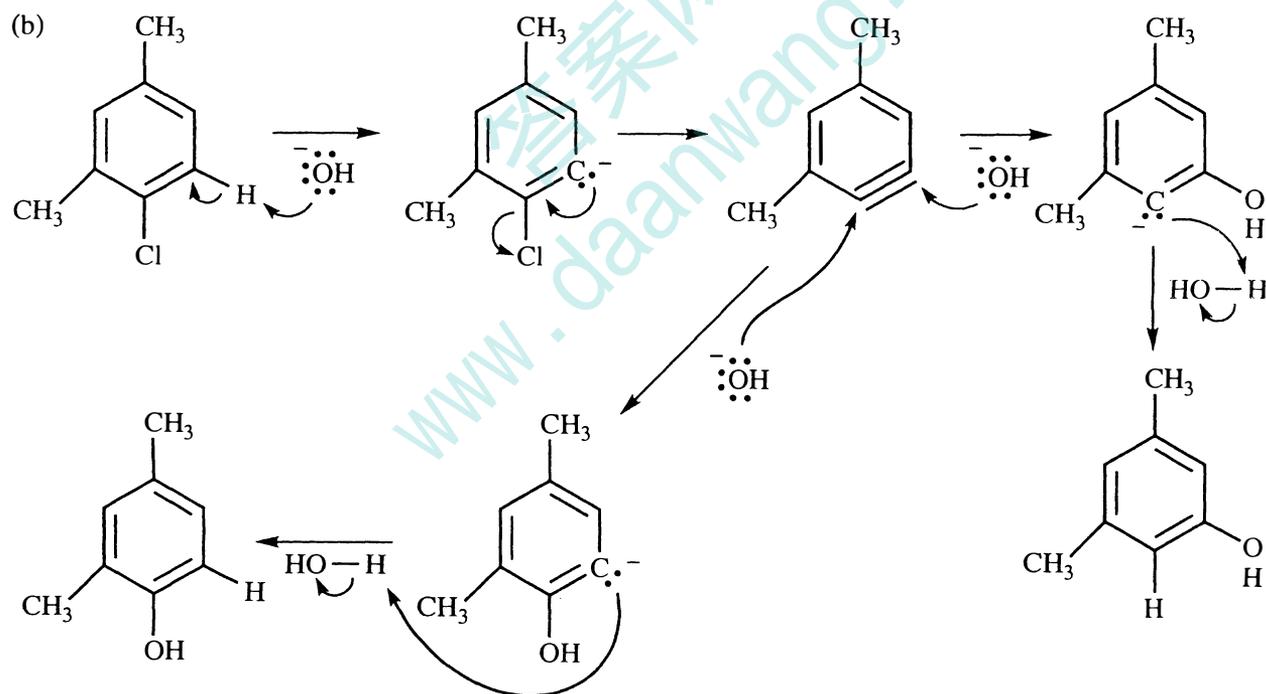
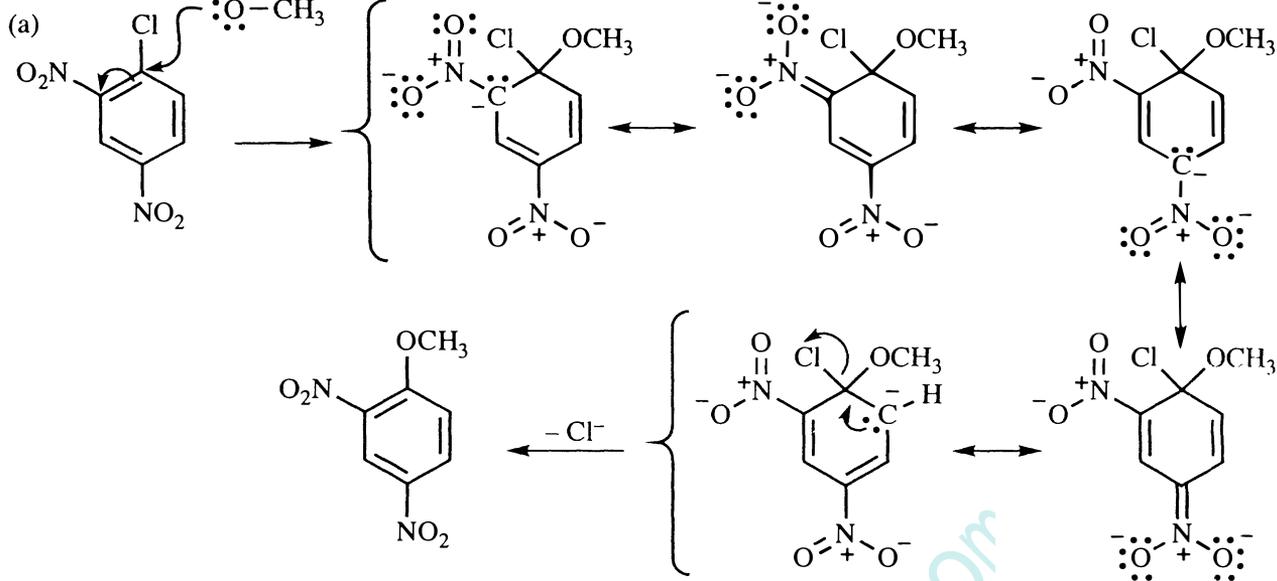
Formation of the anionic sigma complex **A** is the rate-determining (slow) step in nucleophilic aromatic substitution. The loss of fluoride ion occurs in a subsequent fast step where the nature of the leaving group does not affect the overall reaction rate. In the S_N1 or S_N2 mechanisms, however, the carbon-fluorine bond is breaking in the rate-determining step, so the poor leaving group ability of fluoride does indeed affect the rate.



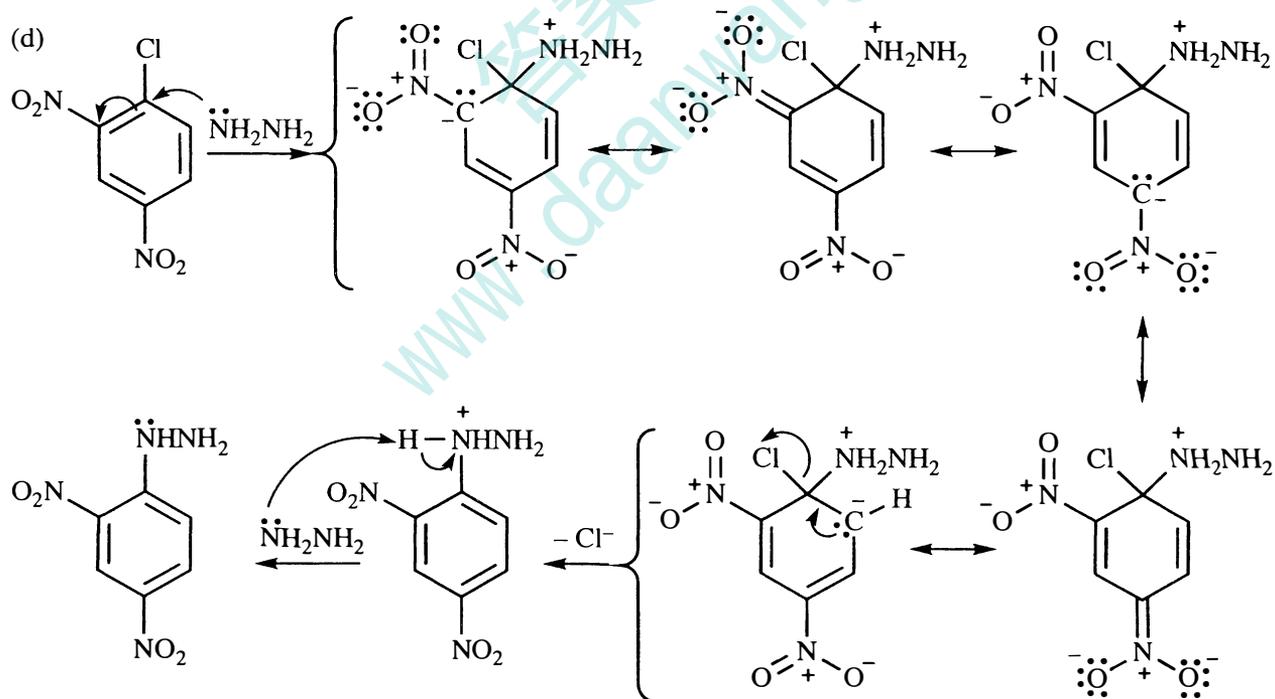
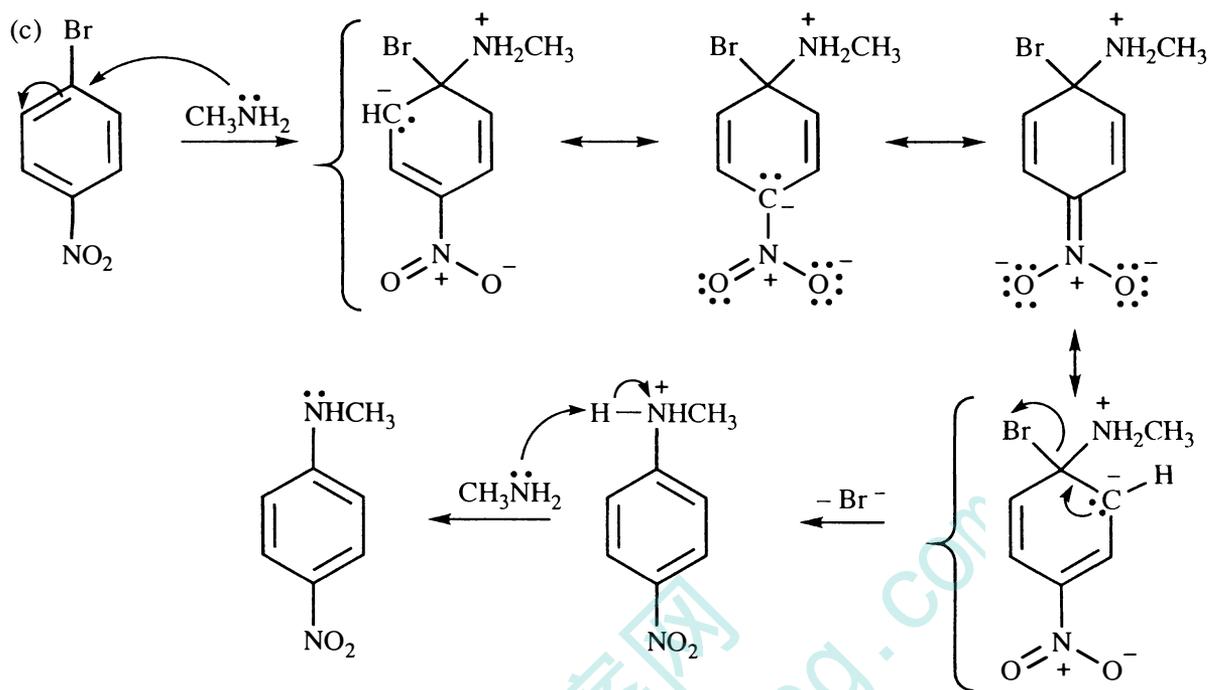
17-24



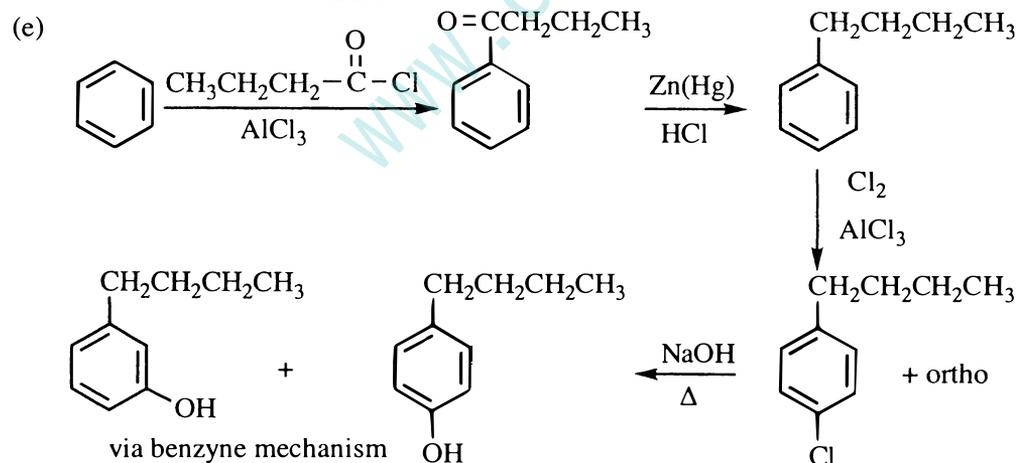
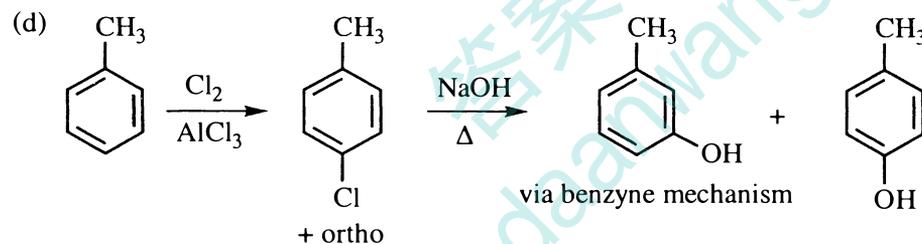
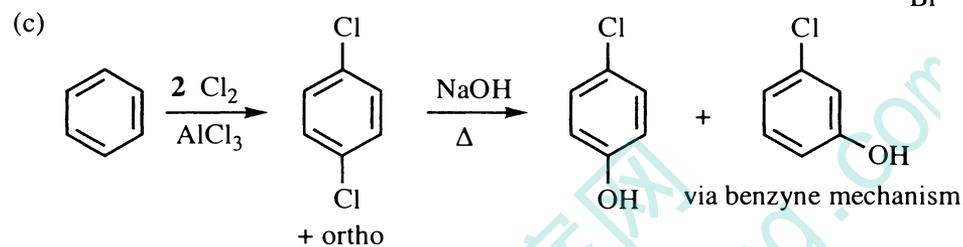
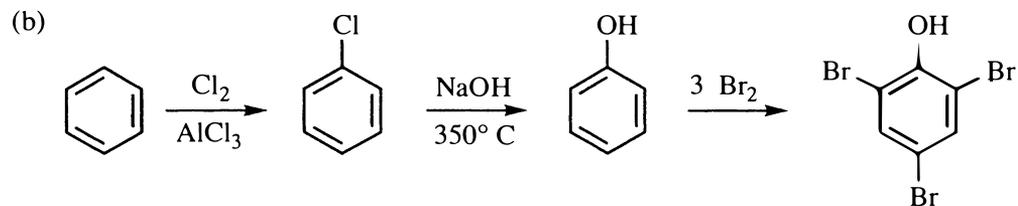
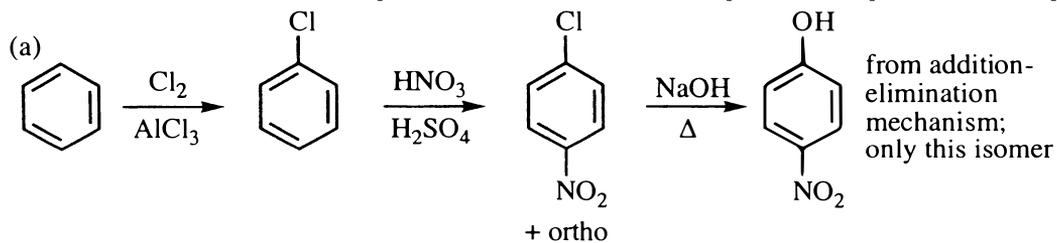
17-25



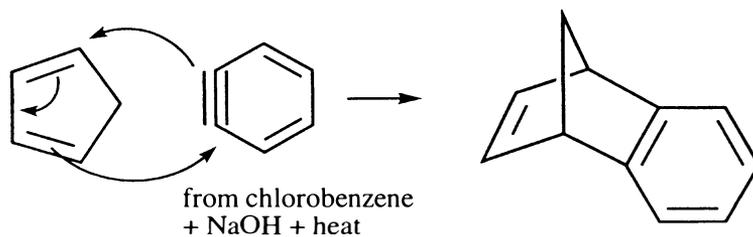
17-25 continued



17-26 Assume an acidic workup to each of these reactions to produce the phenol, not the phenoxide ion.

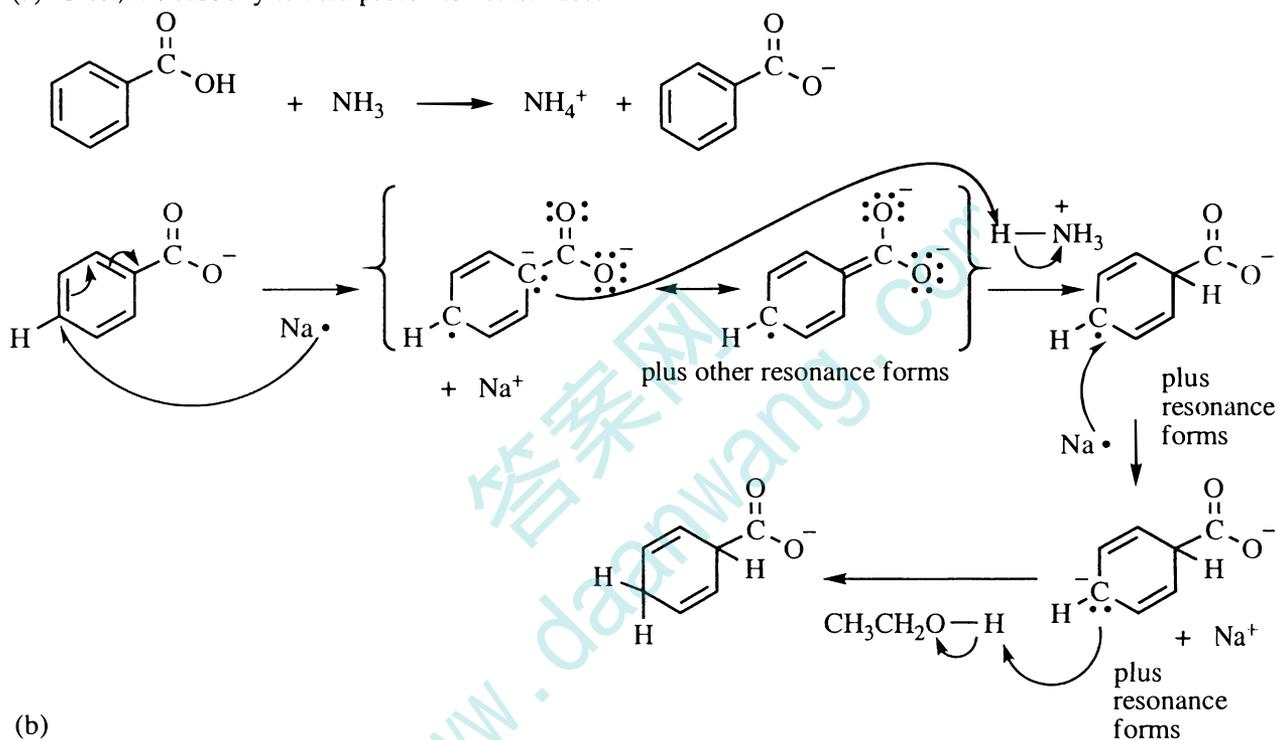


17-27

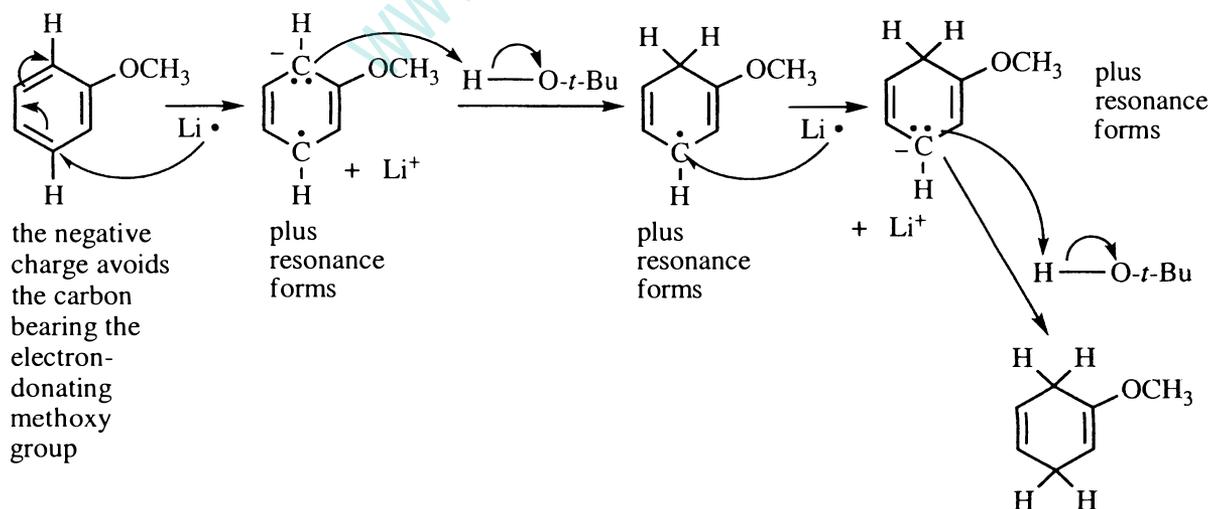


17-28

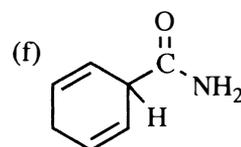
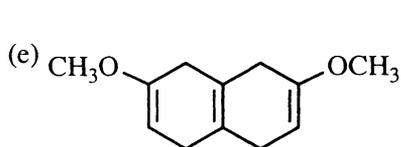
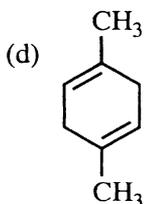
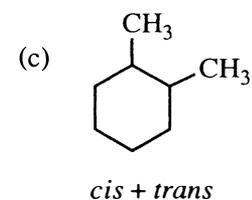
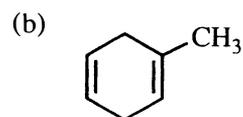
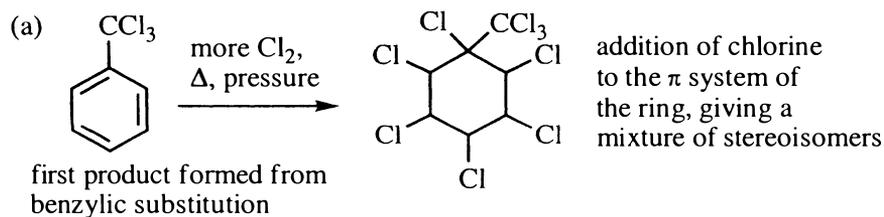
(a) First, the carboxylic acid proton is neutralized.



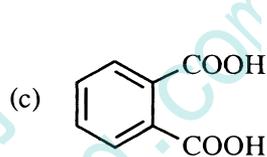
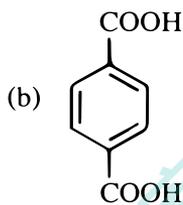
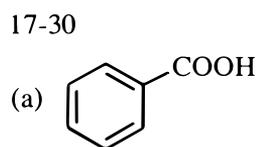
(b)



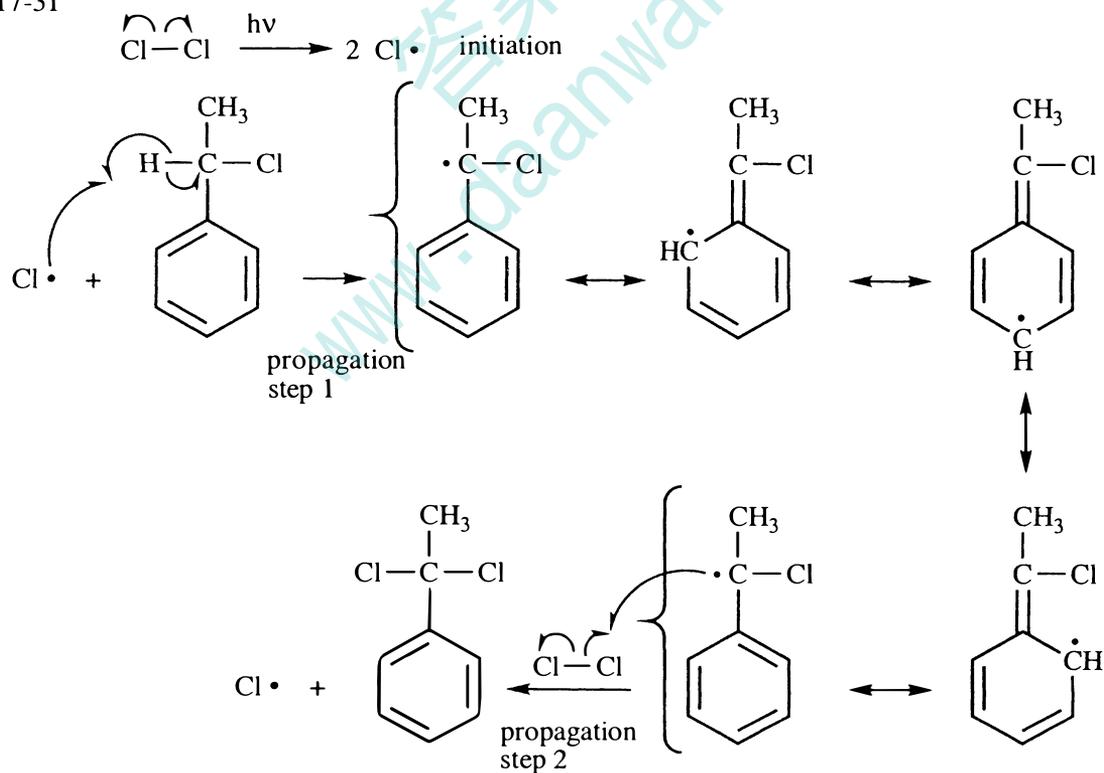
17-29



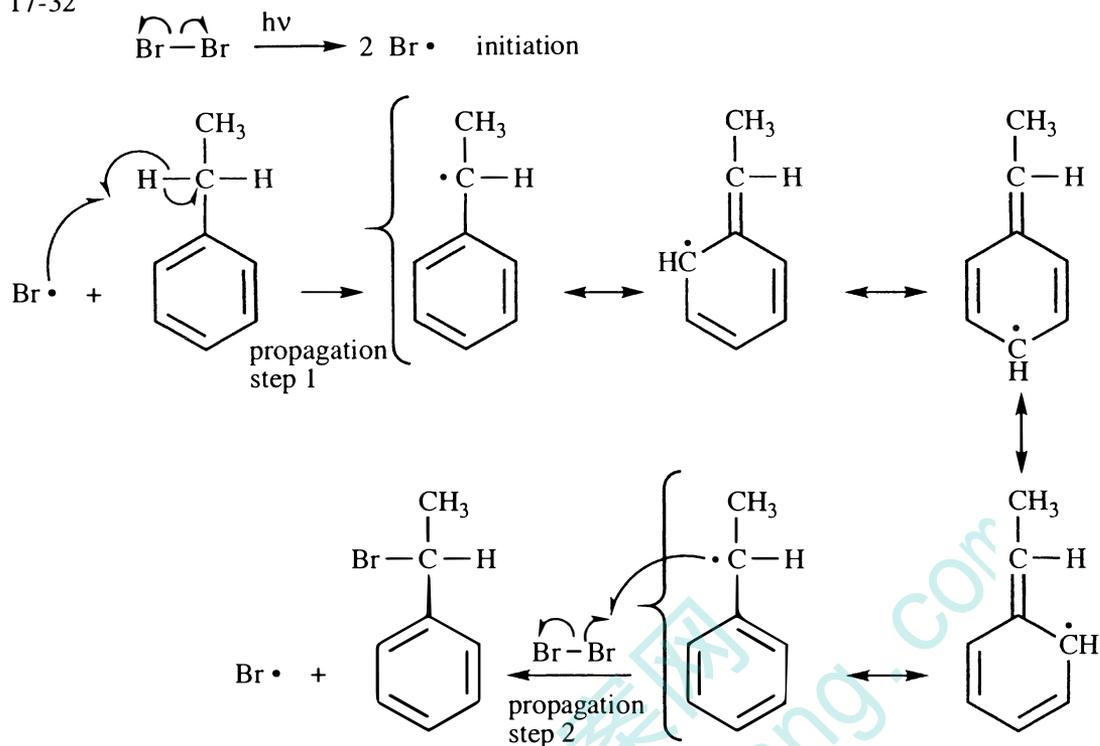
17-30



17-31



17-32



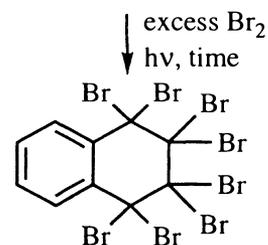
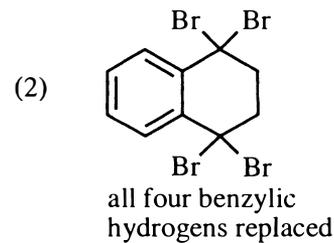
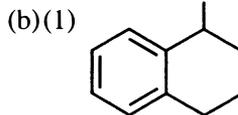
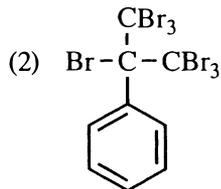
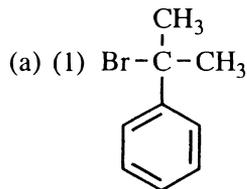
17-33 A statistical mixture would give 2 : 3 or 40% : 60% α to β . To calculate the relative reactivities, the percents must be corrected for the numbers of each type of hydrogen.

$$\alpha: \frac{56\%}{2\text{H}} = 28 \text{ relative reactivity}$$

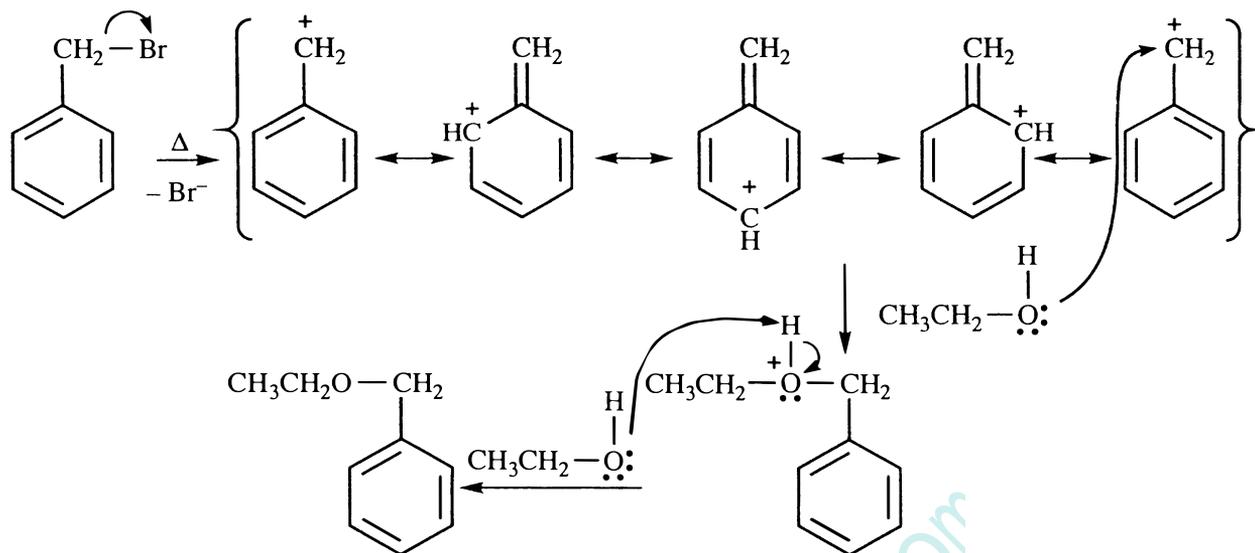
$$\beta: \frac{44\%}{3\text{H}} = 14.7 \text{ relative reactivity}$$

The reactivity of α to β is $\frac{28}{14.7} = 1.9$ to 1

17-34 Replacement of aliphatic hydrogens with bromine can be done under free radical substitution conditions, but reaction at aromatic carbons is unfavorable because of the very high energy of the aryl radical. Benzylic substitution is usually the only product observed.



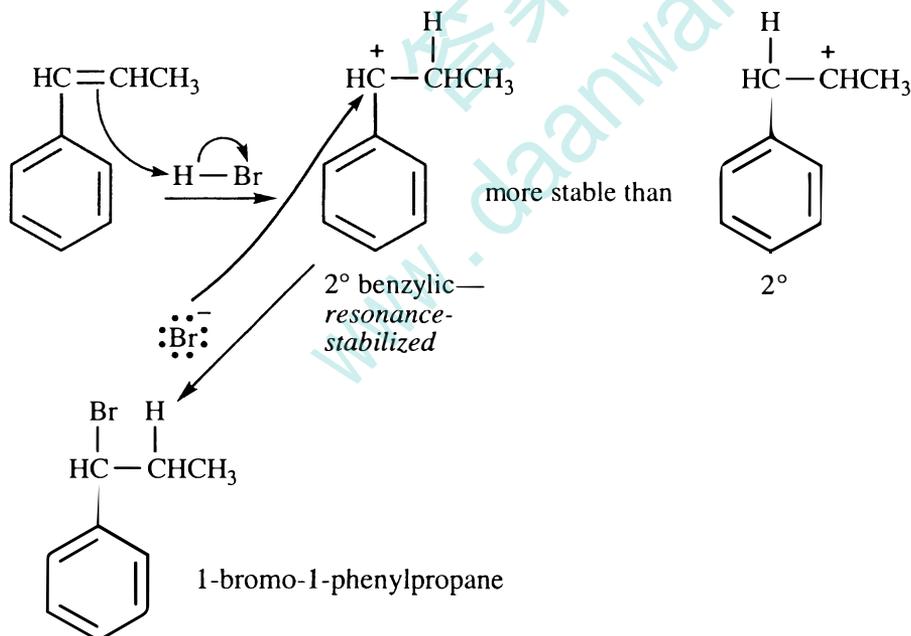
17-35



17-36

(a) Benzylic cations are stabilized by resonance and are much more stable than regular alkyl cations. The product is 1-bromo-1-phenylpropane.

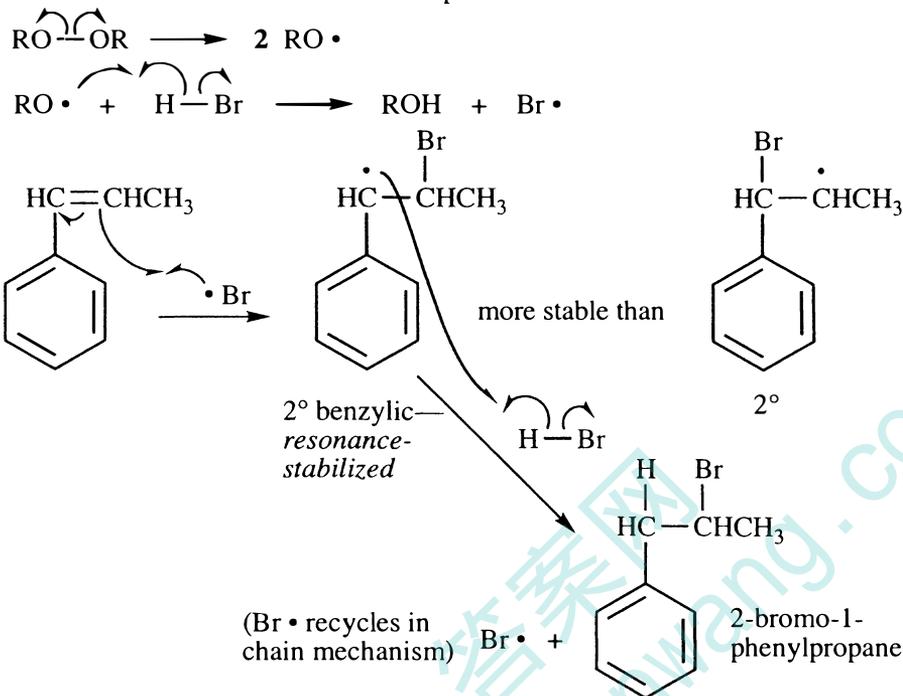
(b)



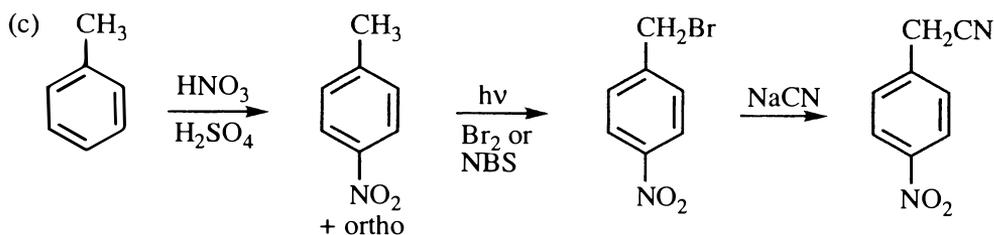
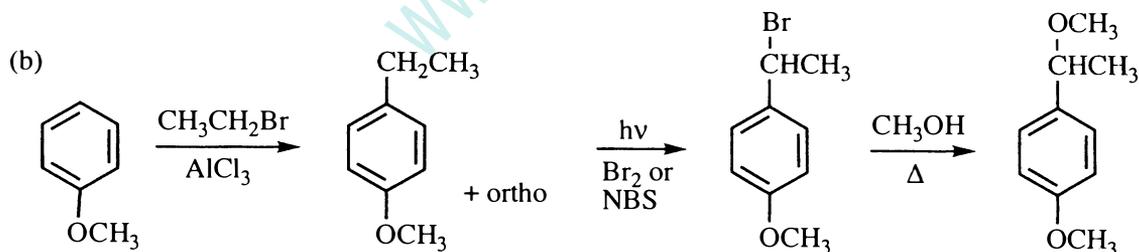
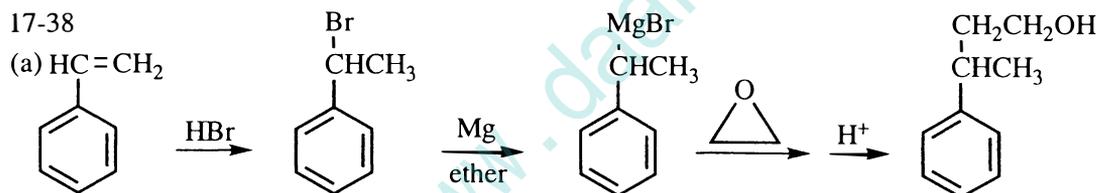
17-37

(a) The combination of HBr with a free-radical initiator generates bromine radicals and leads to anti-Markovnikov orientation. (Recall that whatever species adds *first* to an alkene determines orientation.) The product will be 2-bromo-1-phenylpropane.

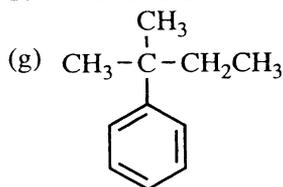
(b) Assume the free-radical initiator is a peroxide.



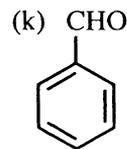
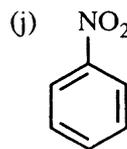
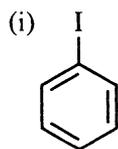
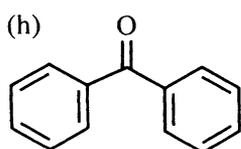
17-38



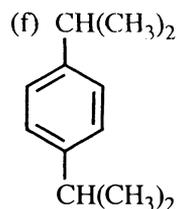
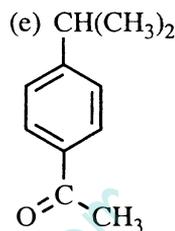
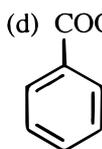
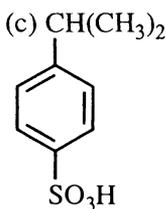
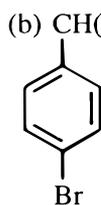
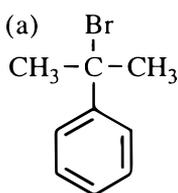
17-44 continued



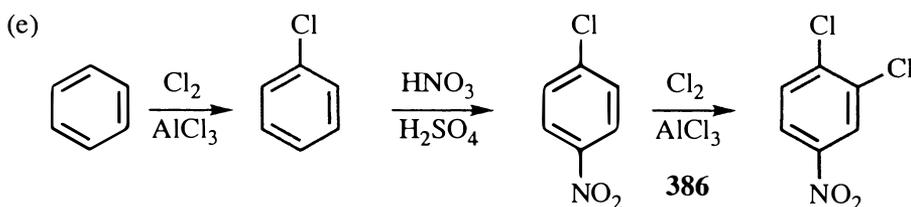
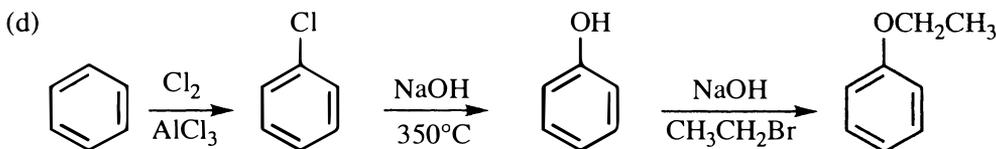
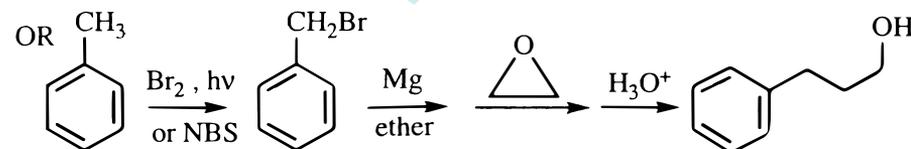
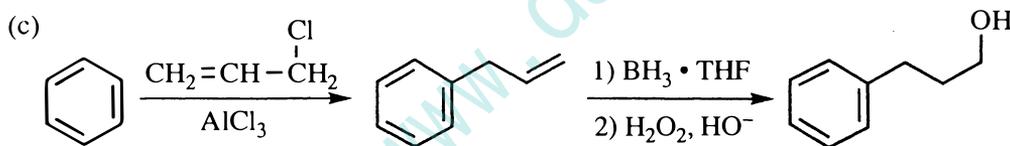
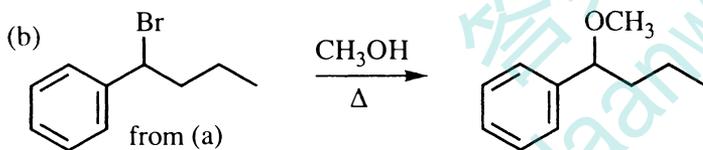
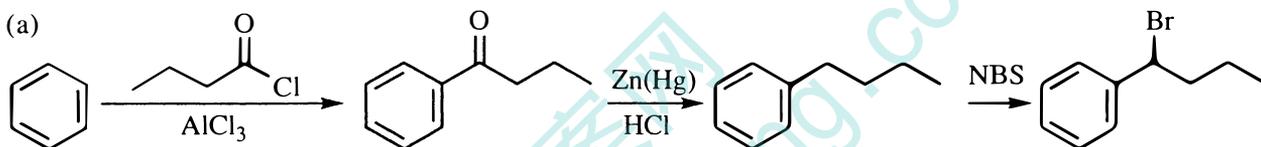
rearrangement



17-45 Products from substitution at the ortho position will be minor because of the steric bulk of the isopropyl group.

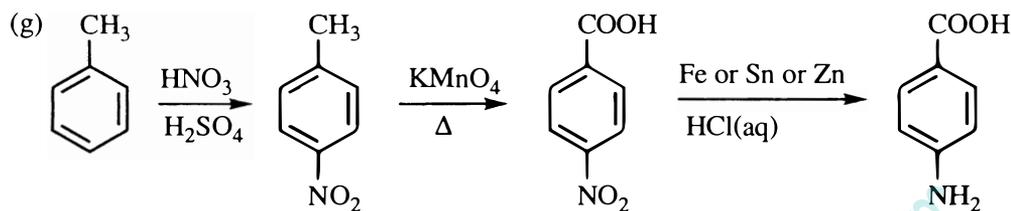
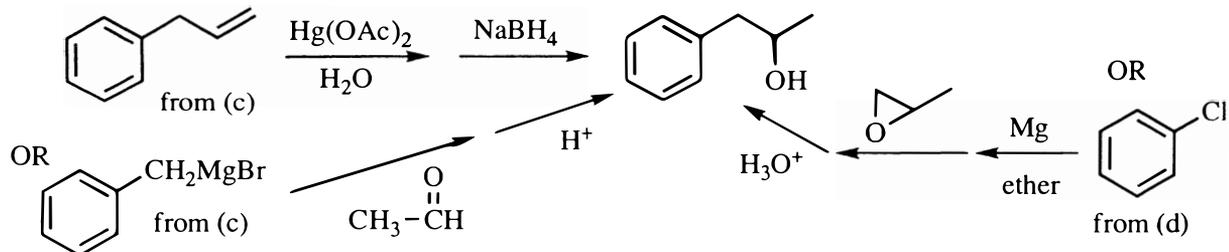


17-46

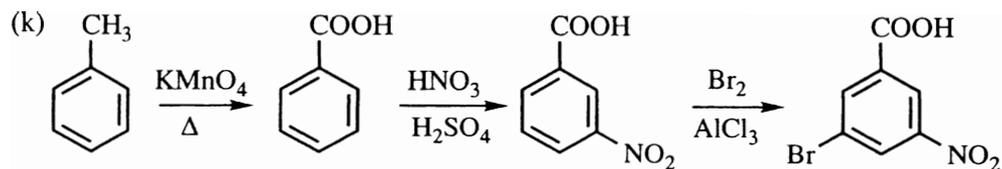
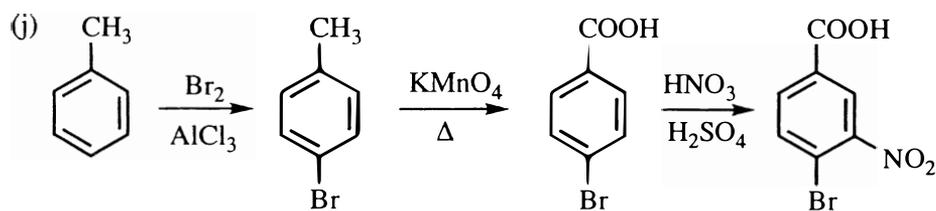
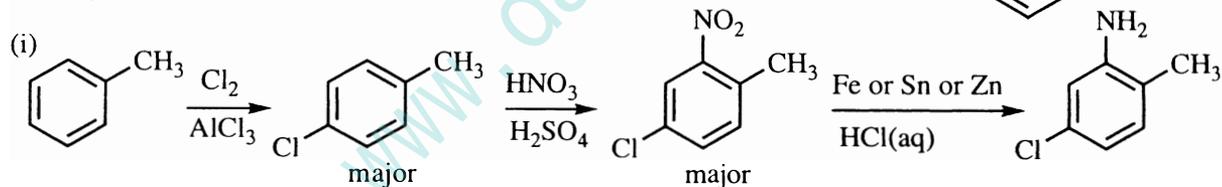
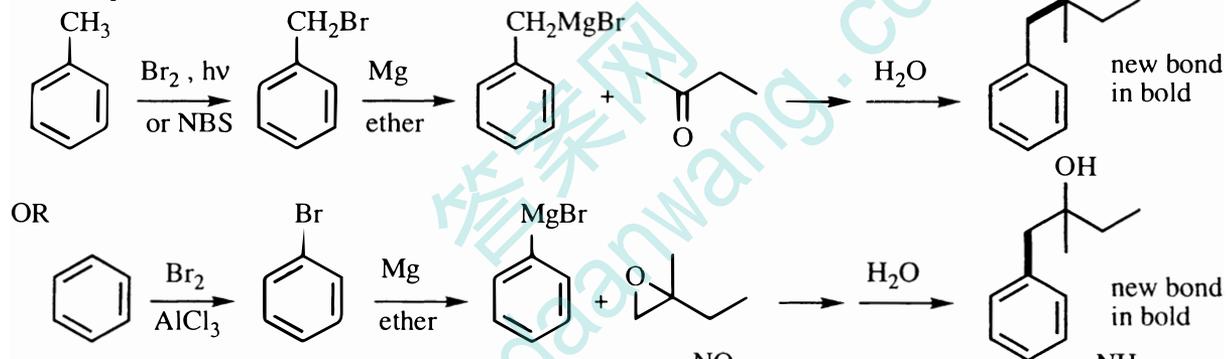


17-46 continued

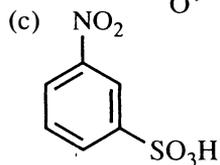
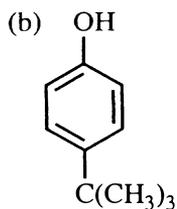
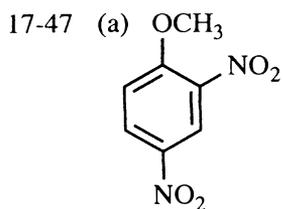
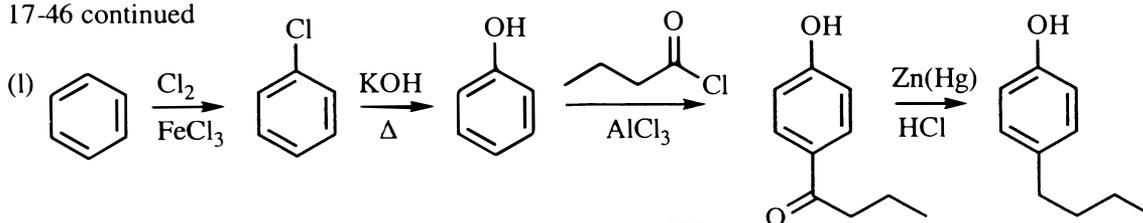
(f) three methods



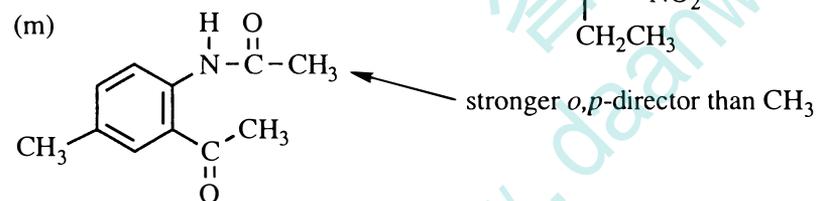
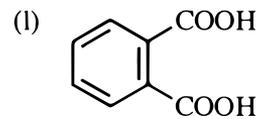
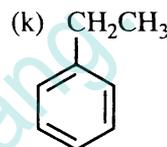
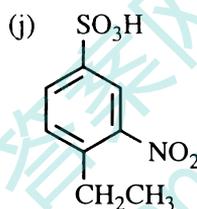
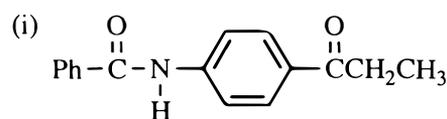
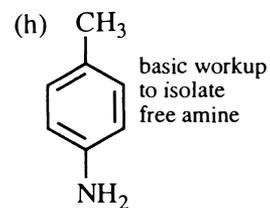
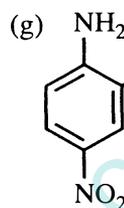
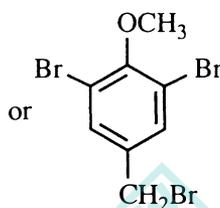
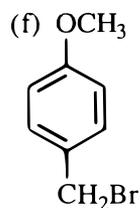
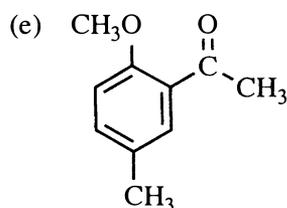
(h) two possible methods



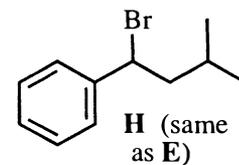
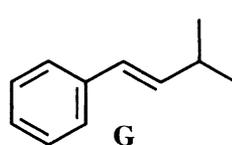
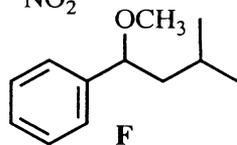
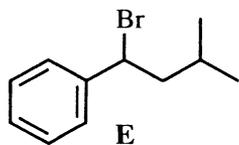
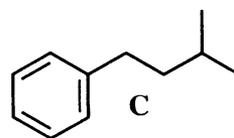
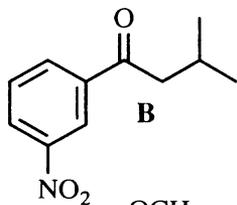
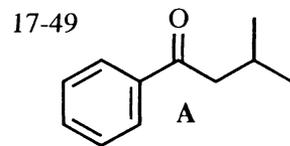
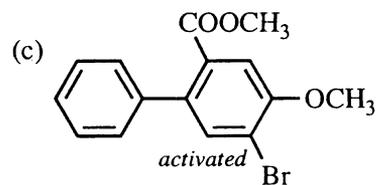
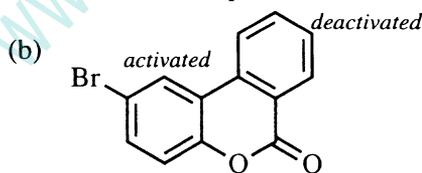
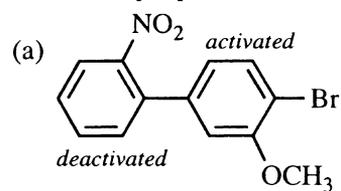
17-46 continued



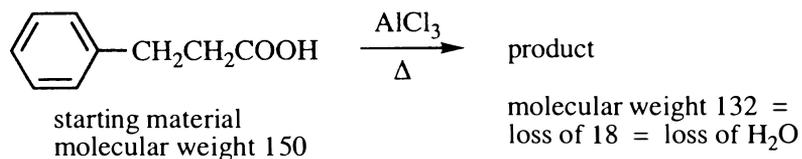
(d) no reaction: Friedel-Crafts acylation does not occur on rings with strong deactivating groups like NO₂



17-48 Major products are shown. Other isomers are possible.



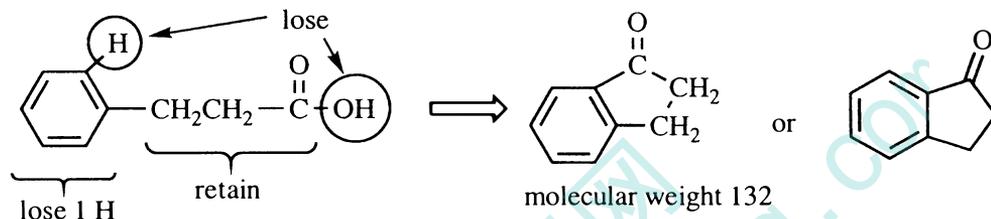
17-50



IR spectrum: The dominant peak is the carbonyl at 1710 cm⁻¹. No COOH stretch.

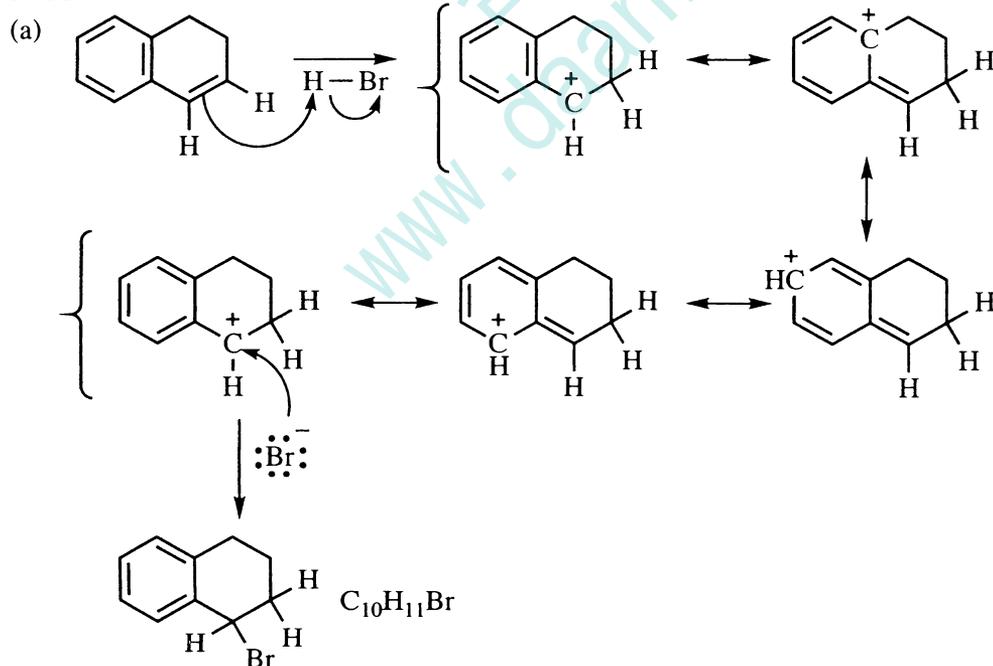
NMR spectrum: The splitting is complicated but the integration is helpful. In the region of δ 2.6-3.2, there are two signals each with integration value of 2H; these must be the two adjacent methylenes, CH₂CH₂. The aromatic region from δ 7.3-7.8 has integration of 4H, so the ring must be disubstituted.

Carbon NMR: Four of the aromatic signals are tall, indicating C—H; two are short, with no attached hydrogens, also showing a disubstituted benzene. Also indicated are carbons in a carbonyl and two methylenes.



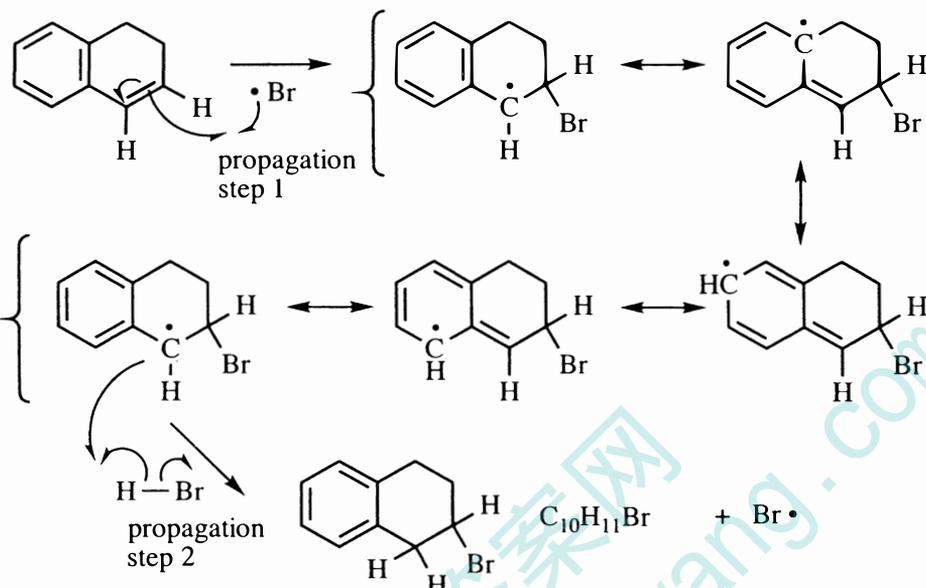
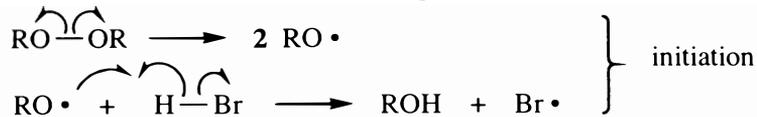
The product must be the cyclized ketone, formed in an intramolecular Friedel-Crafts acylation.

17-51

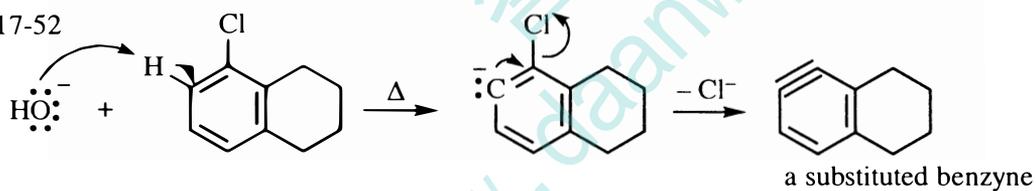


17-51 continued

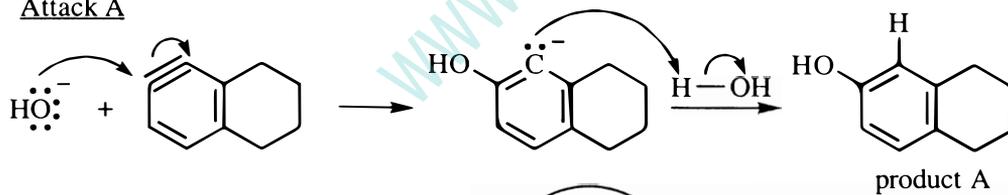
(b) Assume the free-radical initiator is a peroxide.



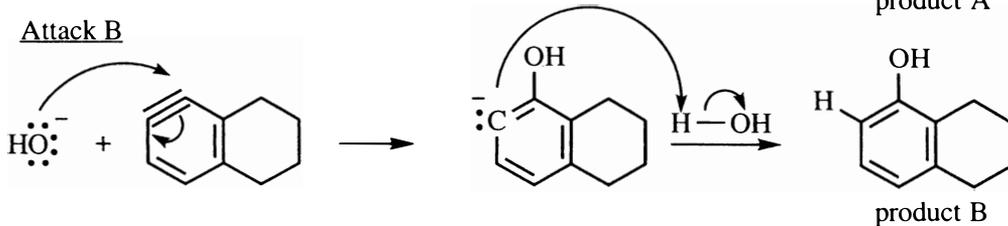
17-52



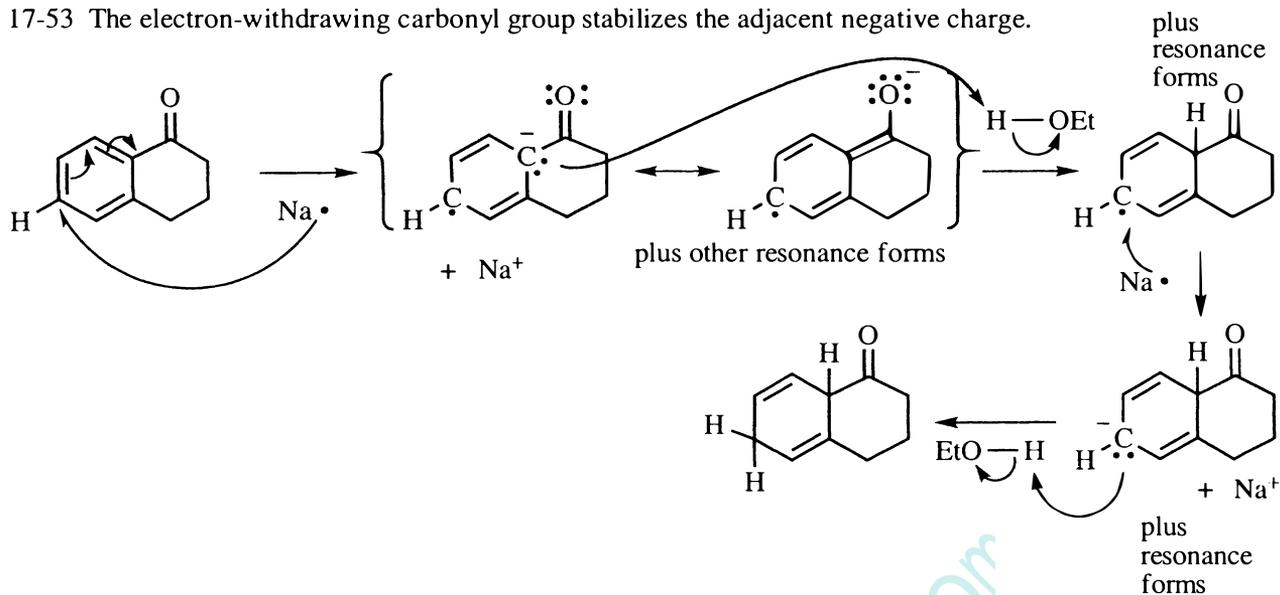
Attack A



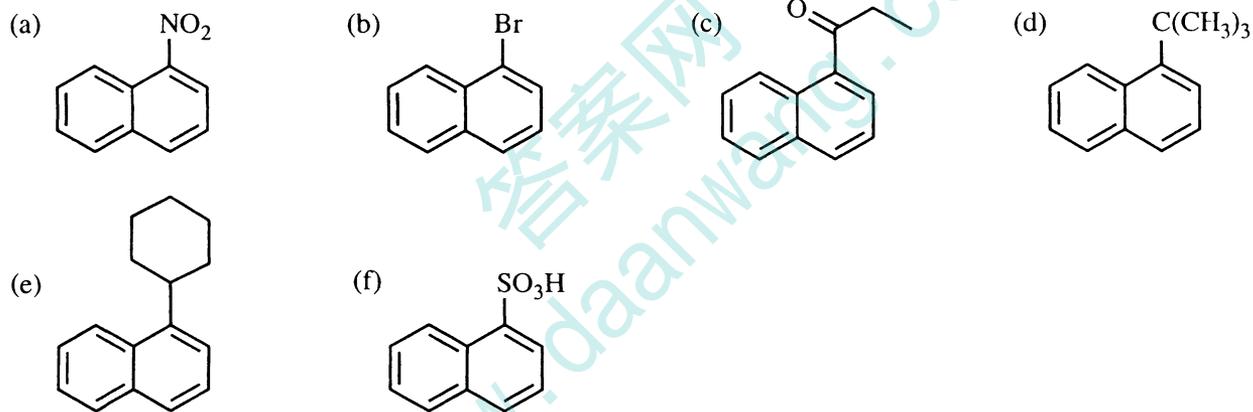
Attack B



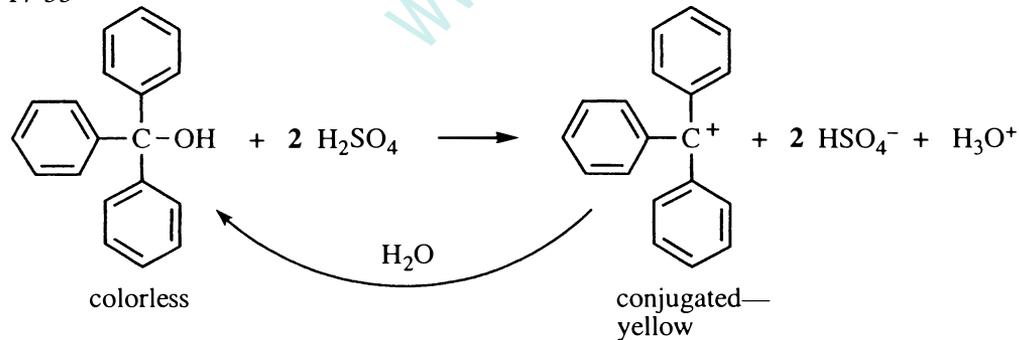
17-53 The electron-withdrawing carbonyl group stabilizes the adjacent negative charge.



17-54

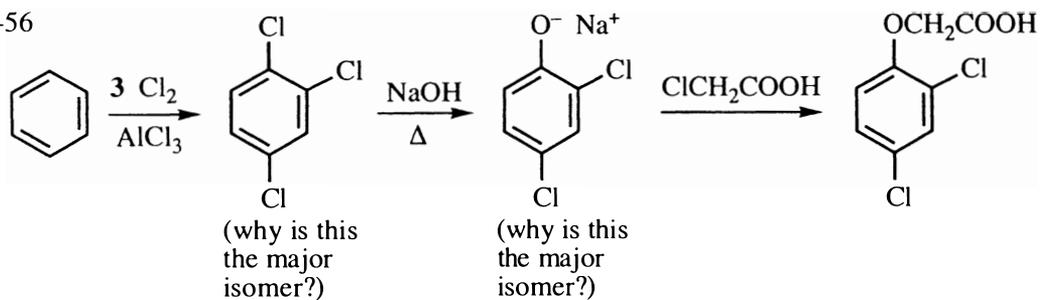


17-55



Concentrated sulfuric acid "dehydrates" the alcohol, producing a highly conjugated, colored carbocation, and protonates the water to prevent the reverse reaction. Upon adding more water, however, there are too many water molecules for the acid to protonate, and triphenylmethanol is regenerated.

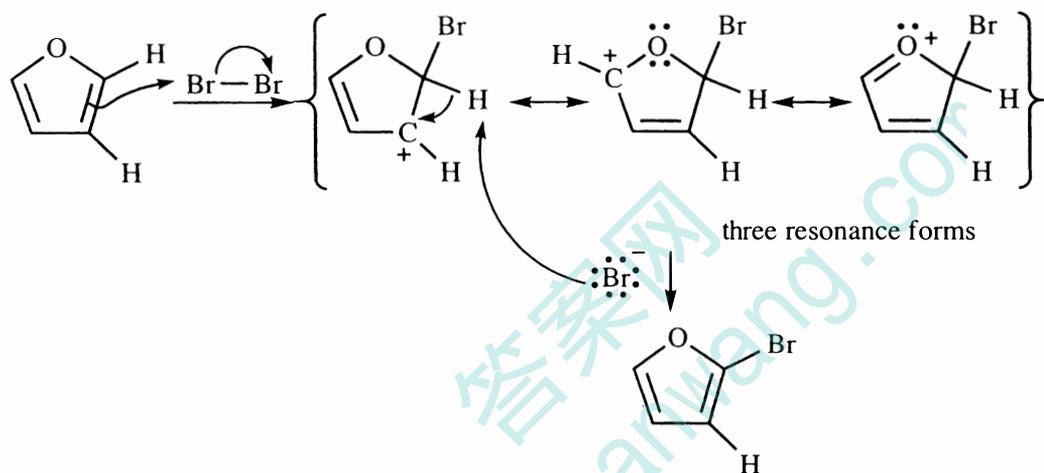
17-56



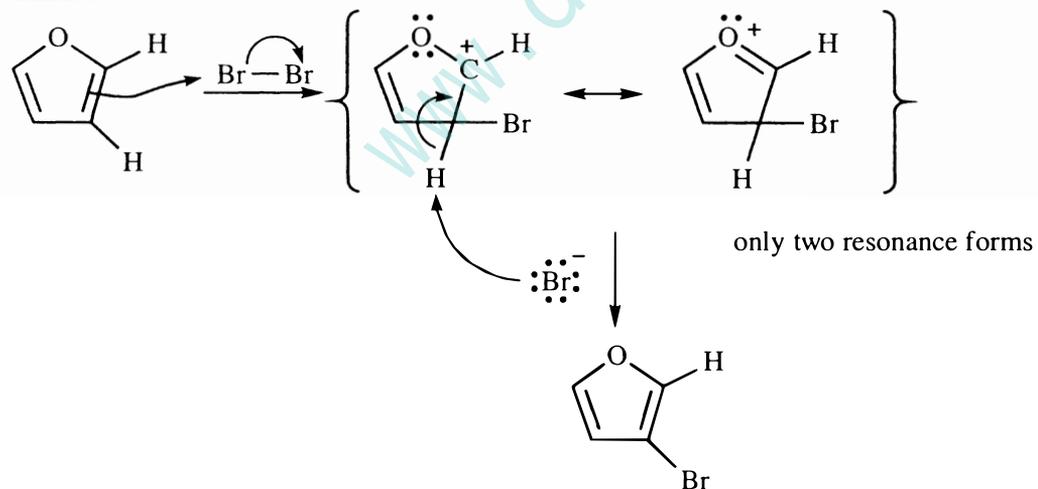
17-57

(a)

bromination at C-2

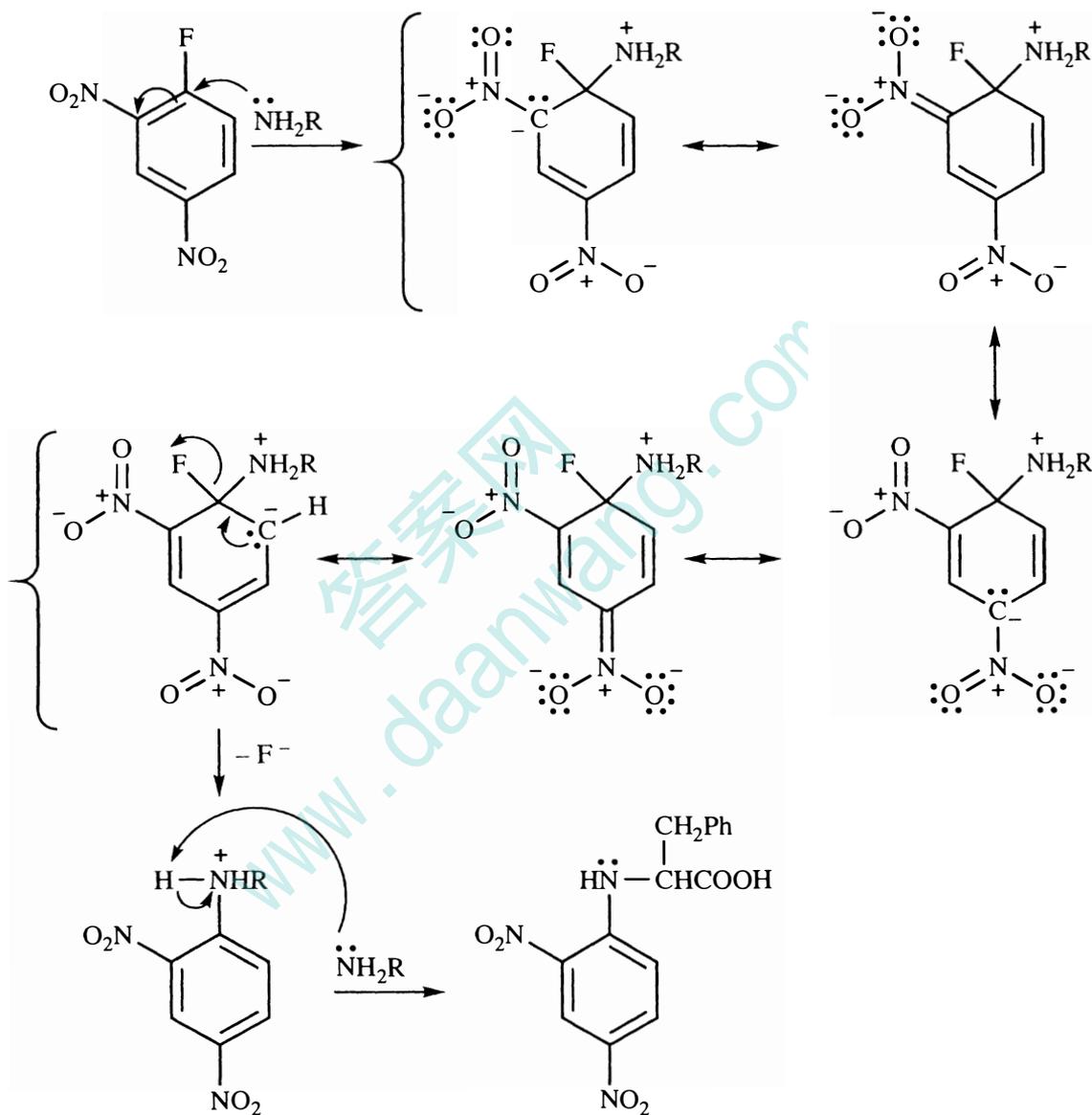
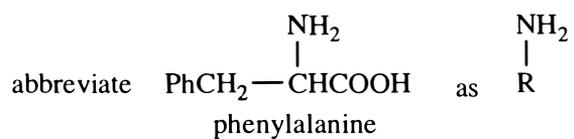


bromination at C-3

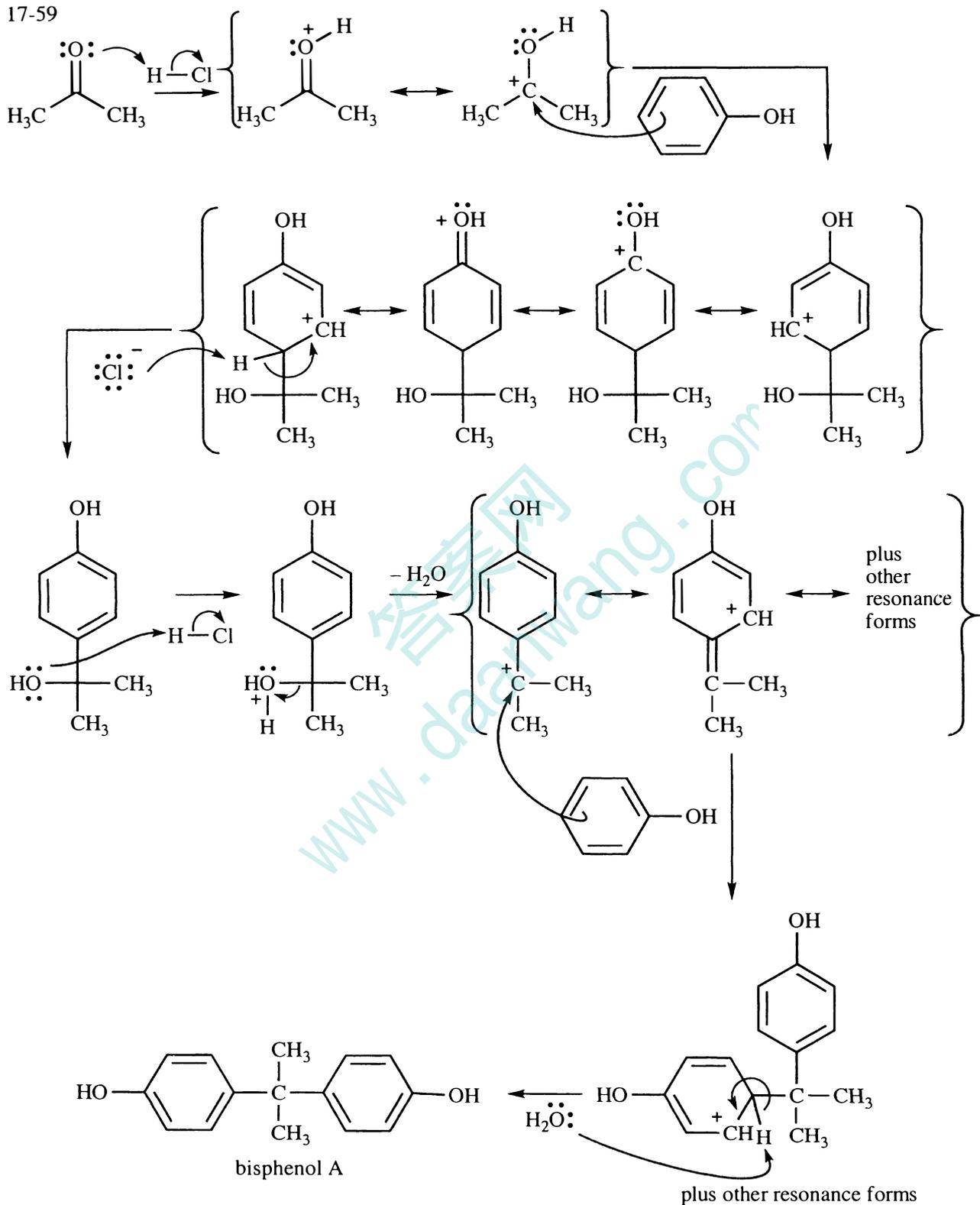


(b) Attack at C-2 gives an intermediate stabilized by three resonance forms, as opposed to only two resonance forms stabilizing attack at C-3. Bromination at C-2 will occur more readily.

17-58



17-59

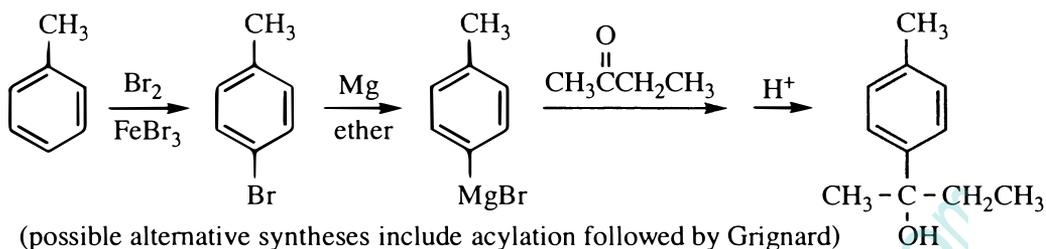


17-60

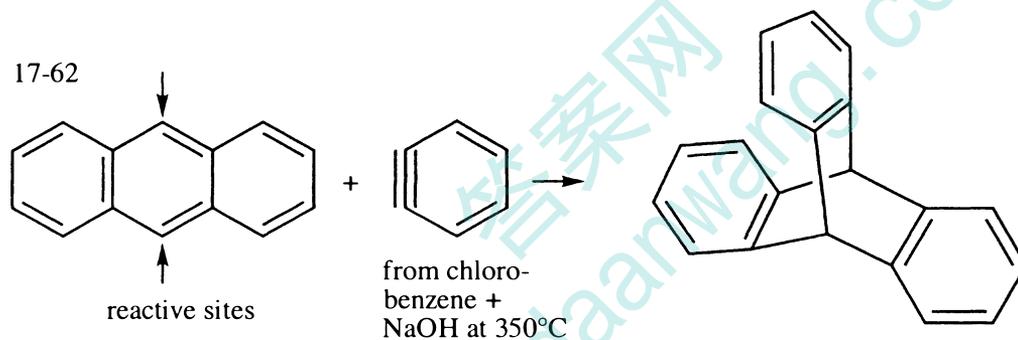
(a) This is an example of kinetic versus thermodynamic control of a reaction. At low temperature, the kinetic product predominates: in this case, almost a 1 : 1 mixture of ortho and para. These two isomers must be formed at approximately equal rates at 0° C. At 100° C, however, enough energy is provided for the *desulfonation* to occur rapidly; the large excess of the para isomer indicates the para is more stable, even though it is formed initially at the same rate as the ortho.

(b) The product from the 0° C reaction will equilibrate as it is warmed, and at 100° C will produce the same ratio of products as the reaction which was run initially at 100° C.

17-61

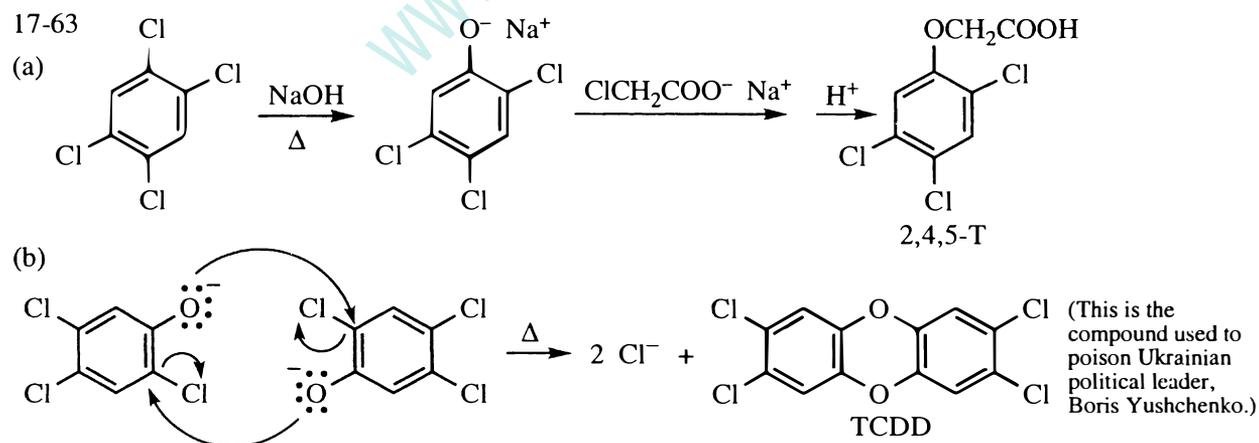


17-62



As we saw in Chapter 16, the carbons of the center ring of anthracene are susceptible to electrophilic addition, leaving two isolated benzene rings on the ends. Benzyne is such a reactive dienophile that the reluctant anthracene is forced into a Diels-Alder reaction.

17-63

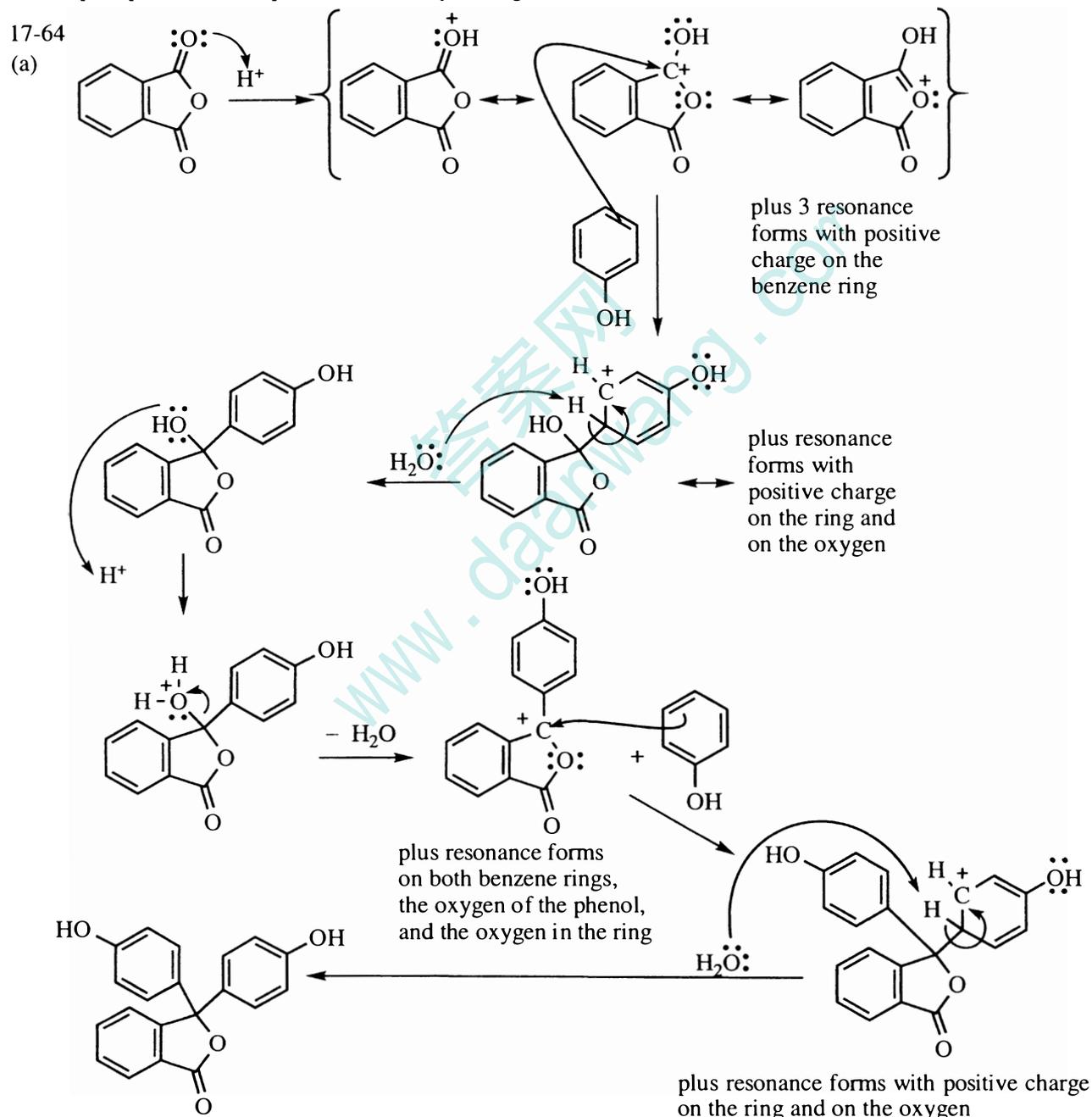


Two nucleophilic aromatic substitutions form a new six-membered ring. (Though not shown here, this reaction would follow the standard addition-elimination mechanism.)

17-63 continued

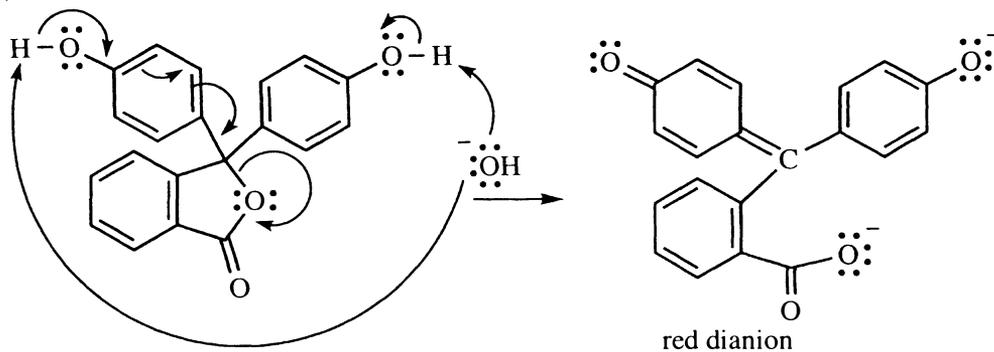
(c) To minimize formation of TCDD during synthesis: 1) keep the solutions dilute; 2) avoid high temperature; 3) replace chloroacetate with a more reactive molecule like bromoacetate or iodoacetate; 4) add an excess of the haloacetate.

To separate TCDD from 2,4,5-T at the end of the synthesis, take advantage of the acidic properties of 2,4,5-T. The 2,4,5-T will dissolve in an aqueous solution of a weak base like NaHCO_3 . The TCDD will remain insoluble and can be filtered or extracted into an organic solvent like ether or dichloromethane. The 2,4,5-T can be precipitated from aqueous solution by adding acid.

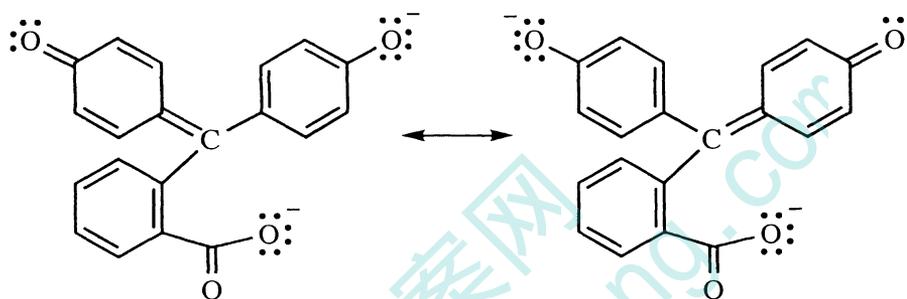


17-64 continued

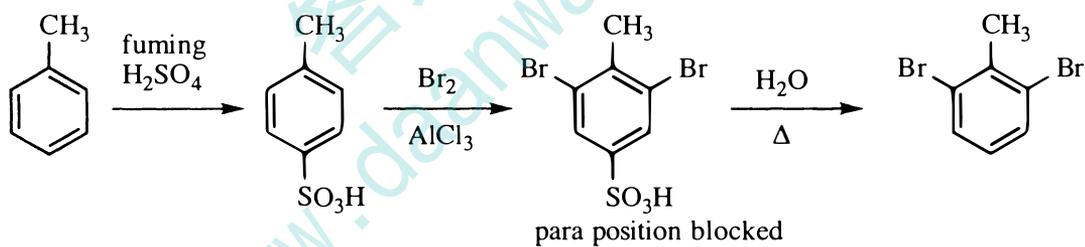
(b)



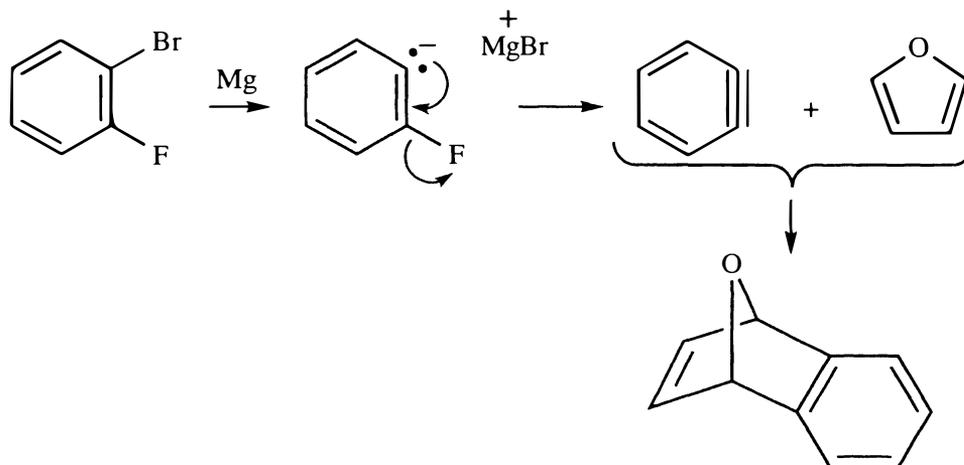
(c)



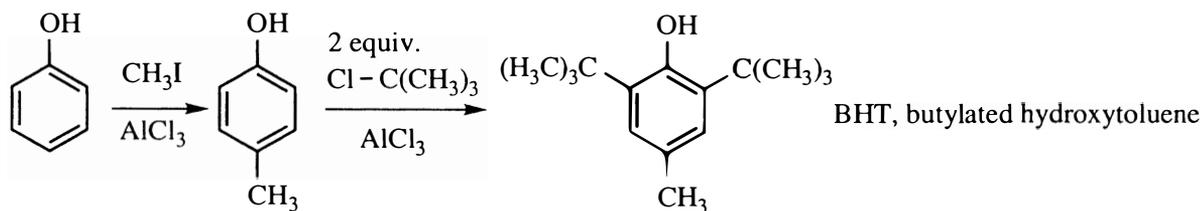
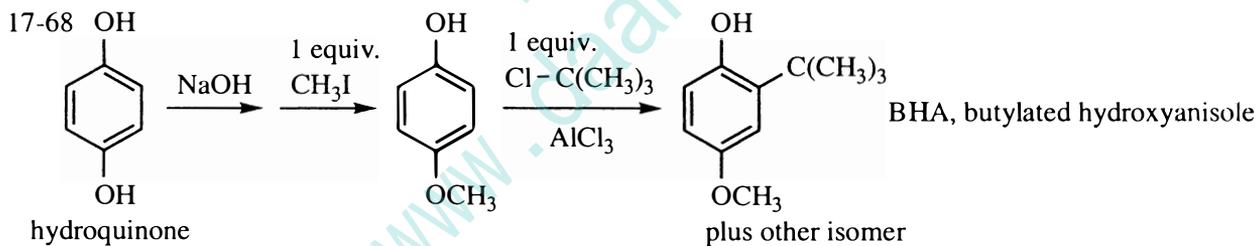
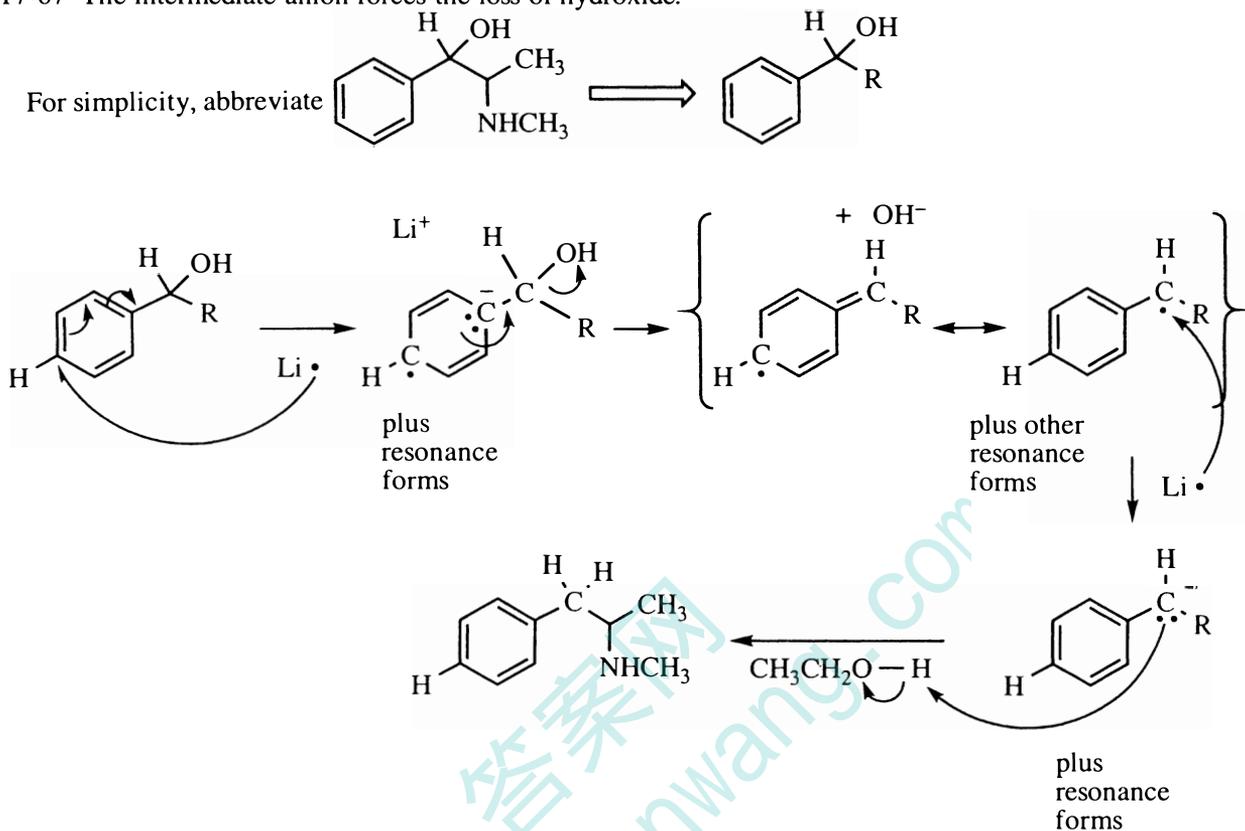
17-65



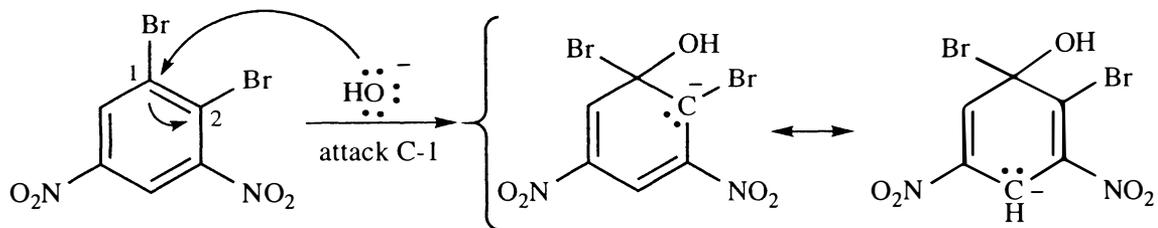
17-66 A benzyne must have been generated from the Grignard reagent.



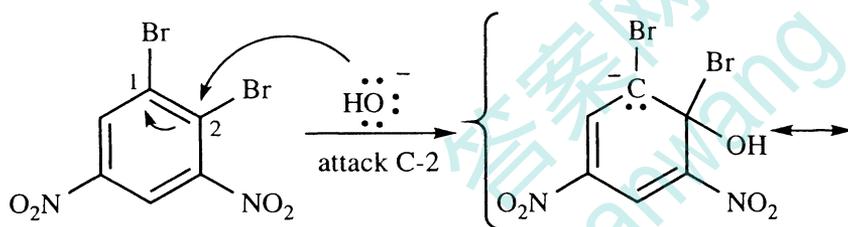
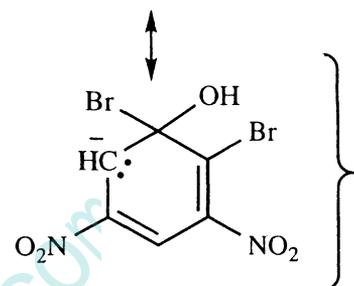
17-67 The intermediate anion forces the loss of hydroxide.



17-69 Solve the problem by writing the mechanism. (See the solution to problem 17-25(a) for an identical mechanism.)

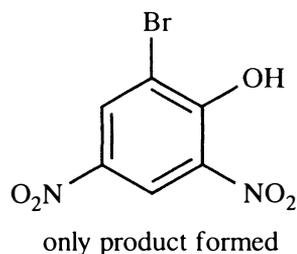
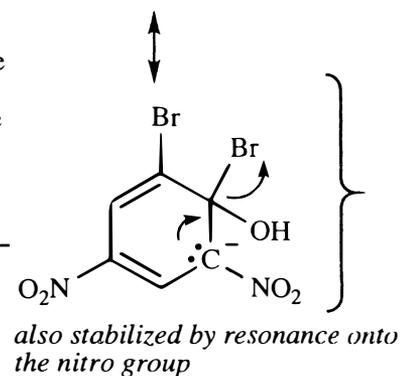


Hydroxide attack on C-1 puts the negative charge on carbons that do not have the NO₂ groups, so these anions are not stabilized.



Hydroxide attack on C-2 puts the negative charge on carbons with nitro groups, thereby increasing the stabilization by delocalizing the negative charge. This intermediate is formed preferentially.

also stabilized by resonance onto the nitro group



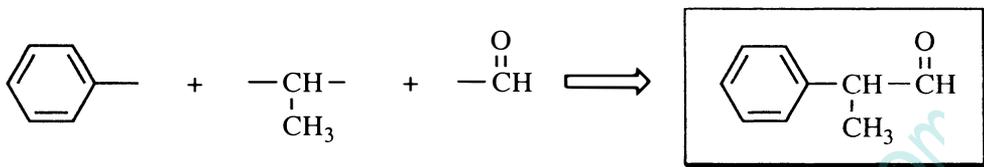
CHAPTER 18—KETONES AND ALDEHYDES

18-1

- (a) 5-hydroxyhexan-3-one; ethyl β -hydroxypropyl ketone
 (b) 3-phenylbutanal; β -phenylbutyraldehyde
 (c) *trans*-2-methoxycyclohexancarbaldehyde (or (*R,R*) if you named this enantiomer); no common name
 (d) 6,6-dimethylcyclohexa-2,4-dienone; no common name

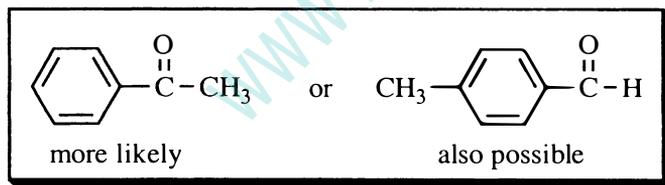
18-2

- (a) $C_9H_{10}O \Rightarrow$ 5 elements of unsaturation
 1H doublet (very small coupling constant) at δ 9.7 \Rightarrow aldehyde hydrogen, next to CH
 5H multiple peaks at δ 7.2-7.4 \Rightarrow monosubstituted benzene
 1H multiplet at δ 3.6 and 3H doublet at δ 1.4 \Rightarrow CHCH₃

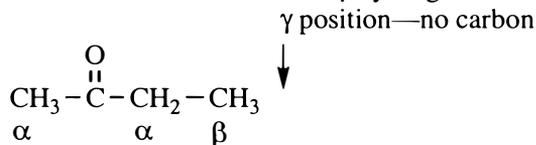


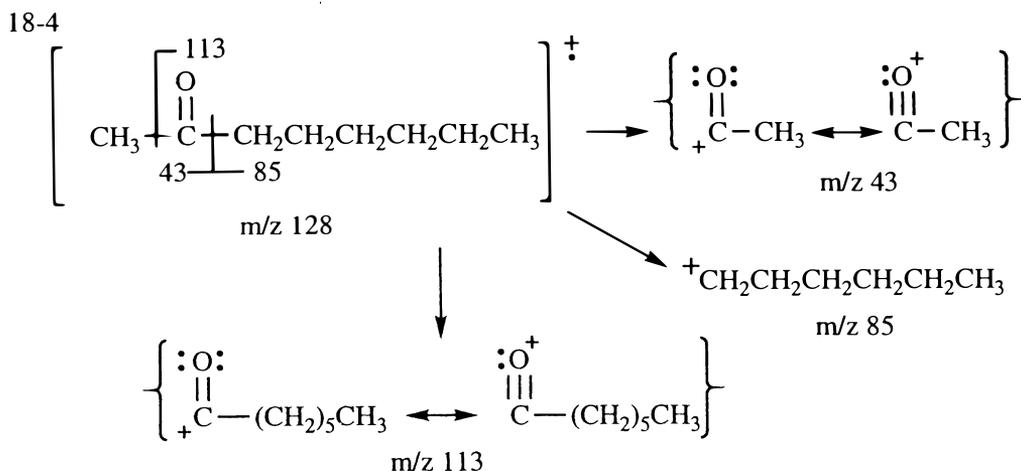
The splitting of the hydrogen on carbon-2, next to the aldehyde, is worth examining. In its overall shape, it looks like a quartet due to the splitting from the adjacent CH₃. A closer examination of the peaks shows that each peak of the quartet is split into two peaks: this is due to the splitting from the aldehyde hydrogen. The aldehyde hydrogen and the methyl hydrogens are not equivalent, so it is to be expected that the coupling constants will not be equal. If a hydrogen is coupled to different neighboring hydrogens by different coupling constants, they must be considered separately, just as you would by drawing a splitting tree for each type of adjacent hydrogen.

- (b) $C_8H_8O \Rightarrow$ 5 elements of unsaturation
 cluster of 4 peaks at δ 128-145 \Rightarrow mono- or para-substituted benzene ring
 peak at δ 197 \Rightarrow carbonyl carbon (the small peak height suggests a ketone rather than an aldehyde)
 peak at δ 26 \Rightarrow methyl next to carbonyl or benzene

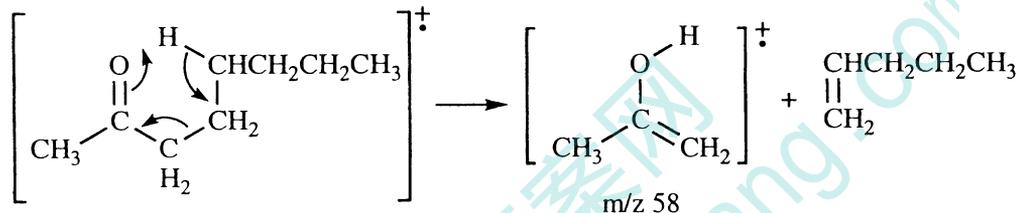


18-3 A compound has to have a hydrogen on a γ carbon (or other atom) in order for the McLafferty rearrangement to occur. Butan-2-one has no γ -hydrogen.





McLafferty rearrangement



18-5

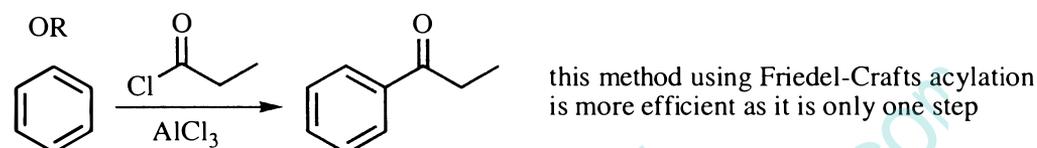
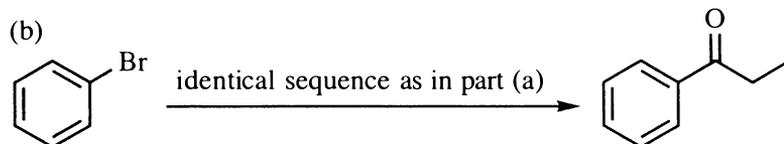
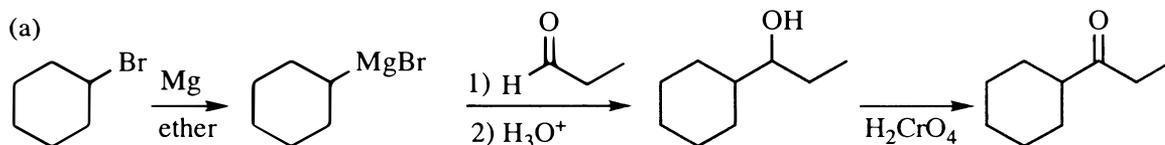
The first value is the π to π^* ; the second value is the n to π^* . The values are approximate.

- (a) < 200 nm; 280 nm; this simple ketone should have values similar to acetone
- (b) 230 nm; 310 nm; conjugated system (210) plus 2 alkyl groups (20) = 230; the value of 310 nm is similar to Figure 18-7: ketone (280 nm base value) plus 30 nm for the conjugated double bond = 310 nm
- (c) 280 nm; 360 nm; conjugated system (210) plus 1 extra double bond (30) plus 4 alkyl groups (40) = 280; similar reasoning for the other transition, starting with an average base value of 290
- (d) 270 nm; 350 nm; same as in (c) except only 3 alkyl groups instead of 4

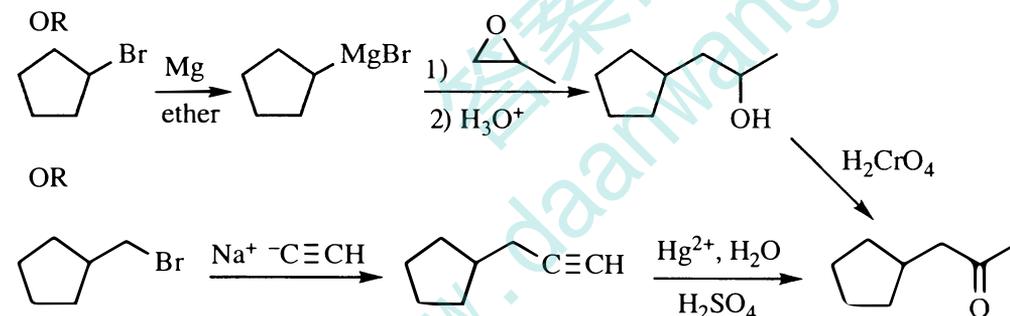
REMINDERS ABOUT SYNTHESIS PROBLEMS:

1. There may be more than one legitimate approach to a synthesis, especially as the list of reactions gets longer.
2. Begin your analysis by comparing the target to the starting material. If the product has more carbons than the reactant, you will need to use one of the small number of reactions that form carbon-carbon bonds.
3. Where possible, work backwards from the target back to the starting material.
4. **KNOW THE REACTIONS.** There is no better test of whether you know the reactions than attempting synthesis problems.

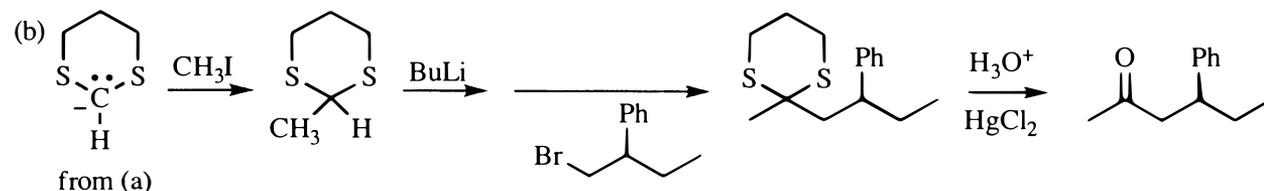
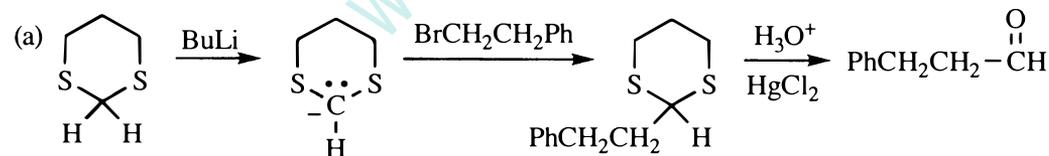
18-6 All three target molecules in this problem have more than six carbons, so all answers will include carbon-carbon-bond-forming reactions. So far, there are three types of reactions that form carbon-carbon bonds: the Grignard reaction, S_N2 substitution by an acetylide ion, and the Friedel-Crafts reactions (alkylation and acylation) on benzene.



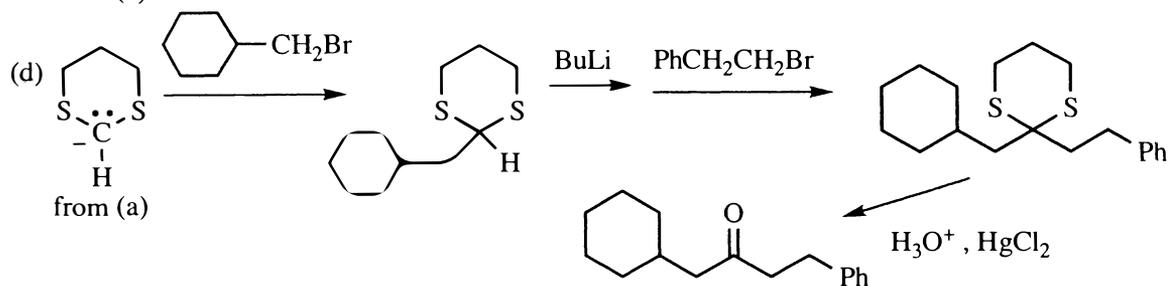
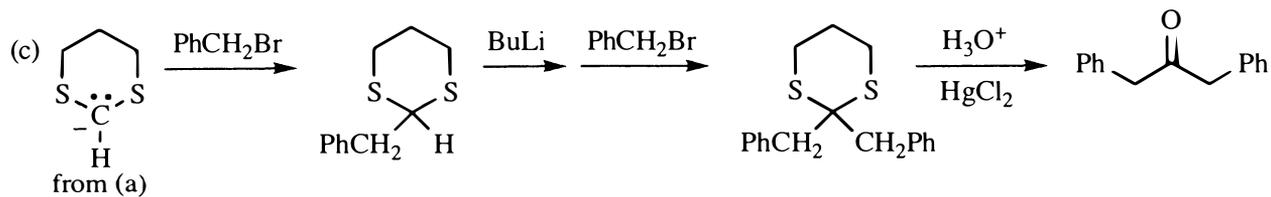
(c) a synthesis as in part (a) could also be used here



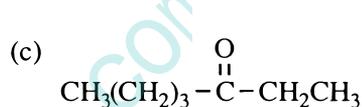
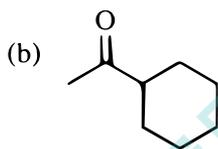
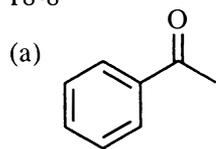
18-7



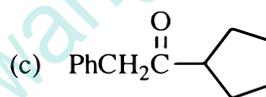
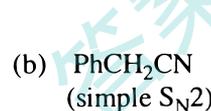
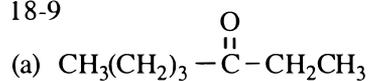
18-7 continued



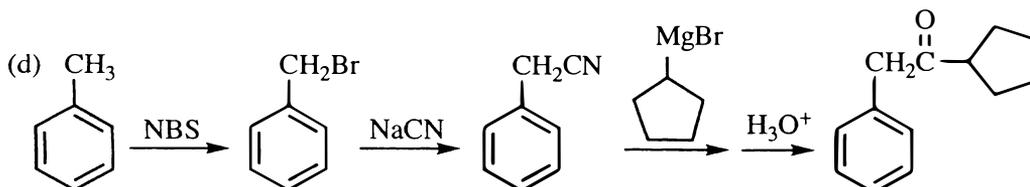
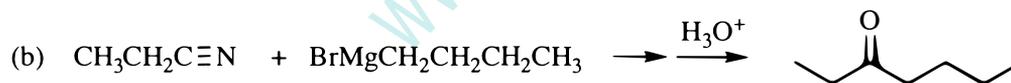
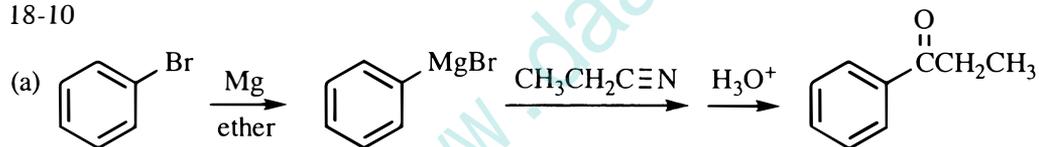
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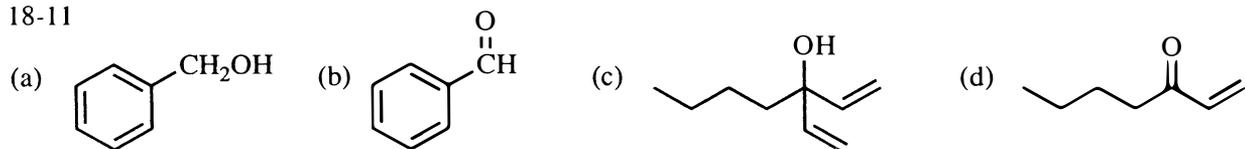
18-9



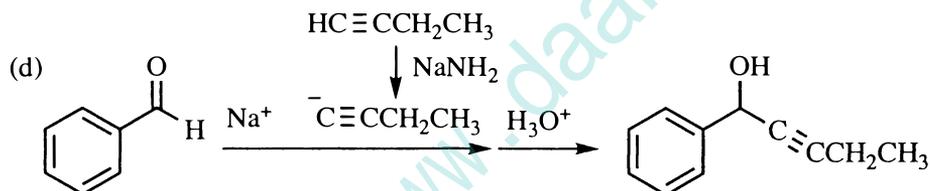
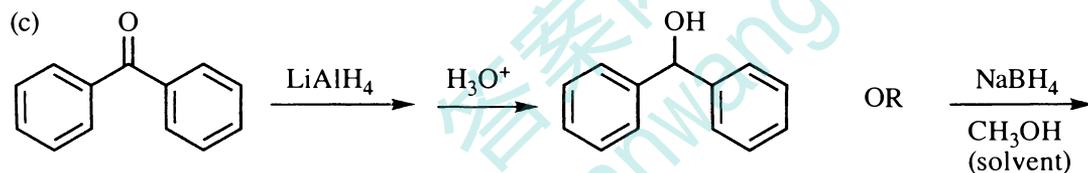
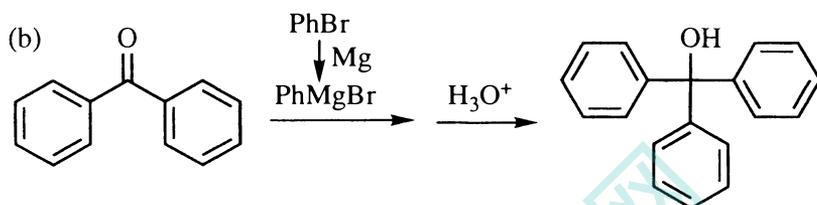
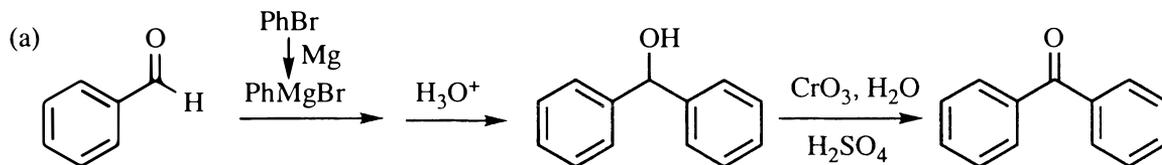
18-10



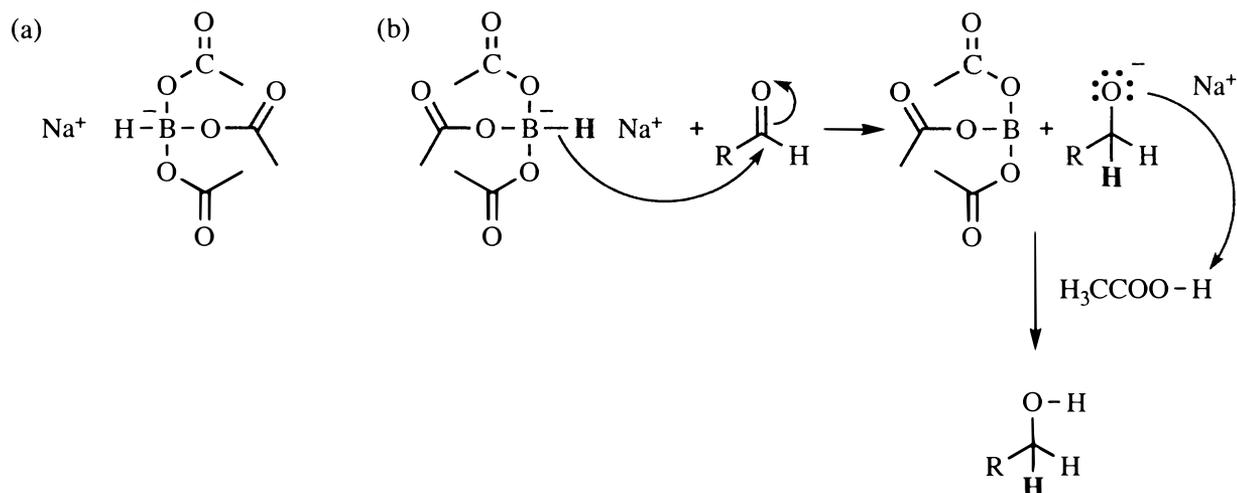
18-11



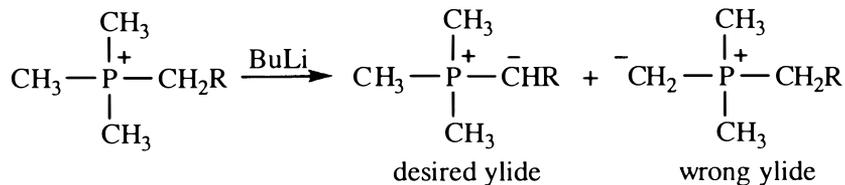
18-12 Review the reminders on p. 402. There are often more than one correct way to do syntheses, but a more direct route with fewer steps is usually better.



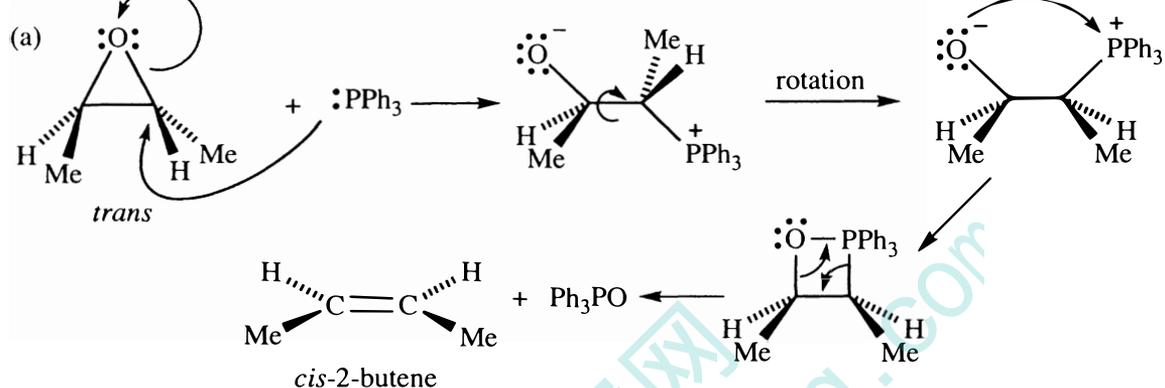
18-13 The triacetoxyborohydride ion is similar to borohydride, BH_4^- , where three acetoxy groups have replaced three hydrides.



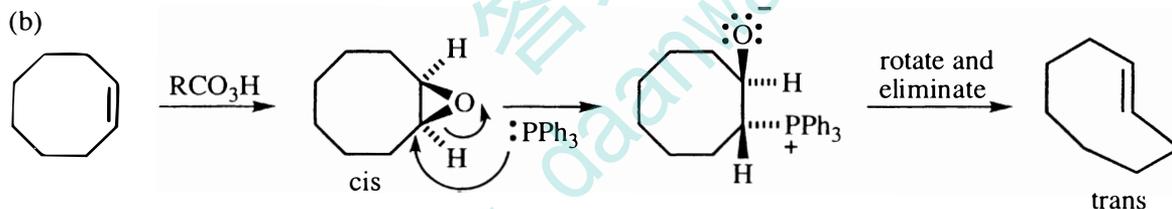
18-14 Trimethylphosphine has α -hydrogens that could be removed by butyllithium, generating undesired ylides.



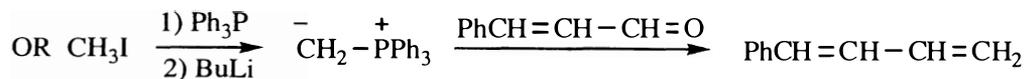
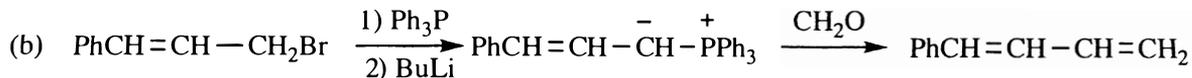
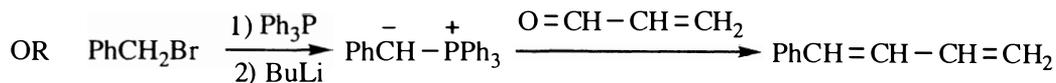
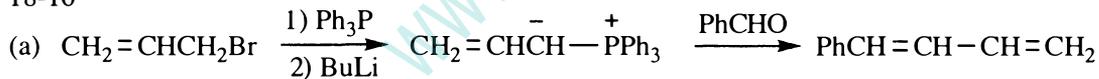
18-15



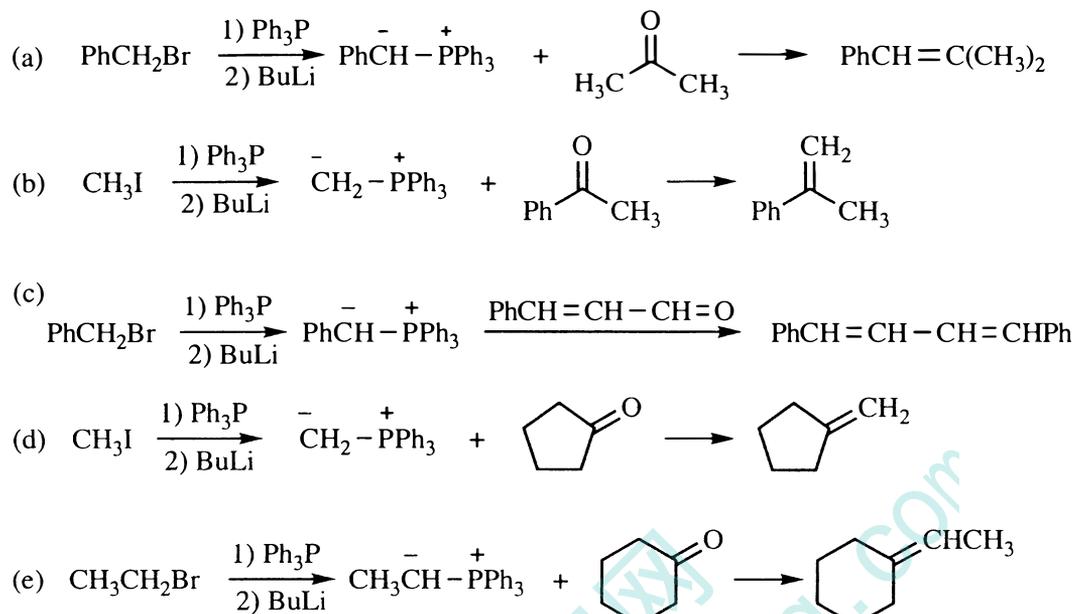
The stereochemistry is inverted. The nucleophile triphenylphosphine must attack the epoxide in an anti fashion, yet the triphenylphosphine oxide must eliminate with syn geometry.



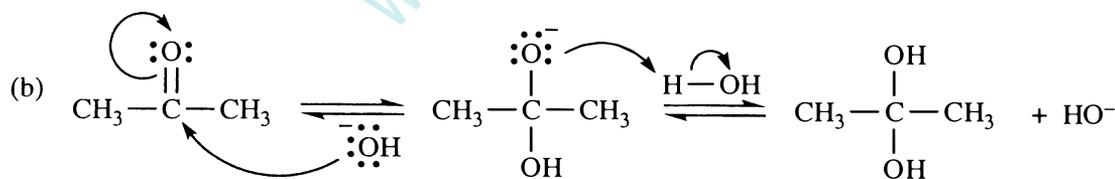
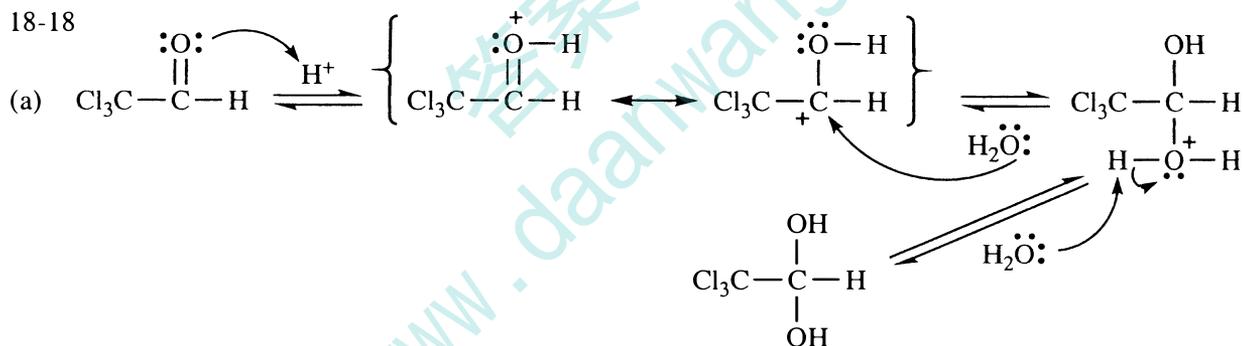
18-16



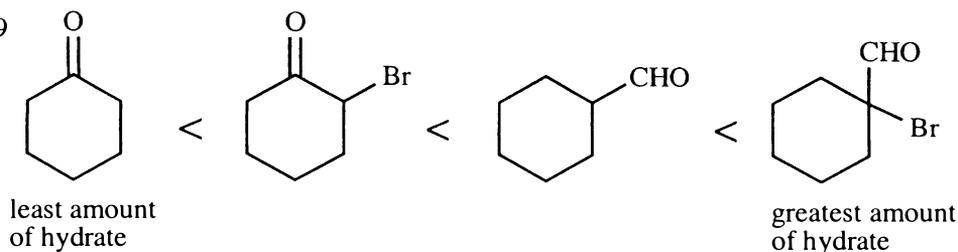
18-17 Many alkenes can be synthesized by two different Wittig reactions (as in the previous problem). The ones shown here form the phosphonium salt from the less hindered alkyl halide.



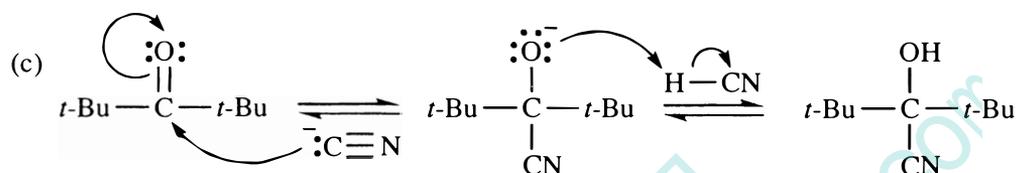
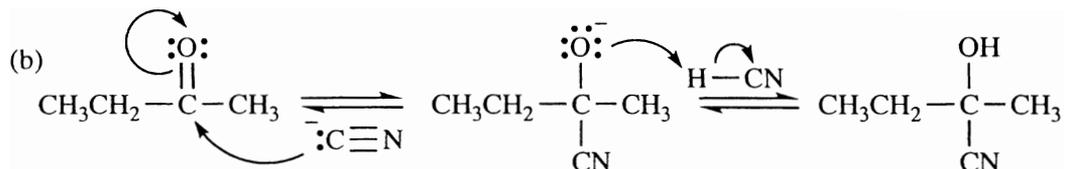
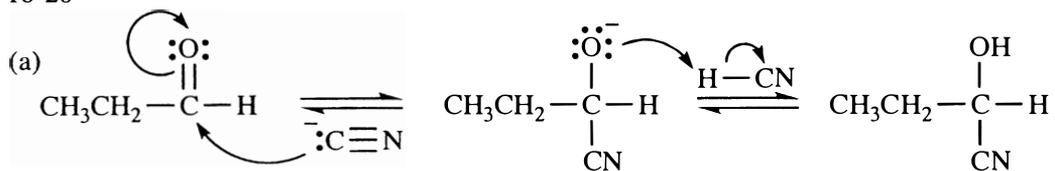
18-18



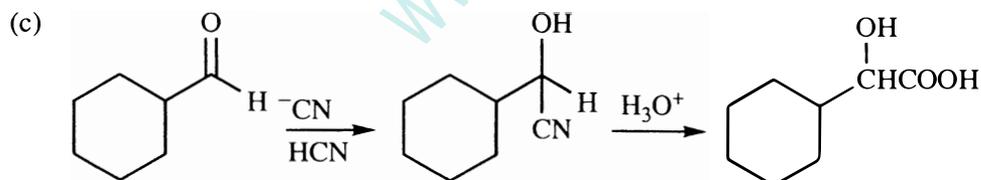
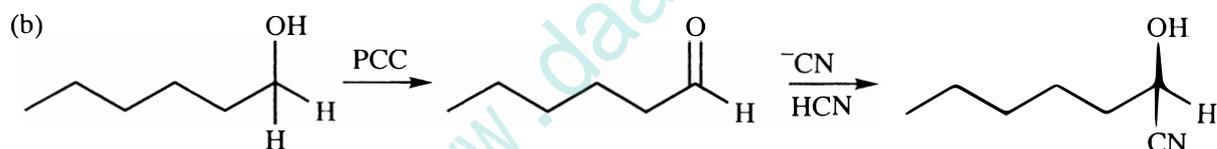
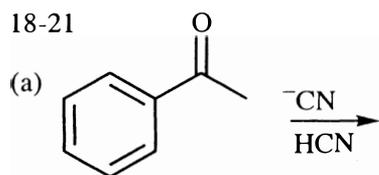
18-19



18-20



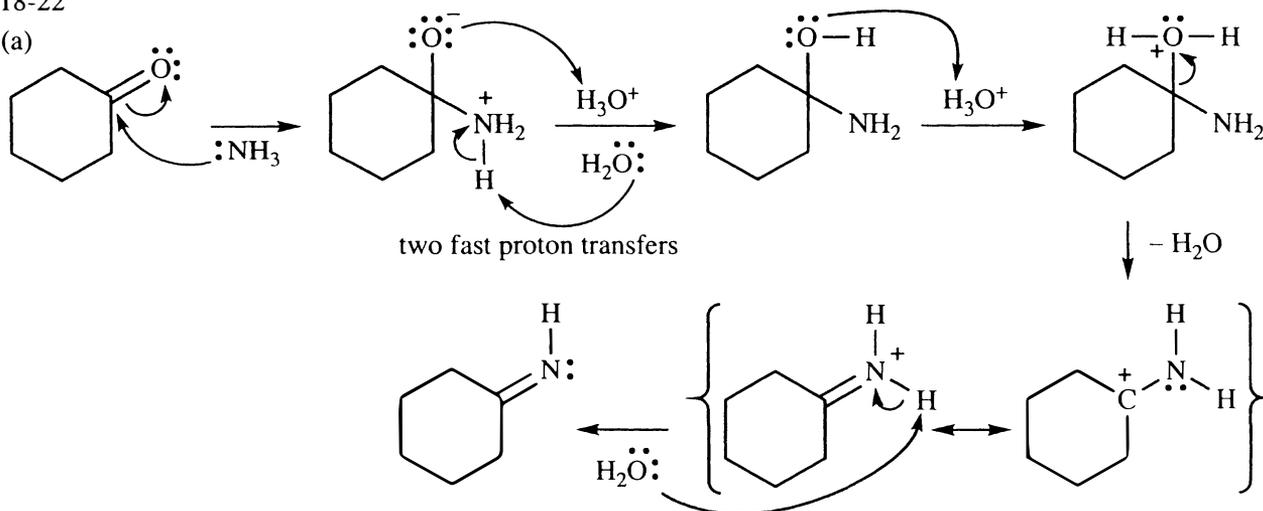
18-21



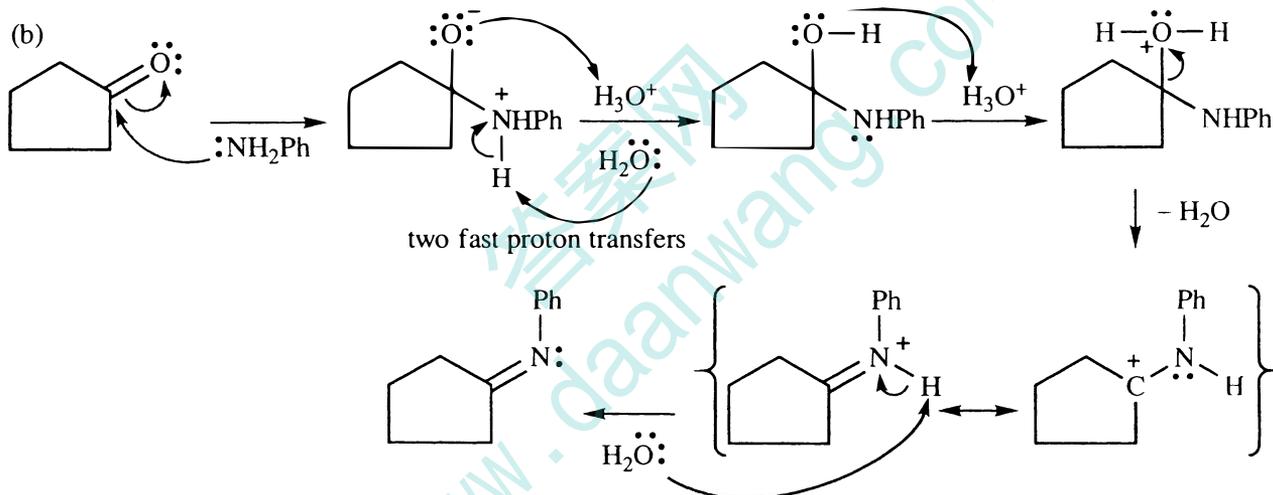
Note: Mechanisms of nucleophilic attack at carbonyl carbon frequently include species with both positive and negative charges. These species are very short-lived as each charge is quickly neutralized by a rapid proton transfer; in fact, these steps are the fastest of the whole mechanism. In most cases, this Solutions Manual will show these *two* steps as occurring at the same time, even though you have been admonished to show *all* steps of a mechanism separately. The practice of showing these proton transfers in one step is legitimate as long as it is understood that these are *two* fast steps.

18-22

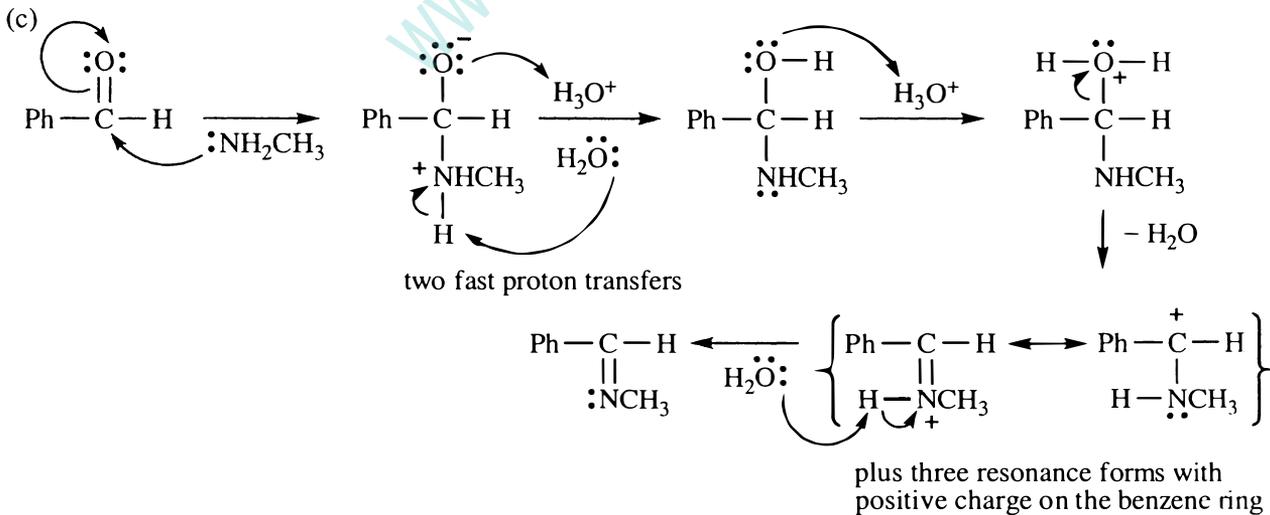
(a)



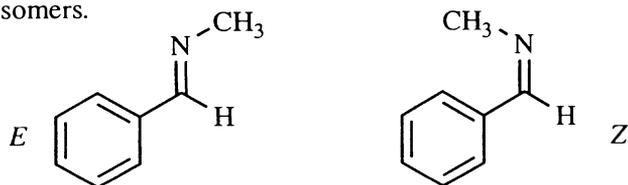
(b)



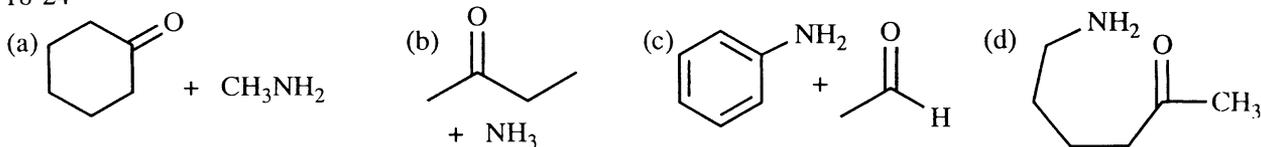
(c)



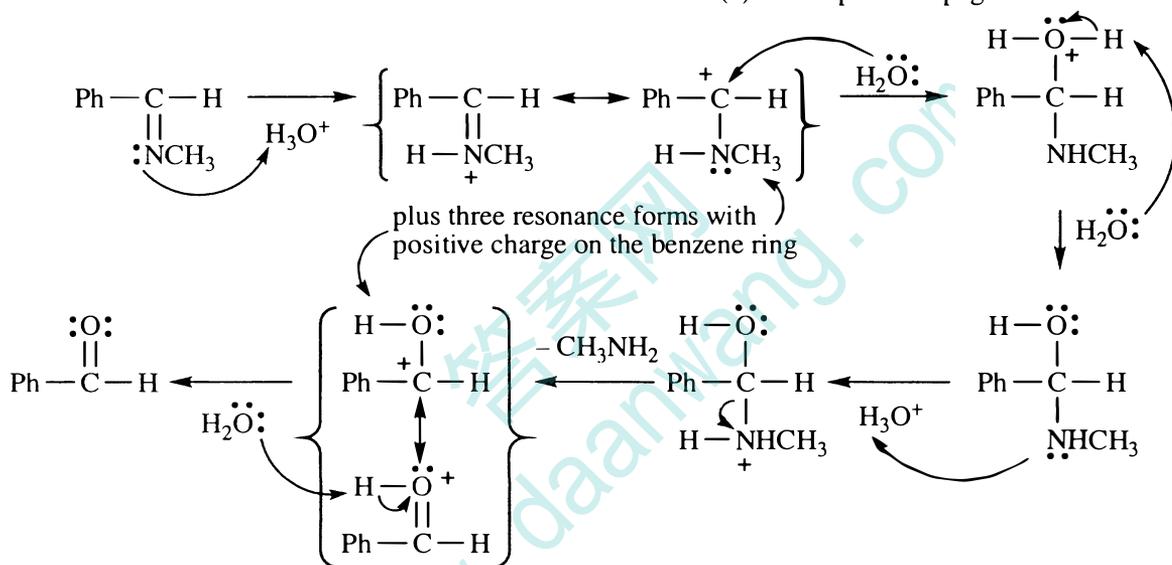
18-23 Whenever a double bond is formed, stereochemistry must be considered. The two compounds are the *Z* and *E* isomers.



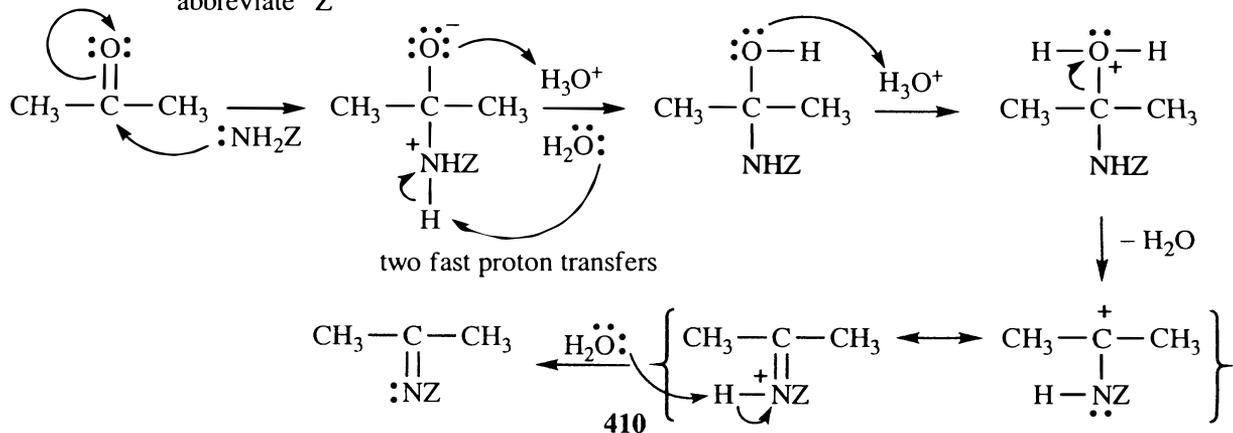
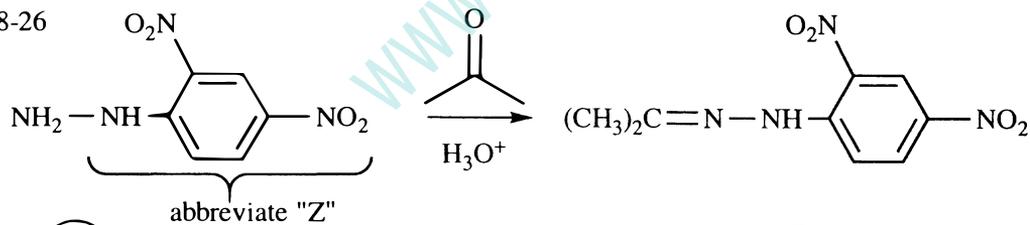
18-24



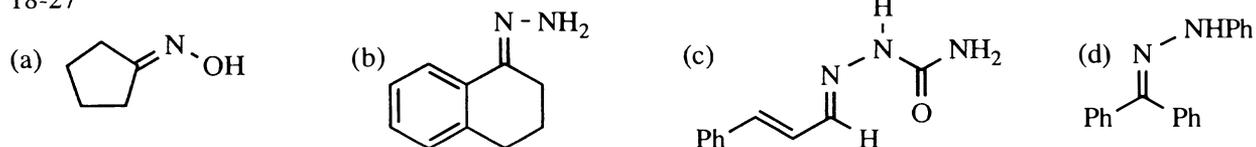
18-25 This mechanism is the reverse of the one shown in 18-22(c) on the previous page.



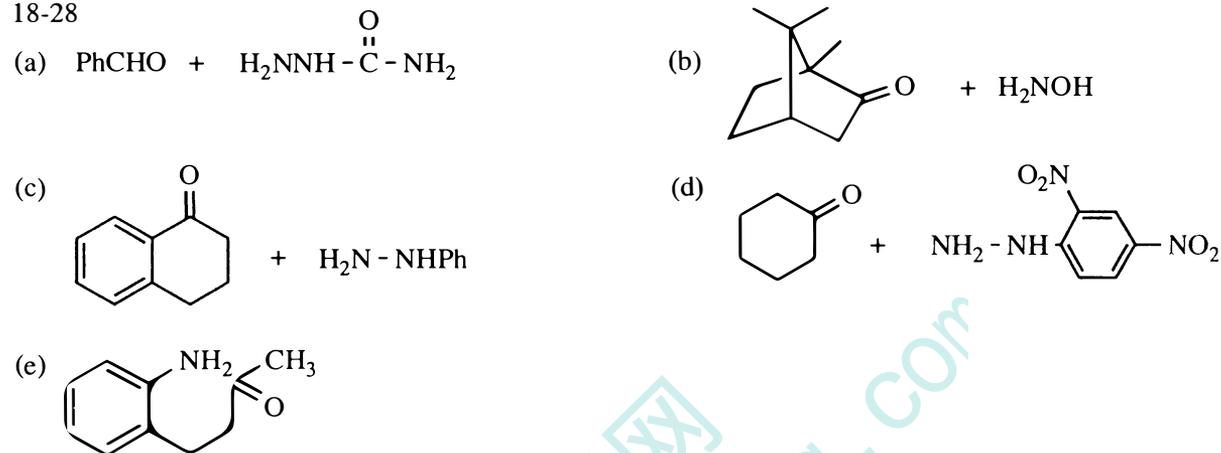
18-26



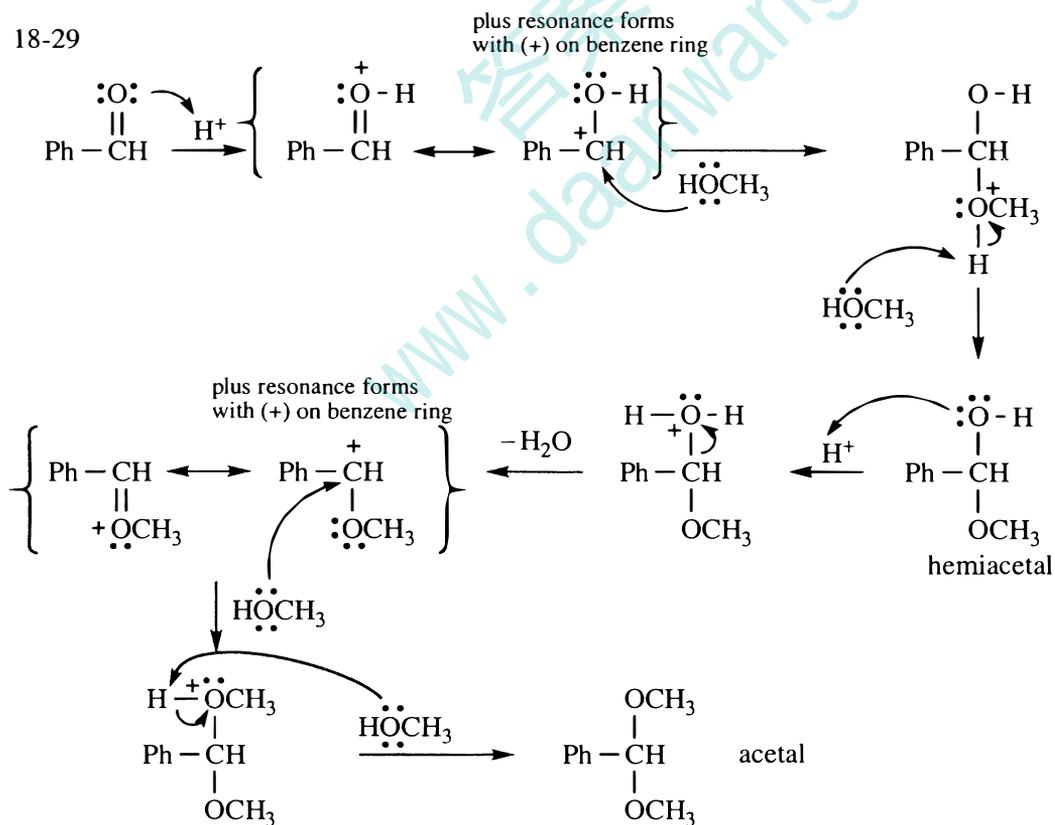
18-27



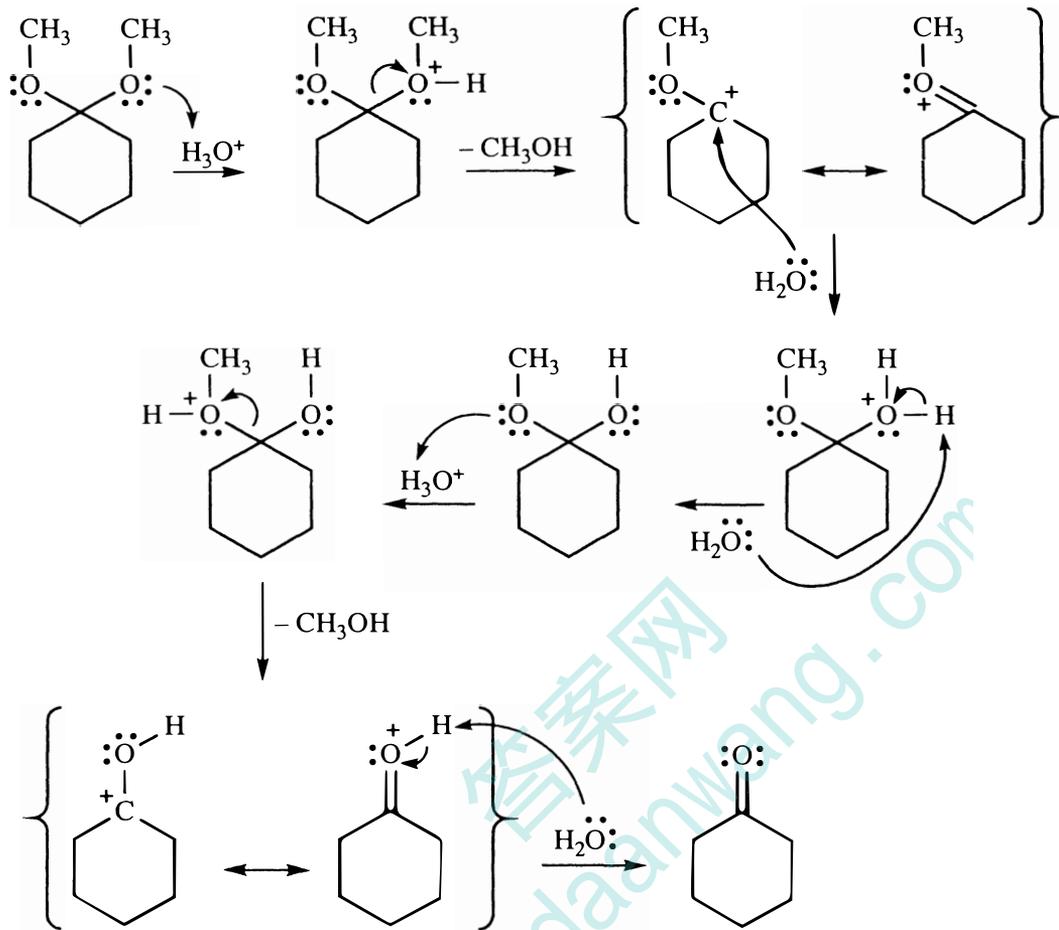
18-28



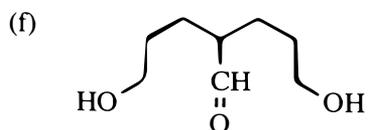
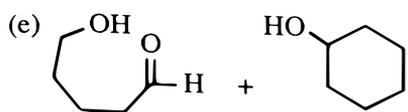
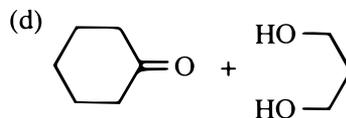
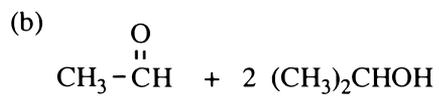
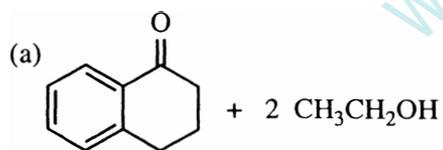
18-29



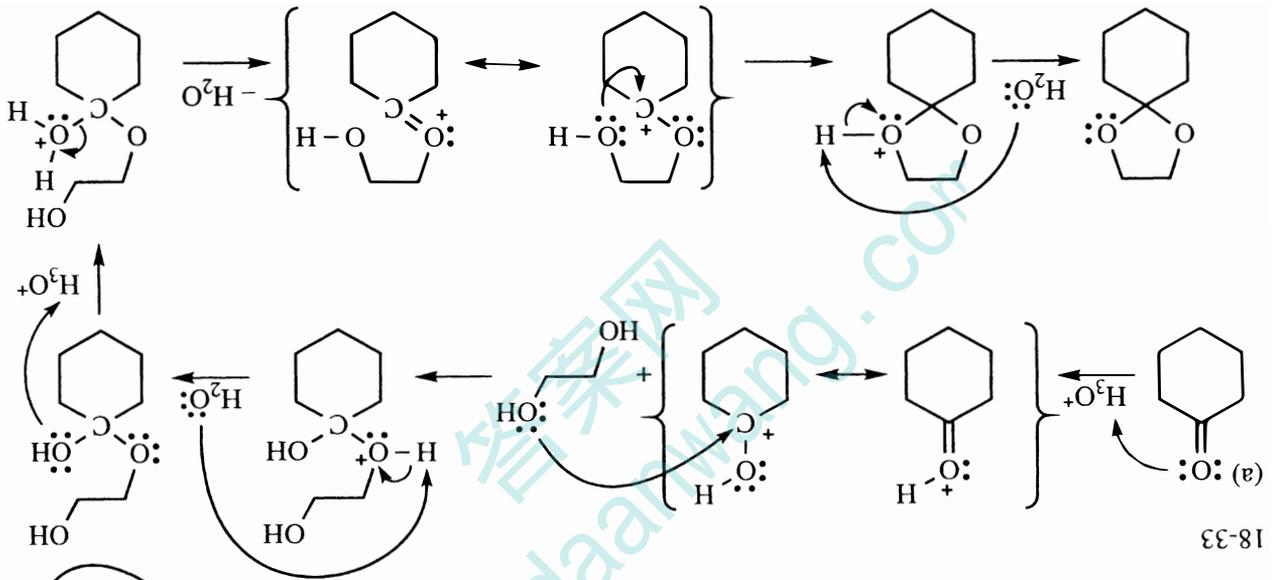
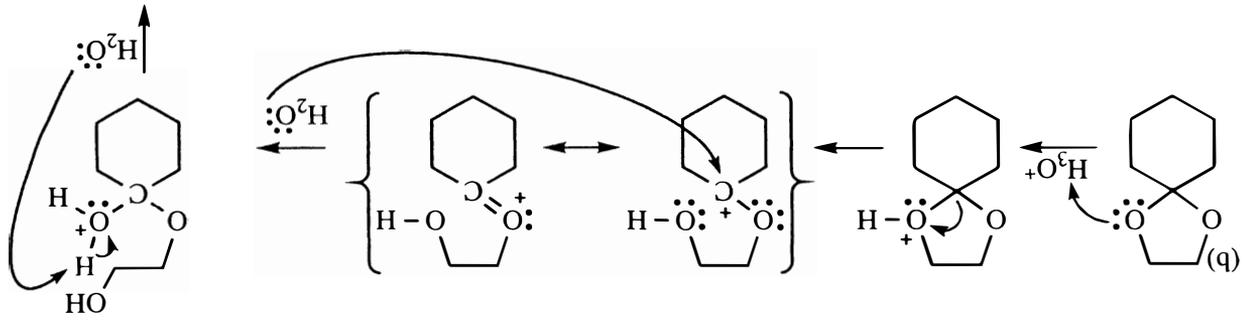
18-30



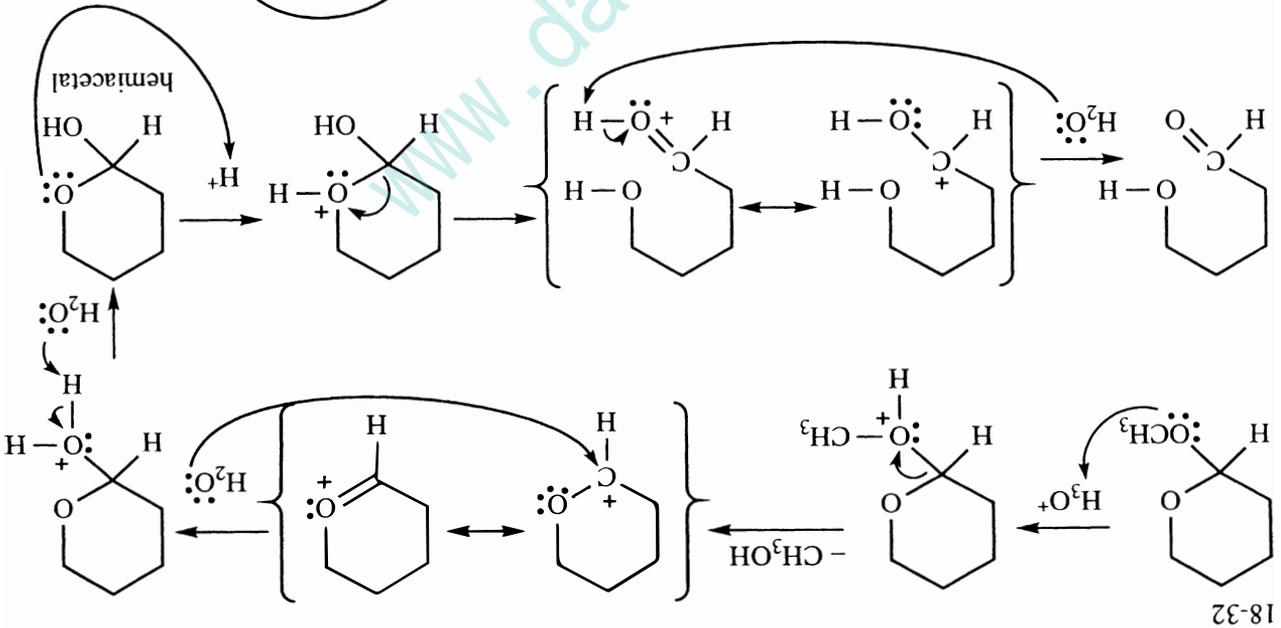
18-31



hydrolysis mechanism
continued on next page



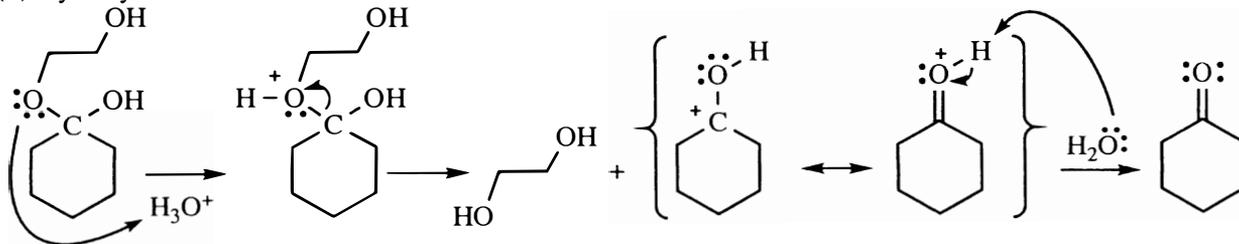
18-33



18-32

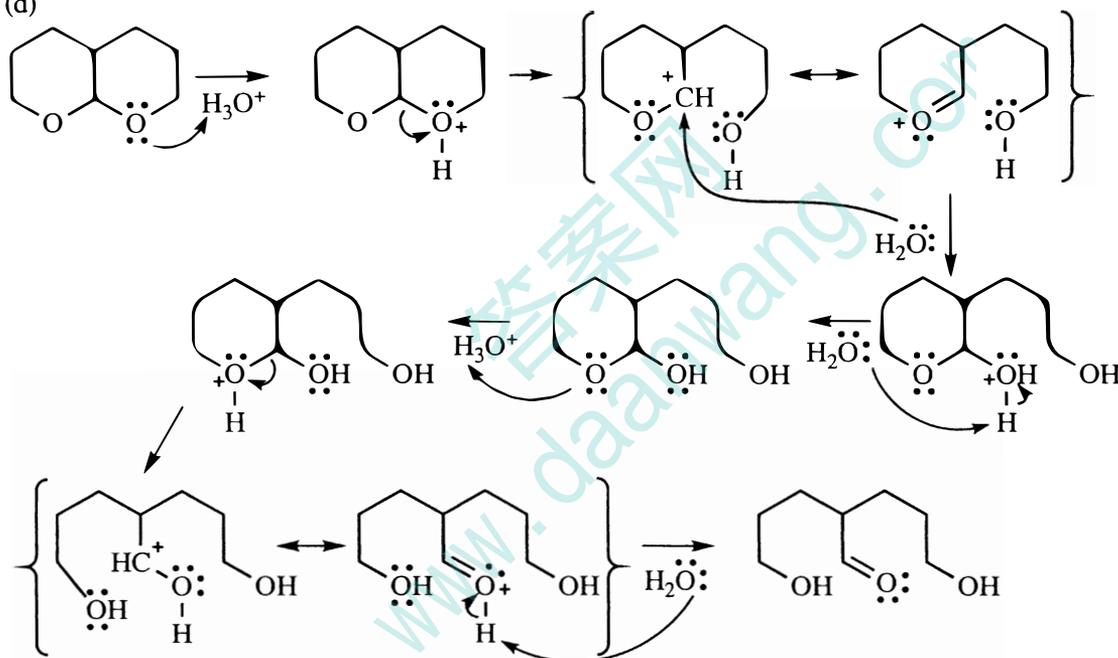
18-33 continued

(b) hydrolysis mechanism continued

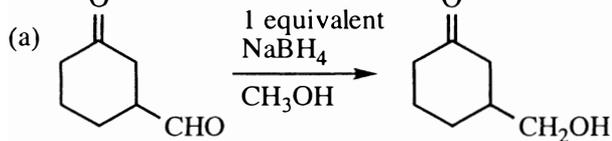


(c) The mechanisms of formation of an acetal and hydrolysis of an acetal are identical, just the reverse order. This has to be true because this process is an equilibrium: if the forward steps follow a minimum energy path, then the reverse steps have to follow the identical minimum energy path. This is the famous Principle of Microscopic Reversibility, text section 8-4A.

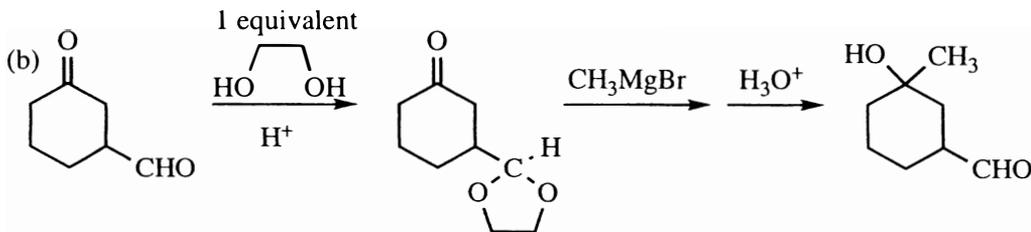
(d)



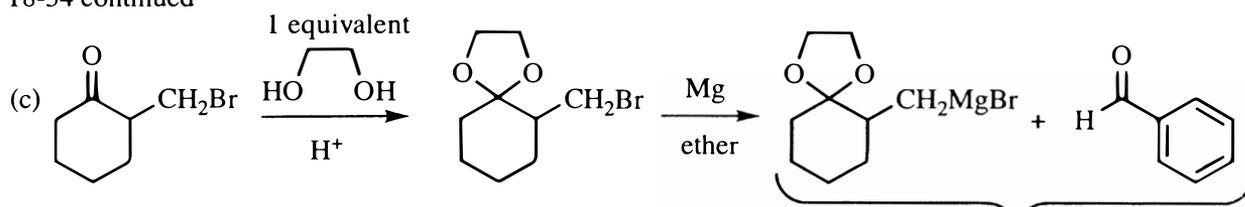
18-34



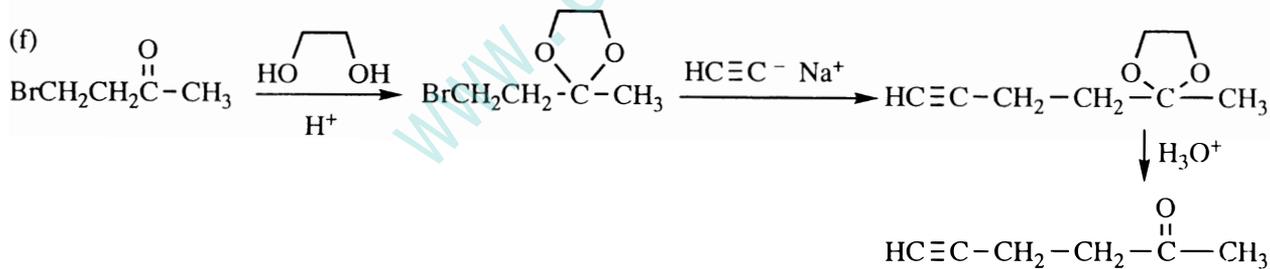
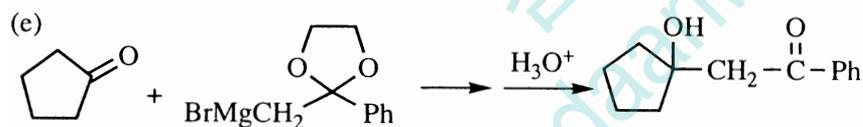
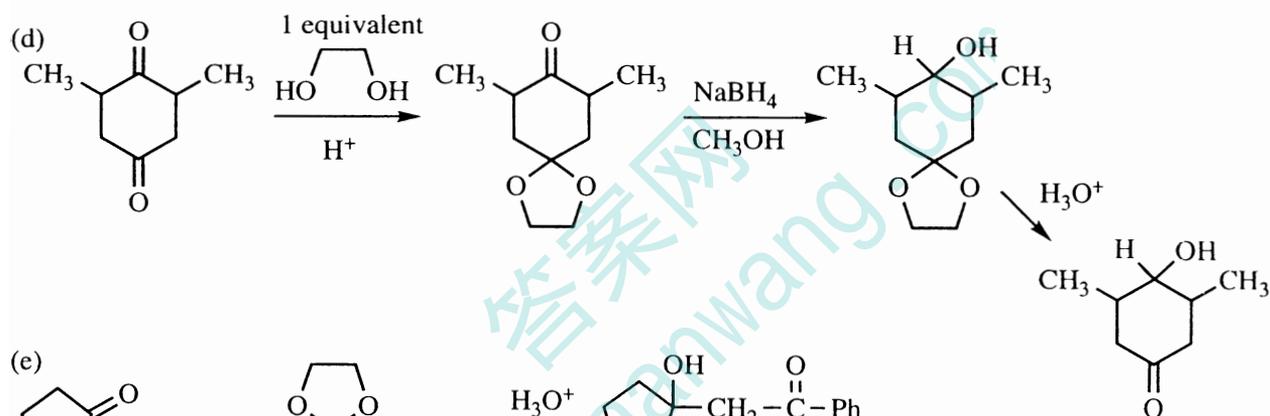
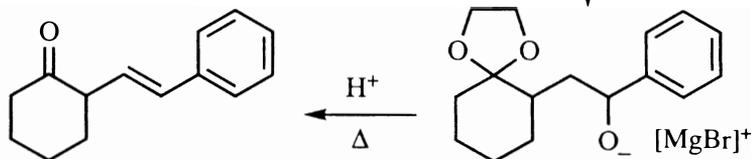
Aldehydes are reduced faster than ketones (keeping this reaction cold will increase selectivity). Alternatively, sodium triacetoxyborohydride could be used for this reduction; see problem 18-13.



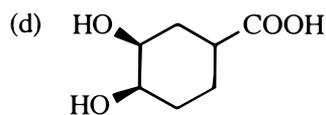
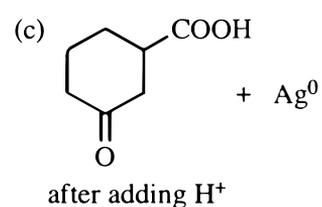
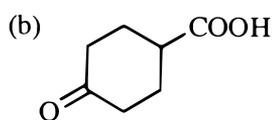
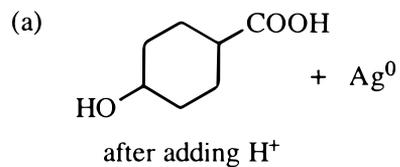
18-34 continued



The last step protonates the oxygen, dehydrates the alcohol, and hydrolyzes the acetal.

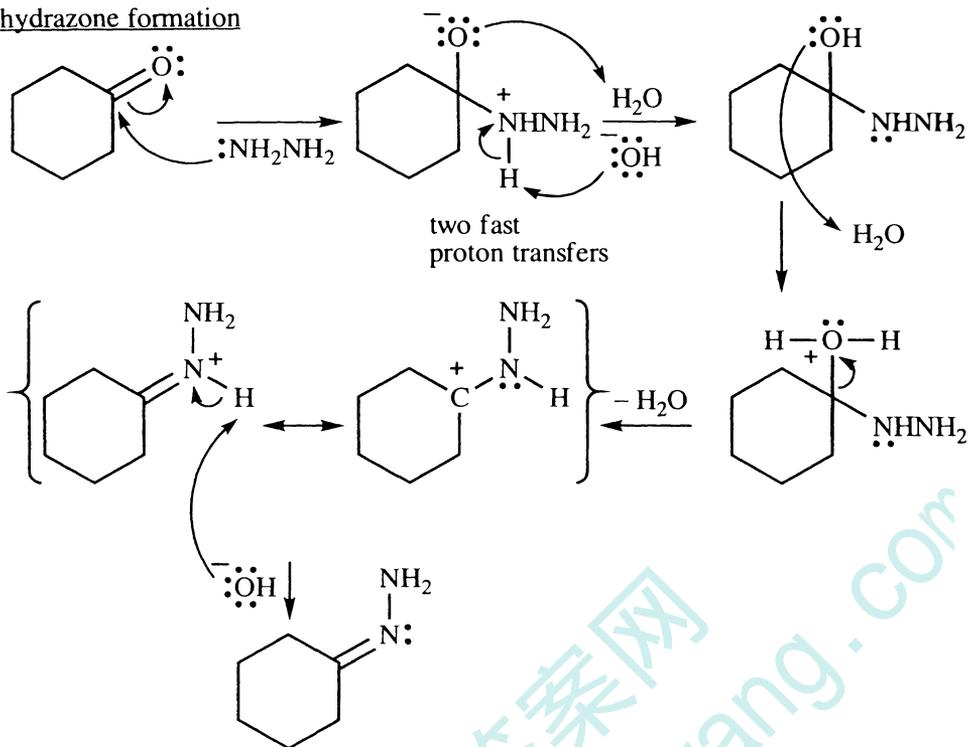


18-35

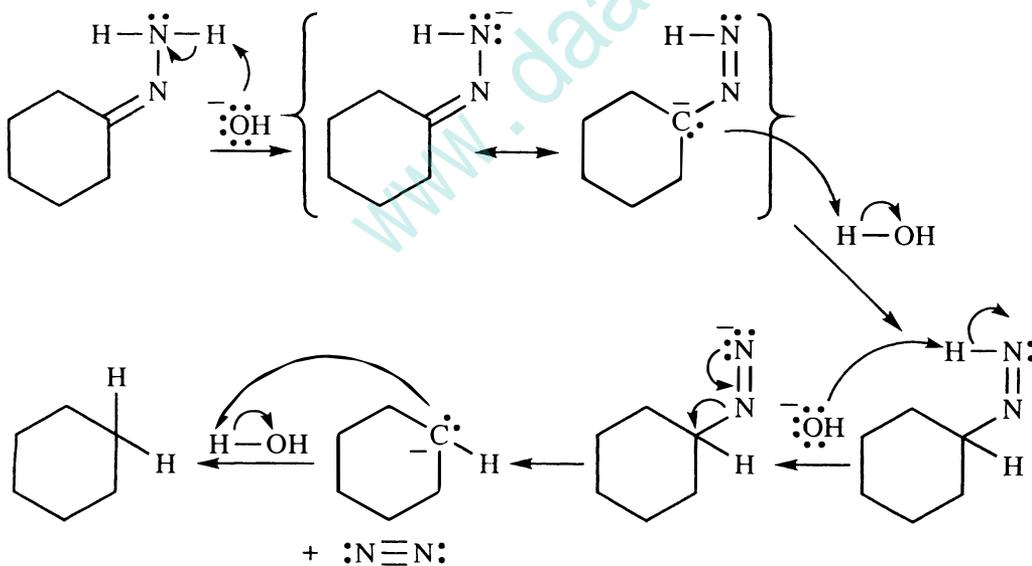


18-36

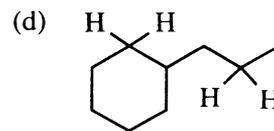
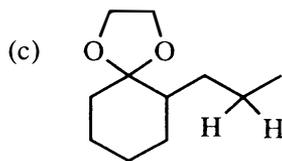
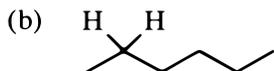
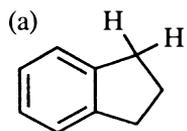
hydrazone formation



reduction of the hydrazone



18-37

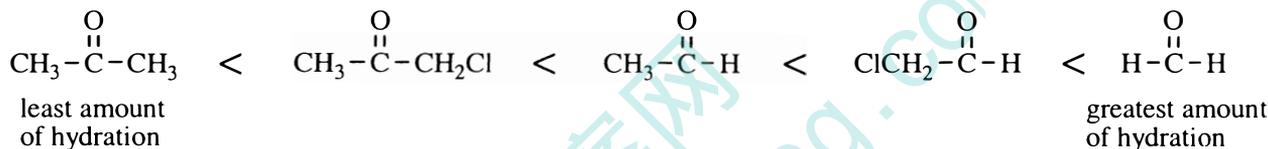


18-38 Please refer to solution 1-20, page 12 of this Solutions Manual.

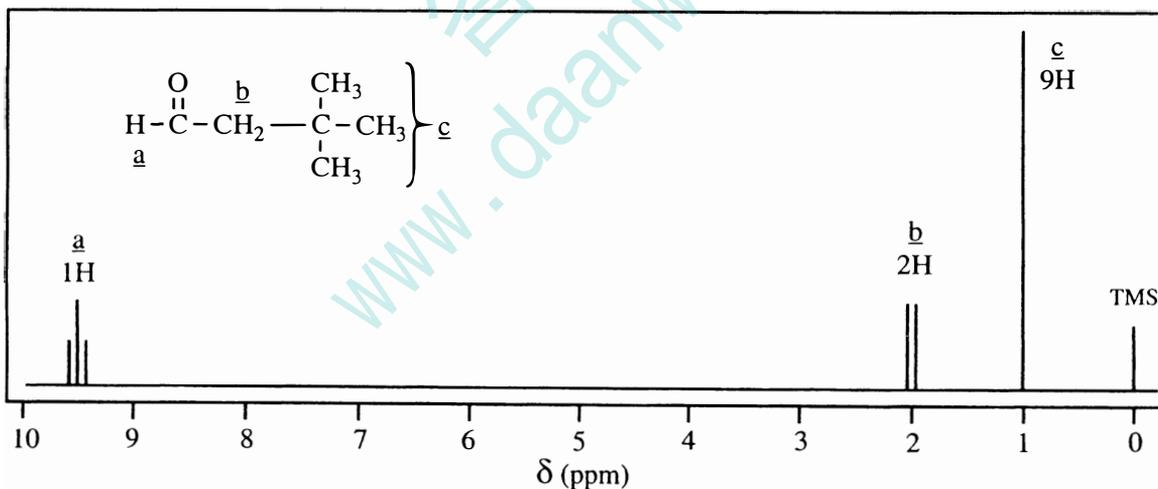
18-39 IUPAC names first; then common names. Please see the note on p. 136 of this Solutions Manual regarding placement of position numbers.

- | | |
|--|--|
| (a) heptan-2-one; methyl <i>n</i> -pentyl ketone | (g) 4-bromo-2-methylhexanal; no common name |
| (b) heptan-4-one; di- <i>n</i> -propyl ketone | (h) 3-phenylprop-2-enal; cinnamaldehyde |
| (c) heptanal; no simple common name | (i) hexa-2,4-dienal; no common name |
| (d) benzophenone; diphenyl ketone | (j) 3-oxopentanal; no common name |
| (e) butanal; butyraldehyde | (k) 3-oxocyclopentanecarbaldehyde; no common name |
| (f) propanone; acetone (IUPAC accepts "acetone") | (l) <i>cis</i> -2,4-dimethylcyclopentanone; no common name |

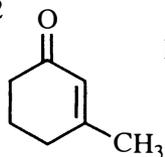
18-40 In order of increasing equilibrium constant for hydration:



18-41



18-42



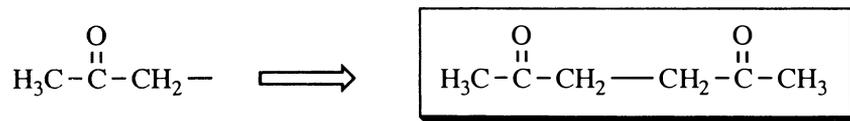
By comparison with similarly substituted molecules shown in the text:

$$\begin{aligned} \pi \rightarrow \pi^* & \text{ base value (210) plus 3 alkyl groups (30) = 240 nm} \\ n \rightarrow \pi^* & \text{ 300-320 nm} \end{aligned}$$

18-43

$C_6H_{10}O_2$ indicates two elements of unsaturation.

The IR absorption at 1708 cm^{-1} suggests a ketone, or possibly two ketones since there are two oxygens and two elements of unsaturation. The NMR singlets in the ratio of 2 : 3 indicate a highly symmetric molecule. The singlet at δ 2.15 is probably methyl next to carbonyl, and the singlet at δ 2.67 integrating to two is likely to be CH_2 on the other side of the carbonyl.

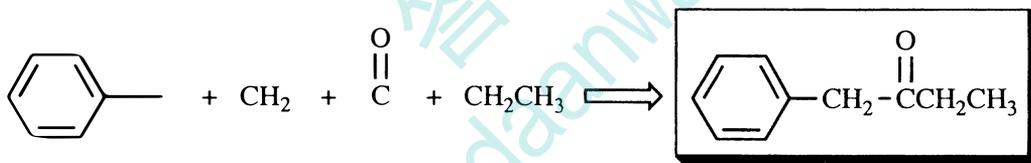


Since the molecular formula is double this fragment, the molecule must be twice the fragment.

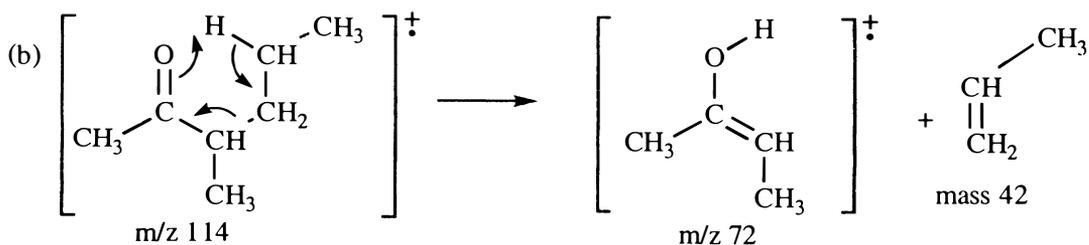
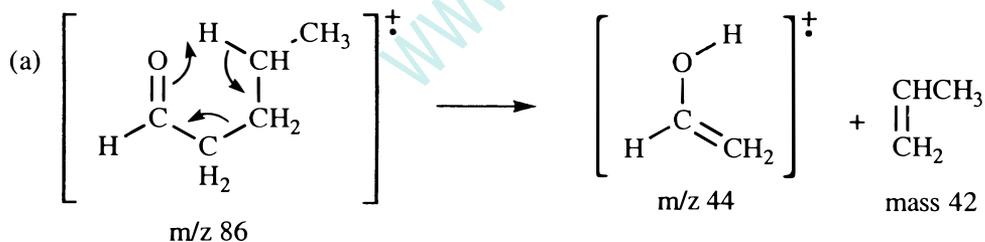
Two questions arise. Why is the integration 2 : 3 and not 4 : 6? Integration provides a *ratio*, not absolute numbers, of hydrogens. Why don't the two methylenes show splitting? Adjacent, *identical* hydrogens, with identical chemical shifts, do not split each other; the signals for ethane or cyclohexane appear as singlets.

18-44 The formula $C_{10}H_{12}O$ indicates 5 elements of unsaturation. A solid 2,4-DNP derivative suggests an aldehyde or a ketone, but a negative Tollens test precludes the possibility of an aldehyde; therefore, the unknown must be a ketone.

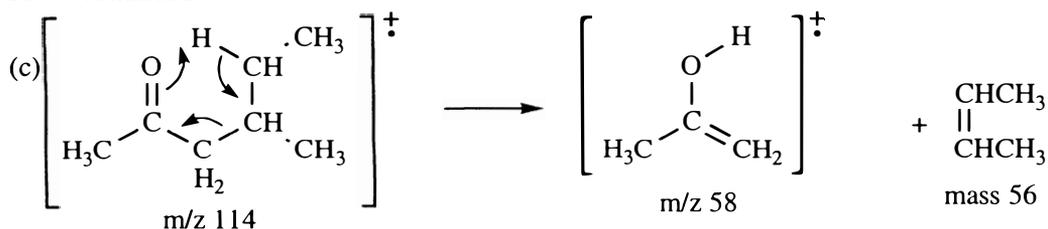
The NMR shows the typical ethyl pattern at δ 1.0 (3H, triplet) and δ 2.5 (2H, quartet), and a monosubstituted benzene at δ 7.3 (5H, multiplet). The singlet at δ 3.7 is a CH_2 , but quite far downfield, apparently deshielded by two groups. Assemble the pieces:



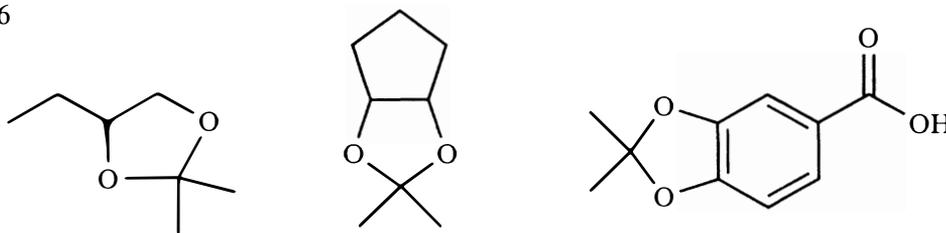
18-45



18-45 continued



18-46



18-47

A molecular ion of m/z 70 means a fairly small molecule. A solid semicarbazone derivative and a negative Tollens test indicate a ketone. The carbonyl (CO) has mass 28, so $70 - 28 = 42$, enough mass for only 3 more carbons. The molecular formula is probably C_4H_6O (mass 70); with two elements of unsaturation, we can infer the presence of a double bond or a ring in addition to the carbonyl.

The IR shows a strong peak at 1790 cm^{-1} , indicative of a ketone in a small ring. No peak in the $1600\text{--}1650\text{ cm}^{-1}$ region shows the absence of an alkene. The only possibilities for a small ring ketone containing four carbons are these:



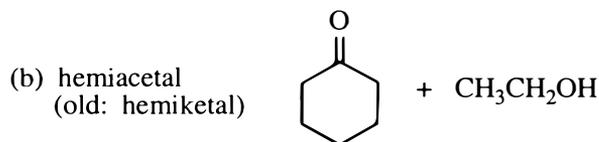
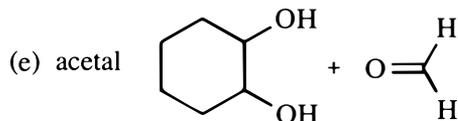
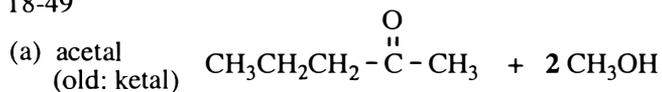
The HNMR can distinguish these. No methyl doublet appears in the NMR spectrum, ruling out **B**. The NMR does show a 4H triplet at δ 3.1; this signal comes from the two methylenes (C-2 and C-4) adjacent to the carbonyl, split by the two hydrogens on C-3. The signal for the methylene at C-3 appears at δ 2.0, roughly a quintet because of splitting by four neighboring protons.

The unknown is cyclobutanone, **A**. The symmetry indicated by the carbon NMR rules out structure **B**. The IR absorption of the carbonyl at 1790 cm^{-1} is characteristic of small ring ketones; ring strain strengthens the carbon-oxygen double bond, increasing its frequency of vibration. (See Section 12-9 in the text.)

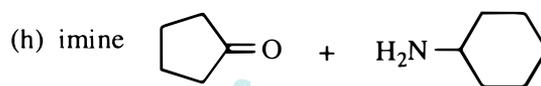
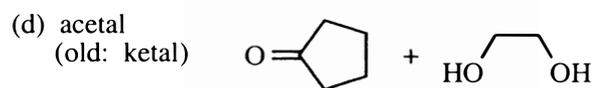
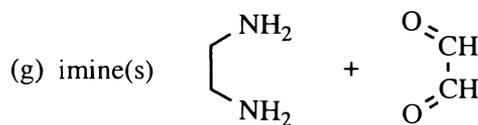
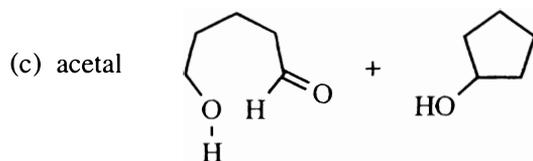
18-48

- (a) The conjugated diene has a maximum at 235 nm (see Solved Problem 15-3) and the ketone has a maximum at about 237 nm, so the π to π^* transition cannot be used to differentiate the compounds.
 (b) The ketone has an n to π^* transition around 315 nm that the diene cannot have.

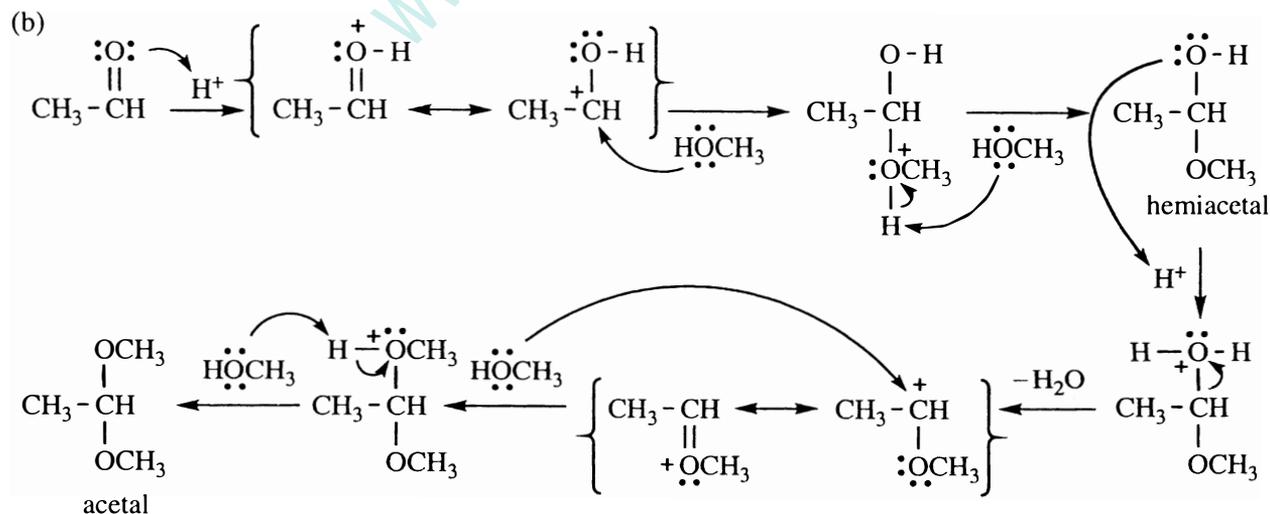
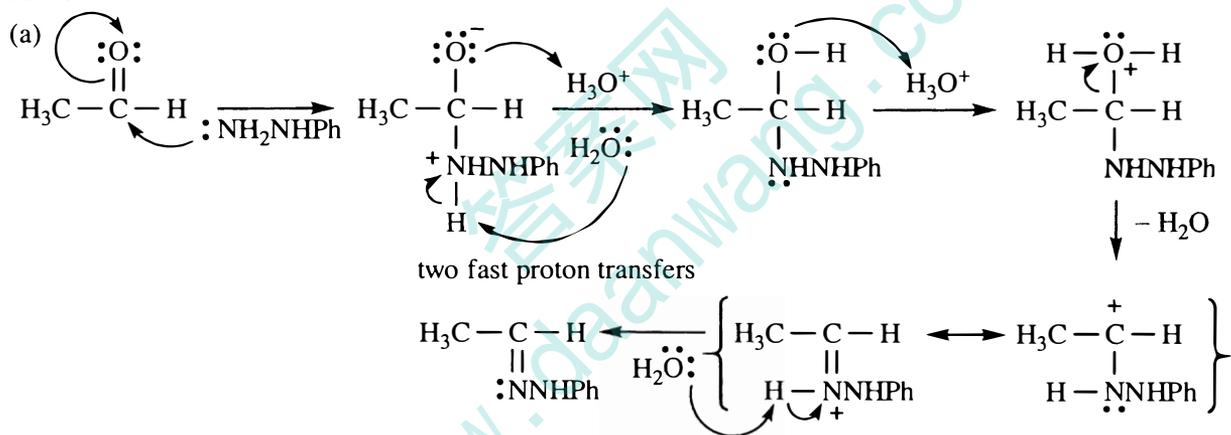
18-49

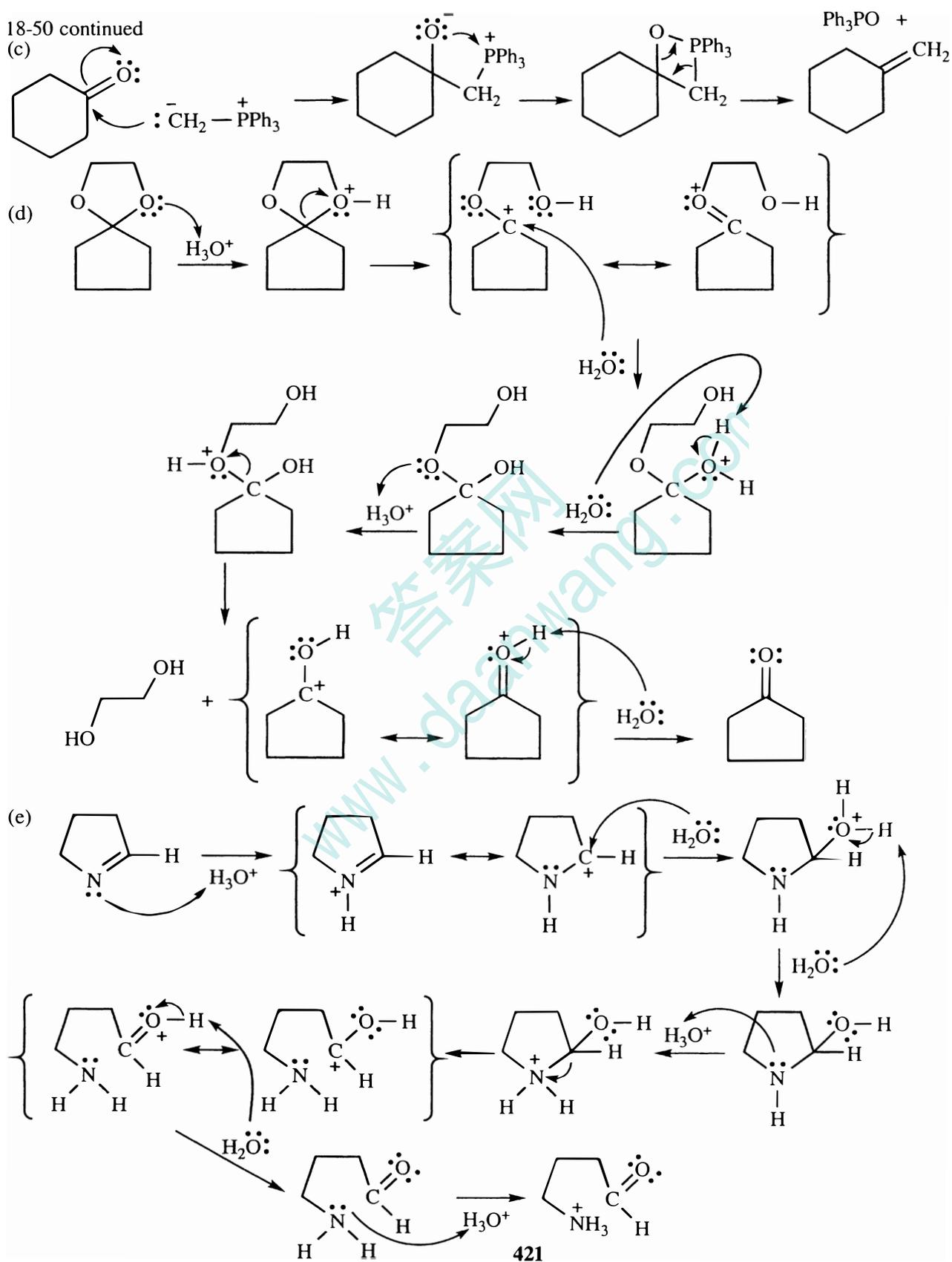


(f) diether, inert to hydrolysis

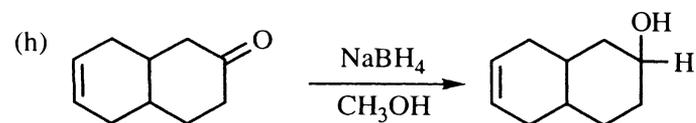
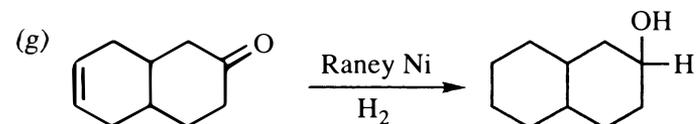
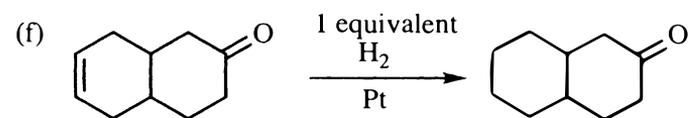
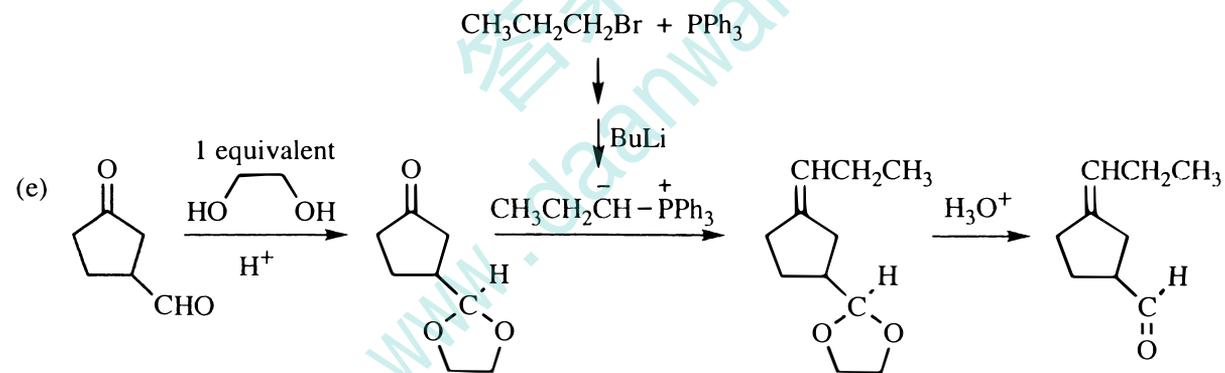
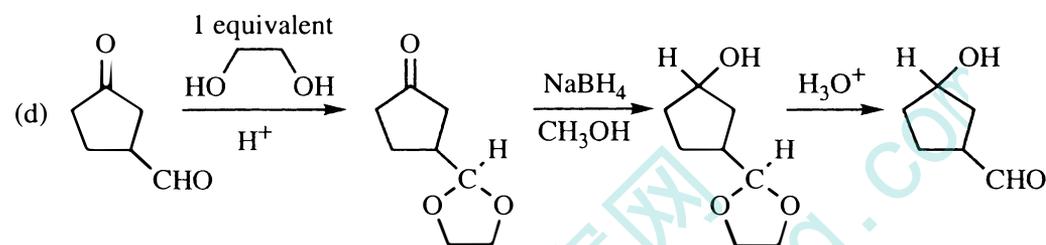
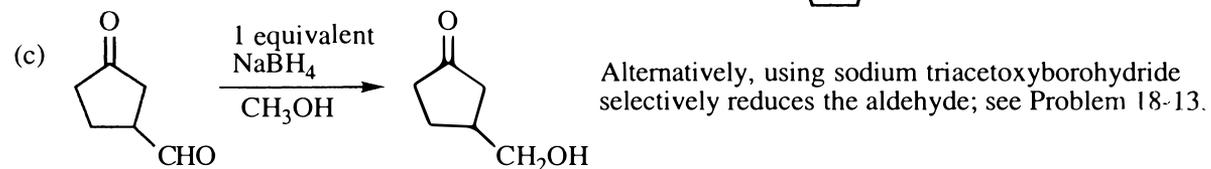
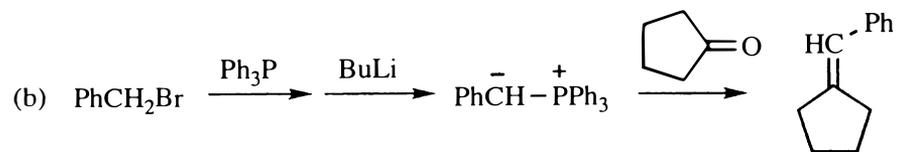
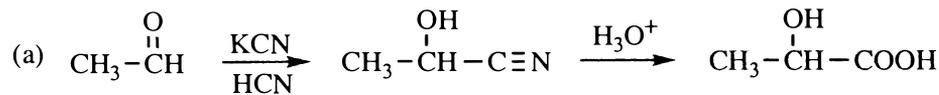


18-50

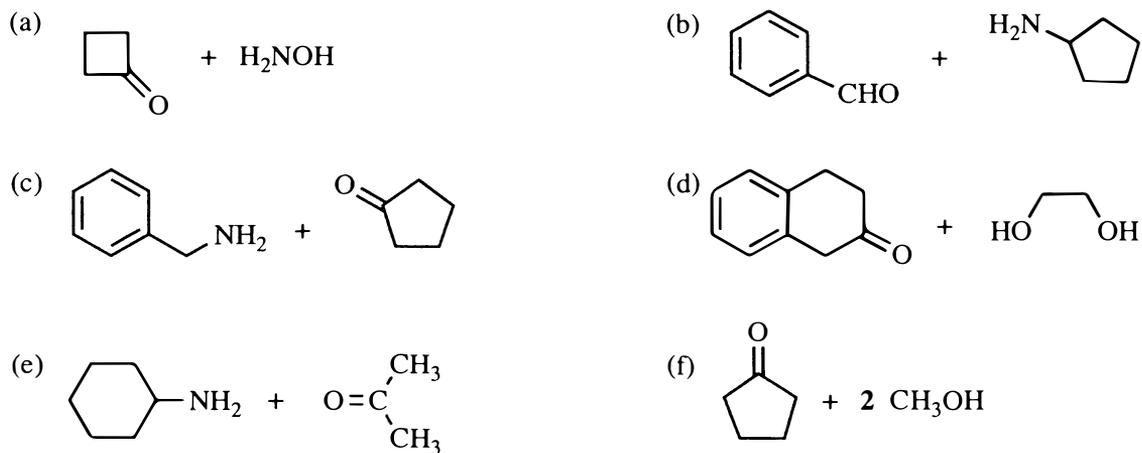




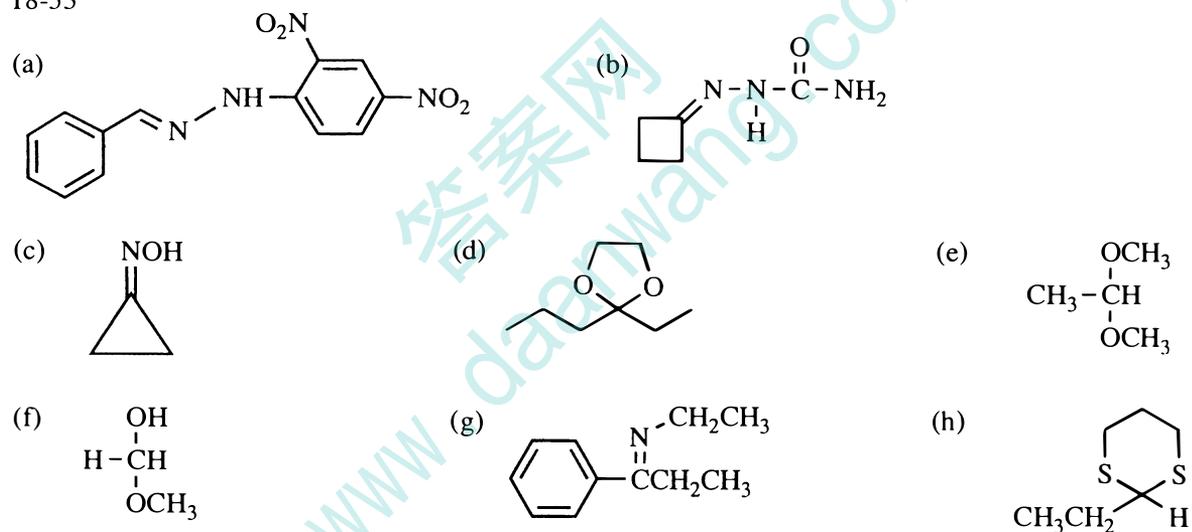
18-51



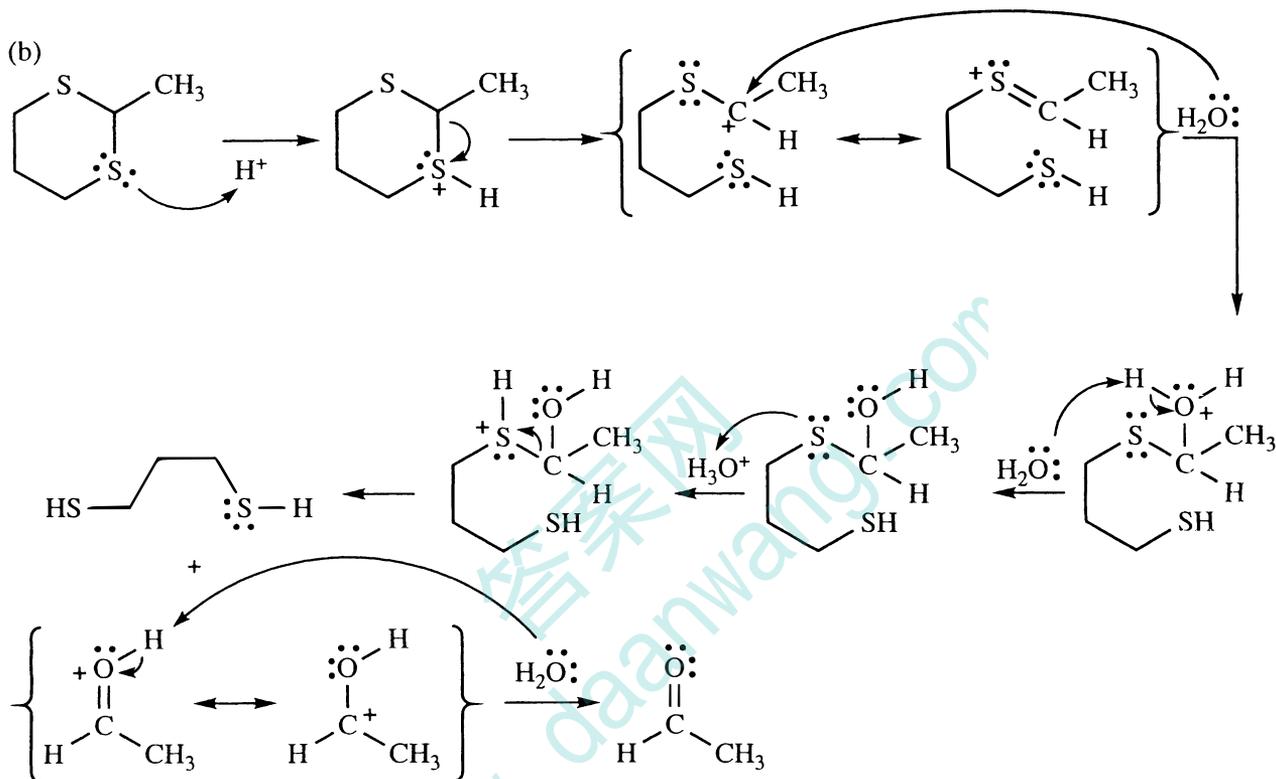
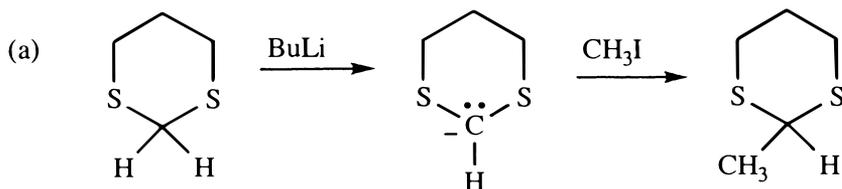
18-52 All of these reactions would be acid-catalyzed.



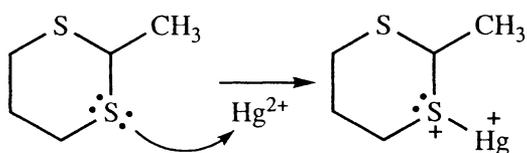
18-53



18-54

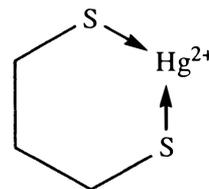


(c) Mercuric ion, Hg^{2+} , assists the hydrolysis in two ways. First, mercuric ion is a Lewis acid of moderate strength, performing the same function as a proton from a protic acid.



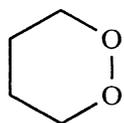
The effectiveness of Hg^{2+} as a Lewis acid is partly due to its charge: even complexed with a sulfur, the mercury atom still has a positive charge, attracting the sulfur's electrons.

A second explanation for mercuric ion's effectiveness in hydrolysis of thioacetals lies in the complex formed between the ion and the two sulfur atoms. This stable complex effectively removes $\text{HSCH}_2\text{CH}_2\text{SH}$ from the equilibrium, shifting the equilibrium to product. (An example of whose principle? His initials are "Le Châtelier".)



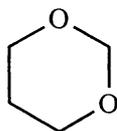
Thiols are often referred to as "mercaptans" because of their ability to CAPTURE MERCURY.

18-55 The key to this problem is understanding that the relative proximity of the two oxygens can dramatically affect their chemistry.



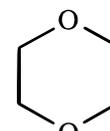
1,2-dioxane

The "second" isomer described: two oxygens connected by a sigma bond are a peroxide. The O—O bond is easily cleaved to give radicals. In the presence of organic compounds, radical reactions can be explosive.



1,3-dioxane

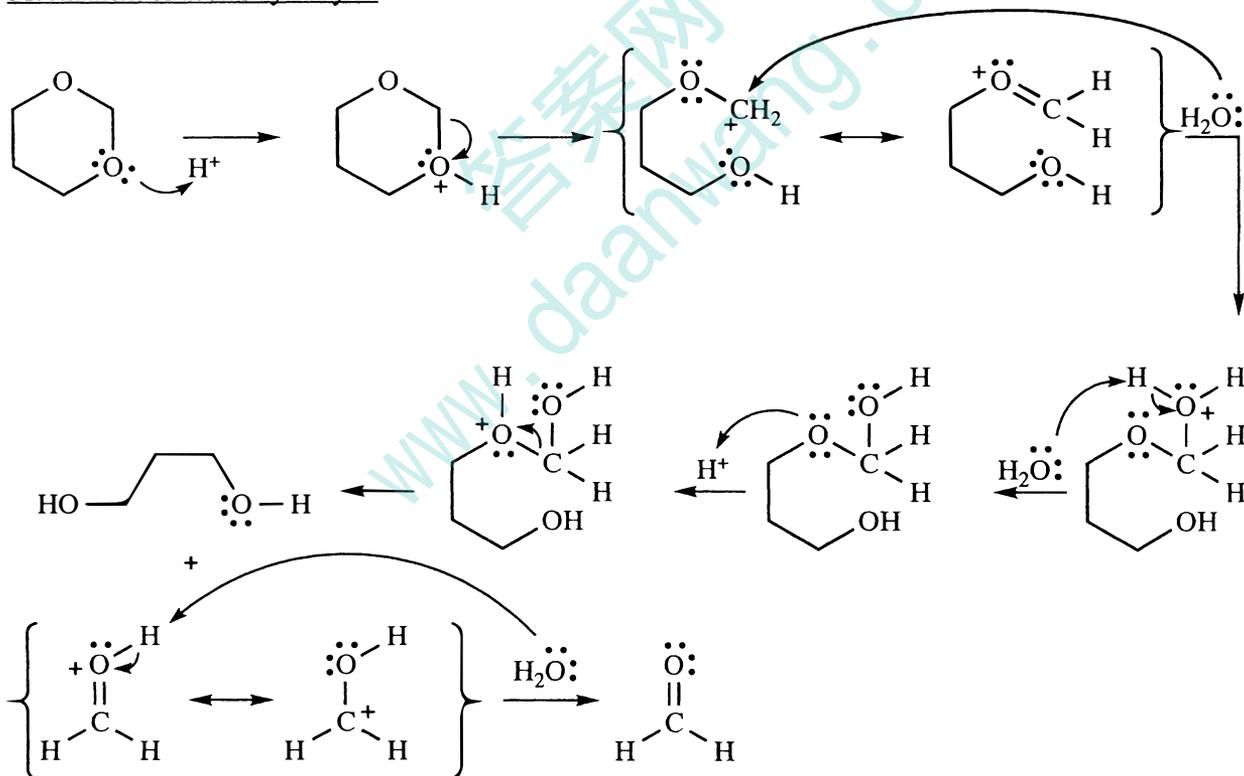
The "third" isomer described: two oxygens bonded to the same sp^3 carbon constitute an acetal which is hydrolyzed in aqueous acid. See the mechanism below.



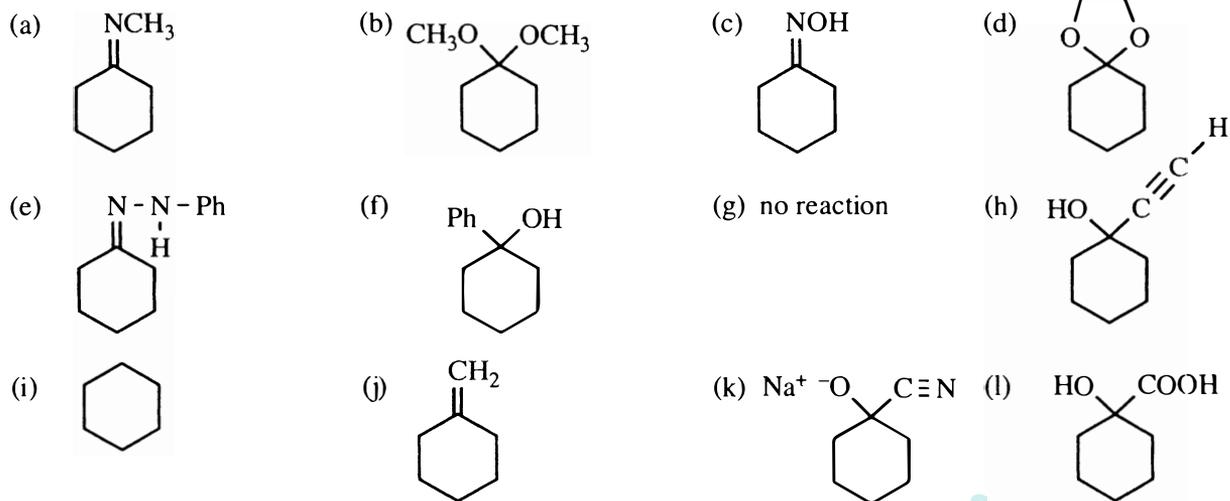
1,4-dioxane

The "first" isomer described: an excellent solvent (although toxic), these oxygens are far enough apart to act independently. It is a simple ether.

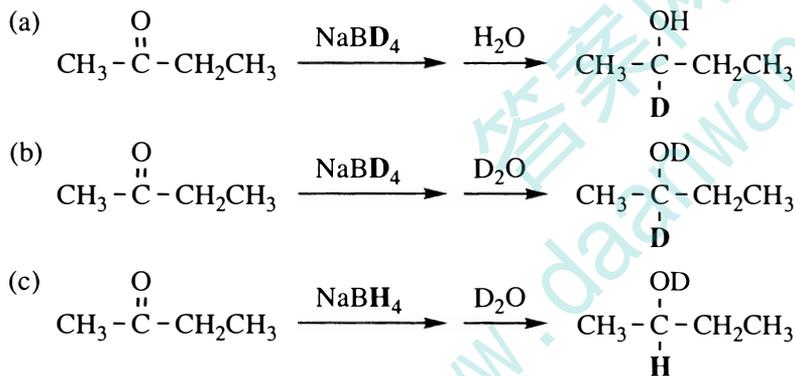
Mechanism of acetal hydrolysis



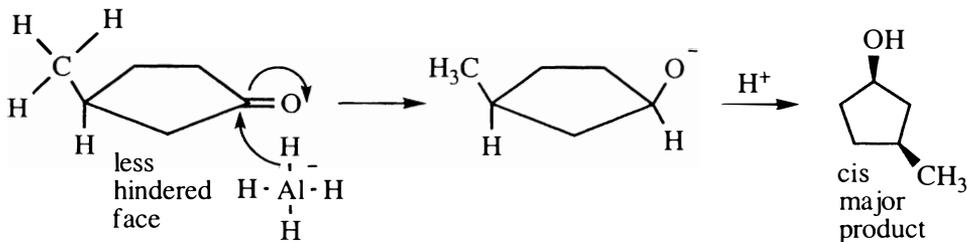
18-56



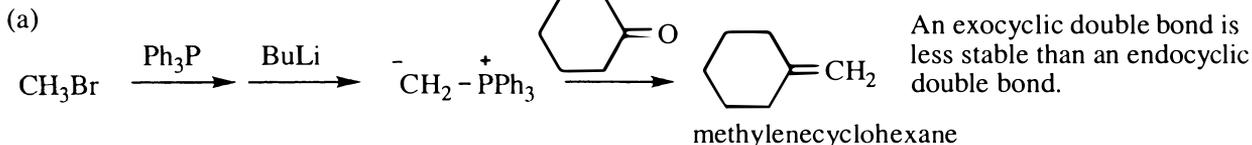
18-57 The new bond to carbon comes from the NaBH_4 or NaBD_4 , shown in bold below. The new bond to oxygen comes from the protic solvent.



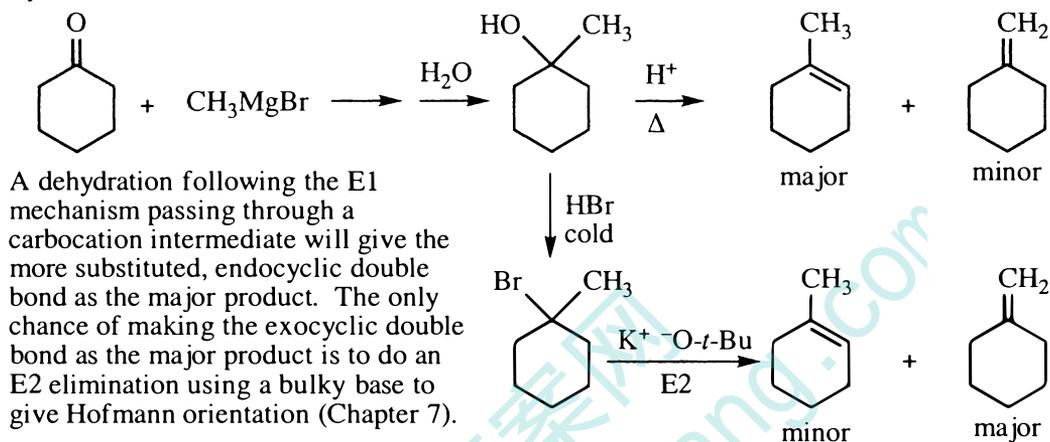
18-58 While hydride is a small group, the actual chemical species supplying it, AlH_4^- , is fairly large, so it prefers to approach from the less hindered side of the molecule, that is, the side opposite the methyl. This forces the oxygen to go to the same side as the methyl, producing the *cis* isomer as the major product.



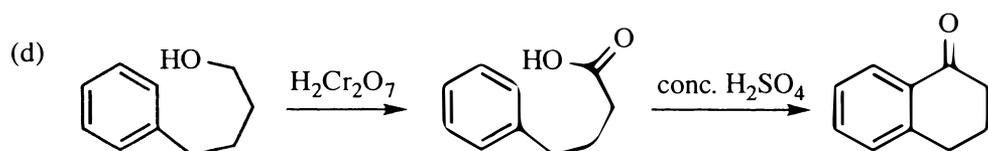
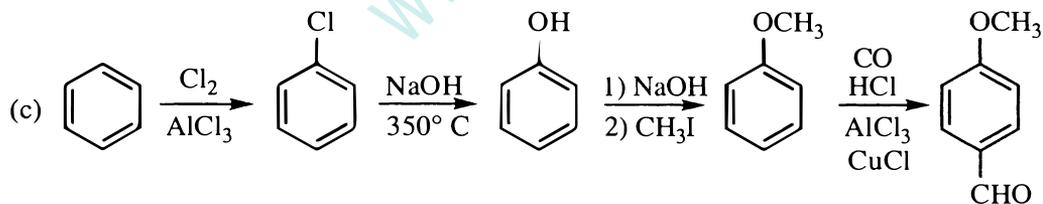
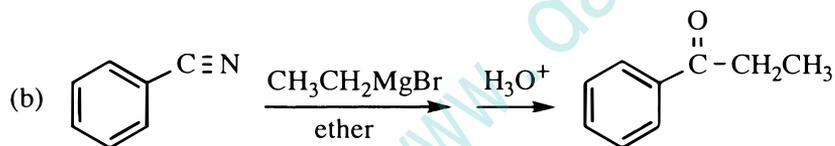
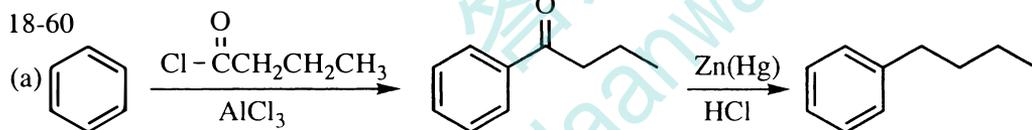
18-59



(b) The difficulty in synthesizing methylenecyclohexane from cyclohexanone without using the Wittig reaction rests in the stability of the double bond inside the ring (endocyclic) versus outside the ring (exocyclic).

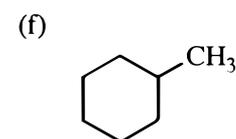
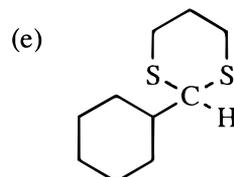
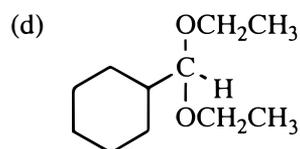
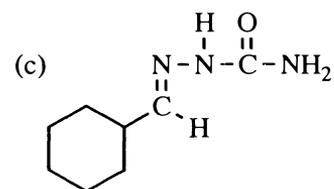
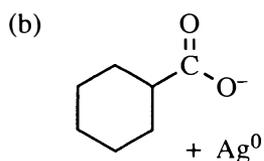
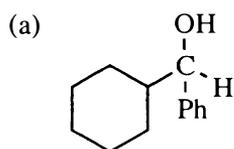


18-60

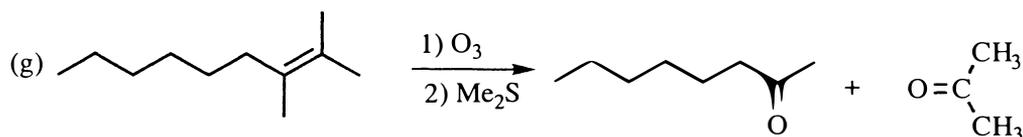
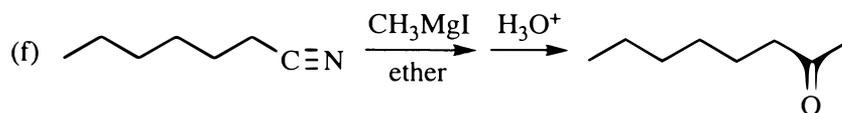
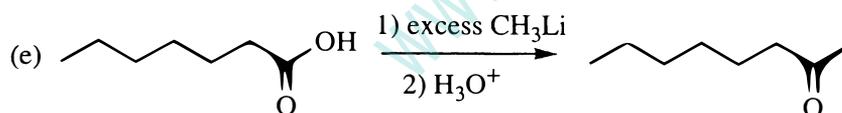
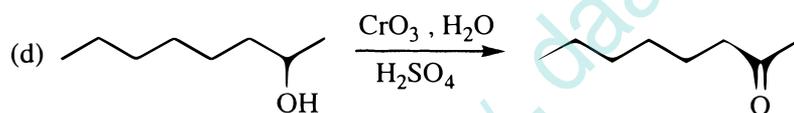
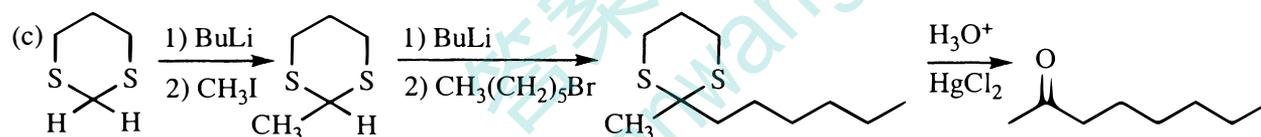
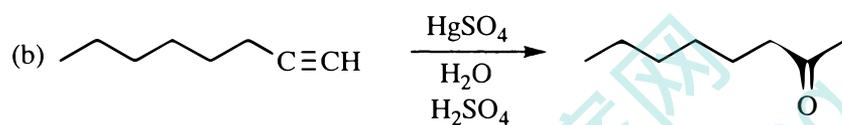
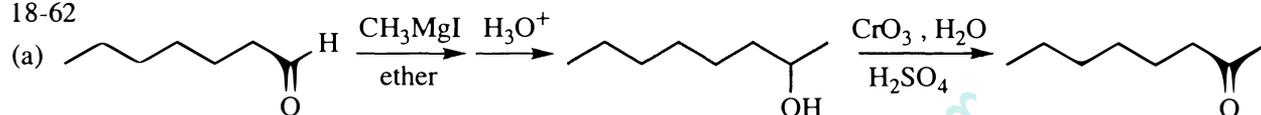


Alternatively, the acid chloride could be made with SOCl_2 , then cyclized by Friedel-Crafts acylation with AlCl_3 .

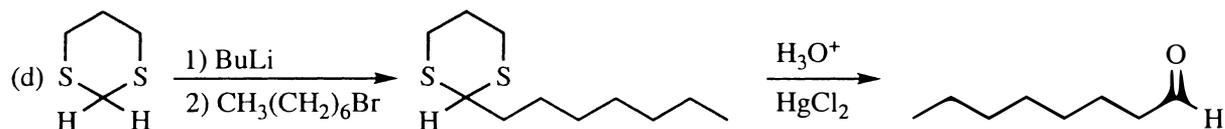
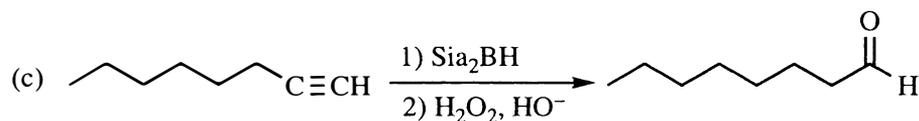
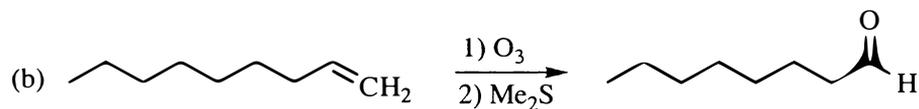
18-61



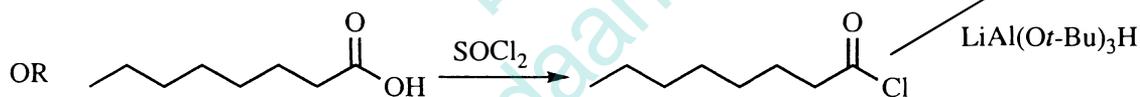
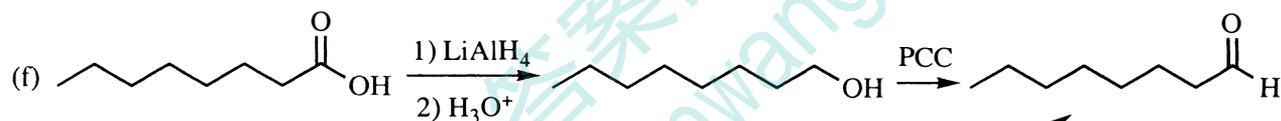
18-62



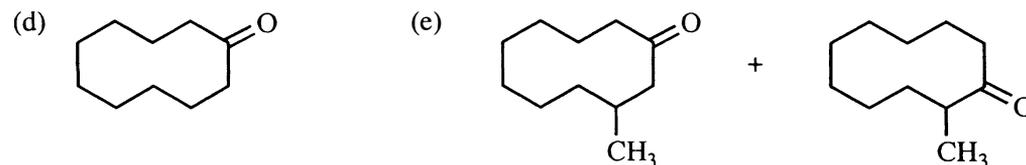
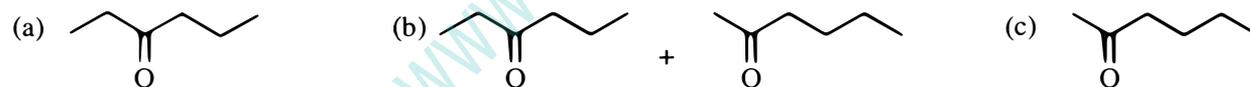
18-63



(This reaction needs a solvent like THF to keep all reactants in solution.)



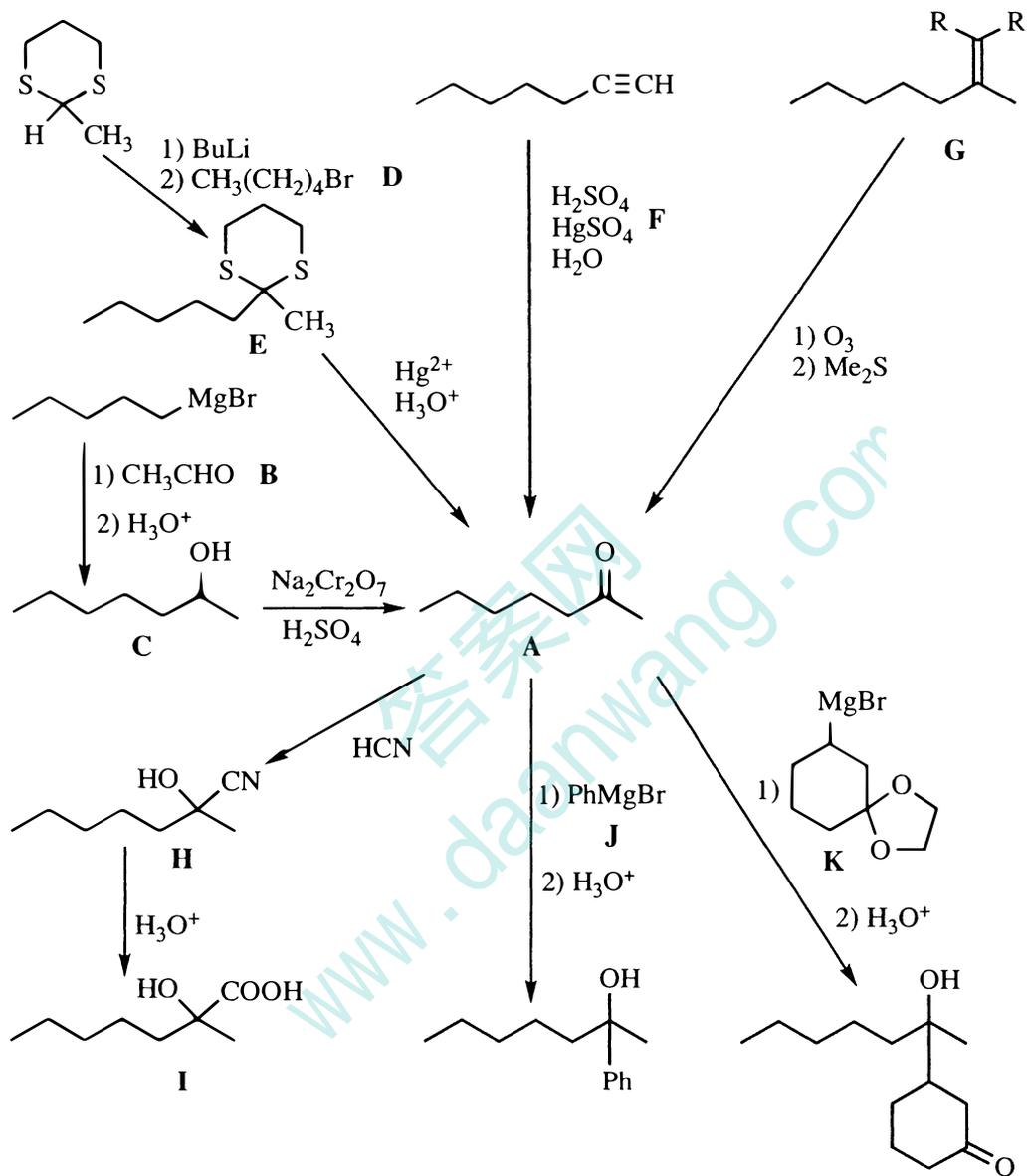
18-64



18-65

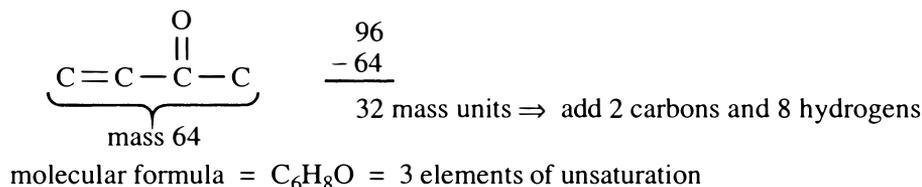
- (a) ketone: no reaction
- (b) aldehyde: positive
- (c) enol of an aldehyde—tautomerizes to aldehyde in base: positive
- (d) hemiacetal of an aldehyde in equilibrium with the aldehyde in base: positive
- (e) acetal—stable in base: no reaction
- (f) hemiacetal of an aldehyde in equilibrium with the aldehyde in base: positive

18-66 The structure of **A** can be deduced from its reaction with **J** and **K**. What is common to both products of these reactions is the heptan-2-ol part; the reactions must be Grignard reactions with heptan-2-one, so **A** must be heptan-2-one.



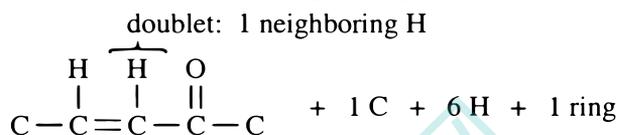
18-67 The very strong π to π^* absorption at 225 nm in the UV spectrum suggests a conjugated ketone or aldehyde. The IR confirms this: strong, conjugated carbonyl at 1690 cm^{-1} and small alkene at 1610 cm^{-1} . The absence of peaks at $2700\text{-}2800\text{ cm}^{-1}$ shows that the unknown is not an aldehyde.

The molecular ion at 96 leads to the molecular formula:

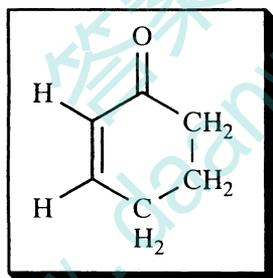


Two elements of unsaturation are accounted for in the enone. The other one is likely a ring.

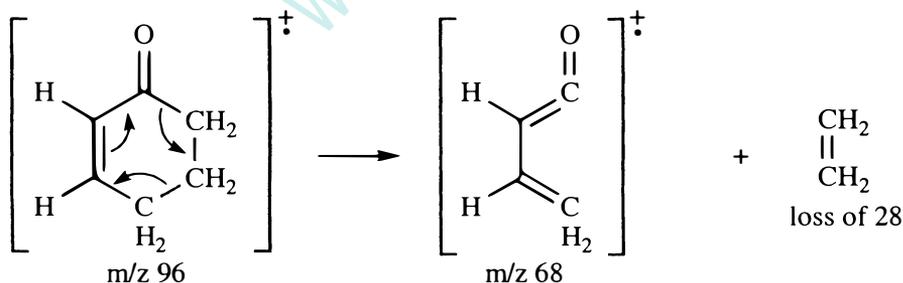
The NMR shows two vinyl hydrogens. The doublet at δ 6.0 says that the two hydrogens are on neighboring carbons (two peaks = one neighboring H).



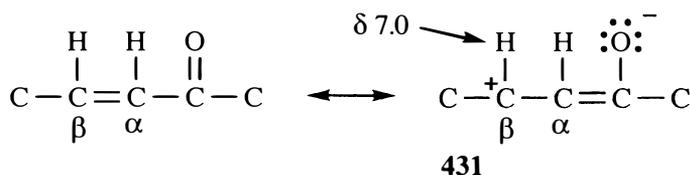
No methyls are apparent in the NMR, so the 6H group of peaks at δ 2.0-2.4 is most likely 3 CH_2 groups. Combining the pieces:



The mass spectral fragmentation can be explained by a "retro" or reverse Diels-Alder fragmentation:

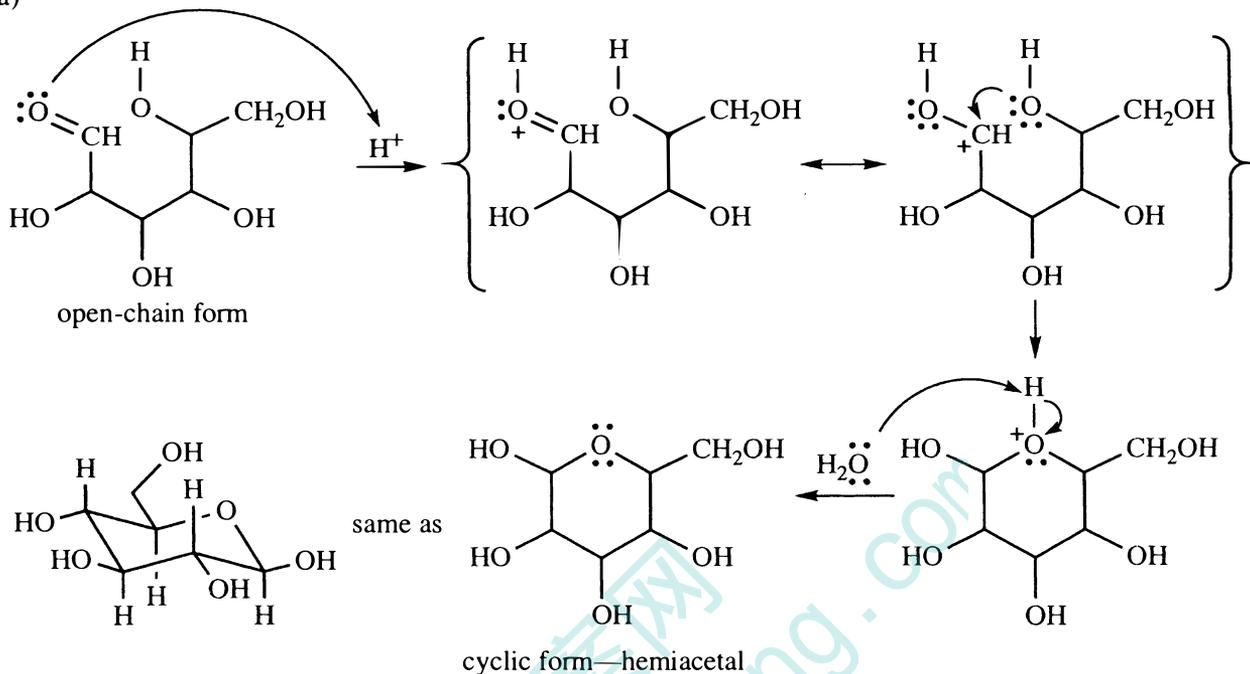


In the HNMR, one of the vinyl hydrogens appears at δ 7.0. This is typical of an α,β -unsaturated carbonyl because of the resonance form that shows deshielding of the β -hydrogen.

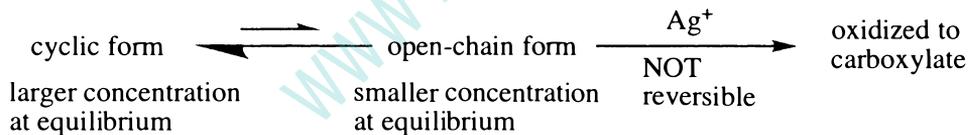


18-68 Building a model will help visualize this problem.

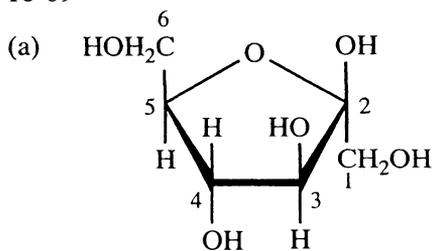
(a)



(b) Yes, the cyclic form of glucose will give a positive Tollens test. In the basic solution of the Tollens test, the hemiacetal is in equilibrium with the open-chain aldehyde with the cyclic form in much larger concentration. However, it is the open-chain aldehyde that reacts with silver ion, so even though there is only a small amount of open-chain form present at any given time, as more of the open-chain form is oxidized by silver ion, more cyclic form will open to replace the consumed open-chain form. Eventually all of the cyclic form will be dragged kicking and screaming through the open-chain form to be oxidized to the carboxylate. Le Châtelier's Principle strikes again!

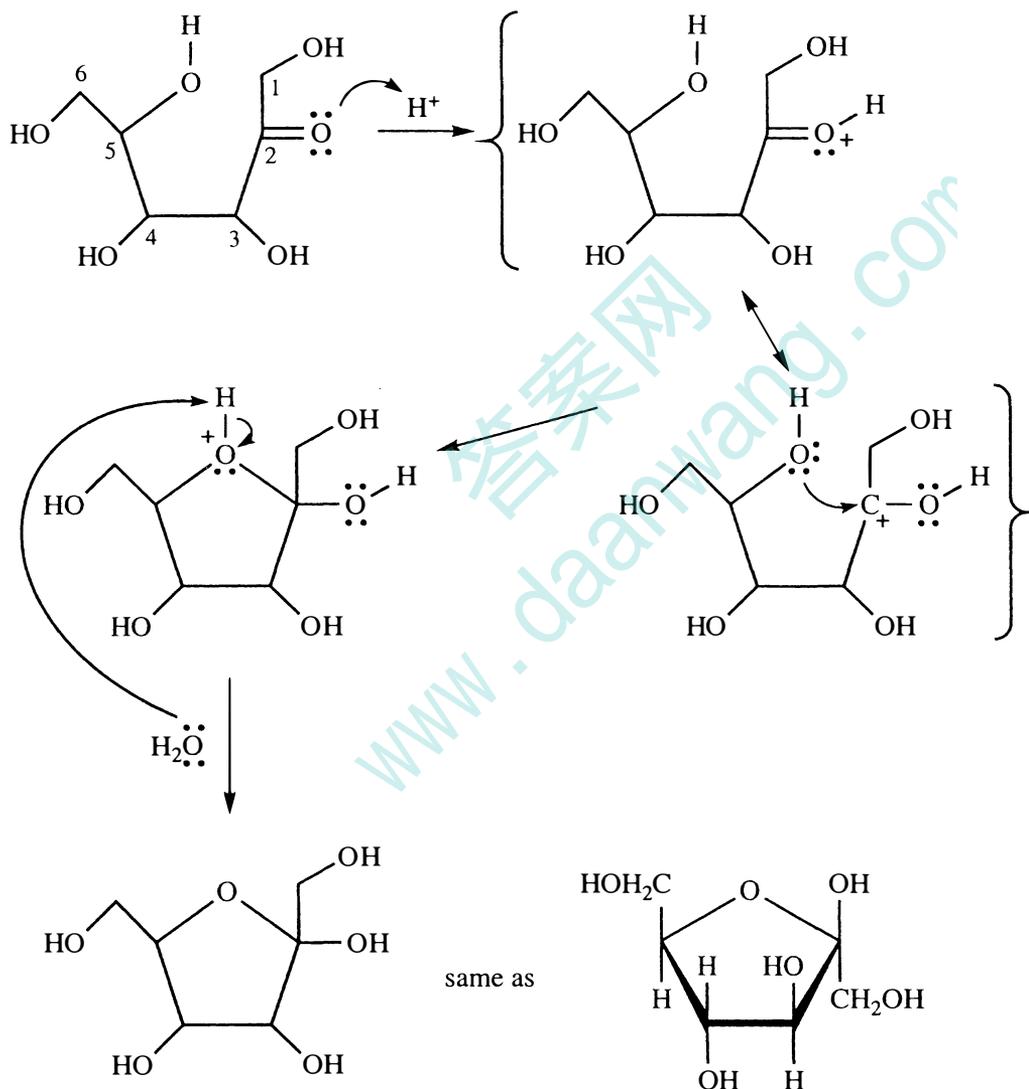


18-69

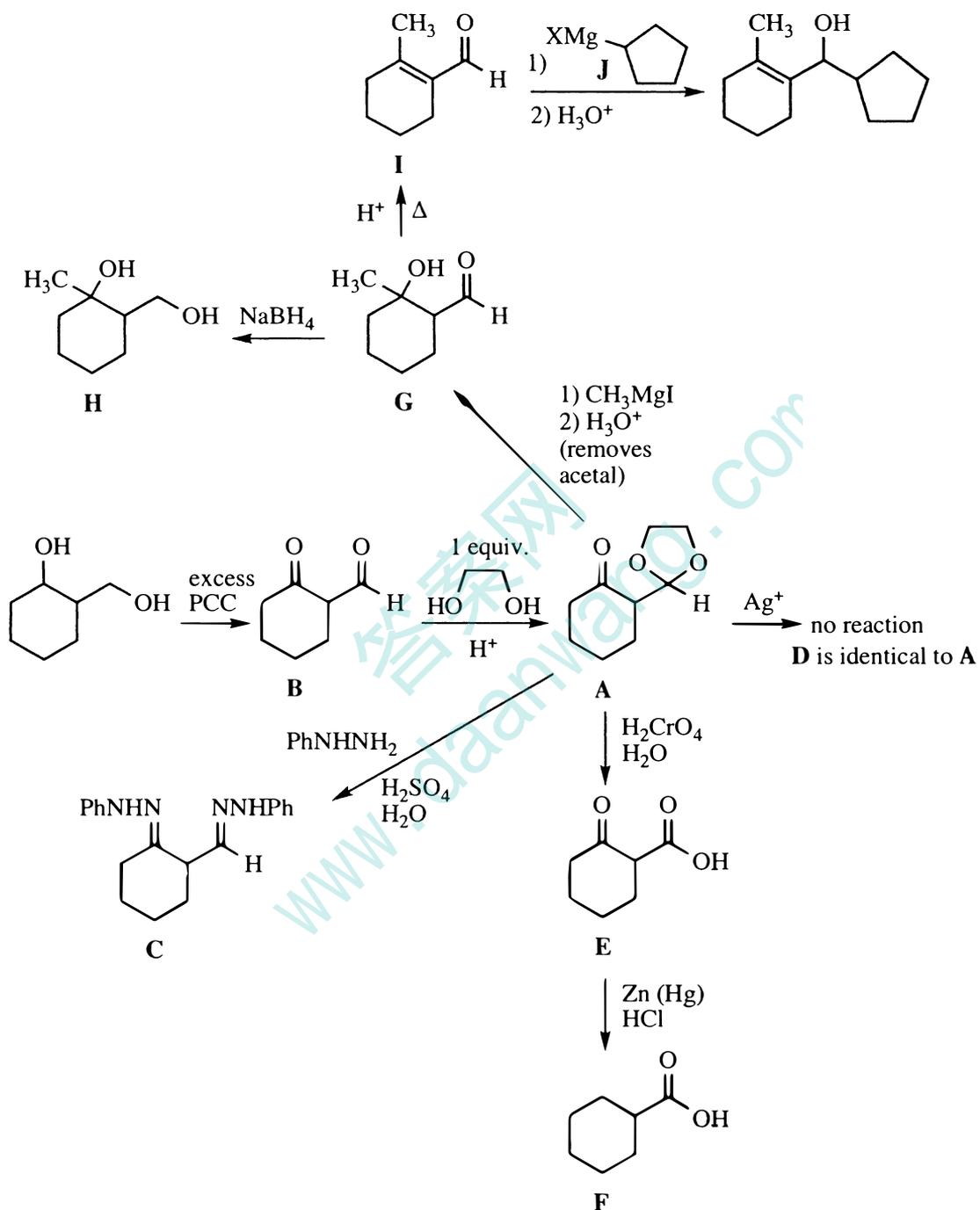


Any carbon with two oxygens bonded to it with single bonds belongs to the acetal family. If one of the oxygen groups is an OH, then the functional group is a hemiacetal. Thus, the functional group at C-2 is a hemiacetal. (The old name for this group is hemiketal as it came from a ketone.)

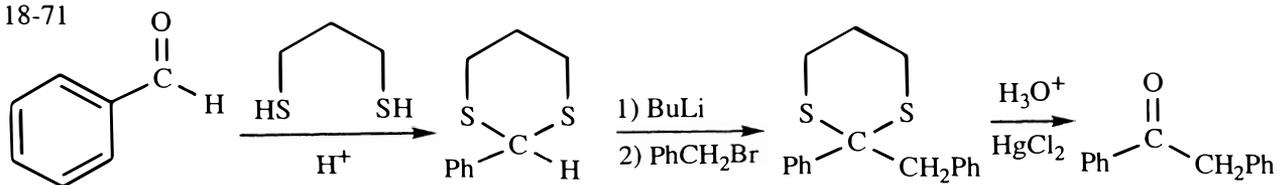
(b) Models will help. Ignore stereochemistry for the mechanism.



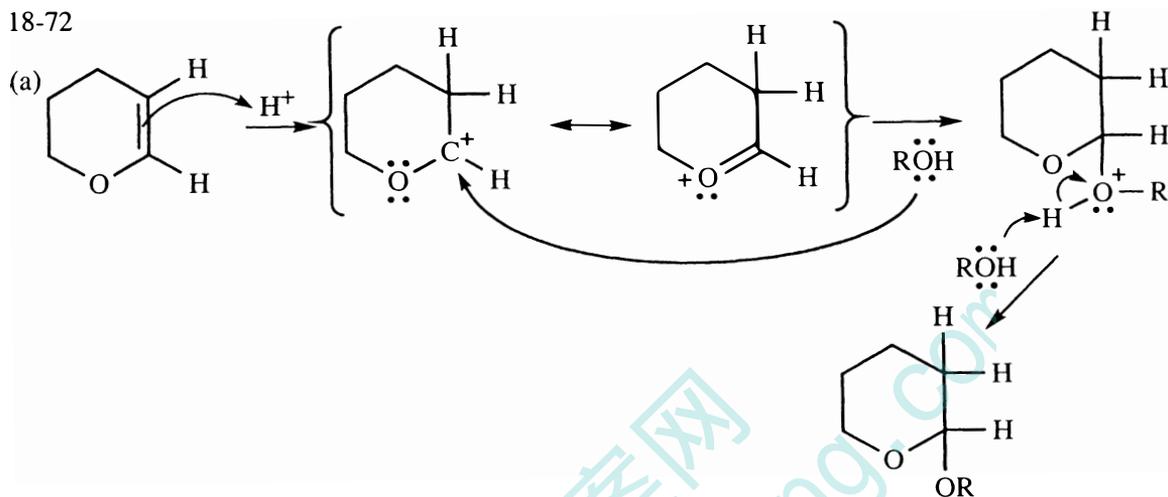
18-70 Recall that "dilute acid" means an aqueous solution, and aqueous acid will remove acetals.



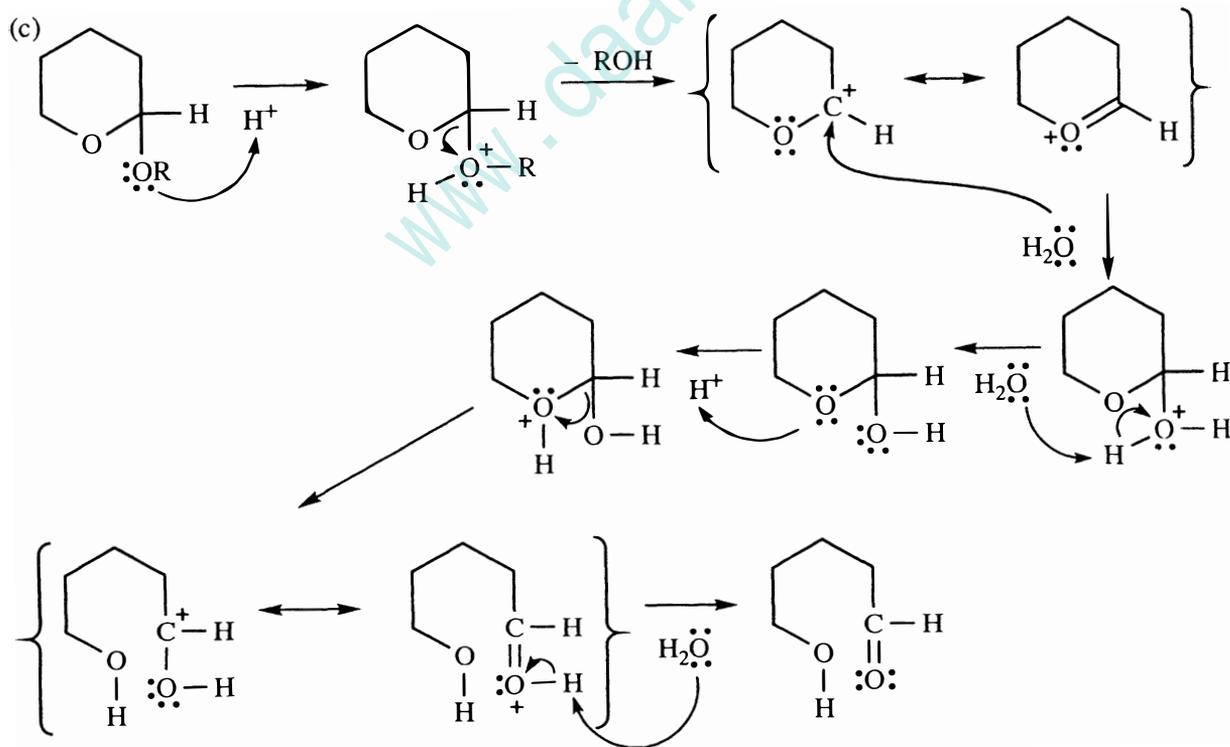
18-71



18-72

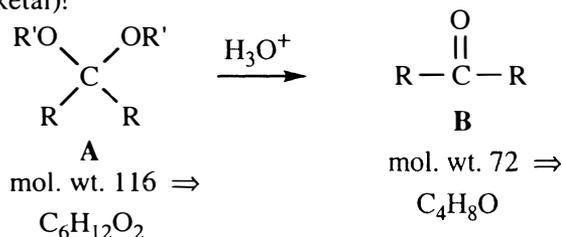


(b) This is not an ether, but rather an acetal, stable to base but reactive with aqueous acid.

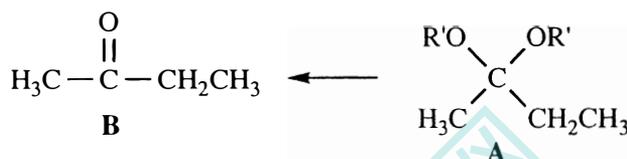


18-73

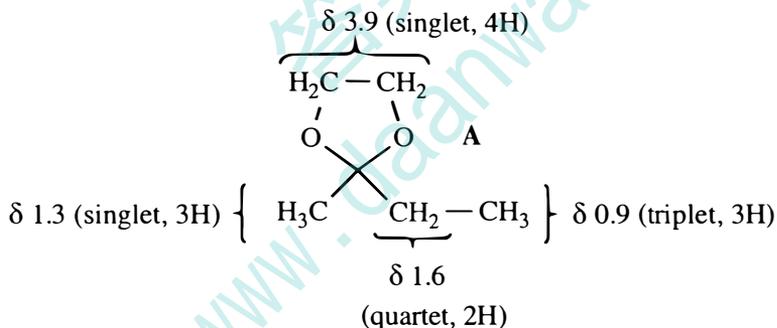
(a) First, deduce what functional groups are present in **A** and **B**. The IR of **A** shows no alkene and no carbonyl: the strongest peak is at 1060 cm^{-1} , possible a C—O bond. After acid hydrolysis of **A**, the IR of **B** shows a carbonyl at 1715 cm^{-1} : a ketone. (If it were an aldehyde, it would have aldehyde C—H around $2700\text{--}2800\text{ cm}^{-1}$, absent in the spectrum of **B**.) What functional group has C—O bonds and is hydrolyzed to a ketone? An acetal (ketal)!



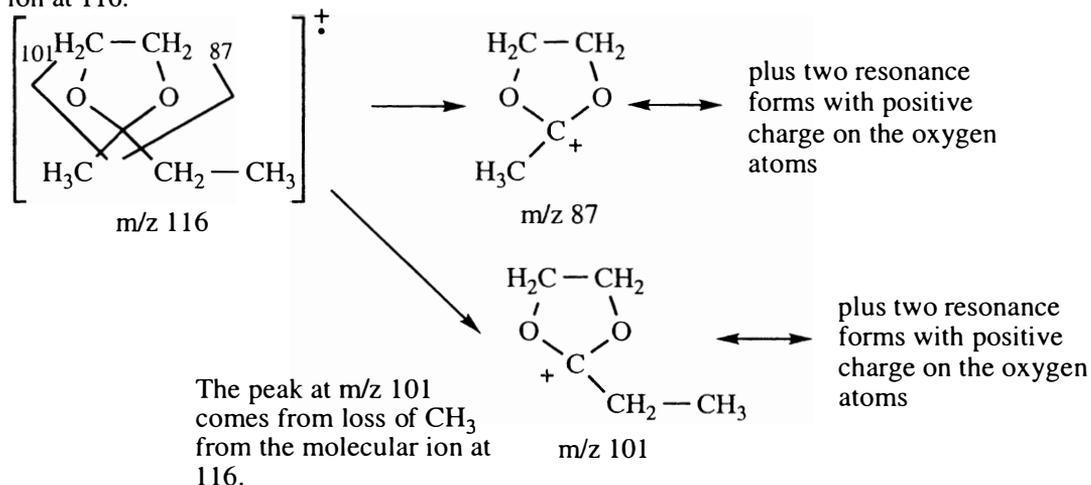
There is only one ketone of formula $\text{C}_4\text{H}_8\text{O}$: butan-2-one.



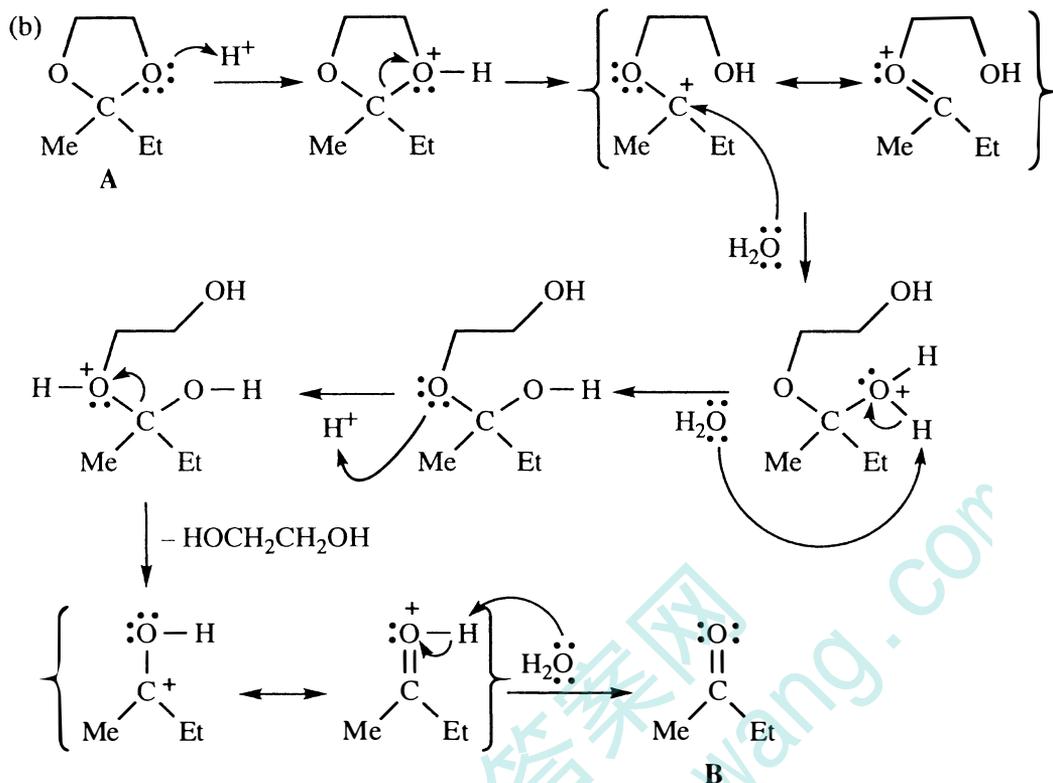
A must have the same alkyl groups as **B**. **A** has one element of unsaturation and is missing only C_2H_4 from the partial structure above. The most likely structure is the ethylene ketal. Is this consistent with the NMR?



What about the peaks in the MS at m/z 87 and 101? The 87 peak is the loss of 29 from the molecular ion at 116.



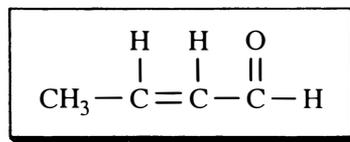
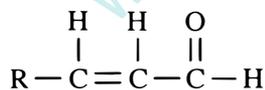
18-73 continued



18-74 The strong UV absorption at 220 nm indicates a conjugated aldehyde or ketone. The IR shows a strong carbonyl at 1690 cm^{-1} , alkene at 1625 cm^{-1} , and two peaks at 2720 cm^{-1} and 2810 cm^{-1} —aldehyde!



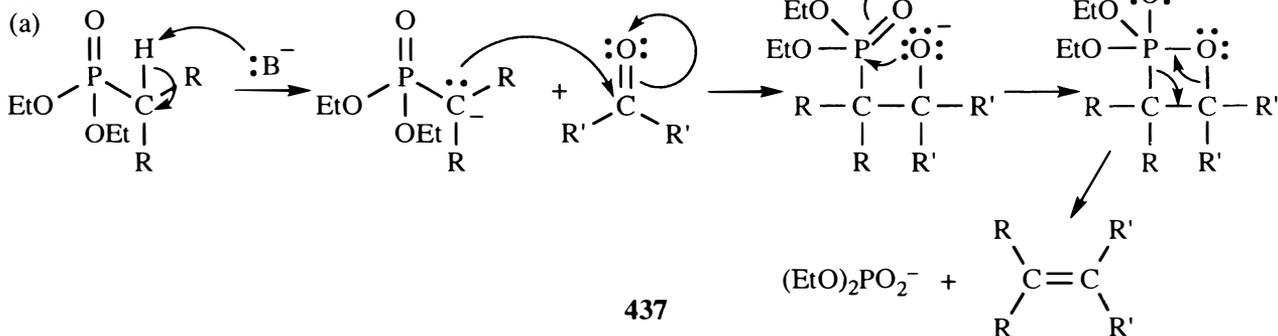
The NMR shows the aldehyde proton at $\delta 9.5$ split into a doublet, so it has one neighboring H. There are only two vinyl protons, so there must be an alkyl group coming off the β carbon:



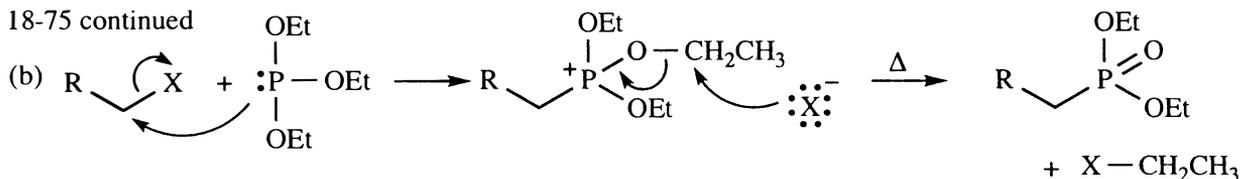
The only other NMR signal is a 3H doublet: R must be methyl.

"crotonaldehyde"

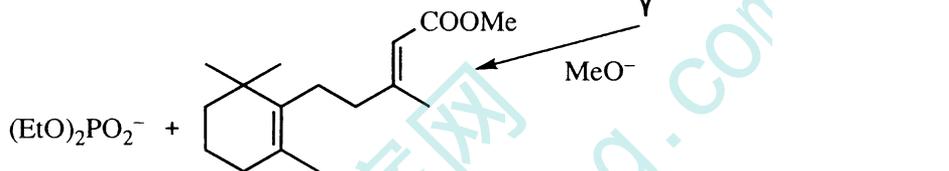
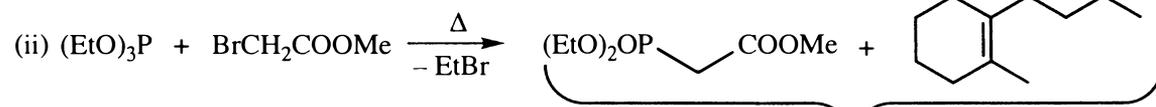
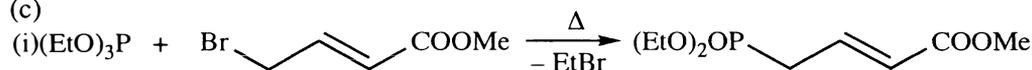
18-75



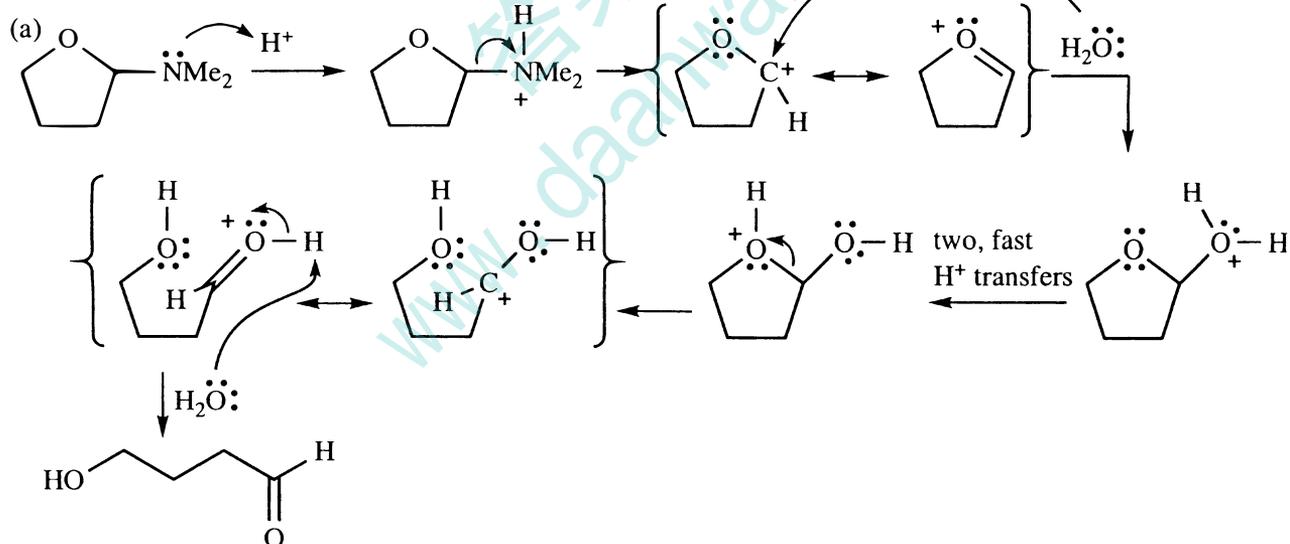
18-75 continued



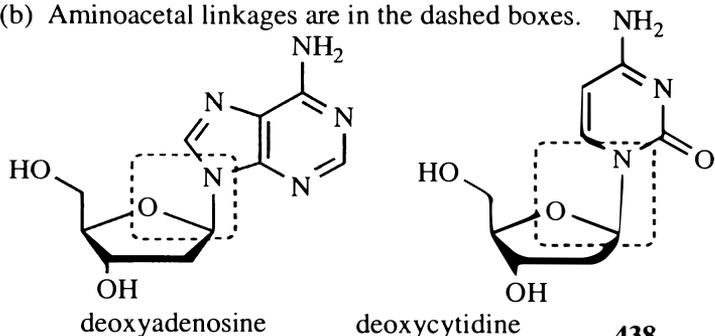
(c)



18-76



(b) Aminoacetal linkages are in the dashed boxes.

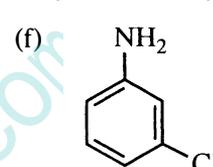
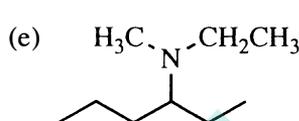
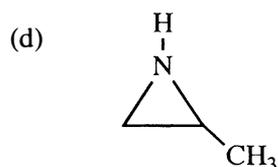
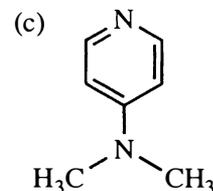
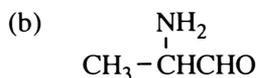
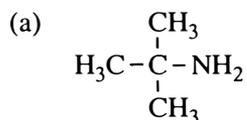


(c) The first step in the mechanism in part (a) is protonation of the amine's electron pair. The nitrogens of the DNA nucleosides, however, are part of aromatic rings, and the electron pairs are required for the aromaticity of the ring. (See the solution to problem 16-42 for a description of the aromaticity of these nucleoside bases.) Protonation of the nitrogen will not occur unless the acid is extremely strong; dilute acids will not protonate the N and therefore the nucleoside will be stable.

CHAPTER 19—AMINES

19-1 These compounds satisfy the criteria for aromaticity (planar, cyclic π system, and the Huckel number of $4n + 2 \pi$ electrons): pyrrole, imidazole, indole, pyridine, 2-methylpyridine, pyrimidine, and purine. The systems with 6 π electrons are: pyrrole, imidazole, pyridine, 2-methylpyridine, and pyrimidine. The systems with 10 π electrons are: indole and purine. The other nitrogen heterocycles shown are not aromatic because they do not have cyclic π systems.

19-2



19-3

- (a) pentan-2-amine (b) *N*-methylbutan-2-amine
 (c) 3-aminophenol (or *meta*-) (d) 3-methylpyrrole
 (e) *trans*-cyclopentane-1,2-diamine (f) *cis*-3-aminocyclohexanecarbaldehyde

19-4

- (a) resolvable: there are two asymmetric carbons; carbon does not invert
 (b) not resolvable: the nitrogen is free to invert
 (c) not resolvable: it is symmetric
 (d) not resolvable: even though the nitrogen is quaternary, one of the groups is a proton which can exchange rapidly, allowing for inversion
 (e) resolvable: the nitrogen is quaternary and cannot invert when bonded to carbons

19-5 In order of increasing boiling point (increasing intermolecular hydrogen bonding):

- (a) triethylamine and *n*-propyl ether have the same b.p. < di-*n*-propylamine
 (b) dimethyl ether < dimethylamine < ethanol
 (c) trimethylamine < diethylamine < diisopropylamine

19-6 Listed in order of increasing basicity. (See Appendix 2 for a discussion of acidity and basicity.)

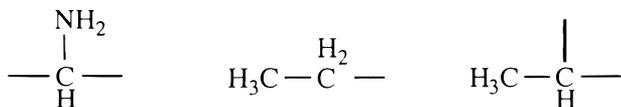
- (a) $\text{PhNH}_2 < \text{NH}_3 < \text{CH}_3\text{NH}_2 < \text{NaOH}$
 (b) *p*-nitroaniline < aniline < *p*-methylaniline (*p*-toluidine)
 (c) pyrrole < aniline < pyridine
 (d) 3-nitropyrrole < pyrrole < imidazole

19-7

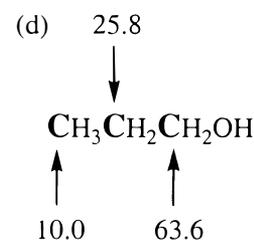
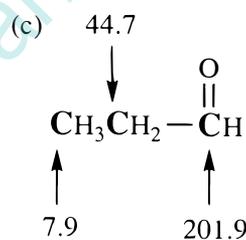
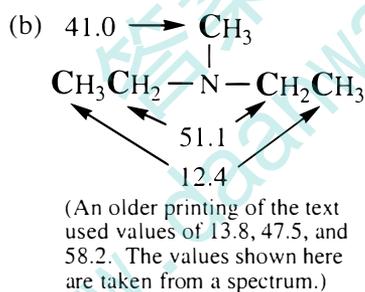
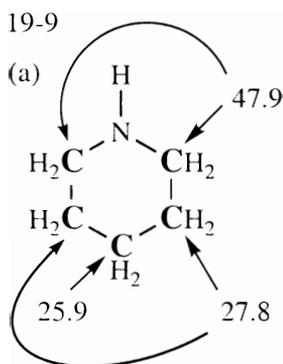
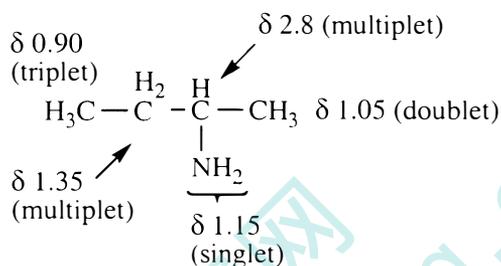
- (a) secondary amine: one peak in the 3200-3400 cm^{-1} region, indicating NH
 (b) primary amine: two peaks in the 3200-3400 cm^{-1} region, indicating NH_2
 (c) alcohol: strong, broad peak around 3400 cm^{-1}

19-8 A compound with formula $C_4H_{11}N$ has no elements of unsaturation. The proton NMR shows five types of H, with the NH_2 appearing as a broad peak at δ 1.15, meaning that there are four different groups of hydrogens on the four carbons. The carbon NMR also shows four carbons, so there is no symmetry in this structure; that is, it does not contain a *t*-butyl group or an isopropyl group.

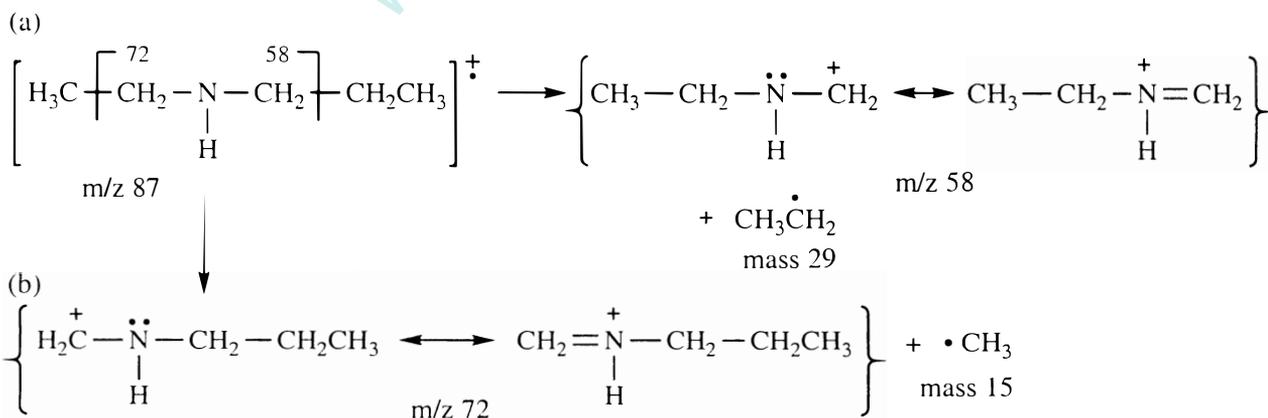
The multiplet farthest downfield is a CH deshielded by the nitrogen; integration shows it to be one H. There is a 2H multiplet at δ 1.35, the broad NH_2 peak at δ 1.15, a 3H doublet at δ 1.05, and a 3H triplet at δ 0.90. The latter two signals must represent methyl groups next to a CH and a CH_2 respectively. So far:



The pieces shown above have one carbon too many, so there must be one carbon that is duplicated: the only possible one is the CH, and the structure reveals itself.



19-10

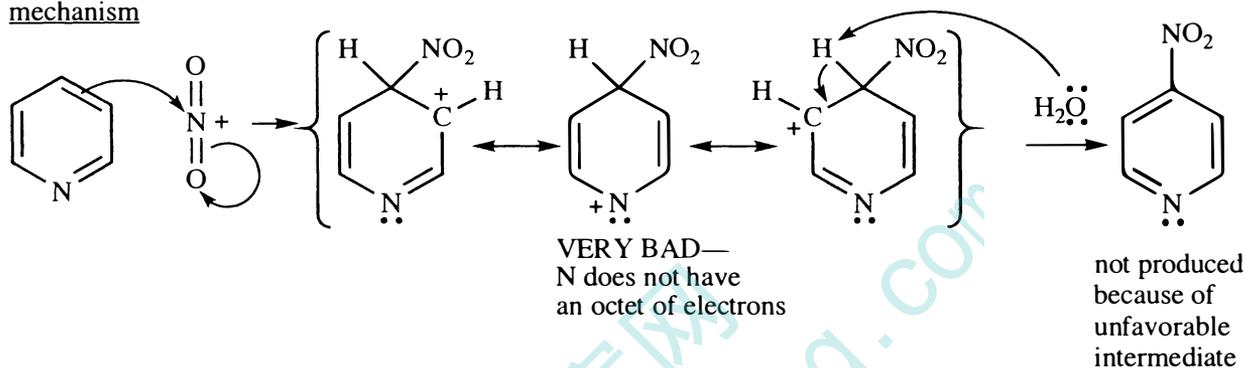


(c) The fragmentation in (a) occurs more often than the one in (b) because of stability of the radicals produced along with the iminium ions. Ethyl radical is much more stable than methyl radical, so pathway (a) is preferred.

19-11 Nitration at the 4-position of pyridine is not observed for the same reason that nitration at the 2-position is not observed: the intermediate puts some positive character on an electron-deficient nitrogen, and electronegative nitrogen hates that. (It is important to distinguish this type of positive nitrogen without a complete octet of electrons, from the quaternary nitrogen, also positively charged but with a full octet. It is the number of electrons around atoms that is most important; the charge itself is less important.)

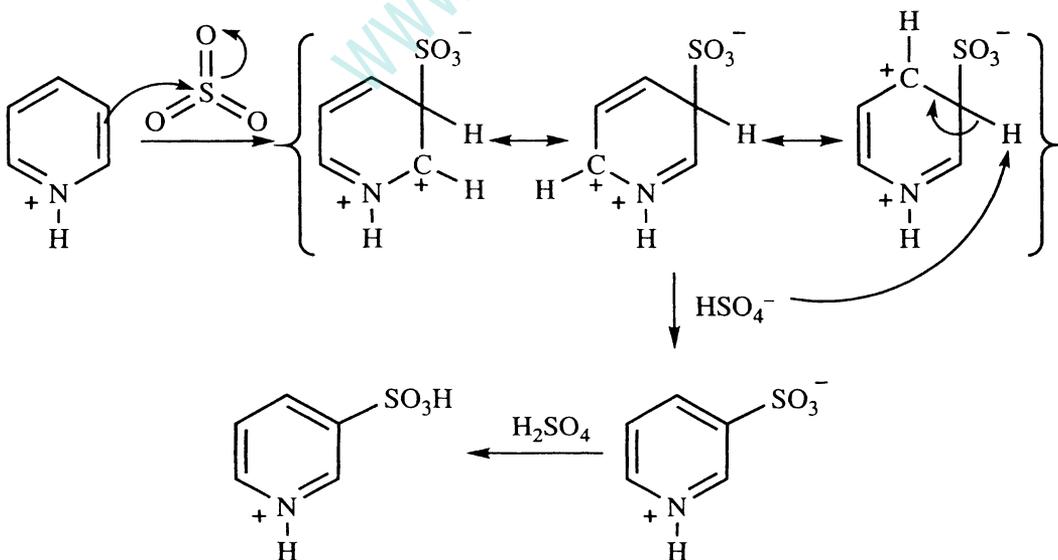


mechanism

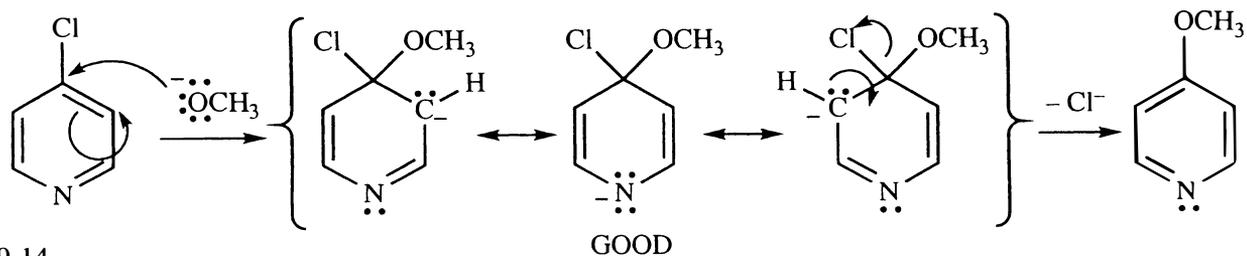


19-12 Any electrophilic attack, including sulfonation, is preferred at the 3-position of pyridine because the intermediate is more stable than the intermediate from attack at either the 2-position or the 4-position. (Resonance forms of the sulfonate group are not shown, but remember that they are important!)

The N of pyridine is basic, and in the strong acid mixture, it will be protonated as shown here. That is part of the reason that pyridine is so sluggish to react: the ring already has a positive charge, so attack of an electrophile is slowed.

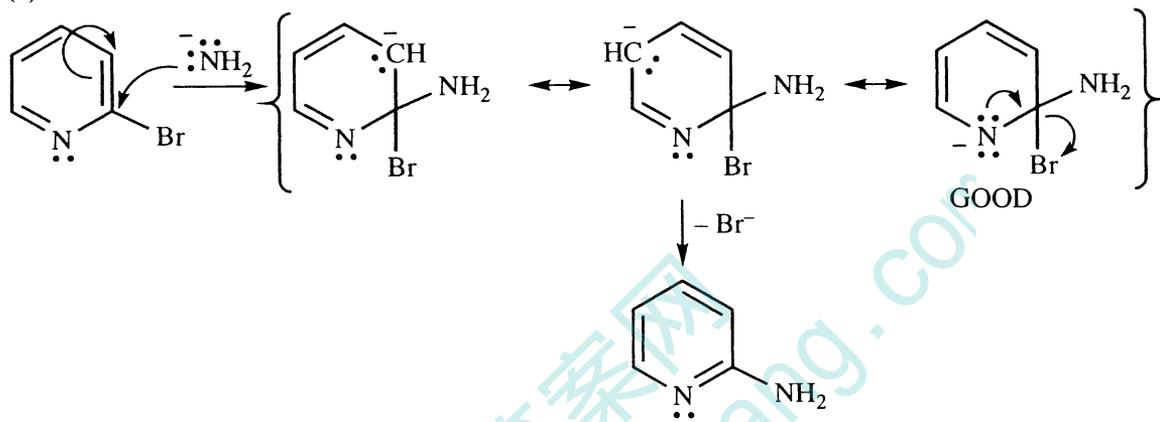


19-13

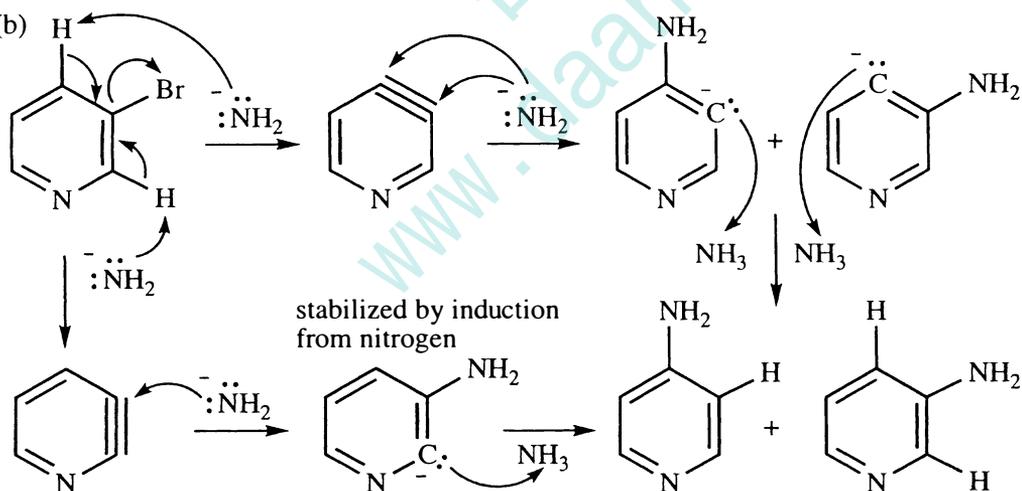


19-14

(a)



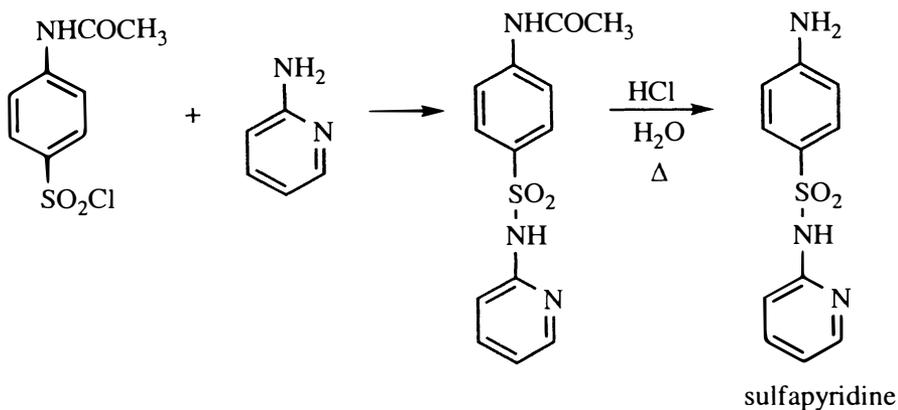
(b)



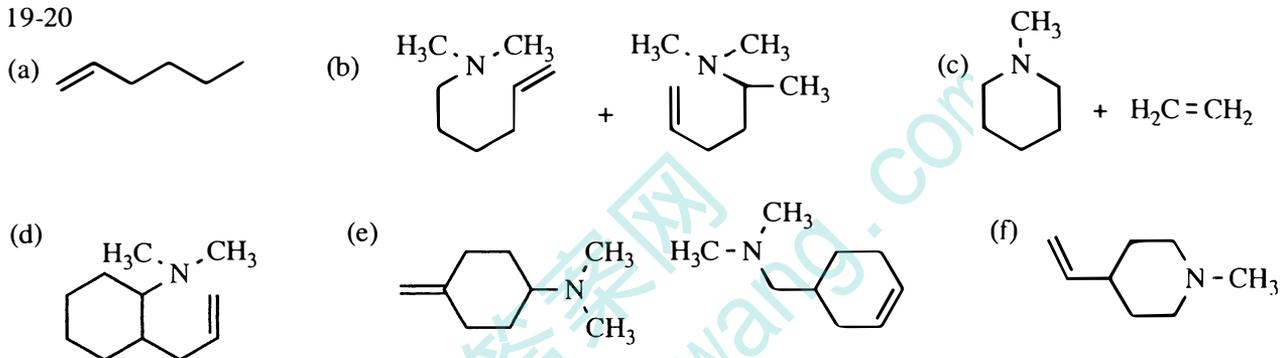
This is a benzyne-type mechanism. (For simplicity above, two steps of benzyne generation are shown as one step: first, a proton is abstracted by amide anion, followed by loss of bromide.) Amide ion is a strong enough base to remove a proton from 3-bromopyridine as it does from a halobenzene. Once a benzyne is generated (two possibilities), the amide ion reacts quickly, forming a mixture of products.

Why does the 3-bromo follow this extreme mechanism while the 2-bromo reacts smoothly by the addition-elimination mechanism? Stability of the intermediate! Negative charge on the electronegative nitrogen makes for a more stable intermediate in the 2-bromo substitution. No such stabilization is possible in the 3-bromo case.

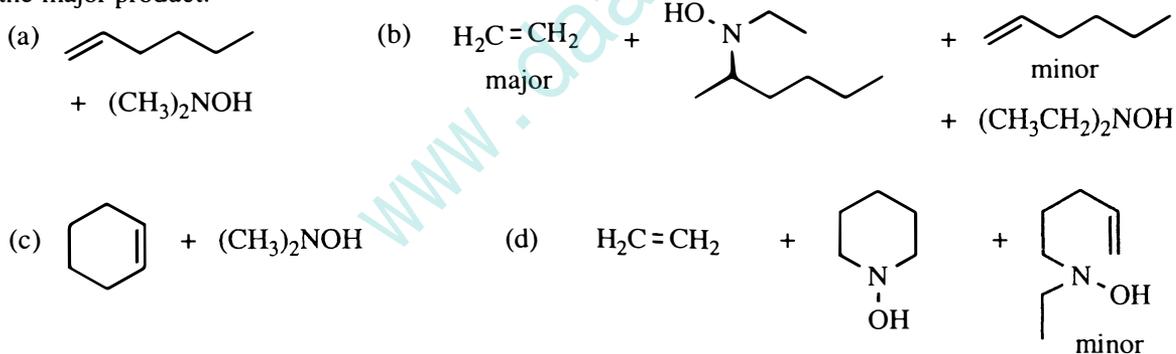
19-19 continued



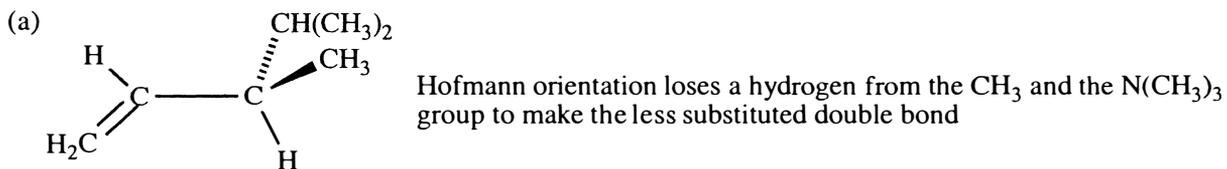
19-20



19-21 Orientation of the Cope elimination is similar to Hofmann elimination: the *less* substituted alkene is the major product.

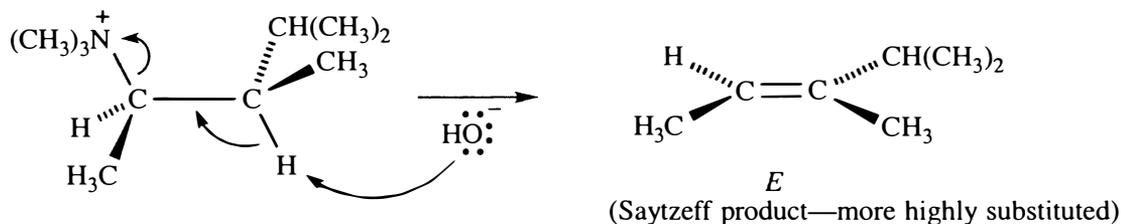


19-22 The key to this problem is to understand that Hofmann elimination occurs via an E2 mechanism requiring *anti* coplanar stereochemistry, whereas Cope elimination requires *syn* coplanar stereochemistry.

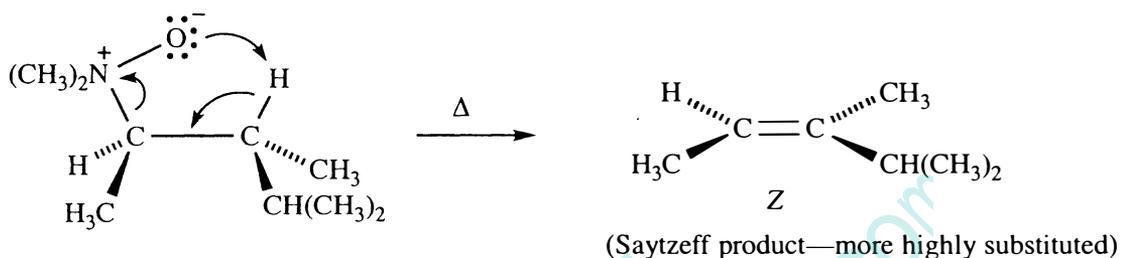


19-22 continued

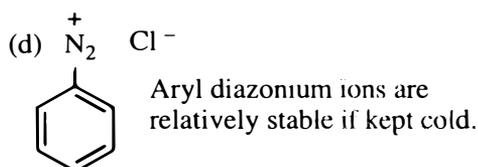
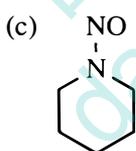
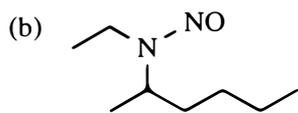
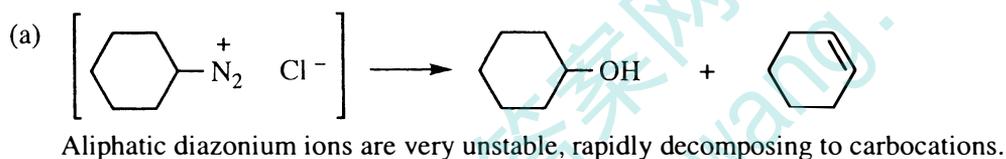
(b) Hofmann elimination



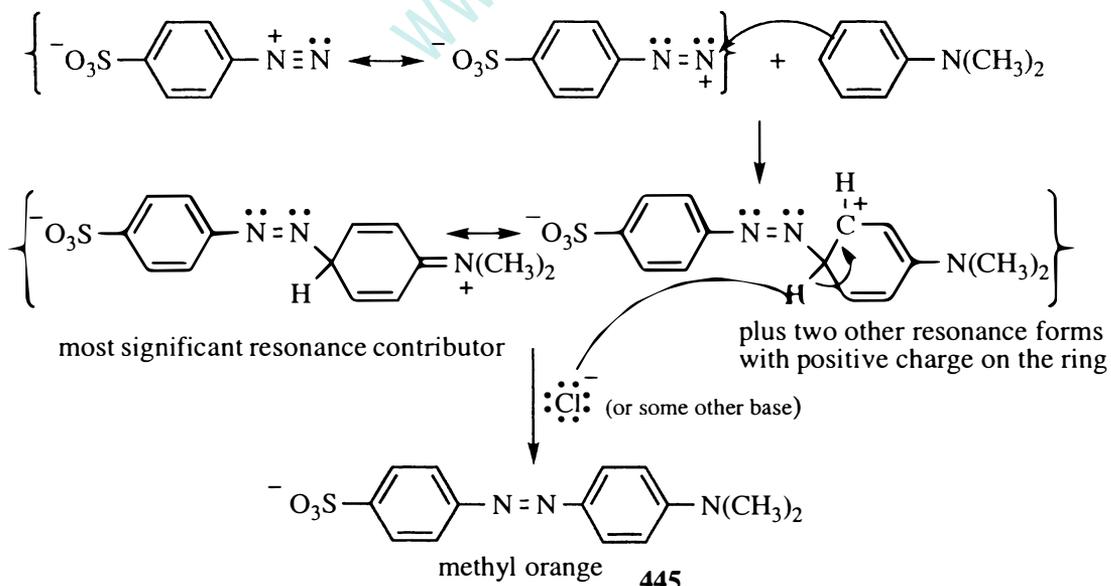
Cope elimination



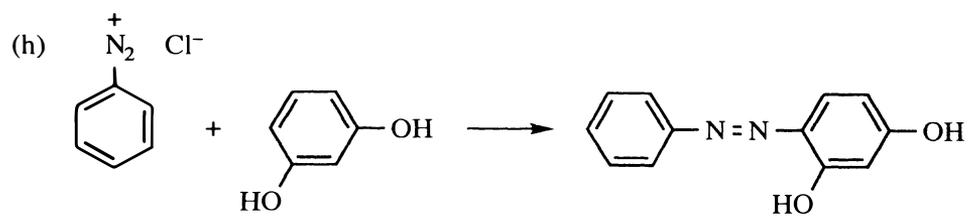
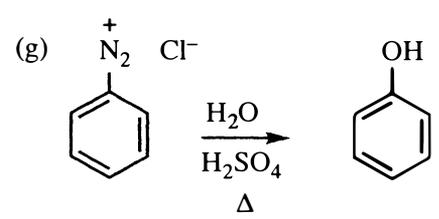
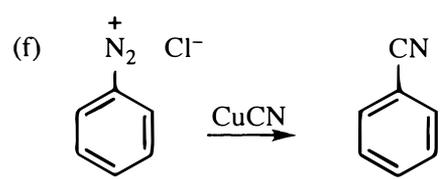
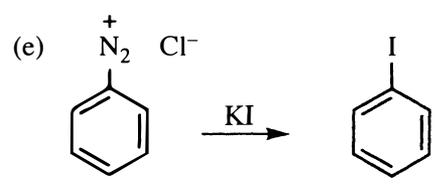
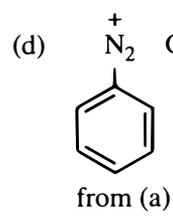
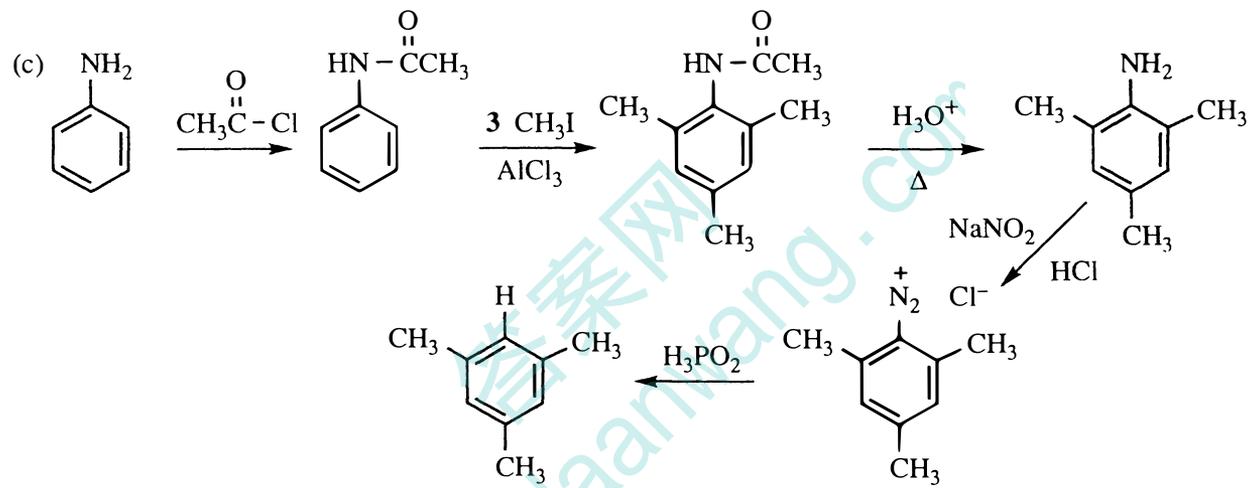
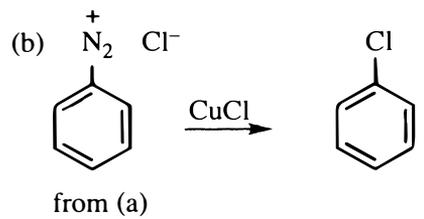
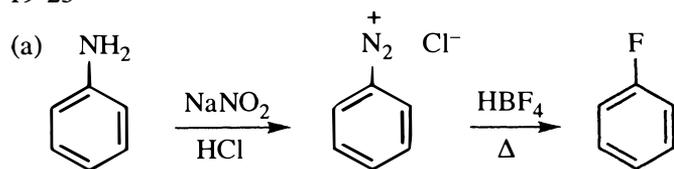
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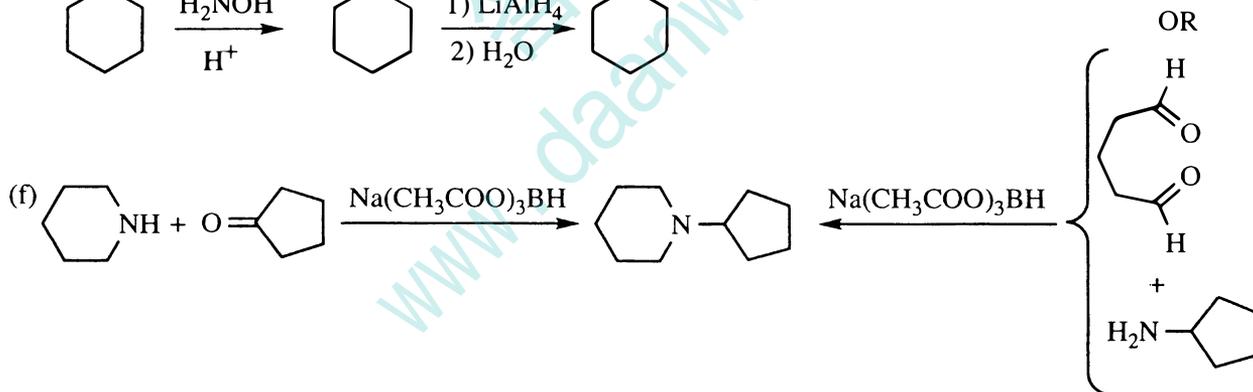
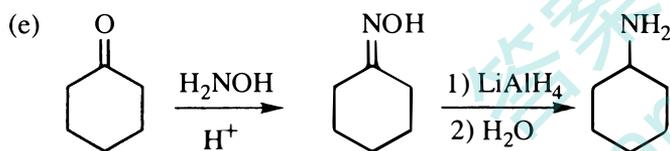
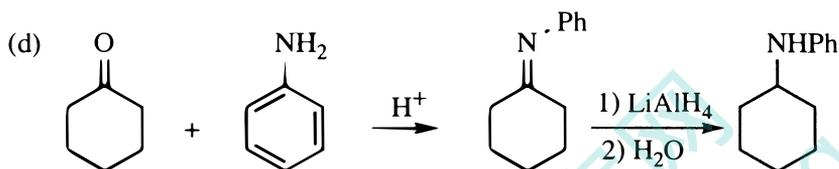
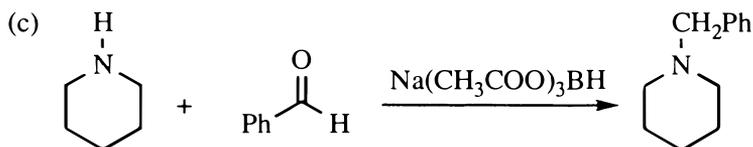
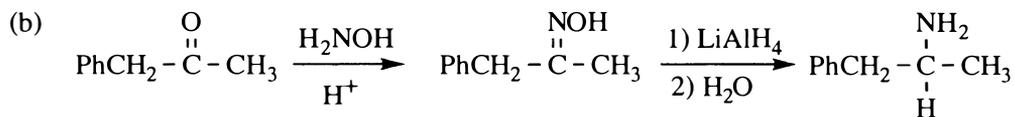
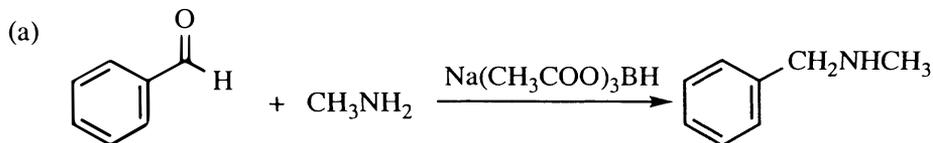
19-24 The diazonium ion can do aromatic substitution like any other electrophile.



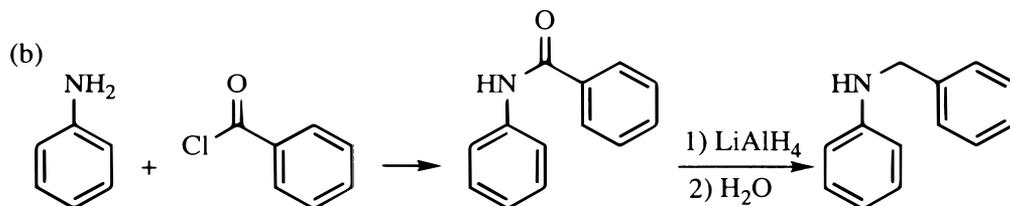
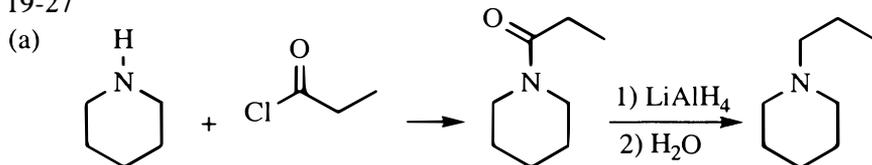
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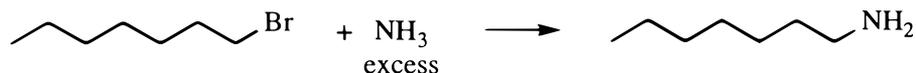
19-26 General guidelines for choice of reagent for reductive amination: use LiAlH_4 when the imine or oxime is isolated. Use $\text{Na}(\text{CH}_3\text{COO})_3\text{BH}$ in solution when the imine or iminium ion is not isolated. Alternatively, catalytic hydrogenation works in most cases.



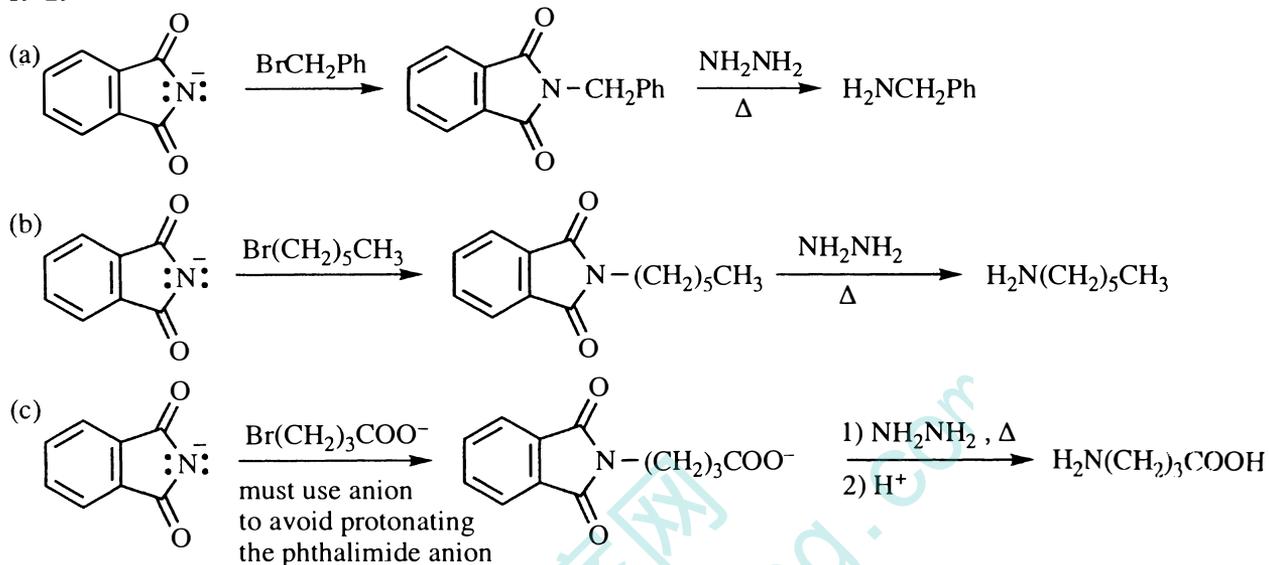
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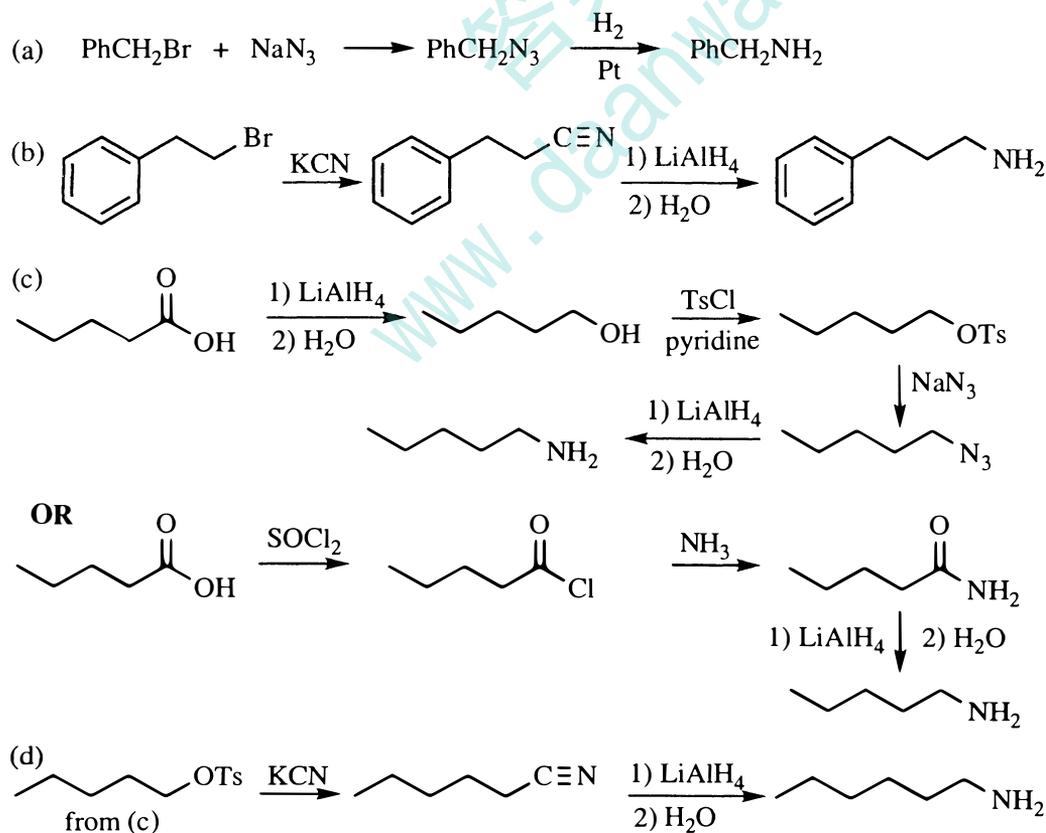
19-28 Use a large excess of ammonia to avoid multiple alkylations of each nitrogen.



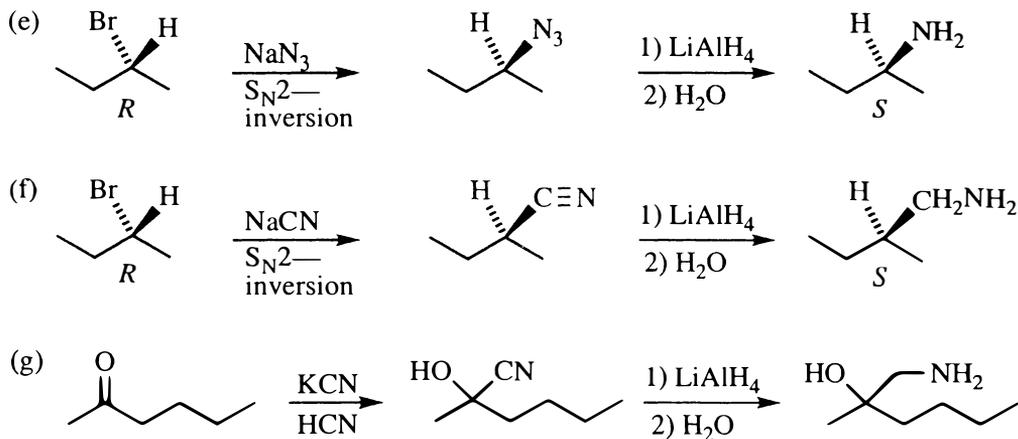
19-29



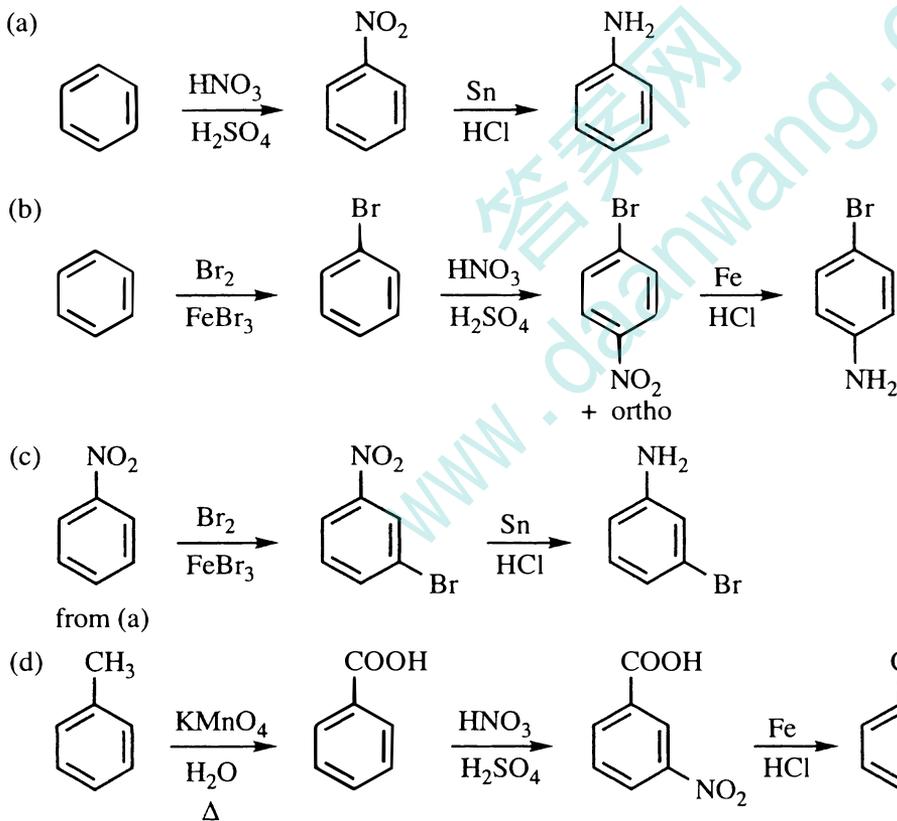
19-30 Assume that LiAlH_4 or $\text{H}_2/\text{catalyst}$ can be used interchangeably.



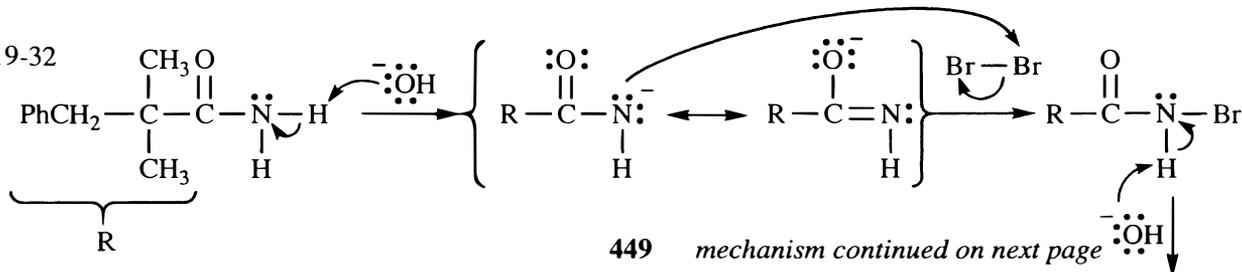
19-30 continued



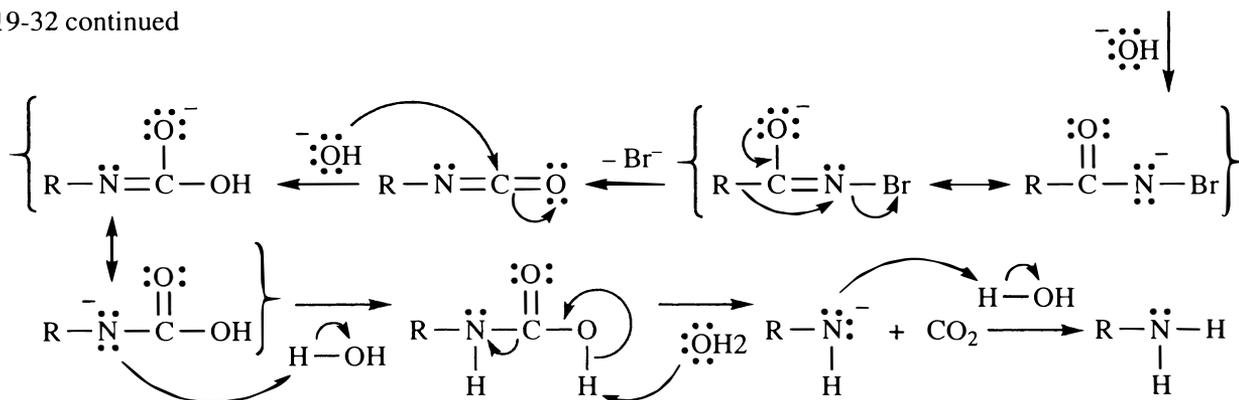
19-31 To reduce nitroaromatics, the reducing reagents (H_2 plus a metal catalyst, or a metal plus HCl) can be used virtually interchangeably. Assume a workup in base to give the free amine final product.



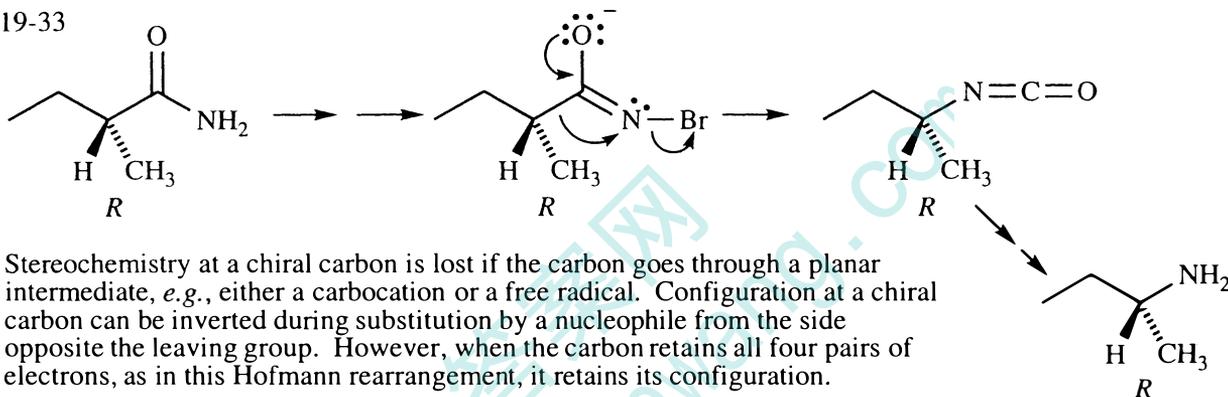
19-32



19-32 continued



19-33

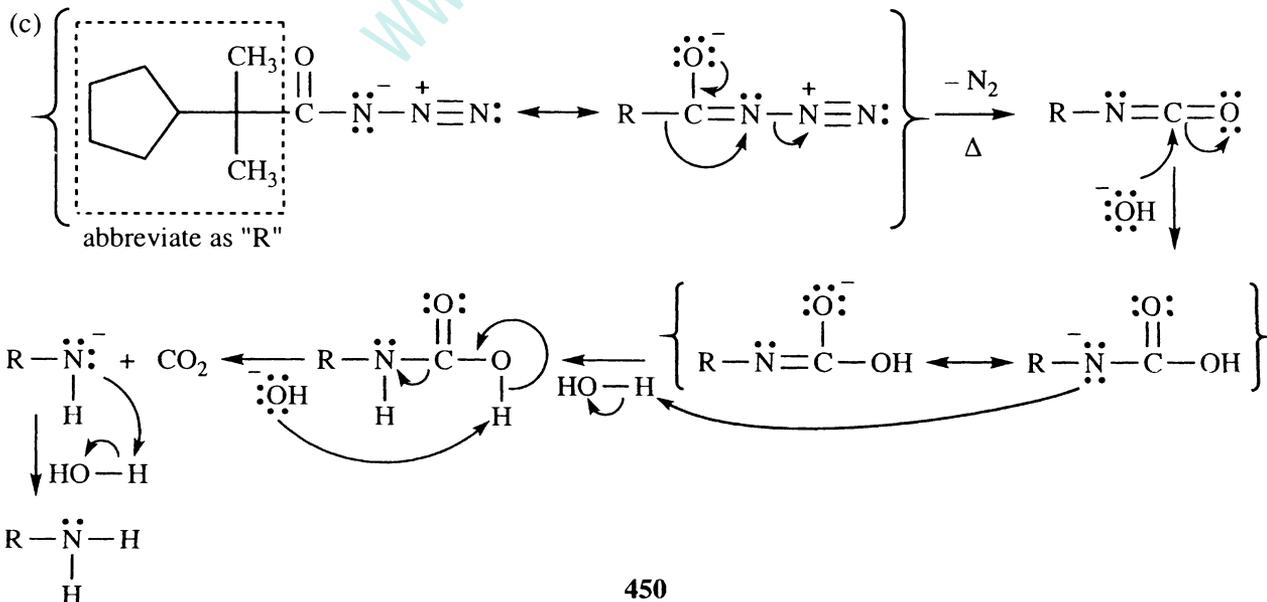


Stereochemistry at a chiral carbon is lost if the carbon goes through a planar intermediate, *e.g.*, either a carbocation or a free radical. Configuration at a chiral carbon can be inverted during substitution by a nucleophile from the side opposite the leaving group. However, when the carbon retains all four pairs of electrons, as in this Hofmann rearrangement, it retains its configuration.

19-34

(a) The acyl azide of the Curtius rearrangement is similar to the N-bromoamide of the Hofmann rearrangement in that both have an amide nitrogen with a good leaving group attached. Subsequent alkyl migration to the isocyanate and hydrolysis through the carbamic acid to the amine are identical in both mechanisms.

(b) The leaving group in the Curtius rearrangement is N_2 gas, one of the best leaving groups known "to man or beast", as we used to say.

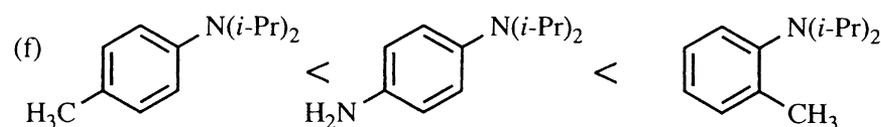
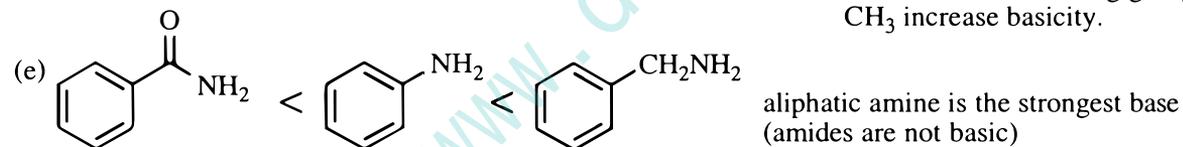
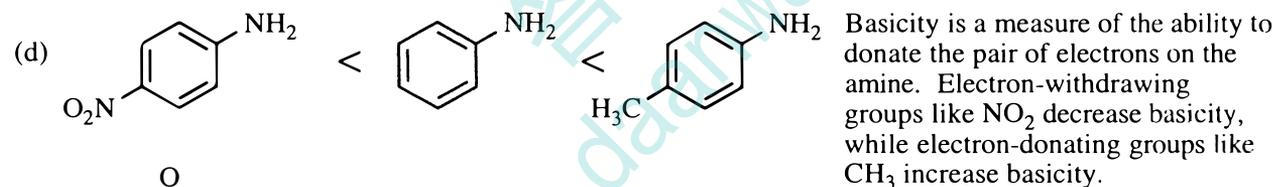
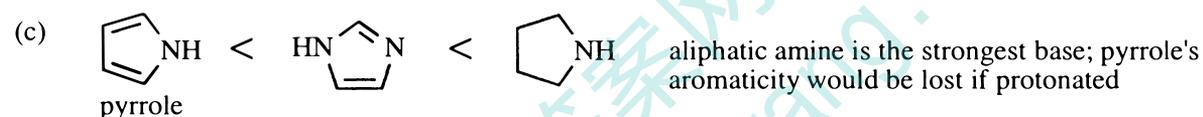
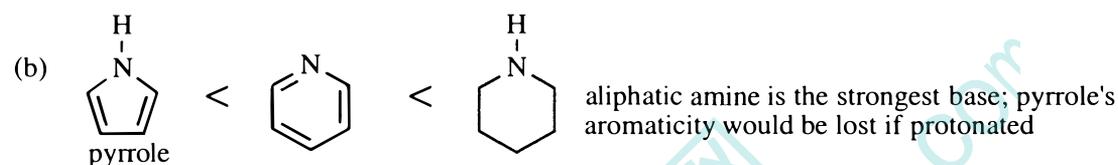


19-35 Please refer to solution 1-20, page 12 of this Solutions Manual.

19-36

- (a) primary amine; 2,2-dimethylpropan-1-amine, or neopentylamine
- (b) secondary amine; *N*-methylpropan-2-amine, or isopropylmethylamine
- (c) tertiary heterocyclic amine and a nitro group; 3-nitropyridine
- (d) quaternary heterocyclic ammonium ion; *N,N*-dimethylpiperidinium iodide
- (e) tertiary aromatic amine oxide; *N*-ethyl-*N*-methylaniline oxide
- (f) tertiary aromatic amine; *N*-ethyl-*N*-methylaniline
- (g) tertiary heterocyclic ammonium ion; pyridinium chloride
- (h) secondary amine; *N*,4-diethylhexan-3-amine

19-37 Shown in order of increasing basicity. In sets a-c, the aliphatic amine is the strongest base.

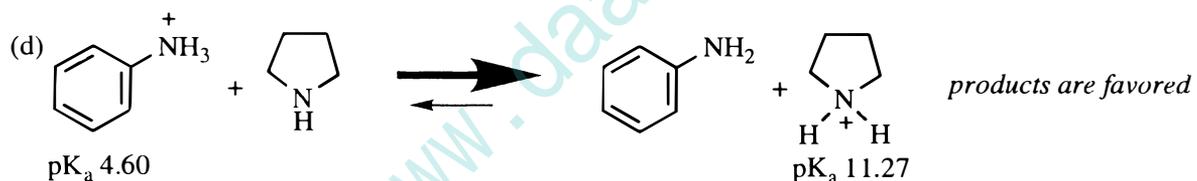
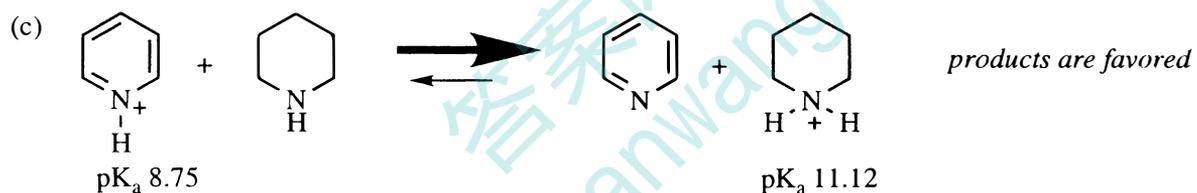
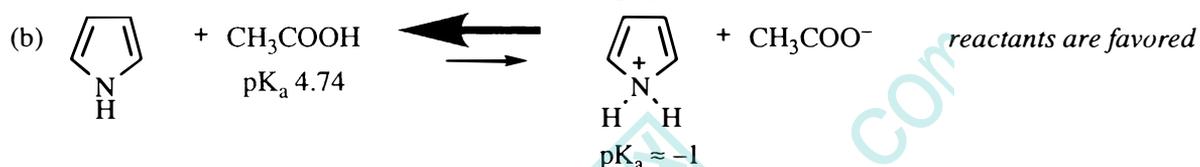
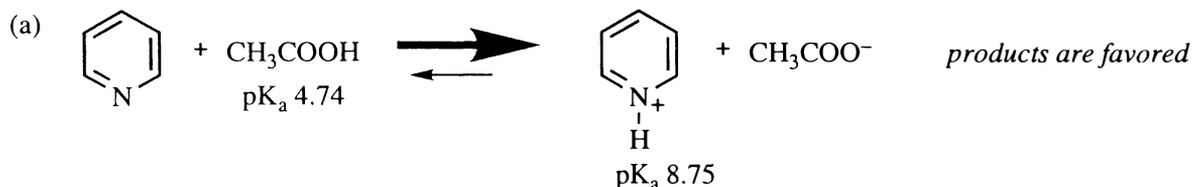


Congratulations if you got this one right! CH₃ is only slightly electron-donating by induction so the first structure puts the least electron density on the N. The second structure is more basic (by about 1 pK unit) because NH₂ is electron-donating by resonance. The last structure is the strongest base for a completely different reason: steric inhibition of resonance. (See the last topic in Appendix Two of this Manual.) The ortho methyl interferes with the isopropyl substituents on N and it forces the NR₂ out of planarity with the ring, so that the electron pair on the N is not conjugated with the aromatic pi system. Essentially, this N becomes an aliphatic amine. The pK_b of 2-methyl-*N,N*-diethylaniline is 6.9, about 2.5 pK units more basic than aniline. It is not as strong a base as a tertiary aliphatic amine because the aromatic ring is somewhat electron withdrawing by induction, yet the ortho methyl reduces the pi overlap of the nitrogen's electrons to make the N significantly more basic.

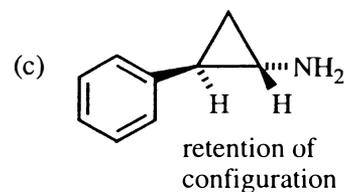
19-38

- (a) not resolvable: planar
 (b) resolvable: asymmetric carbon
 (c) not resolvable: symmetric
 (d) resolvable: nitrogen inversion is very slow
 (e) not resolvable: symmetric
 (f) resolvable: asymmetric nitrogen, unable to invert
 (g) not resolvable in conditions where the proton on N can exchange
 (h) resolvable: asymmetric nitrogen, unable to invert

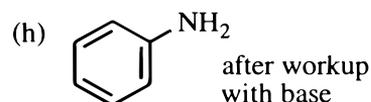
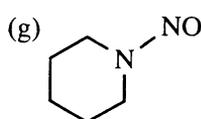
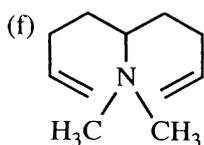
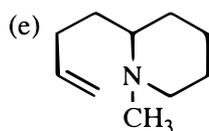
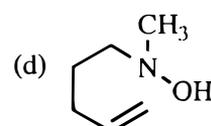
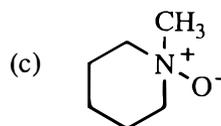
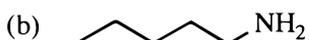
19-39 The values of pK_b of amines or pK_a of the conjugate acids can be obtained from Table 19-3. The side of the reaction with the weaker acid and base will be favored at equilibrium. (See Appendix 2 for a discussion of acidity and basicity.)



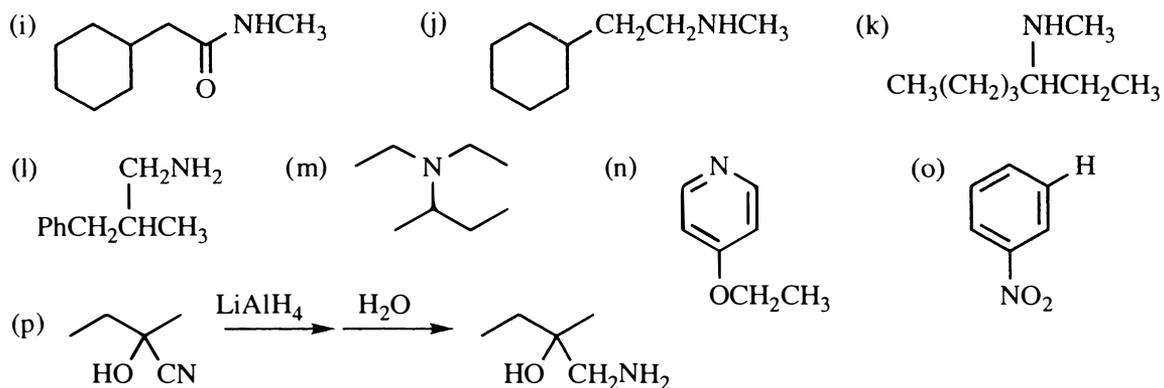
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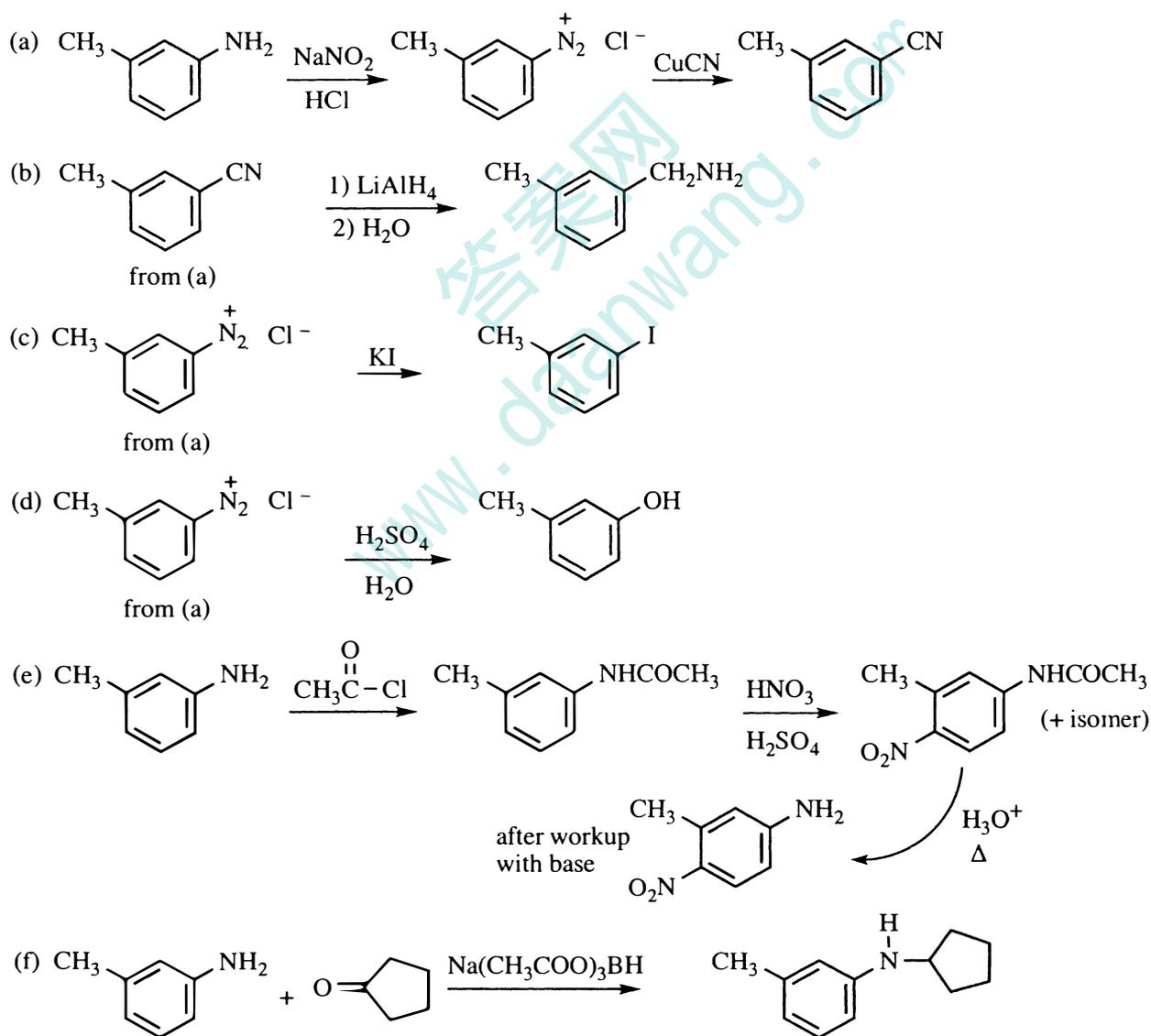
19-41



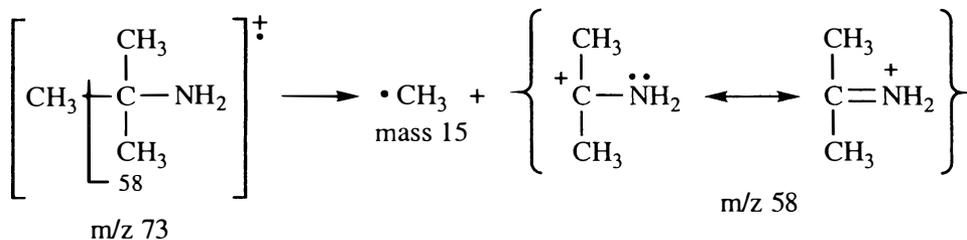
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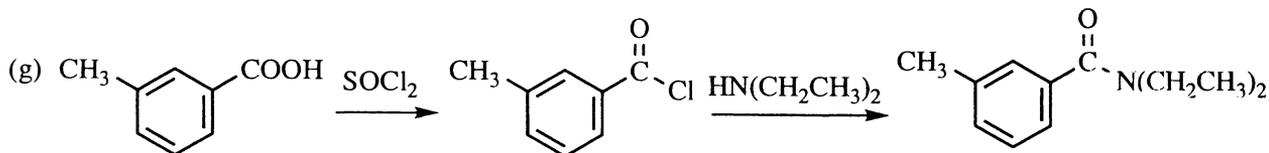
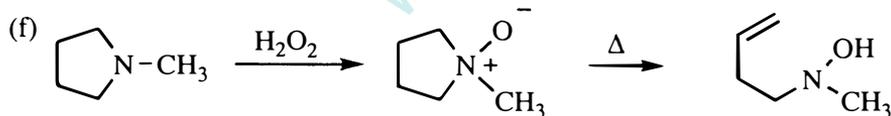
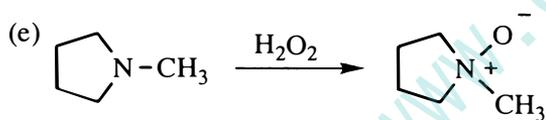
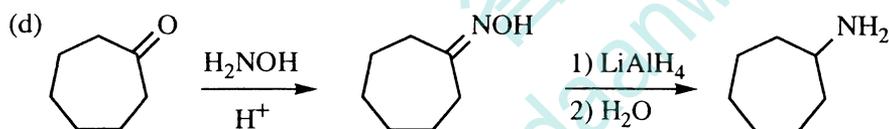
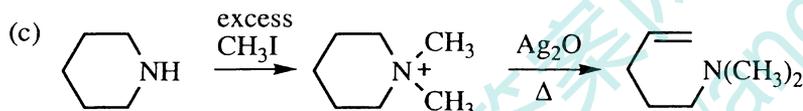
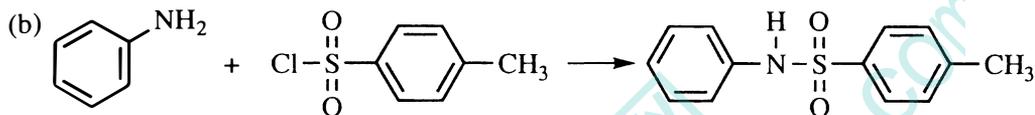
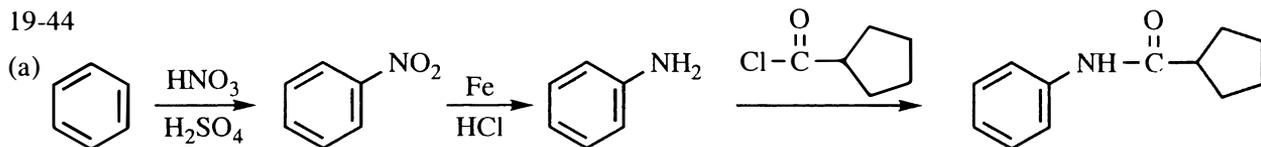
19-42



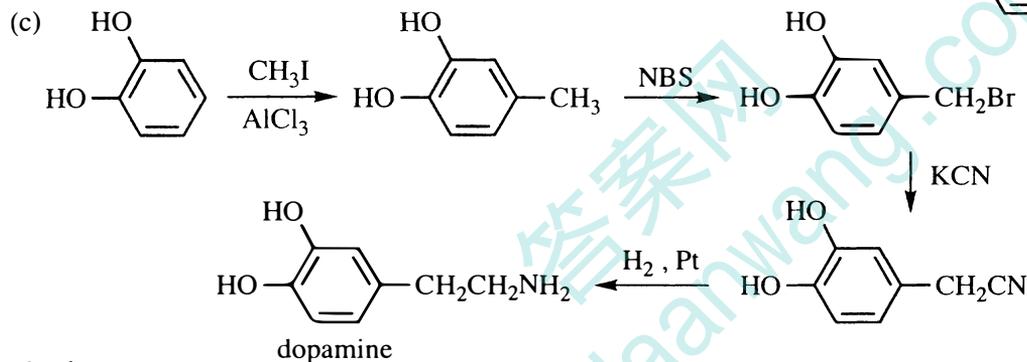
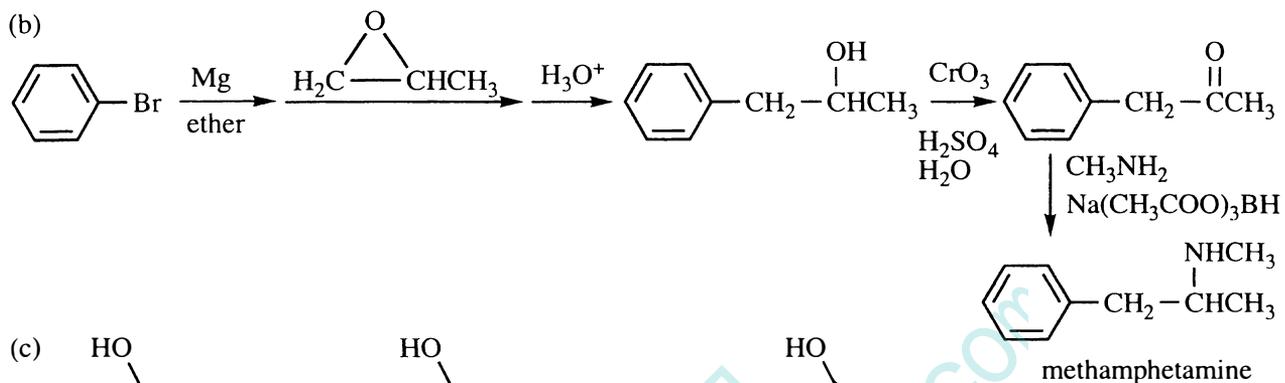
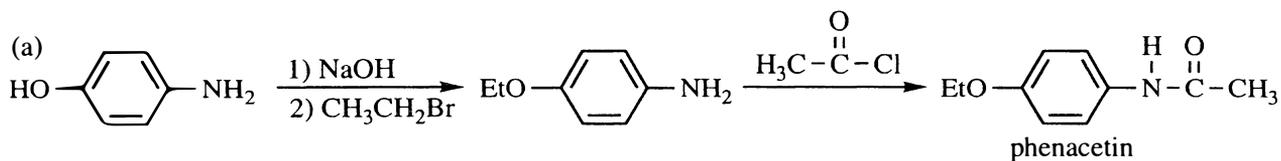
19-43 This fragmentation is favorable because the iminium ion produced is stabilized by resonance. Also, there are three possible cleavages that give the same ion. Both factors combine to make the cleavage facile, at the expense of the molecular ion.



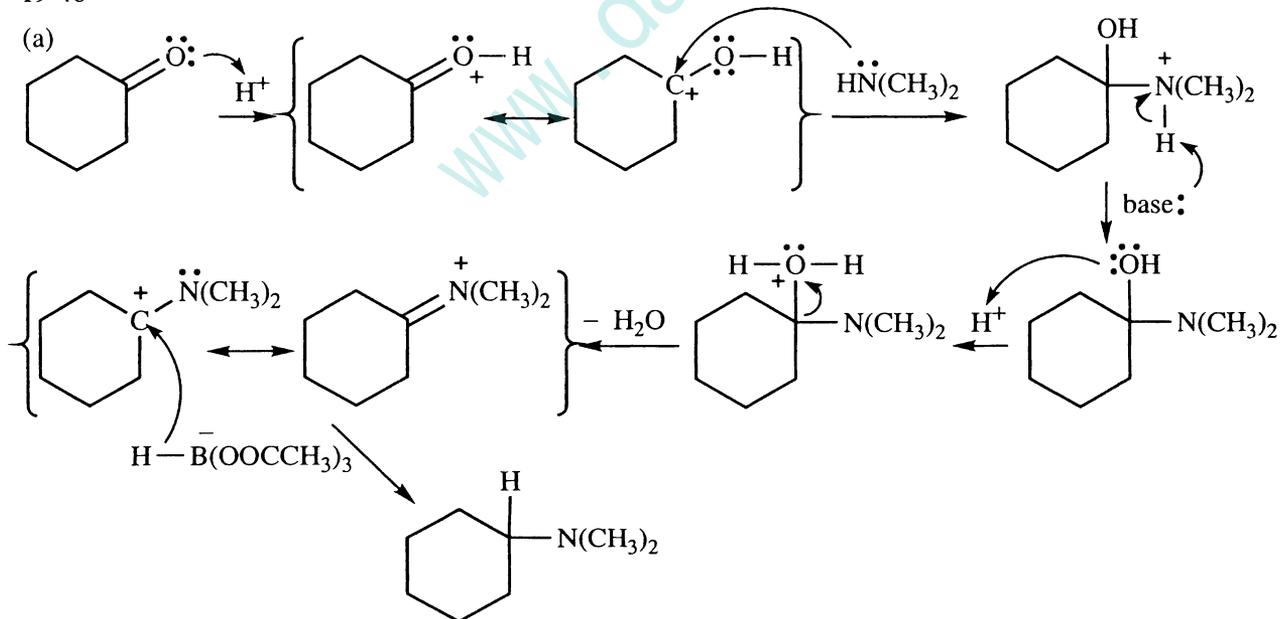
19-44



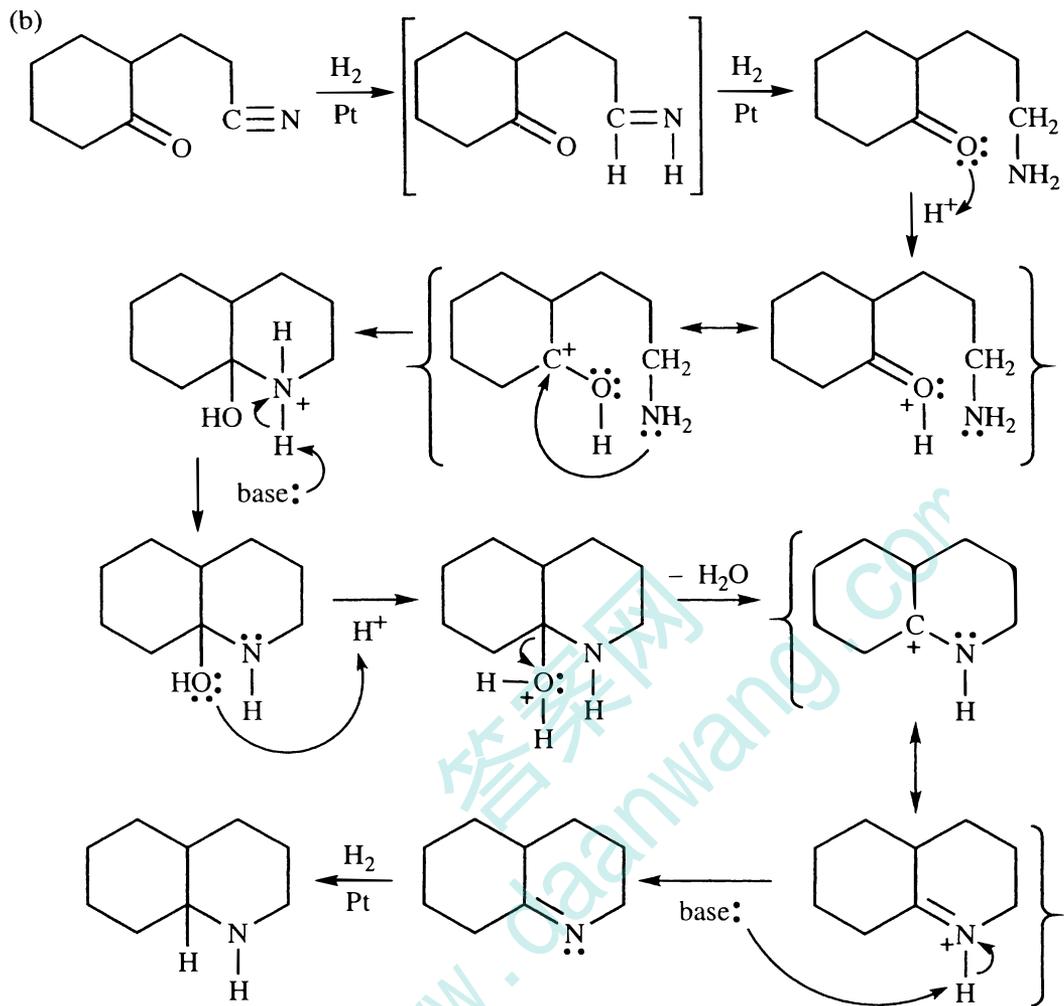
19-45 The problem restricts the starting materials to six carbons or fewer. Always choose starting materials with as many of the necessary functional groups as possible.



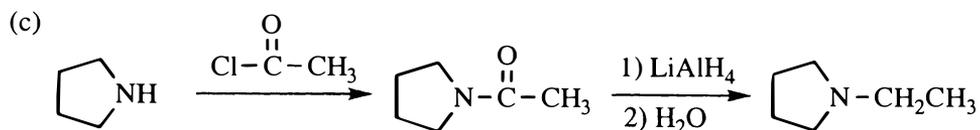
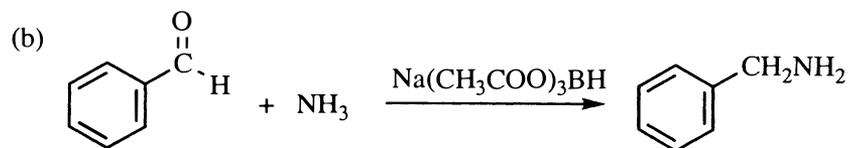
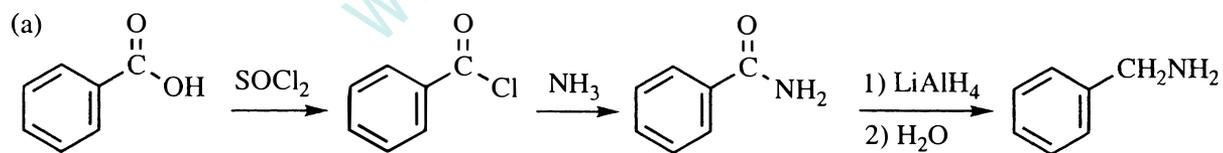
19-46



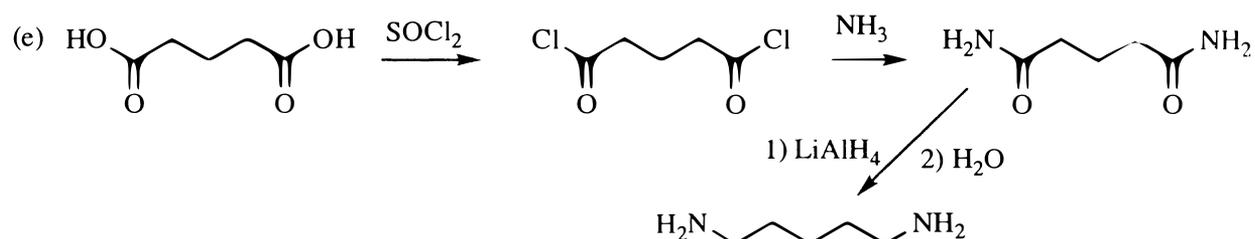
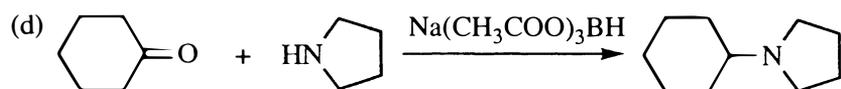
19-46 continued



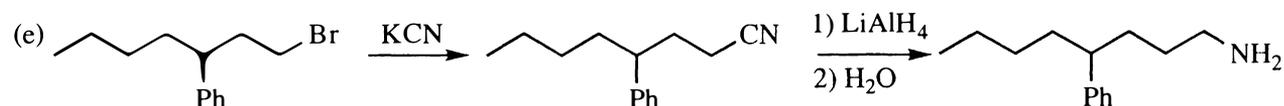
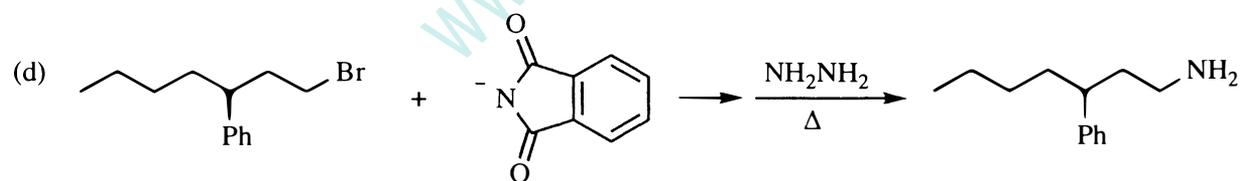
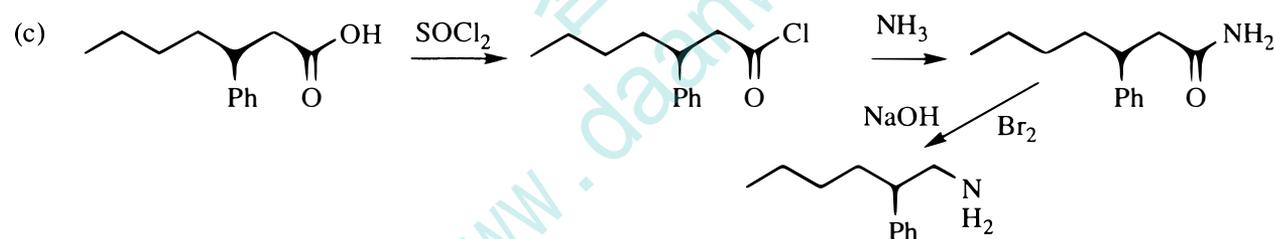
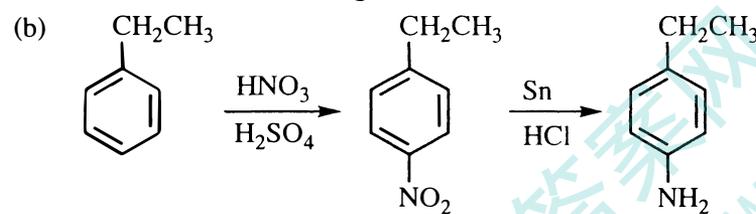
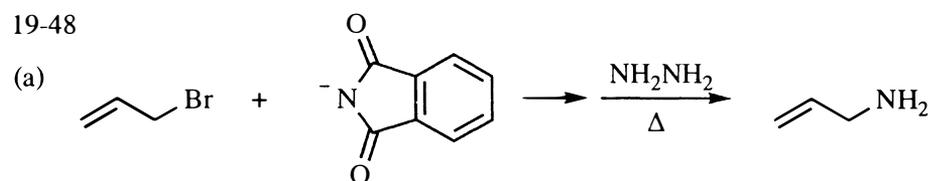
19-47



19-47 continued

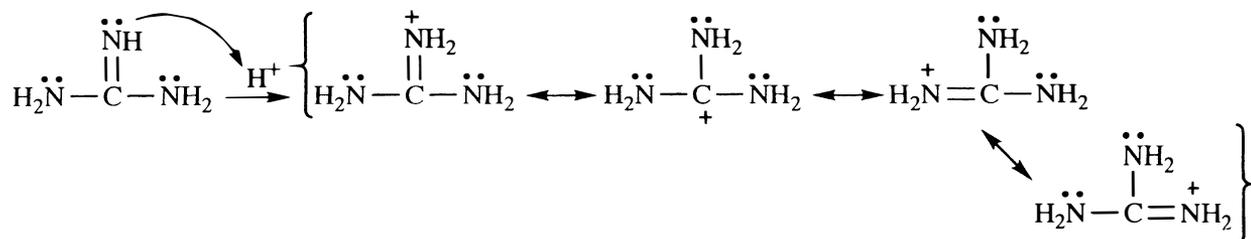


19-48

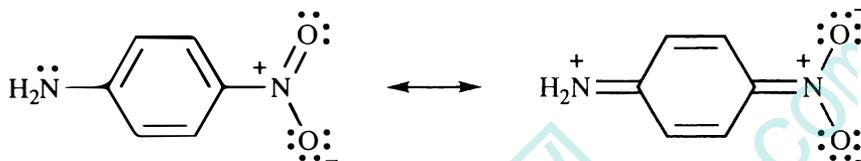


19-49

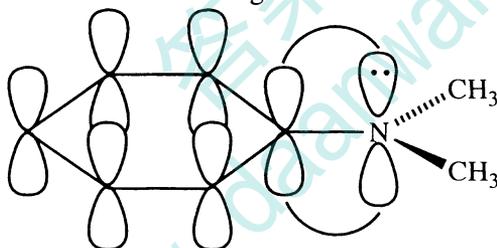
(a) When guanidine is protonated, the cation is greatly stabilized by resonance, distributing the positive charge over all atoms (except H):



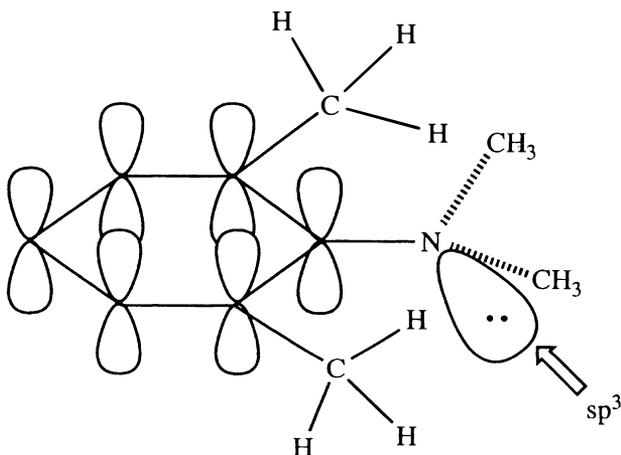
(b) The unprotonated molecule has a resonance form shown below that the protonated molecule cannot have. Therefore, the unprotonated form is stabilized relative to the protonated form. This greater stabilization of the unprotonated form is reflected in weaker basicity.



(c) Anilines are weaker bases than aliphatic amines because the electron pair on the nitrogen is shared with the ring, stabilizing the system. There is a steric requirement, however: the p orbital on the N must be parallel with the p orbitals on the benzene ring in order for the electrons on N to be distributed into the π system of the ring.

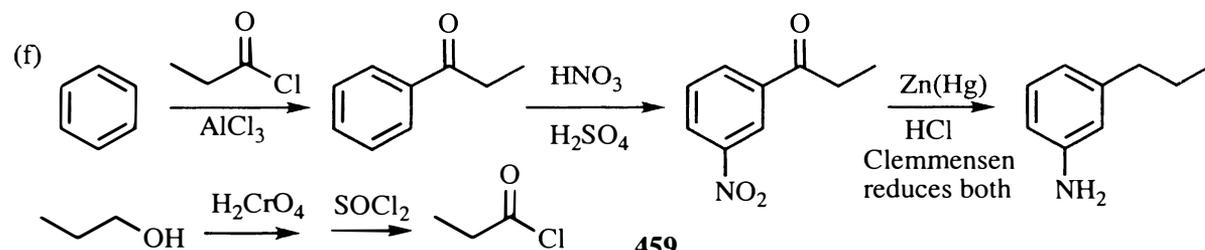
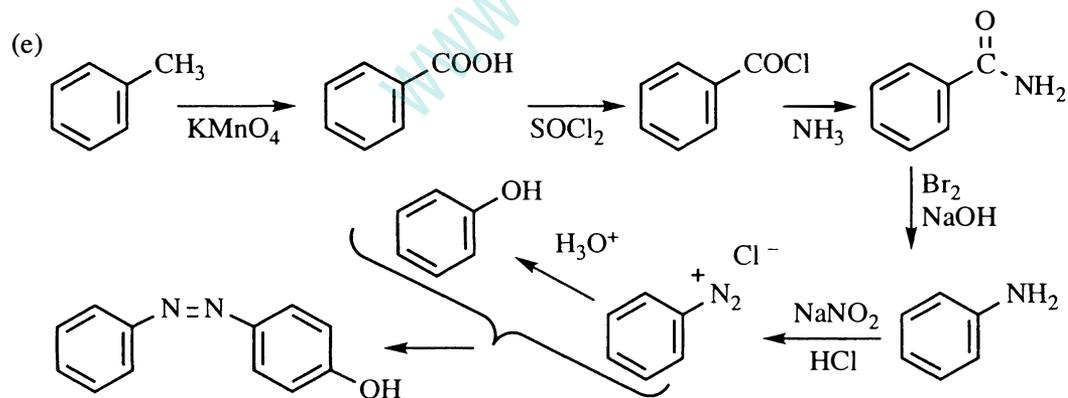
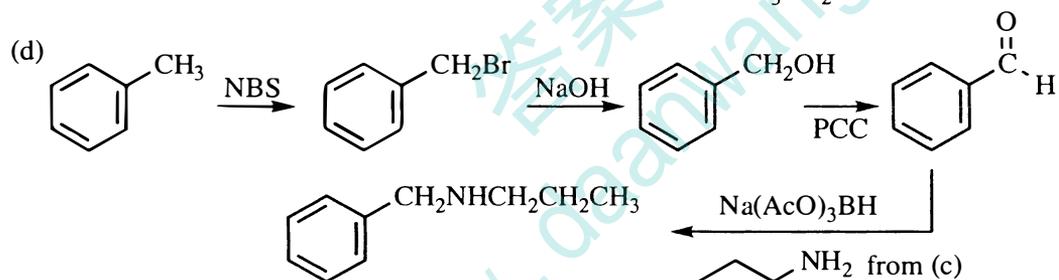
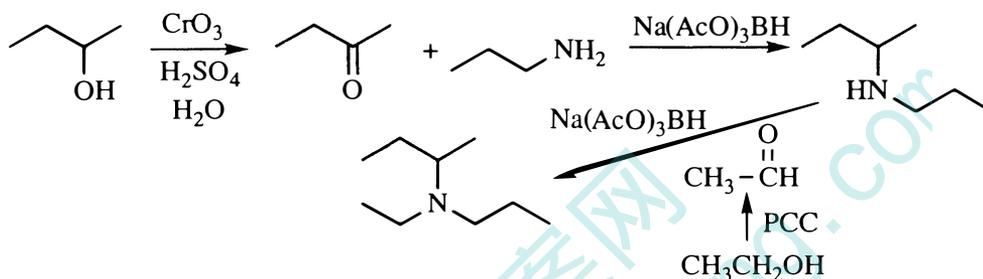
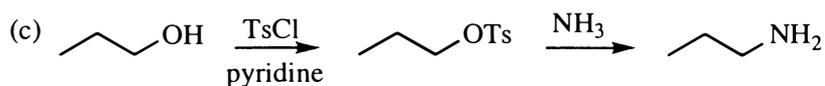
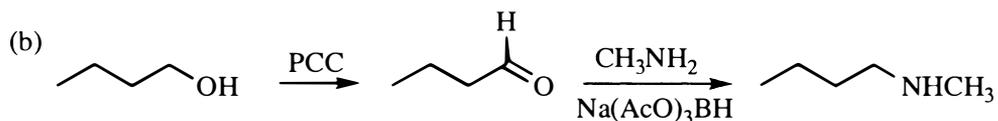
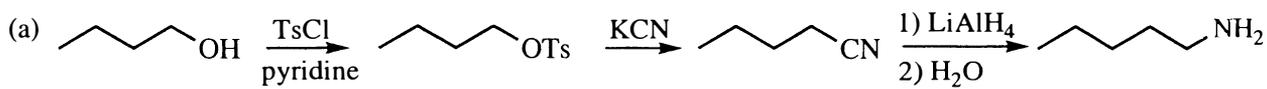


If the orbital on the nitrogen is forced out of this orientation (by substitution on C-2 and C-6, for example), the electrons are no longer shared with the ring. The nitrogen is hybridized sp^3 (no longer any reason to be sp^2), and the electron pair is readily available for bonding \Rightarrow increased basicity.

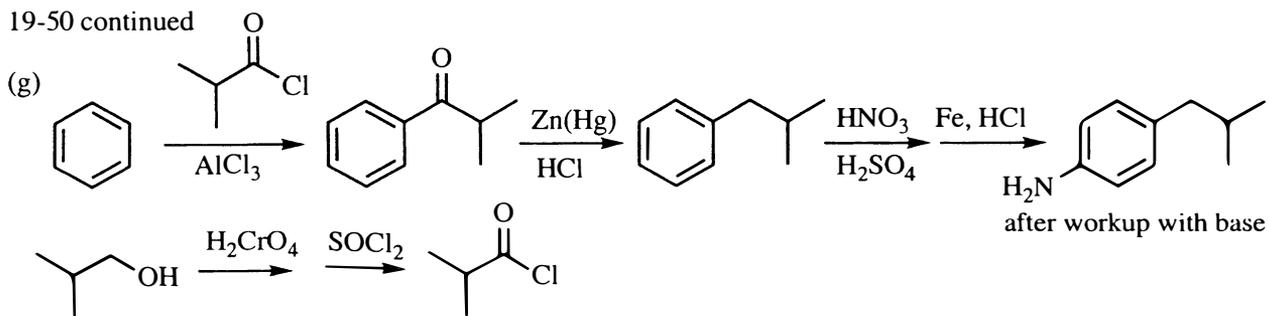


As surprising as it sounds, this aniline is about as basic as a tertiary aliphatic amine, except that the aromatic ring substituent is electron-withdrawing by induction, decreasing the basicity slightly. This phenomenon is called "steric inhibition of resonance". We will see more examples in future chapters. Also, it is the last topic in Appendix 2. (See another example in the solution to 19-37(f).)

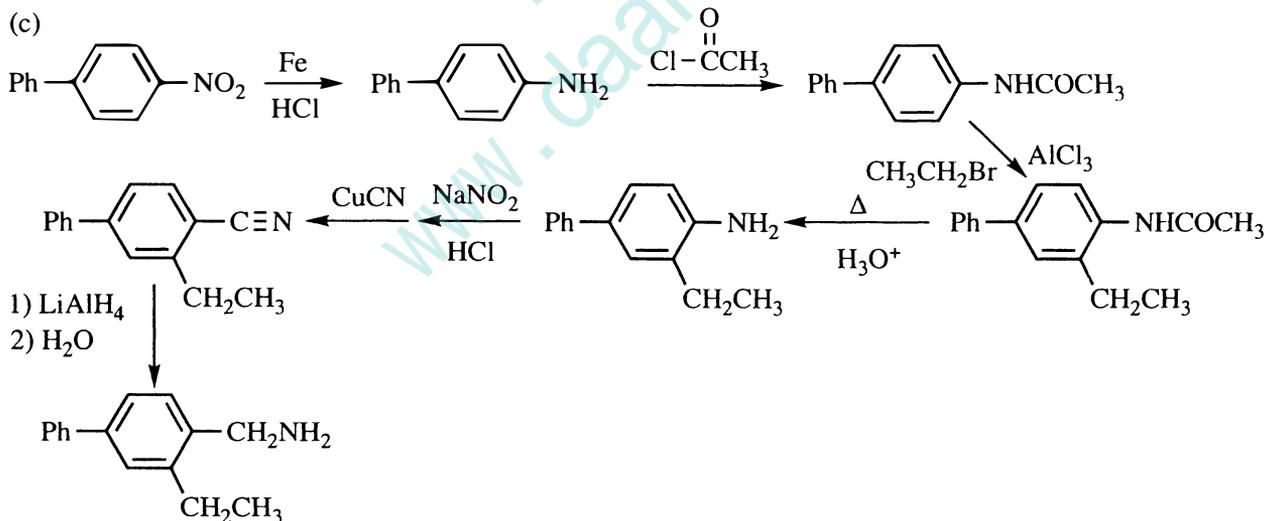
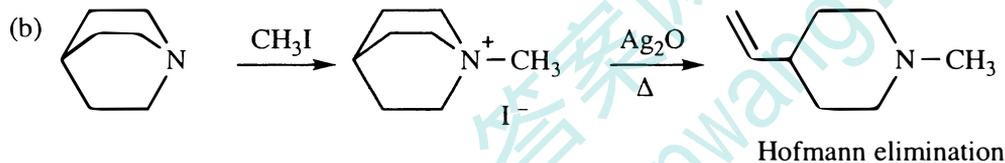
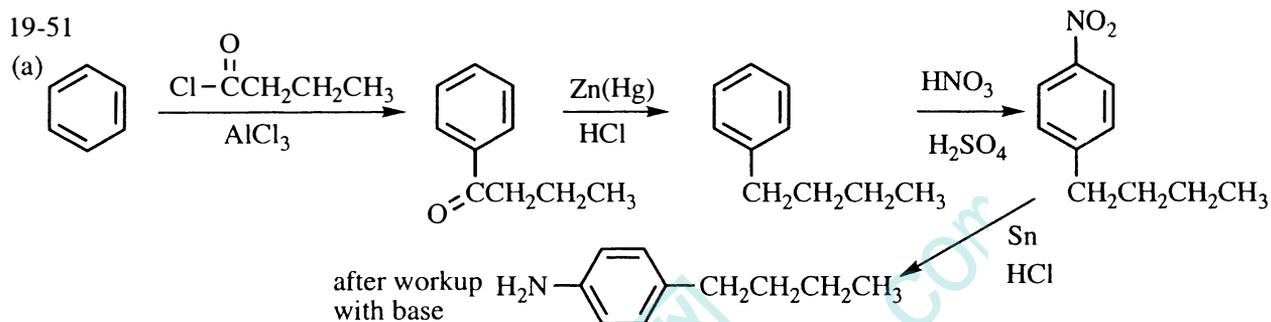
19-50 In this problem, sodium triacetoxyborohydride will be represented as $\text{Na}(\text{AcO})_3\text{BH}$.



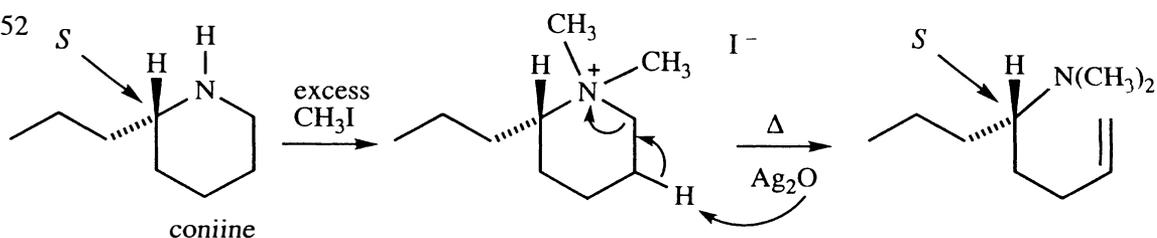
19-50 continued



19-51



19-52



19-53

unknown X

(a)

—fishy odor \Rightarrow amine

—molecular weight 101 \Rightarrow odd number of nitrogens

\Rightarrow if one nitrogen and no oxygen, the remainder is C_6H_{15}

Mass spectrum:

—fragment at 86 = $M - 15$ = loss of methyl \Rightarrow the compound is likely to

have this structural piece: $CH_3 \begin{array}{l} | \\ \text{---} C \text{---} N \\ | \\ \alpha\text{-cleavage} \end{array}$

IR spectrum:

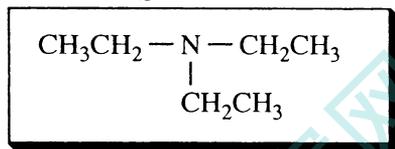
—no OH, no NH \Rightarrow must be a 3° amine

—no C=O or C=C or C \equiv N or NO₂

NMR spectrum:

—only a triplet and quartet, integration about 3 : 2 \Rightarrow ethyl group(s) only

assemble the evidence: $C_6H_{15}N$, 3° amine, only ethyl in the NMR:



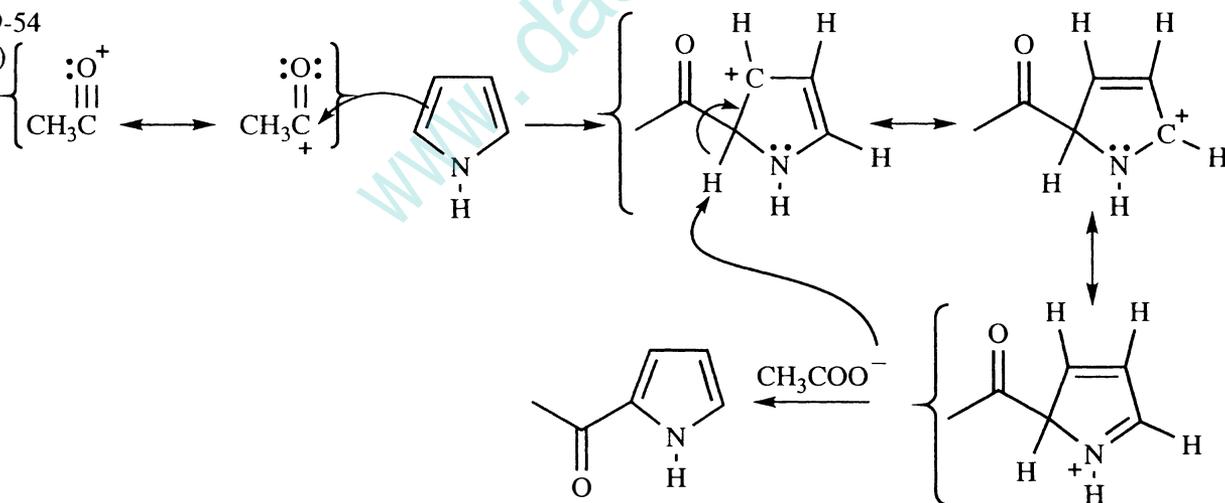
(b) React the triethylamine with HCl. The pure salt is solid and odorless.



(c) Washing her clothing in dilute acid like vinegar (dilute acetic acid) or dilute HCl would form a water-soluble salt as shown in (b). Normal washing will remove the water-soluble salt.

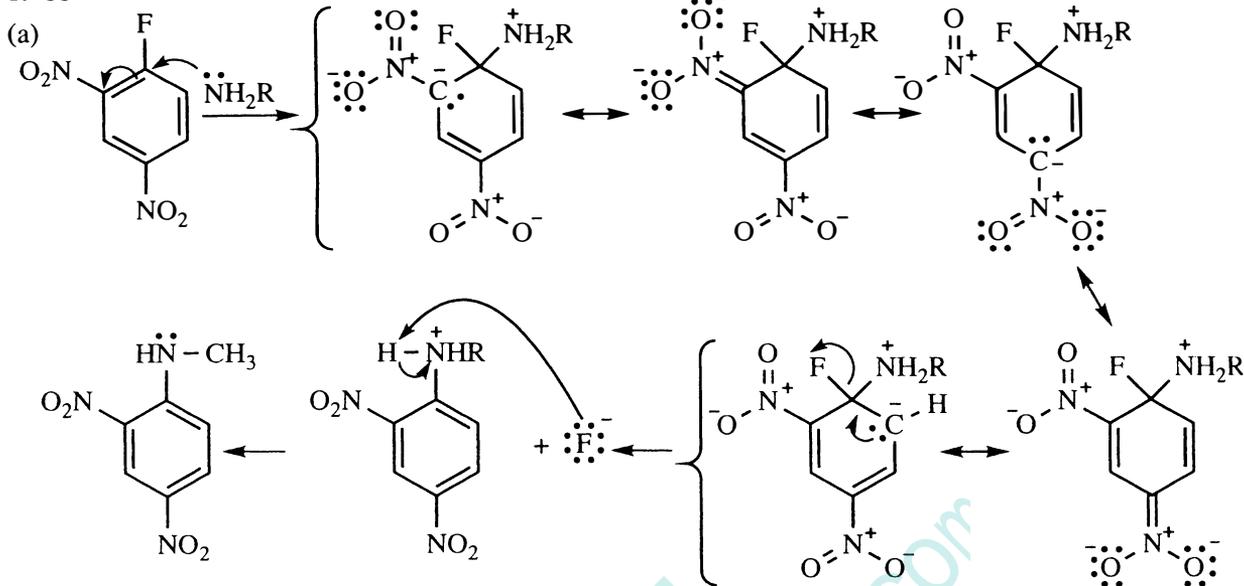
19-54

(a)

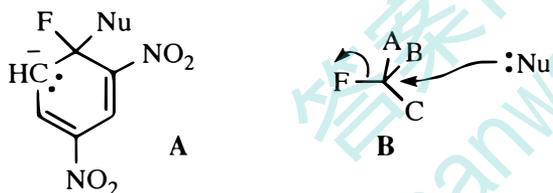


(b) Both answers can be found in the resonance forms of the intermediate, in particular, the resonance form that shows the positive charge on the N. This is the major resonance contributor; what is special about it is that every atom has a full octet, the best of all possible conditions. That does not arise in the benzene intermediate, so it must be easier to form the intermediate from pyrrole than from benzene. Also, acylation at the 3-position puts positive charge at the 2-position and on the N, but never on the other side of the ring, so this substitution has only two resonance forms. The intermediate from acylation at the 3-position is therefore not as stable as the intermediate from acylation at the 2-position.

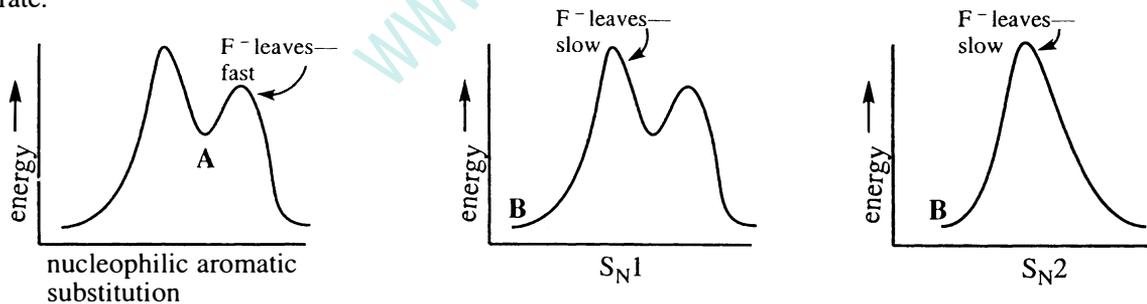
19-55



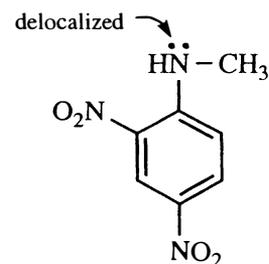
(b) Why is fluoride ion a good leaving group from A but not from B (either by S_N1 or S_N2)?



Formation of the anionic sigma complex A is the rate-determining (slow) step in nucleophilic aromatic substitution. The loss of fluoride ion occurs in a subsequent fast step where the nature of the leaving group does not affect the overall reaction rate. In the S_N1 or S_N2 mechanisms, however, the carbon-fluorine bond is breaking in the rate-determining step, so the poor leaving group ability of fluoride does indeed affect the rate.



(c) Amines can act as nucleophiles as long as the electron pair on the N is available for bonding. The initial reactant, methylamine, CH_3NH_2 , is a very reactive nucleophile. However, once the N is bonded to the benzene ring, the electron pair is delocalized onto the ring, especially with such strong electron-withdrawing groups like NO_2 in the ortho and para positions. The electrons on N are no longer available for bonding so there is no danger of it acting as a nucleophile in another reaction.



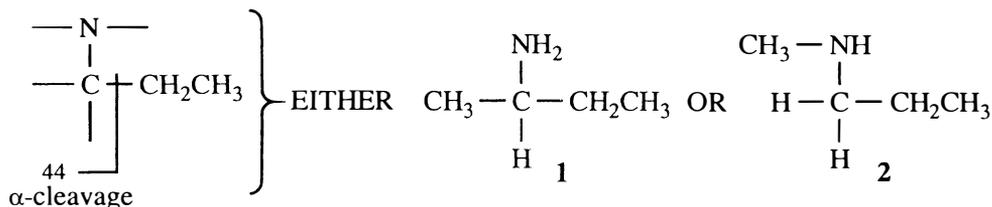
19-56 **Compound A**

Mass spectrum:

—molecular ion at 73 = odd mass = odd number of nitrogens;

if one nitrogen and no oxygen present \Rightarrow molecular formula $C_4H_{11}N$

—base peak at 44 is $M - 29 \Rightarrow$ this fragment must be present:



IR spectrum:

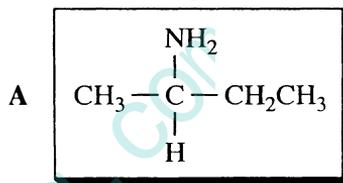
—two peaks around 3300 cm^{-1} indicate a 1° amine; no indication of oxygen

NMR spectrum:

—two exchangeable protons suggest NH_2 present

—1H multiplet at δ 2.8 means a CH—NH_2

The structure of **A** must be the same as **1** above:



Compound B

an isomer of **A**, so its molecular formula must also be $C_4H_{11}N$

IR spectrum:

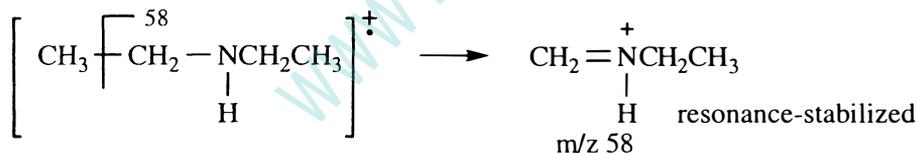
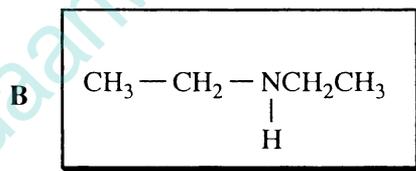
—only one peak at $3300\text{ cm}^{-1} \Rightarrow 2^\circ$ amine

NMR spectrum:

—one exchangeable proton $\Rightarrow \text{NH}$

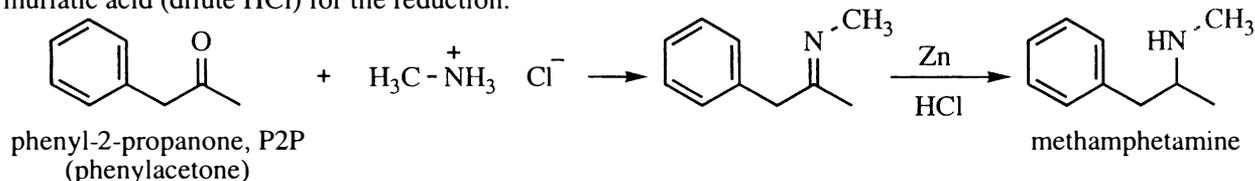
—two ethyls present

The structure of **B** must be:



19-57

(a) The acid-catalyzed condensation of P2P (a controlled substance) with methylamine hydrochloride gives an imine which can be reduced to methamphetamine. The suspect was probably planning to use zinc in muriatic acid (dilute HCl) for the reduction.



(b) The jury acquitted the defendant on the charge of attempted manufacture of methamphetamine. There were legal problems with possible entrapment, plus the fact that he had never opened the bottle of the starting material. The defendant was convicted on several possession charges, however, and was awarded four years of institutional time to study organic chemistry.

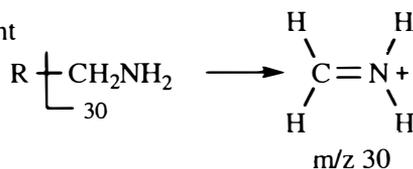
19-58

Mass spectrum:

—molecular ion at 87 = odd mass = odd number of nitrogens present

—if one nitrogen and no oxygens \Rightarrow molecular formula $C_5H_{13}N$

—base peak at m/z 30 \Rightarrow structure must include this fragment



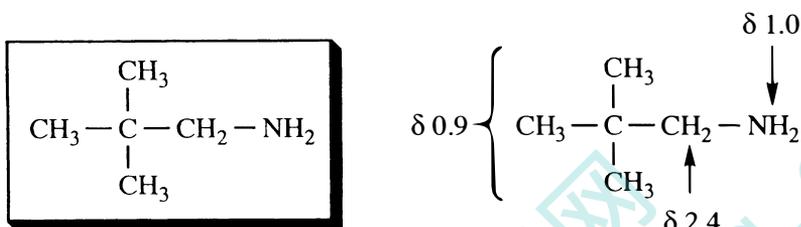
IR spectrum:

—two peaks in the $3300\text{-}3400\text{ cm}^{-1}$ region \Rightarrow 1° amine

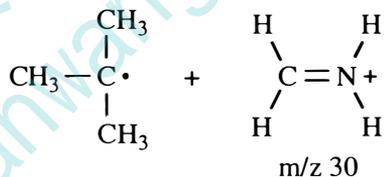
NMR spectrum:

—singlet at δ 0.9 for 9H must be a *t*-butyl group

—2H signal at δ 1.0 exchanges with D_2O \Rightarrow must be protons on N or O



Note that the base peak in the MS arises from cleavage to give these two, relatively stable fragments:



19-59 (a tough problem)

molecular formula $C_{11}H_{16}N_2$ has 5 elements of unsaturation, enough for a benzene ring; no oxygens precludes NO_2 and amide; if $\text{C}\equiv\text{N}$ is present, there are not enough elements of unsaturation left for a benzene ring, so benzene and $\text{C}\equiv\text{N}$ are mutually exclusive

IR spectrum:

—one spike around 3300 cm^{-1} suggests a 2° amine

—no $\text{C}\equiv\text{N}$

—CH and C=C regions suggest an aromatic ring

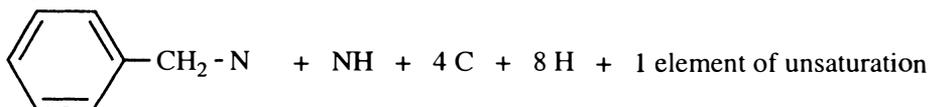
Proton NMR spectrum:

—5H multiplet at δ 7.3 indicates a monosubstituted benzene ring (the fact that all the peaks are huddled around 7.3 precludes N being bonded to the ring)

—1H singlet at δ 2.0 is exchangeable \Rightarrow NH of secondary amine

—2H singlet at δ 3.5 is CH_2 ; the fact that it is so strongly deshielded and unsplit suggests that it is between a nitrogen and the benzene ring

fragments so far:



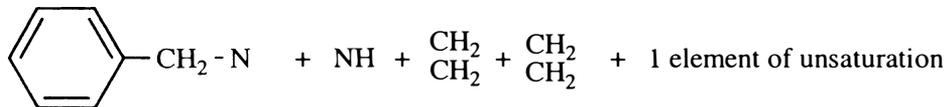
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19-59 continued

Carbon NMR spectrum:

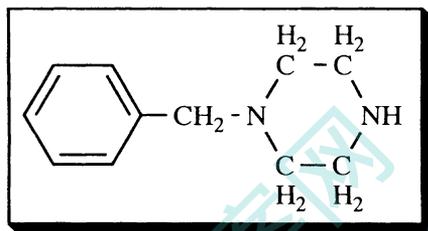
- four signals around δ 125-138 are the aromatic carbons
- the signal at δ 65 is the CH_2 bonded to the benzene
- the other 4 carbons come as two signals at δ 46 and δ 55; each is a triplet, so there are two sets of two equivalent CH_2 groups, each bonded to N to shift it downfield

fragments so far:



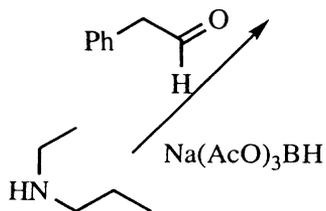
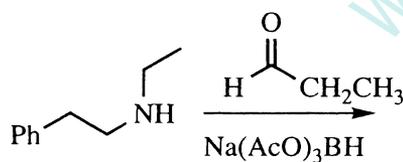
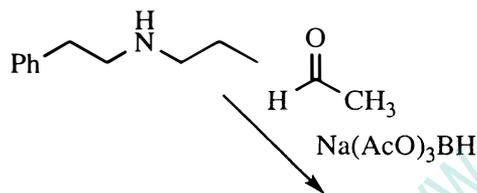
There is no evidence for an alkene in any of the spectra, so the remaining element of unsaturation must be a ring. The simplicity of the NMR spectra indicates a fairly symmetric compound.

Assemble the pieces:

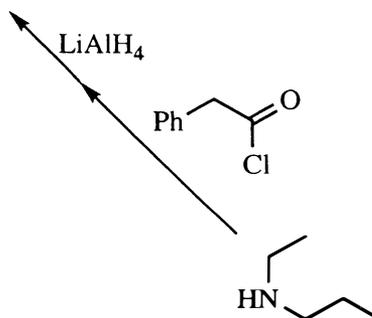
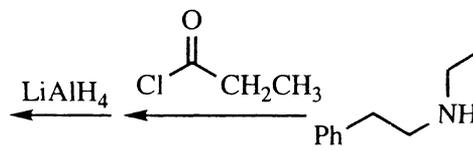
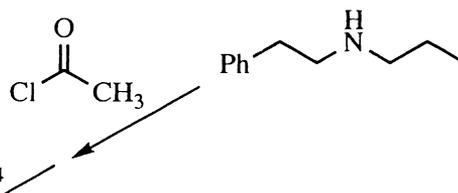


19-60

(a)

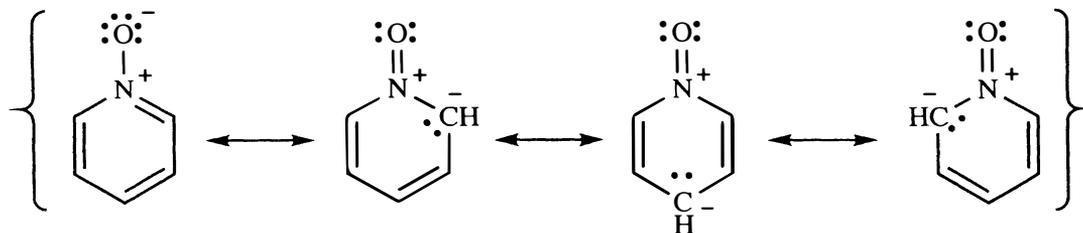


(b)



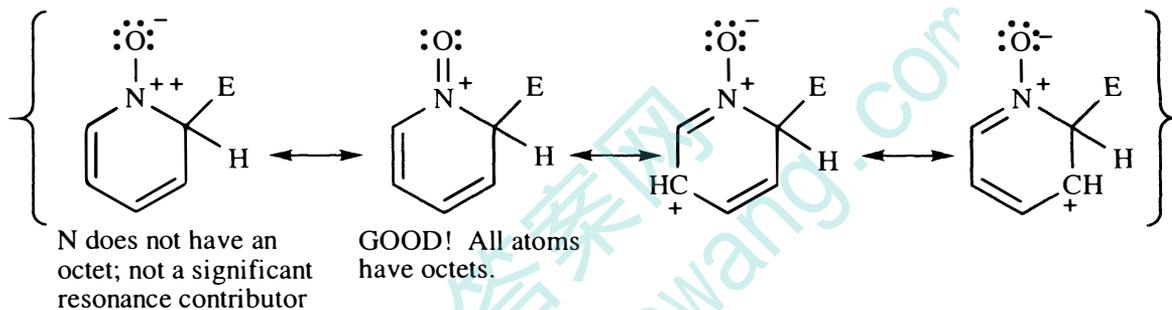
19-61 Not only is substitution at C-2 and C-4 the major products, but substitution occurs under surprisingly mild conditions.

Begin by drawing the resonance forms of pyridine N-oxide:

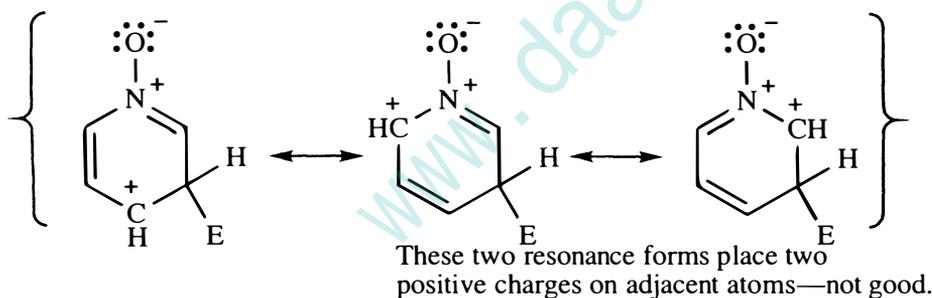


Resonance forms show that the electron density from the oxygen is distributed at C-2 and C-4; these positions would be the likely places for an electrophile to attack.

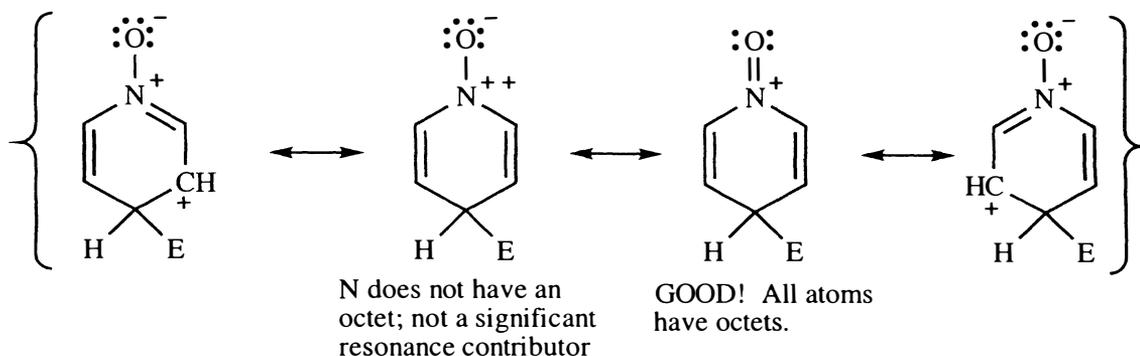
Resonance forms from electrophilic attack at C-2



Resonance forms from electrophilic attack at C-3



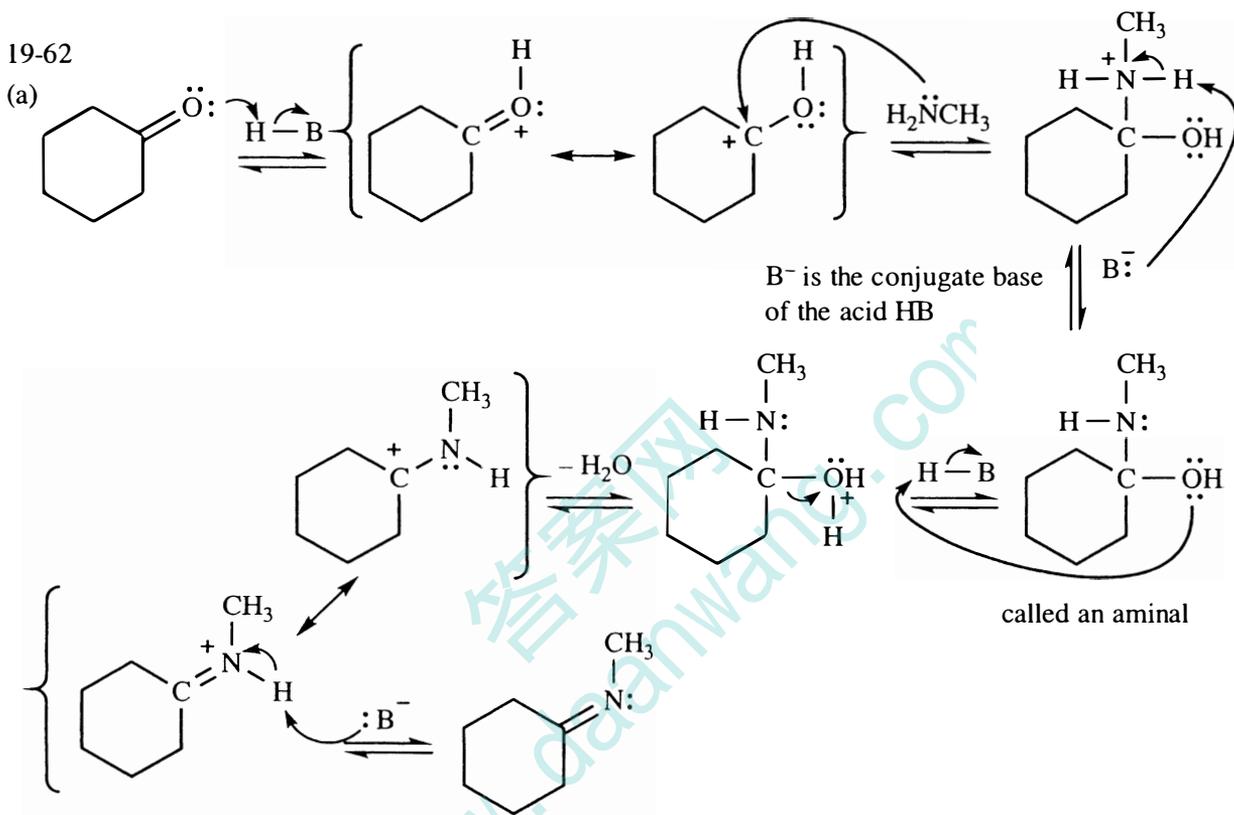
Resonance forms from electrophilic attack at C-4



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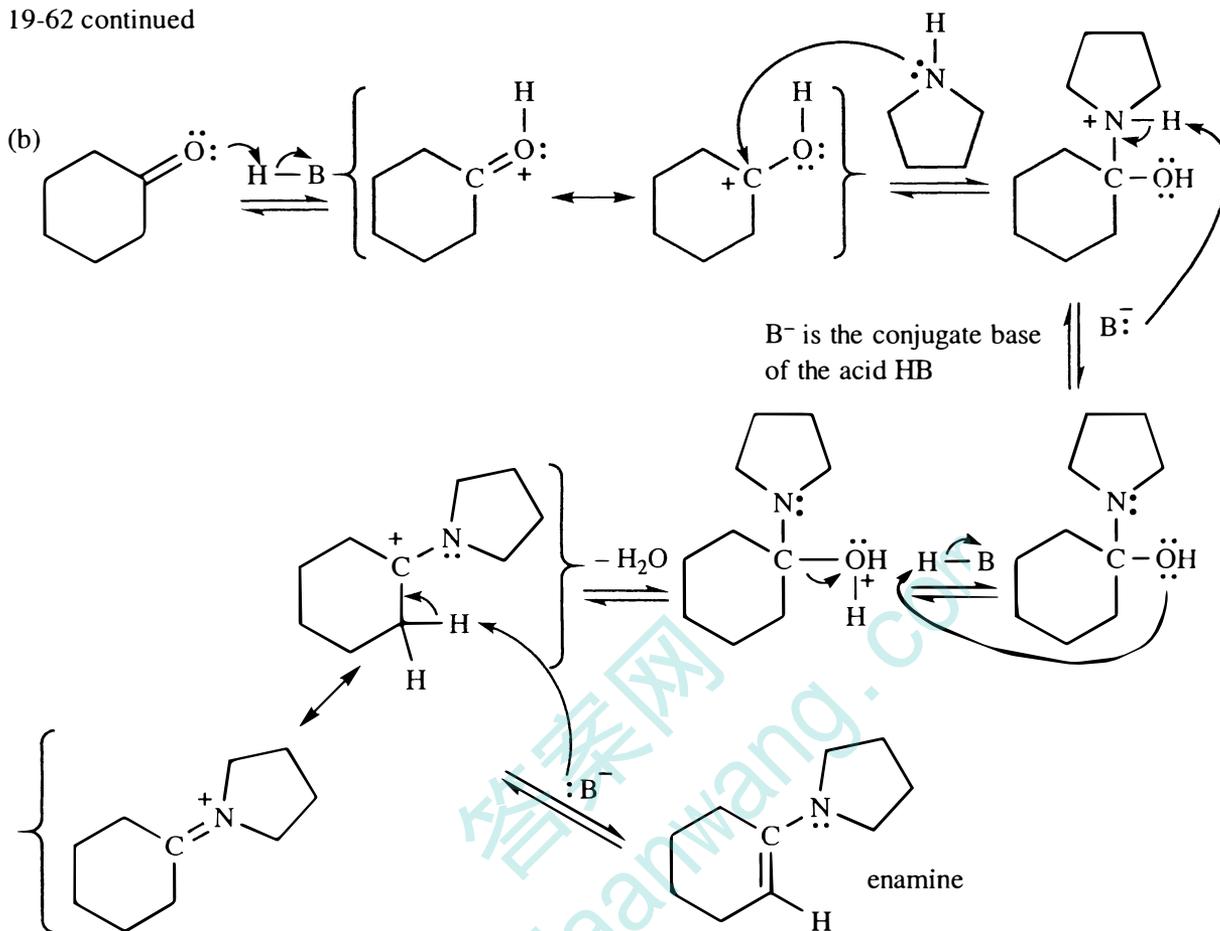
19-61 continued

The resonance forms from electrophilic attack at C-3 are bad; only one of the three is a significant contributor, which means that there is not much resonance stabilization. When the electrophile attacks at C-2 or C-4, however, there are two forms that are good plus one great one that has all atoms with full octets. Clearly, attack at C-2 and C-4 give the most stable intermediates and will be the preferred sites of attack.



continued on next page

19-62 continued

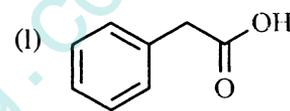
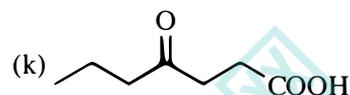
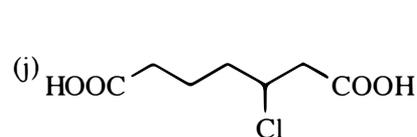
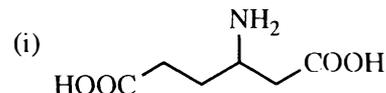
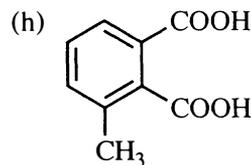
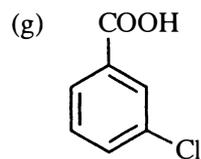
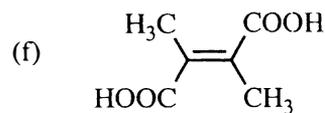
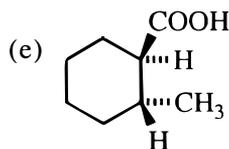
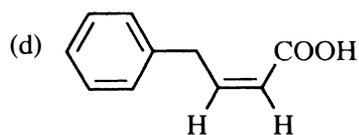
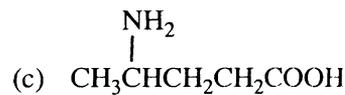
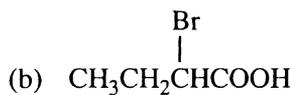
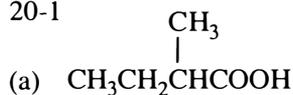


To this point, everything is the same in the two mechanisms.
 But now, there is no H on the N to remove to form the imine.
 The only H that can be removed to form a neutral intermediate
 is the H on C next to the carbocation.

(c) A secondary amine has only one H to give which it loses in the first half of the mechanism to form the neutral intermediate called an aminal, equivalent to a hemiacetal. In the second half of the mechanism, the H on an adjacent carbon is removed to form the neutral product, the enamine. The type of product depends entirely on whether the amine begins with one or two hydrogen atoms.

CHAPTER 20—CARBOXYLIC ACIDS

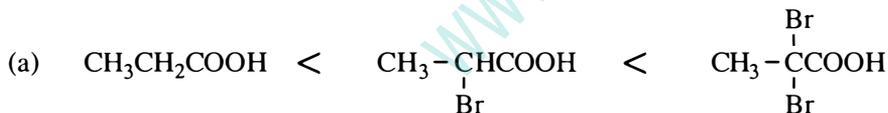
20-1



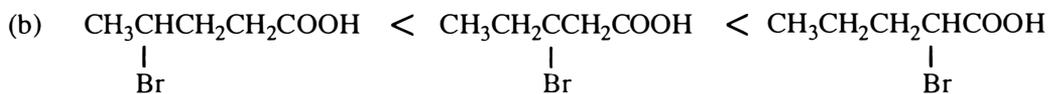
20-2 IUPAC name first; then common name.

- (a) 2-iodo-3-methylpentanoic acid; α -iodo- β -methylvaleric acid
 (b) (Z)-3,4-dimethylhex-3-enoic acid
 (c) 2,3-dinitrobenzoic acid; no common name
 (d) *trans*-cyclohexane-1,2-dicarboxylic acid; (*trans*-hexahydrophthalic acid)
 (e) 2-chlorobenzene-1,4-dicarboxylic acid; 2-chloroterephthalic acid
 (f) 3-methylhexanedioic acid; β -methyladipic acid

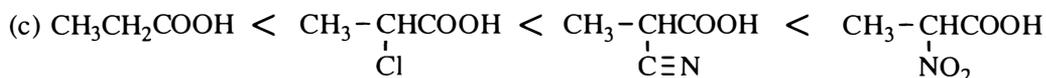
20-3 Listed in order of increasing acid strength (weakest acid first). (See Appendix 2 for a review of acidity.)



The greater the number of electron-withdrawing substituents, the greater the stabilization of the carboxylate ion.

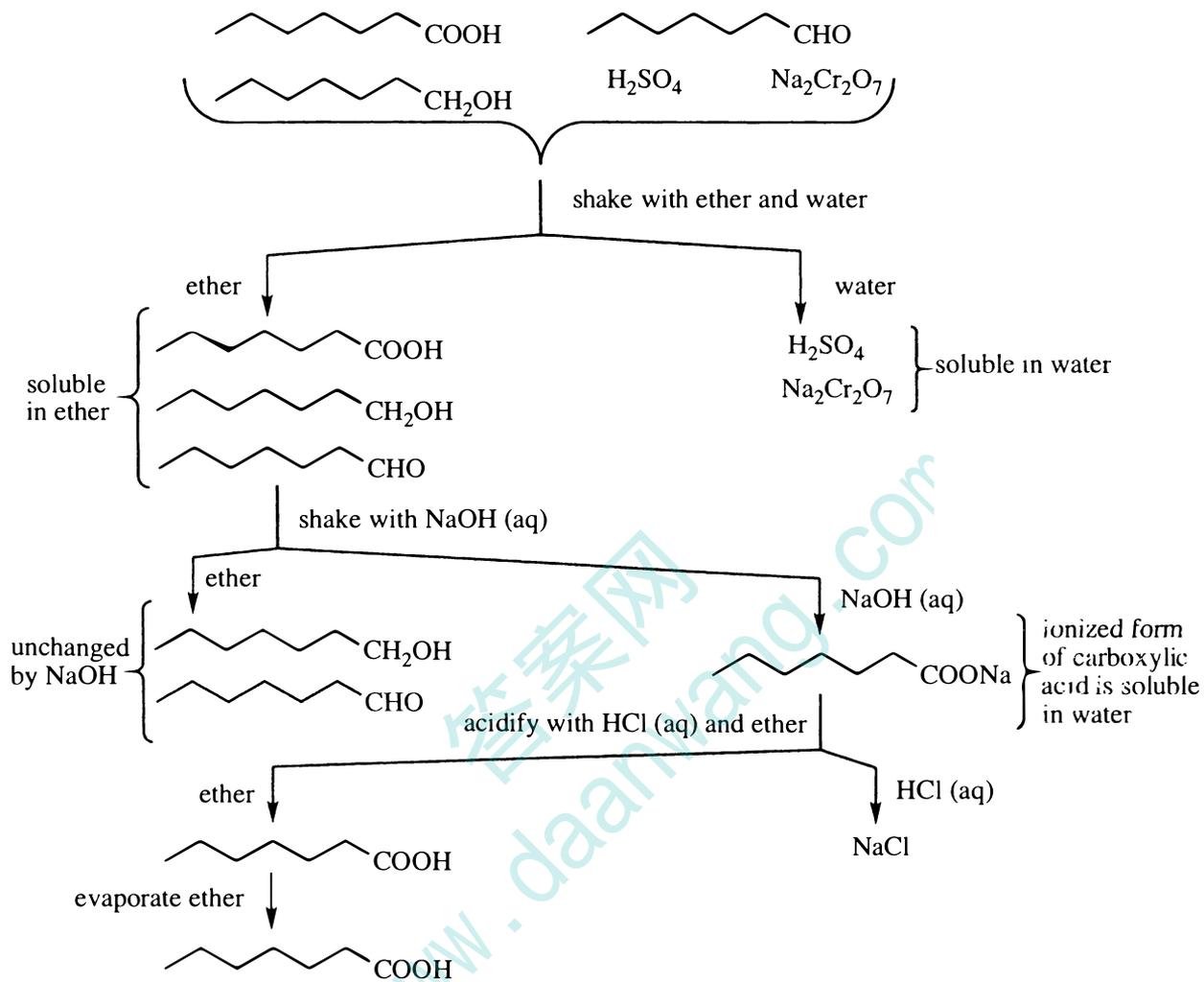


The closer the electron-withdrawing group, the greater the stabilization of the carboxylate ion.

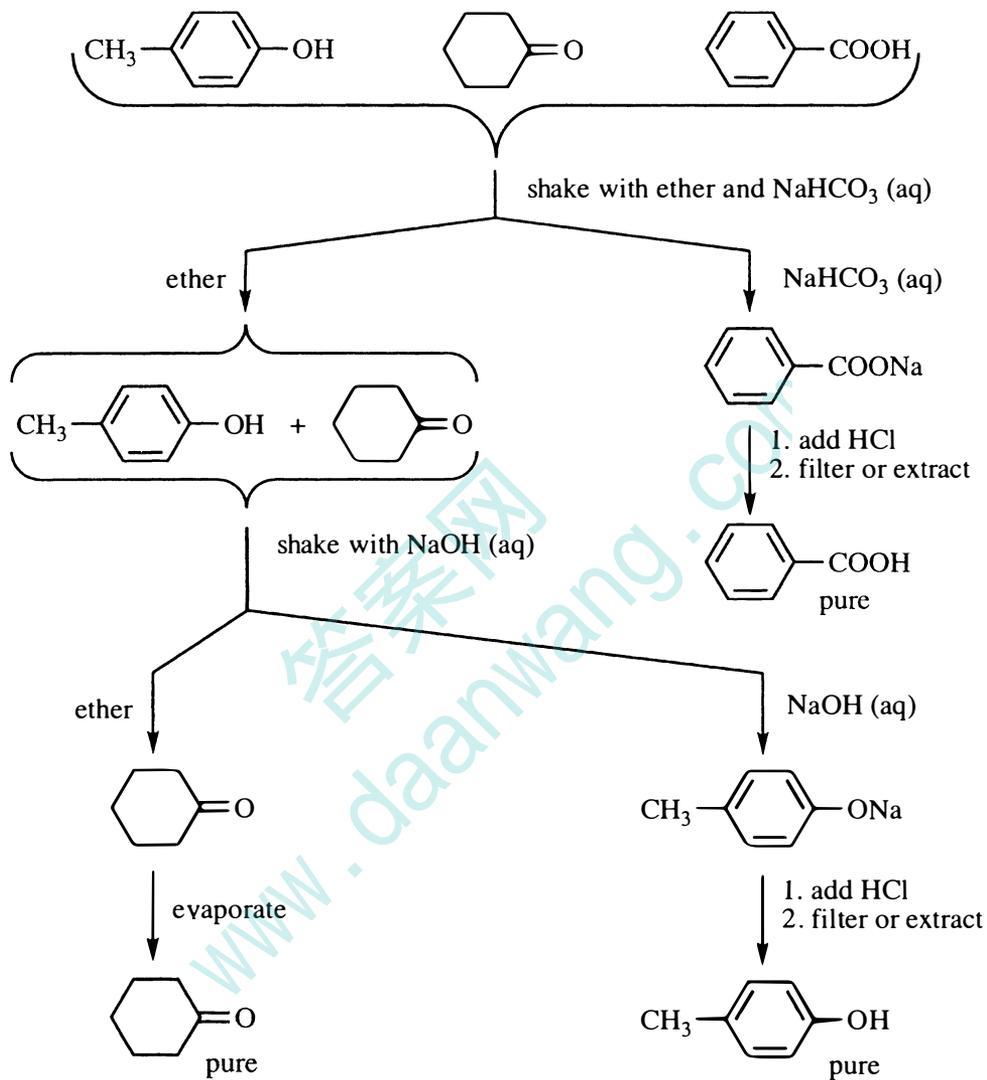


The stronger the electron-withdrawing effect of the substituent, the greater the stabilization of the carboxylate ion.

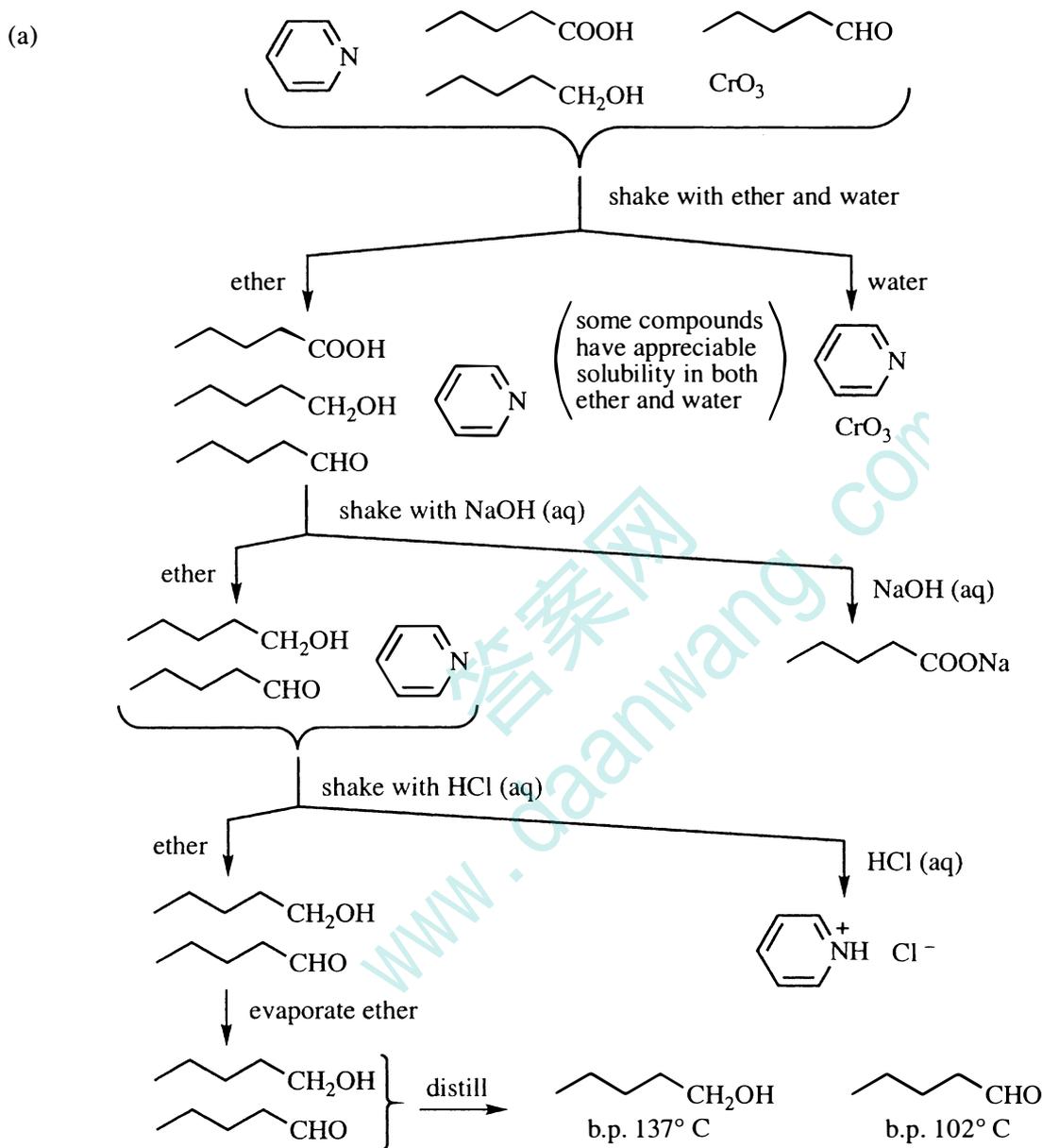
20-4



20-5 The principle used to separate a carboxylic acid (a stronger acid) from a phenol (a weaker acid) is to neutralize with a weak base (NaHCO_3), a base strong enough to ionize the stronger acid but not strong enough to ionize the weaker acid.



20-6 The reaction mixture includes the initial reactant, reagent, desired product, and the overoxidation product—not unusual for an organic reaction mixture.

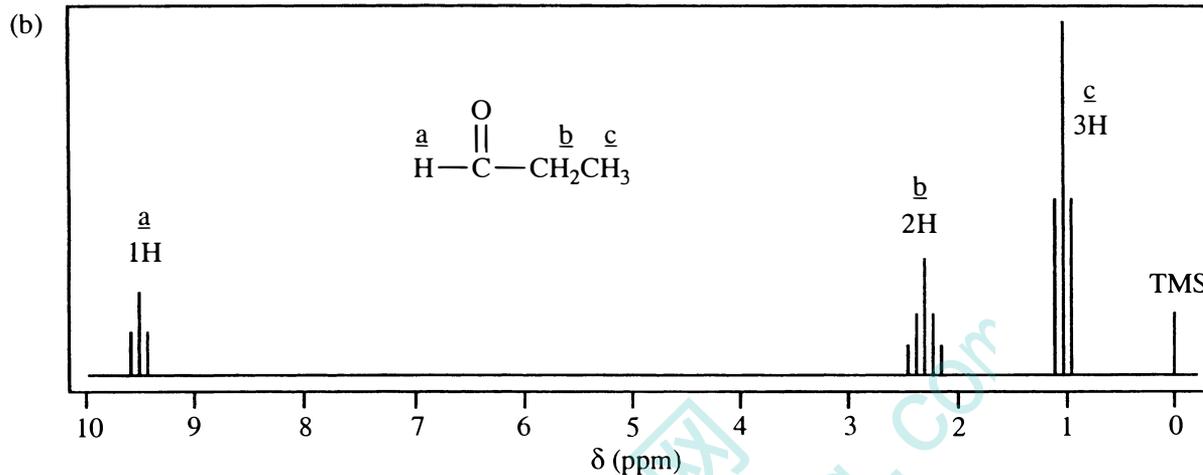
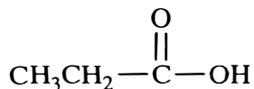


(b) Pentan-1-ol cannot be removed from pentanal by acid-base extraction. These two remaining products can be separated by distillation, the alcohol having the higher boiling point because of hydrogen bonding.

20-7 The COOH has a characteristic IR absorption: a broad peak from 3400-2400 cm^{-1} , with a "shoulder" around 2700 cm^{-1} . The carbonyl stretch at 1695 cm^{-1} is a little lower than the standard 1710 cm^{-1} , suggesting conjugation. The strong alkene absorption at 1650 cm^{-1} also suggests it is conjugated.

20-8

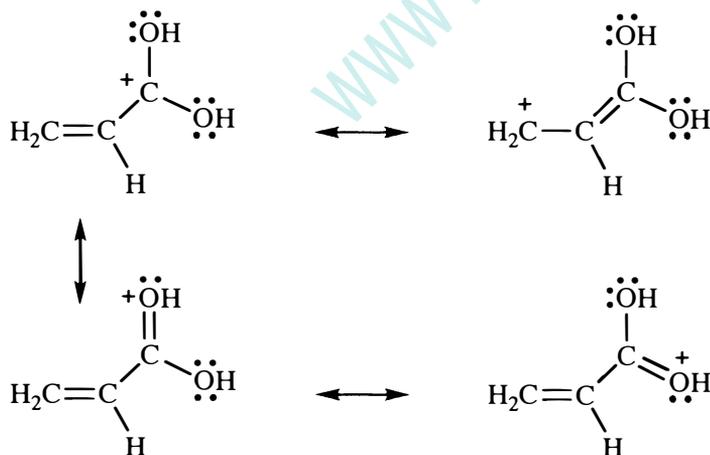
(a) The ethyl pattern is obvious: a 3H triplet at δ 1.15 and a 2H quartet at δ 2.4. The only other peak is the COOH at δ 11.9 (a 2.1 δ unit offset added to 9.8).



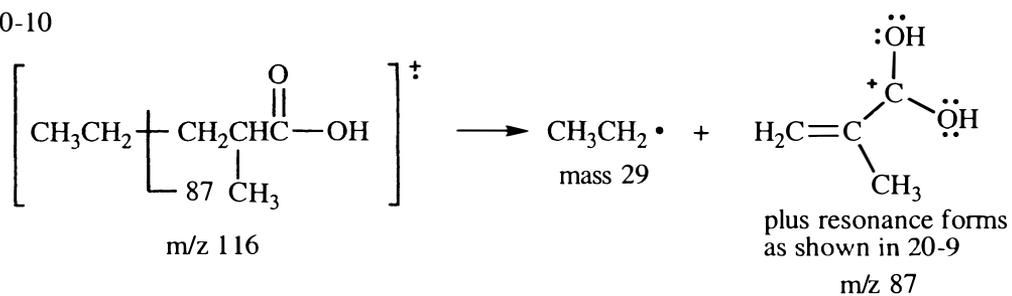
The multiplet between δ 2 and δ 3 is drawn as a pentet as though it were split equally by the aldehyde proton and the CH_2 group. These coupling constants are probably unequal, in which case the actual splitting pattern will be a complex multiplet.

(c) The chemical shift of the aldehyde proton is between δ 9-10, not as far downfield as the carboxylic acid proton. Also, the aldehyde proton is split into a triplet by the CH_2 , unlike the COOH proton which always appears as a singlet. Finally, the CH_2 is split by an extra proton, so it will give a multiplet with complex splitting, instead of the quartet shown in the acid.

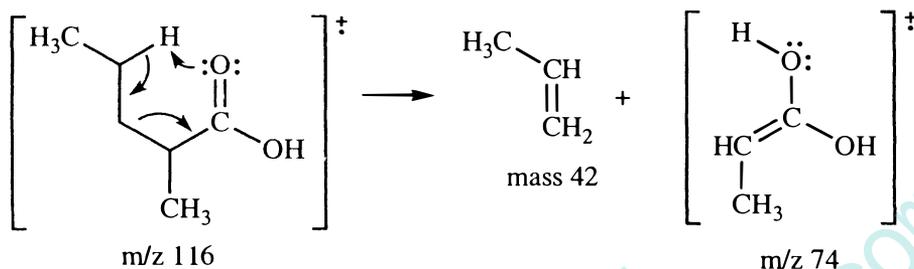
20-9



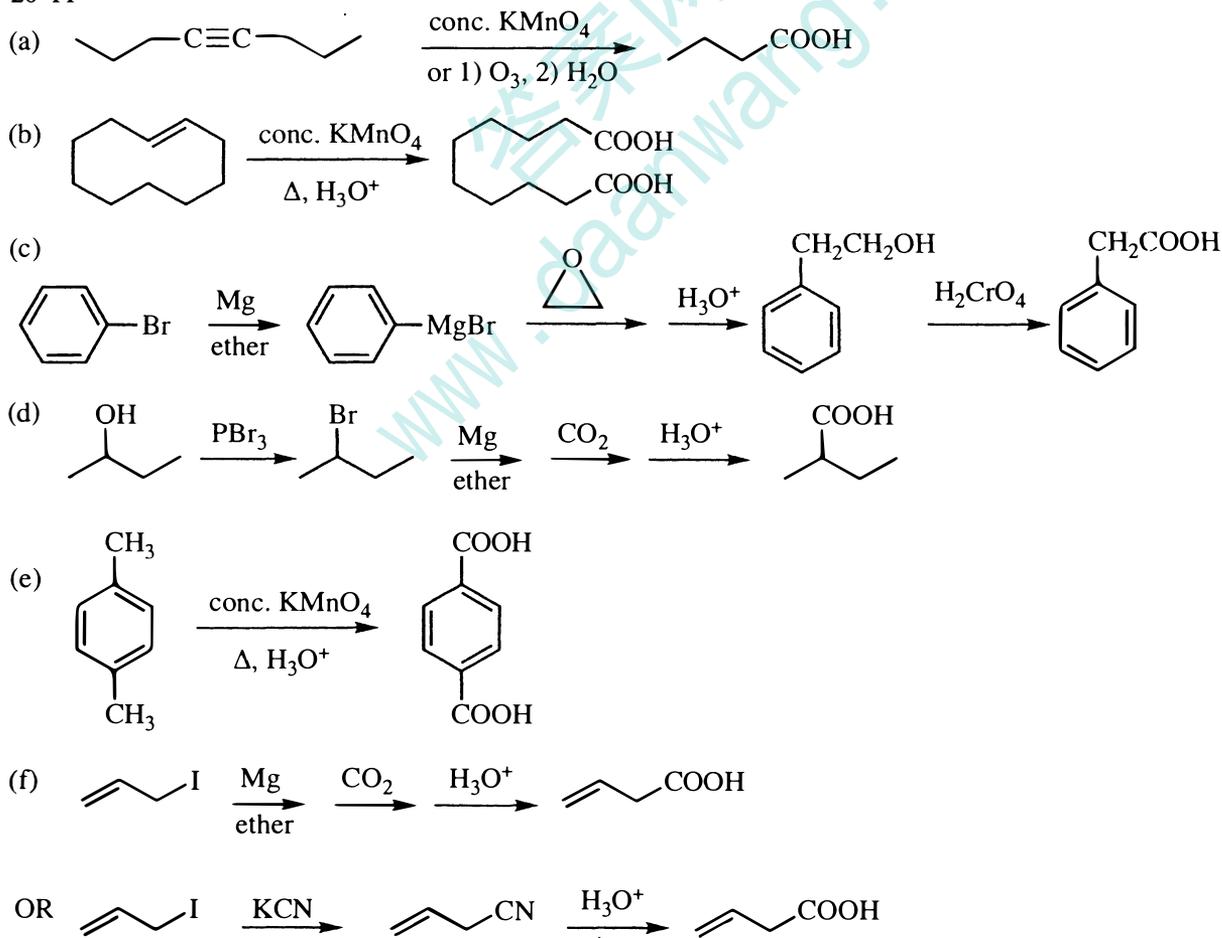
20-10



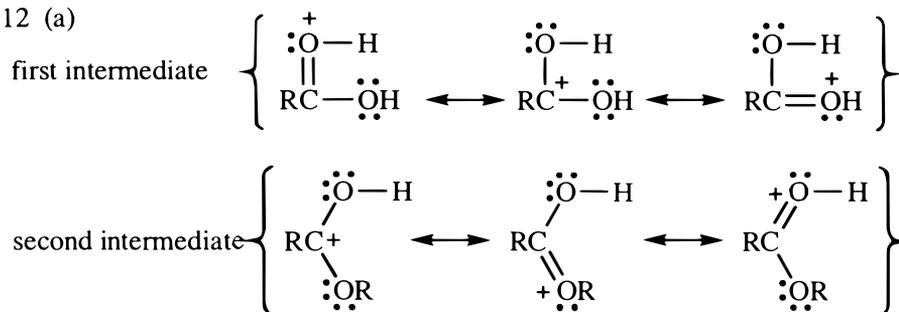
McLafferty rearrangement



20-11



20-12 (a)



(b) The mechanism of acid-catalyzed nucleophilic acyl substitution may seem daunting, but it is simply a succession of steps that are already very familiar to you.

Typically, these mechanisms have six steps: four proton transfers (two on, two off), a nucleophilic attack, and a leaving group leaving, with a little resonance stabilization thrown in that makes the whole thing work. The six steps are labeled in the mechanism below:

Step A proton on (resonance stabilization)

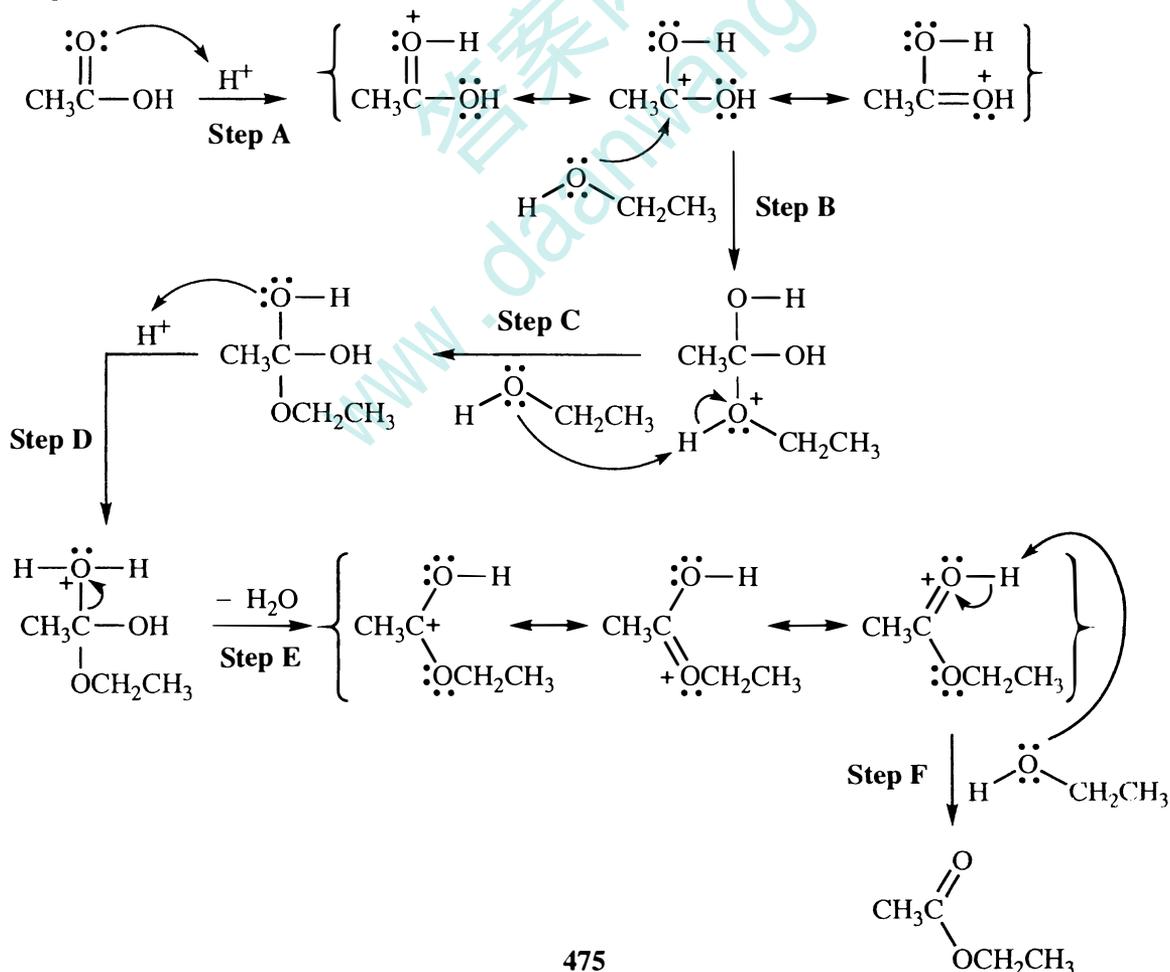
Step B nucleophile attacks

Step C proton off

Step D proton on

Step E leaving group leaves (resonance stabilization)

Step F proton off



20-12 (c) All steps are reversible, which is the reason the Principle of Microscopic Reversibility applies. Applying the steps as outlined on the previous page: (abbreviating OCH_2CH_3 as OEt)

Step A proton on (resonance stabilization)

Step B nucleophile attacks

Step C proton off

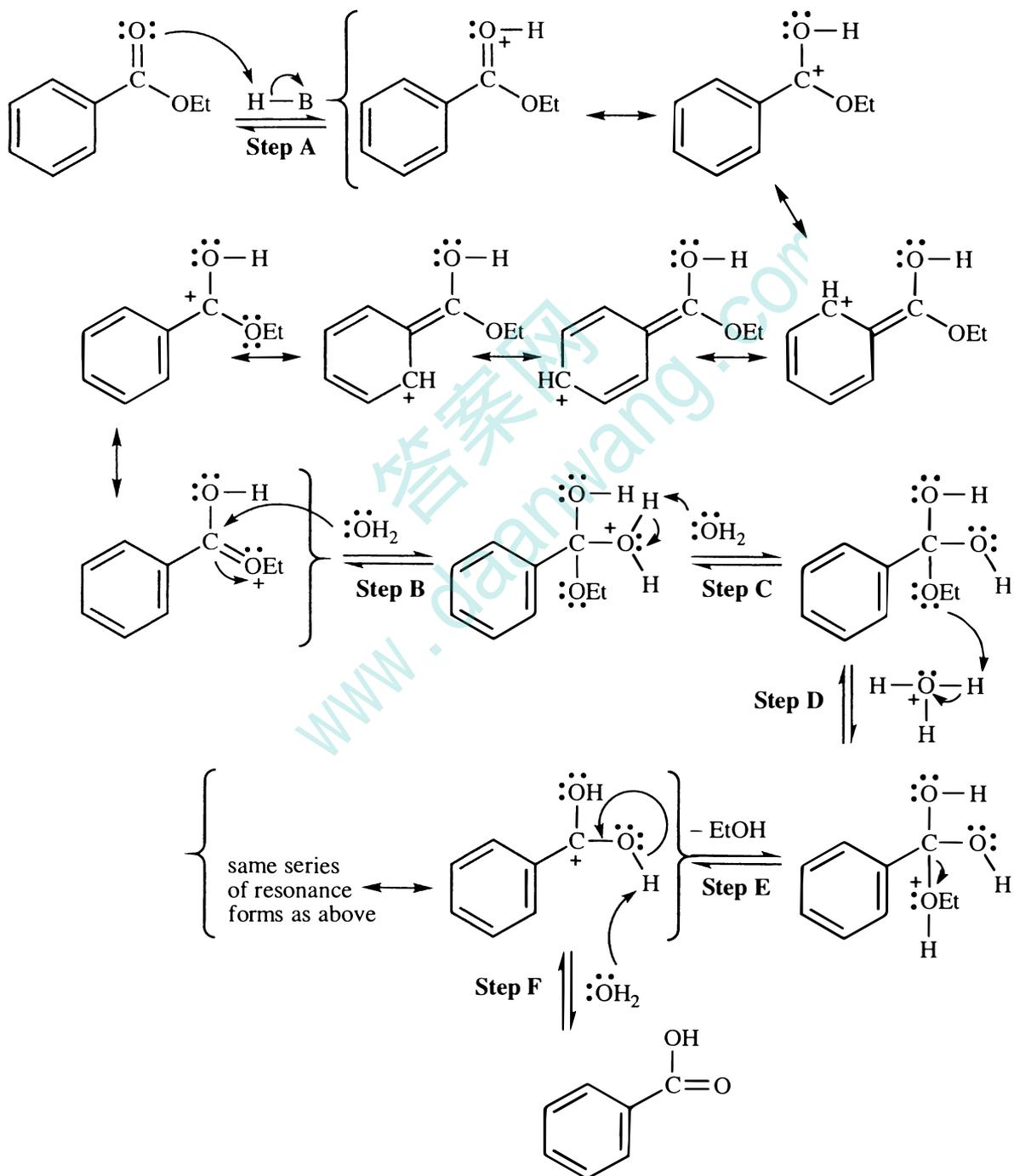
Step D proton on

Step E leaving group leaves (resonance stabilization)

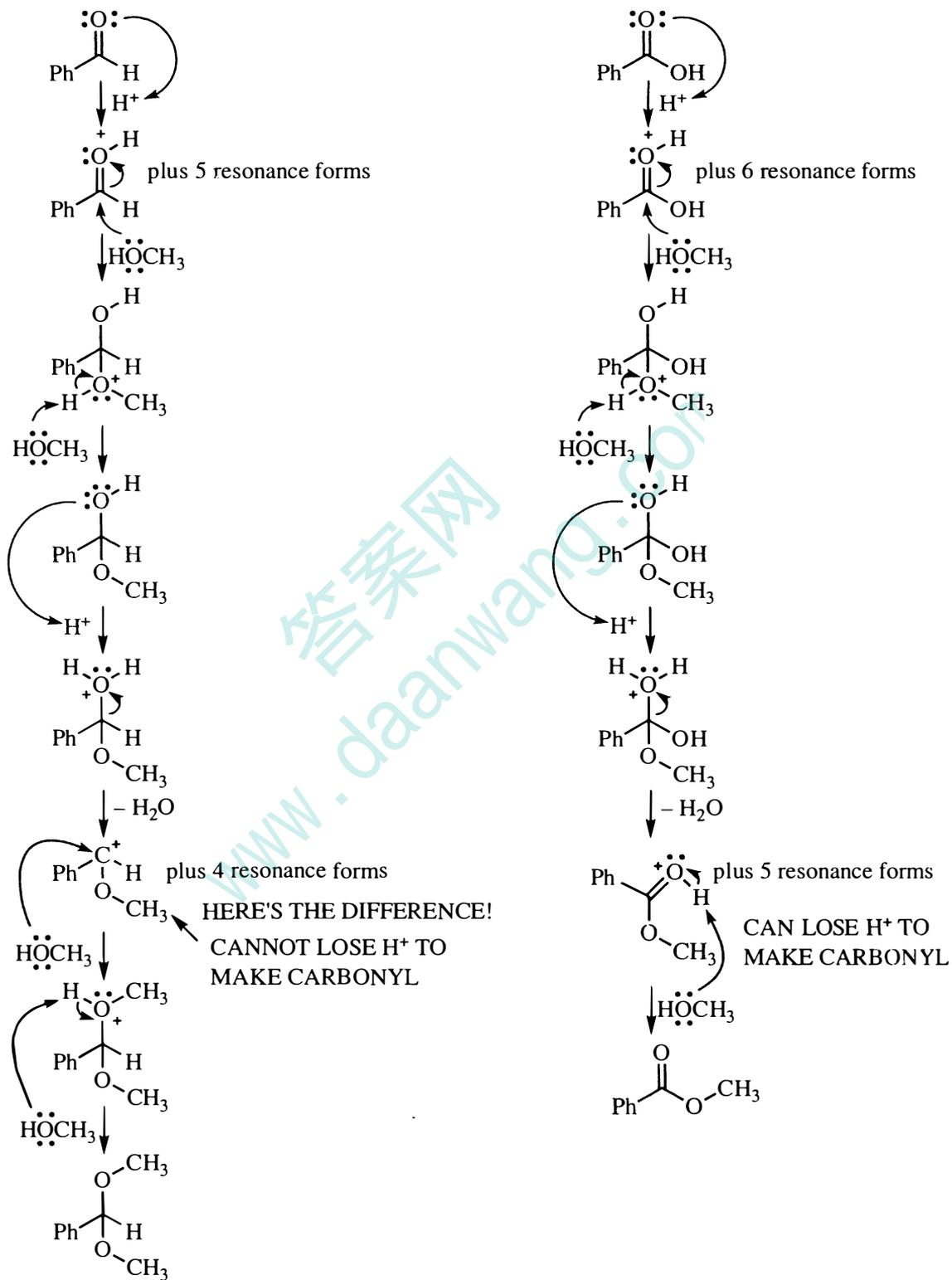
Step F proton off

$\text{H}-\text{B}$ is the acid catalyst

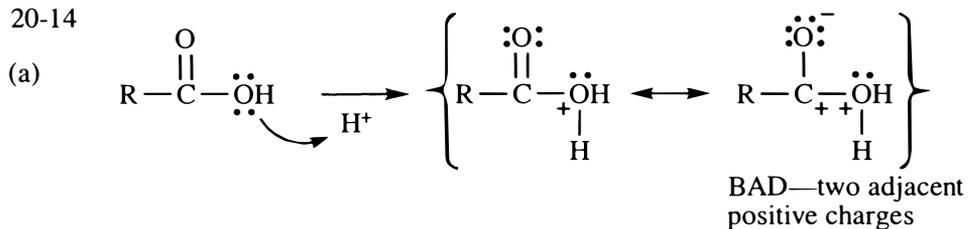
$:\text{B}^-$ is the conjugate base, although in hydrolysis reactions, water usually removes H^+



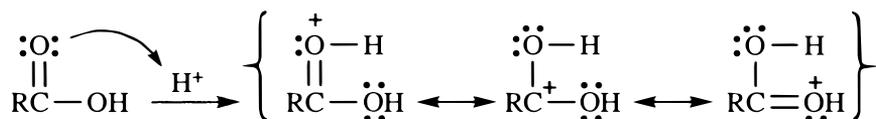
20-13 For the sake of space in this problem, resonance forms will not be drawn, but remember that they are critical!



20-14

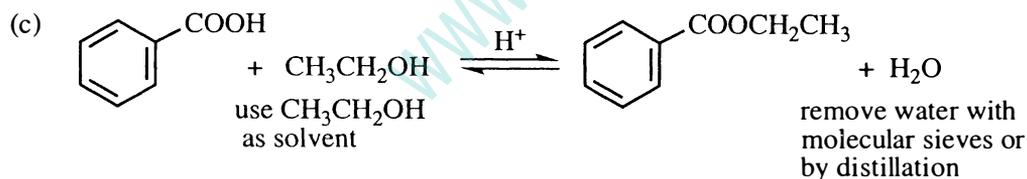
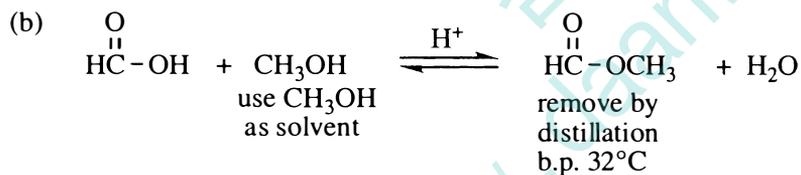
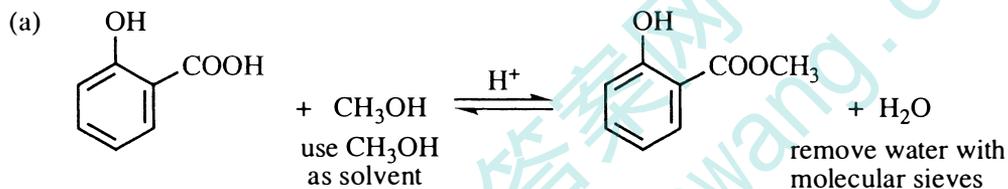


(b) Protonation on the OH gives only two resonance forms, one of which is bad because of adjacent positive charges. Protonation on the C=O is good because of three resonance forms distributing the positive charge over three atoms, with no additional charge separation.



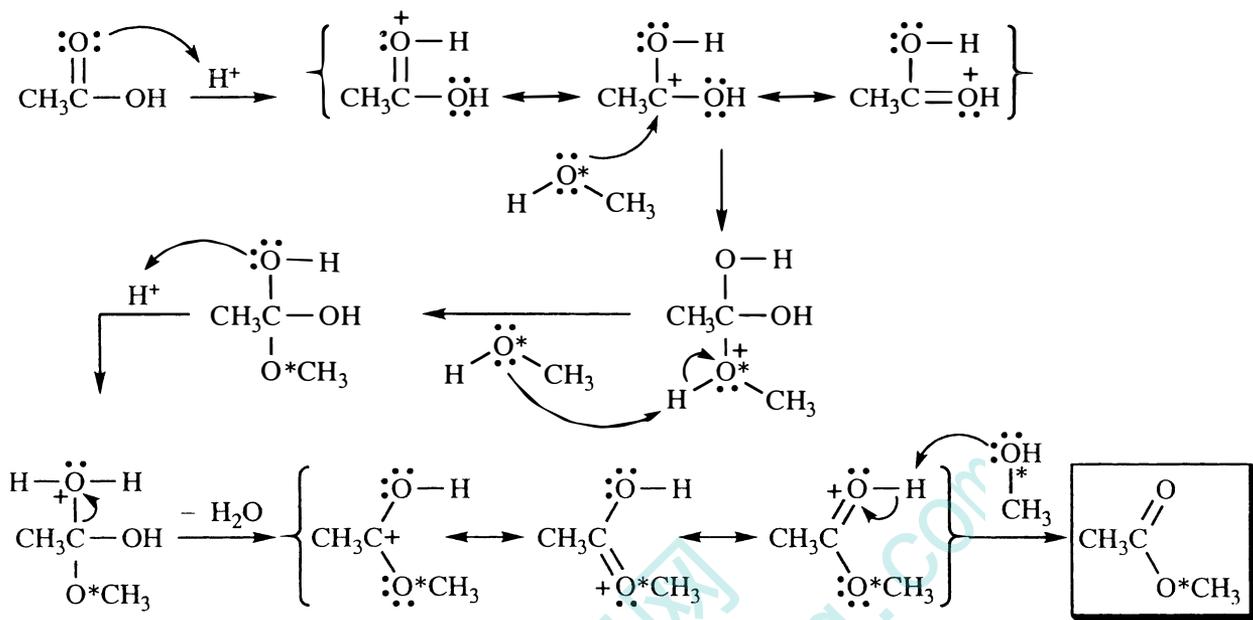
(c) The carbonyl oxygen is more "basic" because, by definition, it reacts with a proton more readily. It does so because the intermediate it produces is more stable than the intermediate from protonation of the OH.

20-15



20-16 The asterisk ("*") denotes the ^{18}O isotope.

(a) and (b)

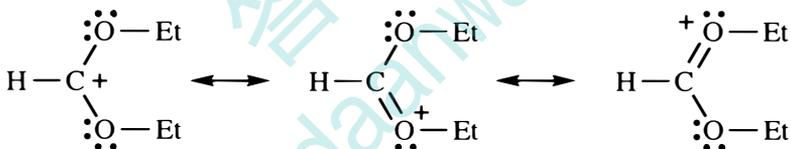


(c) The ^{18}O has two more neutrons, and therefore two more mass units, than ^{16}O . The instrument ideally suited to analyze compounds of different mass is the mass spectrometer.

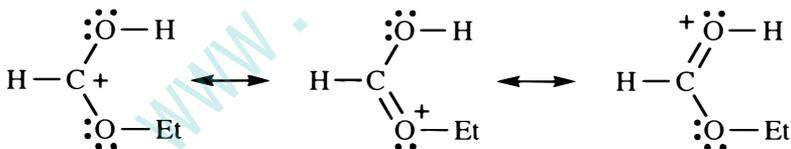
20-17

(a)

first intermediate:

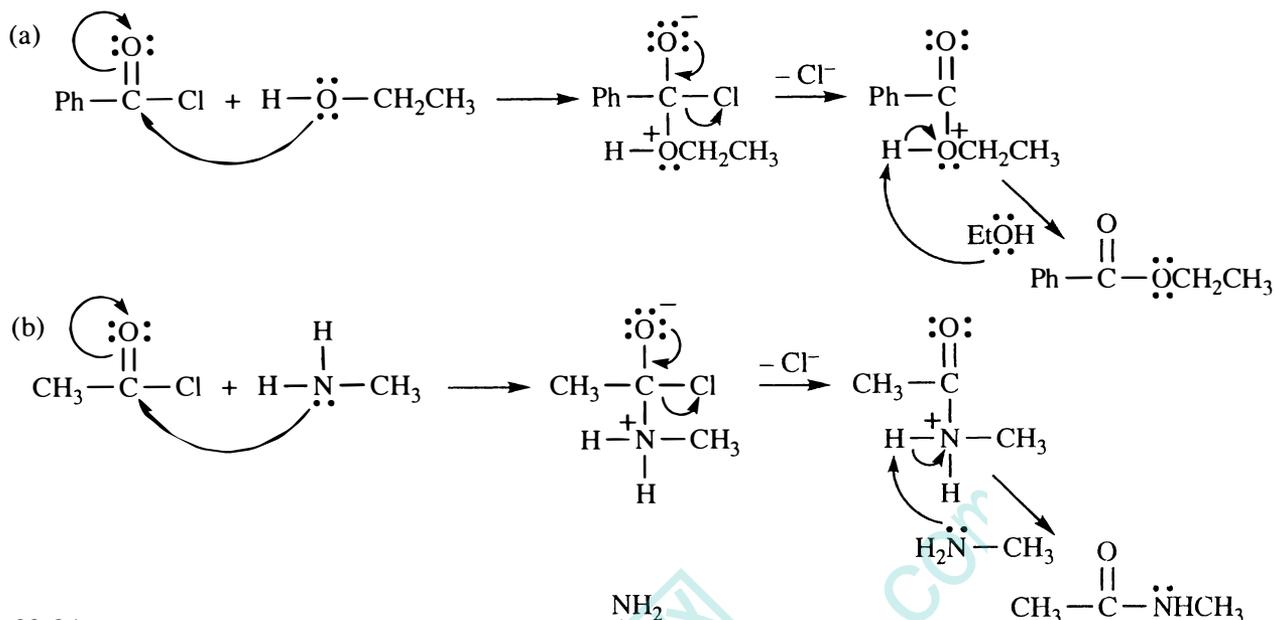


second intermediate:

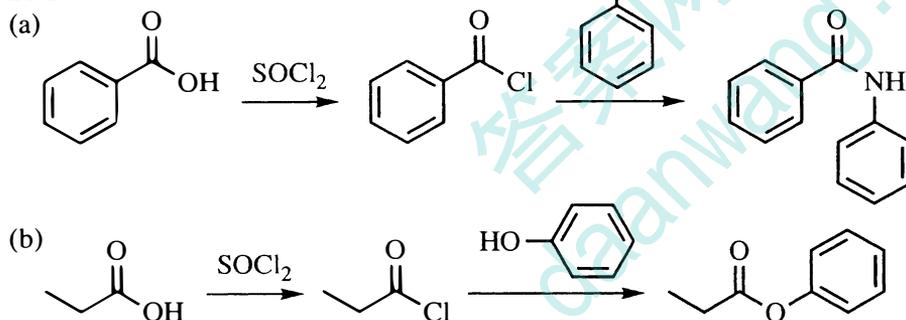


The more resonance forms that can be drawn to represent an intermediate, the more stable the intermediate. The more stable the intermediate, the more easily it can be formed, that is, under milder conditions. These intermediates are highly stabilized due to delocalization of the positive charge over the carbon and both oxygens. A trace of acid is all that is required to initiate this process.

20-23



20-24



20-25 Please refer to solution 1-20, page 12 of this Solution Manual.

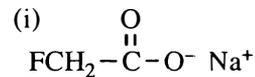
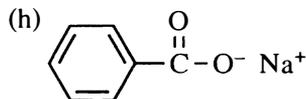
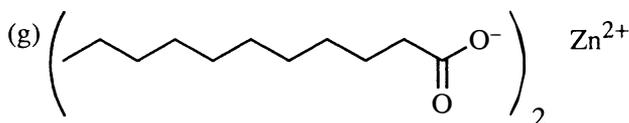
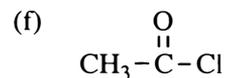
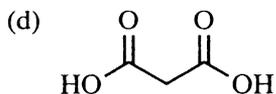
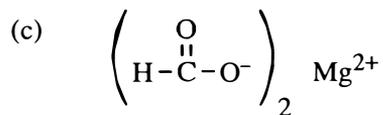
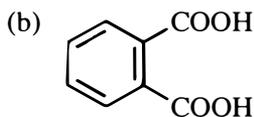
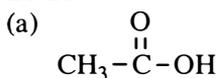
20-26

- | | |
|---|--------------------------------|
| (a) 3-phenylpropanoic acid | (b) 2-methylbutanoic acid |
| (c) 2-bromo-3-methylbutanoic acid | (d) 2-methylbutanedioic acid |
| (e) sodium 2-methylbutanoate | (f) 3-methylbut-2-enoic acid |
| (g) <i>trans</i> -2-methylcyclopentanecarboxylic acid | (h) 2,4,6-trinitrobenzoic acid |
| (i) 7,7-dimethyl-4-oxooctanoic acid | |

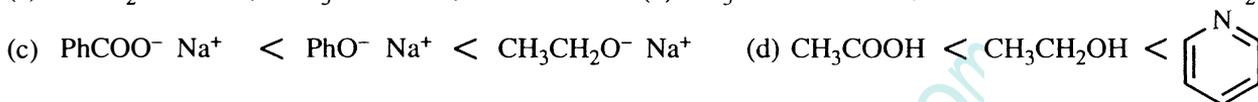
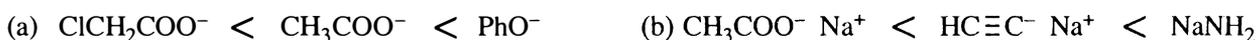
20-27

- | | |
|--|-----------------------------------|
| (a) β -phenylpropionic acid | (b) α -methylbutyric acid |
| (c) α -bromo- β -methylbutyric acid,
or α -bromoisovaleric acid | (d) α -methylsuccinic acid |
| (e) sodium β -methylbutyrate | (f) β -aminobutyric acid |
| (g) <i>o</i> -bromobenzoic acid | (h) magnesium oxalate |
| (i) 4-methoxyphthalic acid | |

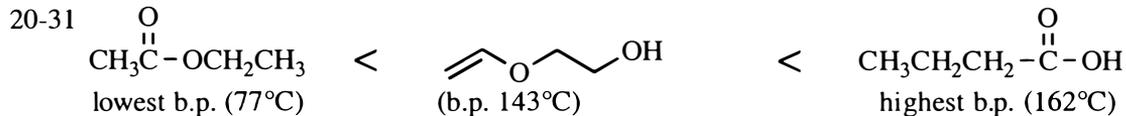
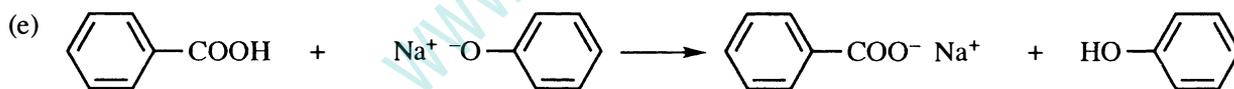
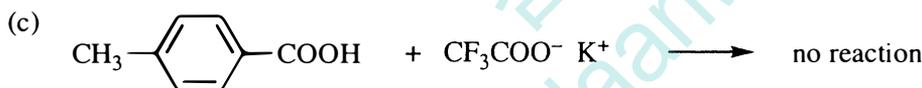
20-28



20-29 Weaker base listed first. (Weaker bases come from stronger conjugate acids.)



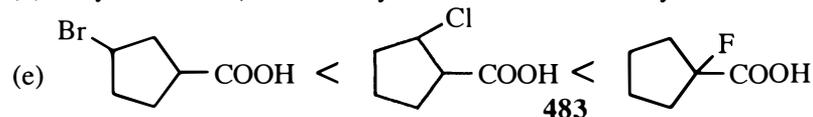
20-30



The ester cannot form hydrogen bonds and will be the lowest boiling. The alcohol can form hydrogen bonds. The carboxylic acid forms two hydrogen bonds and boils as the dimer, the highest boiling among these three compounds.

20-32 Listed in order of increasing acidity (weakest acid first):

- (a) ethanol < phenol < acetic acid
 (b) acetic acid < chloroacetic acid < *p*-toluenesulfonic acid
 (c) benzoic acid < *m*-nitrobenzoic acid < *o*-nitrobenzoic acid
 (d) butyric acid < β-bromobutyric acid < α-bromobutyric acid



EWG = electron-withdrawing group

- Acidity increases with:
1. closer proximity of EWG
 2. great number of EWG
 3. increasing strength (electronegativity) of EWG

20-33 Acetic acid derivatives are often used as a test of electronic effects of a series of substituents: they are fairly easily synthesized (or are commercially available), and pK_a values are easily measured by titration.

Substituents on carbon-2 of acetic acid can express only an inductive effect; no resonance effect is possible because the CH_2 is sp^3 hybridized and no π overlap is possible.

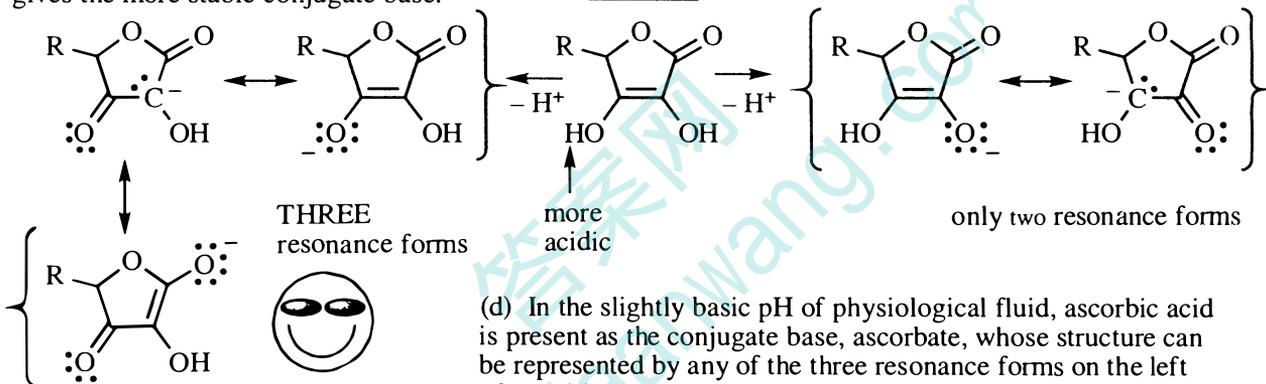
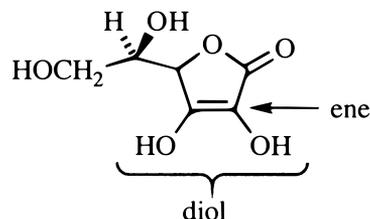
Two conclusions can be drawn from the given pK_a values. First, all four substituents are electron-withdrawing because all four substituted acids are stronger than acetic acid. Second, the magnitude of the electron-withdrawing effect increases in the order: $OH < Cl < CN < NO_2$. (It is always a safe assumption that nitro is the strongest electron-withdrawing group of all the common substituents.)

20-34

(a) Ascorbic acid is not a carboxylic acid. It is an example of a structure called an ene-diol where one of the OH groups is unusually acidic because of the adjacent carbonyl group. See part (c).

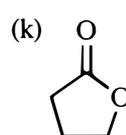
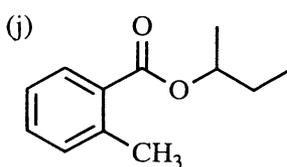
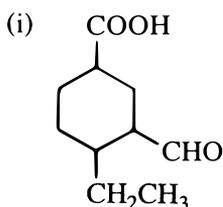
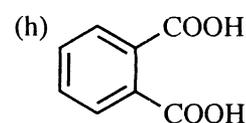
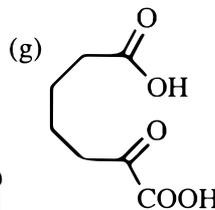
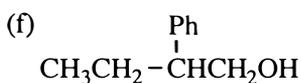
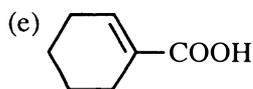
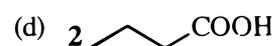
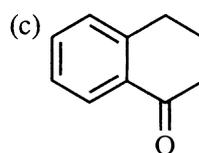
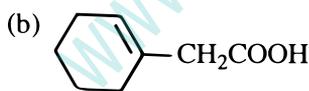
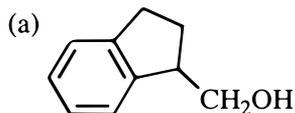
(b) Ascorbic acid, pK_a 4.71, is almost identical to the acidity of acetic acid, pK_a 4.74.

(c) The more acidic H will be the one that, when removed, gives the more stable conjugate base. *start here*

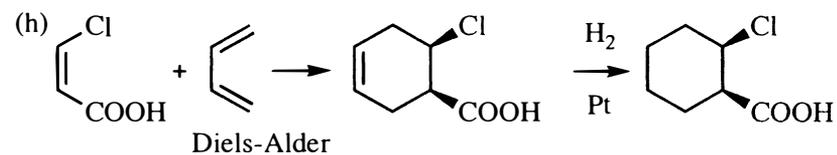
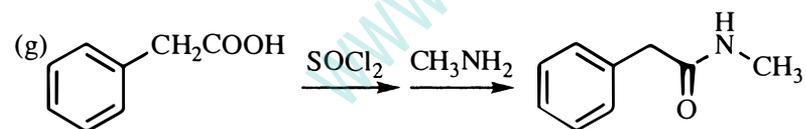
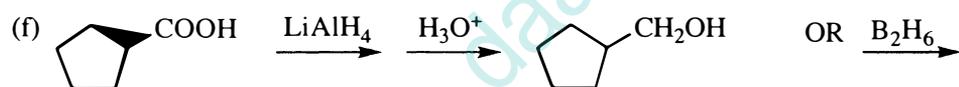
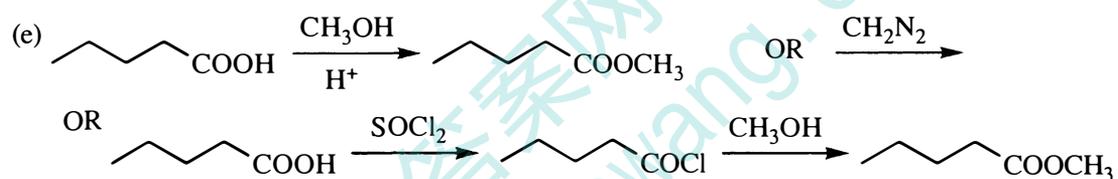
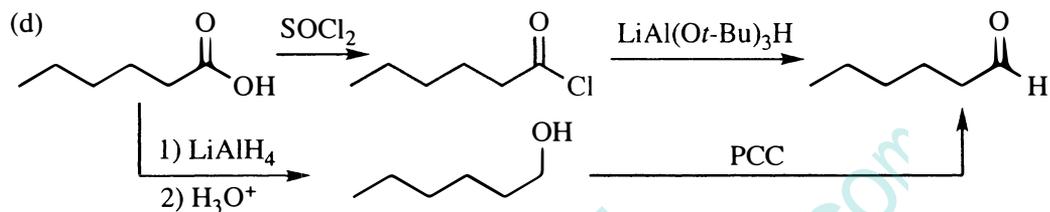
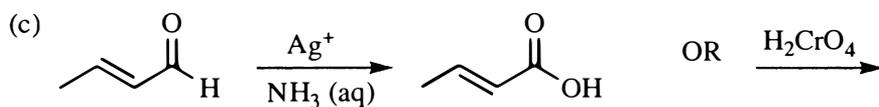
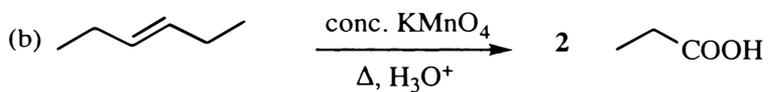
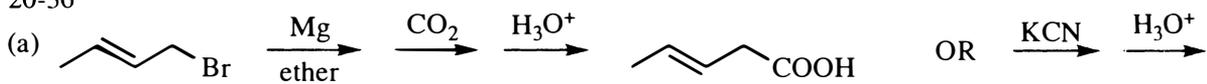


(d) In the slightly basic pH of physiological fluid, ascorbic acid is present as the conjugate base, ascorbate, whose structure can be represented by any of the three resonance forms on the left of part (c).

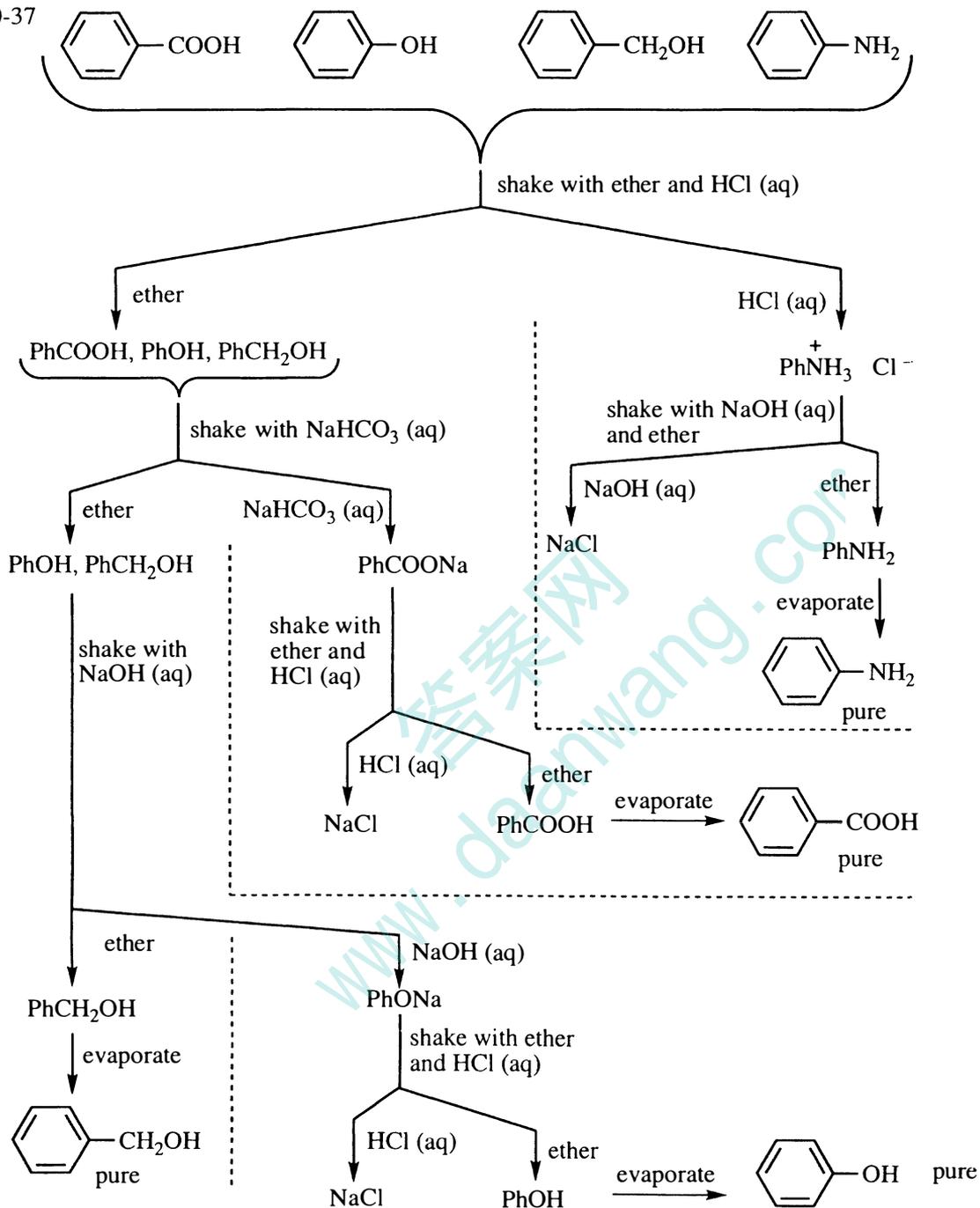
20-35



20-36

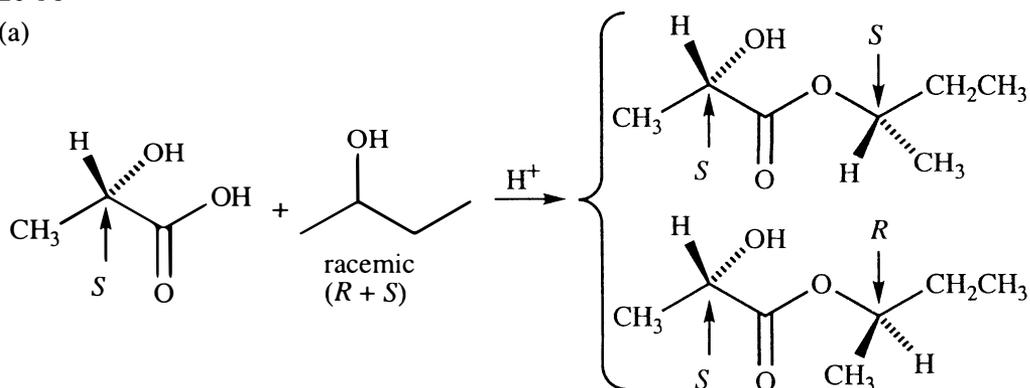


20-37



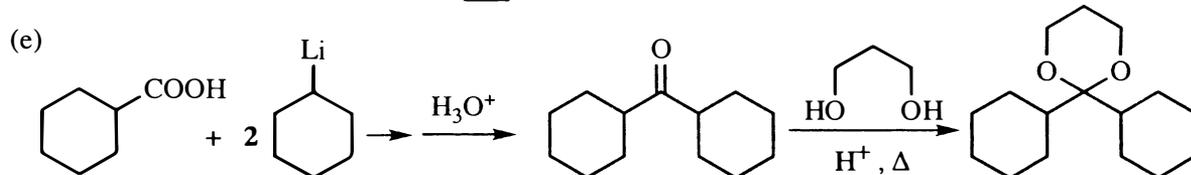
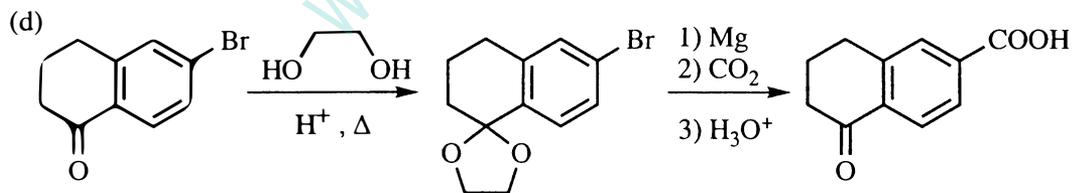
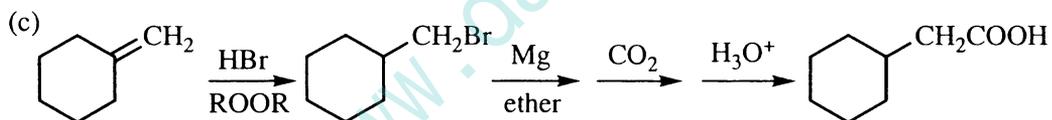
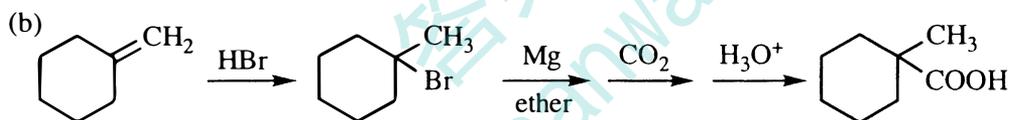
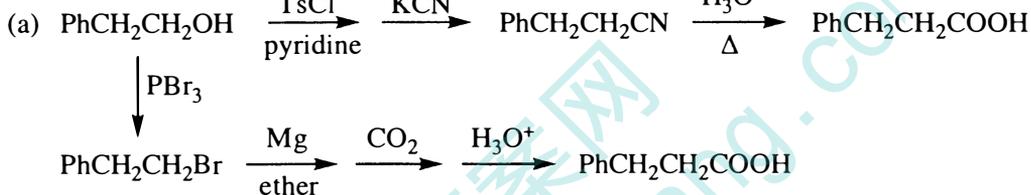
20-38

(a)



(b) Isomers which are *R,S* and *S,S* are diastereomers.

20-39



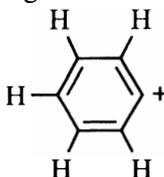
20-40

(a) Mass spectrum:

— m/z 152 \Rightarrow molecular ion \Rightarrow molecular weight 152

— m/z 107 $\Rightarrow M - 45 \Rightarrow$ loss of COOH

— m/z 77 \Rightarrow monosubstituted benzene ring,



IR spectrum:

—3400-2400 cm^{-1} , broad \Rightarrow O—H stretch of COOH

—1700 $\text{cm}^{-1} \Rightarrow$ C=O

—1240 $\text{cm}^{-1} \Rightarrow$ C—O

—1600 $\text{cm}^{-1} \Rightarrow$ aromatic C=C

NMR spectrum:

— δ 6.8-7.3, two signals in the ratio of 2H to 3H \Rightarrow monosubstituted benzene ring

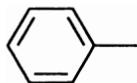
— δ 4.6, 2H singlet \Rightarrow CH₂, deshielded

Carbon NMR spectrum:

— δ 170, small peak \Rightarrow carbonyl

— δ 115-157, four peaks \Rightarrow monosubstituted benzene ring; deshielded peak indicates oxygen substitution on the ring

(b) Fragments indicated in the spectra:

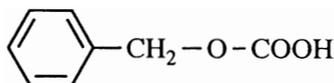
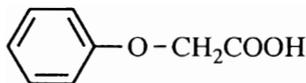


m/z 77

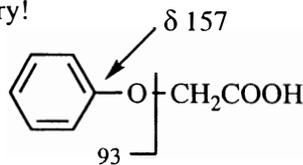
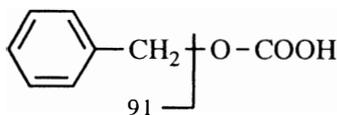
CH₂
 m/z 14

COOH
 m/z 45 and from IR

This appears deceptively simple. The problem is that the mass of these fragments adds to 136, not 152—we are missing 16 mass units \Rightarrow oxygen! Where can the oxygen be? There are only two possibilities:



How can we differentiate? Mass spectrometry!



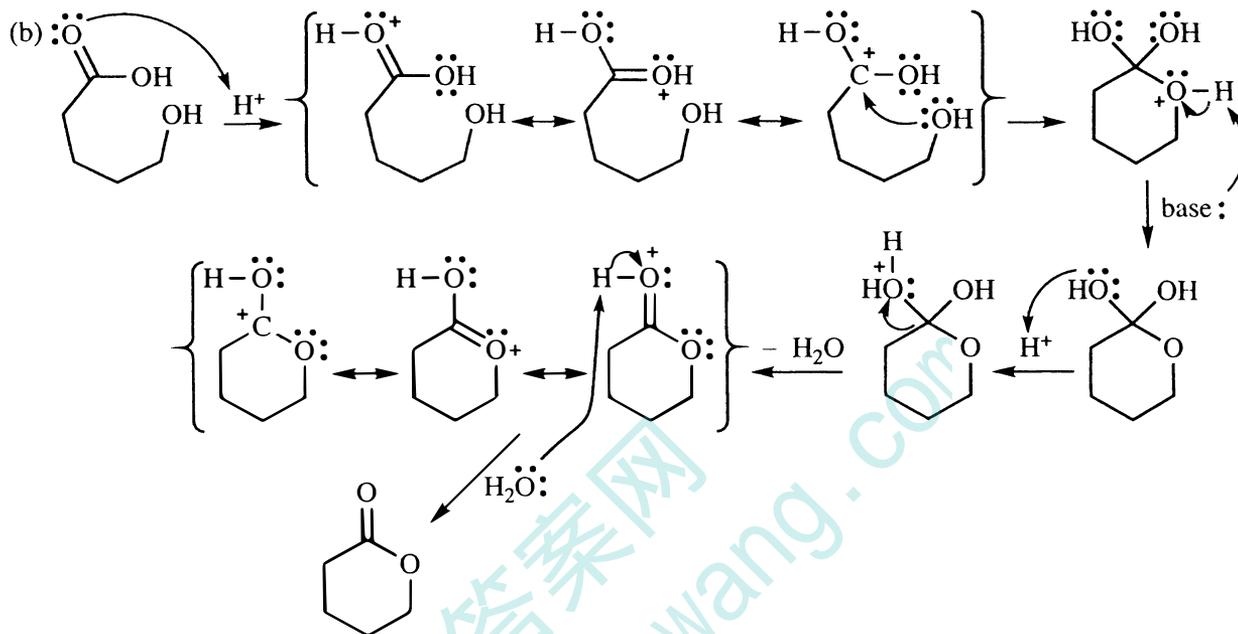
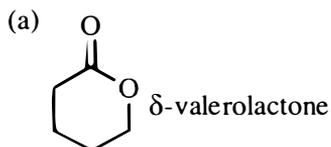
phenoxyacetic acid

This structure is consistent with the peak at δ 157 in the carbon NMR.

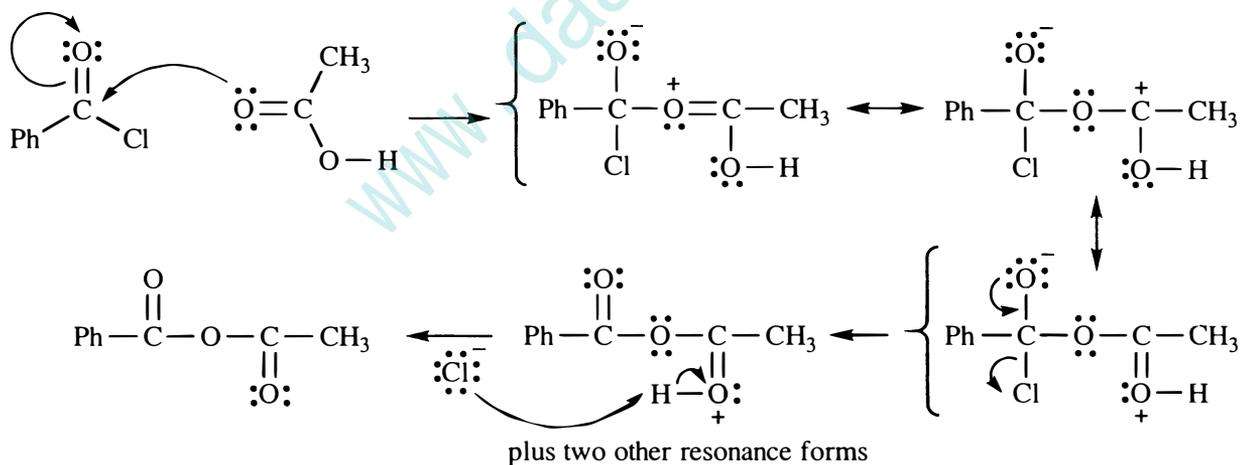
The m/z 93 peak in the MS confirms the structure is **phenoxyacetic acid**. The CH₂ is so far downfield in the NMR because it is between two electron-withdrawing groups, the O and the COOH.

(c) The COOH proton is missing from the proton NMR. Either it is beyond 10 and the NMR was not scanned (unlikely), or the peak was broadened beyond detection because of hydrogen bonding with DMSO.

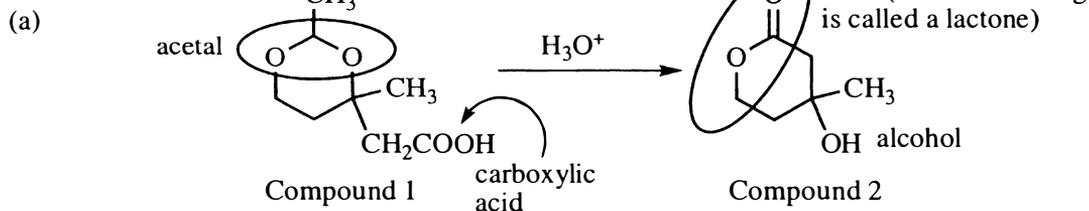
20-41



20-42



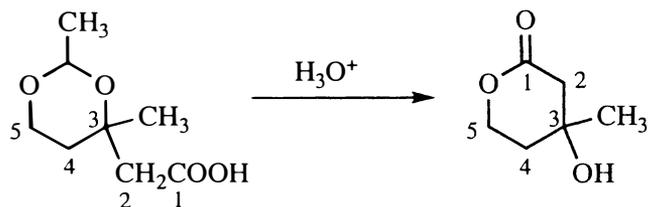
20-43



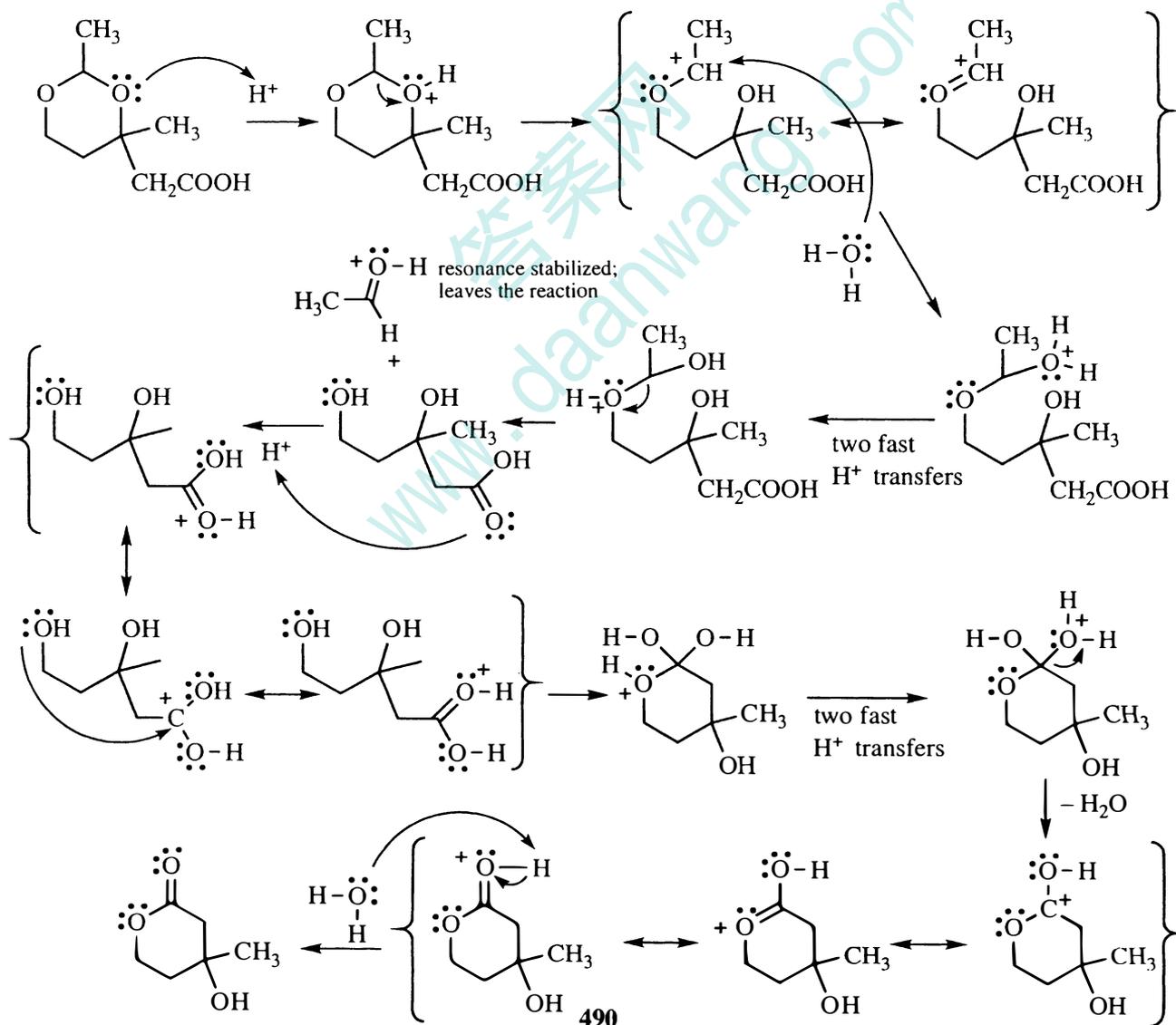
20-43 continued

(b) Compound 1 has 8 carbons, and Compound 2 has 6 carbons. Two carbons have been lost: the two carbons of the acetal have been cleaved. (This is the best way to figure out reactions and mechanisms: find out which atoms of the reactant have become which atoms of the product, then determine what bonds have been broken and formed.)

(c) Acetals are stable to base, so the acetal must have been cleaved when acid was added.



(d) The carbons have been numbered above to help you visualize which atoms in the reactant become which atoms in the product. The overall process requires cleavage of the acetal to expose two alcohols. The 3° alcohol at carbon-3 can be found in the product, so it is the primary alcohol at carbon-5 that reacts with the carboxylic acid to form the lactone.



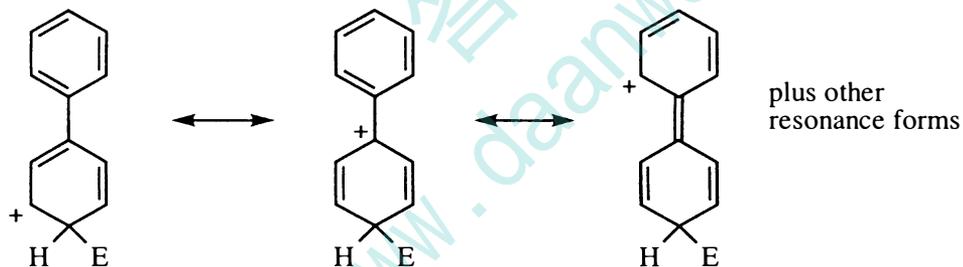
20-44 (A more complete discussion of acidity and electronic effects can be found in Appendix 2.) A few words about the two types of electronic effects: induction and resonance. Inductive effects are a result of polarized σ bonds, usually because of electronegative atom substituents. Resonance effects work through π systems, requiring overlap of p orbitals to delocalize electrons.

All substituents have an inductive effect compared to hydrogen (the reference). Many groups also have a resonance effect; all that is required to have a resonance effect is that the atom or group have at least one p orbital for overlap.

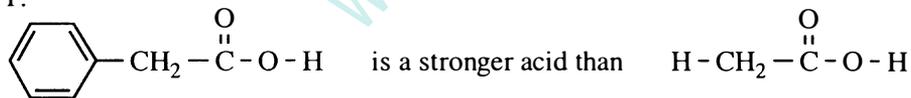
The most interesting groups have both inductive and resonance effects. In such groups, how can we tell the direction of electron movement, that is, whether a group is electron-donating or electron-withdrawing? And do the resonance and inductive effects reinforce or conflict with each other? We can never "turn off" an inductive effect from a resonance effect; that is, any time a substituent is expressing its resonance effect, it is also expressing its inductive effect. We can minimize a group's inductive effect by moving it farther away; inductive effects decrease with distance. The other side of the coin is more accessible to the experimenter: we can "turn off" a resonance effect in order to isolate an inductive effect. We can do this by interrupting a conjugated π system by inserting an sp^3 -hybridized atom, or by making resonance overlap impossible for steric reasons (steric inhibition of resonance).

These three problems are examples of separating inductive effects from resonance effects.

(a) and (b) In electrophilic aromatic substitution, the phenyl substituent is an ortho,para-director because it can stabilize the intermediate from electrophilic attack at the ortho and para positions. The phenyl substituent is electron-donating by resonance.



BUT:

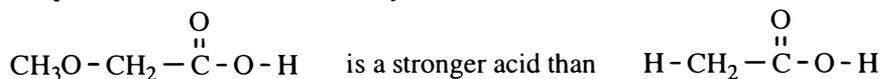


The greater acidity of phenylacetic acid shows that the phenyl substituent is electron-withdrawing, thereby stabilizing the product carboxylate's negative charge. Does this contradict what was said above? Yes and no. What is different is that, since there is no p-orbital overlap between the phenyl group and the carboxyl group because of the CH_2 group in between, the increased acidity must be from a pure *inductive effect*. This structure isolates the inductive effect (which can't be "turned off") from the resonance effect of the phenyl group.

We can conclude three things: (1) phenyl is electron-withdrawing by induction; (2) phenyl is (in this case) electron-donating by resonance; (3) for phenyl, the resonance effect is stronger than the inductive effect (since it is an ortho,para-director).

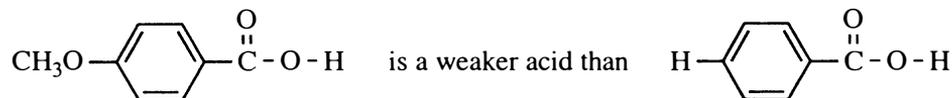
20-44 continued

(c) The simpler case first—induction only:

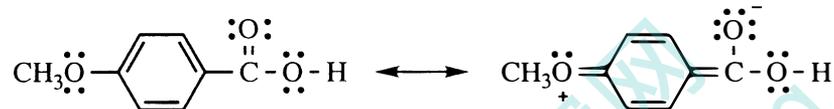


There is no resonance overlap between the methoxy group and the carboxyl group, so this is a pure inductive effect. The methoxy substituent increases the acidity, so methoxy must be electron-withdrawing by induction. This should come as no surprise as oxygen is the second most electronegative element.

The anomaly comes in the decreased acidity of 4-methoxybenzoic acid:

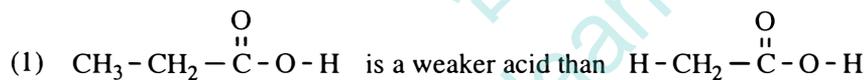


Through resonance, a pair of electrons from the methoxy oxygen can be donated through the benzene ring to the carboxyl group—a stabilizing effect. However, this electron donation *destabilizes* the carboxylate anion as there is already a negative charge on the carboxyl group; the resonance donation intensifies the negative charge. Since the product of the equilibrium would be destabilized relative to the starting material, the proton donation would be less favorable, which we define as a weaker acid.

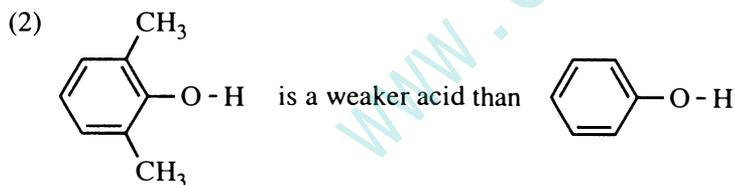


Methoxy is another example of a group which is electron-withdrawing by induction but electron-donating by resonance.

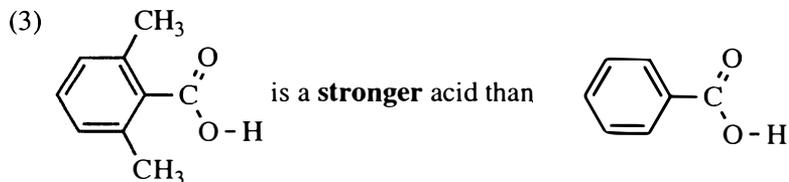
(d) This problem gives three pieces of data to interpret:



Interpretation: the methyl group is electron-donating by induction.



Interpretation: the methyl group is electron-donating by induction. This interpretation is consistent with (1), as expected, since methyl cannot have any resonance effect.

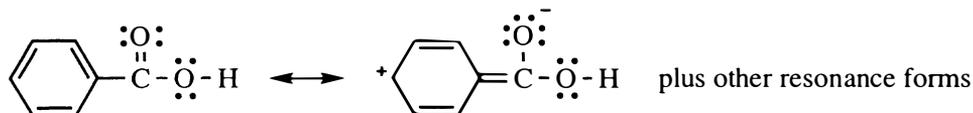


Interpretation: this is the anomaly. Contradictory to the data in (1) and (2), by putting on two methyl groups, the substituent seems to have become electron-withdrawing instead of electron-donating. How?

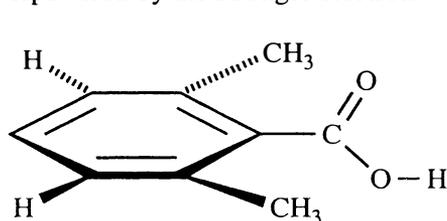
Quick! Turn the page!

20-44 continued

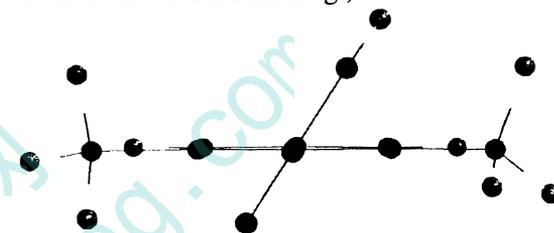
Steric inhibition of resonance! In benzoic acid, the phenyl ring and the carboxyl group are all in the same plane, and benzene is able to donate electrons by resonance overlap through parallel p orbitals. This stabilizes the starting acid (and destabilizes the carboxylate anion) and makes the acid weaker than it would be without resonance.



Putting substituents at the 2- and 6-positions prevents the carboxyl or carboxylate from coplanarity with the ring. Resonance is interrupted, and now the carboxyl group sees a phenyl substituent which cannot stabilize the acid through resonance; the stabilization of the acid is lost. At the same time, the *electron-withdrawing inductive effect* of the benzene ring stabilizes the carboxylate anion. These two effects work together to make this acid unusually strong. (Apparently, the slight electron-donating inductive effect of the methyls is overpowered by the stronger electron-withdrawing inductive effect of the benzene ring.)



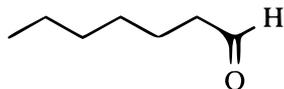
COOH group is perpendicular to the plane of the benzene ring—no resonance interaction.



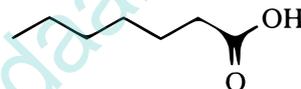
this three-dimensional view down the C-C bond between the COOH and the benzene ring shows that COOH is twisted out of the benzene plane

20-45

(a)



stock bottle

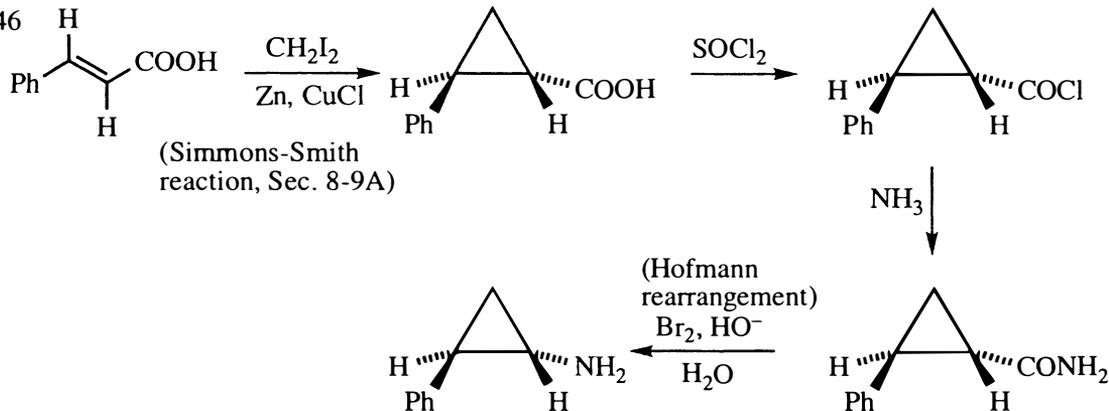


students' samples

(b) The spectrum of the students' samples shows the carboxylic acid present. Contact with oxygen from the air oxidized the sensitive aldehyde group to the acid.

(c) Storing the aldehyde in an inert atmosphere like nitrogen or argon prevents oxidation. Freshly prepared unknowns will avoid the problem.

20-46



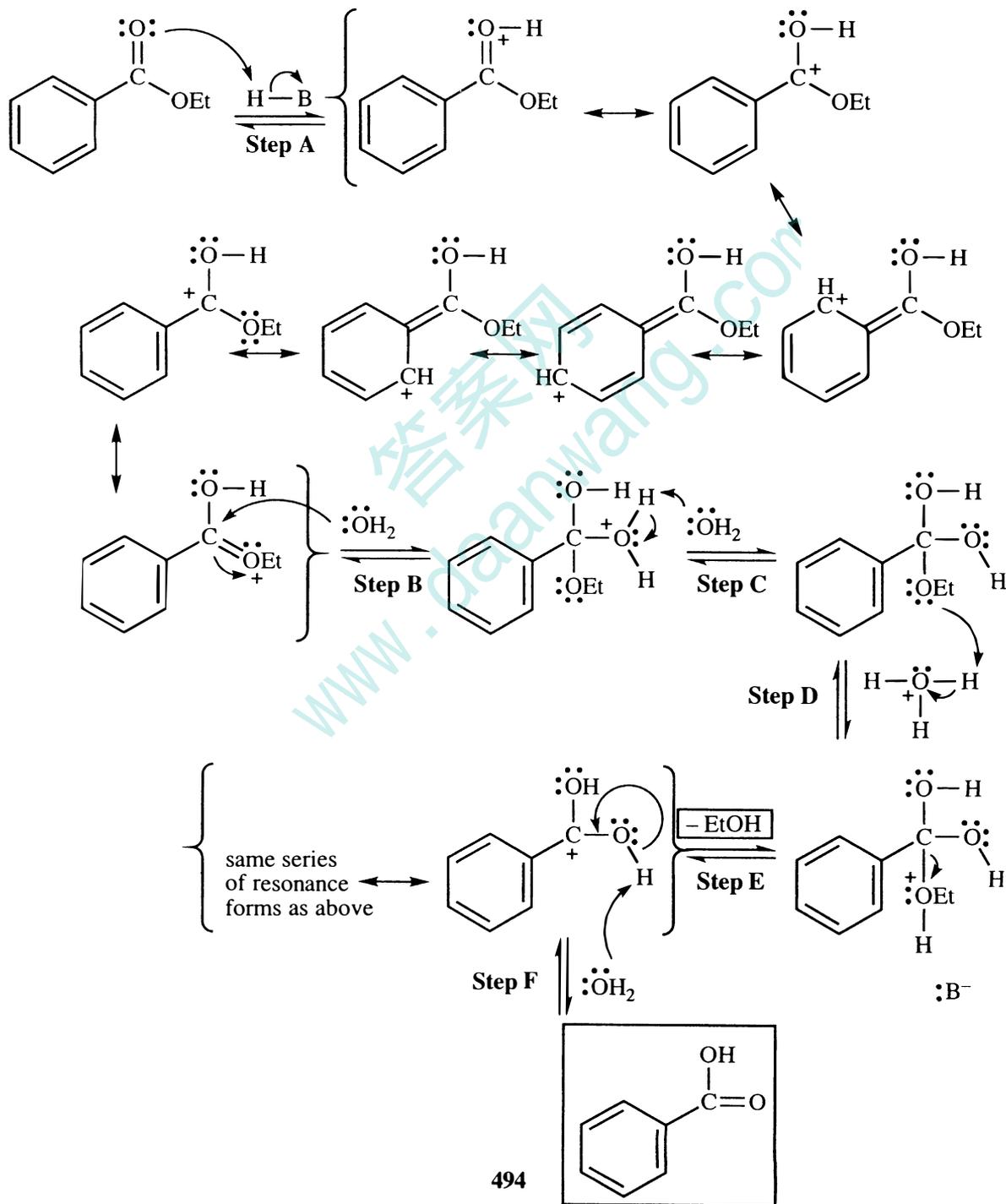
20-47 Products are boxed.

(a) All steps are reversible in an acid-catalyzed ester hydrolysis. (abbreviating OCH_2CH_3 as OEt)

- Step A** proton on (resonance stabilization)
Step B nucleophile attacks
Step C proton off
Step D proton on
Step E leaving group leaves (resonance stabilization)
Step F proton off

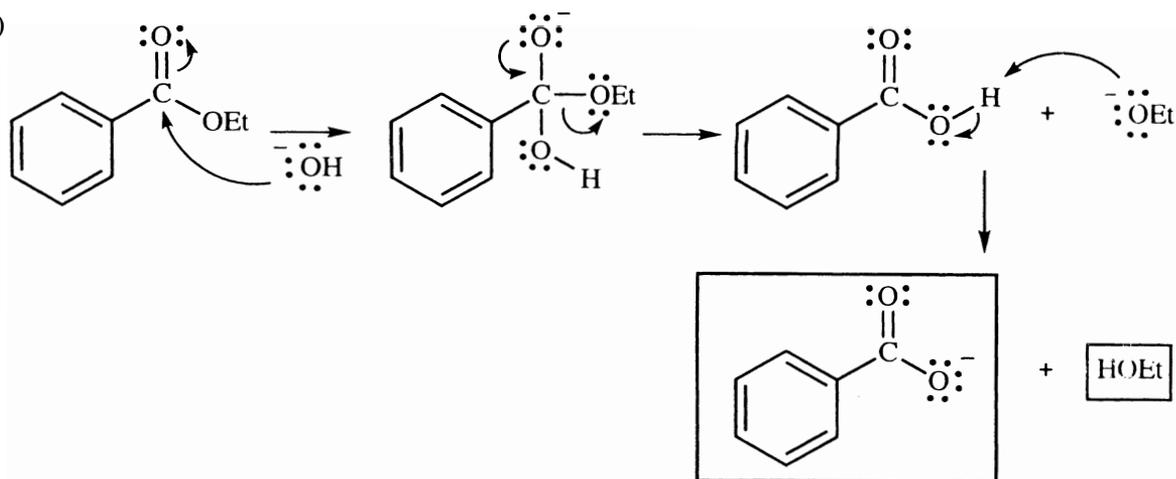
$\text{H}-\text{B}$ is the acid catalyst

$:\text{B}^-$ is the conjugate base, although in hydrolysis reactions, water usually removes H^+

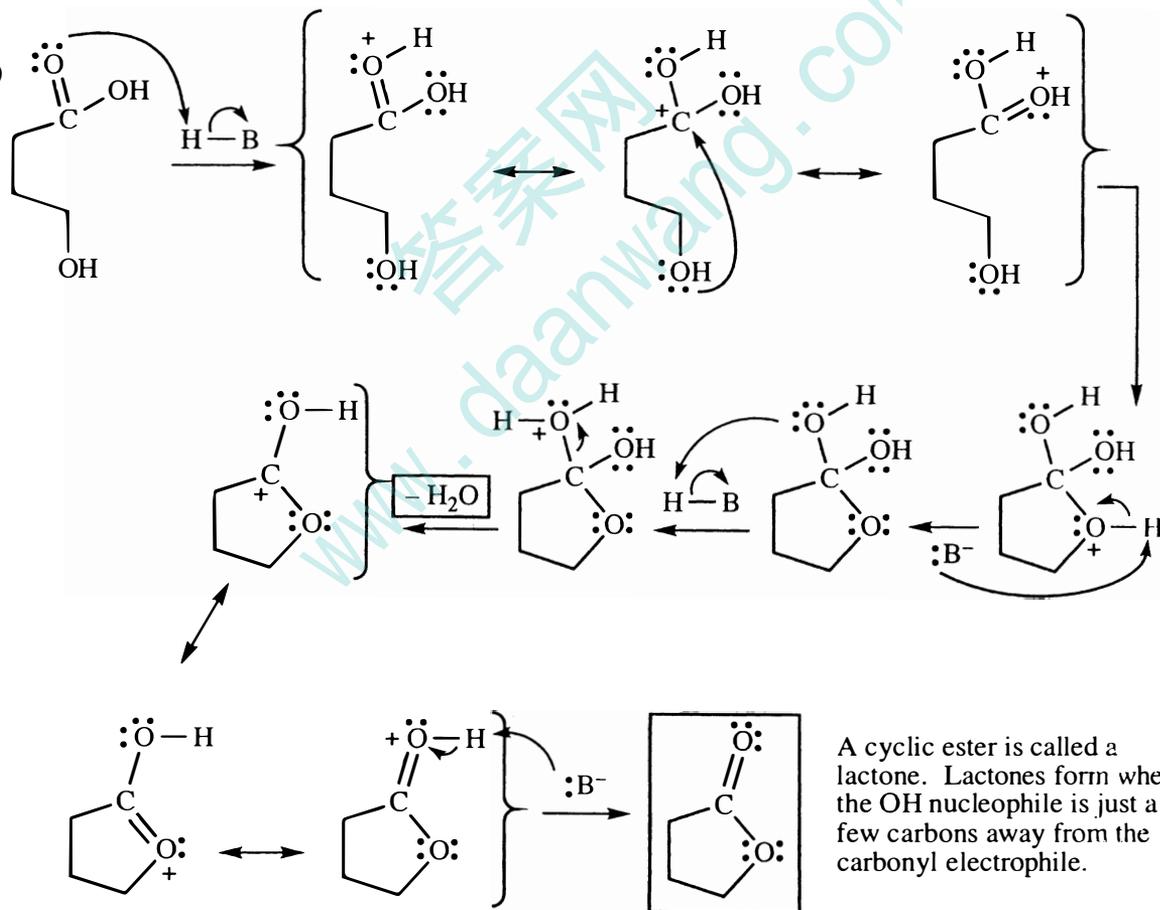


20-47 continued

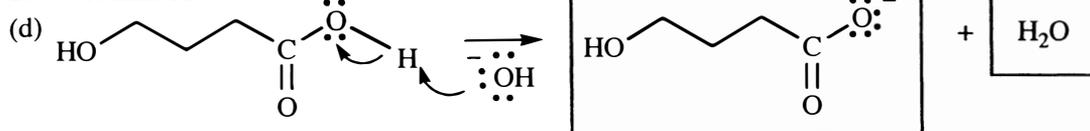
(b)



(c)



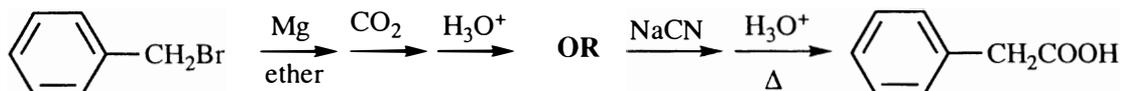
20-47 continued



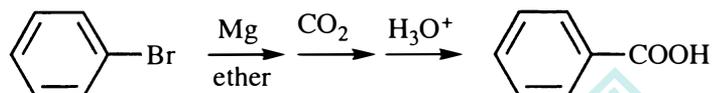
Esters can be formed only in acid, not in base.

20-48 Cyanide substitution is an S_N2 reaction and requires a 1° or 2° carbon with a leaving group. The Grignard reaction is less particular about the type of halide, but is sensitive to, and incompatible with, acidic functional groups and other reactive groups.

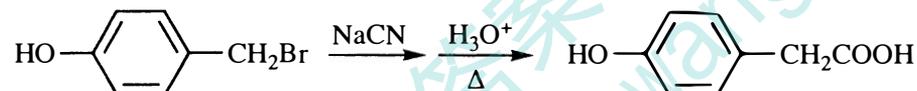
(a) Both methods will work.



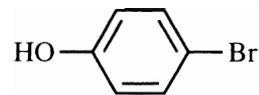
(b) Only Grignard will work. The S_N2 reaction does not work on unactivated benzene rings.



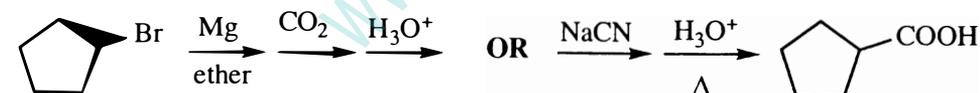
(c) Grignard will fail because of the OH group. The cyanide reaction will work, although an excess of cyanide will need to be added because the first equivalent will deprotonate the phenol.*



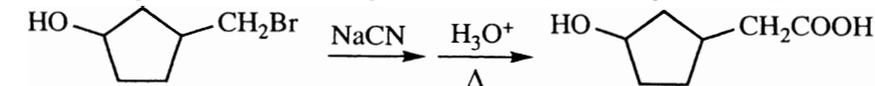
(d) Grignard will fail because of the OH group. The cyanide reaction will fail because S_N2 does not work on unactivated sp^2 carbons. In this case, NEITHER method will work.



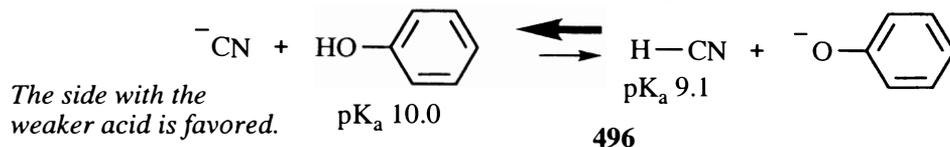
(e) Both methods will work, although cyanide substitution on 2° C will be accompanied by elimination.



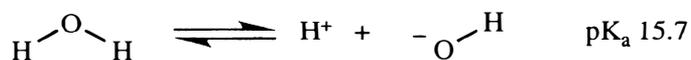
(f) Grignard will fail because of the OH group. The cyanide reaction will work. Since alcohols are much less acidic than phenols, there is no problem with cyanide deprotonating the alcohol.*



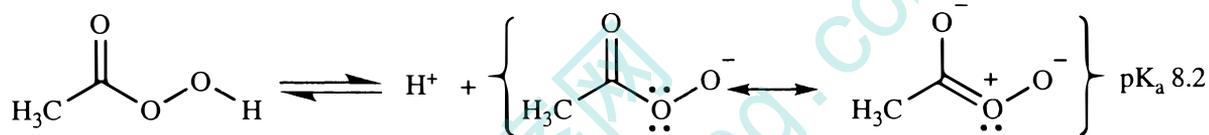
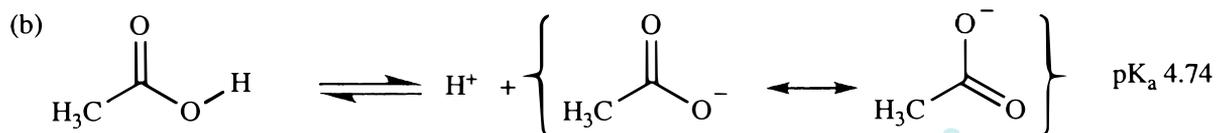
* The pK_a of HCN is 9.1, and the pK_a of phenol is 10.0. Thus cyanide is strong enough to pull off some of the H from the phenol, although the equilibrium would favor cyanide ion and phenol. The pK_a of secondary alcohols is 16-18, so there is no chance that cyanide would deprotonate an alcohol.



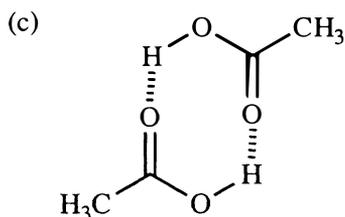
20-49



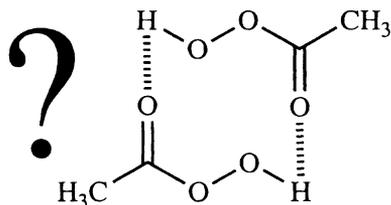
Hydrogen peroxide is four pK units (10^4 times) stronger acid than water, so the hydroperoxide anion, HOO^- , must be stabilized relative to hydroxide. This is from the *inductive effect* of the electronegative oxygen bonded to the O^- ; by induction, the negative charge is distributed over both oxygens. The oxygen in hydroxide has to support the full negative charge with no delocalization.



The reason that carboxylic acids are so acidic (over 10 pK units more acidic than alcohols) is because of the resonance stabilization of the carboxylate anion with two equivalent resonance forms in which all atoms have octets and the negative charge is on the more electronegative atom—the best of all possible resonance worlds. The peroxyacetate anion, however, cannot delocalize the negative charge onto the carbonyl oxygen; that negative charge is stuck out on the end oxygen like a wet nose on a frigid morning. There is some delocalization of the electron density onto the carbonyl, but with all the charge separation, this second form is a minor resonance contributor. This resonance does explain, however, why peroxyacetic acid is more acidic than hydrogen peroxide. It does not come close to acetic acid, though.



Carboxylic acids boil as the dimer, that is, two molecules are held tightly by hydrogen bonding. The dimer is an 8-membered ring with two hydrogen bonds as shown with dashed lines in the diagram. This works because the carbonyl oxygen has significant negative charge, and the $\text{H}-\text{O}$ bond is weak because it is a relatively strong acid. The b.p. is 118°C .



Do peroxyacids boil as the dimer? The author does not know, but there are three reasons to suspect that they do not. First, the b.p. is lower (105°C) instead of higher suggesting that they do not boil as a team but rather individually. Second, the dimer shown is a 10-membered ring—still possible but less likely than 8-membered. Third and most important, the electronic nature of the carbonyl group, as implied in the resonance forms in part (b), places less negative charge on the carbonyl oxygen, and the H is less acidic, suggesting that the hydrogen bonding is much less strong.

20-50

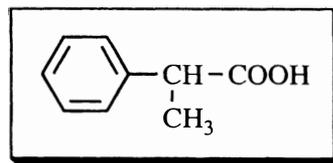
Spectrum A: $C_9H_{10}O_2 \Rightarrow$ 5 elements of unsaturation

δ 11.8, 1H \Rightarrow COOH

δ 7.3, 5H \Rightarrow monosubstituted benzene ring

δ 3.8, 1H quartet \Rightarrow CHCH₃

δ 1.6, 3H doublet \Rightarrow CHCH₃



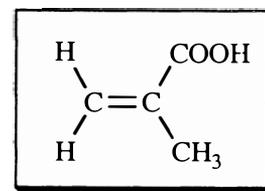
Spectrum B: $C_4H_6O_2 \Rightarrow$ 2 elements of unsaturation

δ 12.1, 1H \Rightarrow COOH

δ 6.2, 1H singlet \Rightarrow H-C=C

δ 5.7, 1H singlet \Rightarrow H-C=C

δ 1.9, 3H singlet \Rightarrow vinyl CH₃ with no H neighbors CH₃-C=C



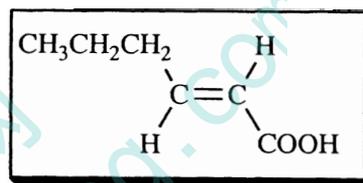
Spectrum C: $C_6H_{10}O_2 \Rightarrow$ 2 elements of unsaturation

δ 12.0, 1H \Rightarrow COOH

δ 7.0, 1H multiplet \Rightarrow H-C=C-COOH

δ 5.7, 1H doublet \Rightarrow C=C-COOH

δ 2.2-0.8 \Rightarrow CH₂CH₂CH₃



must be *trans* due to large coupling constant in doublet at δ 5.7

CHAPTER 21—CARBOXYLIC ACID DERIVATIVES

21-1 IUPAC name first; then common name

- (a) isobutyl benzoate (both IUPAC and common)
- (b) phenyl methanoate; phenyl formate
- (c) methyl 2-phenylpropanoate; methyl α -phenylpropionate
- (d) *N*-phenyl-3-methylbutanamide; β -methylbutyranilide
- (e) *N*-benzylethanamide; *N*-benzylacetamide
- (f) 3-hydroxybutanenitrile; β -hydroxybutyronitrile
- (g) 3-methylbutanoyl bromide; isovaleryl bromide
- (h) dichloroethanoyl chloride; dichloroacetyl chloride
- (i) 2-methylpropanoic methanoic anhydride; isobutyric formic anhydride
- (j) cyclopentyl cyclobutanecarboxylate (both IUPAC and common)
- (k) 5-hydroxyhexanoic acid lactone; δ -caprolactone
- (l) *N*-cyclopentylbenzamide (both IUPAC and common)
- (m) propanedioic anhydride; malonic anhydride
- (n) 1-hydroxycyclopentanecarbonitrile; cyclopentanone cyanohydrin
- (o) *cis*-4-cyanocyclohexanecarboxylic acid; no common name
- (p) 3-bromobenzoyl chloride; *m*-bromobenzoyl chloride
- (q) *N*-methyl-5-aminoheptanoic acid lactam; no common name
- (r) *N*-ethanoylpiperidine; *N*-acetylpiperidine

21-2 An aldehyde has a C—H absorption (usually 2 peaks) at 2700-2800 cm^{-1} . A carboxylic acid has a strong, broad absorption between 2400-3400 cm^{-1} . The spectrum of methyl benzoate has no peaks in this region.

21-3 The C—O single bond stretch in ethyl octanoate appears at 1170 cm^{-1} , while methyl benzoate shows this absorption at 1120 and 1280 cm^{-1} .

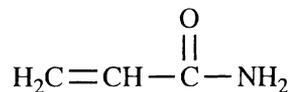
21-4

- (a) acid chloride: single C=O peak at 1800 cm^{-1} ; no other carbonyl comes so high
- (b) primary amide: C=O at 1650 cm^{-1} and two N—H peaks between 3200-3400 cm^{-1}
- (c) anhydride: two C=O absorptions at 1750 and 1820 cm^{-1}

21-5

(a) The formula $\text{C}_3\text{H}_5\text{NO}$ has two elements of unsaturation. The IR spectrum shows two peaks between 3200-3400 cm^{-1} , an NH_2 group. The strong peak at 1670 cm^{-1} is a C=O, and the peak at 1610 cm^{-1} is a C=C. This accounts for all of the atoms.

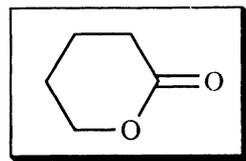
The ^1H NMR corroborates the assignment. The 1H multiplet at δ 5.8 is the vinyl H next to the carbonyl. The 2H multiplet at δ 6.3 is the vinyl hydrogen pair on carbon-3. The 2H singlet at δ 4.8 is the amide hydrogens.



The ^{13}C NMR confirms the structure: two vinyl carbons and a carbonyl.

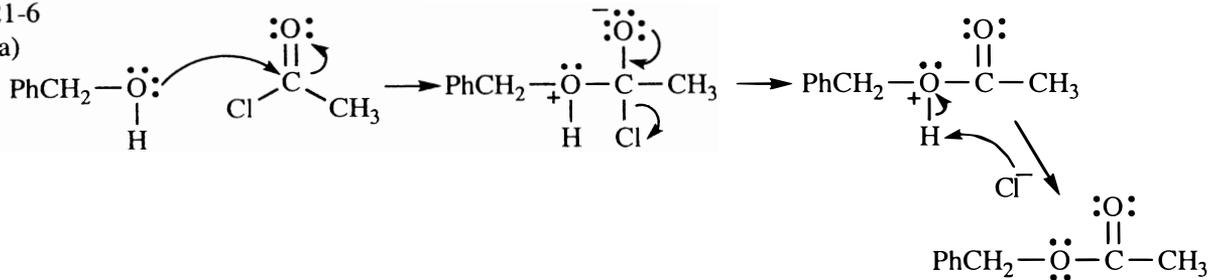
(b) The formula $\text{C}_5\text{H}_8\text{O}_2$ has two elements of unsaturation. The IR spectrum shows no significant OH, so this compound is neither an alcohol nor a carboxylic acid. The strong peak at 1730 cm^{-1} is likely an ester carbonyl. The C—O appears between 1050-1250 cm^{-1} . The IR shows no C=C absorption, so the other element of unsaturation is likely a ring. The carbon NMR spectrum shows the carbonyl carbon at δ 171, the C—O carbon at δ 69, and three more carbons in the aliphatic region, but no carbons in the vinyl region between δ 100-150, so there can be no C=C. The proton NMR shows multiplets of 2H at δ 4.3 and 2.5, most likely CH_2 groups next to oxygen and carbonyl respectively.

The only structure with an ester, four CH_2 groups, and a ring, is δ -valerolactone:

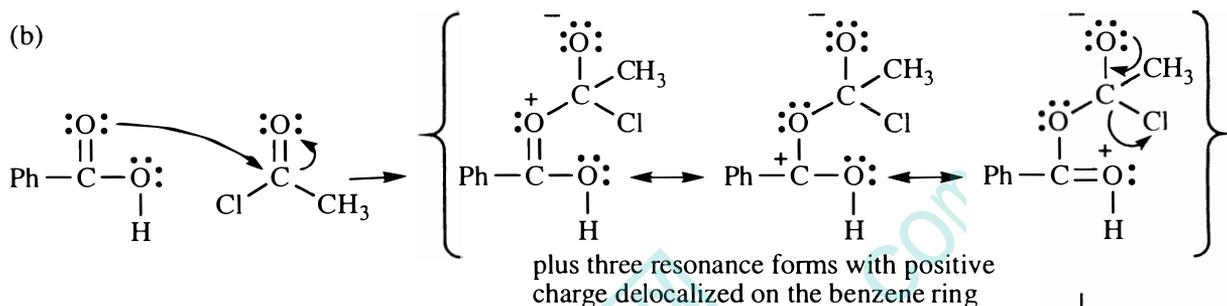


21-6

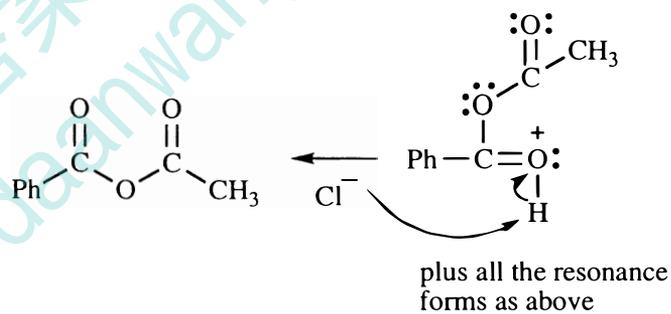
(a)



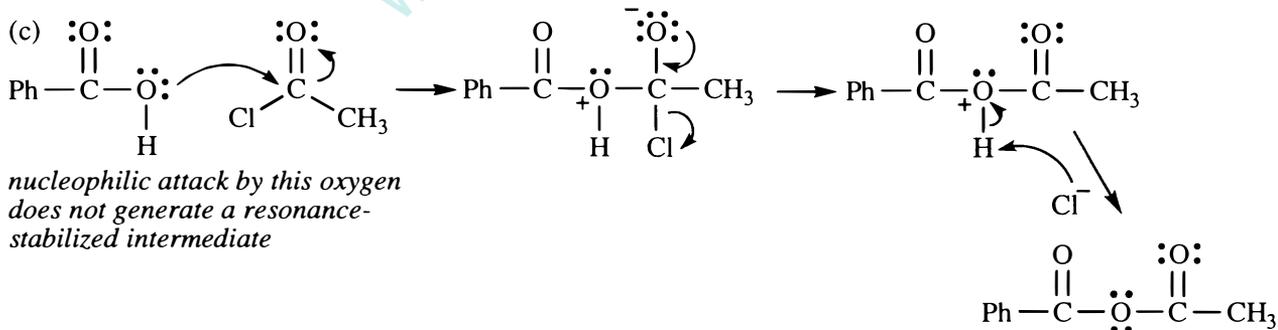
(b)



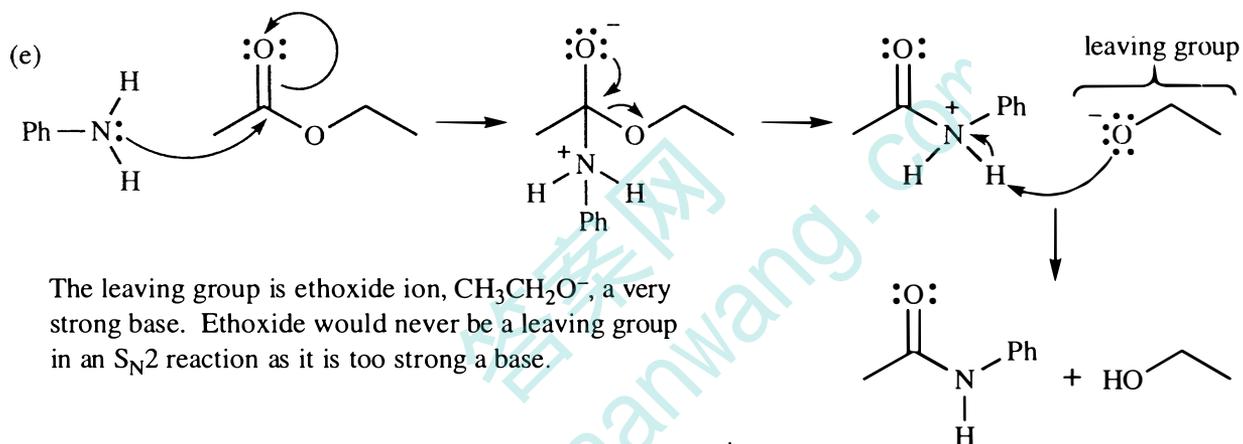
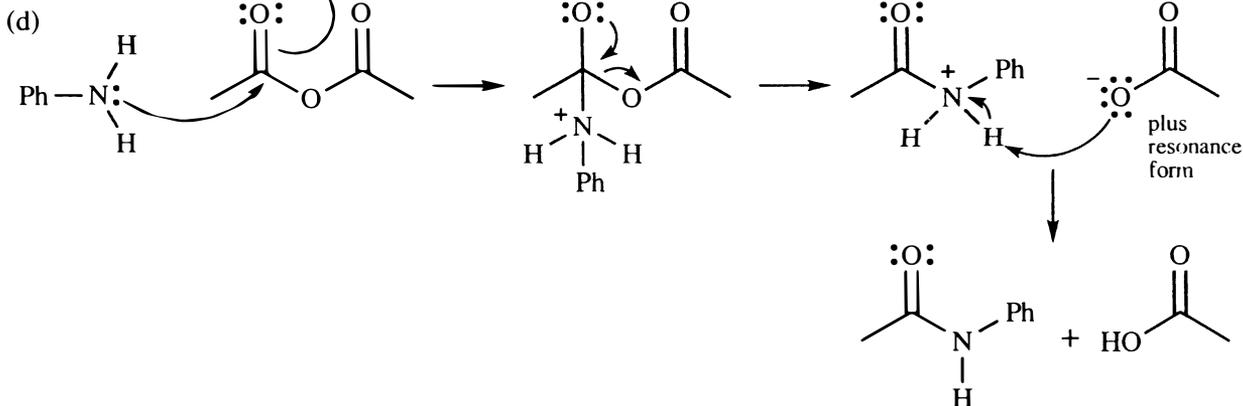
the carbonyl oxygen is more nucleophilic than the single-bonded oxygen because the product is resonance stabilized



(c)



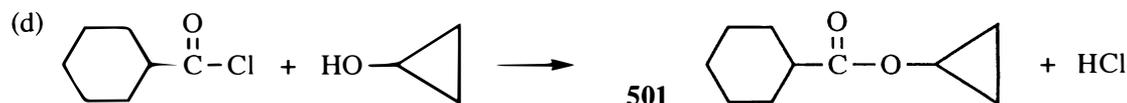
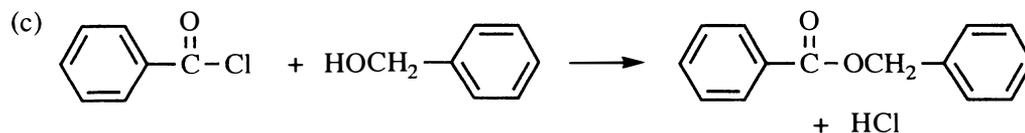
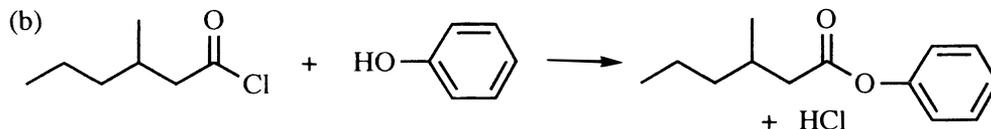
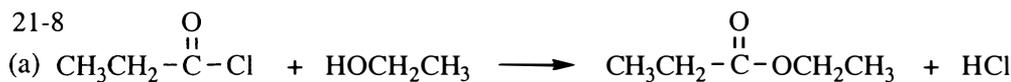
21-6 continued



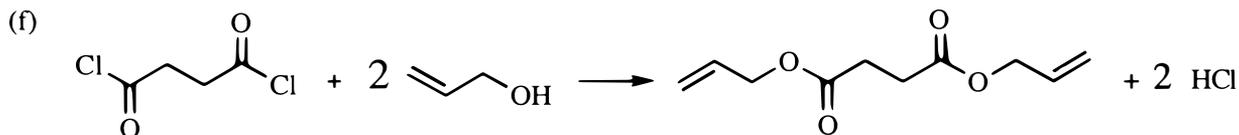
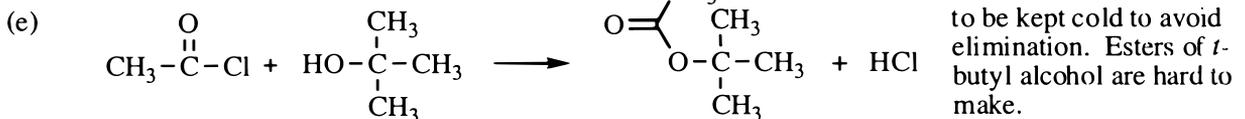
The leaving group is ethoxide ion, $\text{CH}_3\text{CH}_2\text{O}^-$, a very strong base. Ethoxide would never be a leaving group in an $\text{S}_{\text{N}}2$ reaction as it is too strong a base.

21-7 **Figure 21-9 is critical!** Reactions which go from a more reactive functional group to a less reactive functional group ("downhill reactions") will occur readily.

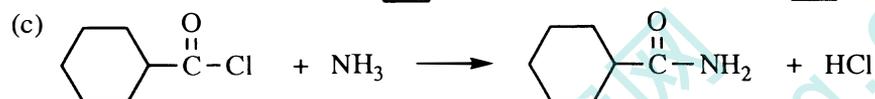
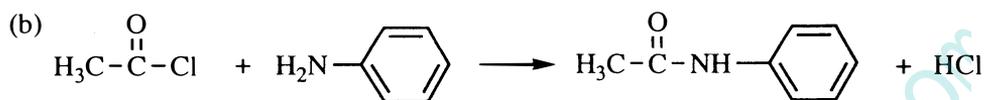
- (a) amide to acid chloride will NOT occur—it is an "uphill" transformation
- (b) acid chloride to amide will occur rapidly
- (c) amide to ester will NOT occur—another "uphill" transformation
- (d) acid chloride to anhydride will occur rapidly
- (e) anhydride to amide will occur rapidly



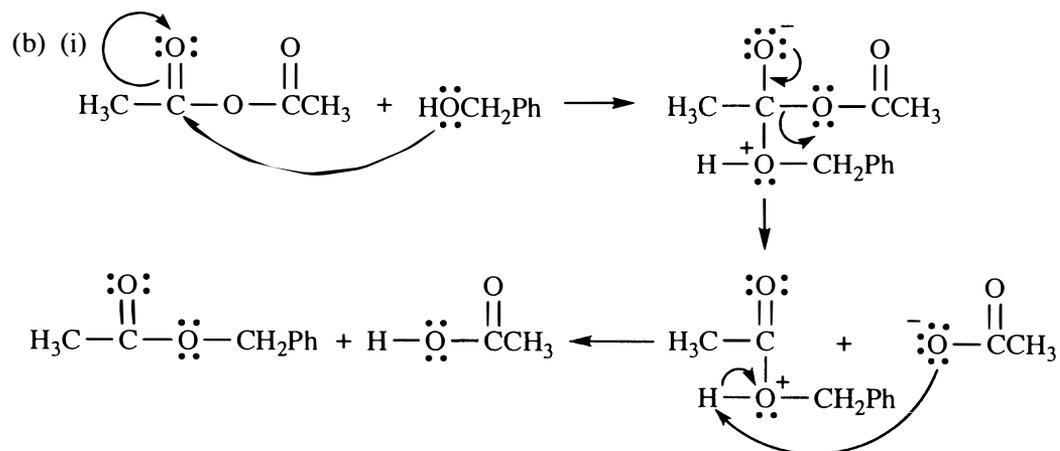
21-8 continued



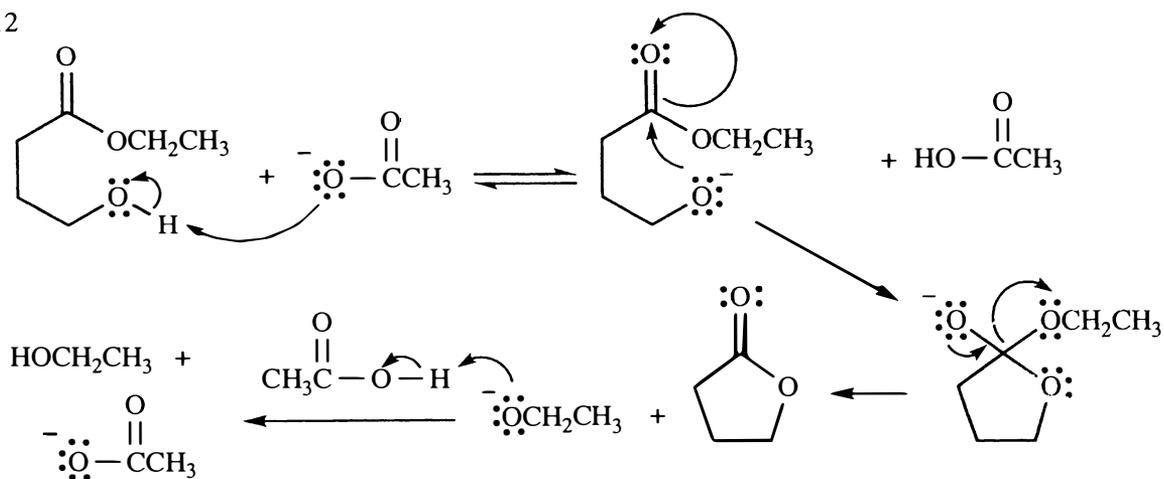
21-9



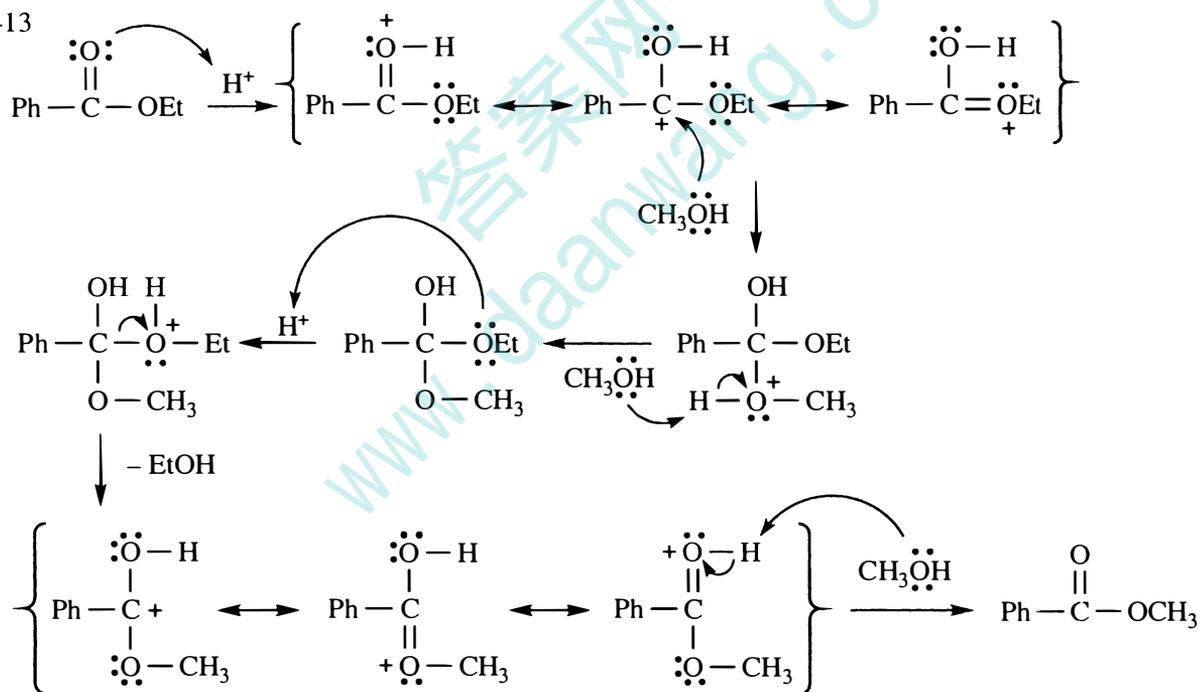
21-10



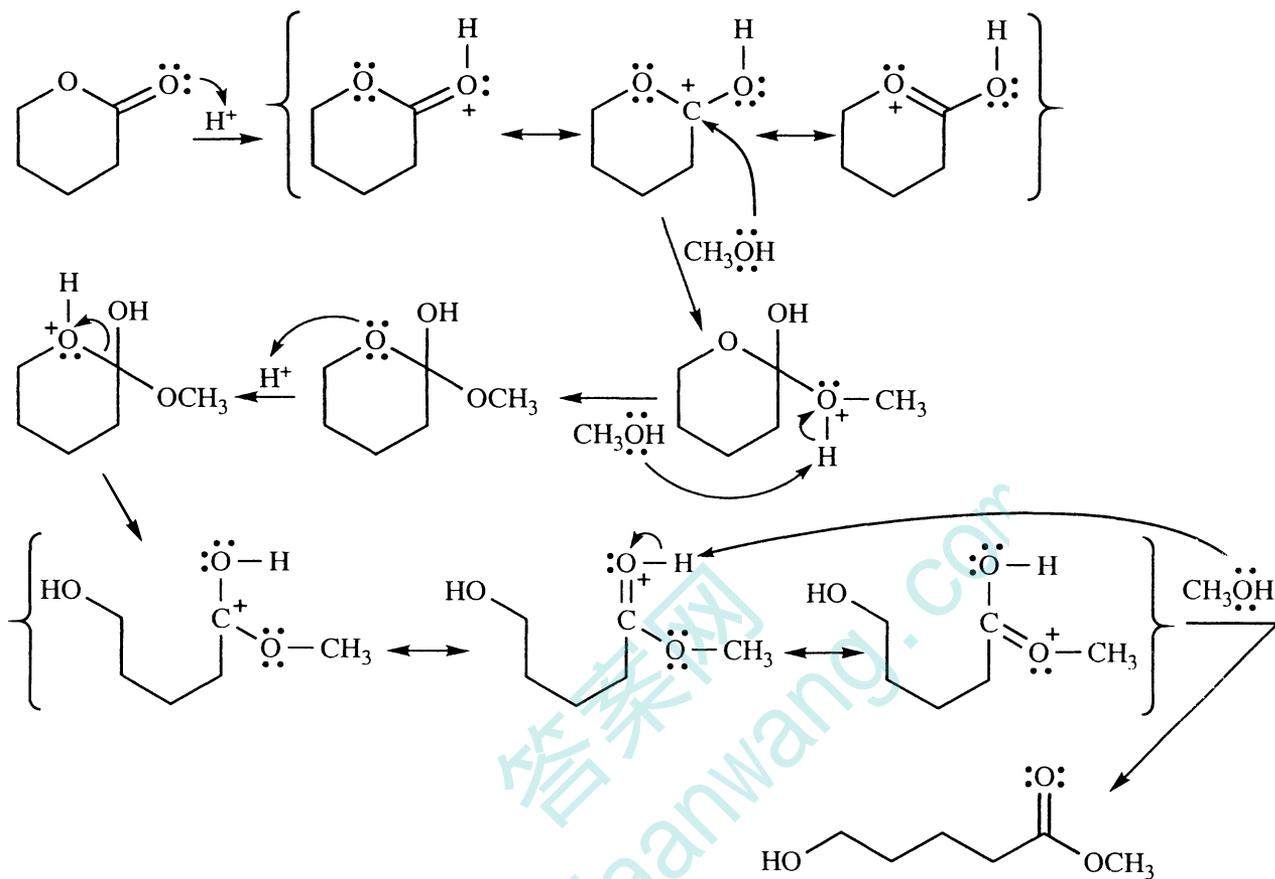
21-12



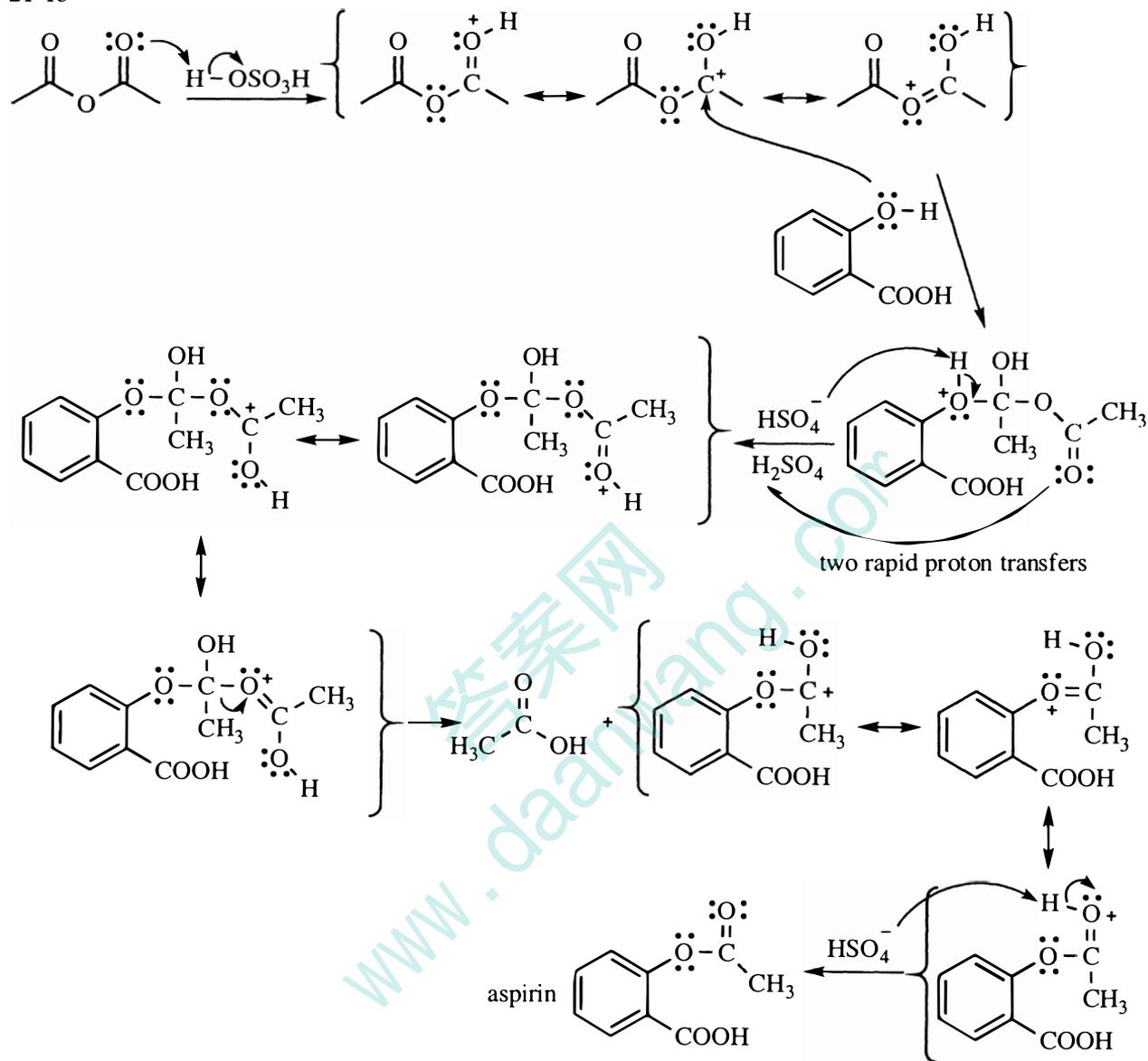
21-13



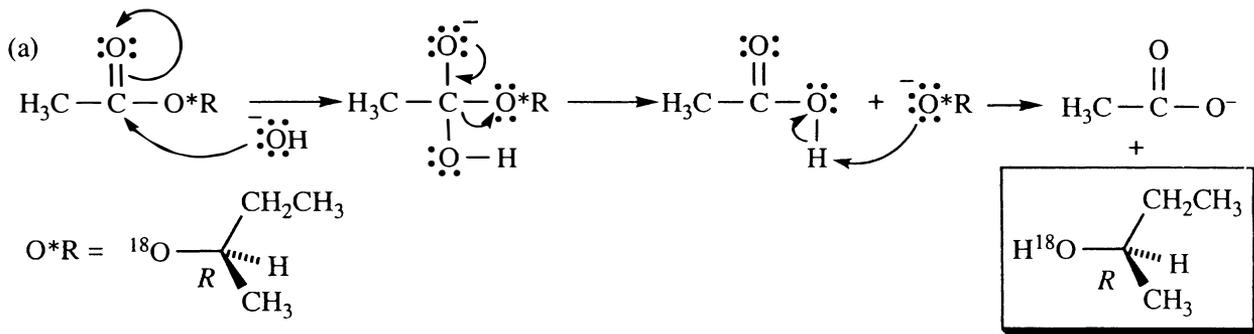
21-14



21-15

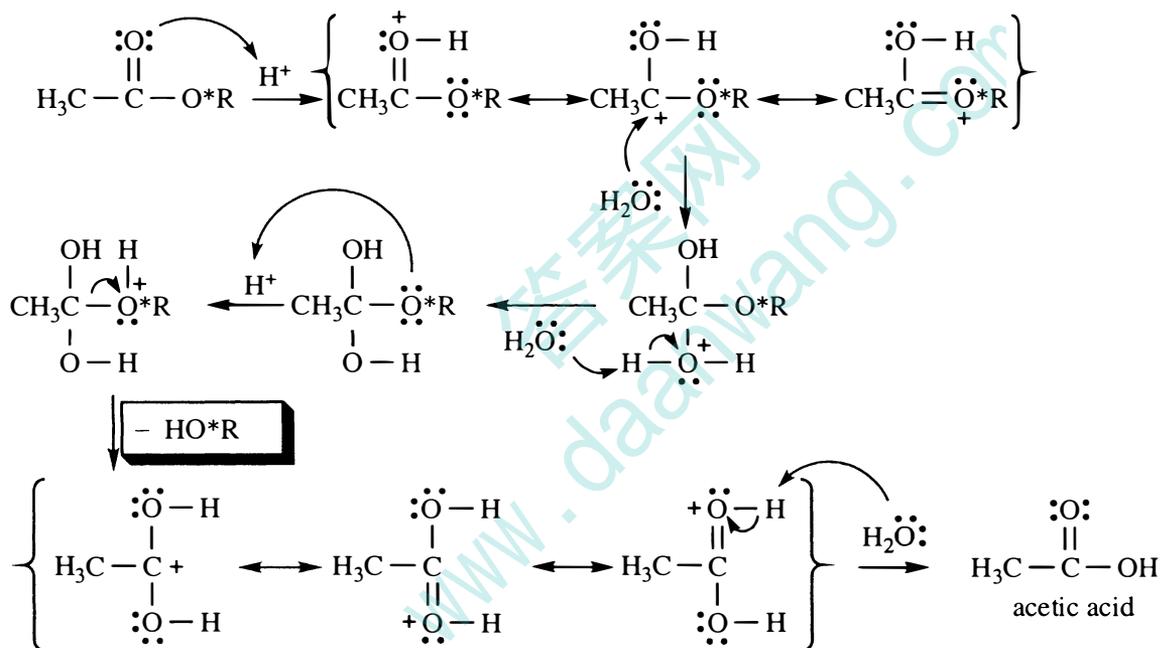


21-16 The asterisk (*) will denote ^{18}O .



The alcohol product contains the ^{18}O label, with none in the carboxylate. The bond between ^{18}O and the tetrahedral carbon with (*R*) configuration did not break, so the configuration is retained.

(b) The products are identical regardless of mechanism.



(c) The ^{18}O has 2 more neutrons in its nucleus than ^{16}O . Mass spectra of these products would show the molecular ion of acetic acid at its standard value of m/z 60, whereas the molecular ion of 2-butanol would appear at m/z 76 instead of m/z 74, proving that the heavy isotope of oxygen went with the alcohol. This demonstrates that the bond between oxygen and the carbonyl carbon is broken, not the bond between the oxygen and the alkyl carbon.

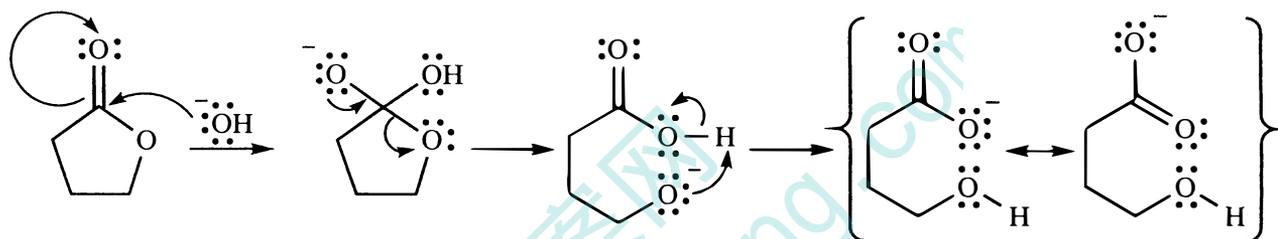
To show if the alcohol was chiral or racemic, measuring its optical activity in a polarimeter and comparing to known values would prove its configuration. (The heavy oxygen isotope has a negligible effect on optical rotation.)

21-17

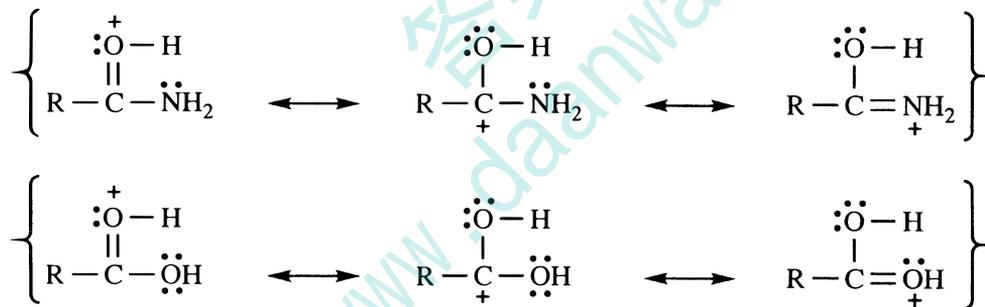
(a) A catalyst is defined as a chemical species that speeds a reaction but is not consumed in the reaction. In the acidic hydrolysis, acid is used in the first and fourth steps of the mechanism but is regenerated in the third and last steps. Acid is not consumed; the final concentration of acid is the same as the initial concentration. In the basic hydrolysis, however, the hydroxide that initially attacks the carbonyl is never regenerated. An alkoxide leaves from the carbonyl, but it quickly neutralizes the carboxylic acid. For every molecule of ester, one molecule of hydroxide is consumed; the base *promotes* the reaction but does not *catalyze* the reaction.

(b) Basic hydrolysis is not reversible. Once an ester molecule is hydrolyzed in base, the carboxylate cannot form an ester. Acid catalysis, however, is an equilibrium: the mixture will always contain some ester, and the yield will never be as high as in basic hydrolysis. Second, long chain fatty acids are not soluble in water until they are ionized; they are soluble only as their sodium salts (soap). Basic hydrolysis is preferred for higher yield and greater solubility of the product.

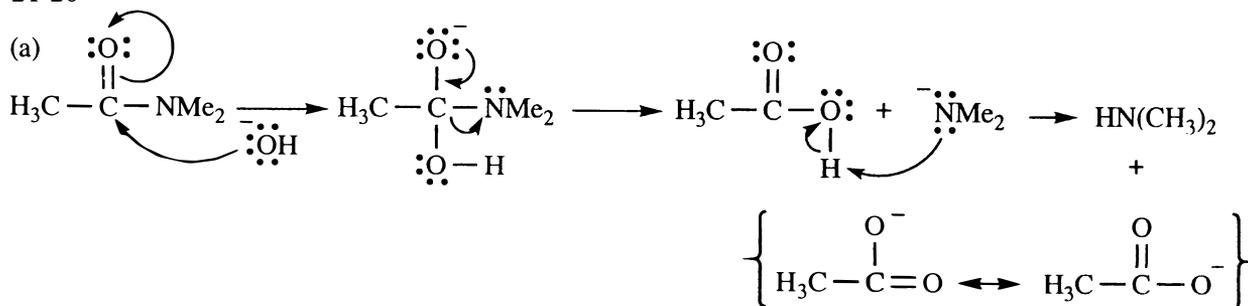
21-18



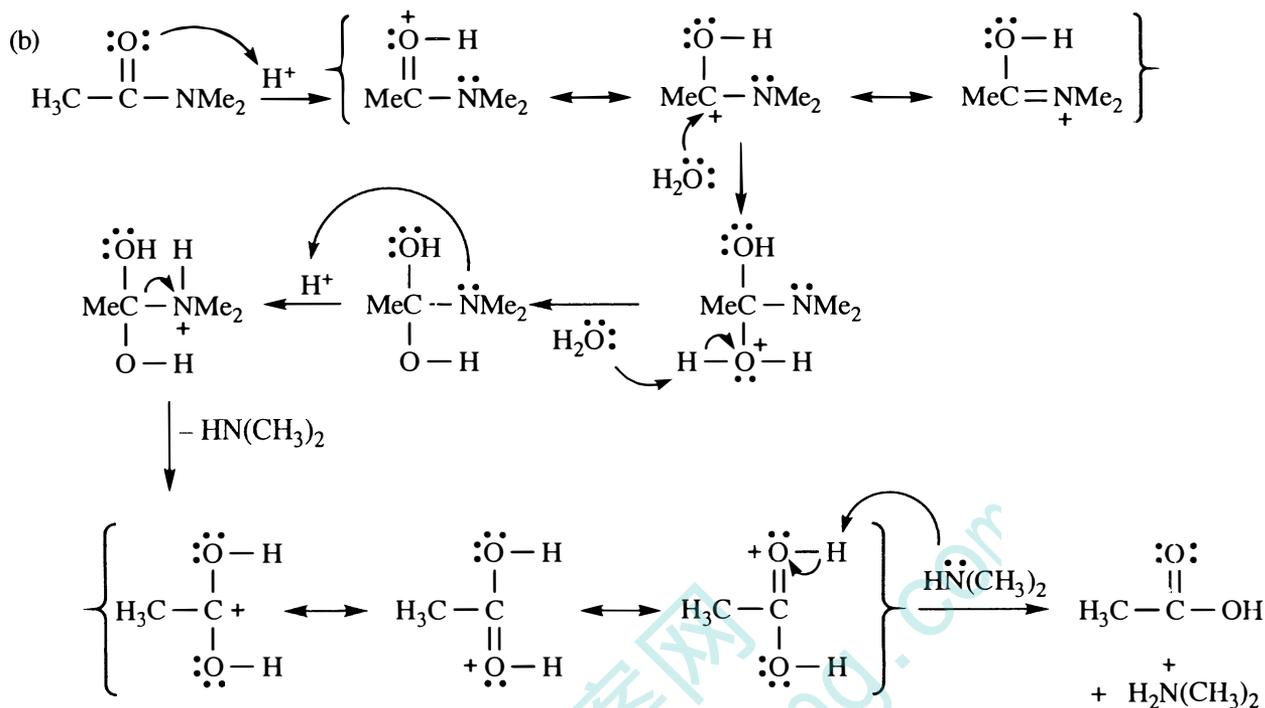
21-19



21-20

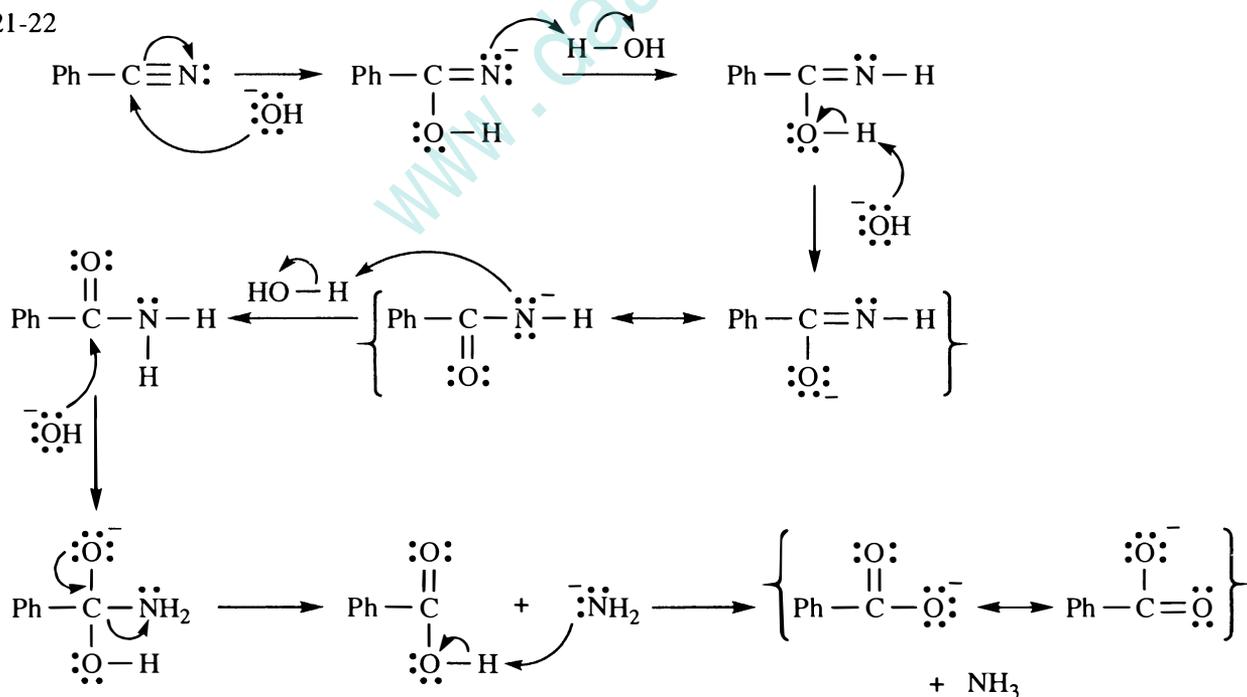


21-20 continued

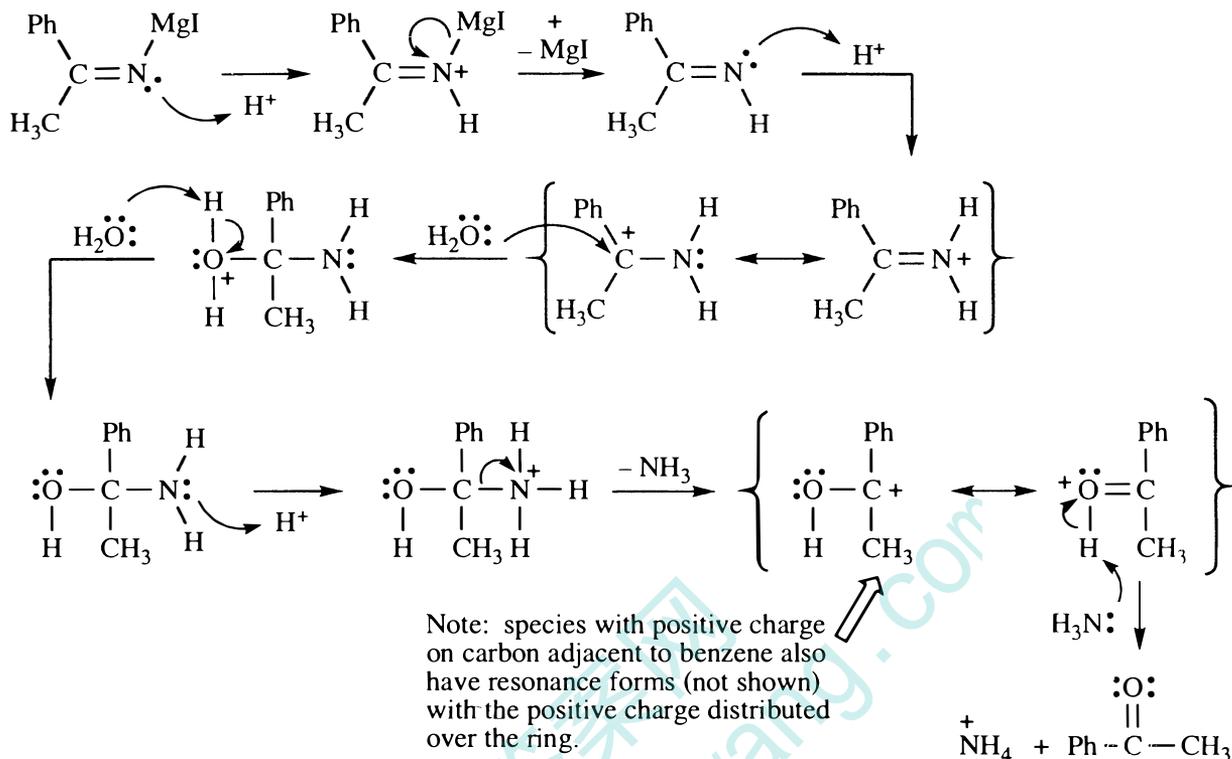


21-21 In the basic hydrolysis (21-20(a)), the step that drives the reaction to completion is the final step, the deprotonation of the carboxylic acid by the amide anion. In the acidic hydrolysis (21-20(b)), protonation of the amine by acid is exothermic and it prevents the reverse reaction by tying up the pair of electrons on the nitrogen so that the amine is no longer nucleophilic.

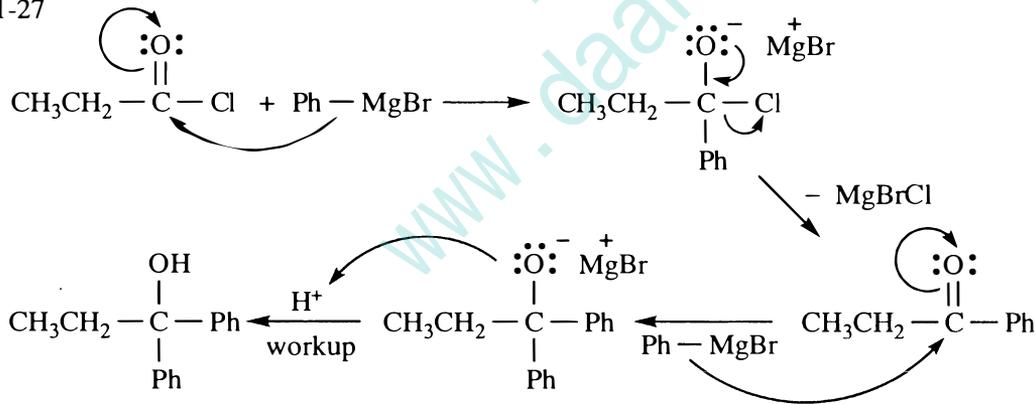
21-22



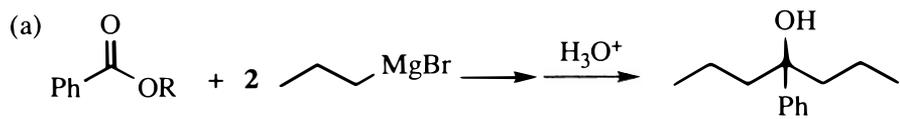
21-26



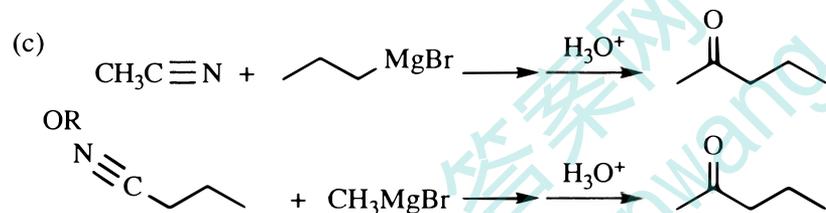
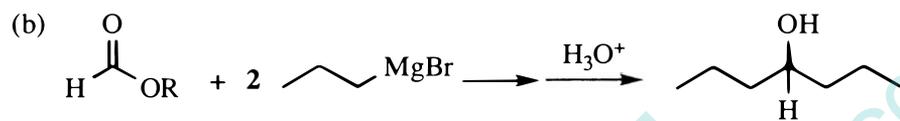
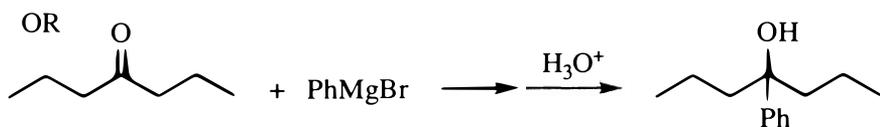
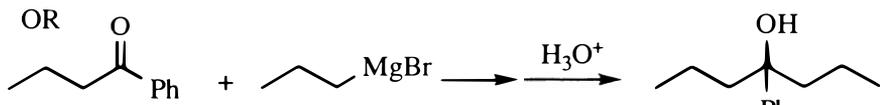
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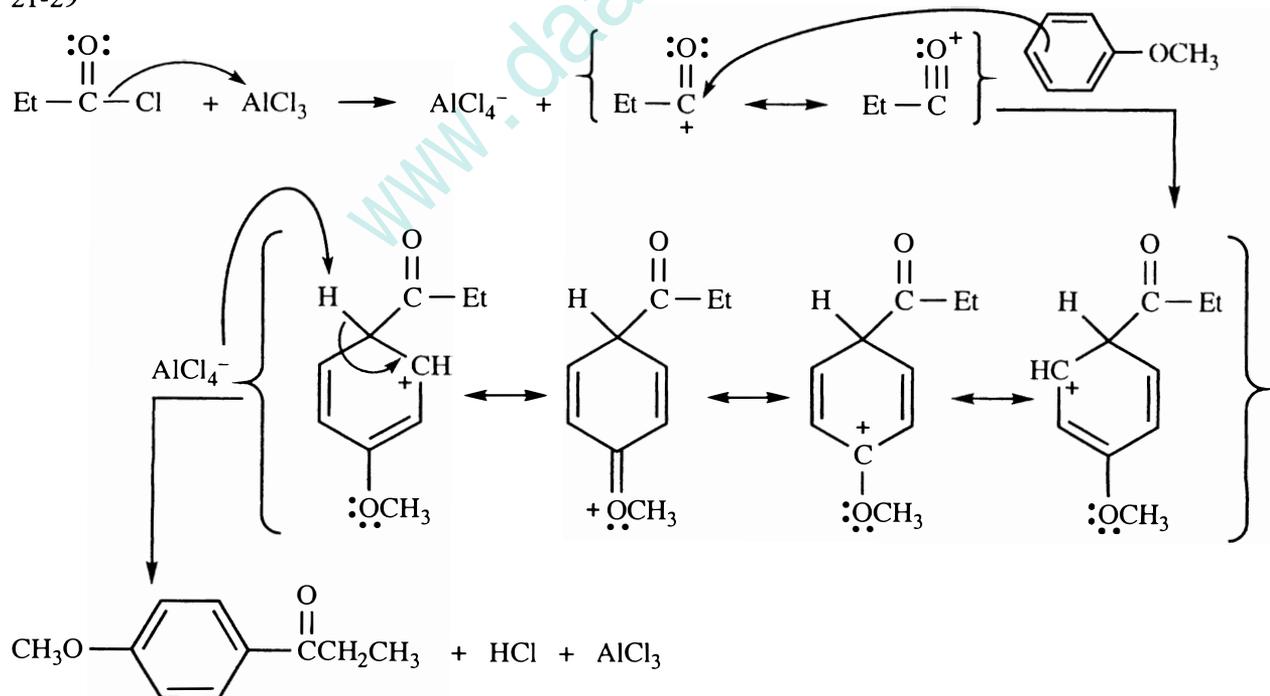
21-28



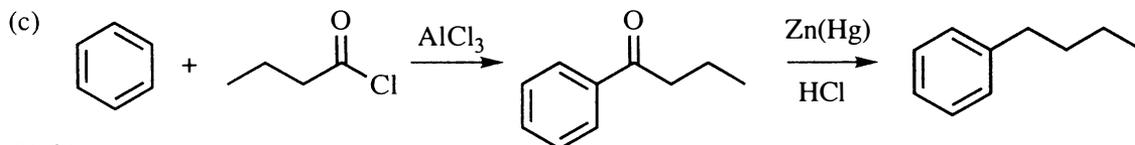
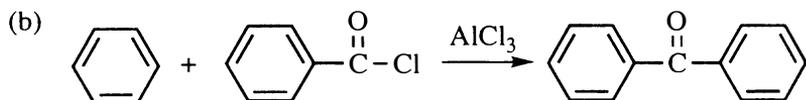
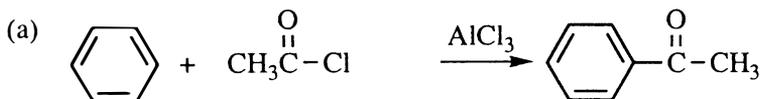
these alcohols can also be synthesized from ketones:



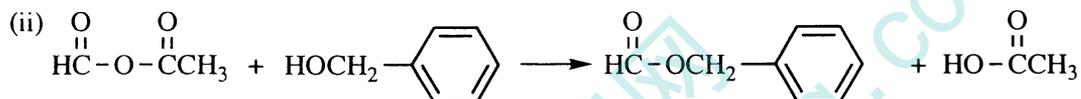
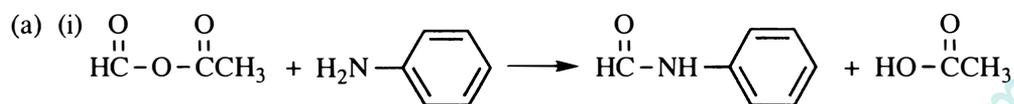
21-29



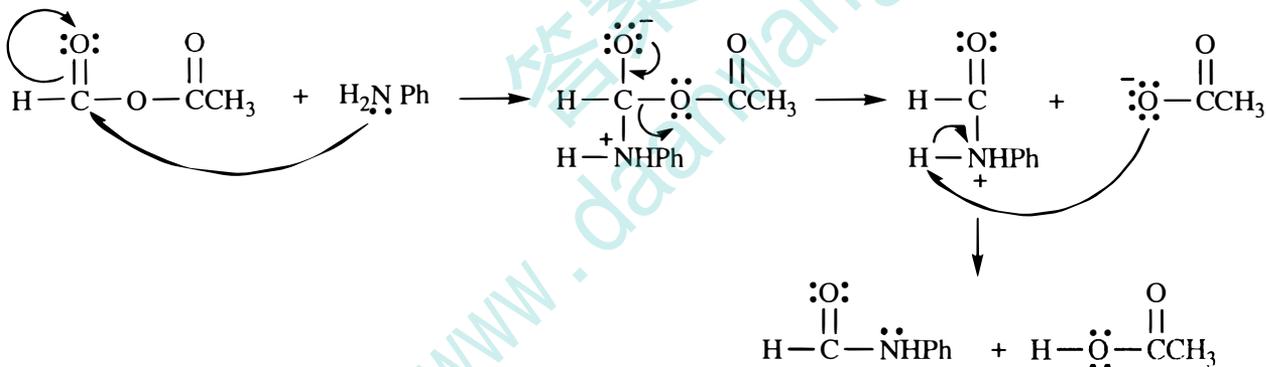
21-30



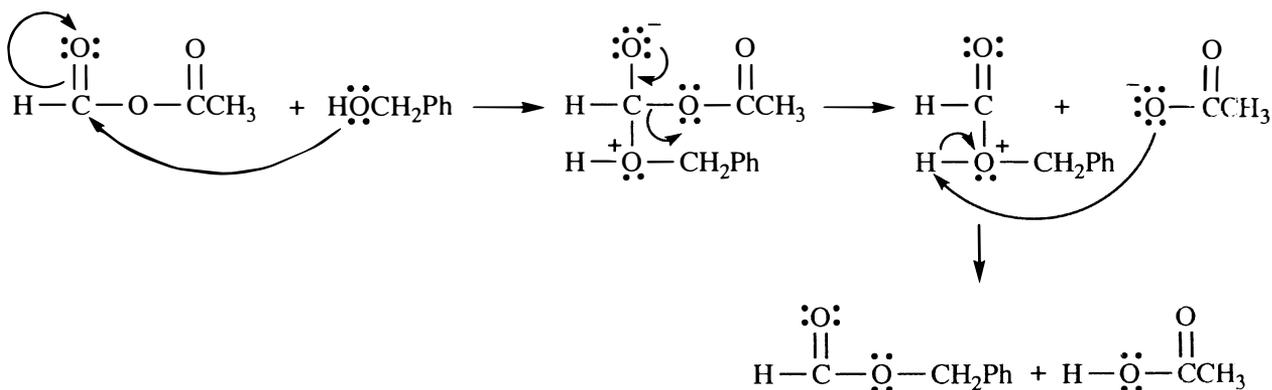
21-31



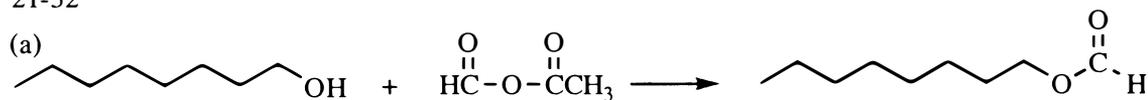
(b) (i)



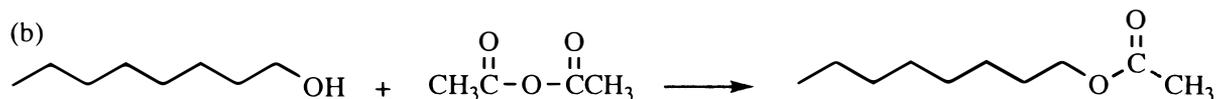
(ii)



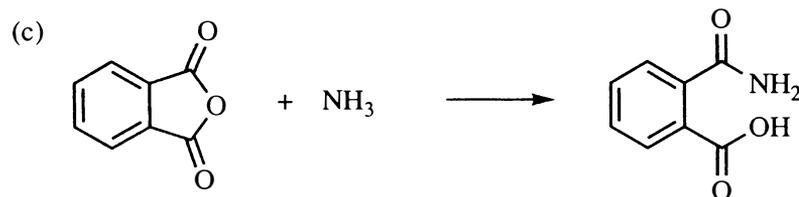
21-32



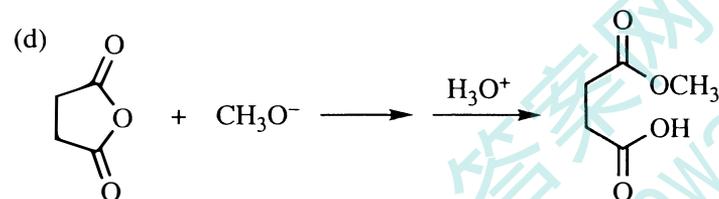
$\text{HC}-\text{Cl}$ does not exist, so acetic formic anhydride is the most practical way to formylate the alcohol.



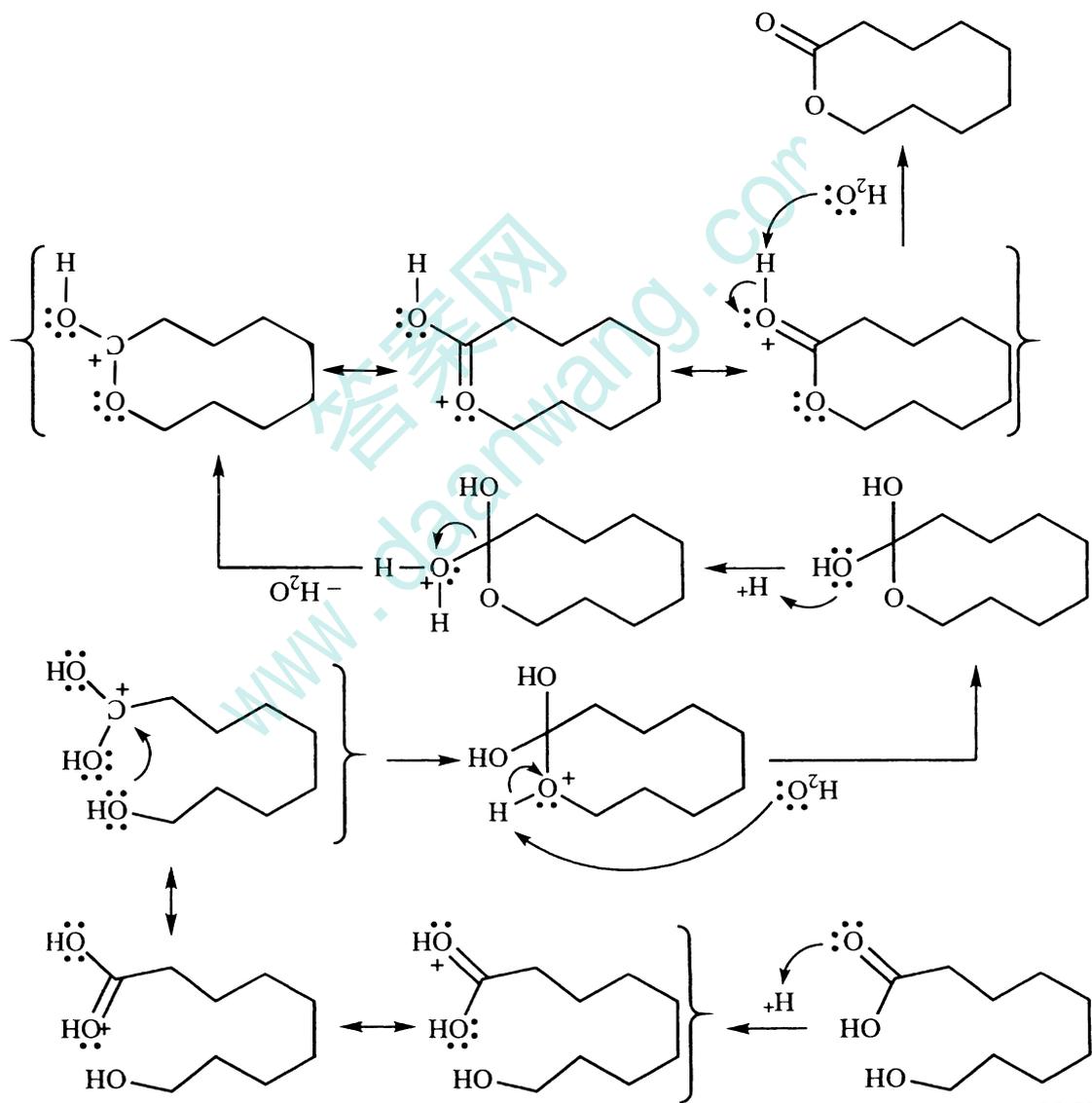
Acetic anhydride is more convenient and less expensive than acetyl chloride.



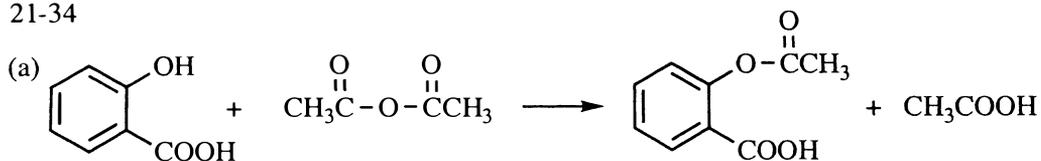
The acid chloride would tend to react at both carbonyls instead of just one; only the anhydride will give this product.



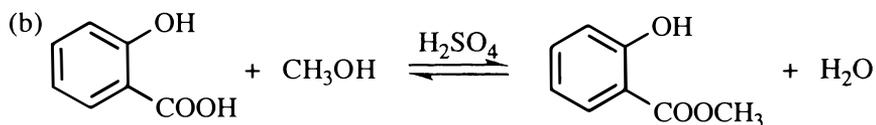
The acid chloride would tend to react at both carbonyls instead of just one; only the anhydride will give this product.



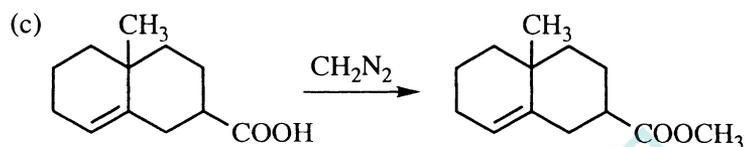
21-34



Generally, acetic anhydride is the optimum reagent for the preparation of acetate esters. Acetyl chloride would also react with the carboxylic acid to form a mixed anhydride.

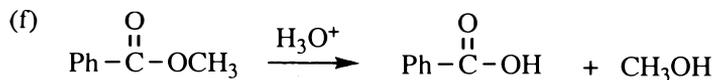
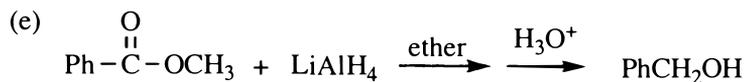
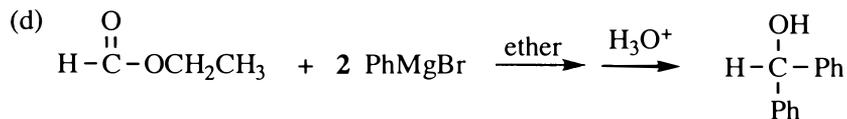
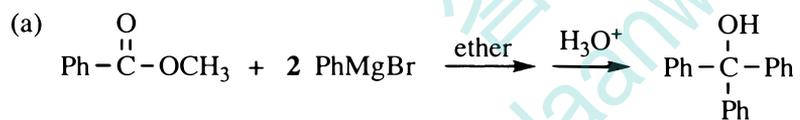


Fischer esterification works well to prepare simple carboxylic esters. The diazomethane method would also react with the phenol, making the phenyl ether.

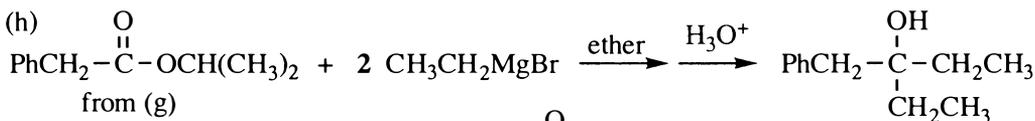
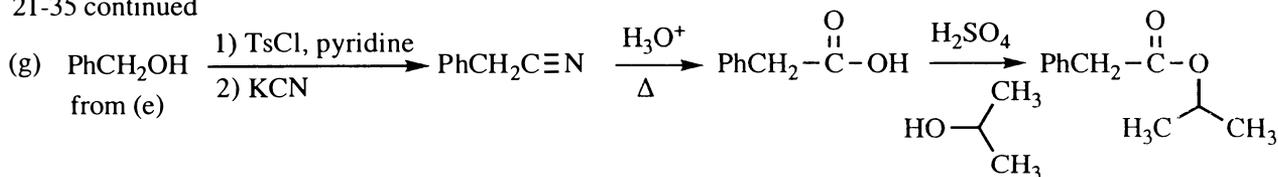


Fischer esterification would make the ester, but in the process, the acidic conditions would risk migrating the double bond into conjugation with the carbonyl group. The diazomethane reaction is run under neutral conditions where double bond migration will not occur.

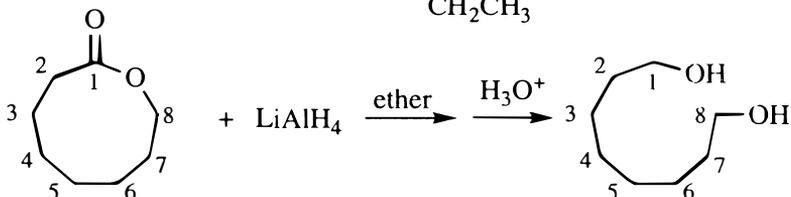
21-35 Syntheses may have more than one correct approach.



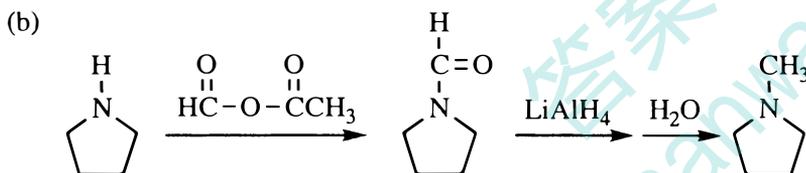
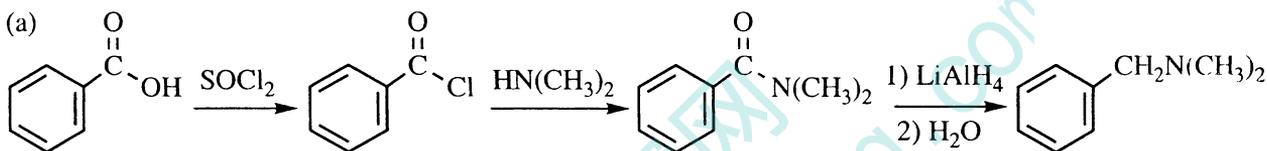
21-35 continued



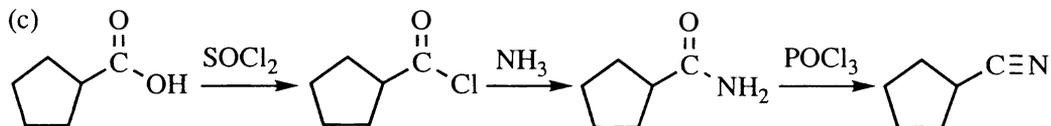
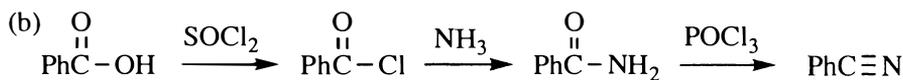
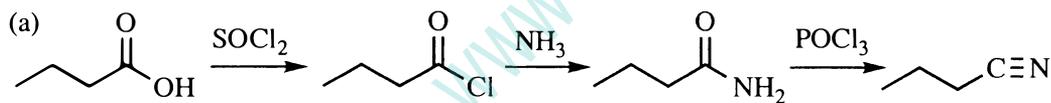
(i) How to make an 8-carbon diol from an ester that has no more than 8 carbons? Make the ester a lactone!



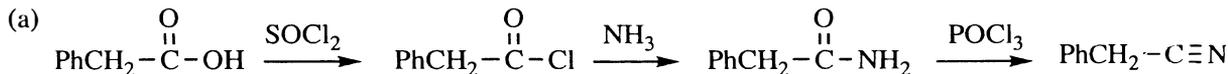
21-36 There may be additional correct approaches to these problems.



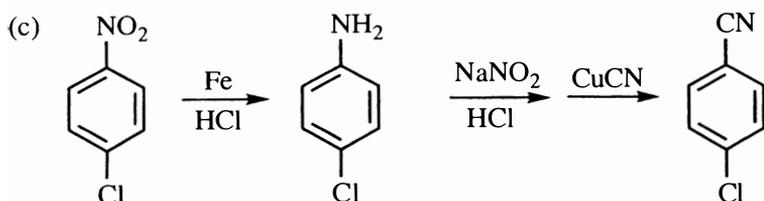
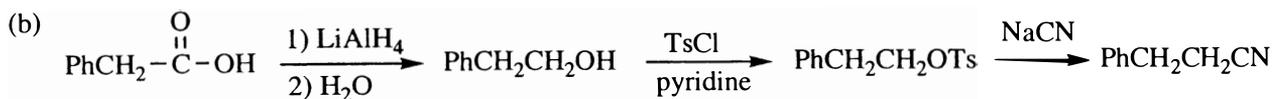
21-37 Prepare the amide, then dehydrate.



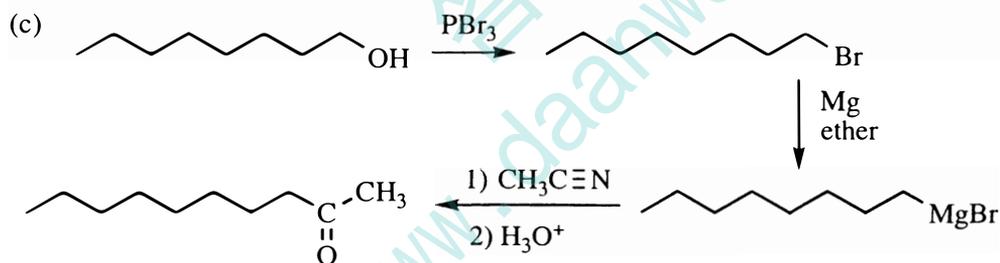
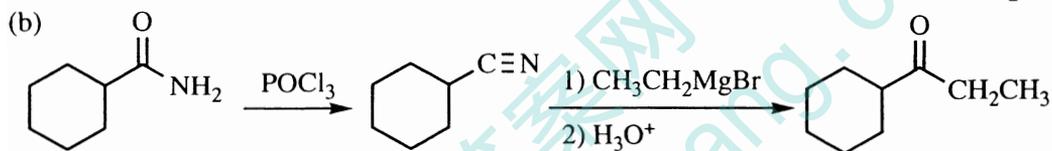
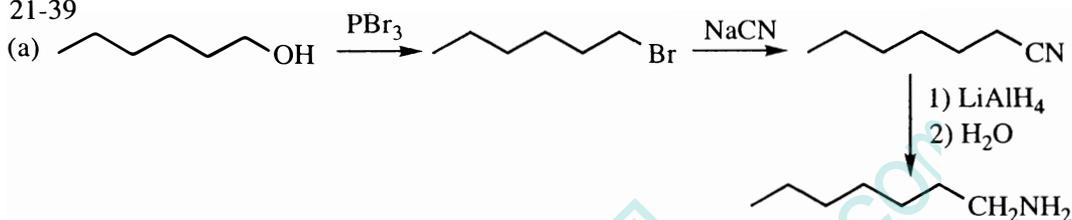
21-38



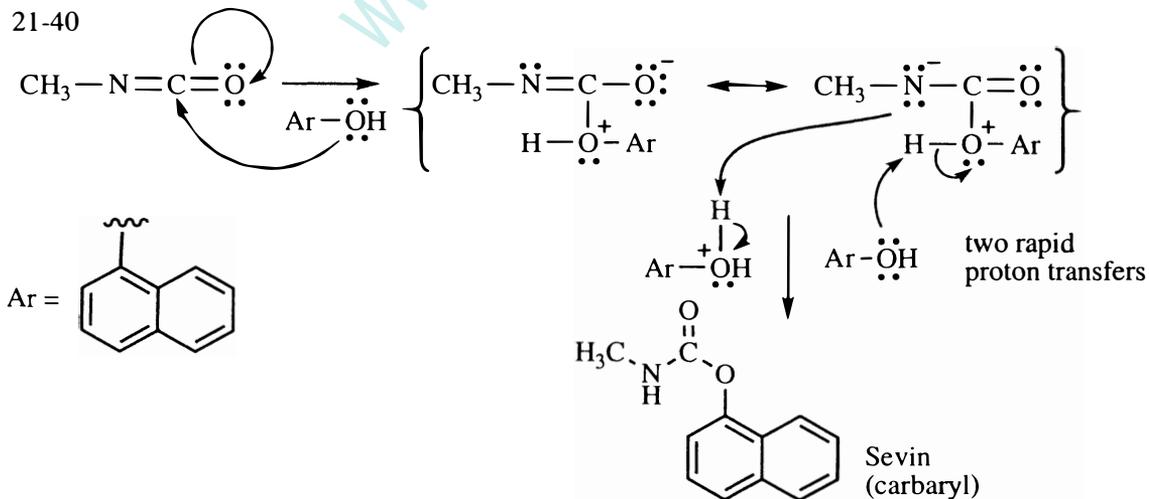
21-38 continued



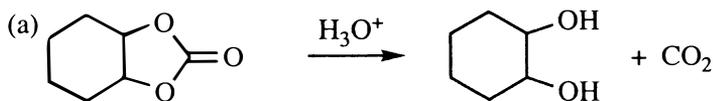
21-39



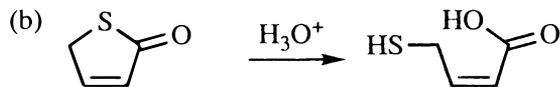
21-40



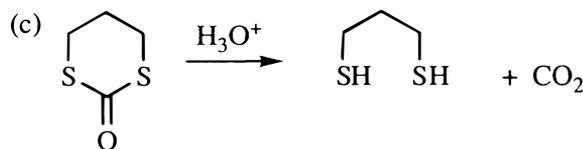
21-41



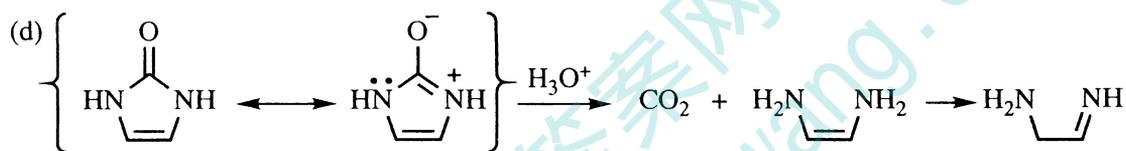
- (i) carbonate ester
(iii) not aromatic



- (i) thiolactone
(iii) not aromatic



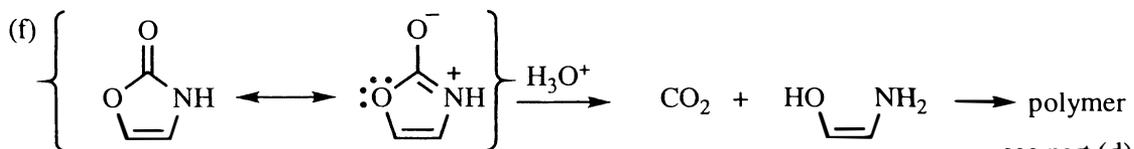
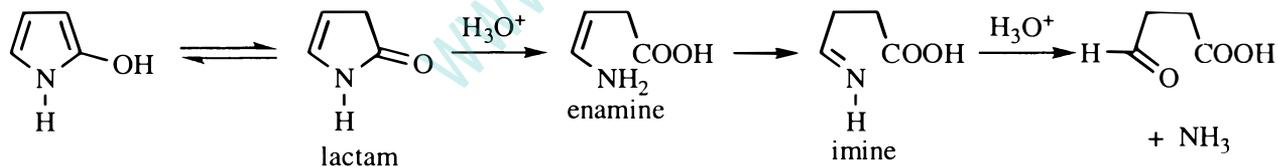
- (i) thiocarbonate ester
(iii) not aromatic



- (i) a substituted urea
(iii) AROMATIC—more easily seen in the resonance form shown

(The enediamine product would not be stable in aqueous acid. It would probably tautomerize to an imine, hydrolyze to ammonia and 2-aminoethanal, then polymerize.)

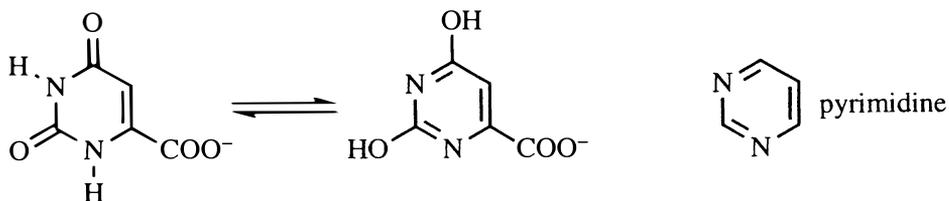
(e) At first glance, this AROMATIC compound does not appear to be an acid derivative. Like any enol, however, its tautomer must be considered.



- (i) a carbamate or urethane
(iii) AROMATIC—more easily seen in the resonance form

21-42

- (a) Carbamoyl phosphate is a mixed anhydride between carbamic acid and phosphoric acid. It would react easily with an amine to form an amide bond (technically, a urea), with phosphate as the leaving group.
 (b) N-Carbamoylaspartate has a carbonyl with two nitrogens on either side; this group is a urea derivative.
 (c) The NH₂ group on one end replaces the OH of a carboxylic acid on the other end; this reaction is a nucleophilic acyl substitution.
 (d) Orotate is aromatic as can be seen readily in the tautomer. It is called a "pyrimidine base" because of its structural similarity to the pyrimidine ring.

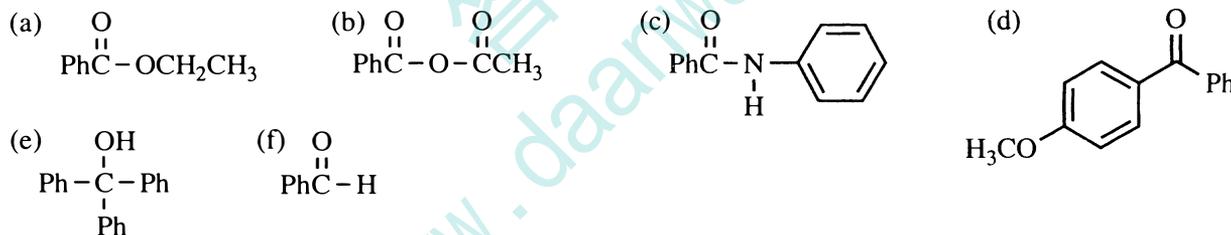


21-43 Please refer to solution 1-20, page 12 of this Solutions Manual.

21-44

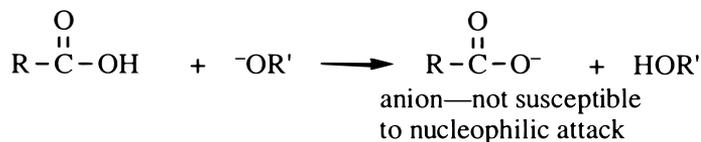
- (a) 3-methylpentanoyl chloride
 (b) benzoic formic anhydride
 (c) acetanilide; *N*-phenylethanamide
 (d) *N*-methylbenzamide
 (e) phenyl acetate; phenyl ethanoate
 (f) methyl benzoate
 (g) benzonitrile
 (h) 4-phenylbutane nitrile; γ -phenylbutyronitrile
 (i) dimethyl isophthalate, or dimethyl benzene-1,3-dicarboxylate
 (j) *N,N*-diethyl-3-methylbenzamide
 (k) 4-hydroxypentanoic acid lactone; γ -valerolactone
 (l) 3-aminopentanoic acid lactam; β -valerolactam

21-45

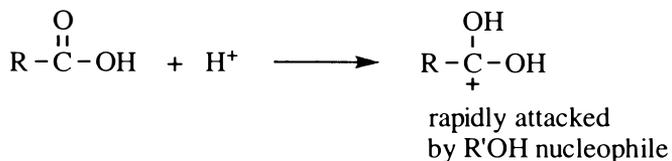


21-46 When a carboxylic acid is treated with a basic reagent, the base removes the acidic proton rather than attacking at the carbonyl (proton transfers are much faster than formation or cleavage of other types of bonds). Once the carboxylate anion is formed, the carbonyl is no longer susceptible to nucleophilic attack: nucleophiles do not attack sites of negative charge. By contrast, in acidic conditions, the protonated carbonyl has a positive charge and is activated to nucleophilic attack.

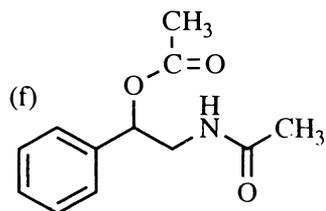
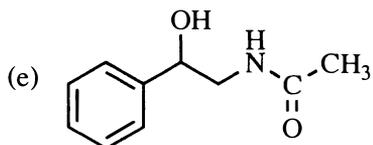
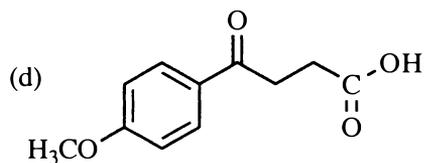
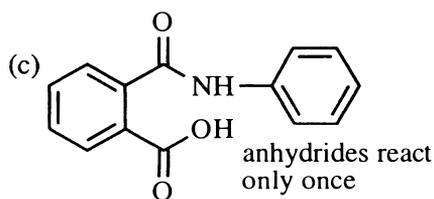
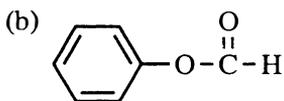
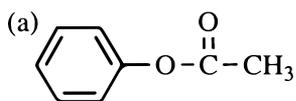
basic conditions



acidic conditions

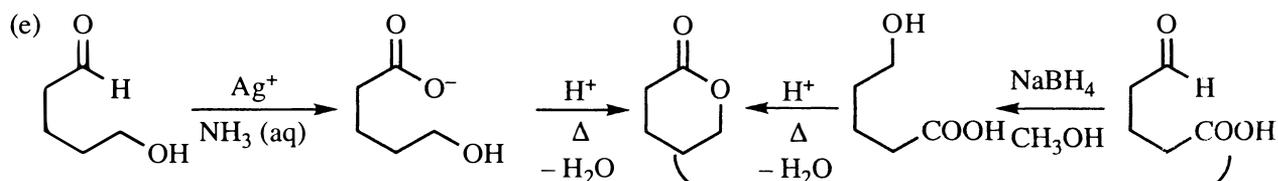
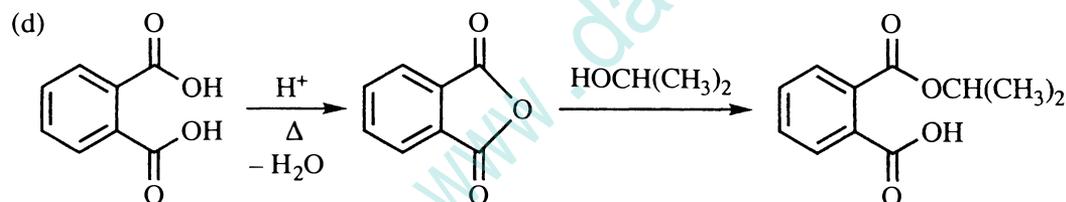
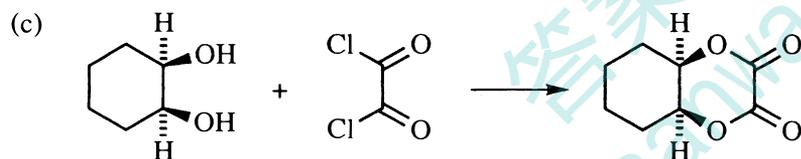
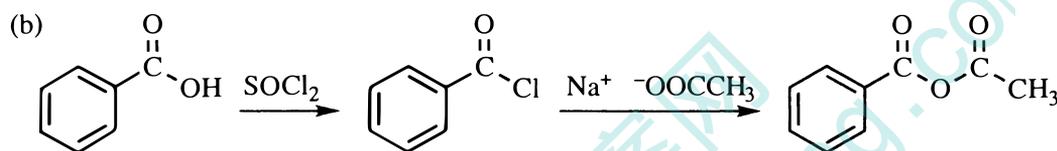


21-47

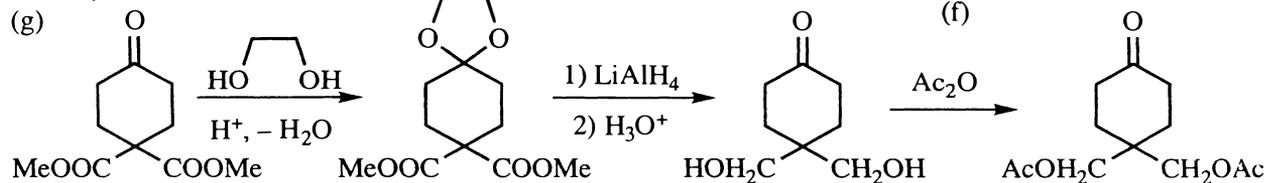


amines are more nucleophilic than alcohols

21-48



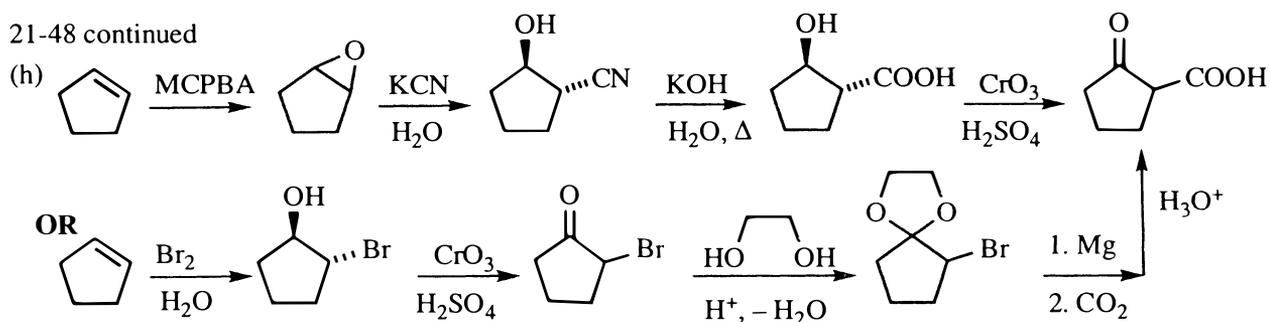
(f) \Rightarrow



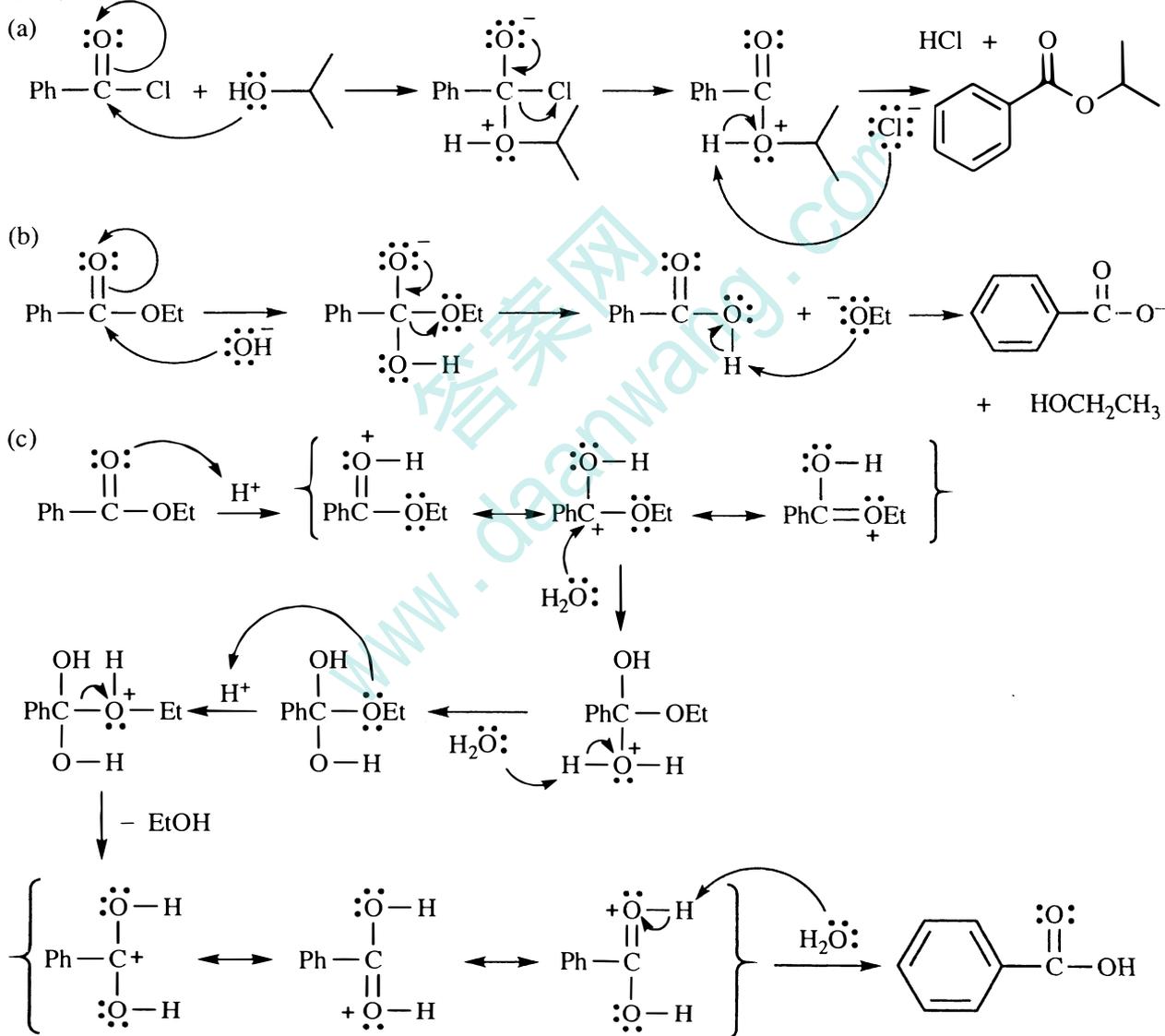
any ester where ethylene glycol displaces methanol will be reduced with LiAlH₄

aqueous acid workup removes ketal protecting group

21-48 continued

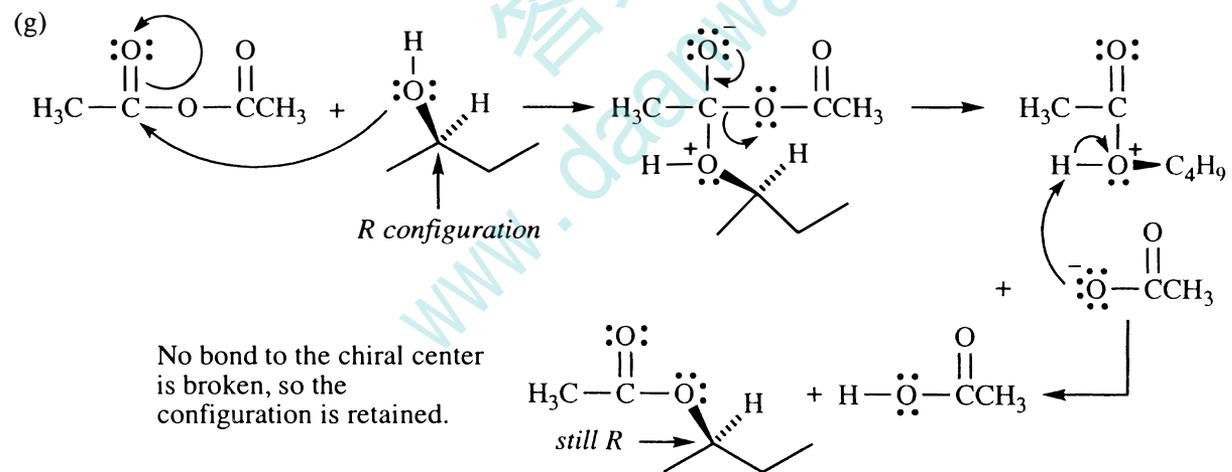
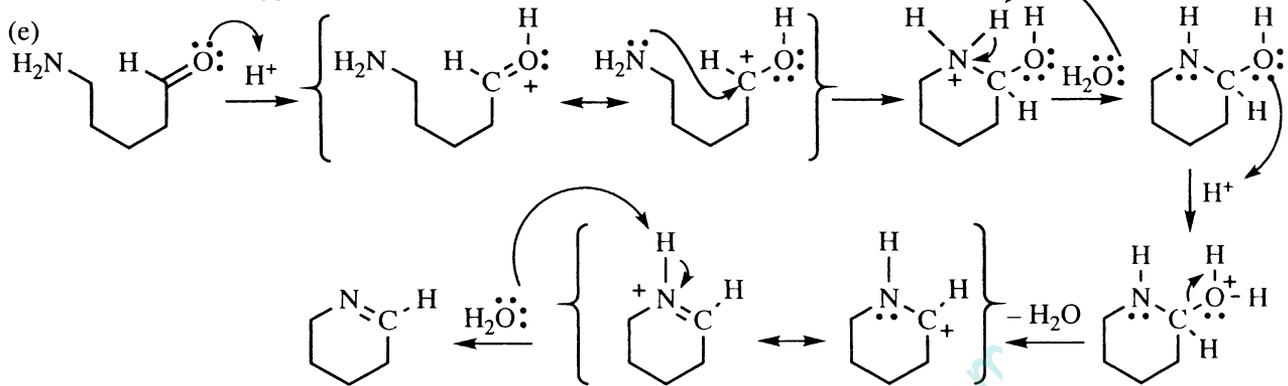
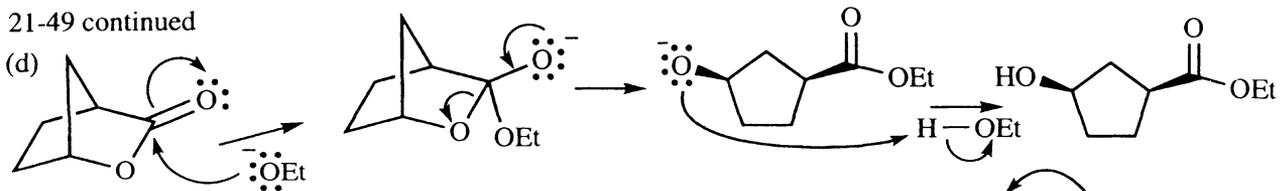


21-49

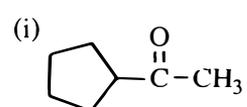
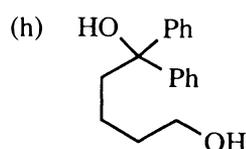
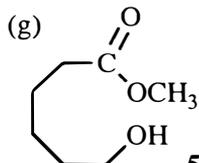
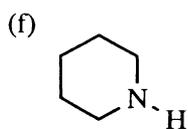
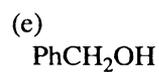
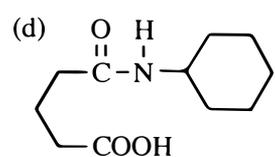
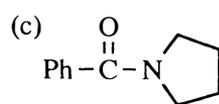
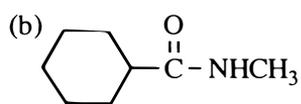
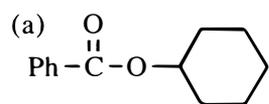


Note: species with positive charge on carbon adjacent to benzene also have resonance forms (not shown) with the positive charge distributed over the ring.

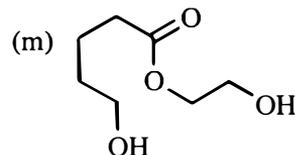
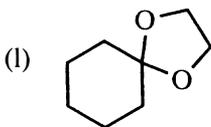
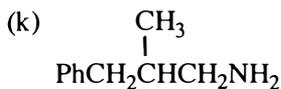
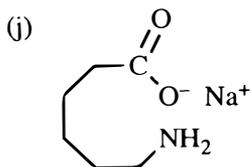
21-49 continued



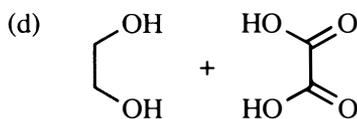
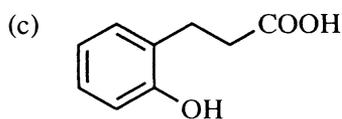
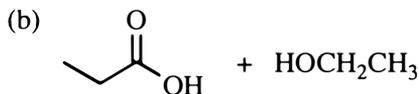
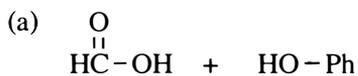
21-50



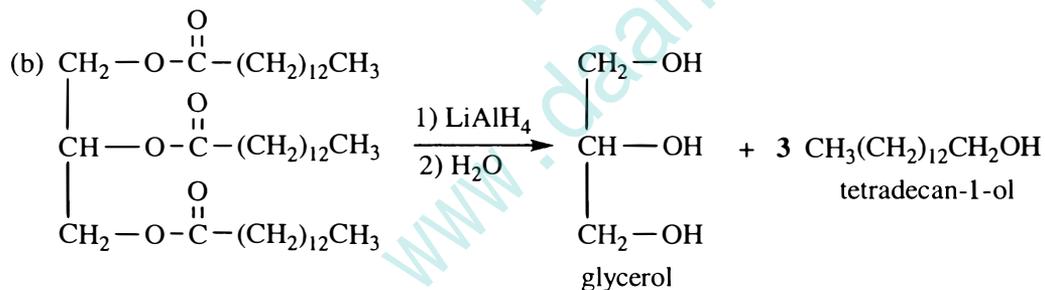
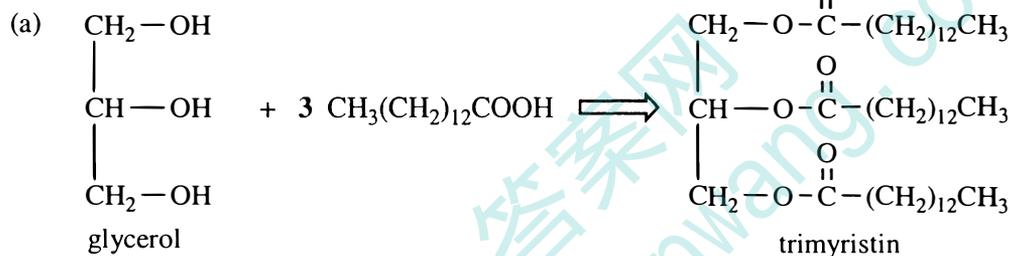
21-50 continued



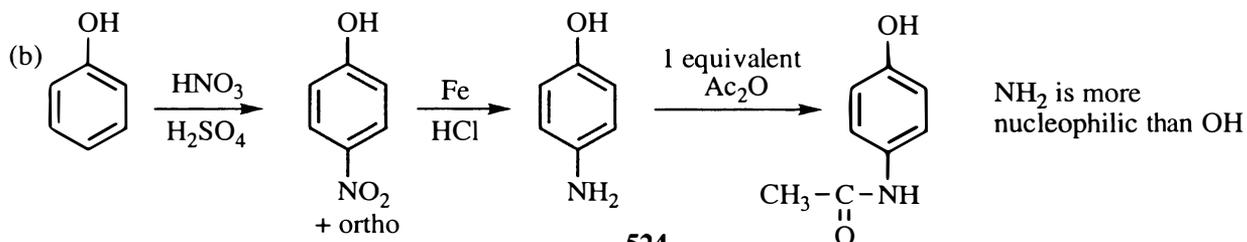
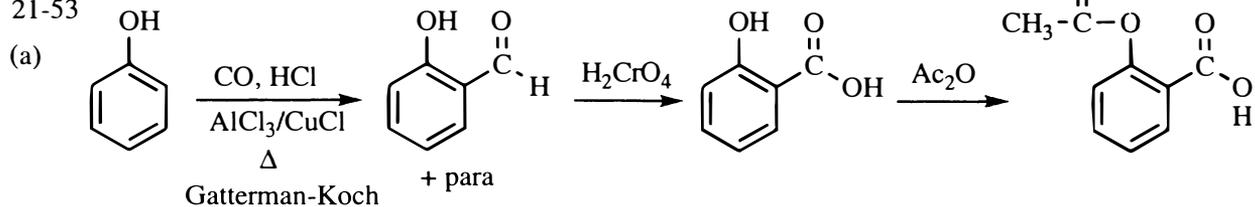
21-51 Products after adding dilute acid in the workup:



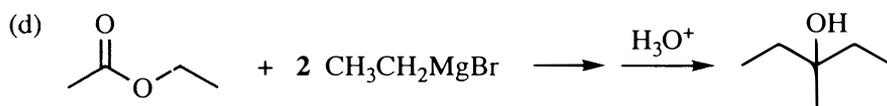
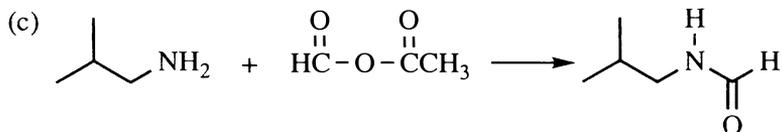
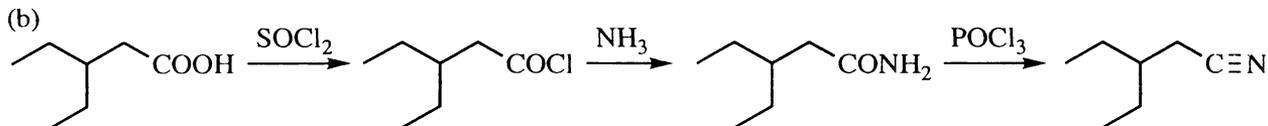
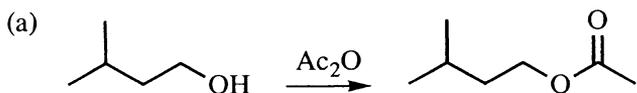
21-52



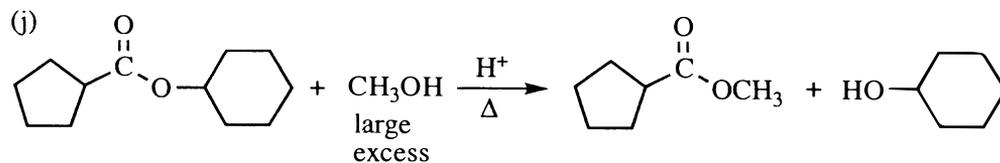
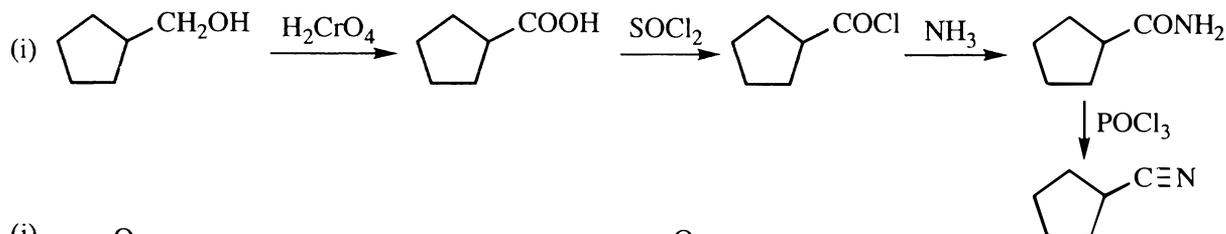
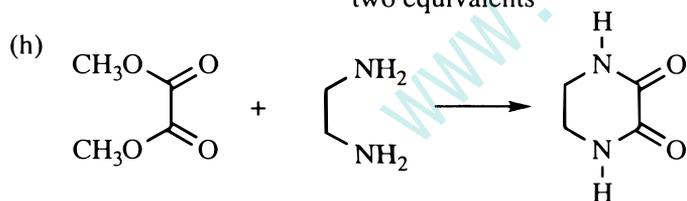
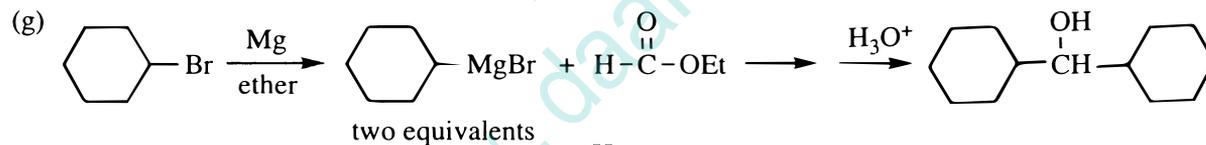
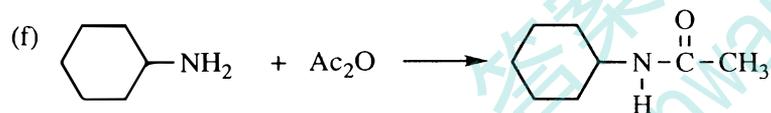
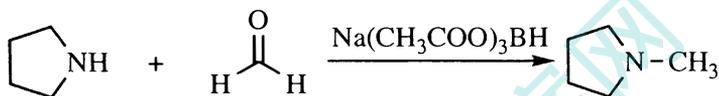
21-53



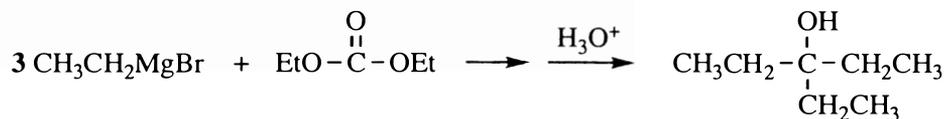
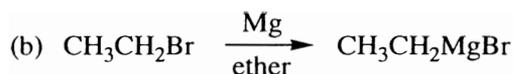
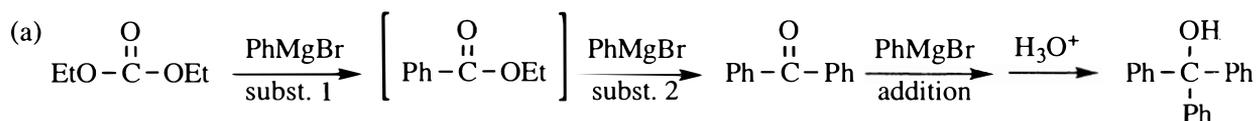
21-54



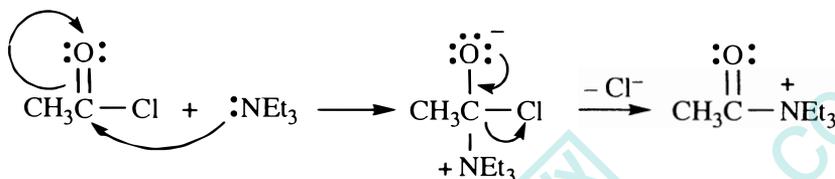
(e) See the solution to 21.36(b) for one method. Here is another: reductive alkylation.



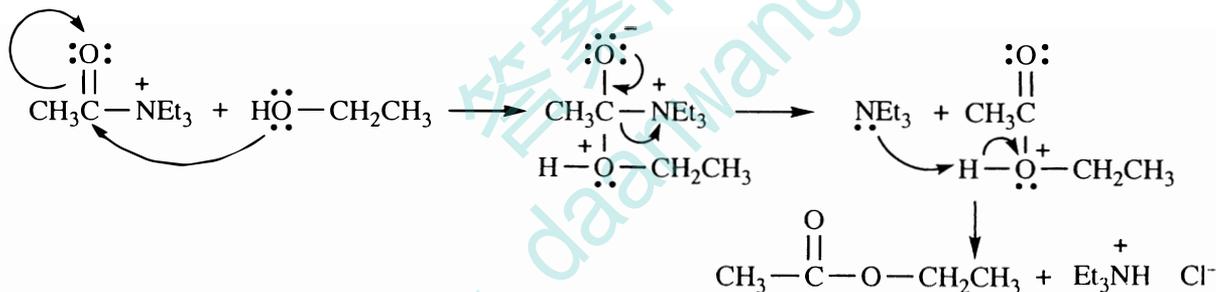
21-55 Diethyl carbonate has *two* leaving groups on the carbonyl. It can undergo *two* nucleophilic acyl substitutions, followed by one nucleophilic addition.



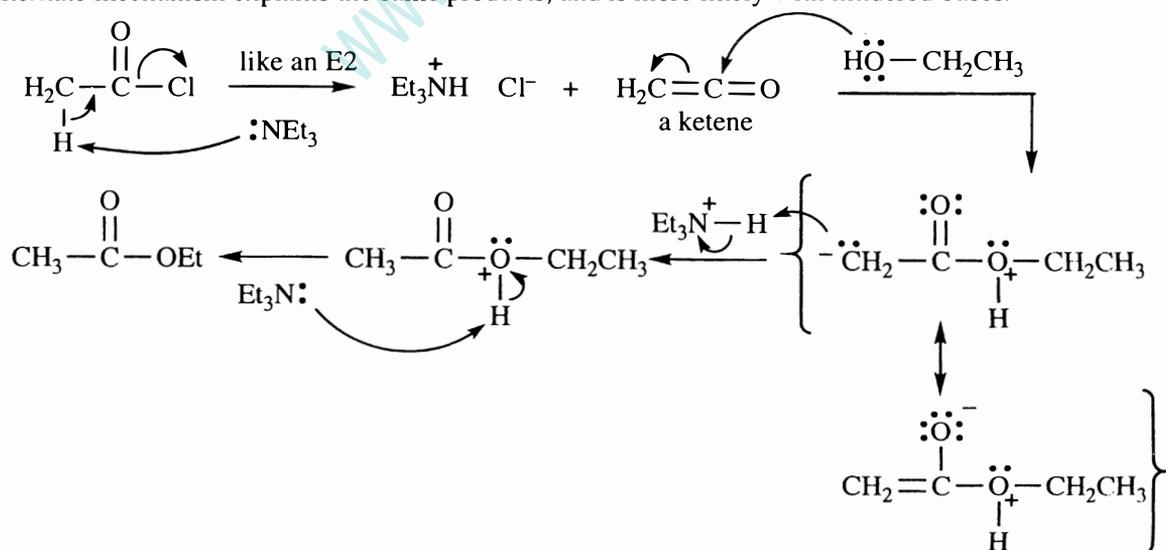
21-56 Triethylamine is nucleophilic, but it has no H on nitrogen to lose, so it forms a salt instead of a stable amide.



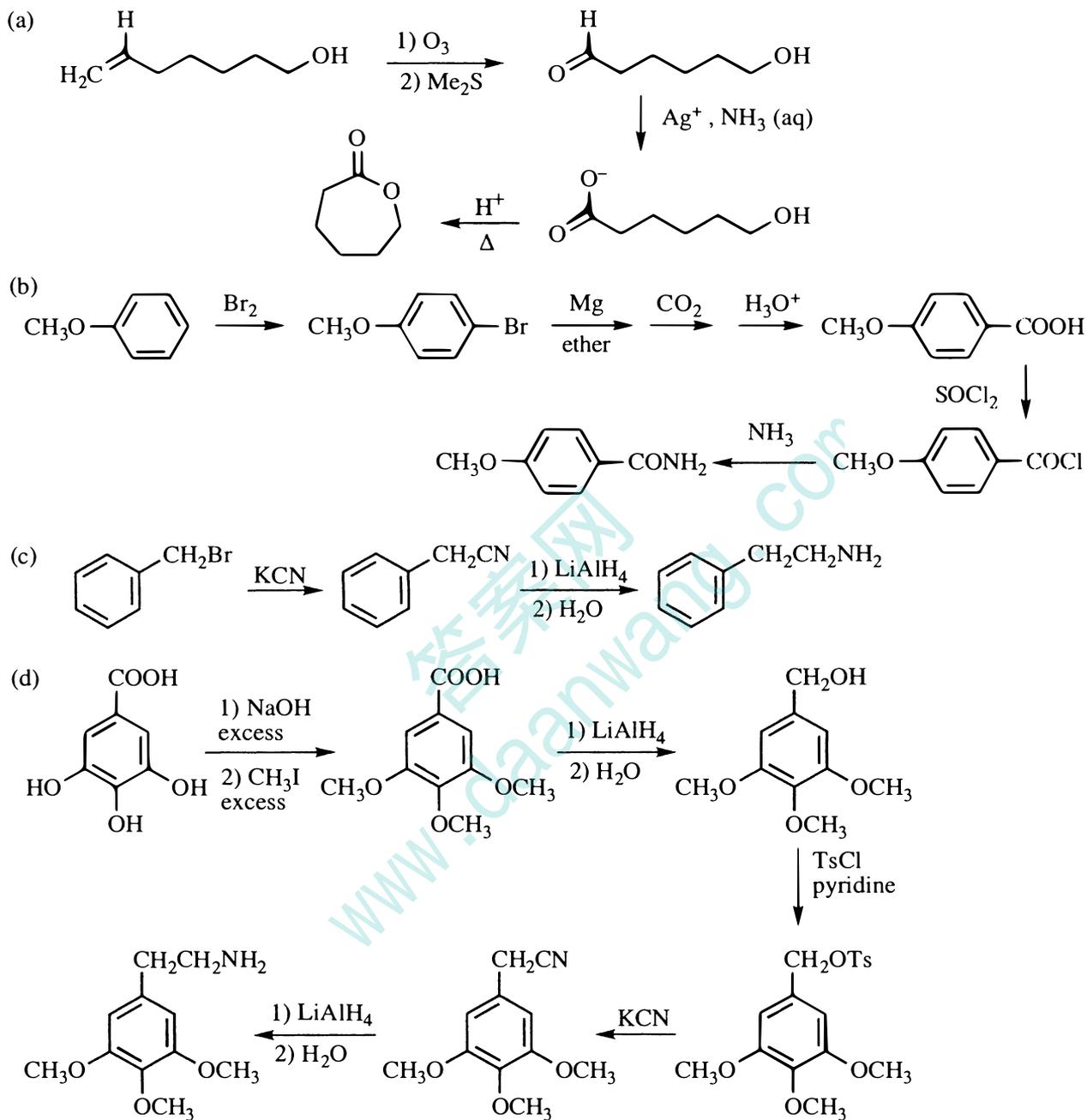
When ethanol is added, it attacks the carbonyl of the salt, with triethylamine as the leaving group.

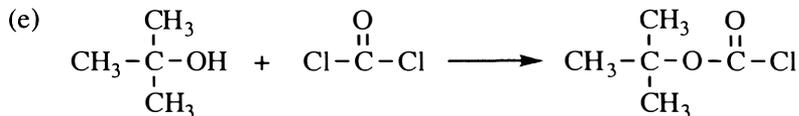
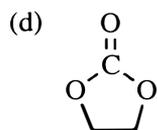
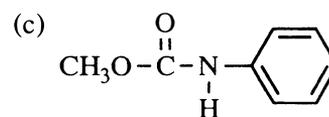
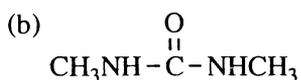
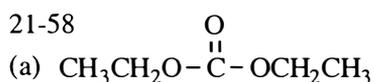


An alternate mechanism explains the same products, and is more likely with hindered bases:



21-57





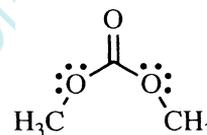
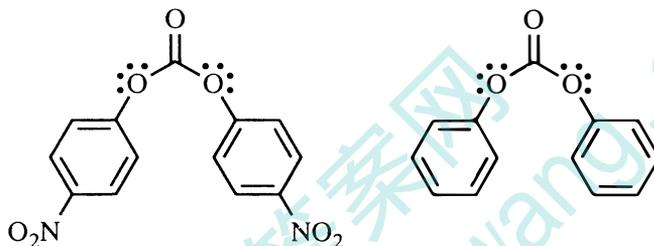
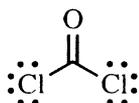
21-59 (a) The rate of these nucleophilic acyl substitution reactions is controlled by two factors: stability of the starting material as determined by the amount of resonance donation from the leaving group into the carbonyl, and the leaving group ability which is determined by the basicity of the leaving group, the least basic being the best leaving group.

LEAST STABLE: no significant sharing of electrons from chlorine

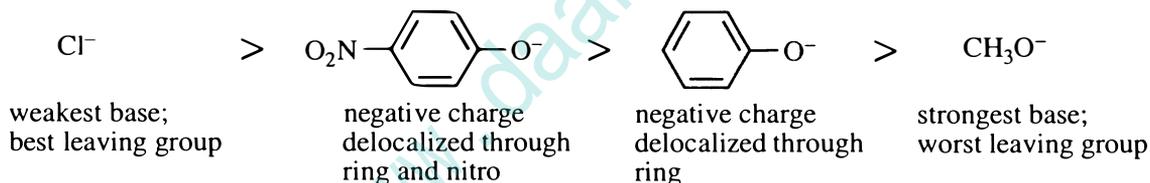
electrons from oxygen are also distributed through the ring and nitro; very little resonance stabilization

electrons from oxygen are also distributed through the ring; small resonance stabilization

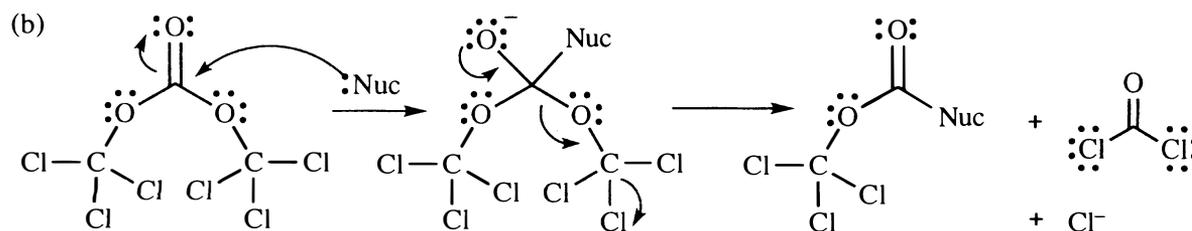
MOST STABLE: most significant resonance donation of electrons from oxygen



leaving group ability and basicity:



The least stable starting material with the best leaving group will be fastest to react. The most stable starting material with the poorest leaving group will be slowest to react.

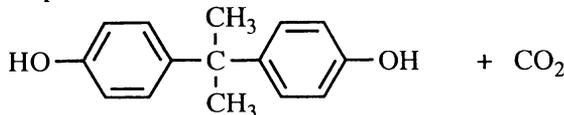


triphosgene

The first step is the standard attack of a nucleophile like CH_3OH at the carbonyl carbon to make the tetrahedral intermediate. The second step is key: the collapse of the tetrahedral intermediate produces one equivalent of phosgene. Attack of a second nucleophile of the other side of triphosgene would release a latent (hidden or trapped) equivalent of phosgene from that side too. Thus, the equivalent of three molecules of phosgene are locked into the triphosgene molecule. Eventually, all six positions would be substituted with methanol producing three molecules of dimethyl carbonate for each molecule of triphosgene.

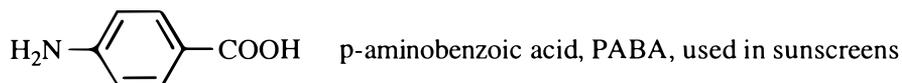
21-61 continued

- (c) (i) The repeating functional group is a carbonate, so the polymer is a polycarbonate (named Lexan®).
 (ii) hydrolysis products:



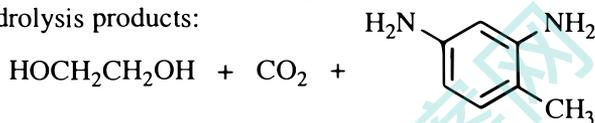
(iii) The phenol monomer would be the same as the hydrolysis product; phosgene or a carbonate ester would be the other monomer.

- (d) (i) The repeating functional group is an amide, so the polymer is a polyamide.
 (ii) hydrolysis product:

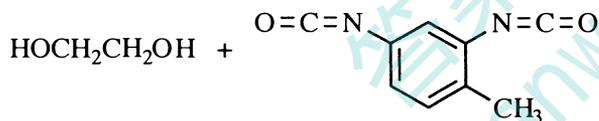


(iii) The monomer could be the same as the hydrolysis product; a reactive derivative of the acid like an ester could also be used.

- (e) (i) The repeating functional group is a urethane, so the polymer is a polyurethane.
 (ii) hydrolysis products:



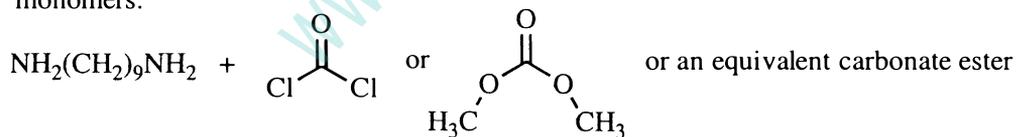
(iii) monomers:



- (f) (i) The repeating functional group is a urea, so the polymer is a polyurea.
 (ii) hydrolysis products:



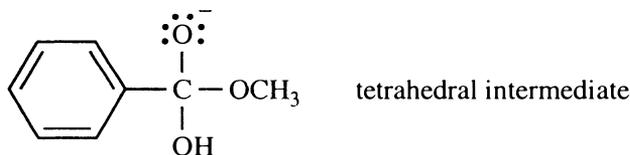
(iii) monomers:



21-62

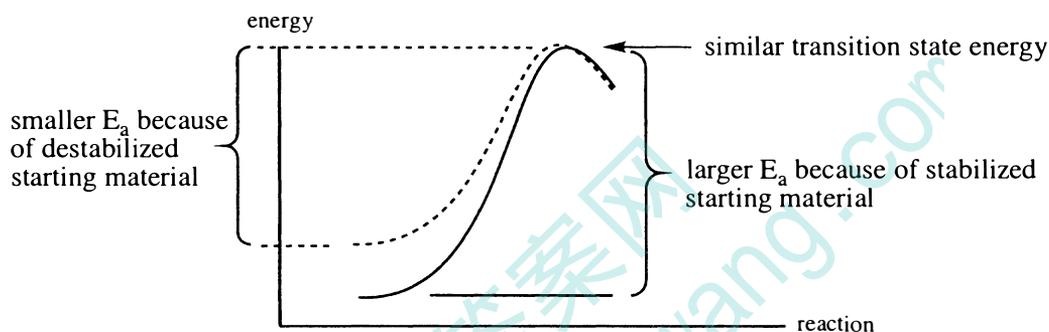
- (a) Both structures are β -lactam antibiotics, a penicillin and a cephalosporin.
 (b) "Cephalosporin N" has a 5-membered, sulfur-containing ring. This belongs in the penicillin class of antibiotics.

21-63 The rate of a reaction depends on its activation energy, that is, the difference in energy between starting material and the transition state. The transition state in saponification is similar in structure, and therefore in energy, to the tetrahedral intermediate:

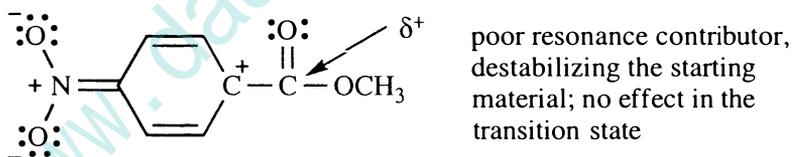


The tetrahedral carbon has no resonance overlap with the benzene ring, so any resonance effect of a substituent on the ring will have very little influence on the energy of the transition state.

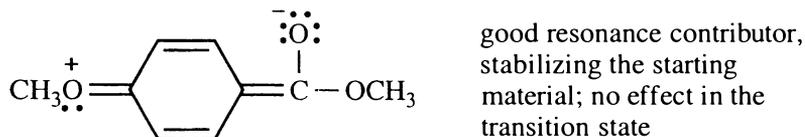
What will have a big influence on the activation energy is whether a substituent stabilizes or destabilizes the starting material. Anything that stabilizes the starting material will therefore increase the activation energy, slowing the reaction; anything that destabilizes the starting material will decrease the activation energy, speeding the reaction.



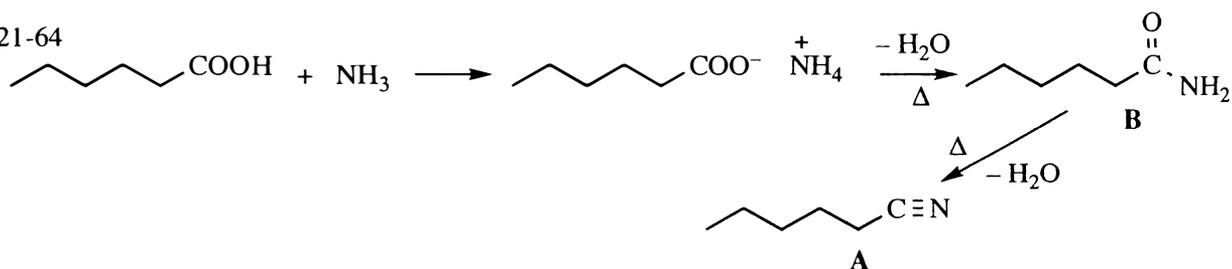
(a) One of the resonance forms of methyl *p*-nitrobenzoate has a positive charge on the benzene carbon adjacent to the positive carbonyl carbon. This resonance form destabilizes the starting material, lowering the activation energy, speeding the reaction.



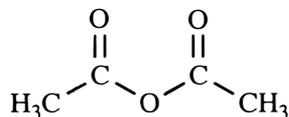
(b) One of the resonance forms of methyl *p*-methoxybenzoate has all atoms with full octets, and negative charge on the most electronegative atom. This resonance form stabilizes the starting material, increasing the activation energy, slowing the reaction.



21-64



21-65 A singlet at δ 2.15 is H on carbon next to carbonyl, the only type of proton in the compound. The IR spectrum shows no OH, and shows two carbonyl absorptions at high frequency, characteristic of an anhydride. Mass of the molecular ion at 102 proves that the anhydride must be acetic anhydride, a reagent commonly used in aspirin synthesis.



Acetic anhydride can be disposed of by hydrolyzing (carefully! exothermic!) and neutralizing in aqueous base.

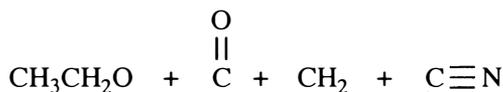
21-66

IR spectrum:

- sharp spike at $2250 \text{ cm}^{-1} \Rightarrow \text{C} \equiv \text{N}$
 - $1750 \text{ cm}^{-1} \Rightarrow \text{C} = \text{O}$
 - $1200 \text{ cm}^{-1} \Rightarrow \text{C} - \text{O}$
- } maybe an ester

NMR spectrum:

- triplet and quartet $\Rightarrow \text{CH}_3\text{CH}_2$
- this quartet at δ 4.3 $\Rightarrow \text{CH}_3\text{CH}_2\text{O}$
- 2H singlet at δ 3.5 \Rightarrow isolated CH_2



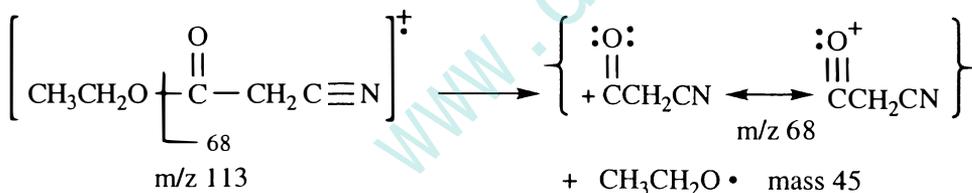
sum of the masses is 113, consistent with the MS

The fragments can be combined in only two possible ways:



The NMR proves the structure to be **A**. If the structure were **B**, the CH_2 between oxygen and the carbonyl would come farther downfield than the CH_2 of the ethyl (deshielded by oxygen and carbonyl instead of by oxygen alone). As this is not the case, the structure cannot be **B**.

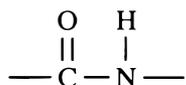
The peak in the mass spectrum at m/z 68 is due to α -cleavage of the ester:



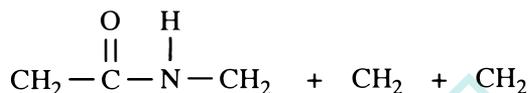
21-67

The formula C_5H_9NO has 2 elements of unsaturation.

IR spectrum: The strongest peak at 1670 cm^{-1} comes low in the carbonyl region; in the absence of conjugation (no alkene peak observed), a carbonyl this low is almost certainly an amide. There is one broad peak in the NH/OH region, hinting at the likelihood of a secondary amide.

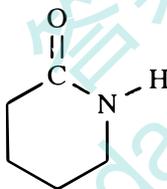


HNMR spectrum: The broad peak at $\delta 7.55$ is exchangeable with D_2O ; this is an amide proton. A broad, 2H peak at $\delta 3.3$ is a CH_2 next to nitrogen. A broad, 2H peak at $\delta 2.4$ is a CH_2 next to carbonyl. The 4H peak at $\delta 1.8$ is probably two more CH_2 groups. There appears to be coupling among these protons but it is not resolved enough to be useful for interpretation. This is often the case when the compound is cyclic, with restricted rotation around carbon-carbon bonds, giving *non-equivalent* (axial and equatorial) hydrogens on the same carbon.



CNMR spectrum: The peak at $\delta 175$ is the $C=O$ of the amide. All of the peaks between $\delta 25$ and $\delta 50$ are aliphatic sp^3 carbons, no sp^2 carbons, so the remaining element of unsaturation cannot be a $C=C$; it must be a ring. The carbon peak farthest downfield is the carbon adjacent to N.

The most consistent structure:

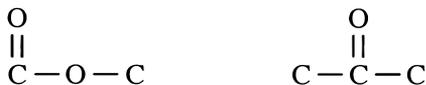


δ -valerolactam

21-69 If you solved this problem, put a gold star on your forehead.

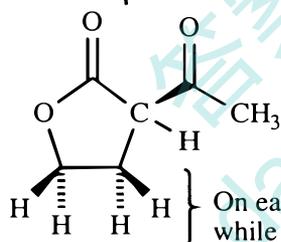
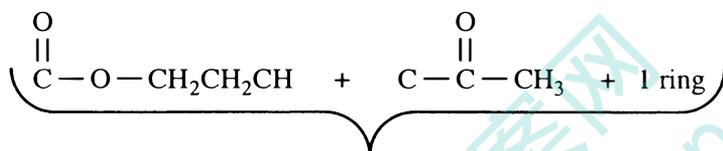
The formula $C_6H_8O_3$ indicates 3 elements of unsaturation.

IR spectrum: The absence of strong OH peaks shows that the compound is neither an alcohol nor a carboxylic acid. There are two carbonyl absorptions: the one about 1770 cm^{-1} is likely a strained cyclic ester (reinforced with the C—O peak around 1150 cm^{-1}), while the one at 1720 cm^{-1} is probably a ketone. (An anhydride also has two peaks, but they are of higher frequency than the ones in this spectrum.)



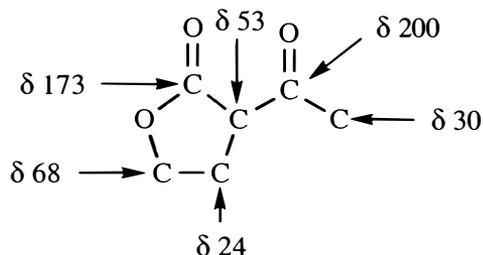
Proton NMR spectrum: The NMR shows four types of protons. The 2H triplet at δ 4.3 is a CH_2 group next to an oxygen on one side, with a CH_2 on the other. The 1H multiplet at δ 3.7 is also strongly deshielded (probably by two carbonyls), a CH next to a CH_2 . The 3H singlet at δ 2.45 is a CH_3 on one of the carbonyls. The remaining two hydrogens are highly coupled, a CH_2 where the two hydrogens are not equivalent. There are no vinyl hydrogens (and no alkene carbon in the carbon NMR), so the remaining element of unsaturation must be a ring.

Assemble the pieces:



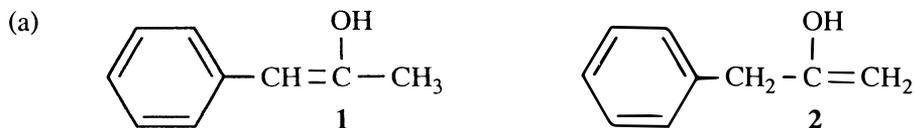
On each carbon, the "up" hydrogen is cis to the acetyl group, while the "down" hydrogen is trans. Thus, the two hydrogens on each of these carbons are not equivalent, leading to complex splitting.

Carbon NMR:



CHAPTER 22
CONDENSATIONS AND ALPHA SUBSTITUTIONS OF CARBONYL COMPOUNDS

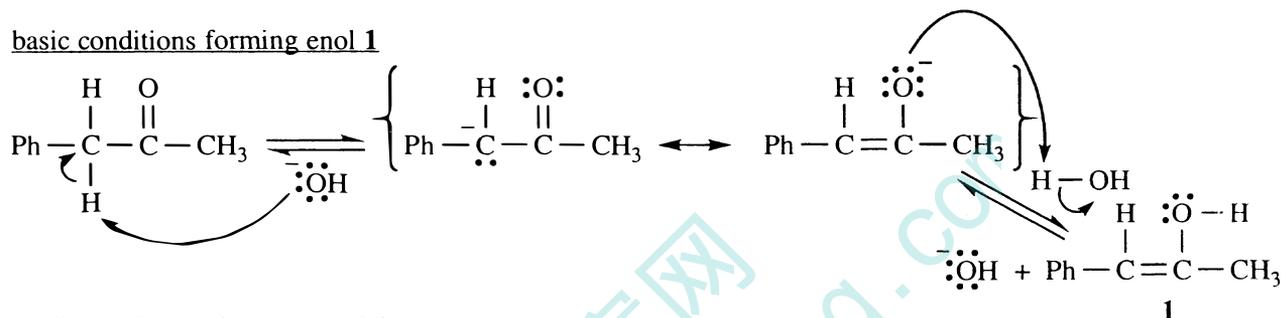
22-1



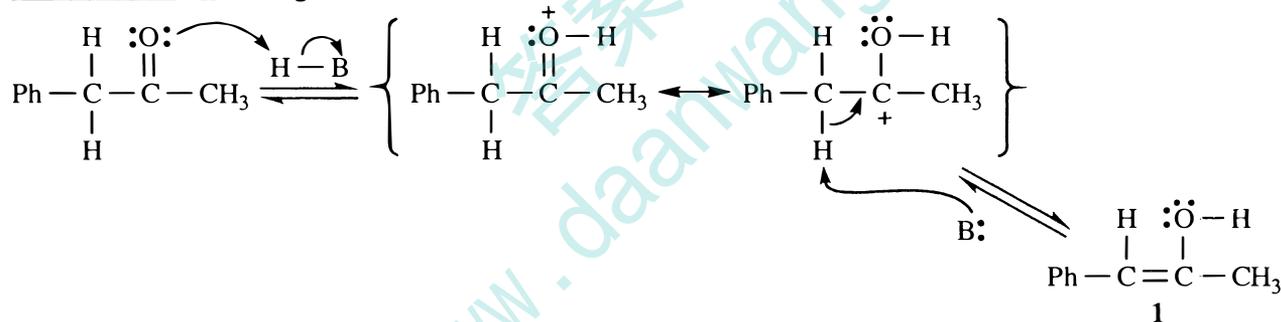
(b) Enol 1 will predominate at equilibrium as its double bond is conjugated with the benzene ring, making it more stable than 2.

(c)

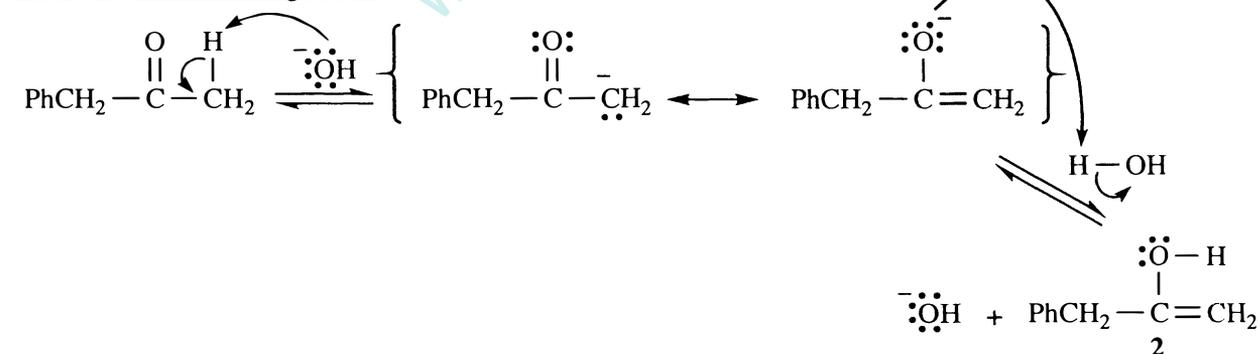
basic conditions forming enol 1



acidic conditions forming enol 1

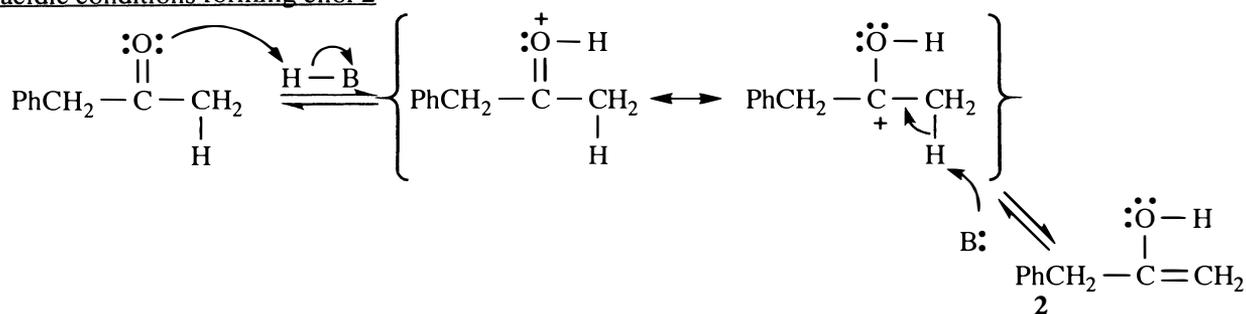


basic conditions forming enol 2

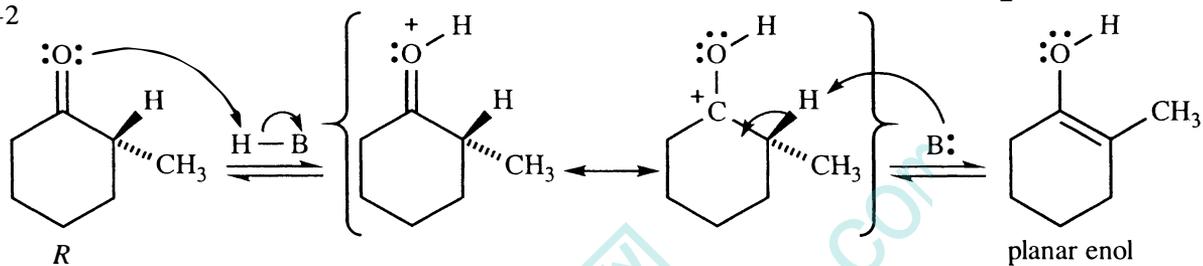


22-1 (c) continued

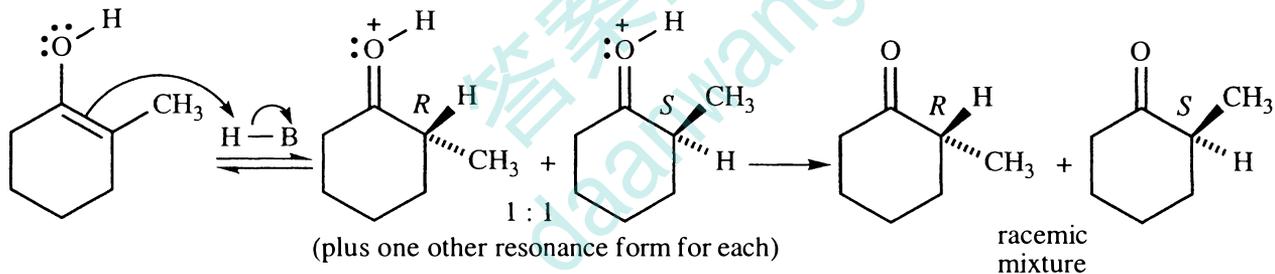
acidic conditions forming enol 2



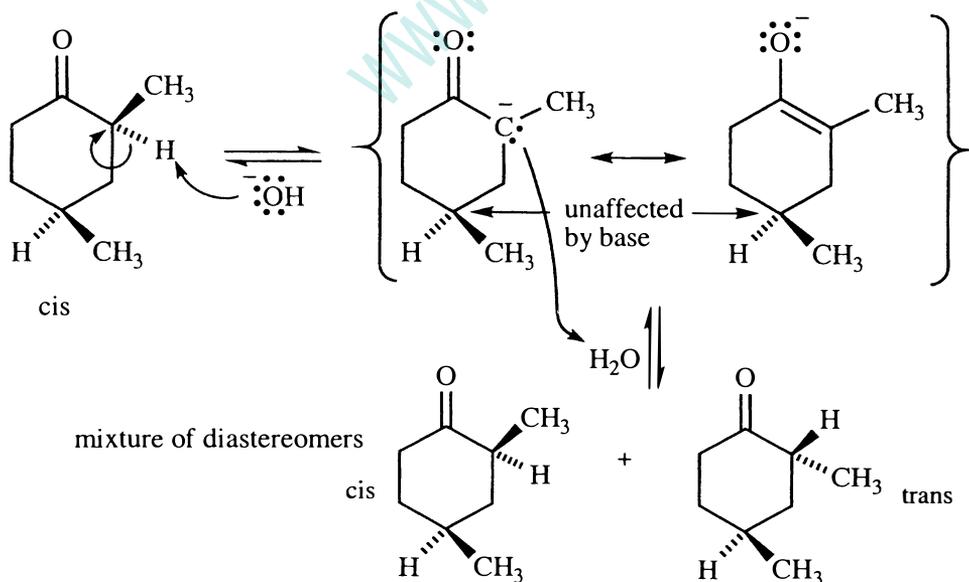
22-2



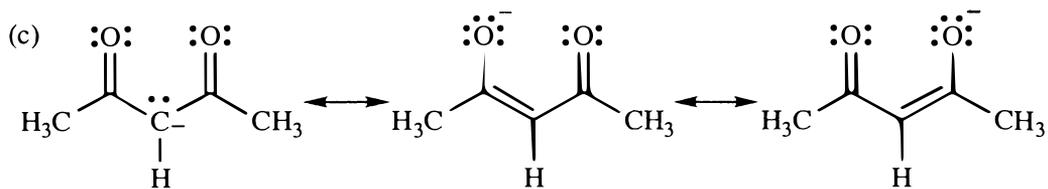
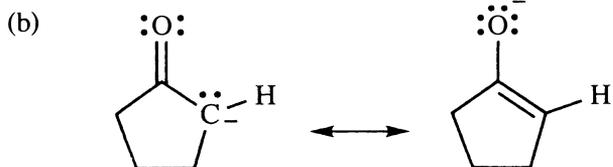
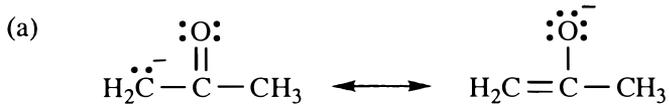
This planar enol intermediate has lost all chirality. Protonation can occur with equal probability at either face of the pi bond leading to racemic product.



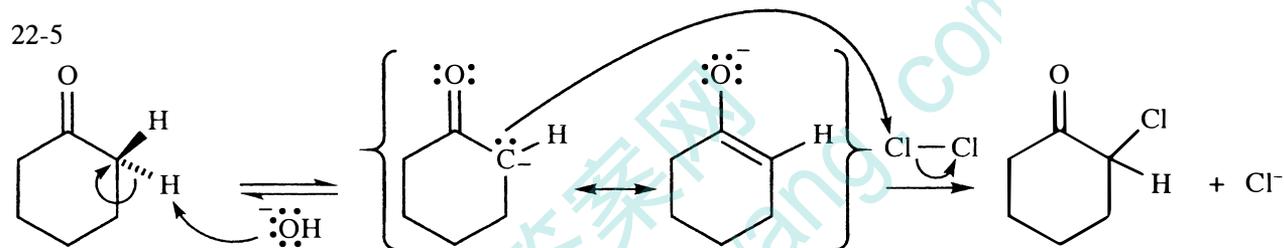
22-3



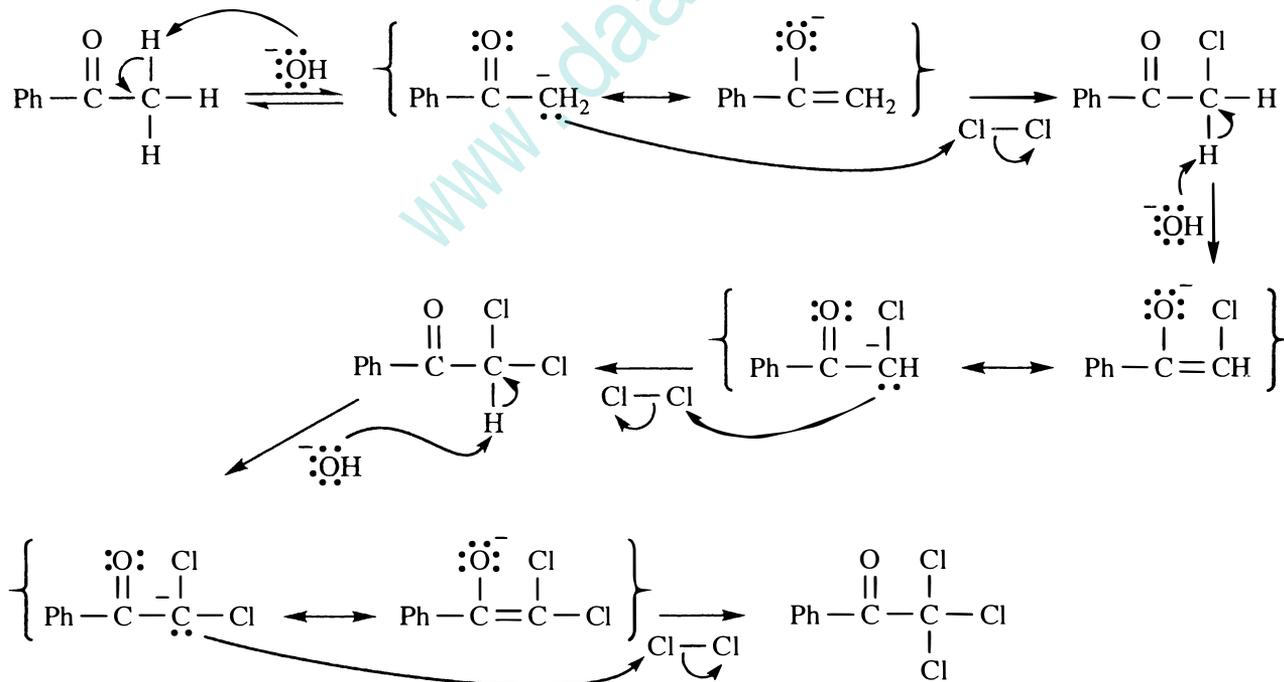
22-4



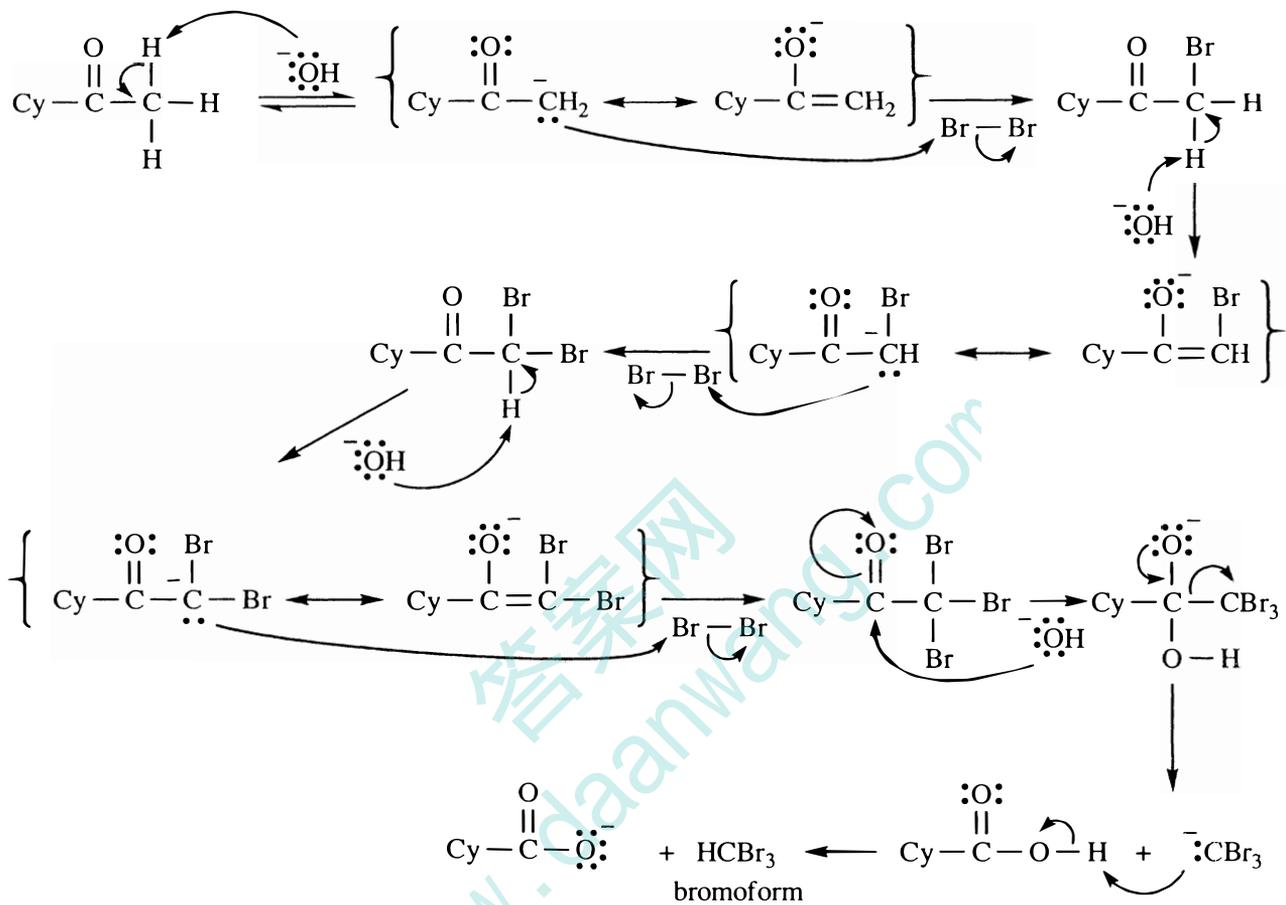
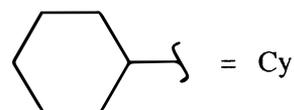
22-5



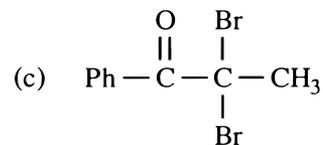
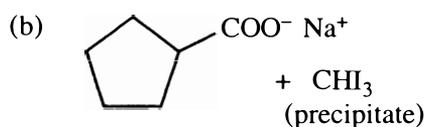
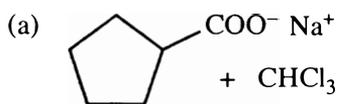
22-6



22-7 For this problem, the cyclohexyl group is abbreviated "Cy".

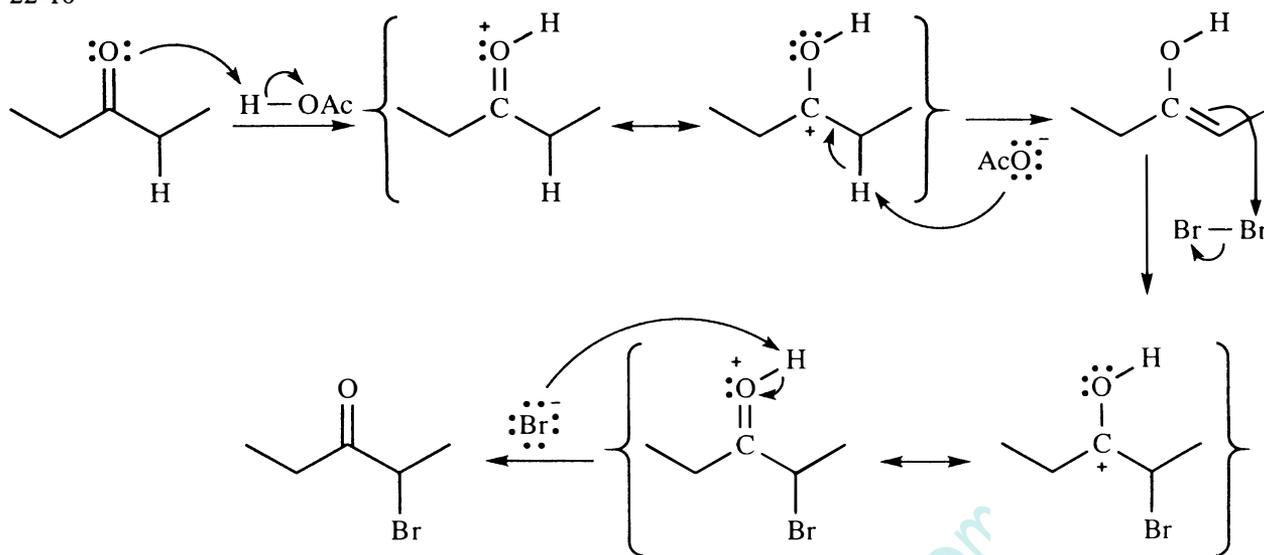


22-8

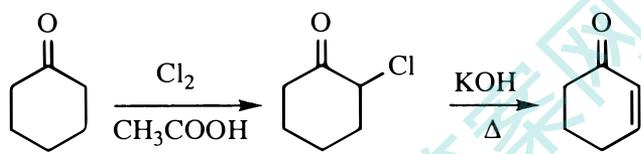


22-9 Methyl ketones, and alcohols which are oxidized to methyl ketones, will give a positive iodoform test. All of the compounds in this problem except pentan-3-one (part (d)) will give a positive iodoform test.

22-10



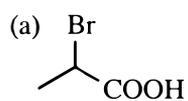
22-11



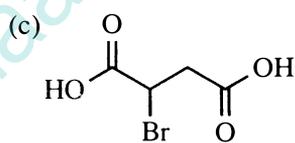
from Solved Problem 22-2

E2 elimination

22-12

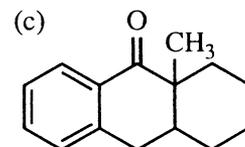
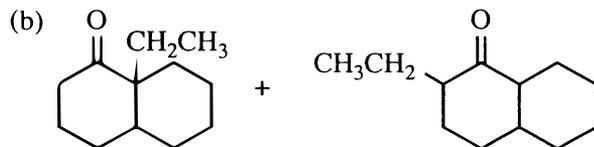
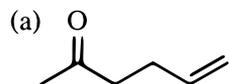


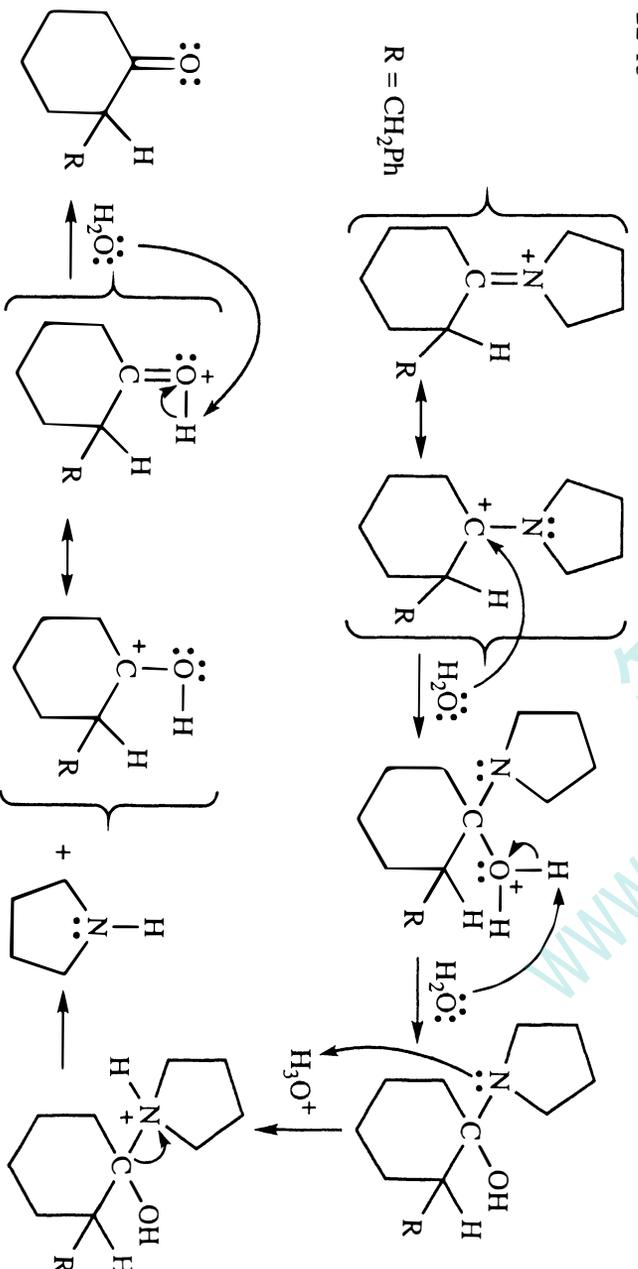
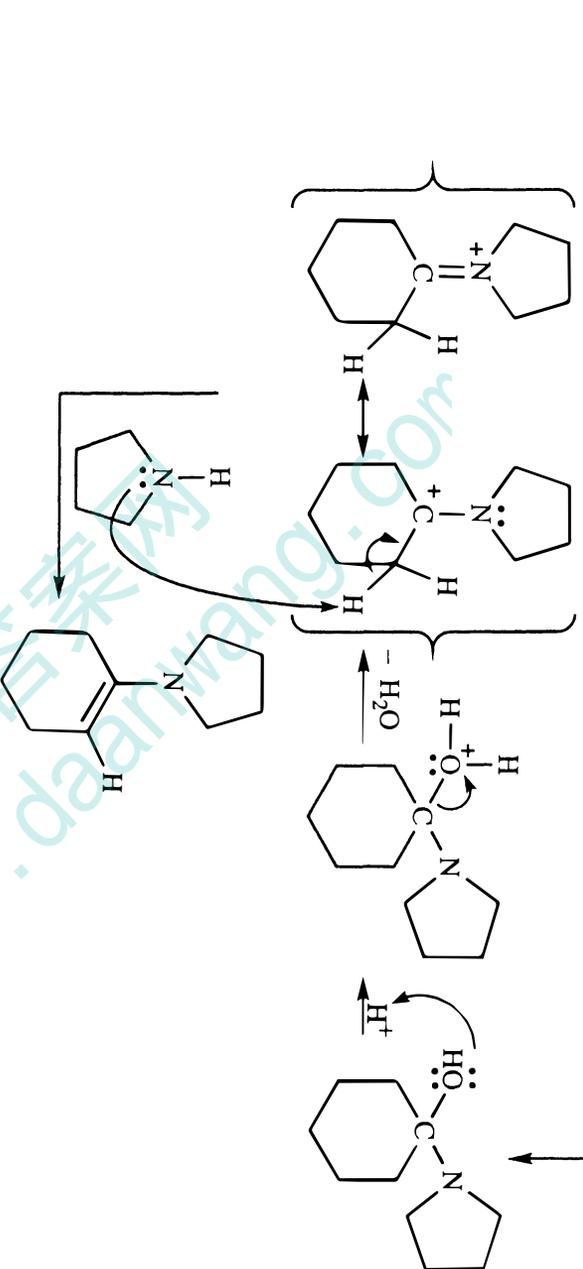
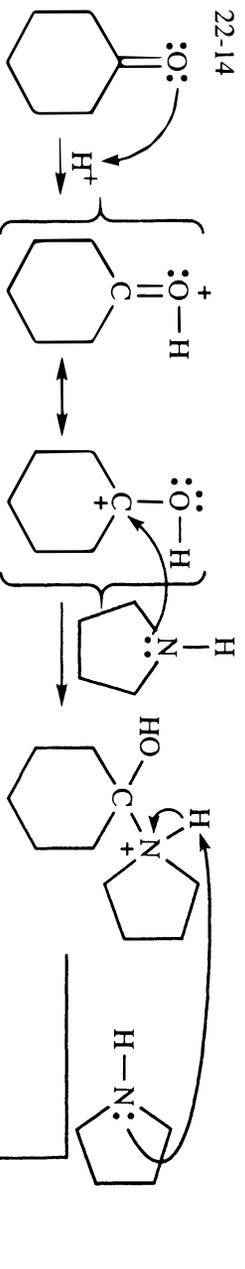
(b) no reaction:
no α -hydrogen



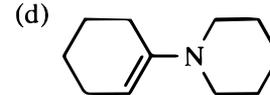
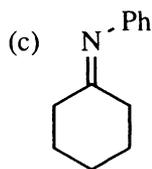
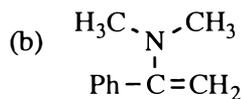
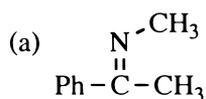
(d) no reaction:
no α -hydrogen

22-13

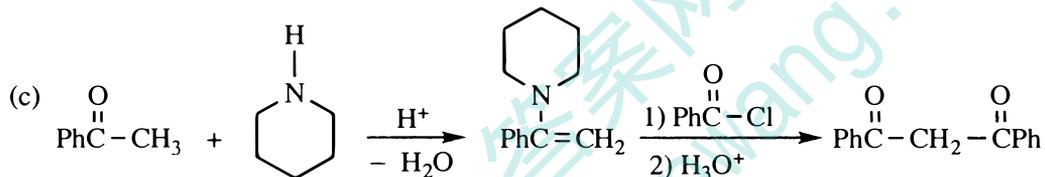
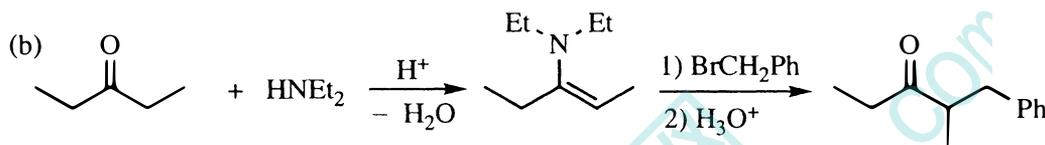
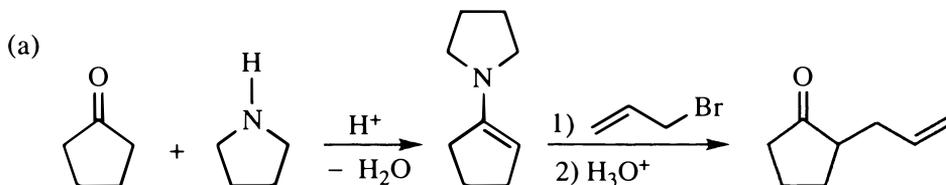




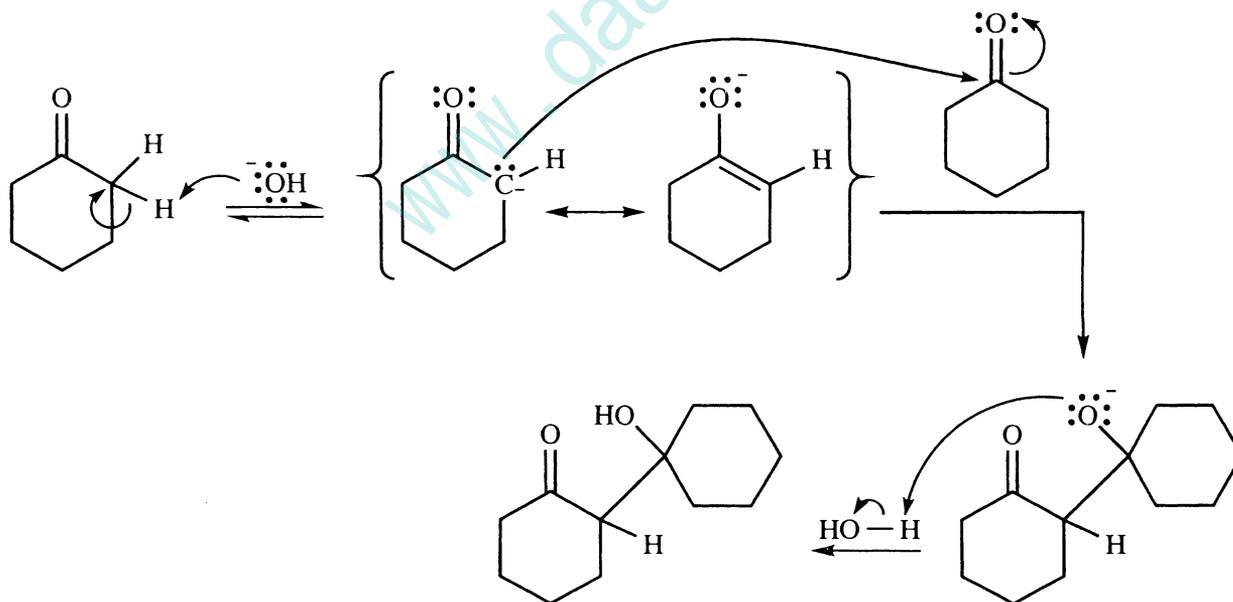
22-16



22-17 Any 2° aliphatic amines can be used for this problem.



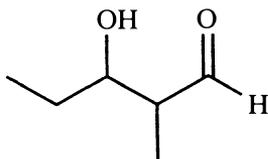
22-18



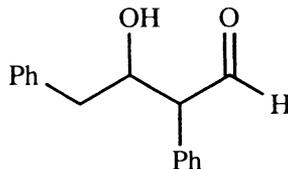
In general, the equilibrium in aldol condensations of ketones favors reactants rather than products. There is significant steric hindrance at both carbons with new bonds, so it is reasonable to conclude that this reaction of cyclohexanone would also favor reactants at equilibrium.

22-19

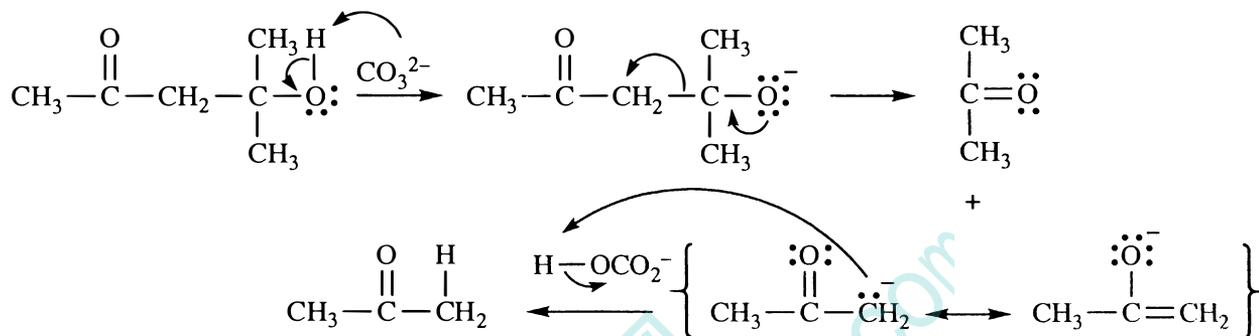
(a)



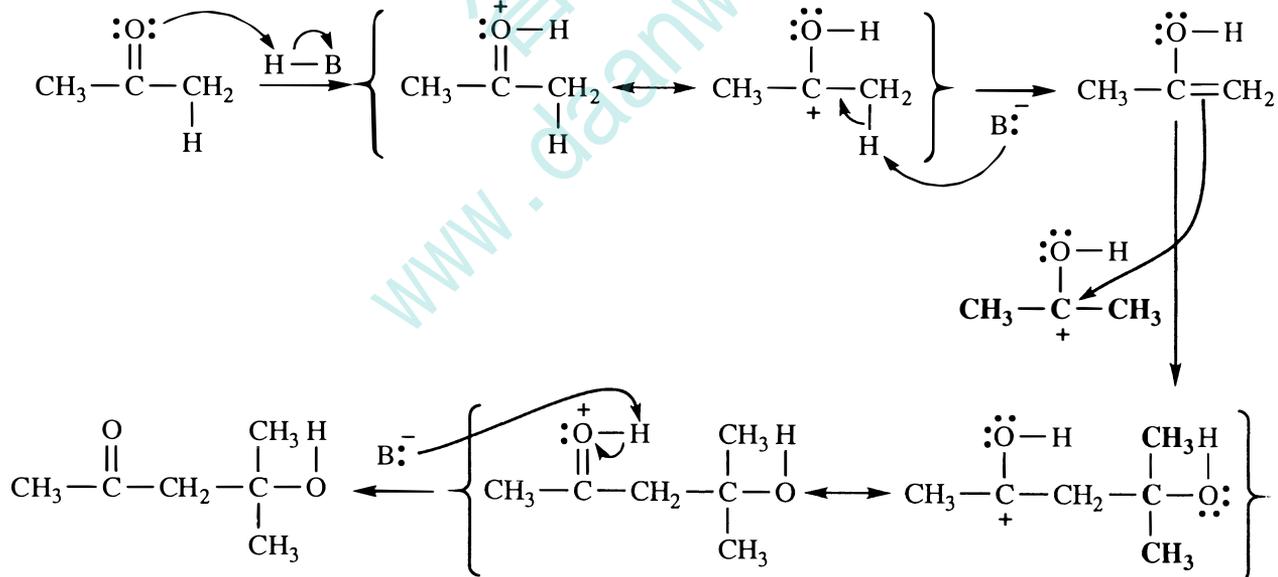
(b)



22-20 All the steps in the aldol condensation are reversible. Adding base to diacetone alcohol promoted the reverse aldol reaction. The equilibrium greatly favors acetone.



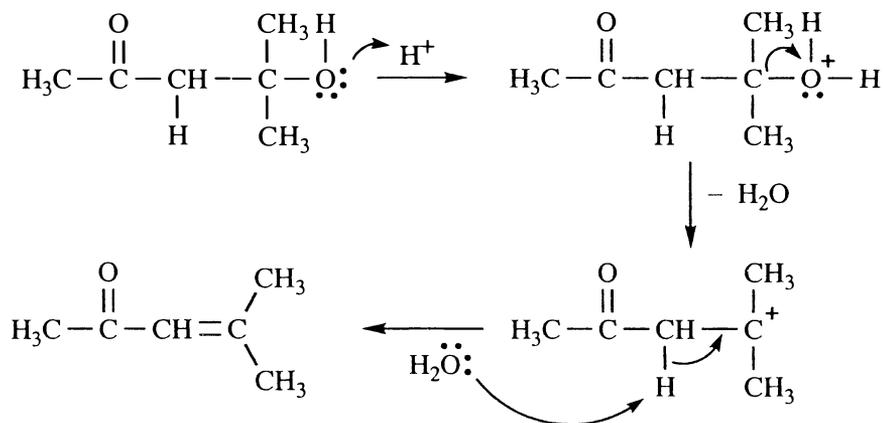
22-21



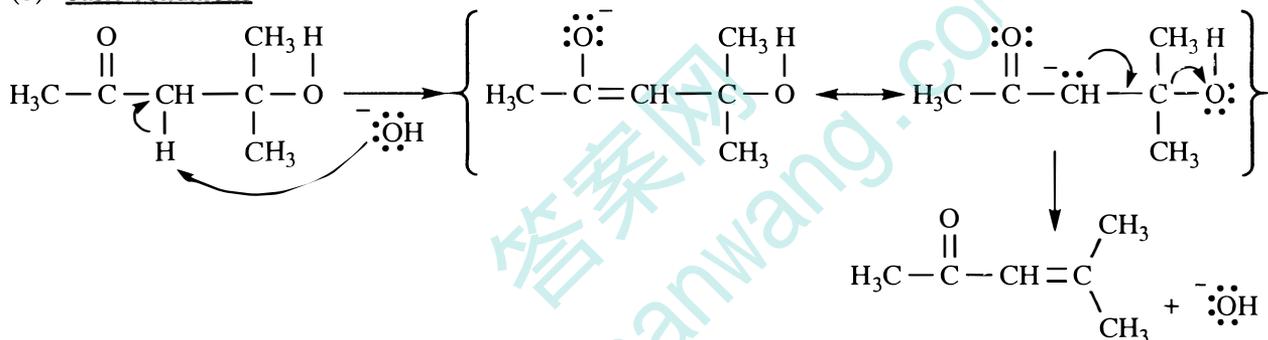
carbons of the electrophile are shown in **bold** just to keep track of which carbons come from which molecule

22-22

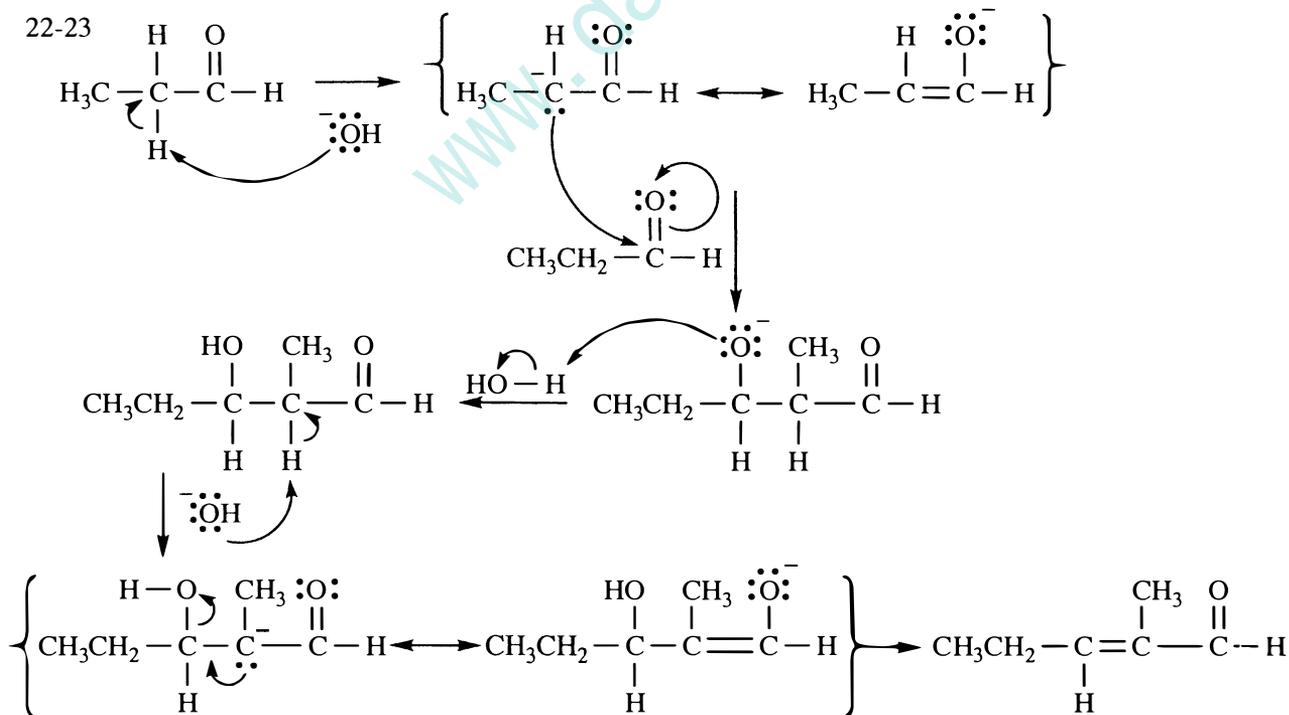
(a) acidic conditions



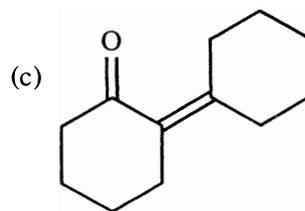
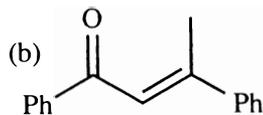
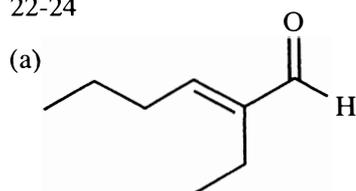
(b) basic conditions



22-23



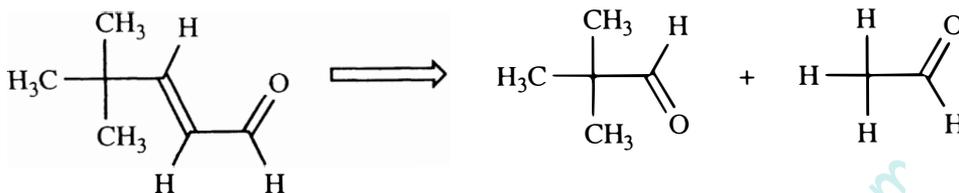
22-24



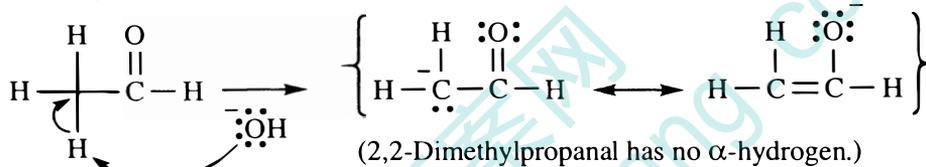
22-25

(a)

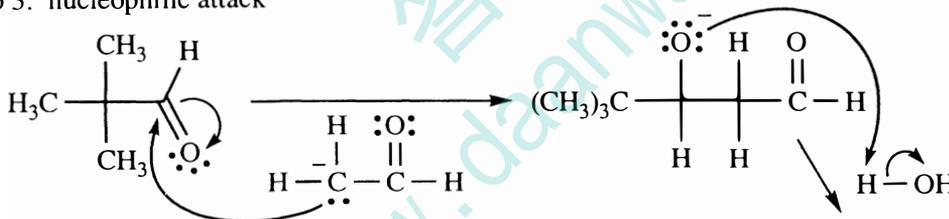
Step 1: carbon skeletons



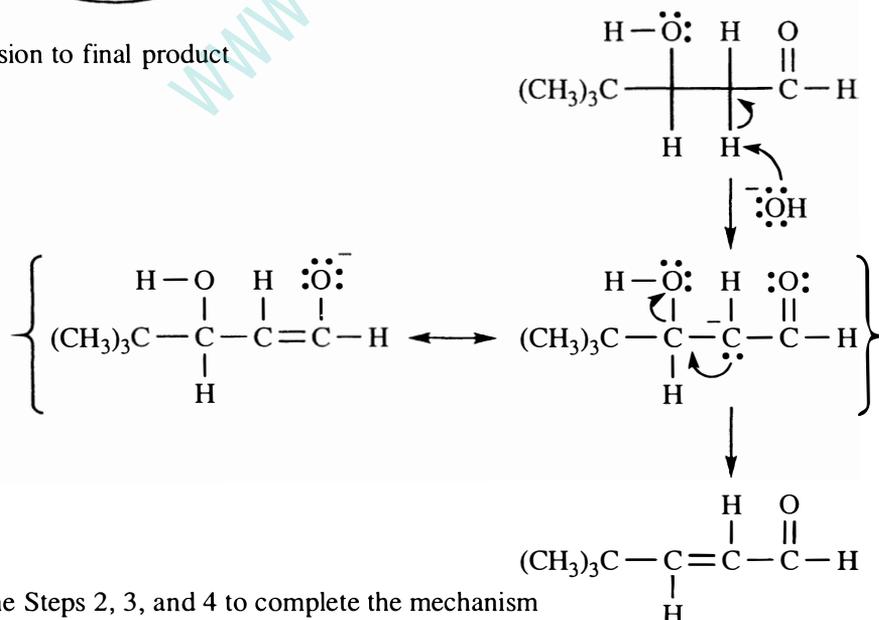
Step 2: nucleophile generation



Step 3: nucleophilic attack



Step 4: conversion to final product

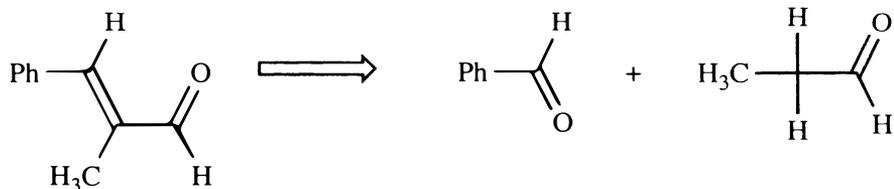


Step 5: combine Steps 2, 3, and 4 to complete the mechanism

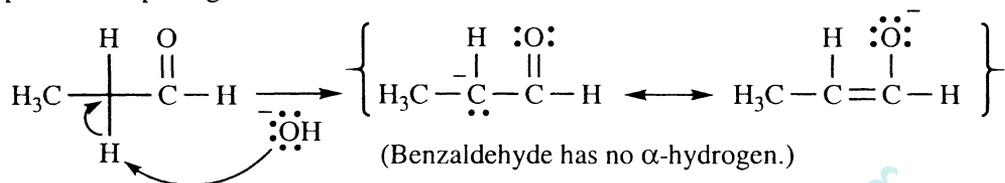
22-25 continued

(b)

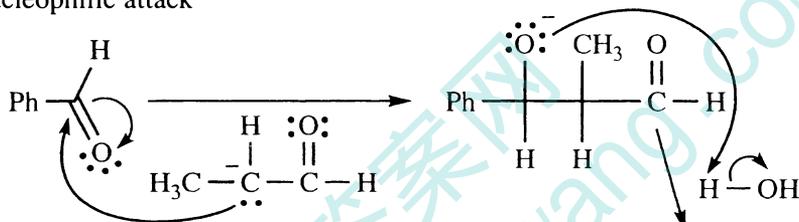
Step 1: carbon skeletons



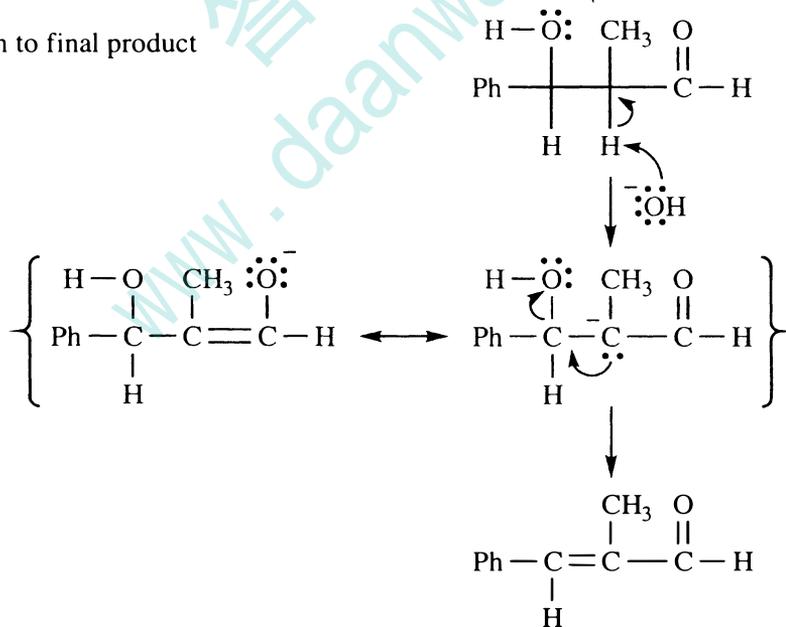
Step 2: nucleophile generation



Step 3: nucleophilic attack



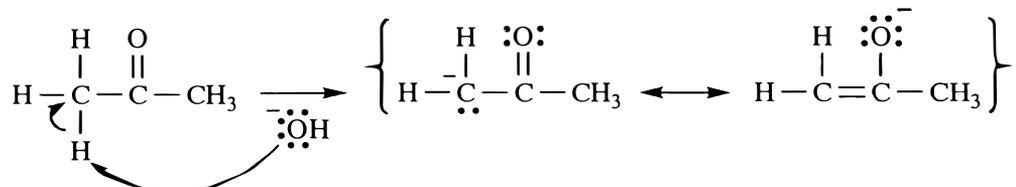
Step 4: conversion to final product



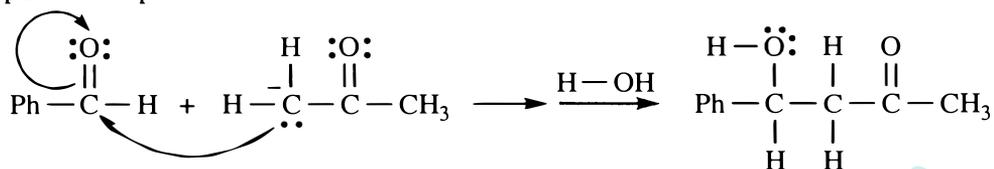
Step 5: combine Steps 2, 3, and 4 to complete the mechanism

22-26 This solution presents the sequence of reactions leading to the product, following the format of the Problem-Solving feature. This is not a complete mechanism.

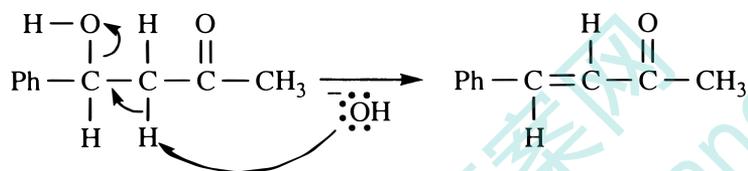
Step 2: generation of the nucleophile



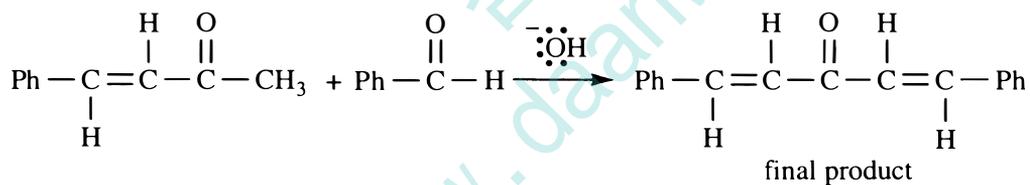
Step 3: nucleophilic attack



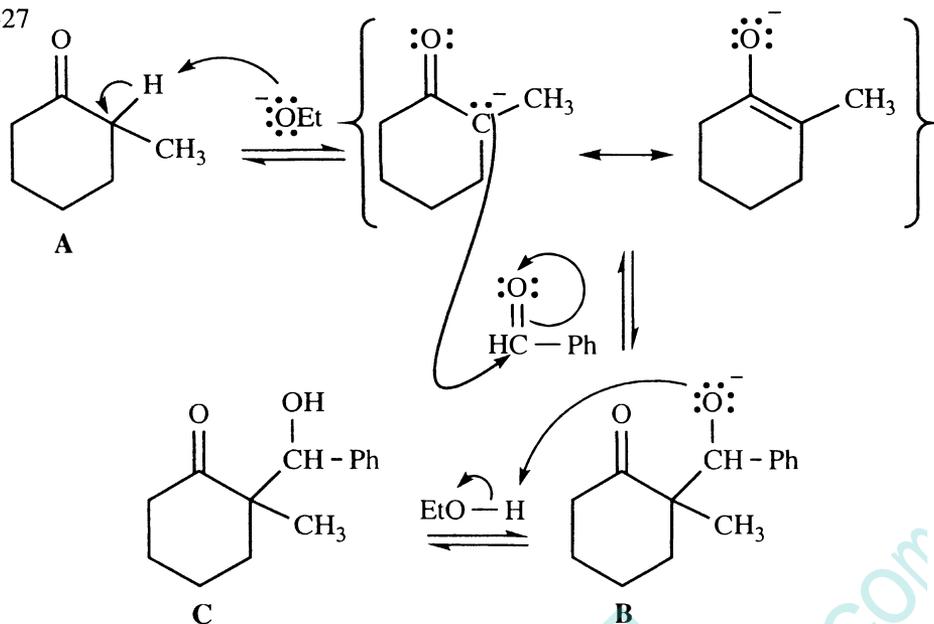
Step 4: dehydration



The same sequence of steps occurs on the other side.



22-27



There are three problems with the reaction as shown:

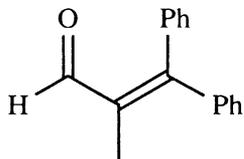
1. Hydrogen on a 3° carbon (structure A) is less acidic than hydrogen on a 2° carbon. The 3° hydrogen will be removed at a slower rate than the 2° hydrogen.

2. Nucleophilic attack by the 3° carbon will be more hindered, and therefore slower, than attack by the 2° carbon. Structure B is quite hindered.

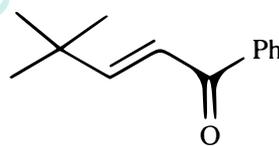
3. Once a normal aldol product is formed, dehydration gives a conjugated system which has great stability. The aldol product C cannot dehydrate because no α -hydrogen remains. Some C will form, but eventually the reverse-aldol process will return C to starting materials which, in turn, will react at the other α -carbon to produce the conjugated system. (This reason is the Kiss of Death for C.)

22-28

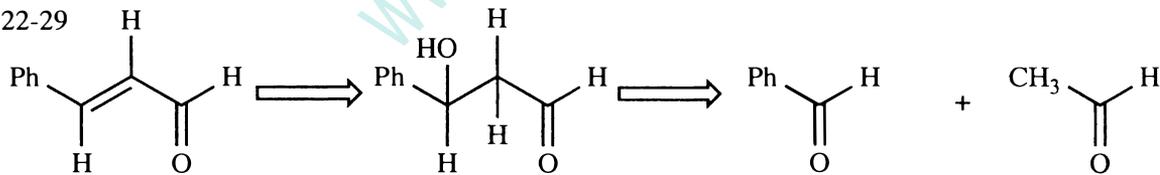
(a)



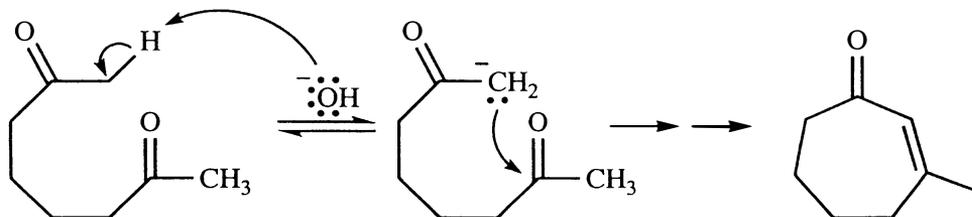
(b)



22-29

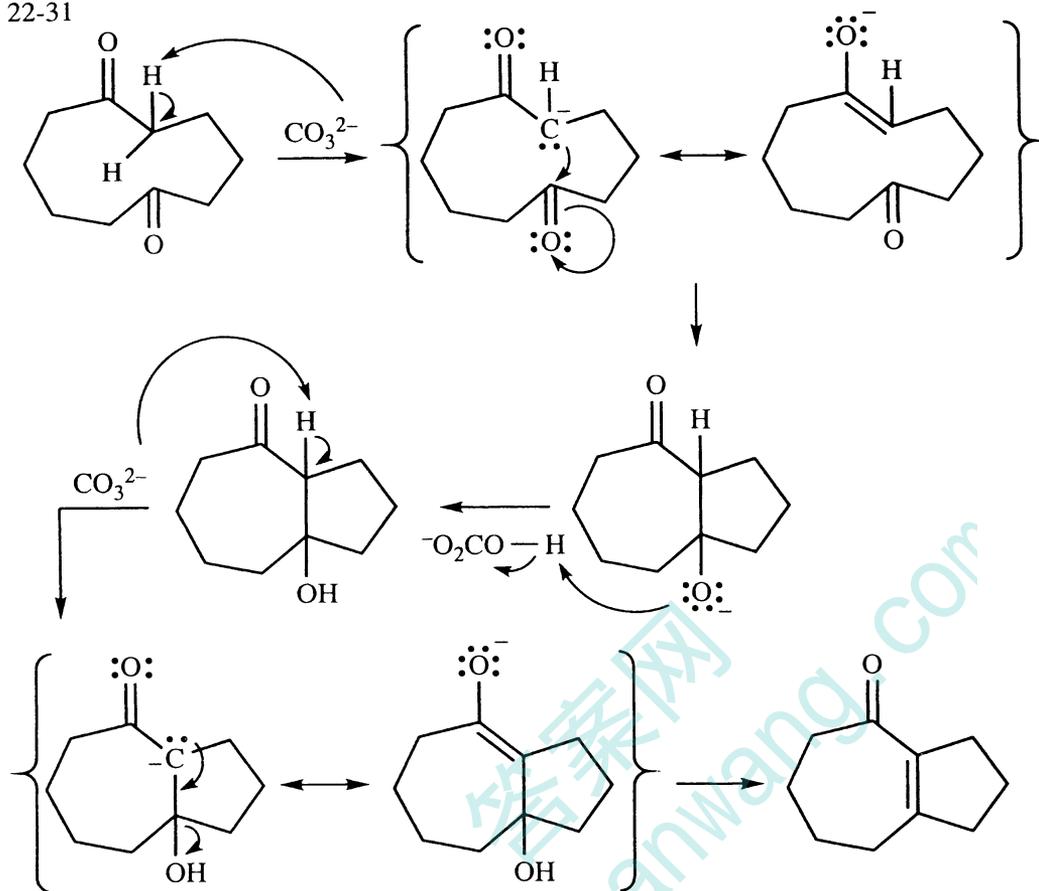


22-30

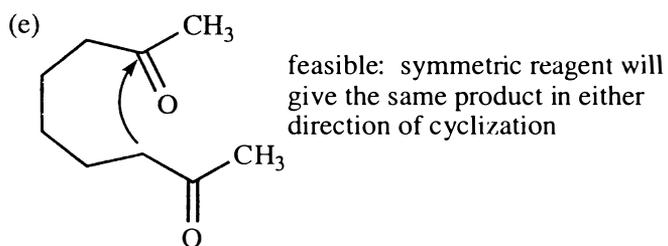
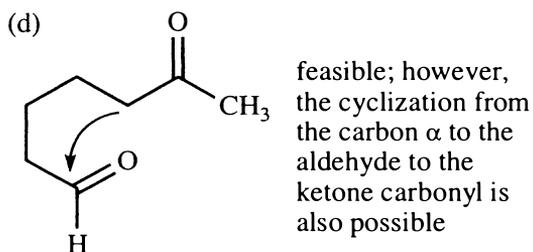
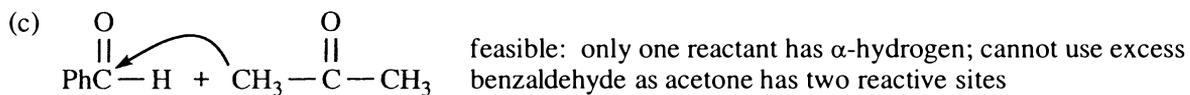
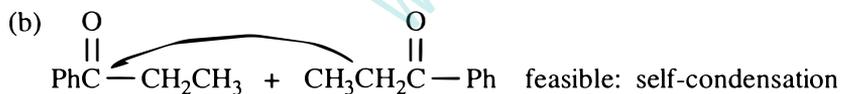
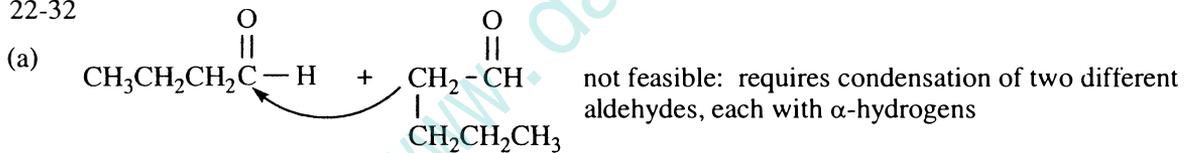


The formation of a seven-membered ring is unfavorable for entropy reasons: the farther apart the nucleophile and the electrophile, the harder time they will have finding each other. If the molecule has a possibility of forming a 5- or a 7-membered ring, it will almost always prefer to form the 5-membered ring.

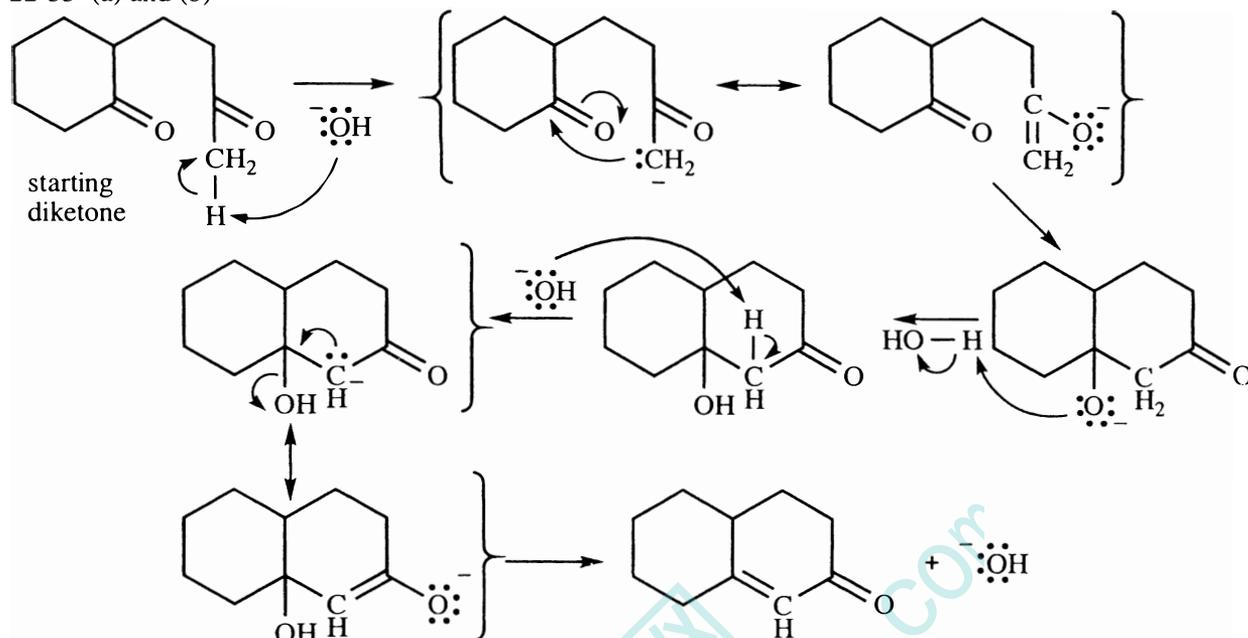
22-31



22-32



22-33 (a) and (b)



22-34

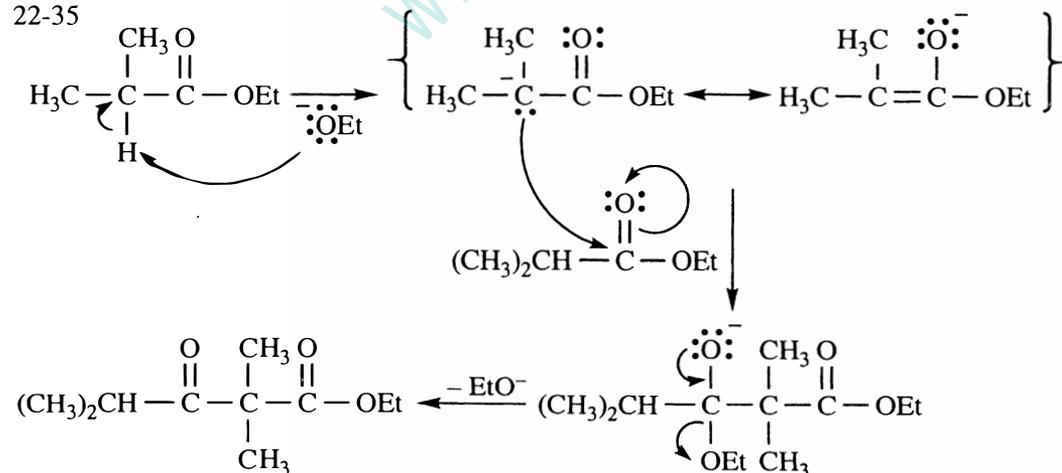
(a) The side reaction with sodium methoxide is transesterification. The starting material, and therefore the product, would be a mixture of methyl and ethyl esters.



(b) Sodium hydroxide would irreversibly saponify the ester, completely stopping the Claisen condensation as the carbonyl no longer has a leaving group attached to it.



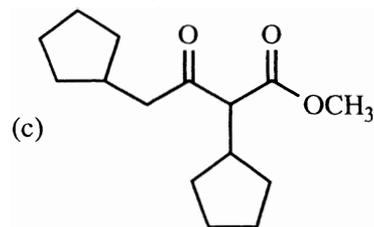
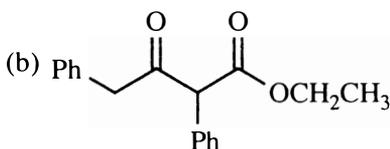
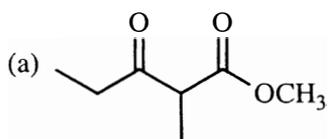
22-35



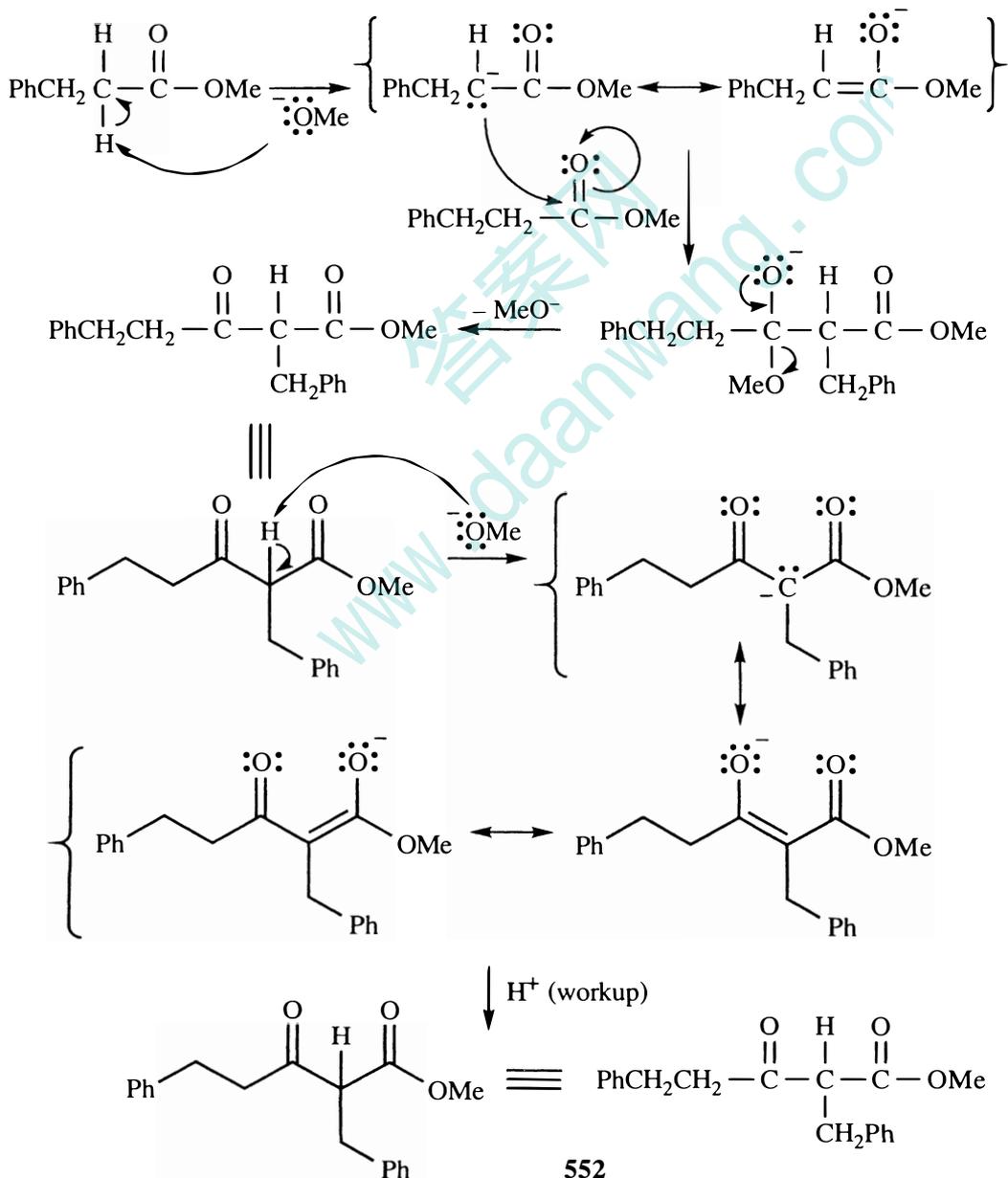
22-35 continued

There are two reasons why this reaction gives a poor yield. The nucleophilic carbon in the enolate is 3° and attack is hindered. More important, the final product has no hydrogen on the α -carbon, so the deprotonation by base which is the driving force in other Claisen condensations cannot occur here. What is produced is an *equilibrium mixture* of product and starting materials; the conversion to product is low.

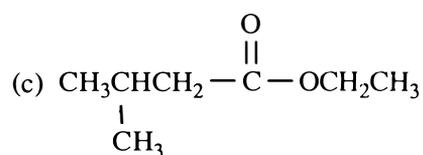
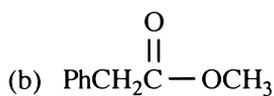
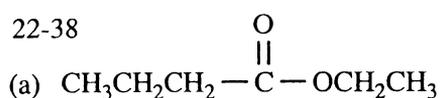
22-36



22-37

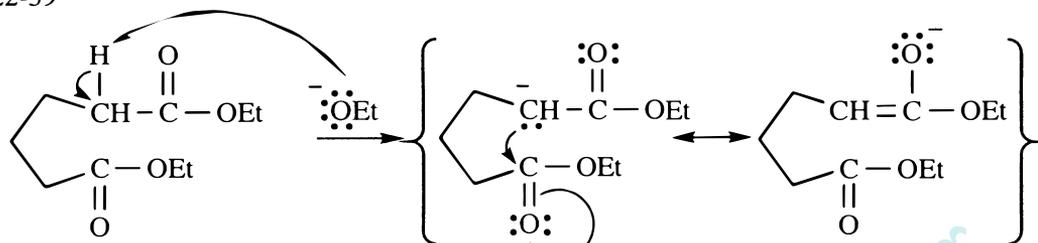


22-38

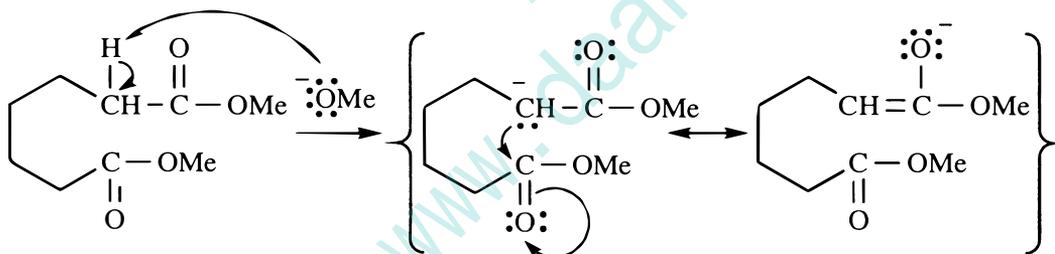
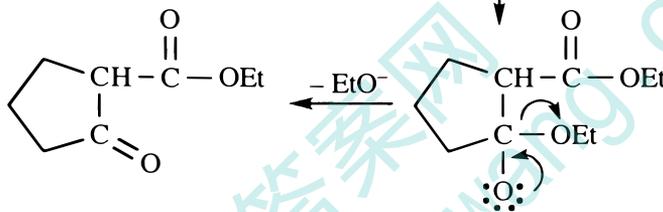


This one would be difficult because the alpha-carbon is hindered.

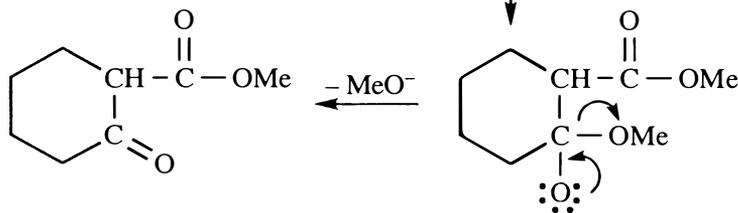
22-39



This is the final product, after removal of the α -hydrogen by ethoxide, followed by reprotonation during the workup.

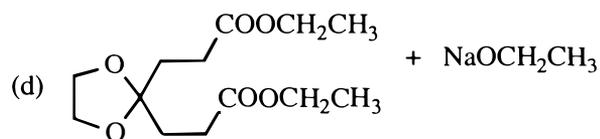
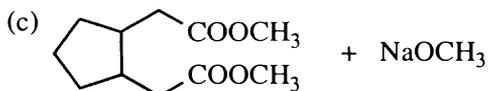
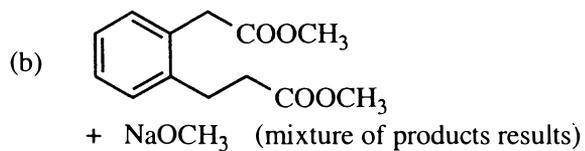


This is the final product, after removal of the α -hydrogen by ethoxide, followed by reprotonation during the workup.



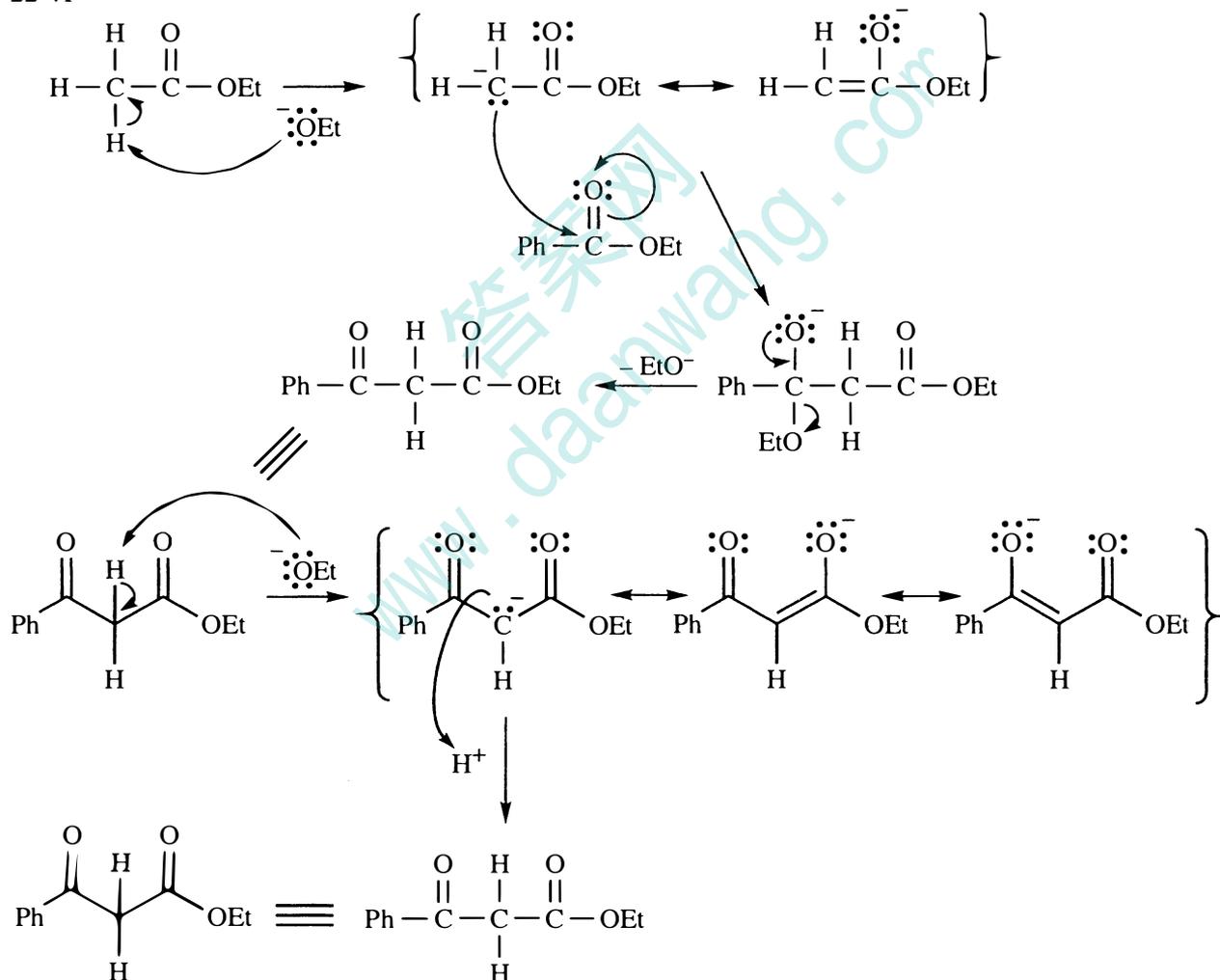
22-40

(a) not possible by Dieckmann—not a β -keto ester

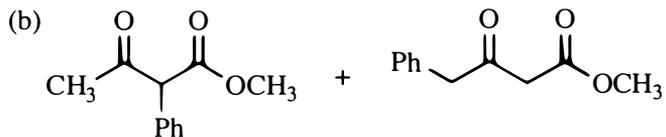
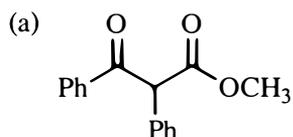


The protecting group is necessary to prevent aldol condensation. Aqueous acid workup removes the protecting group.

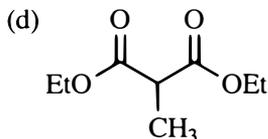
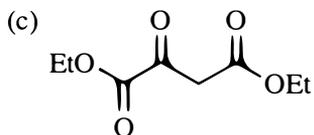
22-41



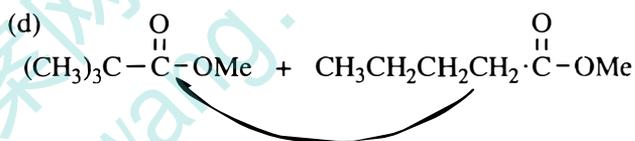
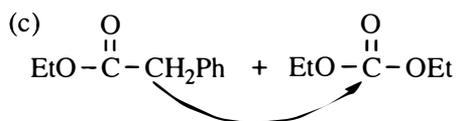
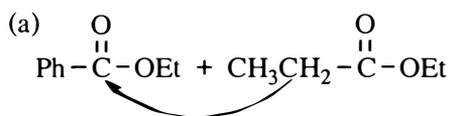
22-42



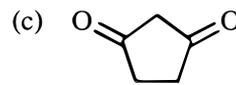
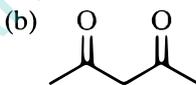
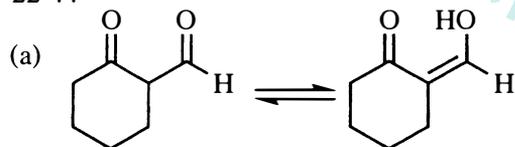
plus 2 self-condensation products—a poor choice because both esters have α -hydrogens



22-43



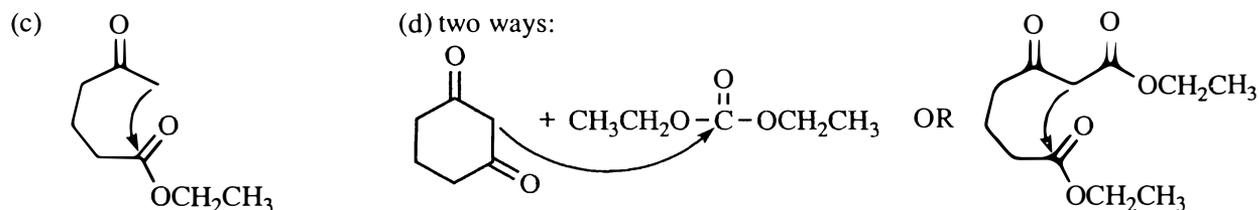
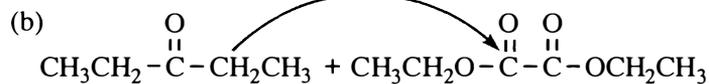
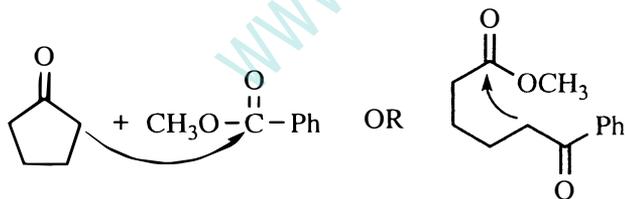
22-44



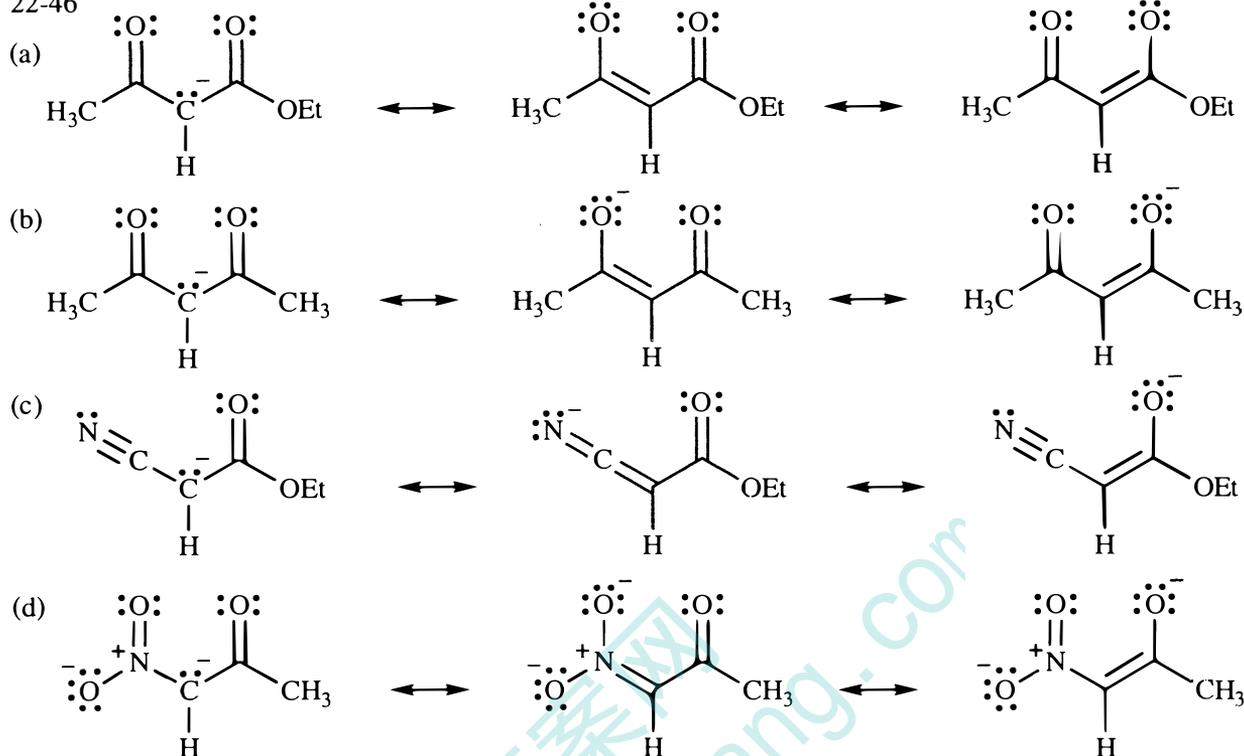
actually present in the enol form:

22-45

(a) two ways:

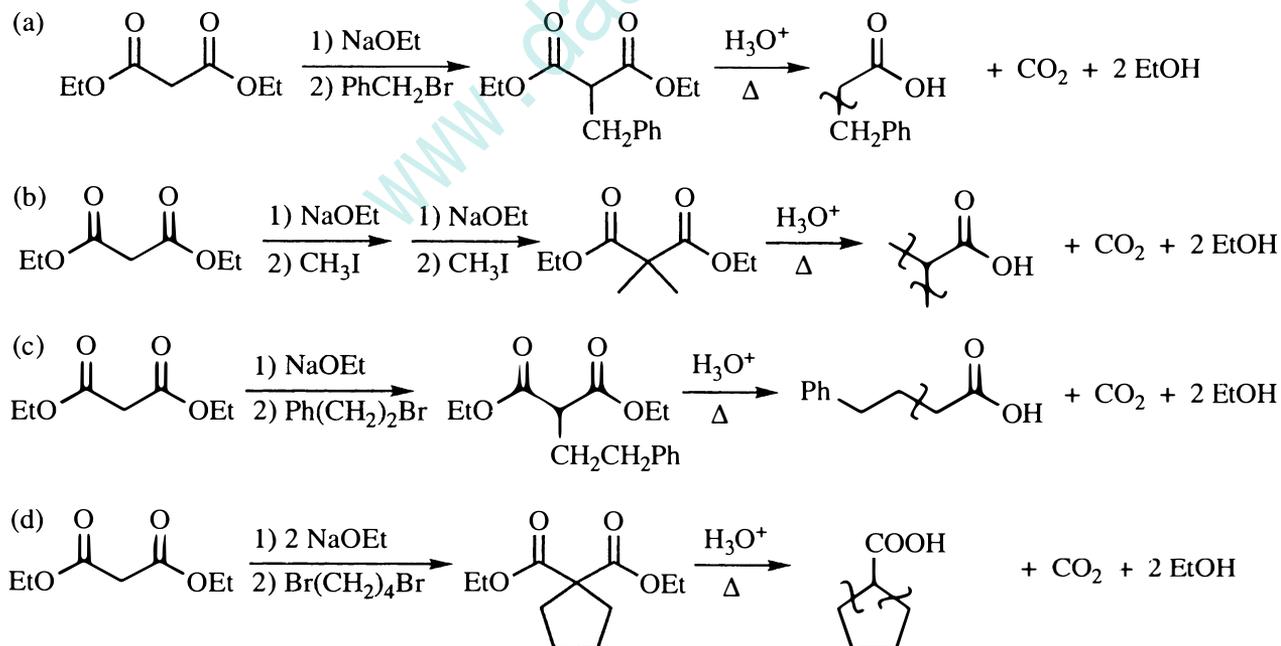


22-46



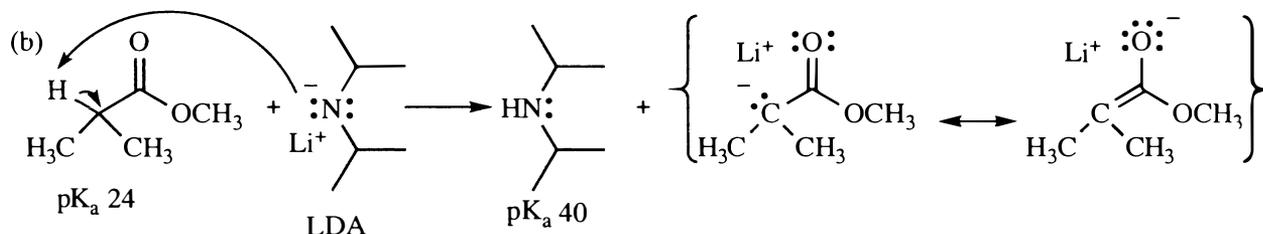
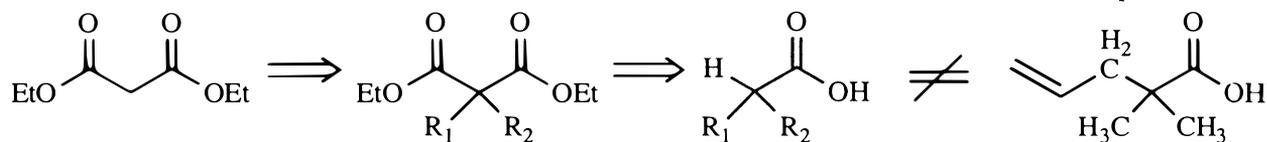
(other resonance forms of the nitro group are not shown)

22-47 In the products, the wavy lines cross the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetic acid.

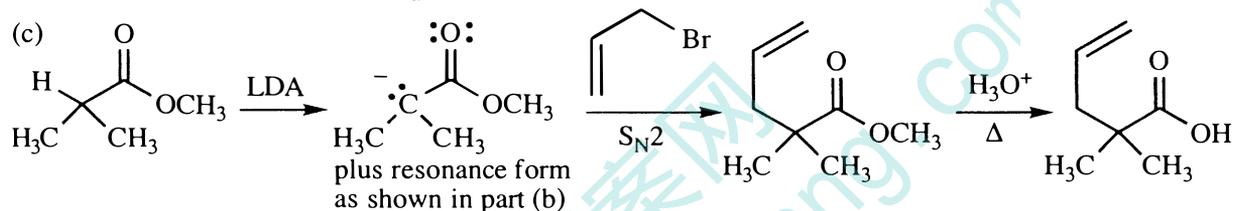


22-48

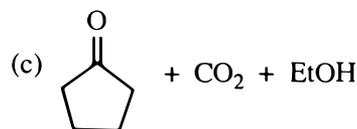
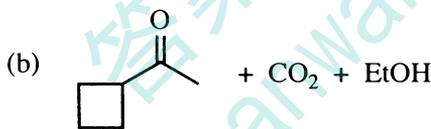
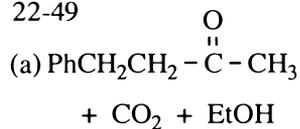
(a) Only two substituent groups plus a hydrogen atom can appear on the alpha carbon after decarboxylation at the end of the malonic ester synthesis. The product shown has three alkyl groups, so it cannot be made by malonic ester synthesis.



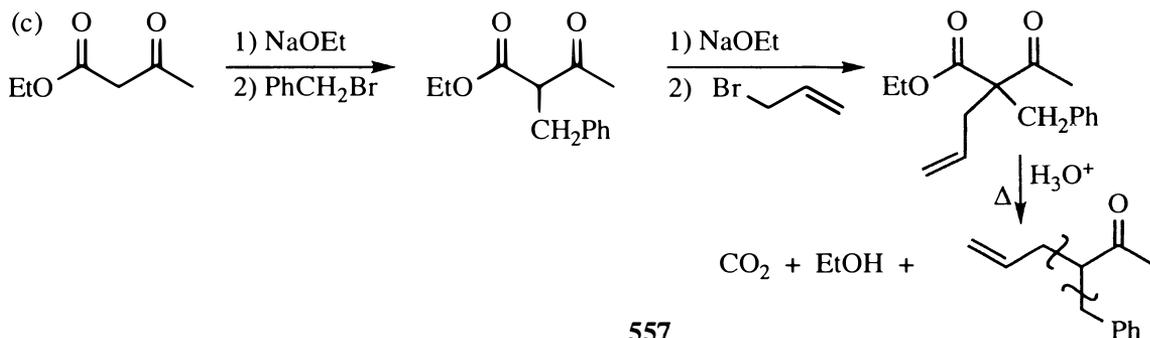
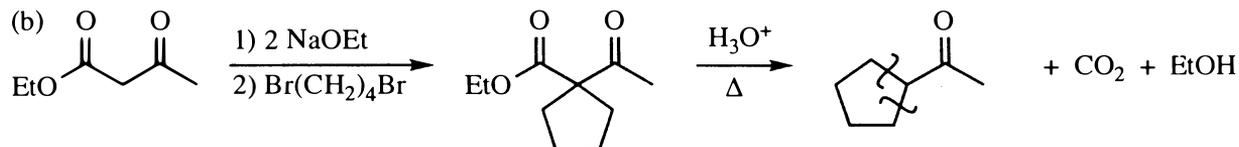
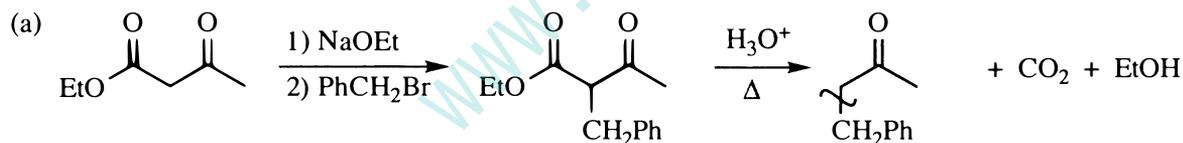
With such a large difference in pK_a values, products are favored $\gg 99\%$.



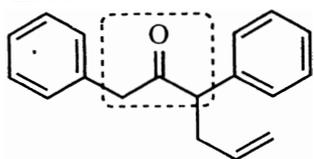
22-49



22-50 In the products, the wavy lines indicate the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetone.

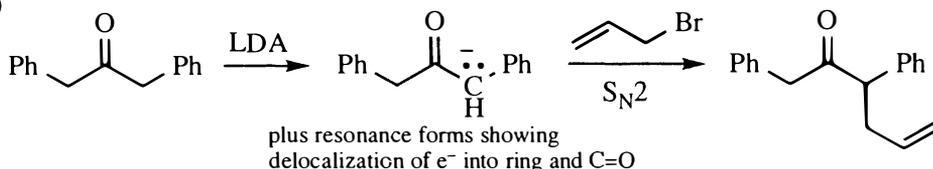


22-51

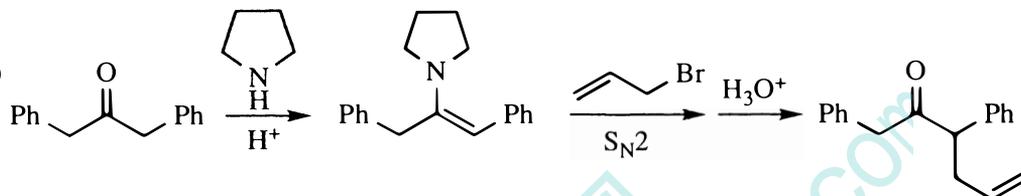


(a) There are two problems with attempting to make this compound by acetoacetic ester synthesis. The acetone "core" of the product is shown in the box. This product would require alkylation at BOTH carbons of the acetone "core" of acetoacetic ester; in reality, only one carbon undergoes alkylation in the acetoacetic ester synthesis. Second, it is not possible to do an S_N2 type reaction on an unsubstituted benzene ring, so neither benzene could be attached by acetoacetic ester synthesis.

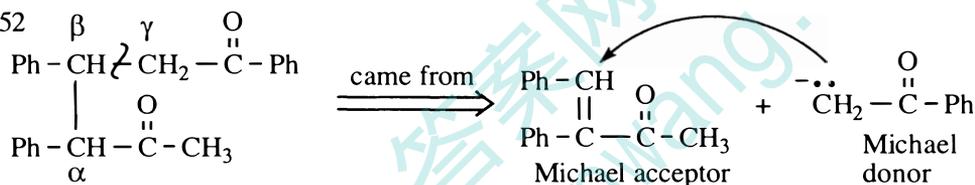
(b)



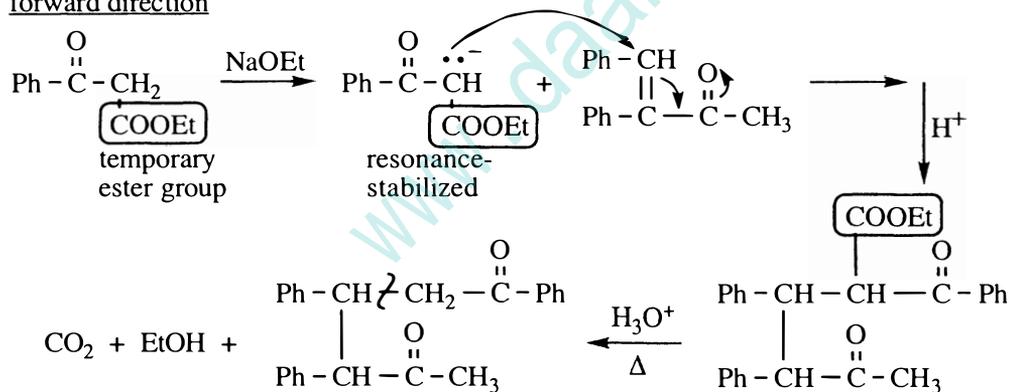
(c)



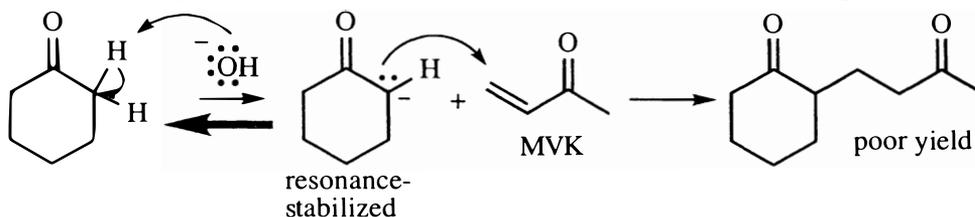
22-52



forward direction



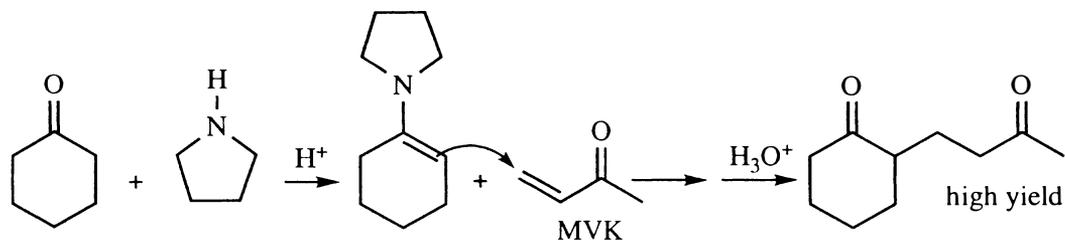
22-53 First, you might wonder why this sequence does not make the desired product:



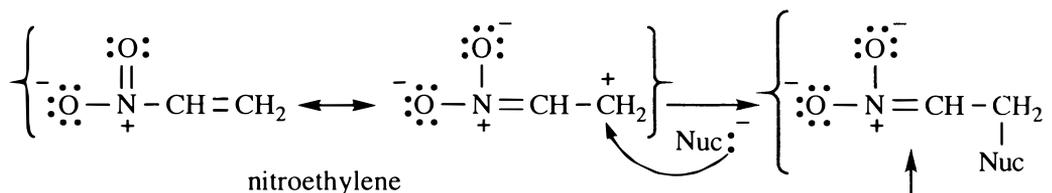
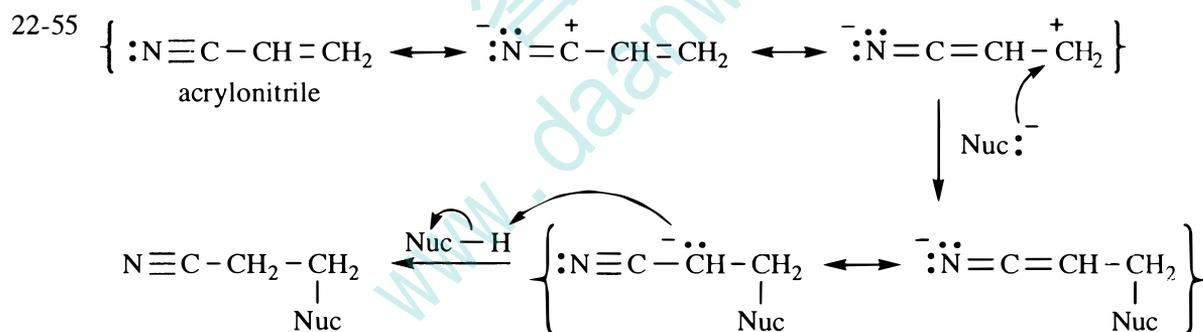
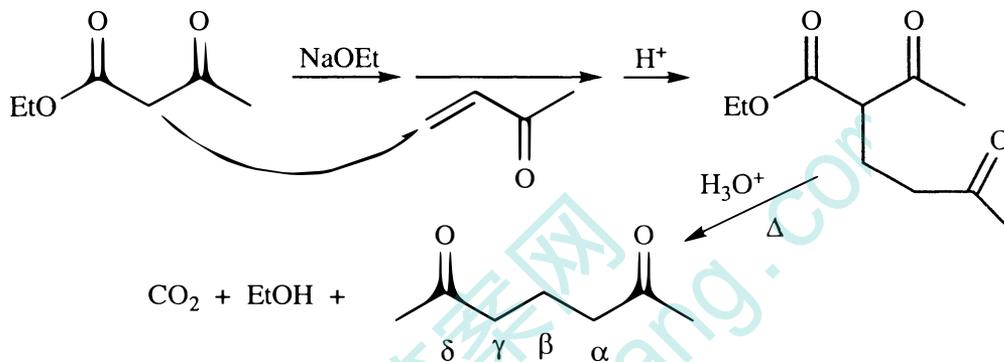
The poor yield in this conjugate addition is due primarily to the numerous competing reactions: the ketone enolate can self-condense (aldol), can condense with the ketone of MVK (aldol), or can deprotonate the methyl of MVK to generate a new nucleophile. The complex mixture of products makes this route practically useless. (continued on next page)

22-53 continued

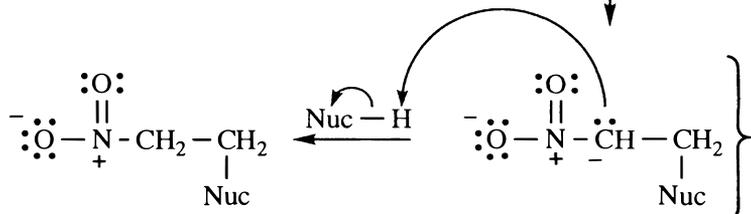
What permits enamines (or other stabilized enolates) to work are: a) the certainty of which atom is the nucleophile, and b) the lack of self-condensation. Enamines can also do conjugate addition:



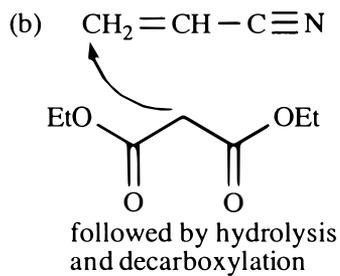
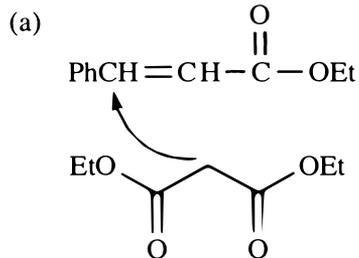
22-54 The enolate of acetoacetic ester can be used in a Michael addition to an α,β -unsaturated ketone like MVK.



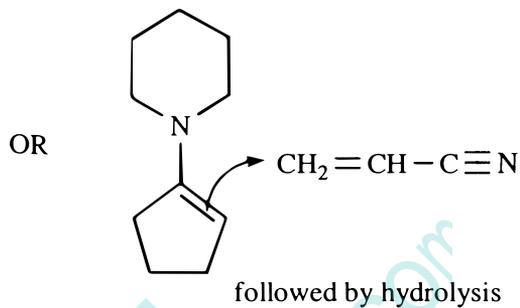
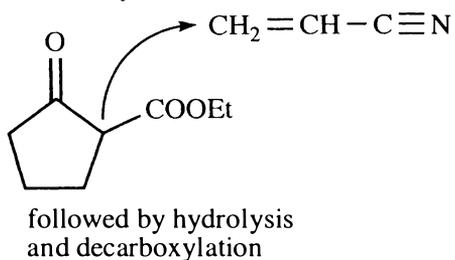
(some resonance forms of the nitro group are not shown)



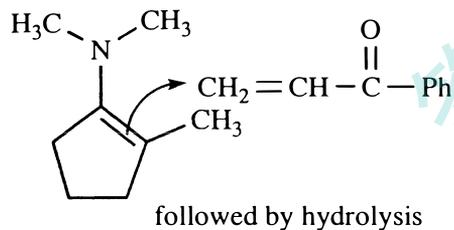
22-56



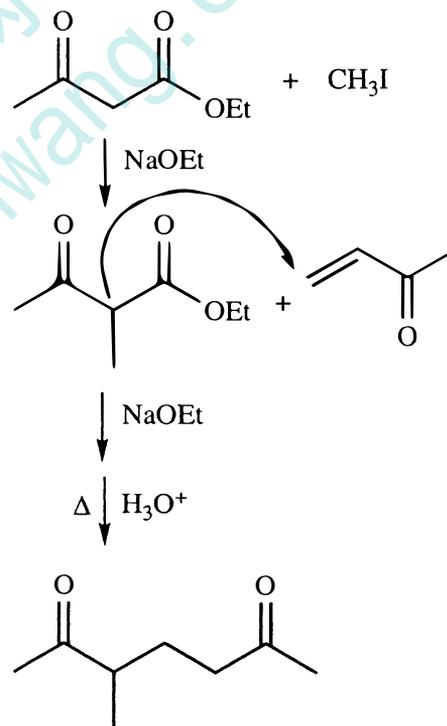
(c) two ways



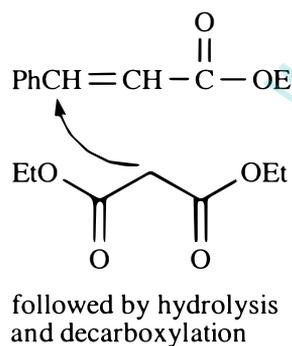
(d)



(e)

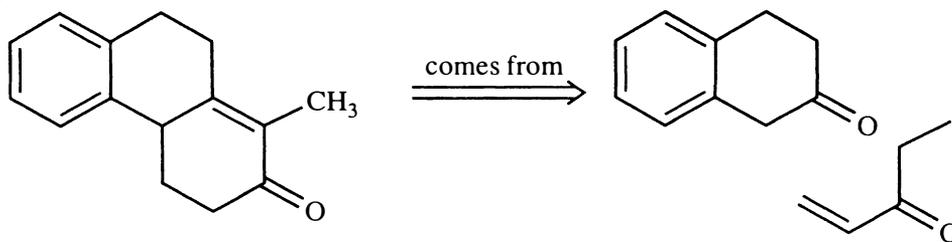


(f)

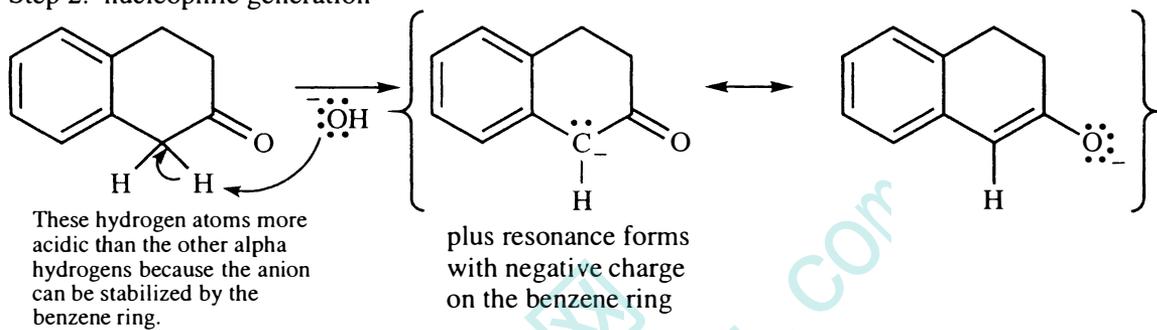


22-57

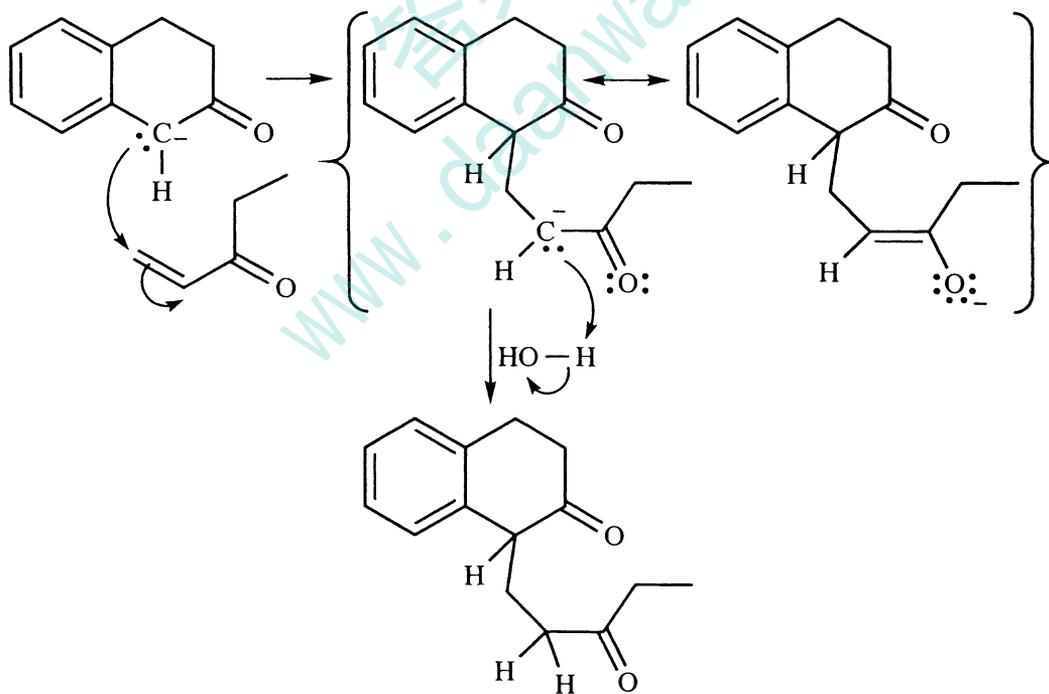
Step 1: carbon skeleton



Step 2: nucleophile generation



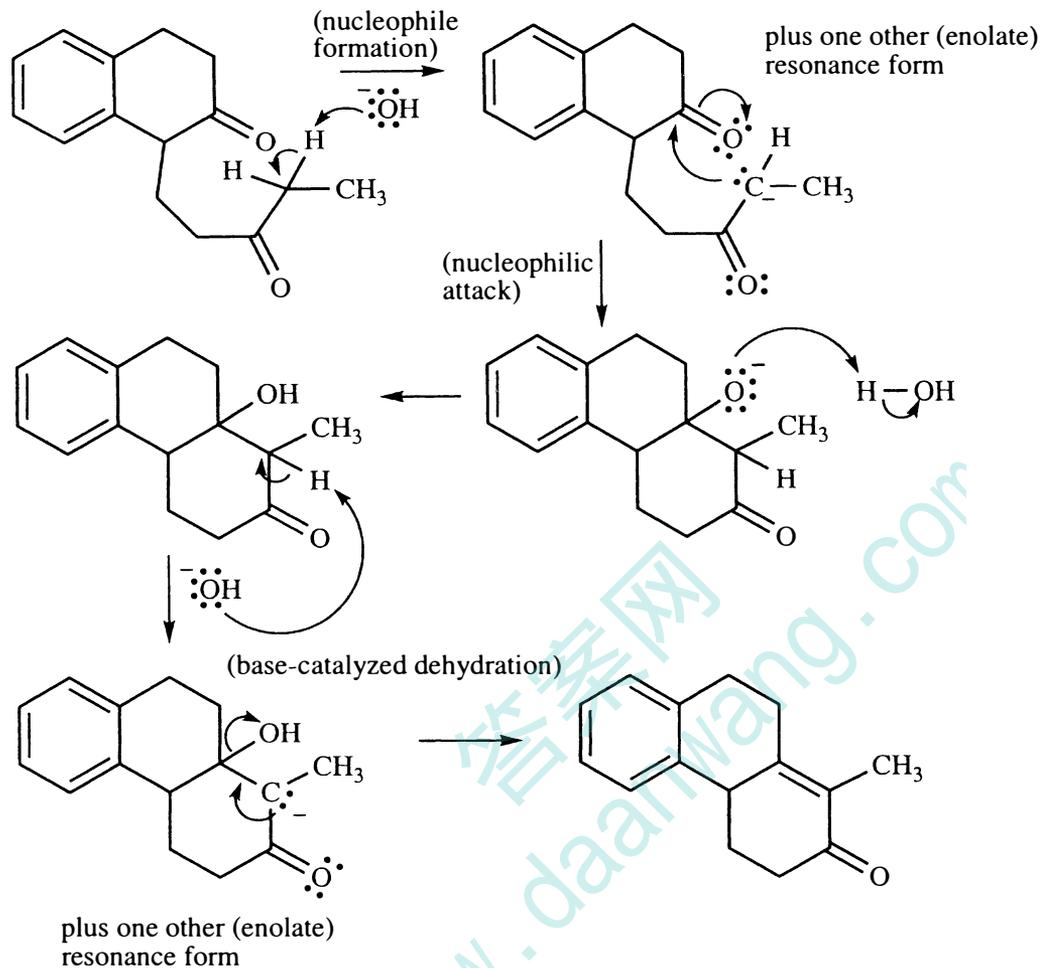
Step 3: nucleophilic attack (Michael addition)



continued on next page

22-57 continued

Step 4: conversion to final product

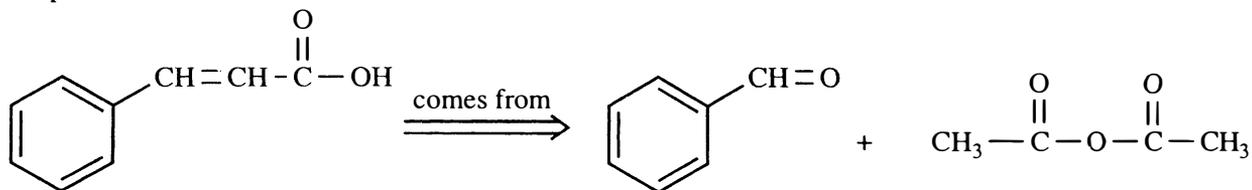


Step 5: The complete mechanism is the combination of Steps 2, 3, and 4. Notice that this mechanism is simply described by:

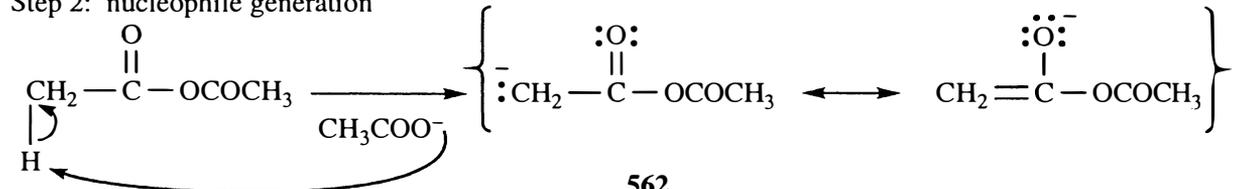
- 1) Enolate formation, followed by Michael addition;
- 2) Aldol condensation, followed by dehydration.

22-58

Step 1: carbon skeleton

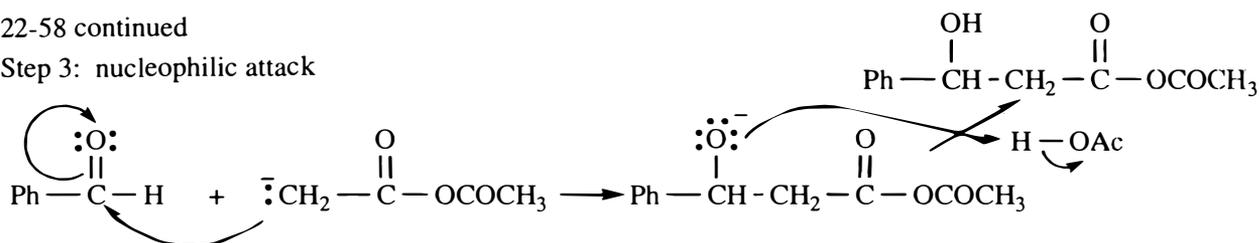


Step 2: nucleophile generation

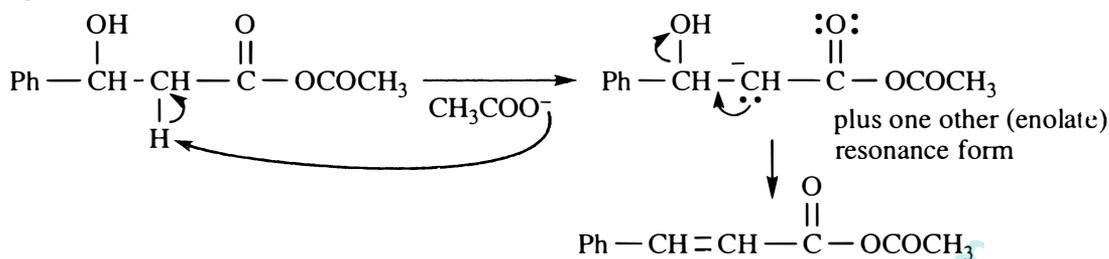


22-58 continued

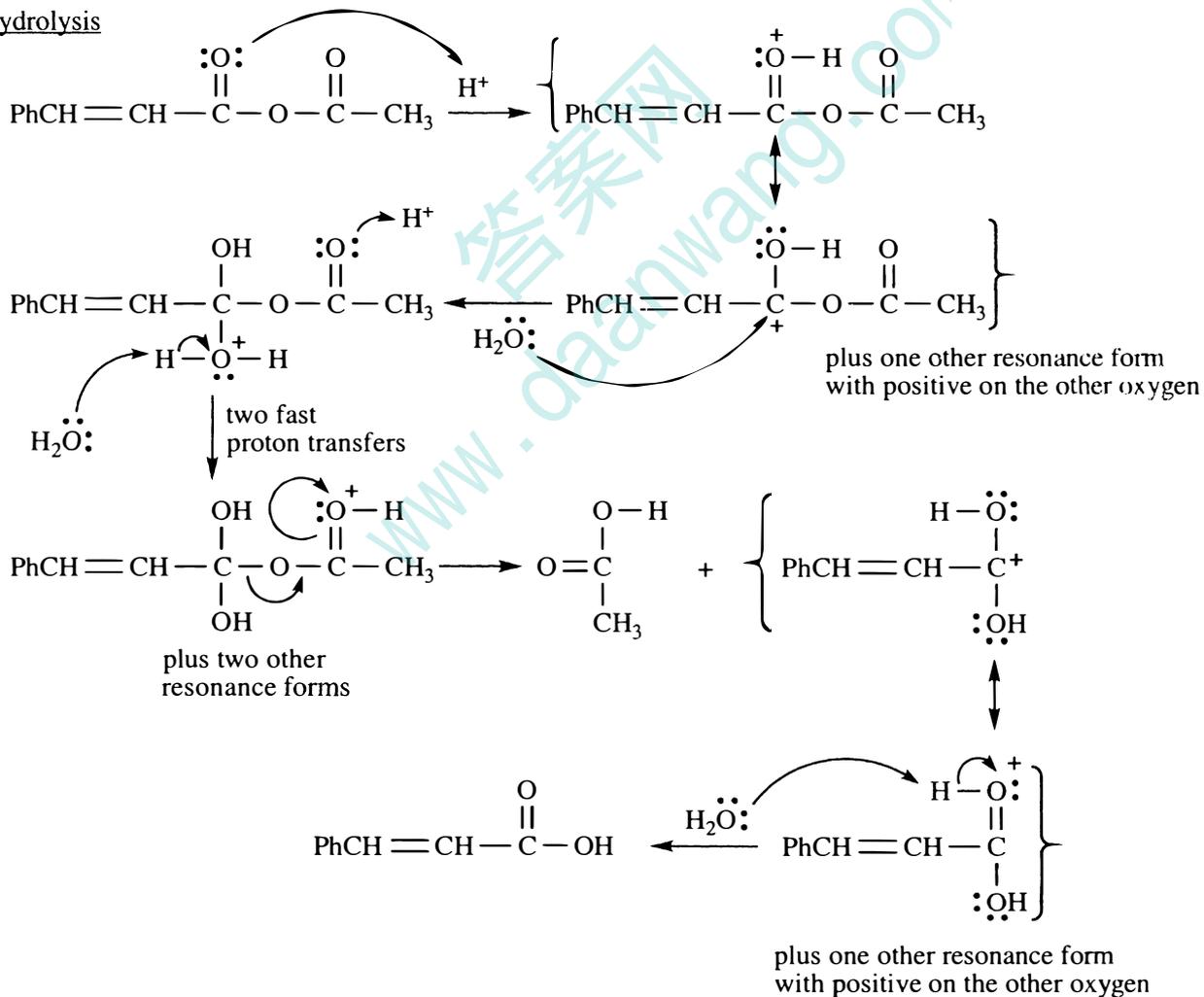
Step 3: nucleophilic attack



Step 4: conversion to final product



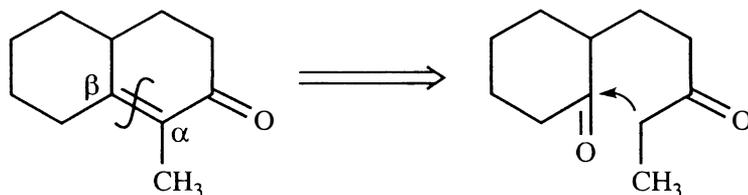
hydrolysis



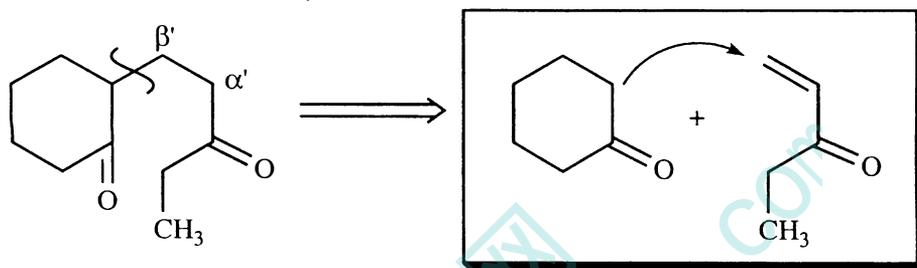
Step 5: The complete mechanism is the combination of Steps 2, 3, and 4.

22-59 The Robinson annulation consists of a Michael addition followed by aldol cyclization with dehydration. In the retrosynthetic direction, disconnect the alkene formed in the aldol/dehydration, then disconnect the Michael addition to discover the reactants.

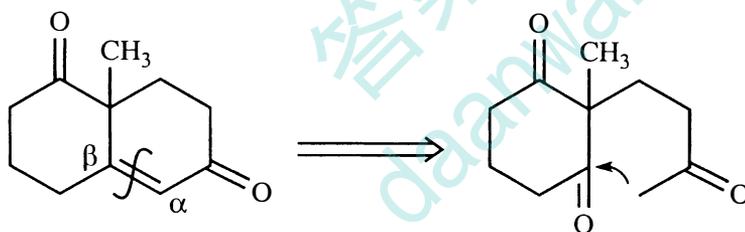
(a) aldol and dehydration forms the α,β double bond:



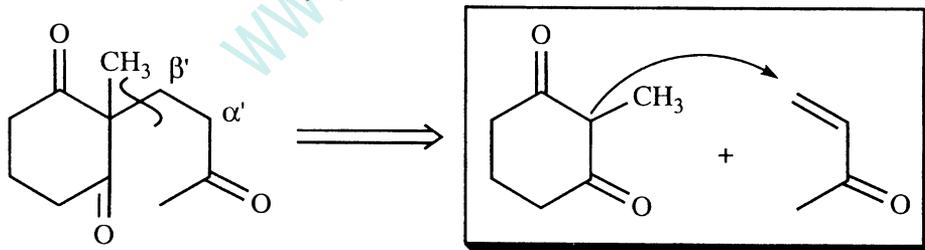
Michael addition forms a bond to the β' carbon:



(b) aldol and dehydration forms the α,β double bond:

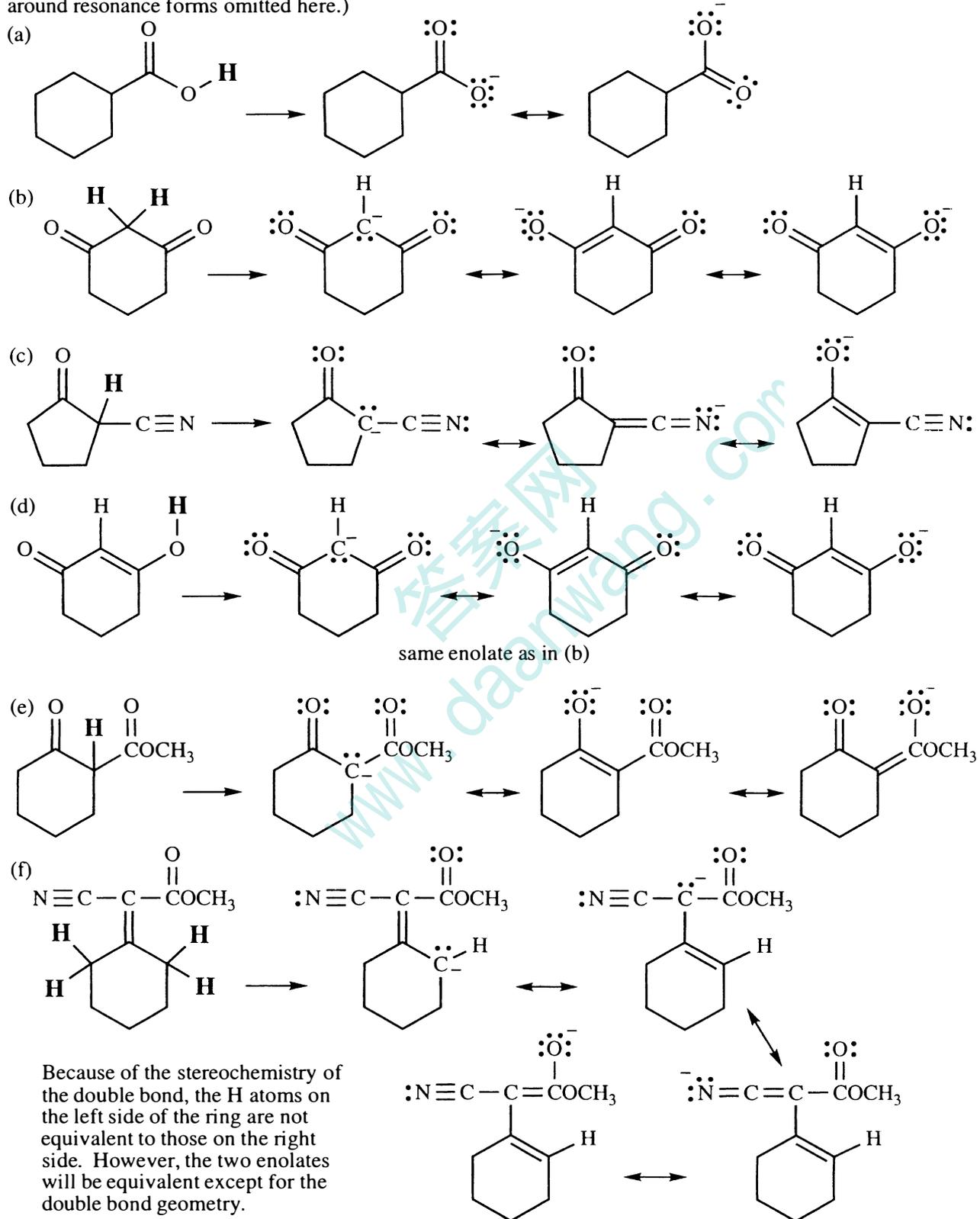


Michael addition forms a bond to the β' carbon:

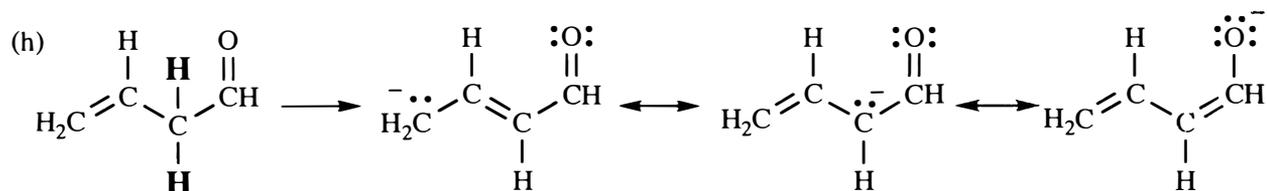
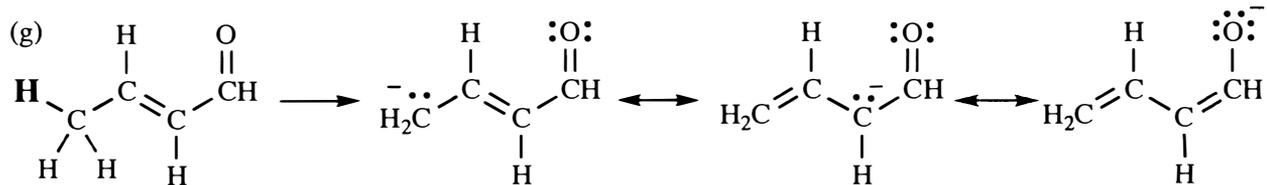


22-60 Please refer to solution 1-20, page 12 of this Solutions Manual.

22-61 The most acidic hydrogens are shown in boldface. (See Appendix 2 for a review of acidity.) (Braces around resonance forms omitted here.)

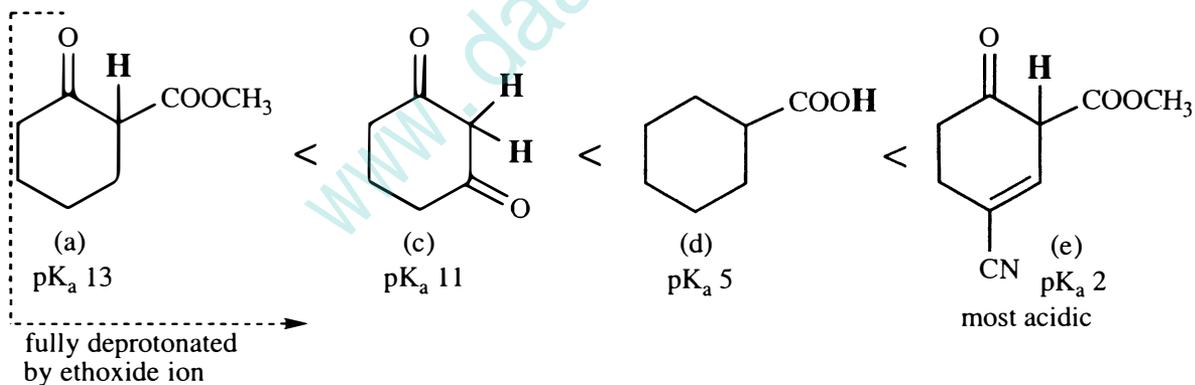
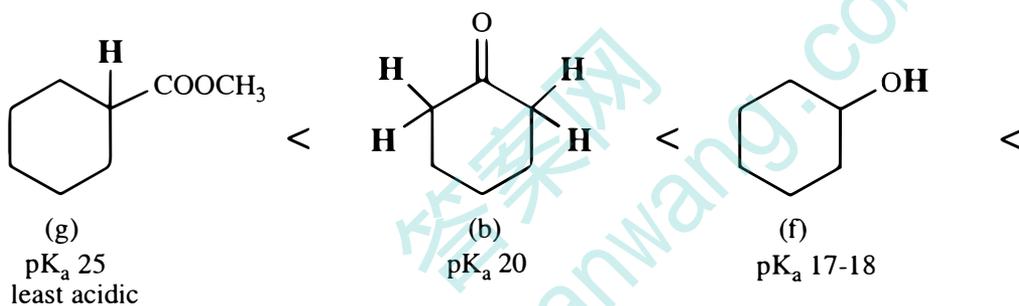


22-61 continued

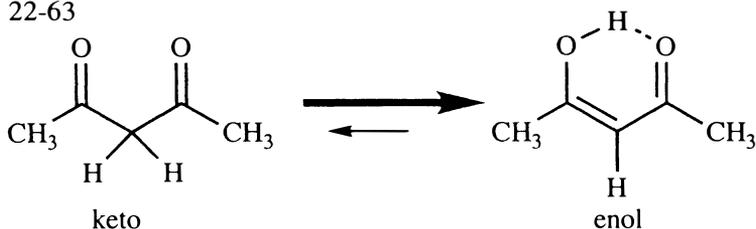


same enolate as in (g)

22-62 In order of increasing acidity. The most acidic protons are shown in boldface. (The approximate pK_a values are shown for comparison.) See Appendix 2 for a review of acidity.

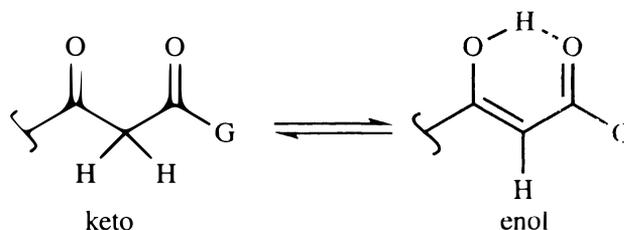


22-63

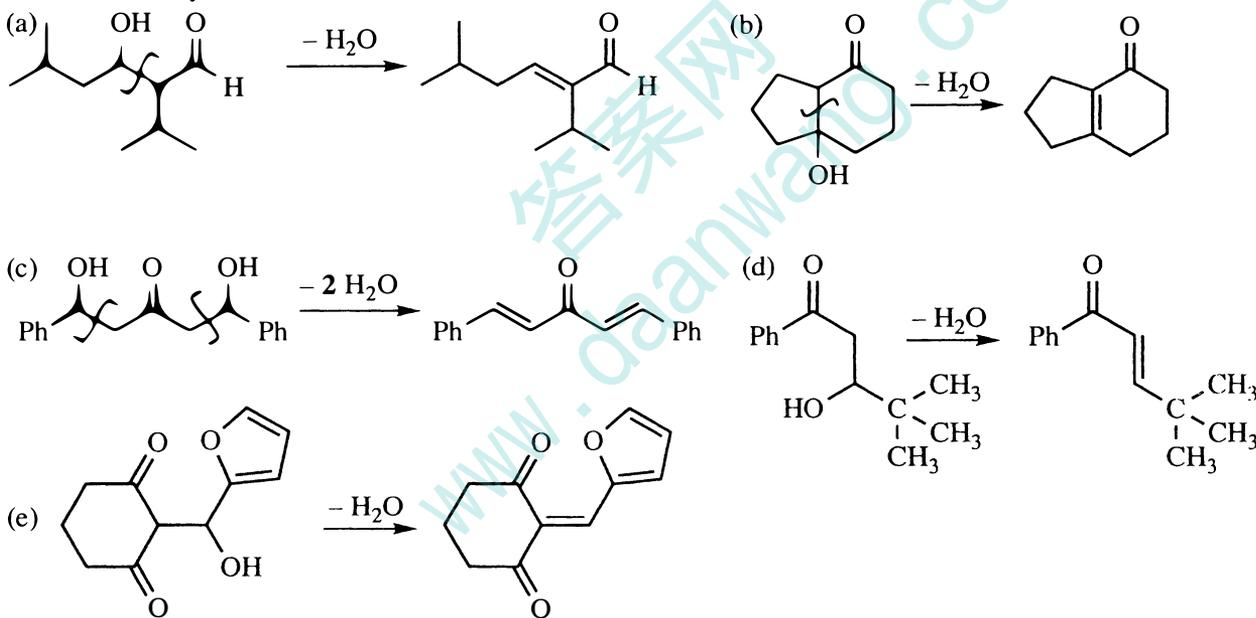


The enol form is stable because of the conjugation and because of intramolecular hydrogen-bonding in a six-membered ring.

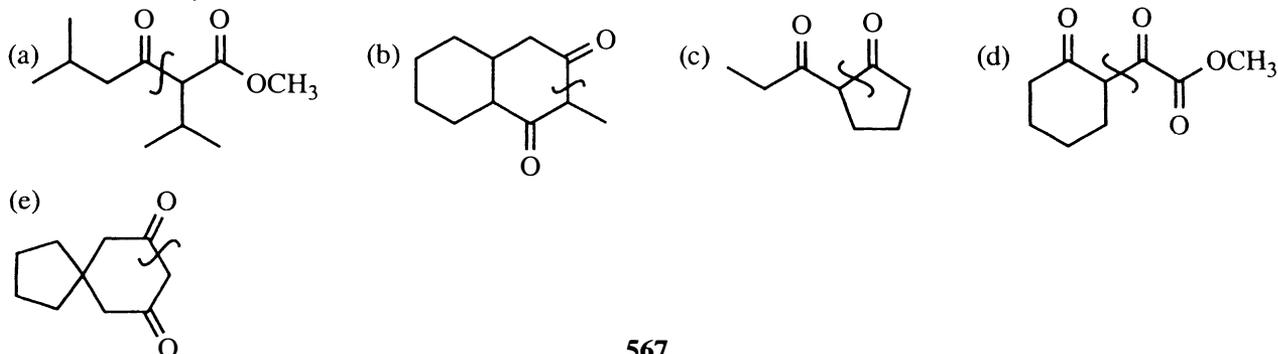
In dicarbonyl compounds in general, the weaker the electron-donating ability of the group G, the more it will exist in the enol form: aldehydes (G = H) are almost completely enolized, then ketones, esters, and finally amides which have virtually no enol content.

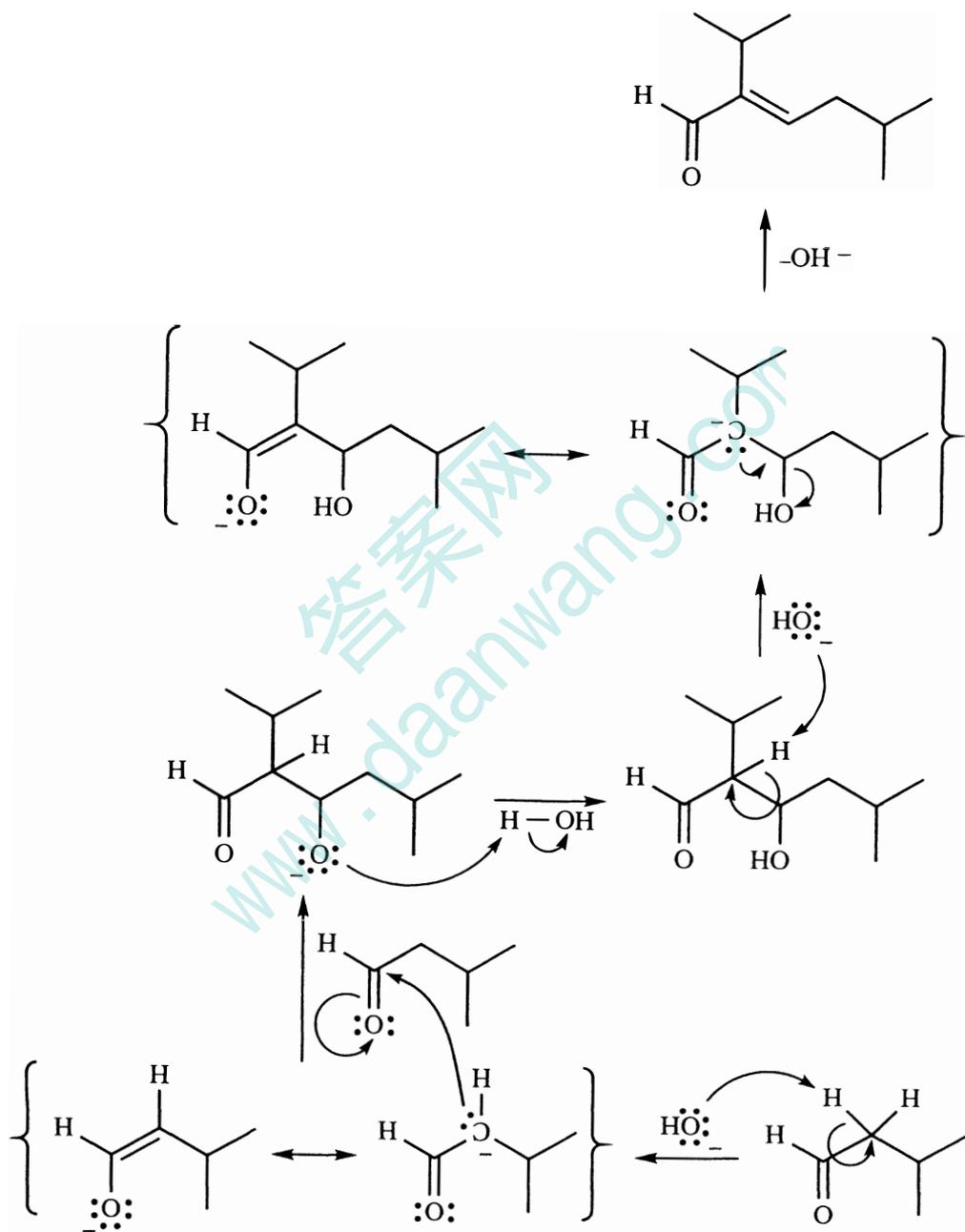


22-64 The wavy line lies across the bond formed in the aldol condensation.

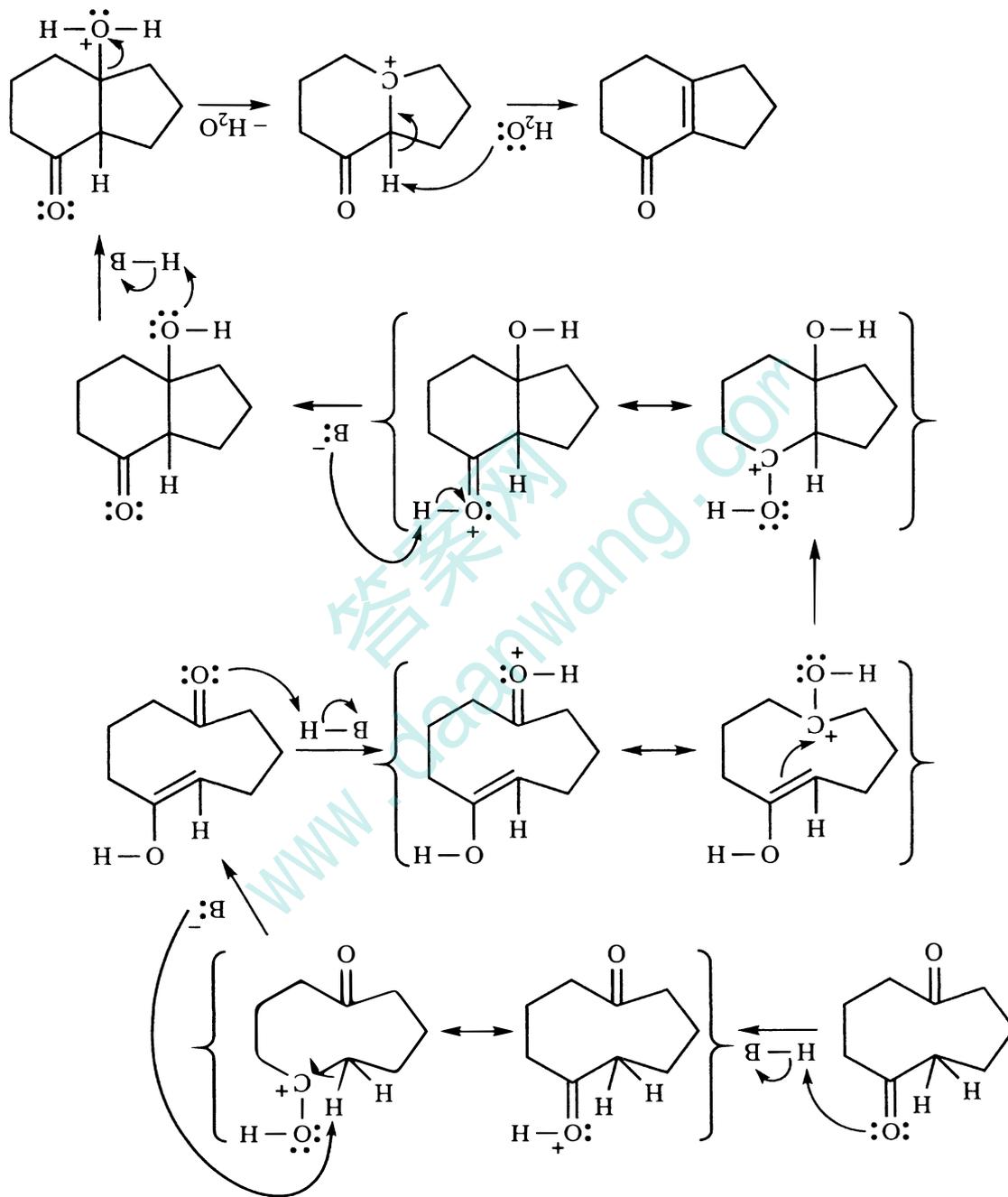


22-65 The wavy line lies across the bond formed in the Claisen condensation.





(a) mechanism of aldol condensation in problem 22-64(a)

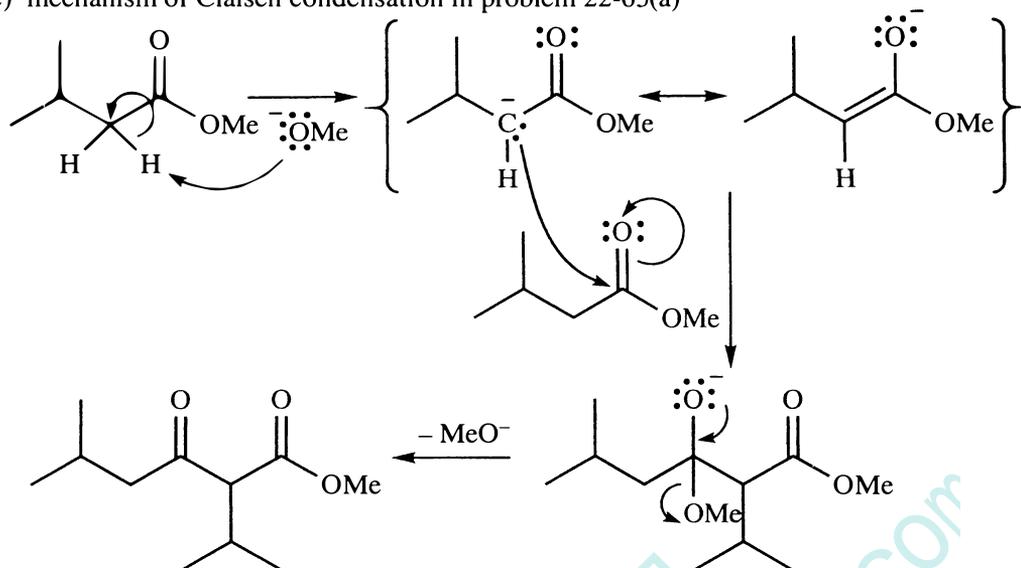


(b) mechanism of aldol condensation in problem 22-64(b)

22-66 continued

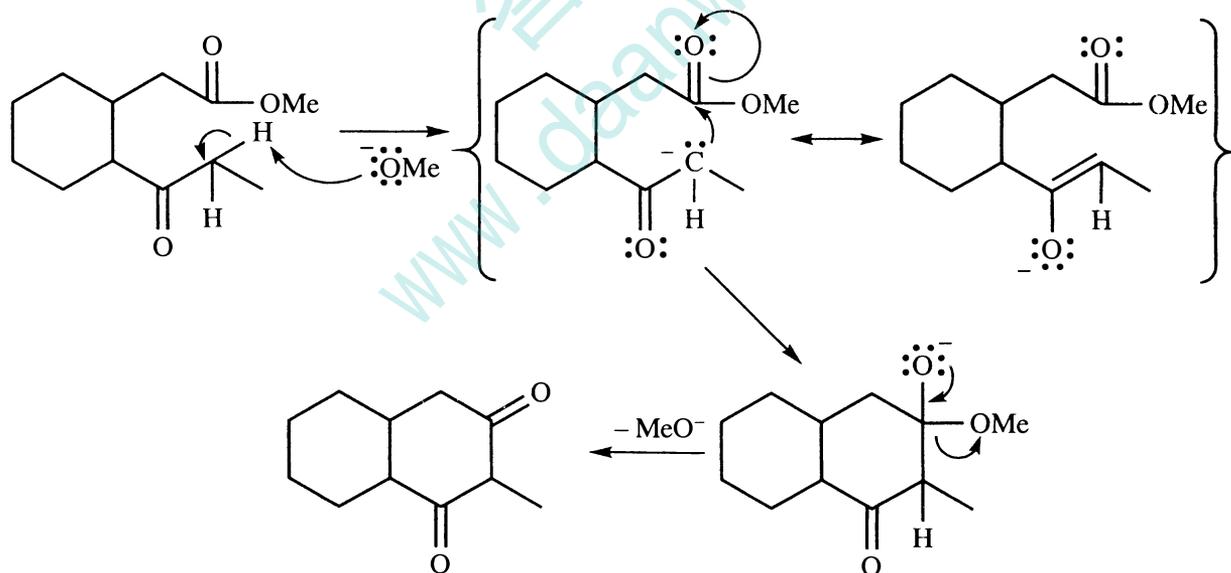
22-66 continued

(c) mechanism of Claisen condensation in problem 22-65(a)



(this product will be deprotonated by methoxide, but regenerated upon acidic workup)

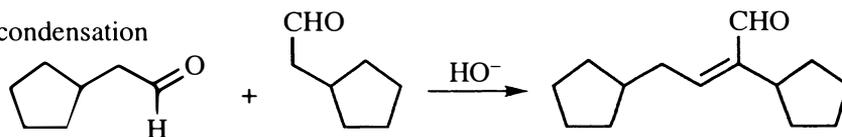
(d) mechanism of Claisen condensation in problem 22-65(b)



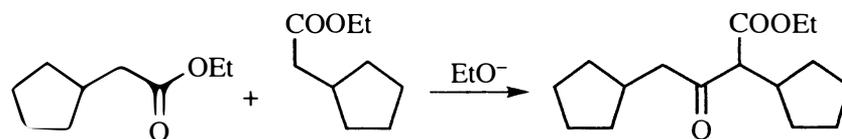
(this product will be deprotonated by methoxide, but regenerated upon acidic workup)

22-67 All products shown are after acidic workup.

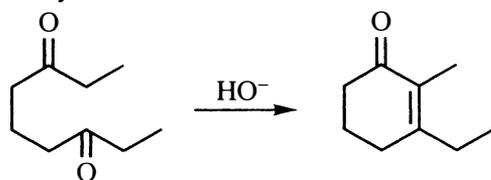
(a) aldol self-condensation



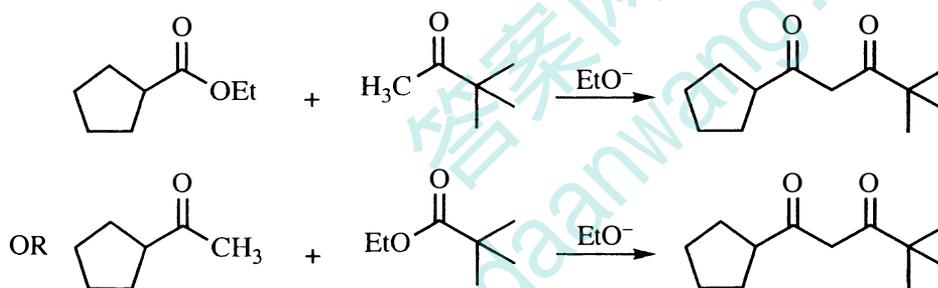
(b) Claisen self-condensation



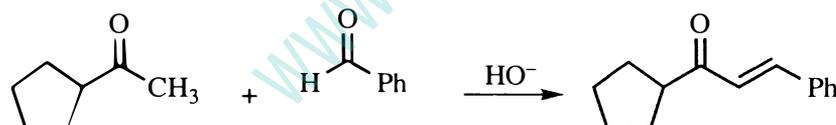
(c) aldol cyclization



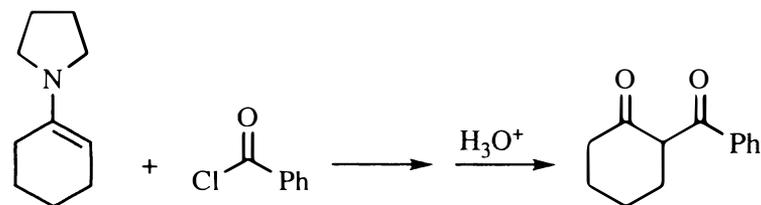
(d) mixed Claisen



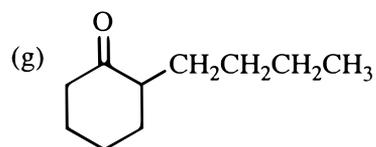
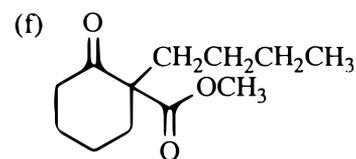
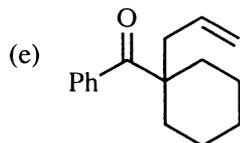
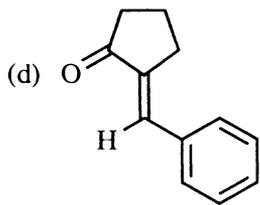
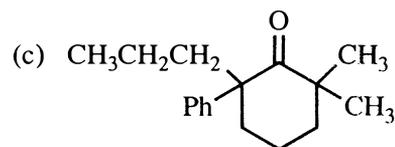
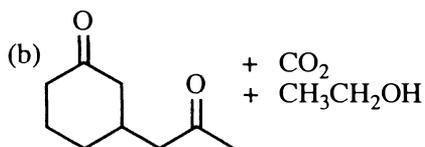
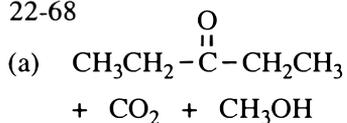
(e) mixed aldol



(f) enamine acylation—attempt at aldol would give self-condensation



22-68

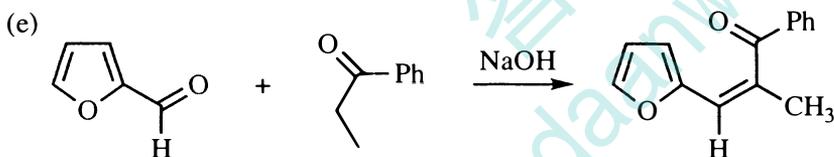
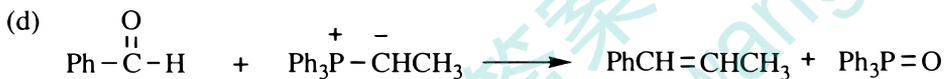


22-69

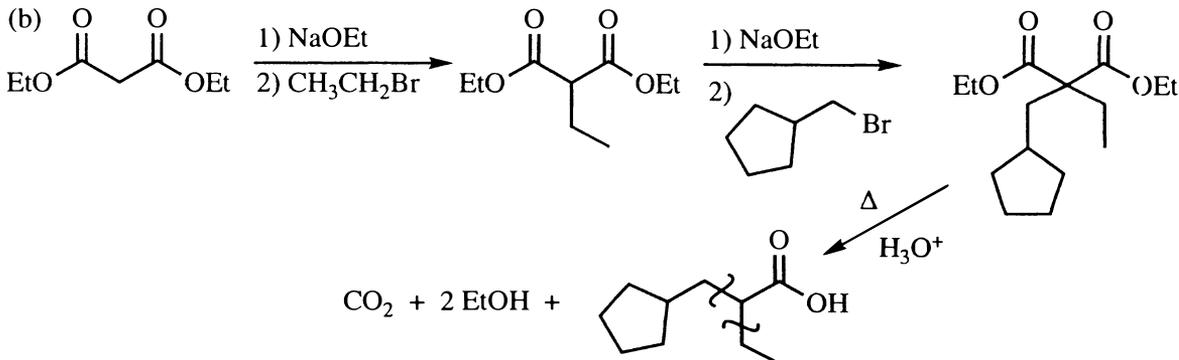
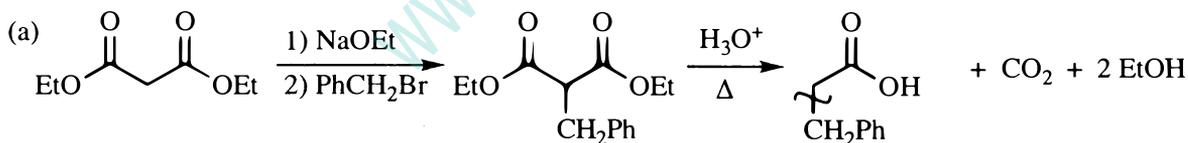
(a) reagents: Br_2, H^+

(b) reagents: $\text{Br}_2, \text{PBr}_3$,
 followed by H_2O

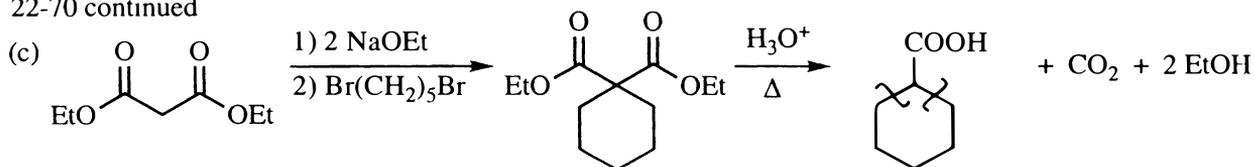
(c) reagents: excess I_2 (or Br_2 or Cl_2),
 NaOH



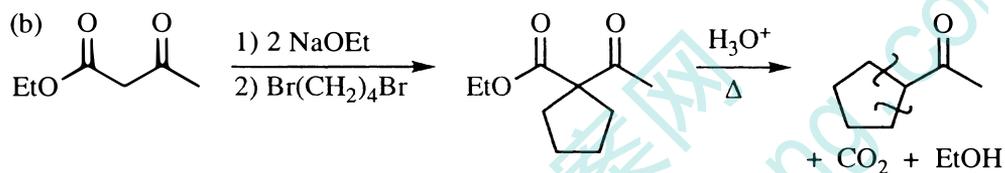
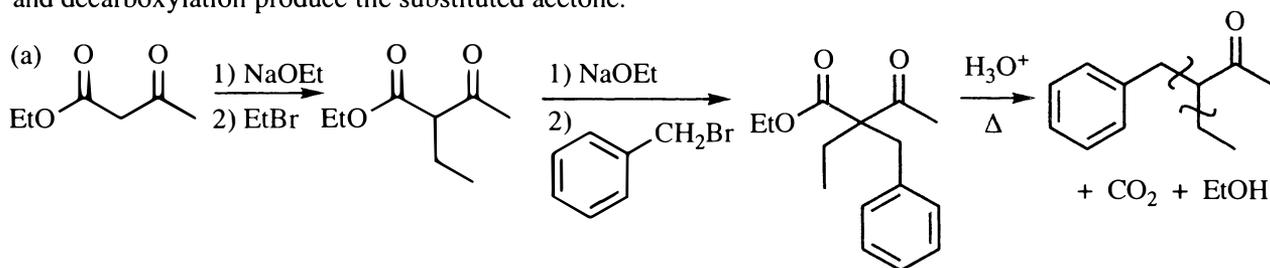
22-70 In the products, the wavy lines indicate the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetic acid.



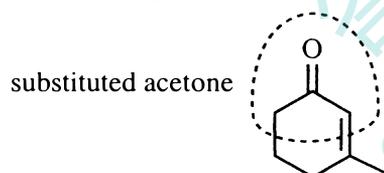
22-70 continued



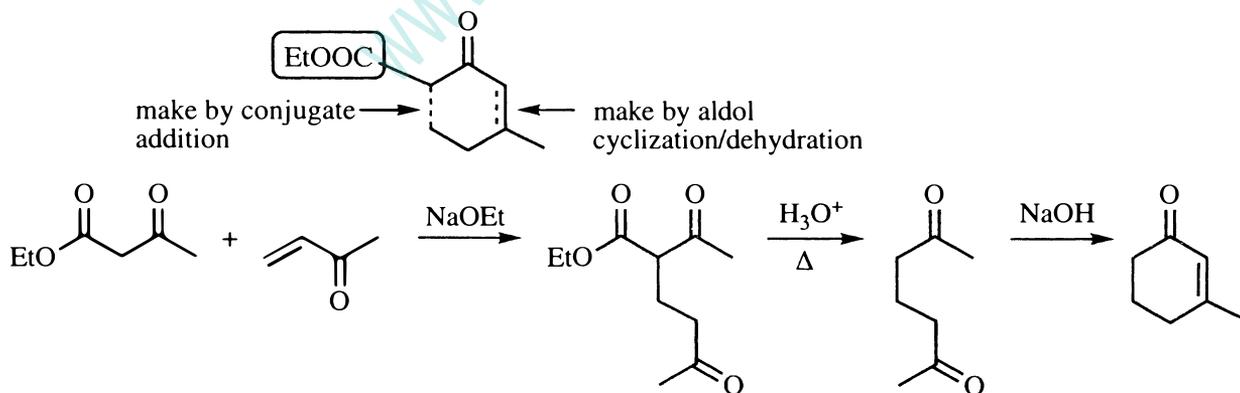
22-71 In the products, the wavy lines indicate the bonds that must be made by alkylation, before hydrolysis and decarboxylation produce the substituted acetone.



(c) The acetoacetic ester synthesis makes substituted acetone, so where is the acetone in this product?

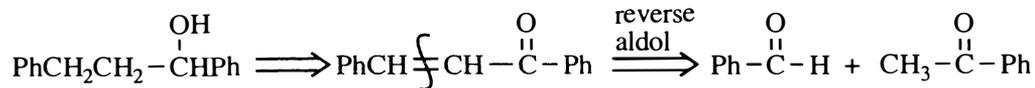


The single bond to this substituted acetone can be made by the acetoacetic ester synthesis. How can we make the α,β double bond? Aldol condensation!

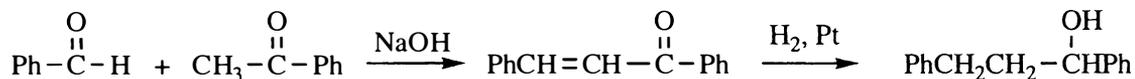


22-72 These compounds are made by aldol condensations followed by other reactions. The key is to find the skeleton made by the aldol.

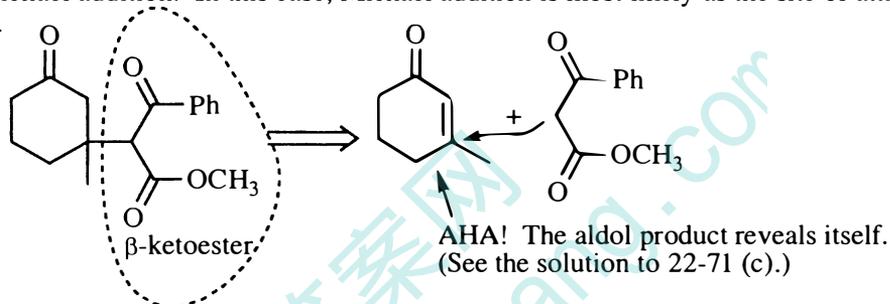
(a) Where is the possible α,β -unsaturated carbonyl in this skeleton?



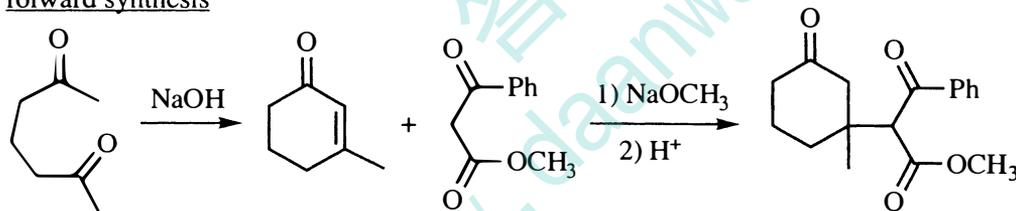
forward synthesis



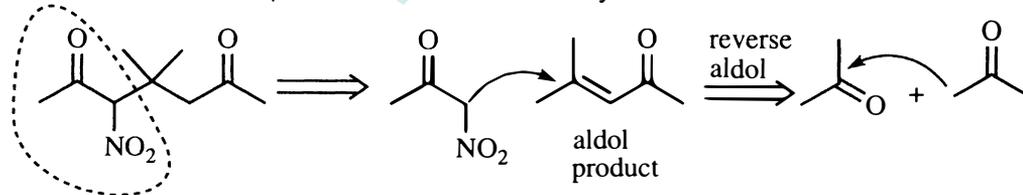
(b) The aldol skeleton is not immediately apparent in this formidable product. What can we see from it? Most obvious is the β -dicarbonyl (β -ketoester) which we know to be a good nucleophile, capable of substitution or Michael addition. In this case, Michael addition is most likely as the site of attack is β to another carbonyl.



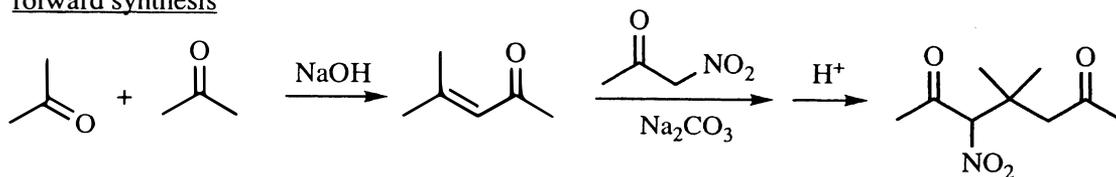
forward synthesis

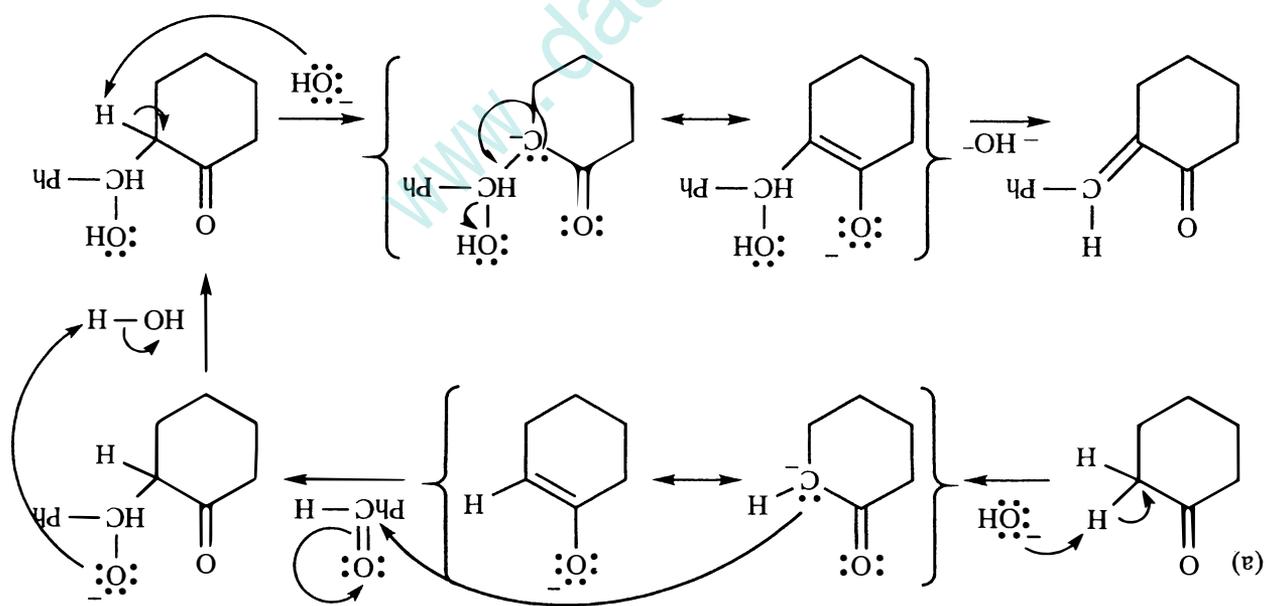
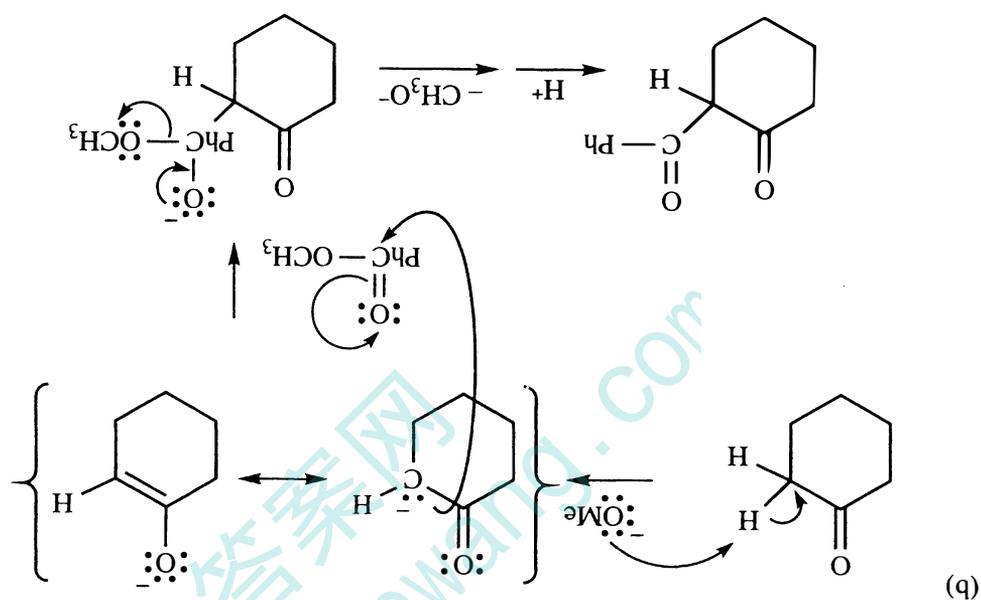


(c) The key in this product is the α -nitroketone, the equivalent of a β -dicarbonyl system, capable of doing Michael addition to the β -carbon of the other carbonyl.



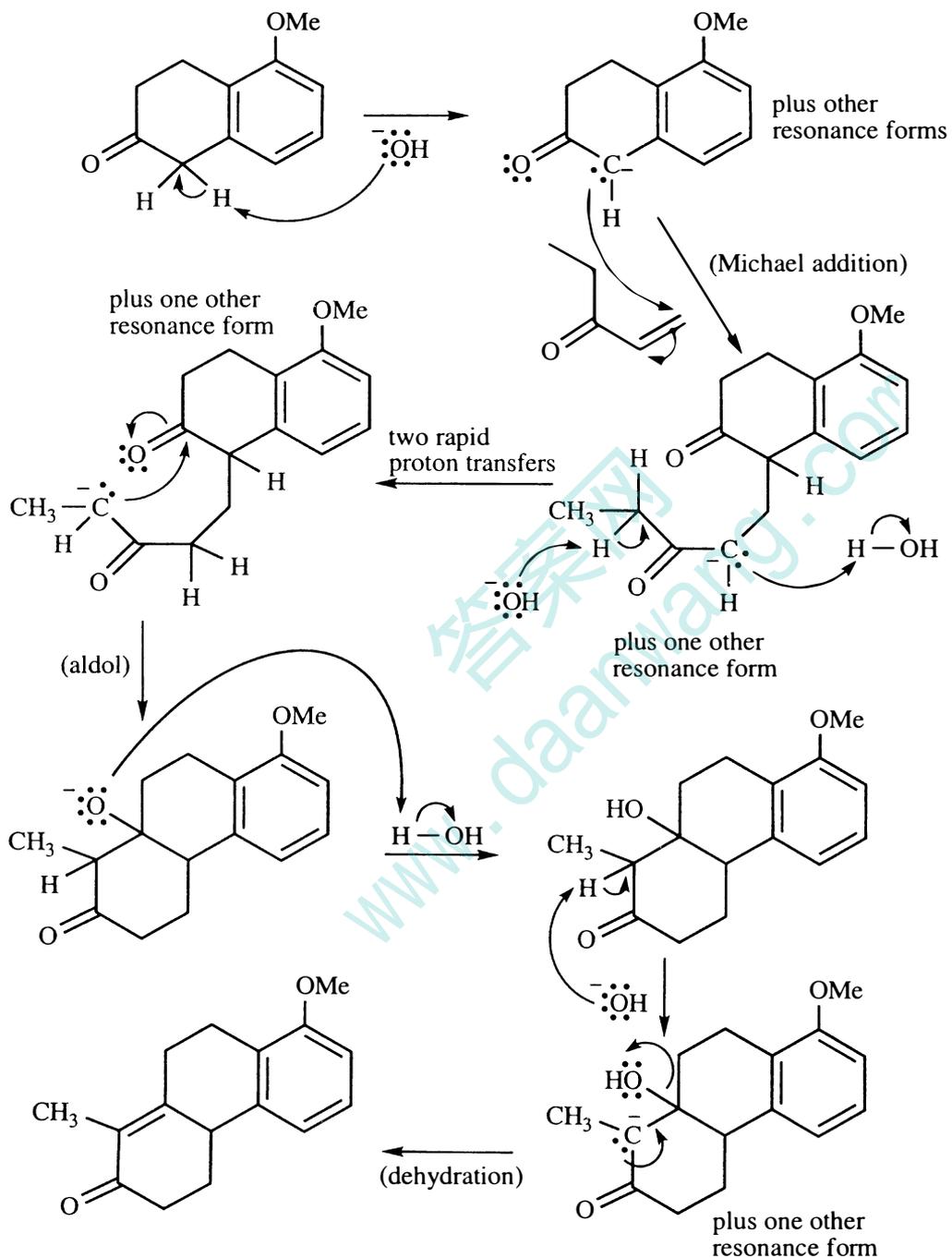
forward synthesis





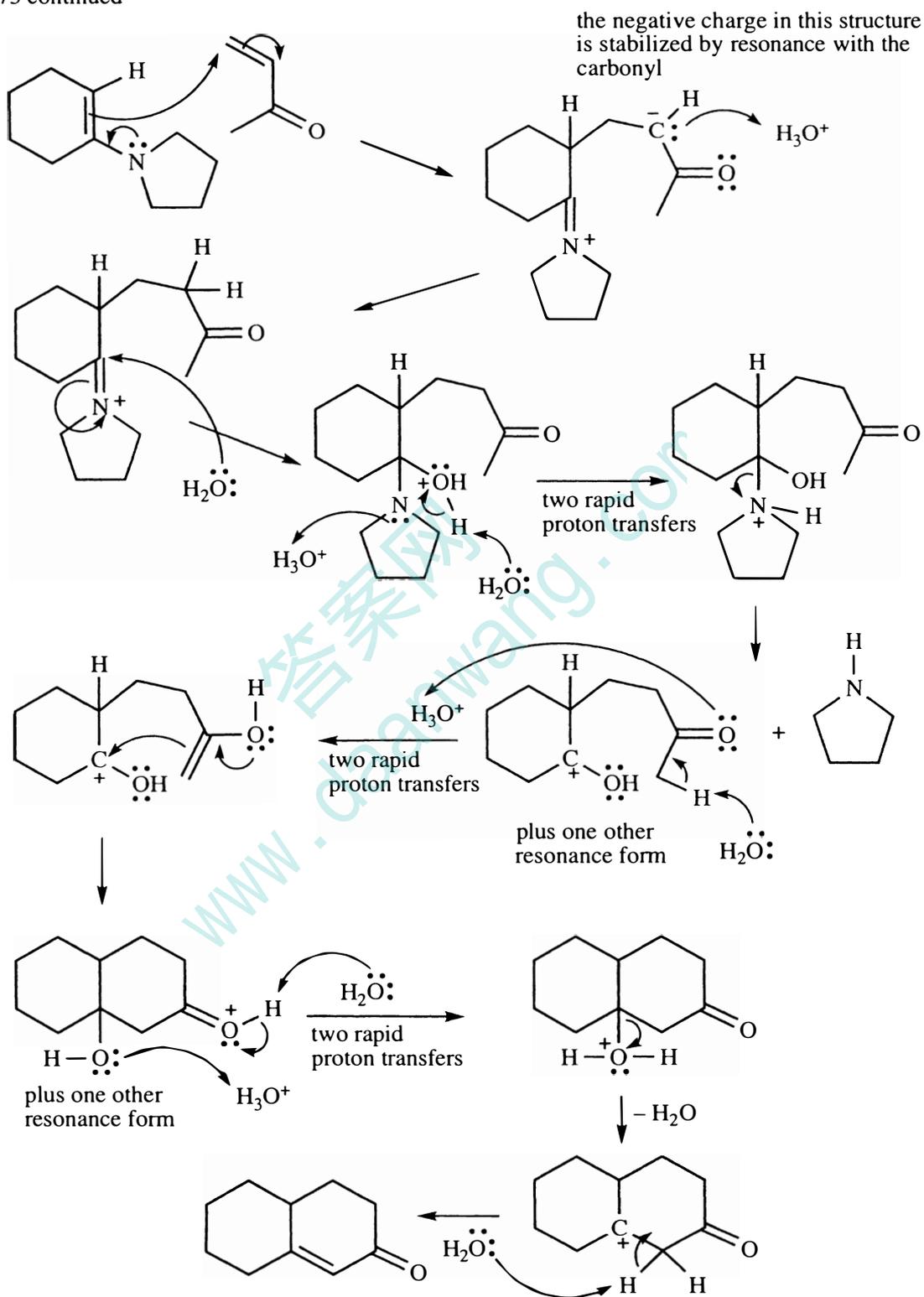
22-73 continued

(c) Robinson annulations are explained most easily by remembering that the first step is a Michael addition, followed by aldol cyclization with dehydration.

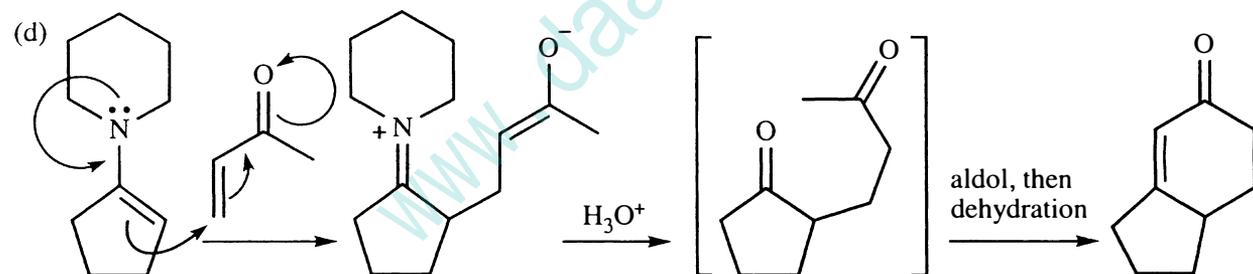
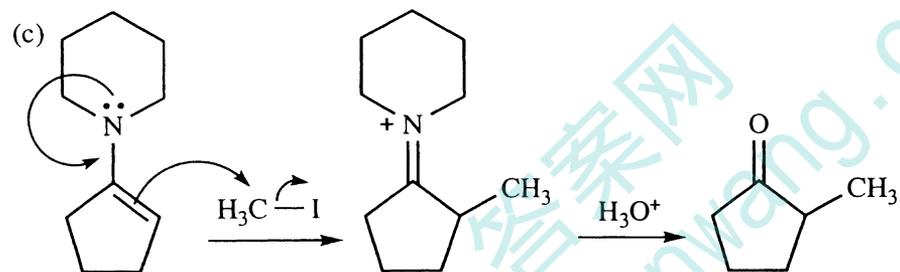
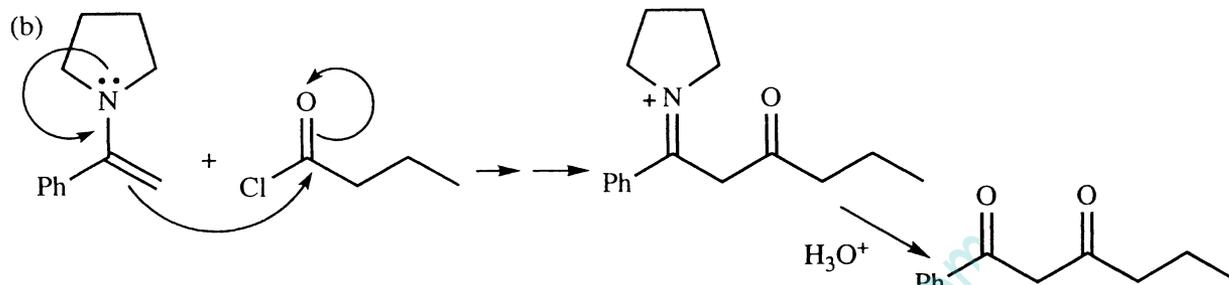
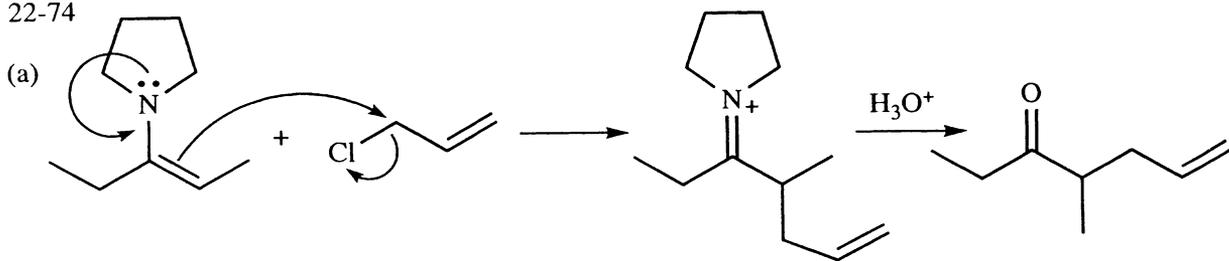


22-73 continued

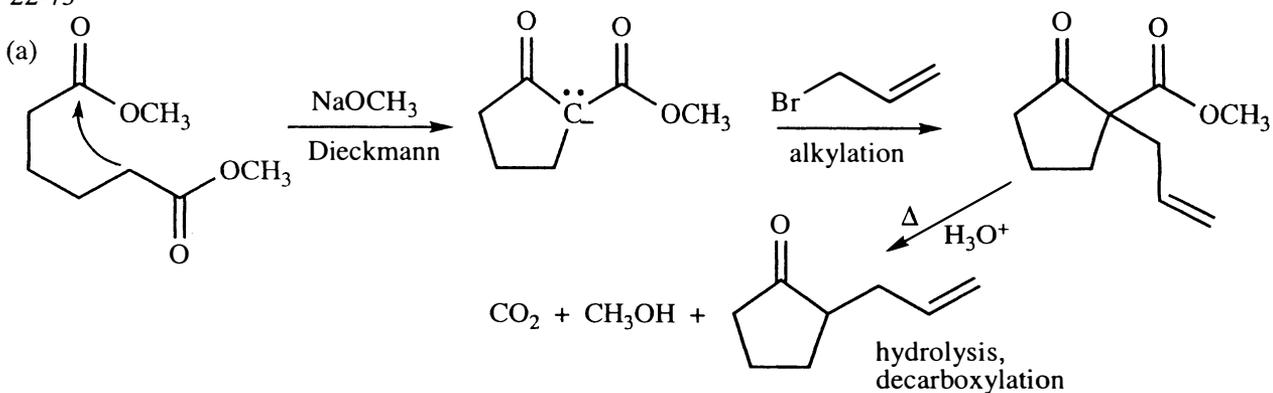
(d)



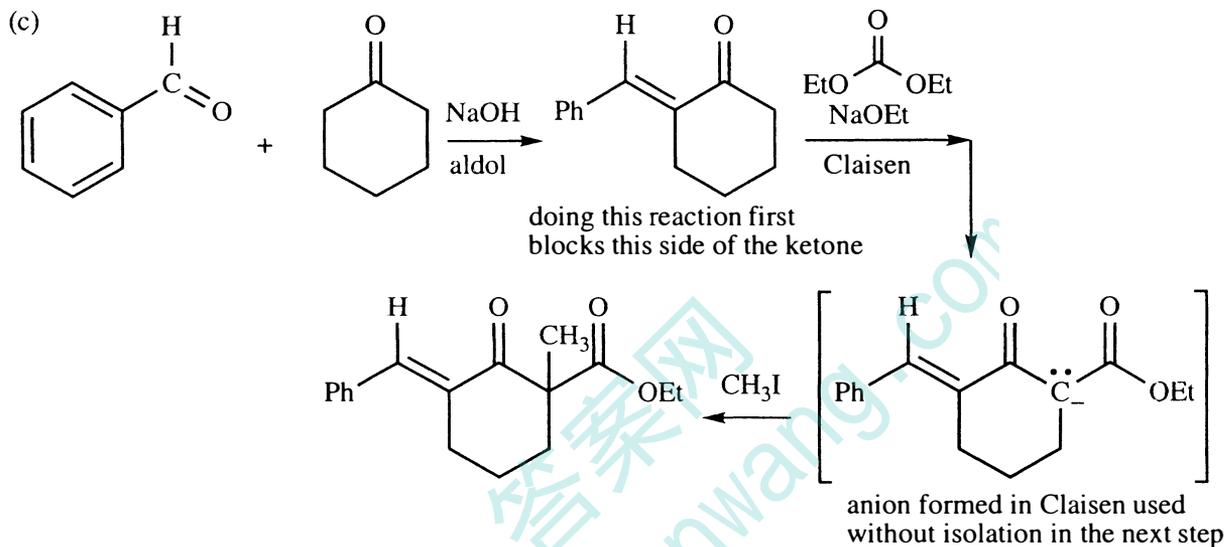
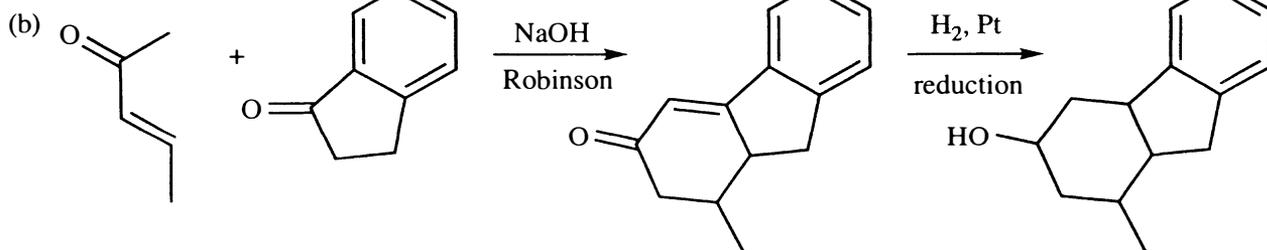
22-74



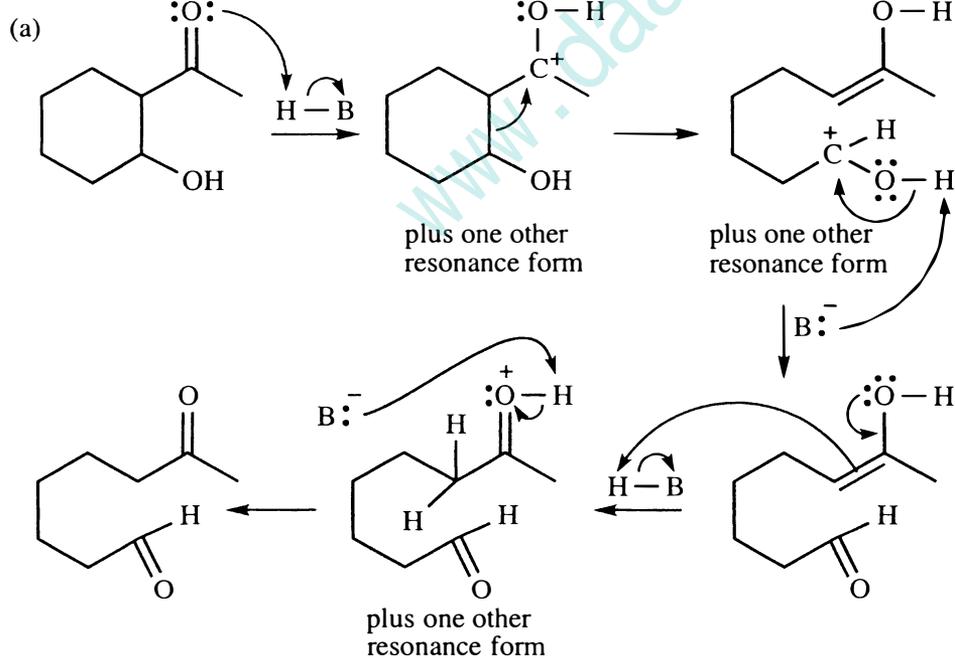
22-75



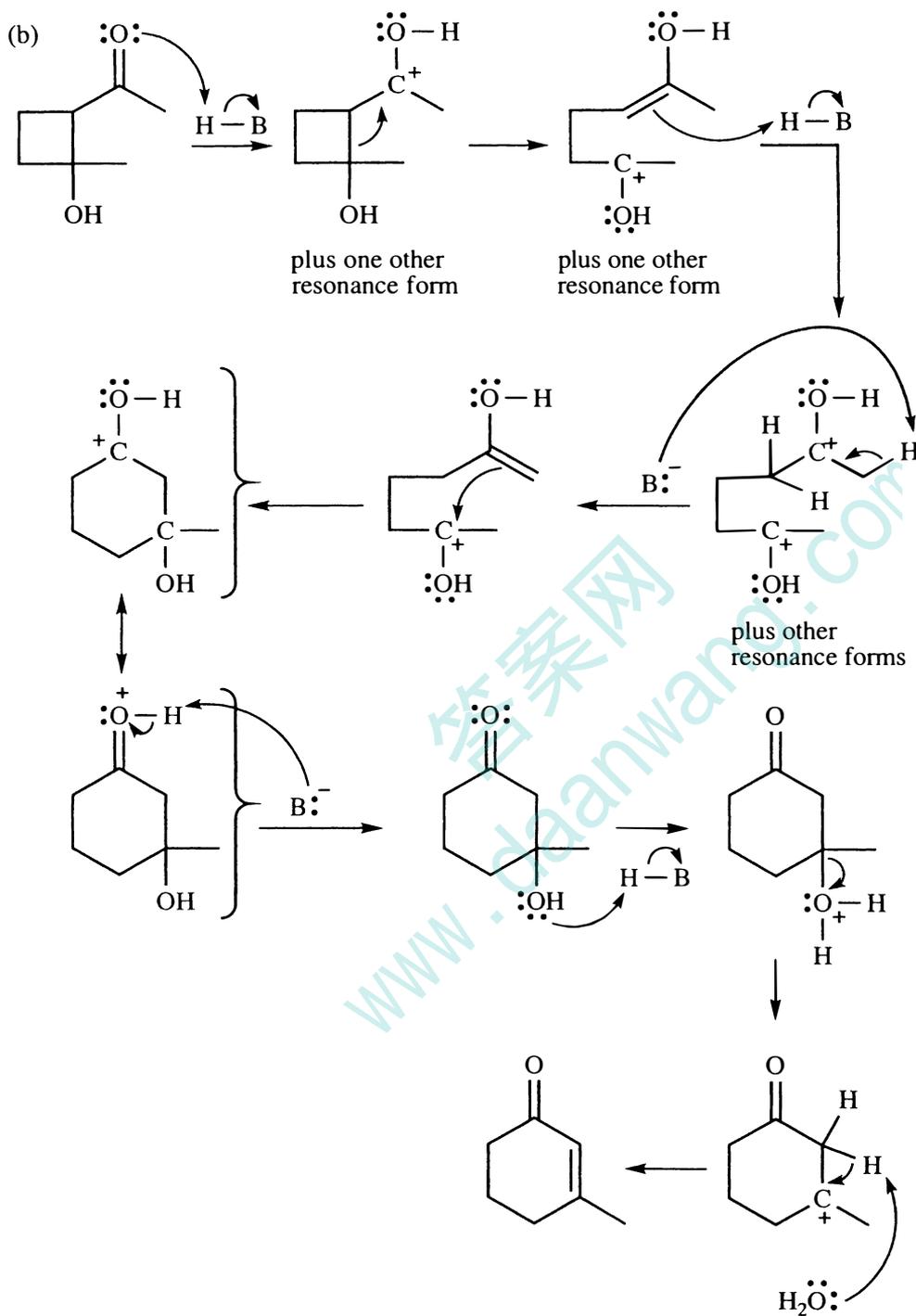
22-75 continued



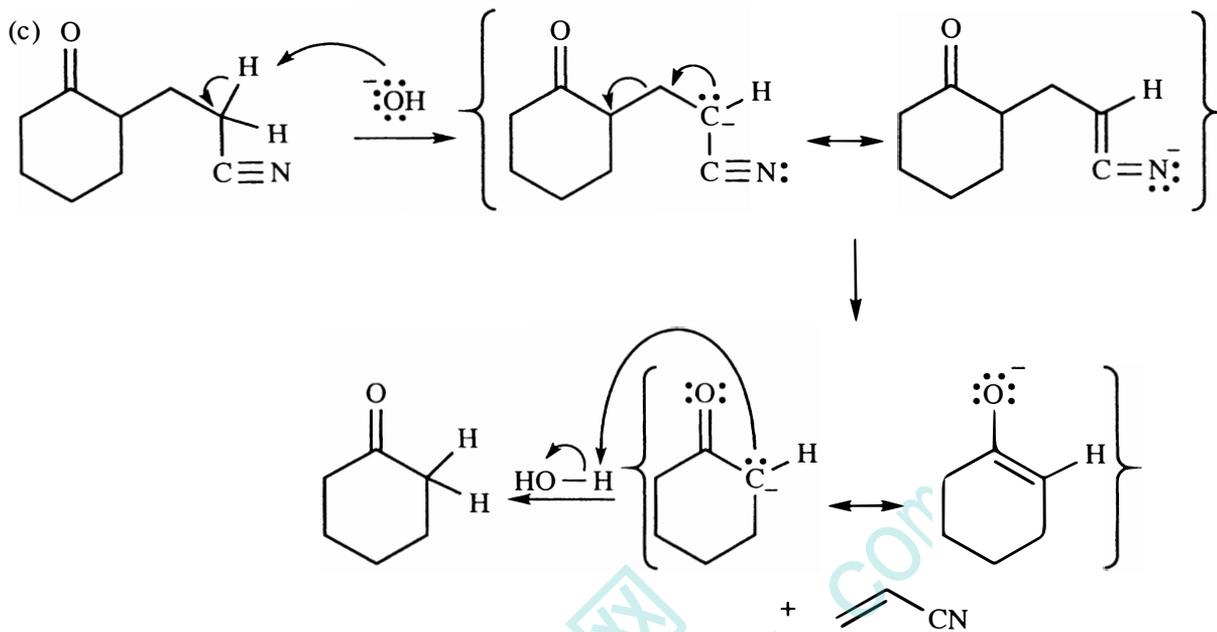
22-76



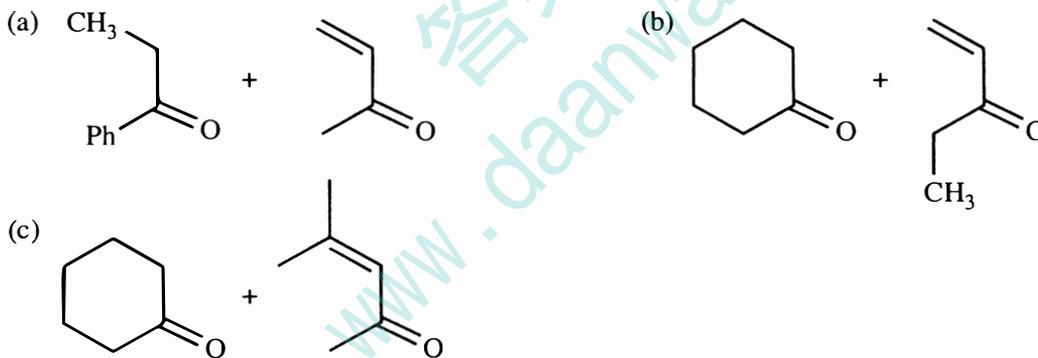
22-76 continued



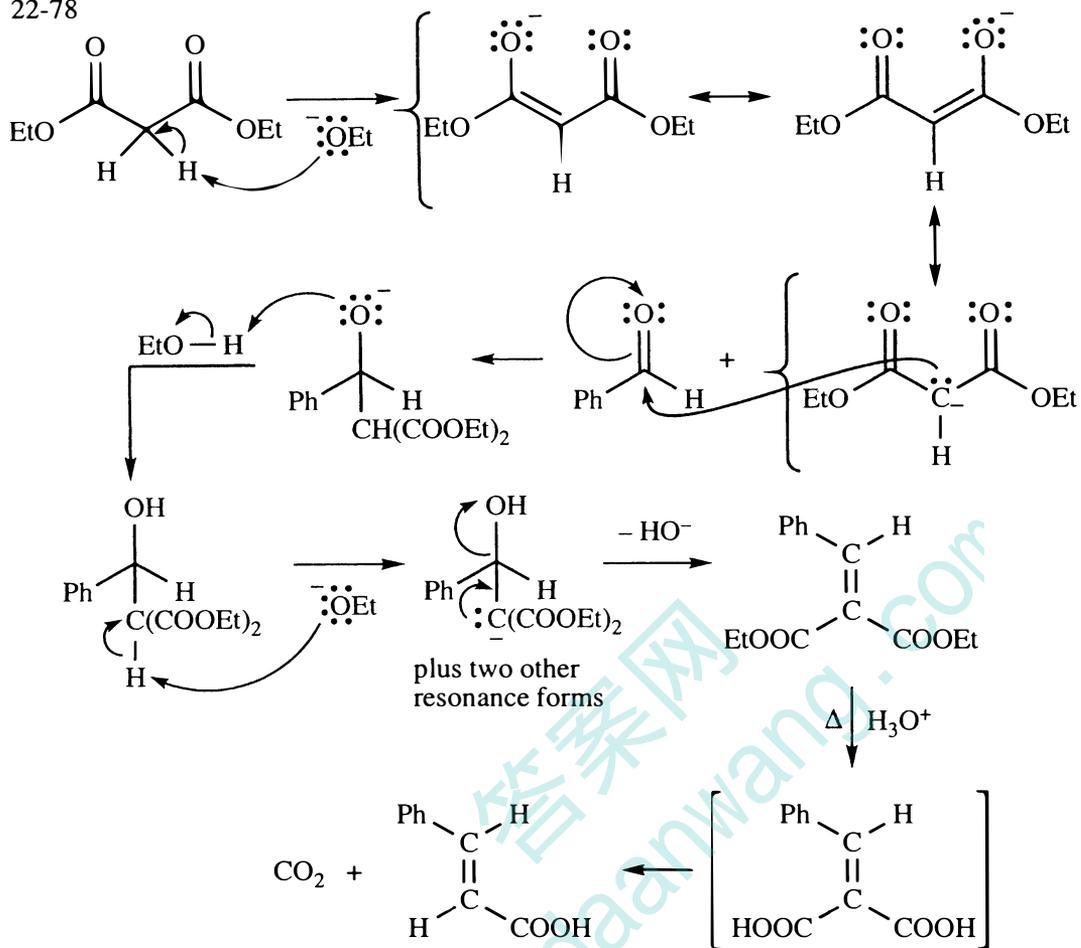
22-76 continued



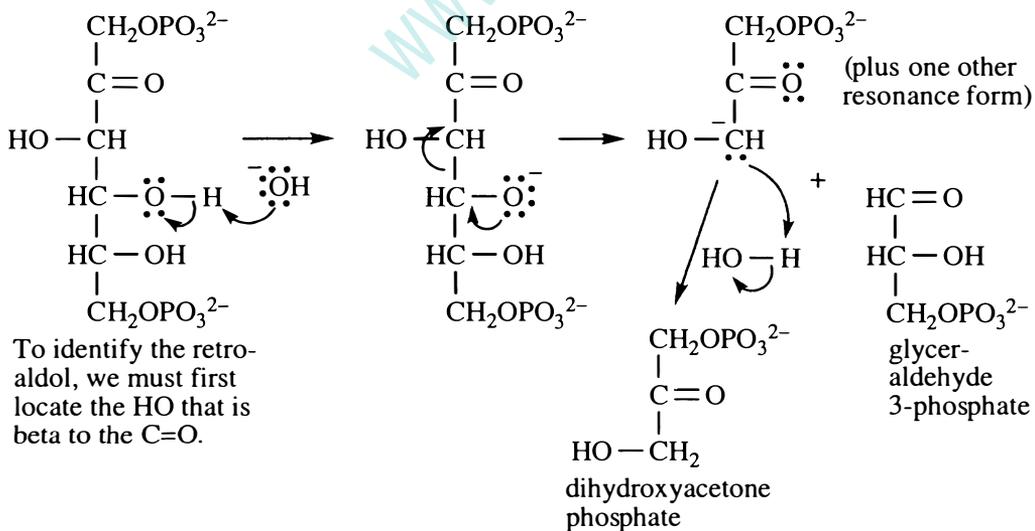
22-77 All of these Robinson annulations are catalyzed by NaOH.



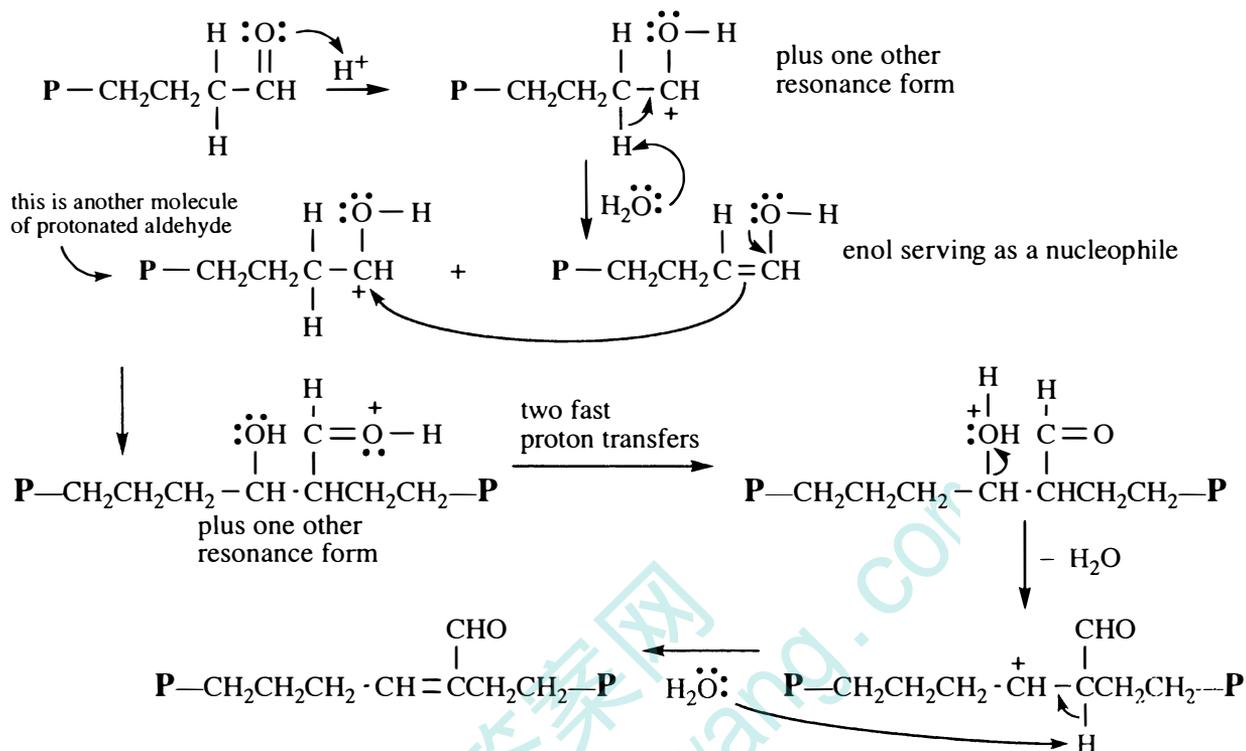
22-78



22-79

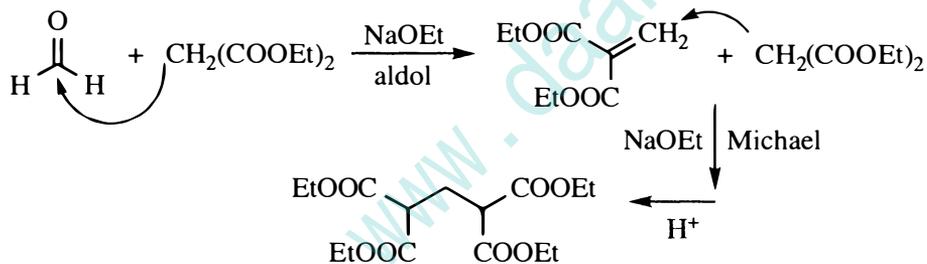


22-80 This is an aldol condensation. **P** stands for a protein chain in this problem.

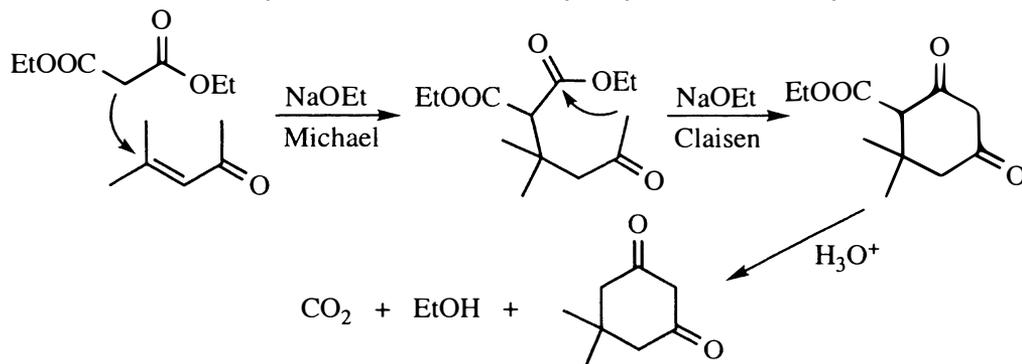


22-81

(a) aldol followed by Michael

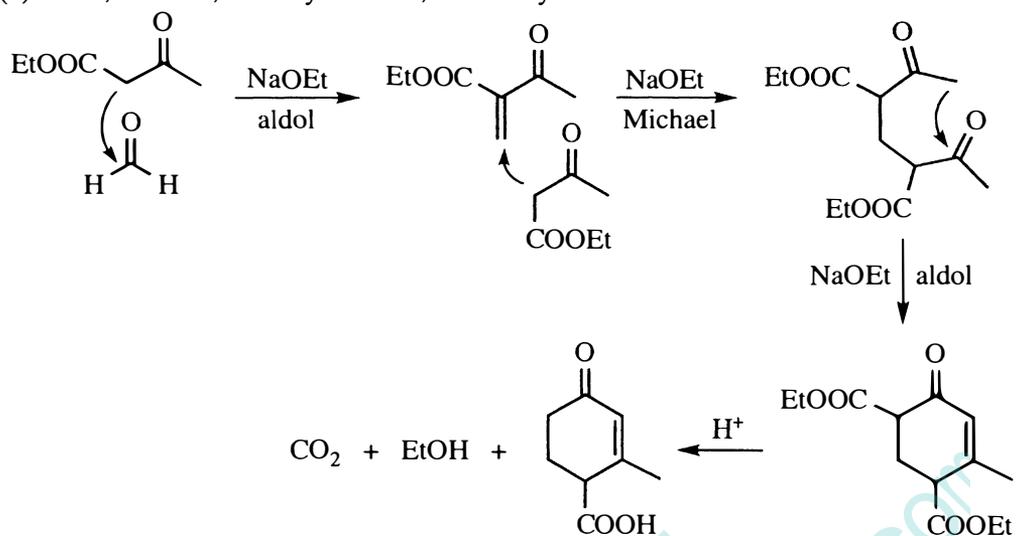


(b) Michael followed by Claisen condensation; hydrolysis and decarboxylation



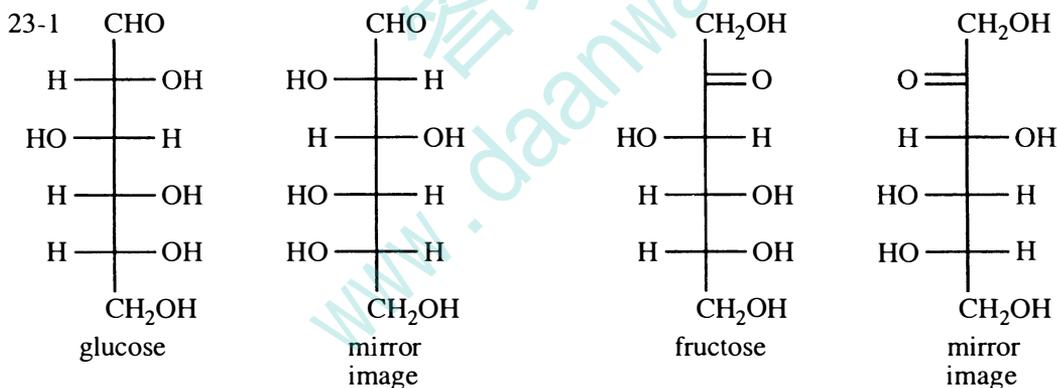
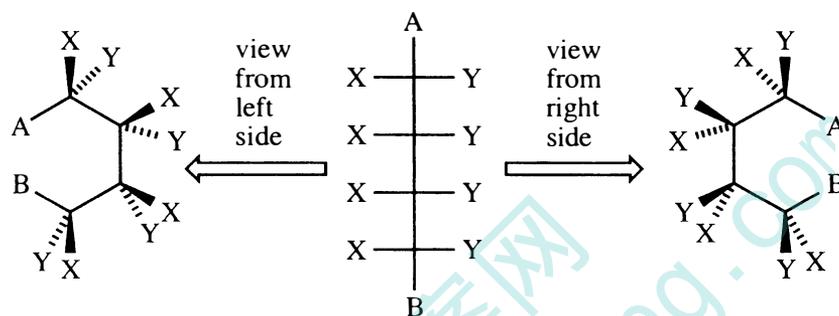
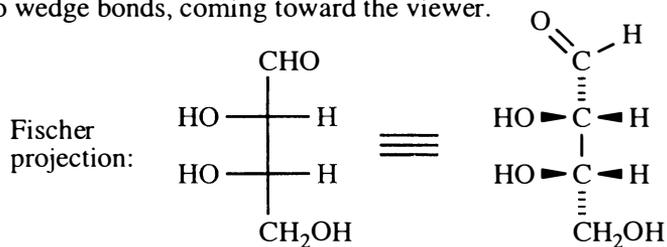
22-81 continued

(c) aldol, Michael, aldol cyclization, decarboxylation

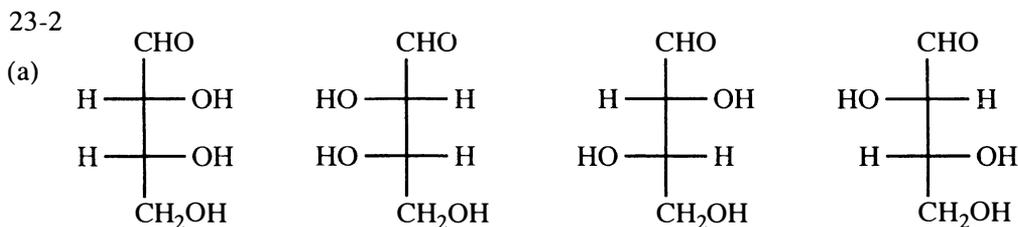


CHAPTER 23—CARBOHYDRATES AND NUCLEIC ACIDS

Reminder about Fischer projections, first introduced in Chapter 5, section 5-10: vertical bonds are equivalent to dashed bonds, going behind the plane of the paper, and horizontal bonds are equivalent to wedge bonds, coming toward the viewer.

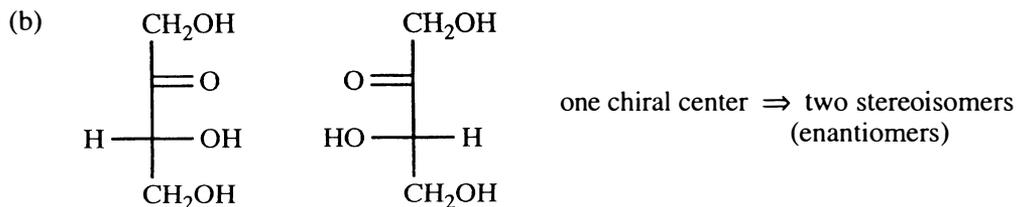


All four of these compounds are chiral and optically active.

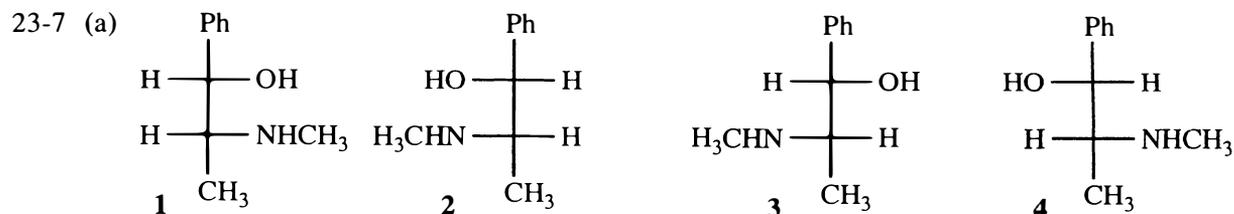
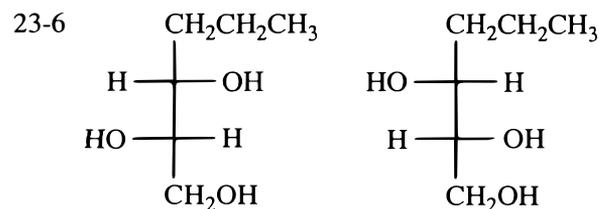
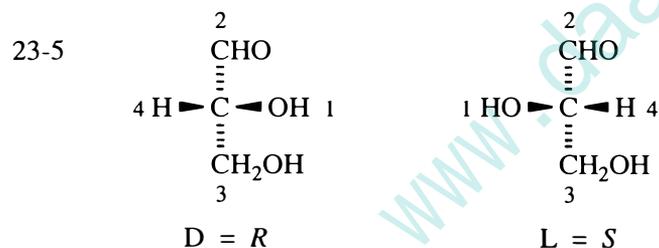
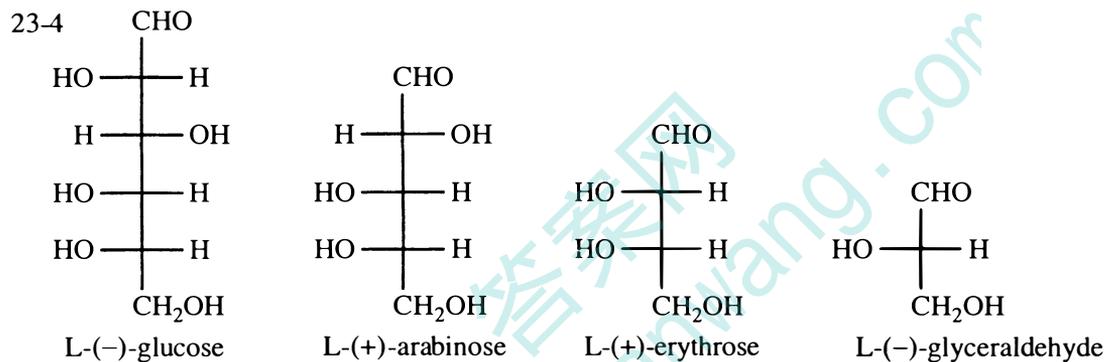
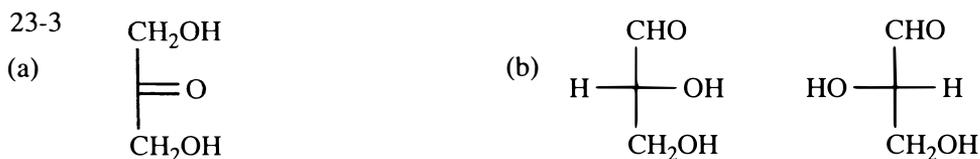


two asymmetric carbons \Rightarrow four stereoisomers (two pairs of enantiomers) if none are meso

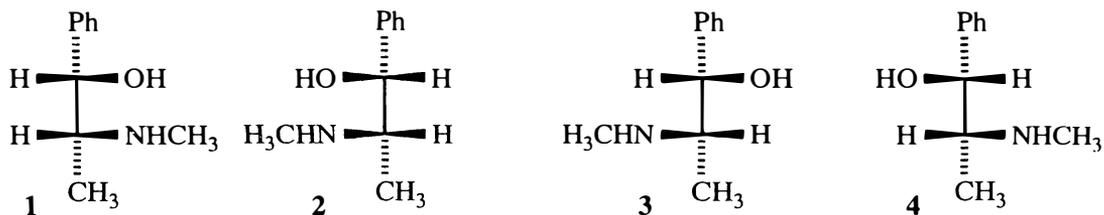
23-2 continued



(c) An aldohexose has four chiral carbons and sixteen stereoisomers. A ketohexose has three chiral carbons and eight stereoisomers.



23-7 (a) continued

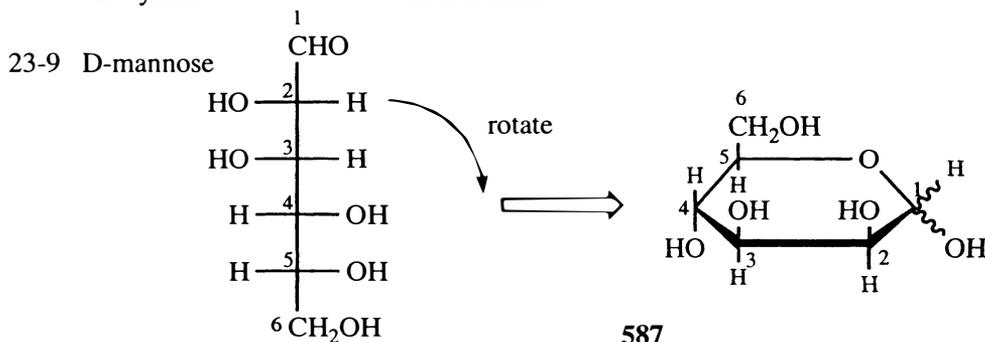
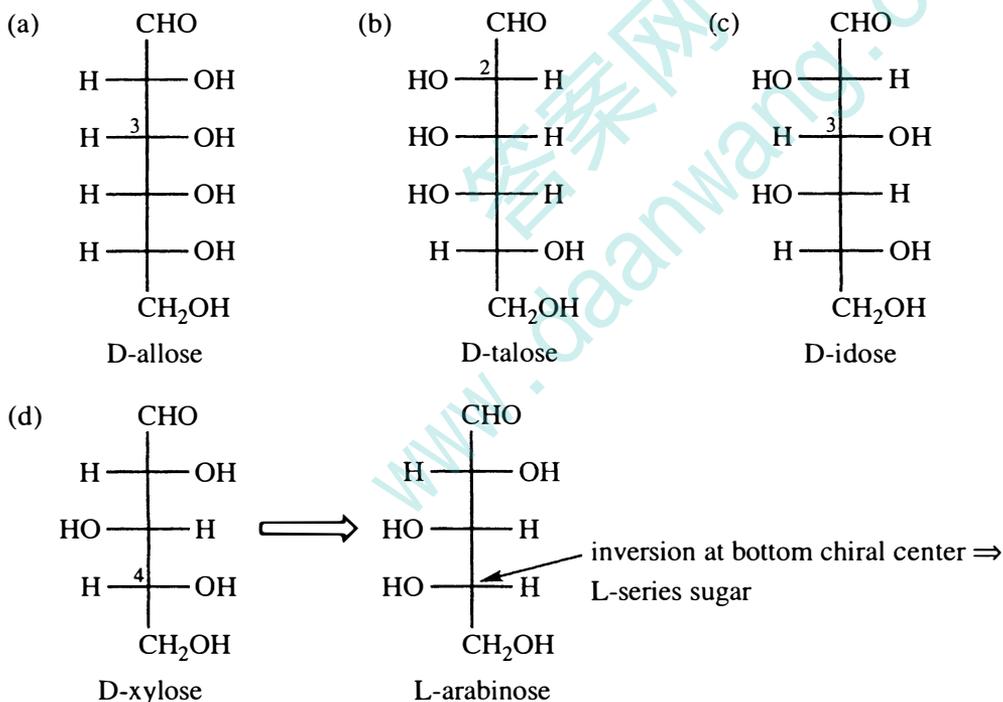


(b) Ephedrine is the *erythro* diastereomer, represented by structures 1 and 2. Structures 3 and 4 represent pseudoephedrine, the *threo* diastereomer.

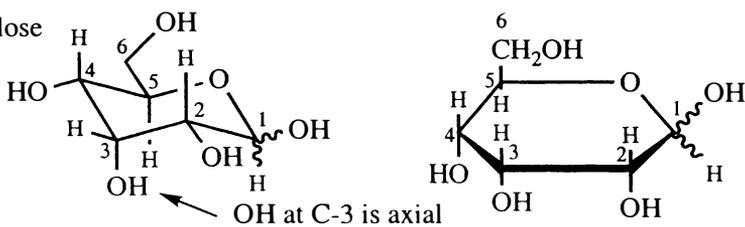
(c) The Fischer-Rosanoff convention assigns D and L to the configuration of the asymmetric carbon at the bottom of the Fischer projection. Structure 1 is D-ephedrine; structure 2 is L-ephedrine; structure 3 is L-pseudoephedrine; and structure 4 is D-pseudoephedrine.

(d) It is not possible to determine which is the (+) or (-) isomer of any compound just by looking at the structure. The only compound that has a direct correlation between the direction of optical rotation and its D or L designation is glyceraldehyde, about which the D and L system was designed. For all other compounds, optical rotation can only be determined by measurement in a polarimeter.

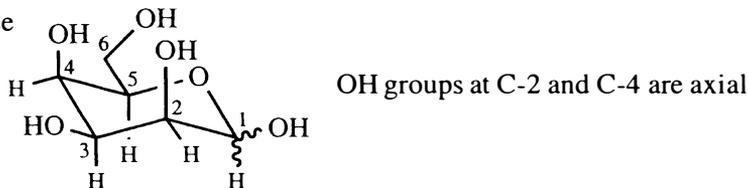
23-8



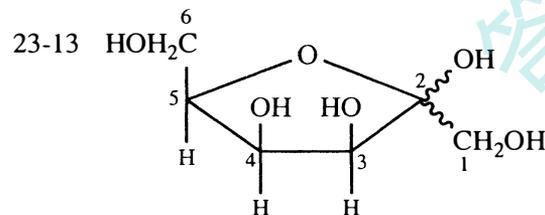
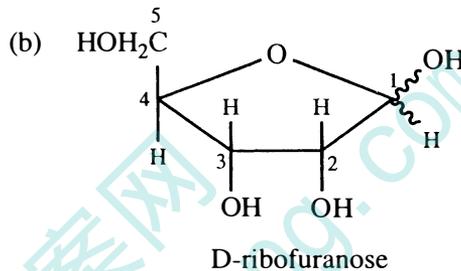
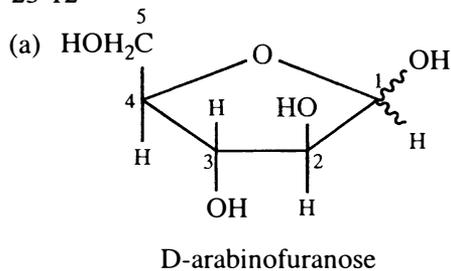
23-10 D-allose



23-11 D-talopyranose

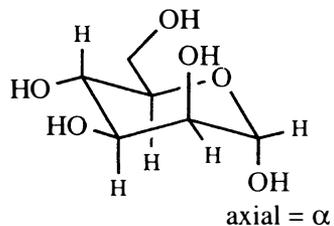


23-12

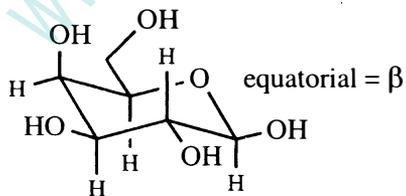


23-14

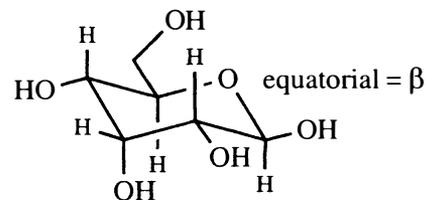
(a) α -D-mannopyranose



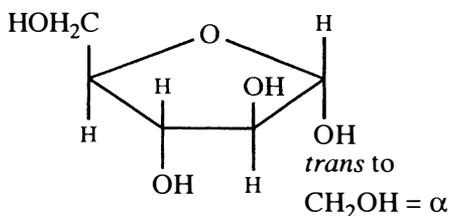
(b) β -D-galactopyranose



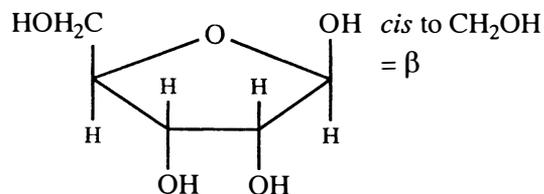
(c) β -D-allopyranose



(d) α -D-arabinofuranose



(e) β -D-ribofuranose



23-15 a = fraction of galactose as the α anomer; b = fraction of galactose as the β anomer

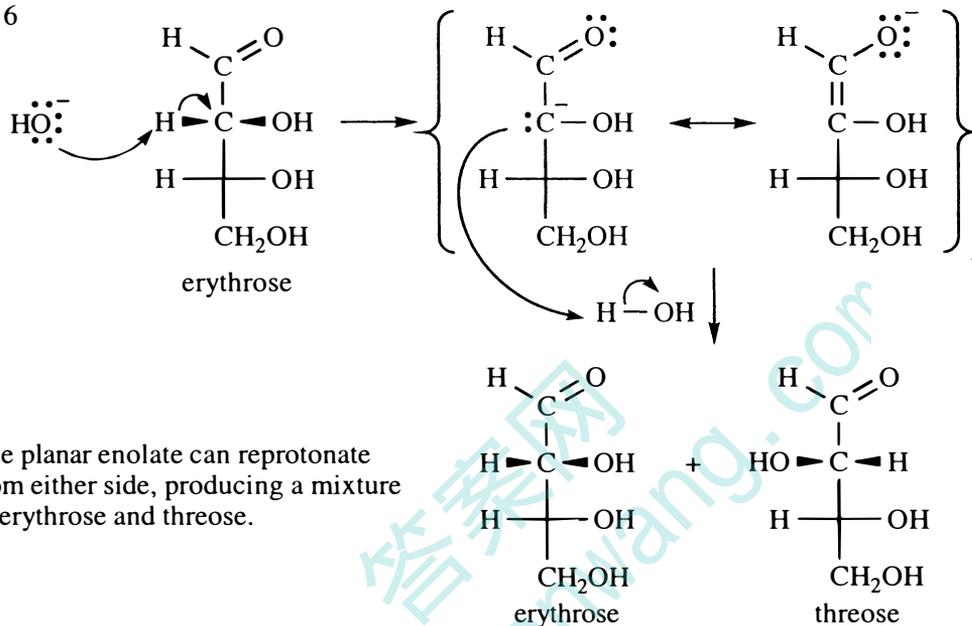
$$a(+150.7^\circ) + b(+52.8^\circ) = +80.2^\circ$$

$$a + b = 1; \quad b = 1 - a$$

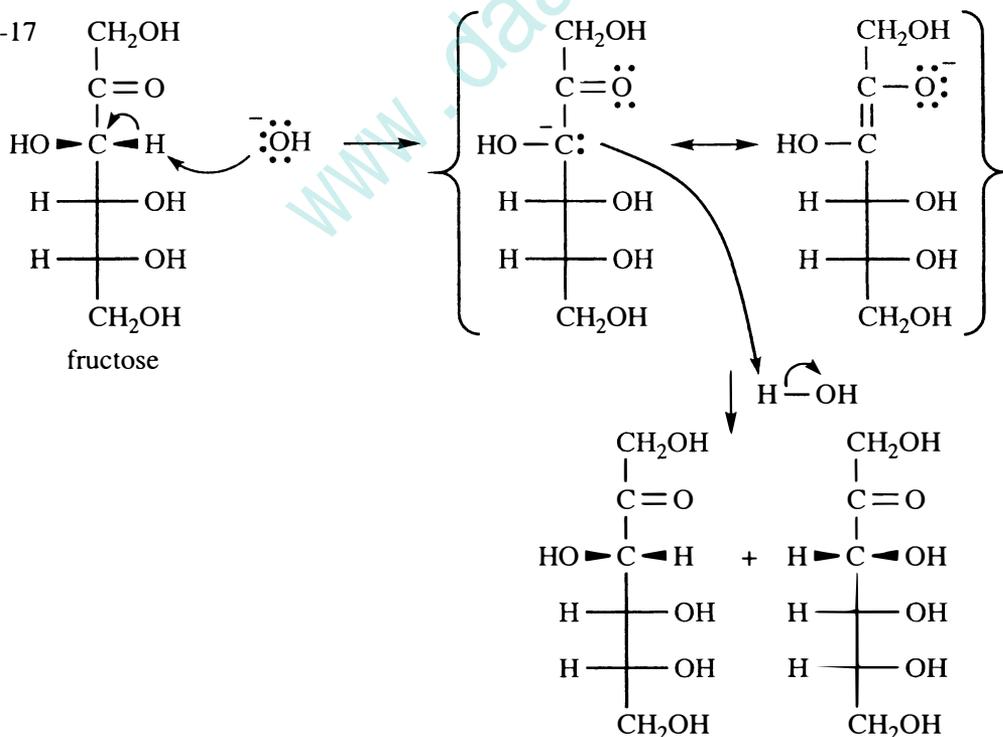
$$a(+150.7^\circ) + (1 - a)(+52.8^\circ) = +80.2^\circ \xrightarrow{\text{solve for "a"}} a = 0.28; \quad b = 0.72$$

The equilibrium mixture contains 28% of the α anomer and 72% of the β anomer.

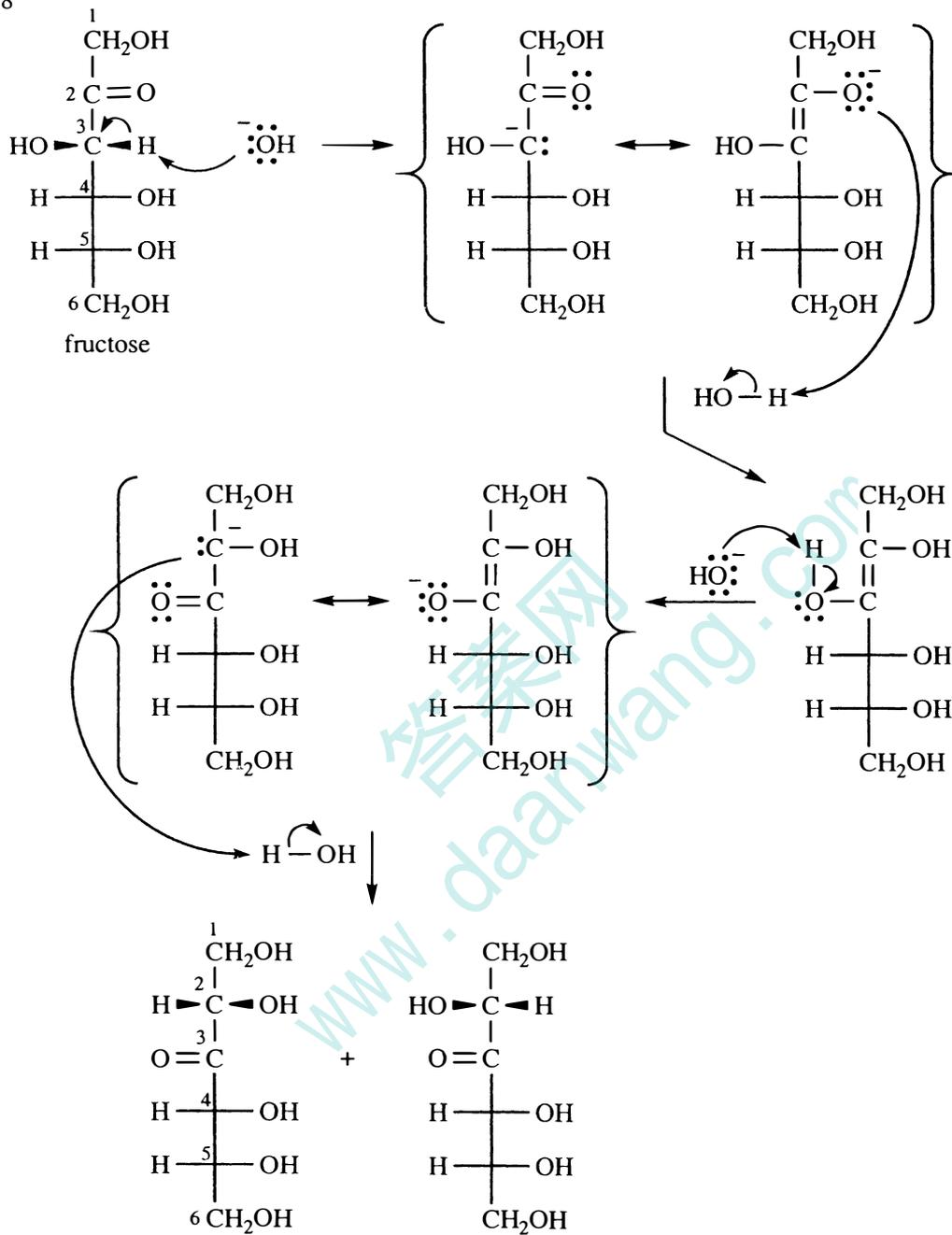
23-16

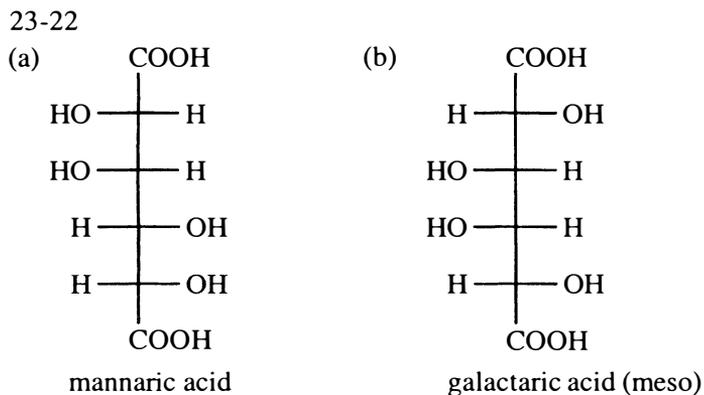
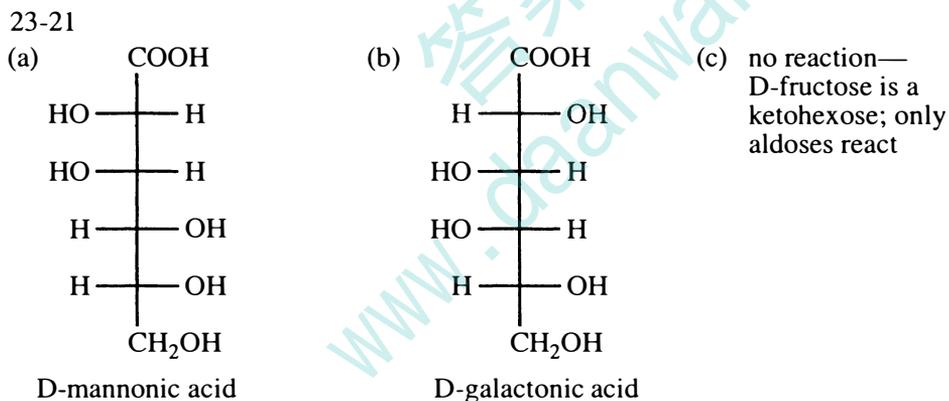
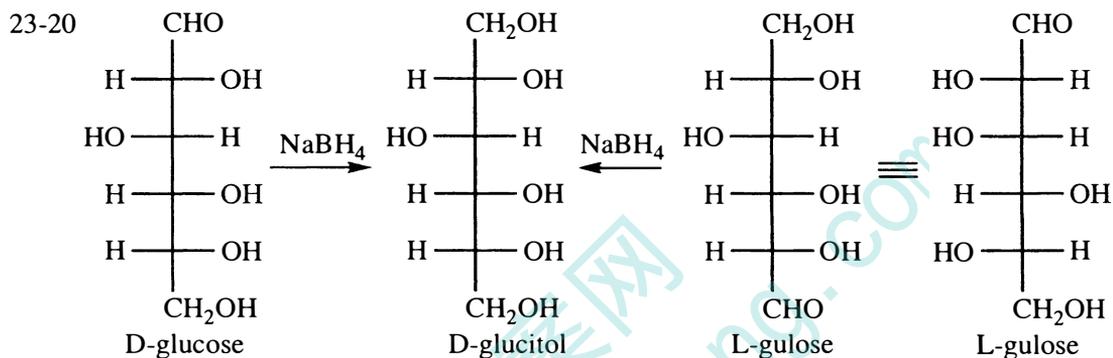
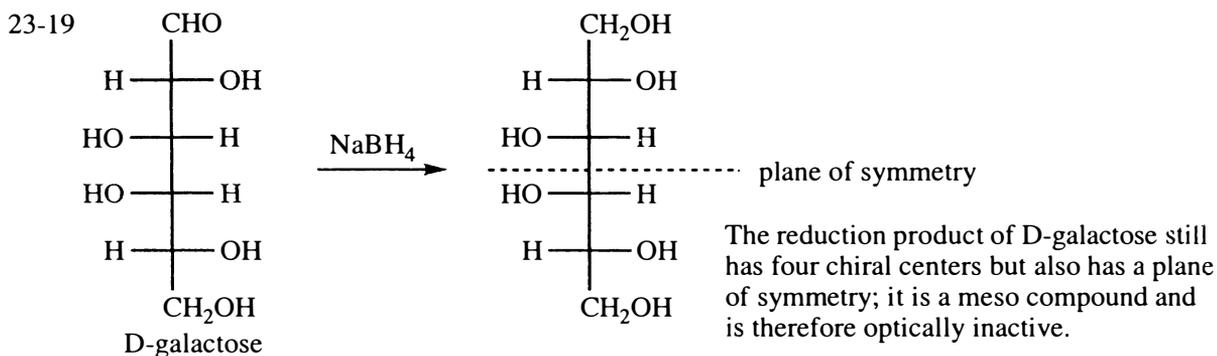


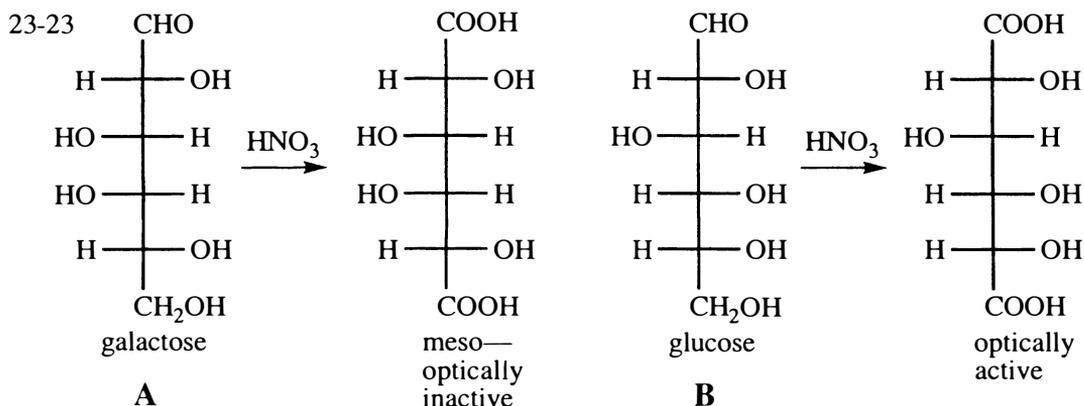
23-17



23-18



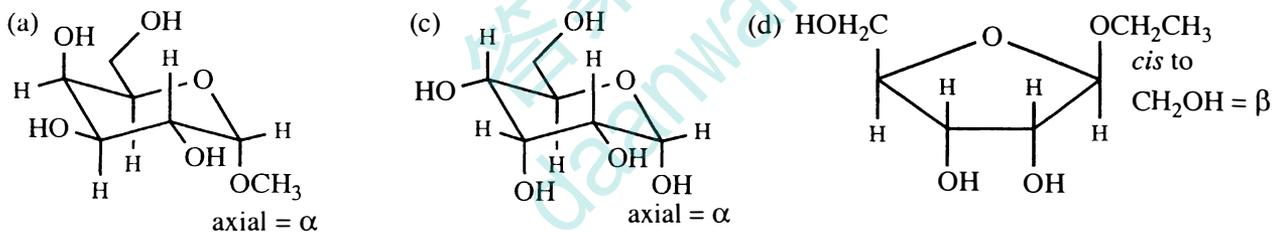




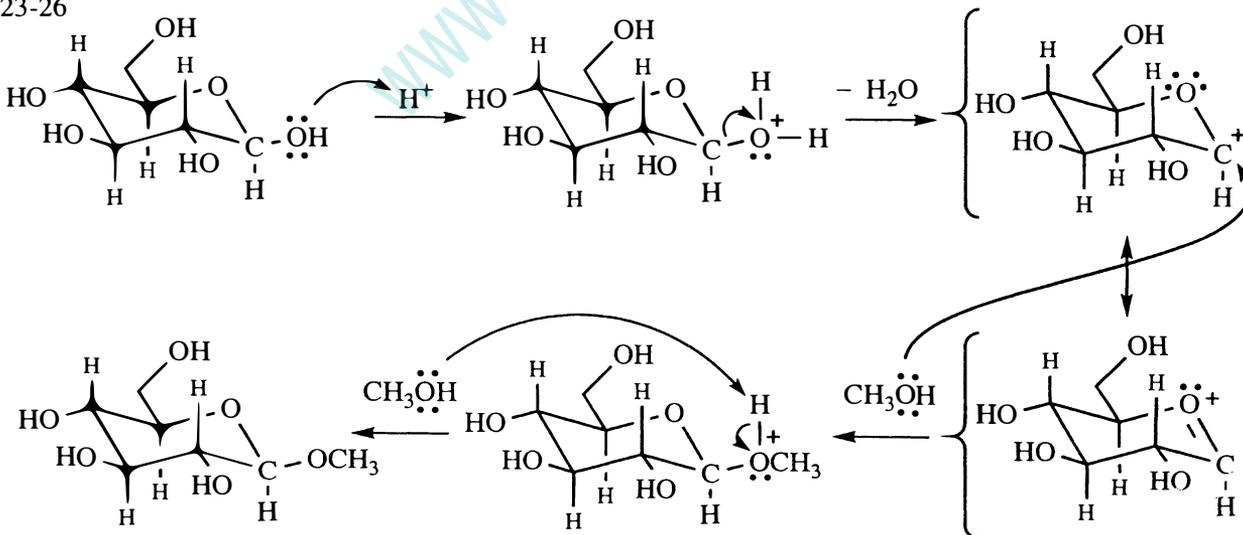
23-24

- (a) not reducing: an acetal ending in "oside"
- (b) reducing: a hemiacetal ending in "ose"
- (c) reducing: a hemiacetal ending in "ose"
- (d) not reducing: an acetal ending in "oside"
- (e) reducing: one of the rings has a hemiacetal
- (f) not reducing: all anomeric carbons are in acetal form

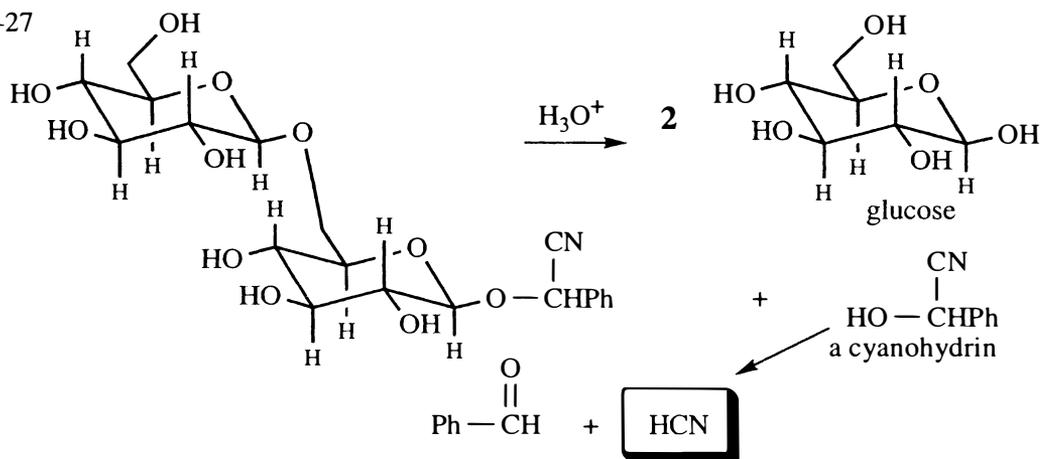
23-25



23-26

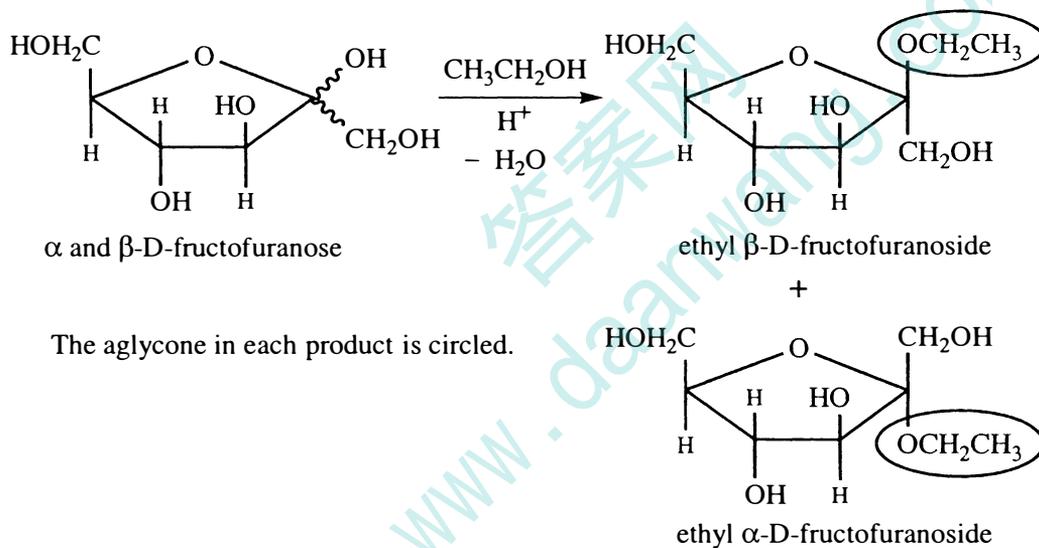


23-27

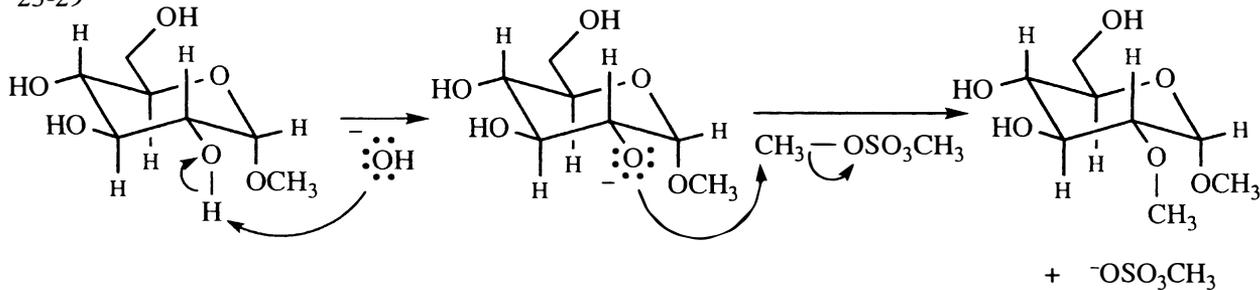


HCN is released from amygdalin. HCN is a potent cytotoxic (cell-killing) agent, particularly toxic to nerve cells.

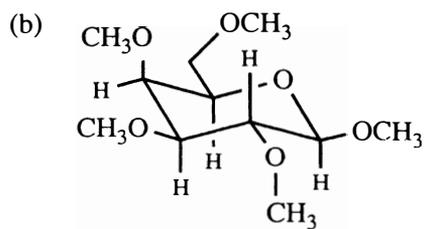
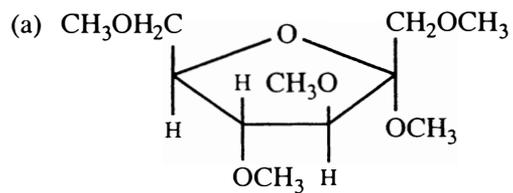
23-28



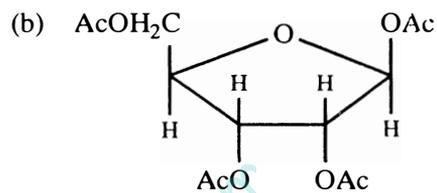
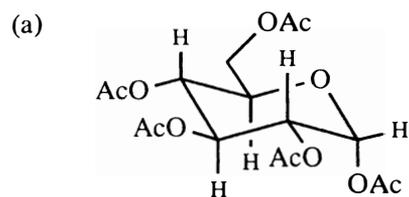
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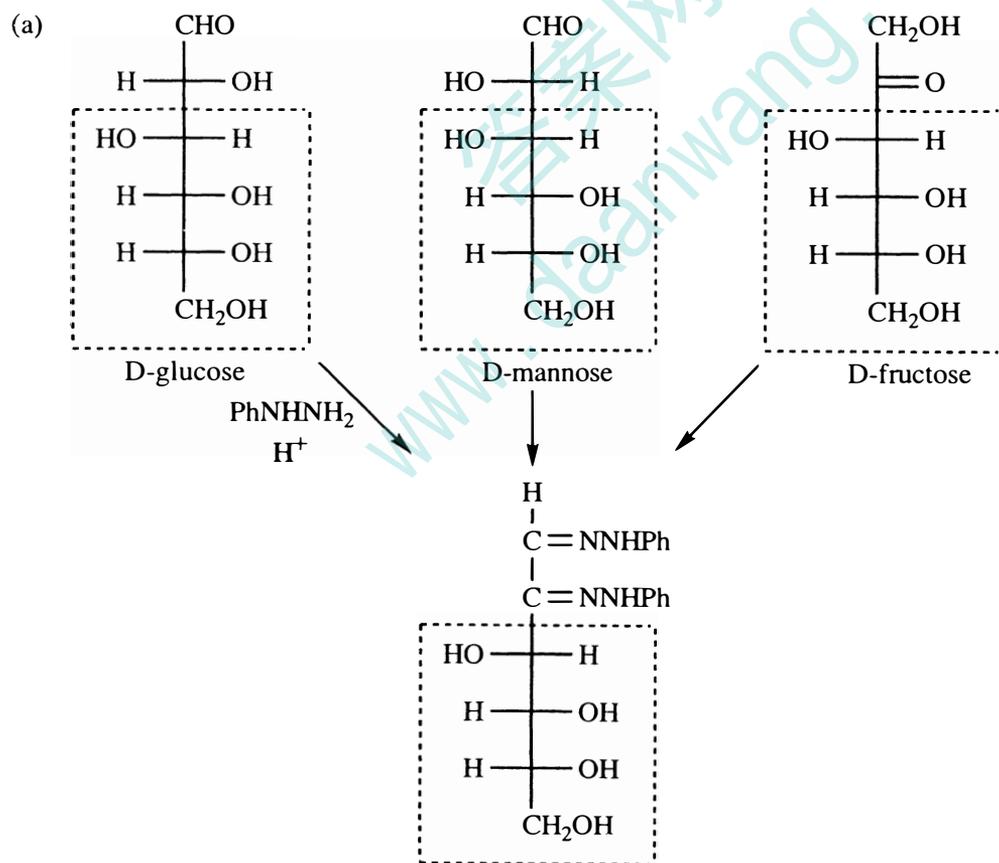
23-30



23-31

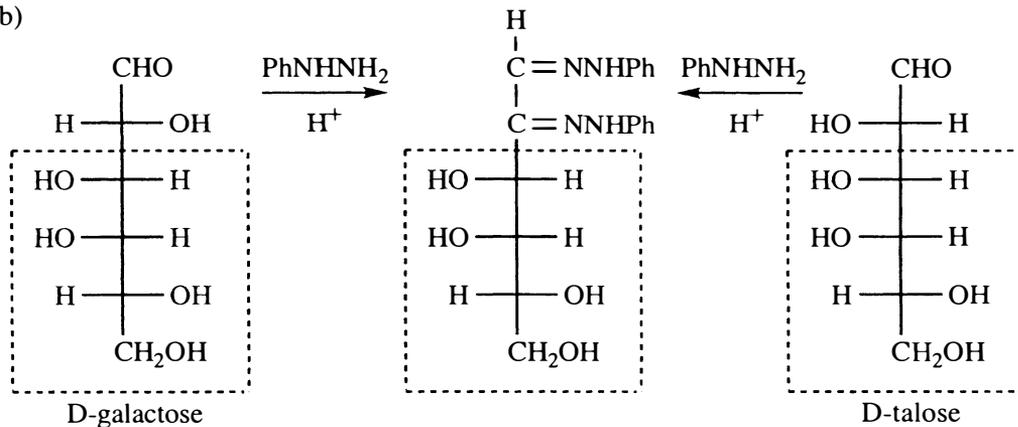


23-32



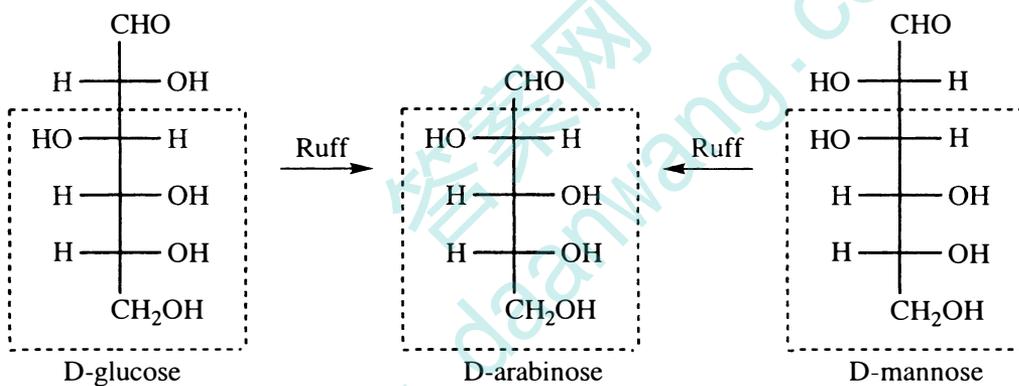
23-32 continued

(b)

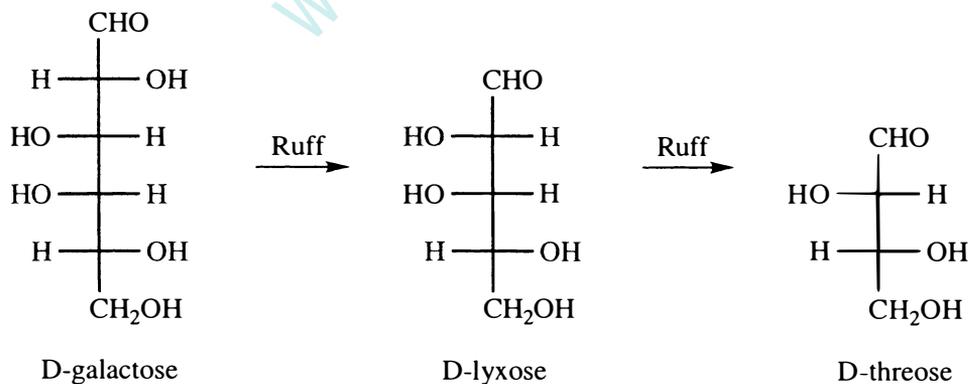


D-Talose must be the C-2 epimer of D-galactose.

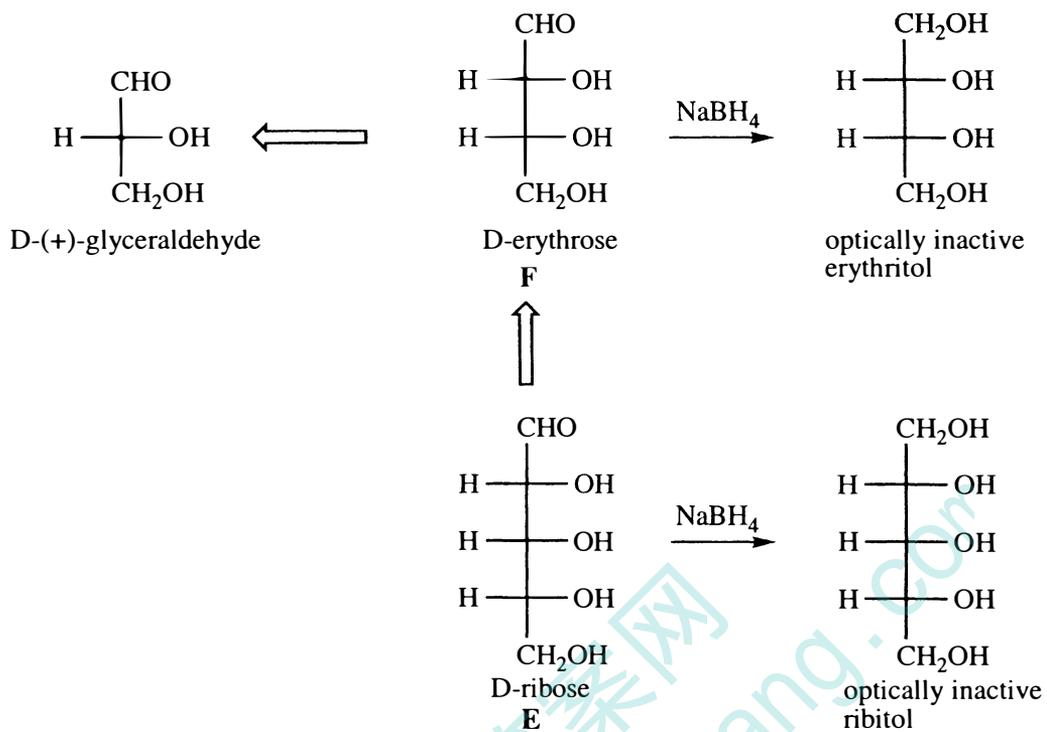
23-33 Reagents for the Ruff degradation are: 1. $\text{Br}_2, \text{H}_2\text{O}$; 2. $\text{H}_2\text{O}_2, \text{Fe}_2(\text{SO}_4)_3$.



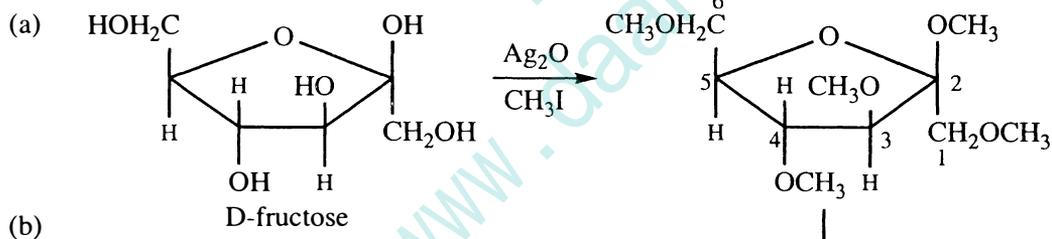
23-34 Reagents for the Ruff degradation are: 1. $\text{Br}_2, \text{H}_2\text{O}$; 2. $\text{H}_2\text{O}_2, \text{Fe}_2(\text{SO}_4)_3$.



23-39 Solve this problem by working backward from (+)-glyceraldehyde.

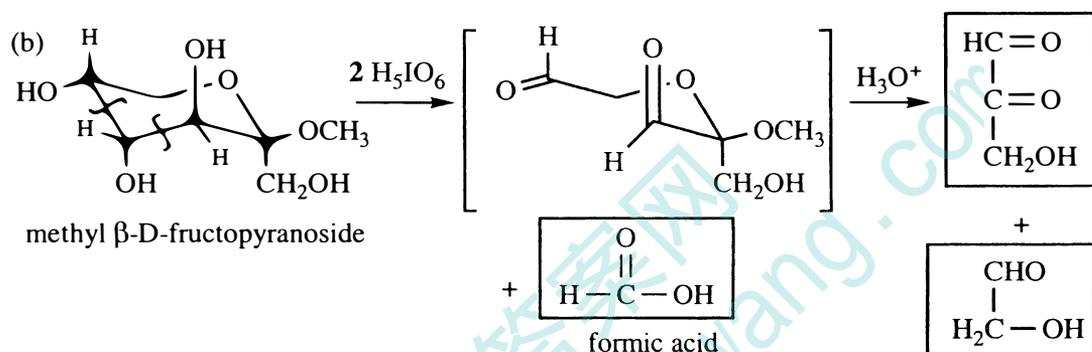
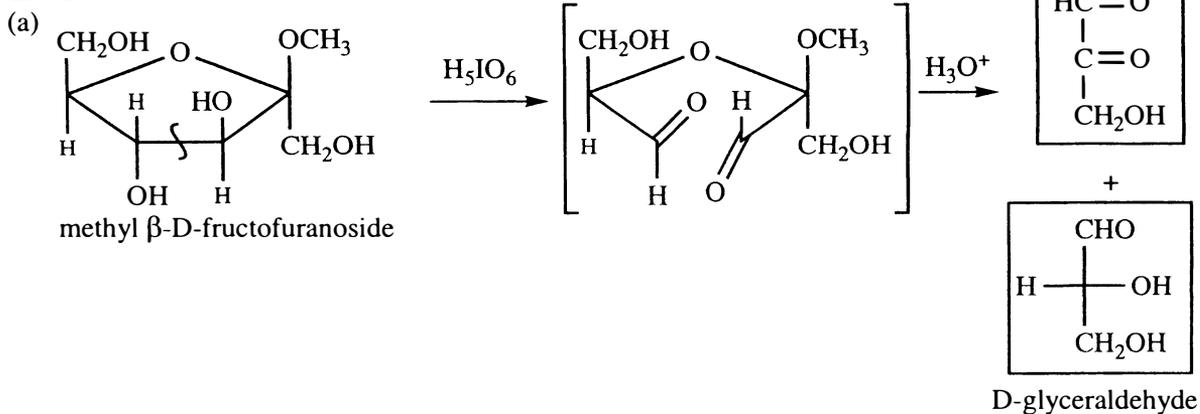


23-40



(c) Determining that the open chain form of fructose is a ketone at C-2 with a free OH at C-5 shows that fructose exists as a furanose hemiacetal.

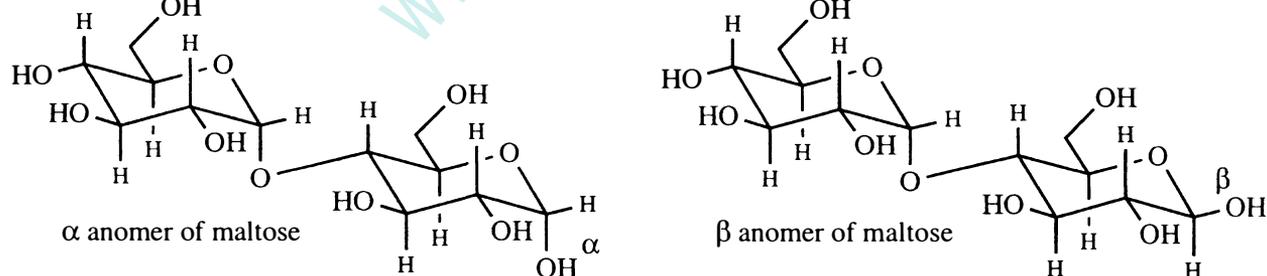
23-41

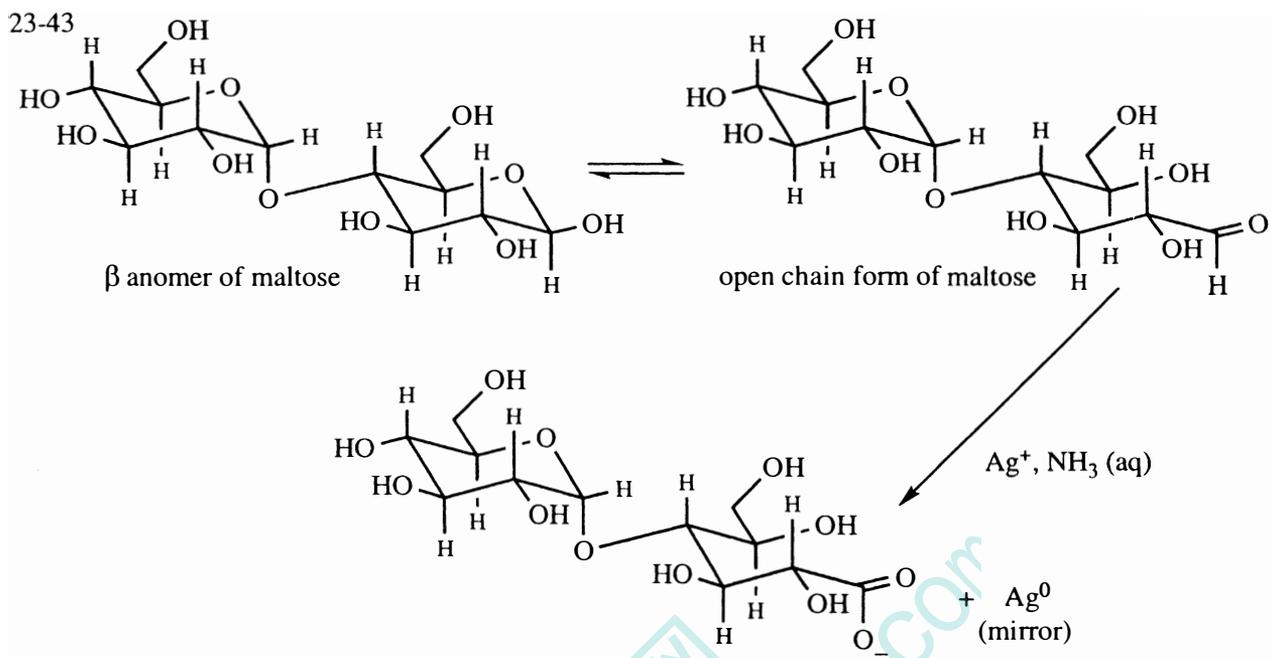


Production of one equivalent of formic acid, and two fragments containing two and three carbons respectively, proves that the glycoside was in a six-membered ring.

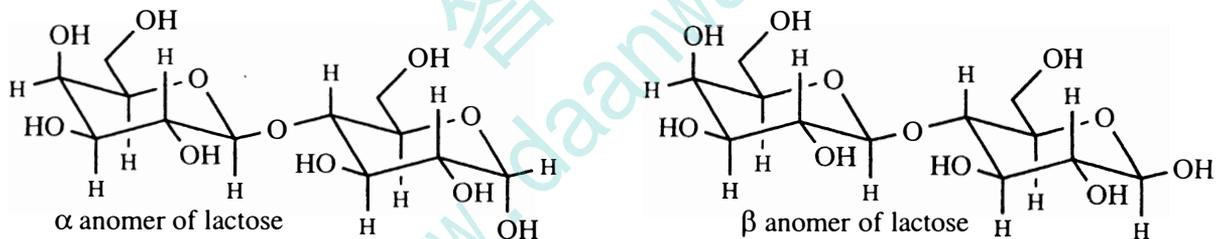
(c) In periodic acid oxidation of an aldohexose glycoside, glyceraldehyde is generated from carbons 4, 5, and 6. If configuration at the middle carbon is D, that means that carbon-5 of the aldohexose must have had the D configuration. On the other hand, if the isolated glyceraldehyde had the L configuration, then the original aldohexose must have been an L sugar.

23-42



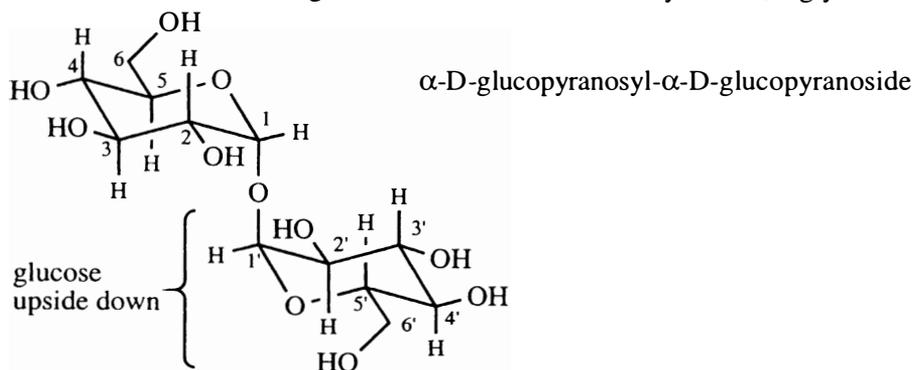


23-44 Lactose is a hemiacetal. Therefore, it can mutarotate and is a reducing sugar.

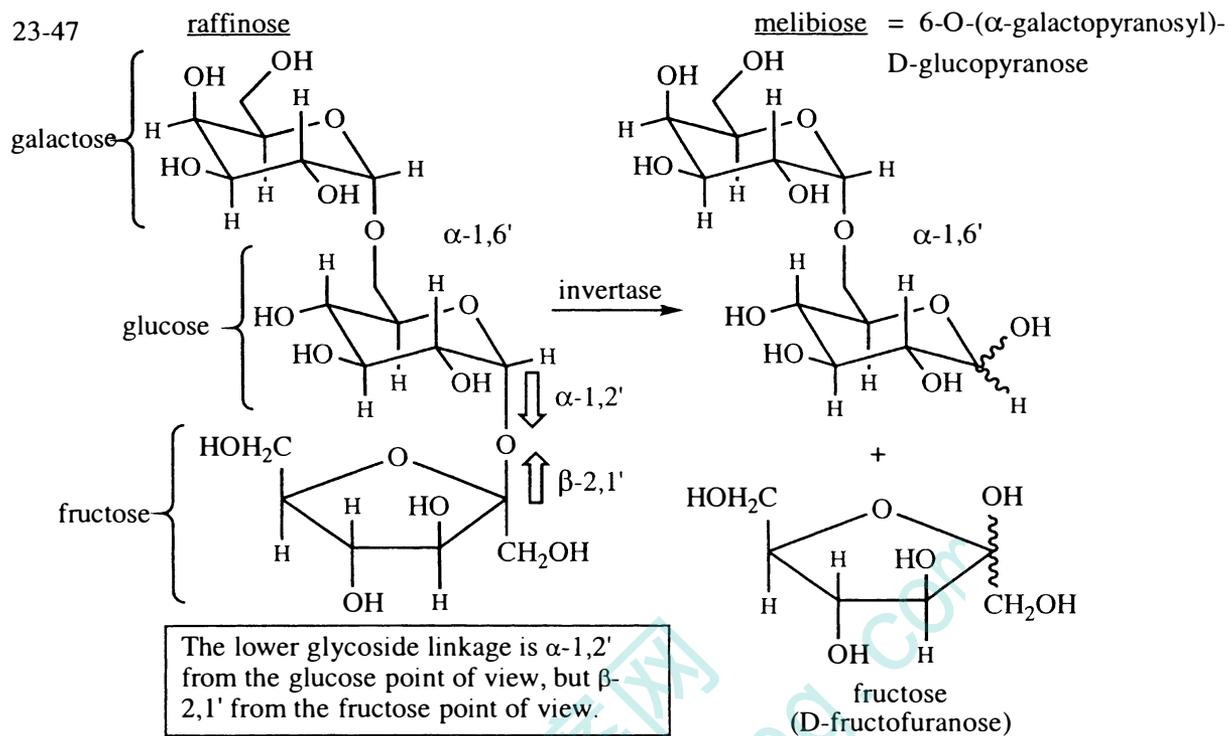


23-45 Gentiobiose is a hemiacetal; in water, the hemiacetal is in equilibrium with the open-chain form and can react as an aldehyde. Gentiobiose can mutarotate and is a reducing sugar.

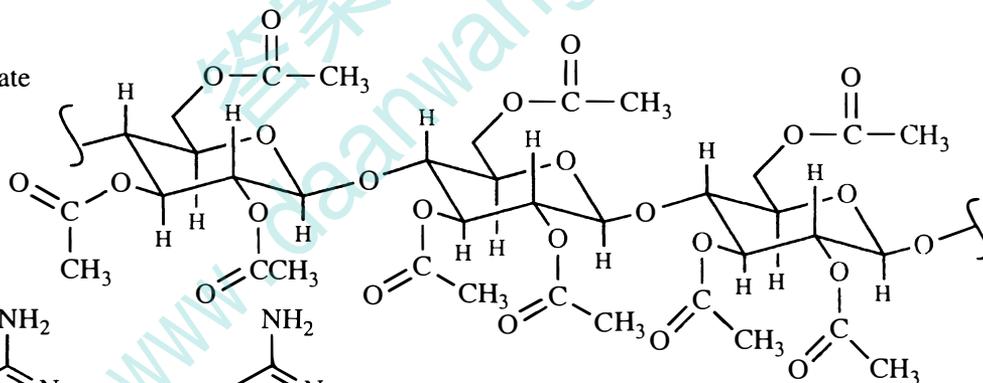
23-46 Trehalose must be two glucose molecules connected by an α -1,1'-glycoside.



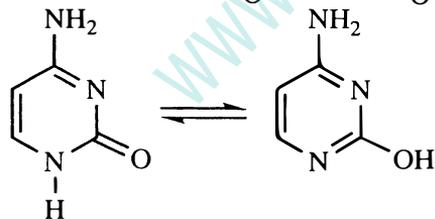
23-47



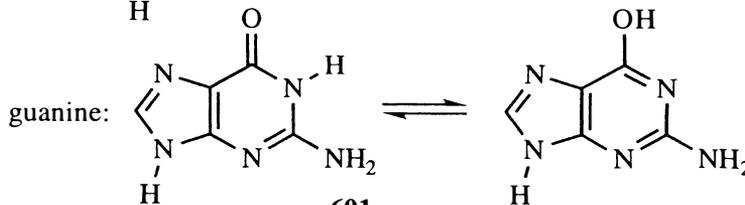
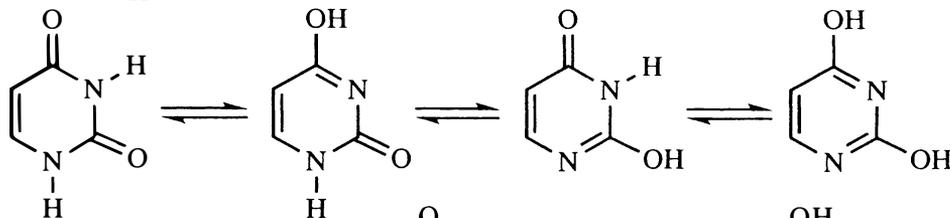
23-48 cellulose acetate



23-49 cytosine:

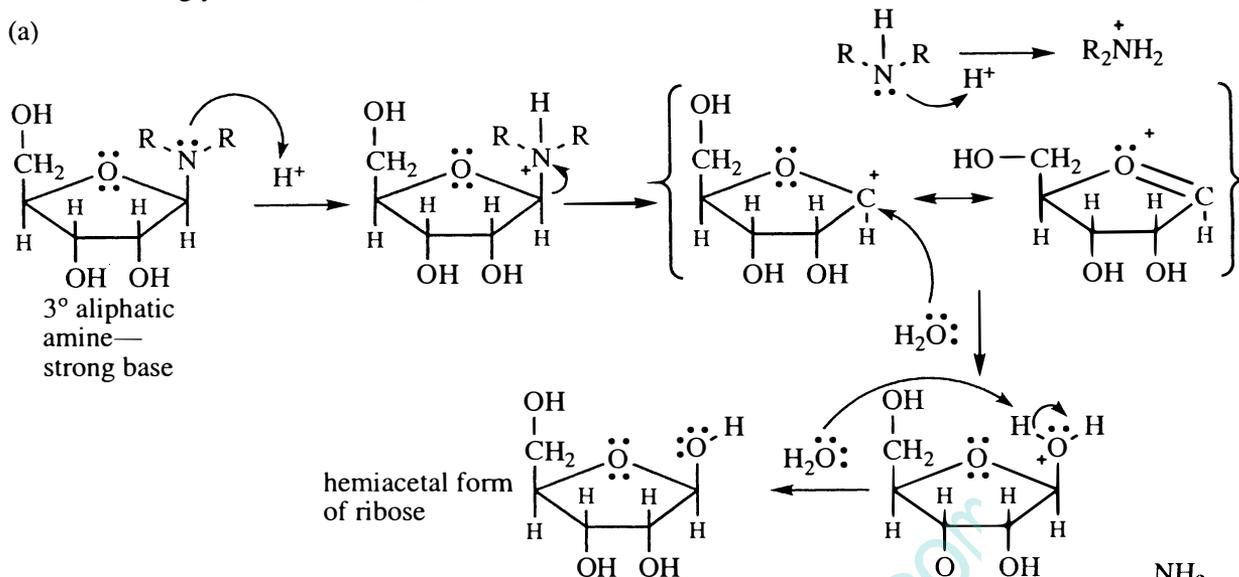


uracil:

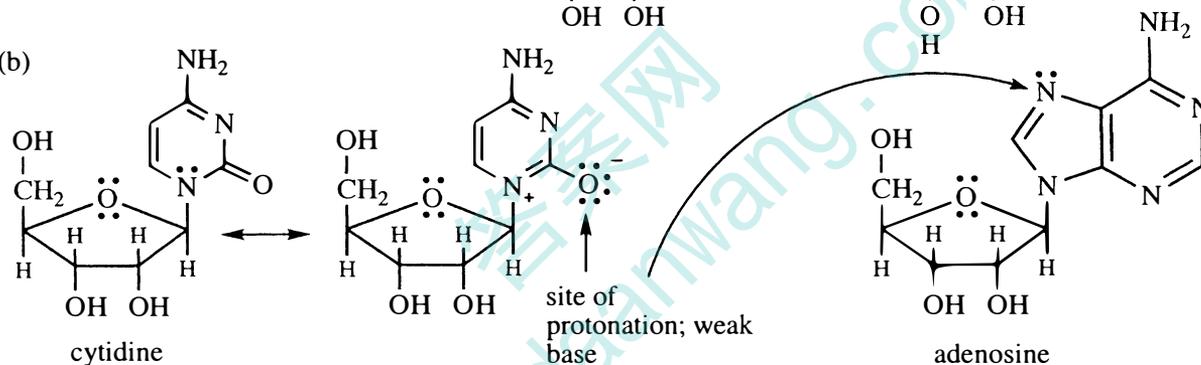


23-50 Aminoglycosides, including nucleosides, are similar to acetals: stable to base, cleaved by acid.

(a)



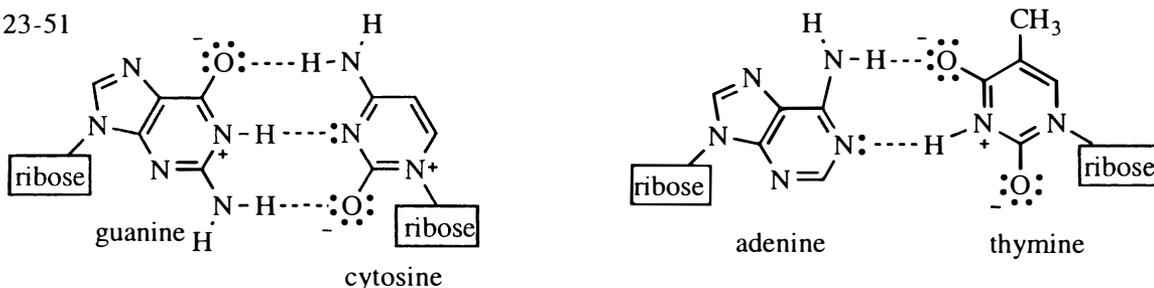
(b)



Nucleosides are less rapidly hydrolyzed in aqueous acid because the site of protonation (the N in adenosine, and in cytidine, the oxygen shown with the negative charge in the second resonance form) is much less basic than the aliphatic amine in an aminoglycoside. Nucleosides require stronger acid, or longer time and higher temperature, to be hydrolyzed.

This is important in living systems as it would cause genetic damage or even death of an organism if its DNA or RNA were too easily decomposed. Organisms go to great length and expend considerable energy to maintain the structural integrity of their DNA.

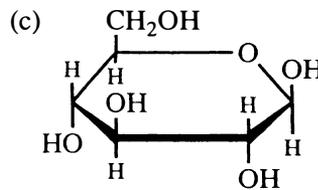
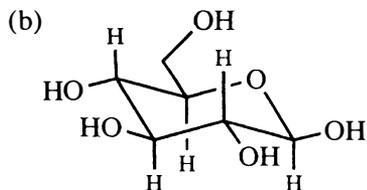
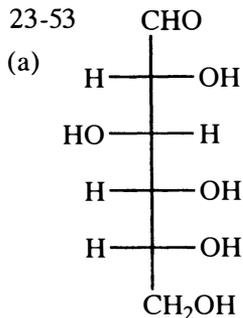
23-51



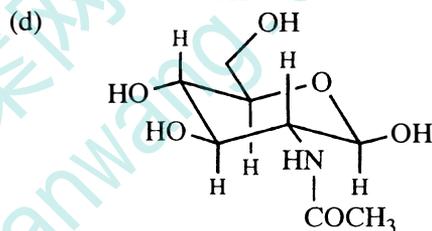
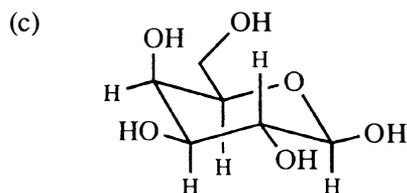
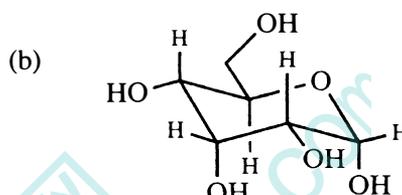
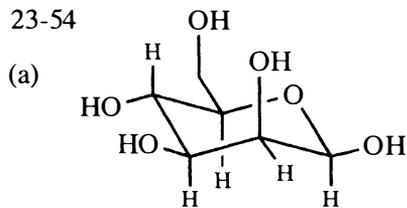
The polar resonance forms show how the hydrogen bonds are particularly strong. Each oxygen has significant negative charge, and in each pair, one H—N is polarized more strongly because the N has positive charge.

23-52 Please refer to solution 1-20, page 12 of this Solutions Manual.

23-53



23-54

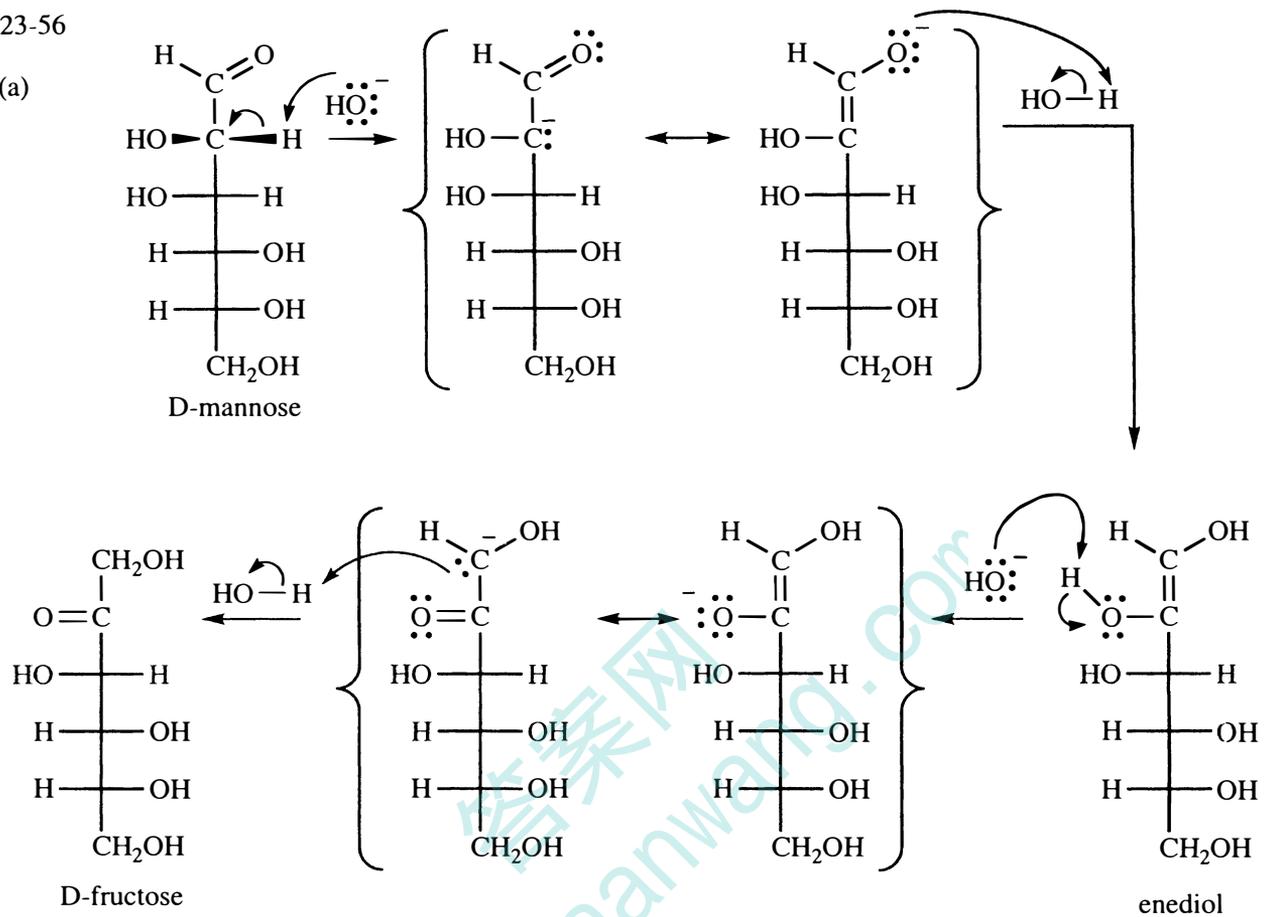


23-55

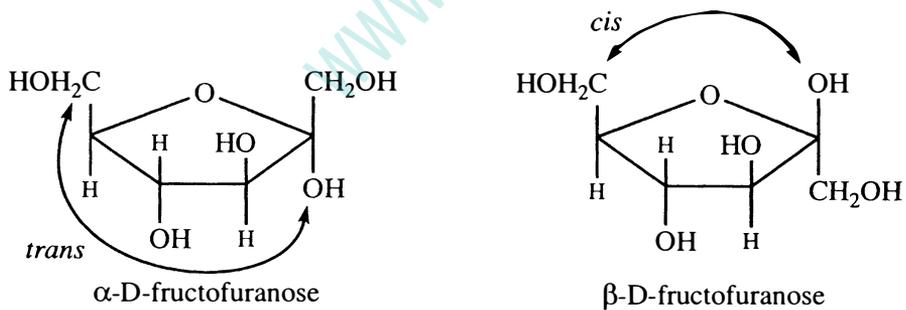
- (a) D-aldohexose (D configuration, aldehyde, 6 carbons)
- (b) D-aldopentose (D configuration, aldehyde, 5 carbons)
- (c) L-ketohexose (L configuration, ketone, 6 carbons)
- (d) L-aldohexose (L configuration, aldehyde, 6 carbons)
- (e) D-ketopentose (D configuration, ketone, 5 carbons)
- (f) L-aldotetrose (L configuration, aldehyde, 4 carbons)
- (g) 2-acetamido D-aldohexose (D configuration, aldehyde, 6 carbons in chain, with acetamido group at C-2)

23-56

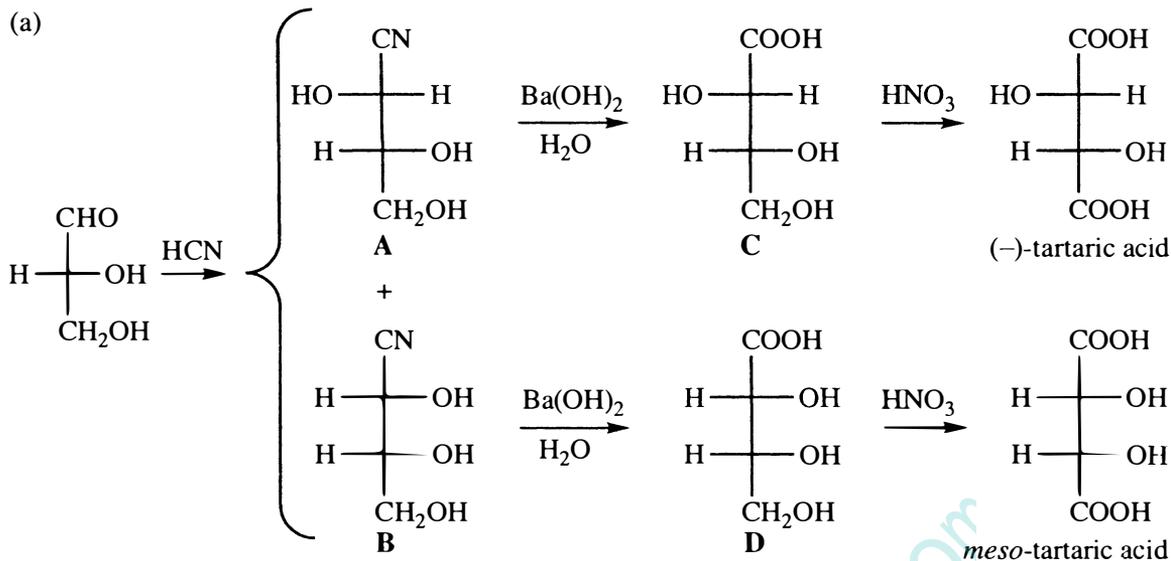
(a)



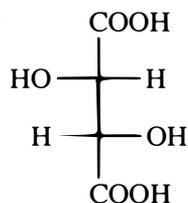
(b) The α isomer has the anomeric OH *trans* to the CH_2OH off of C-5. The β -anomer has these groups *cis*.



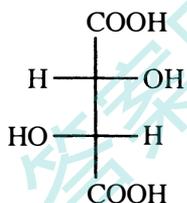
23-57



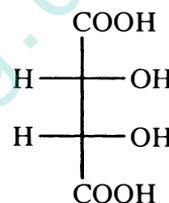
(b)



(*S,S*)-(-)-tartaric acid



(*R,R*)-(+)-tartaric acid



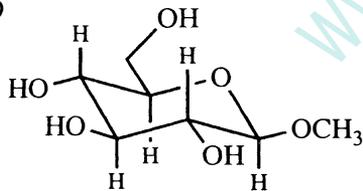
(*R,S*)-*meso*-tartaric acid

23-58

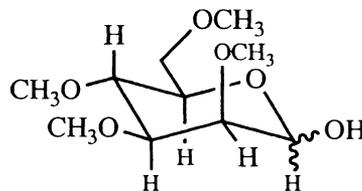
- (a) D-(-)-ribose (b) D-(+)-altrose (c) L-(+)-erythrose (d) L-(-)-galactose (e) L-(+)-idose

23-59

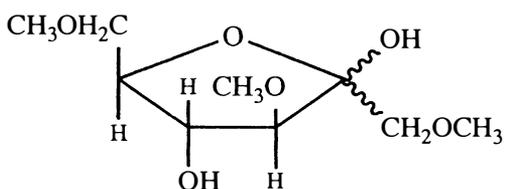
(a)



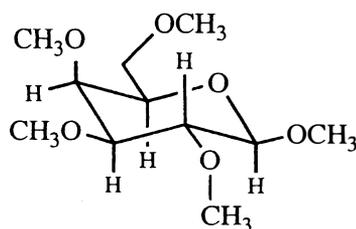
(b)



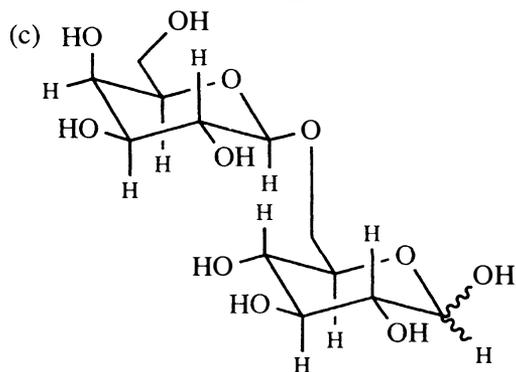
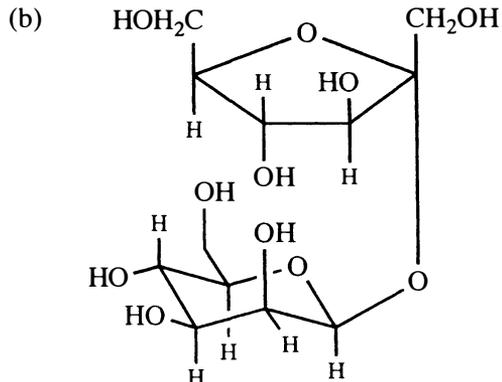
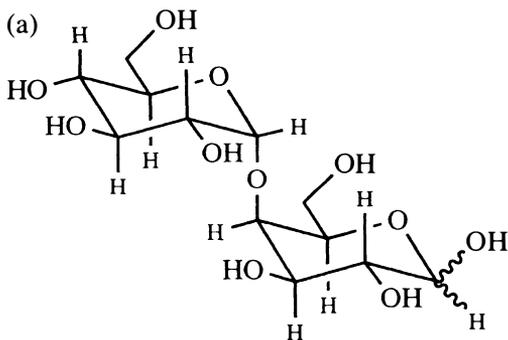
(c)



(d)



23-60



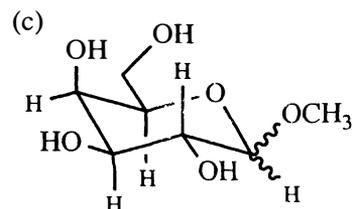
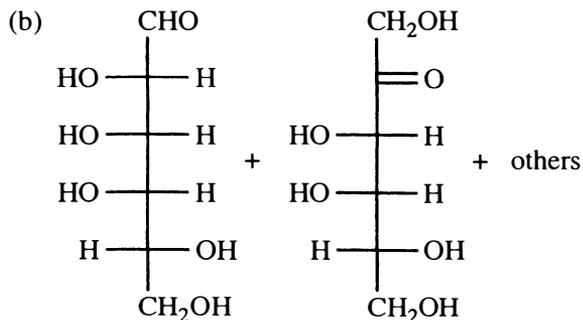
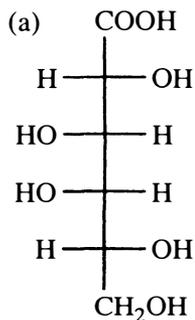
23-61

- (a) methyl β -D-fructofuranoside
 (b) 3,6-di-O-methyl- β -D-mannopyranose
 (c) 4-O-(α -D-fructofuranosyl)- β -D-galactopyranose
 (d) β -D-N-acetylgalactopyranosamine, or 2-acetamido-2-deoxy- β -D-galactopyranose

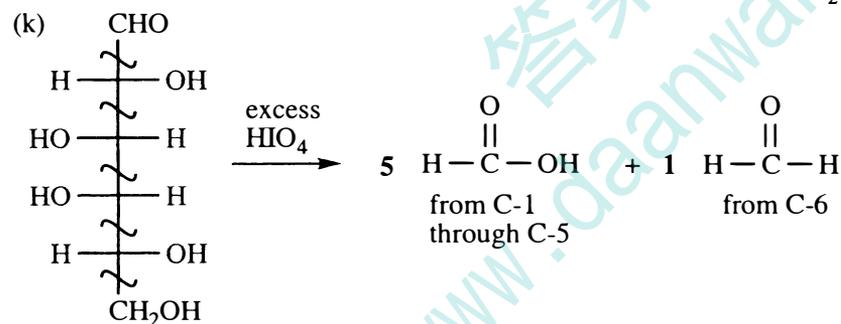
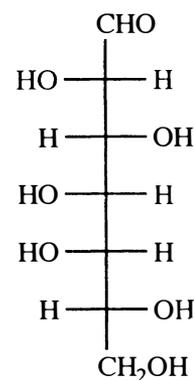
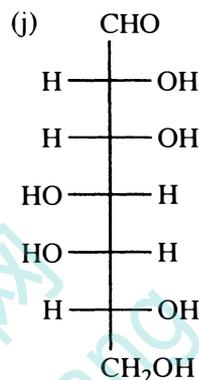
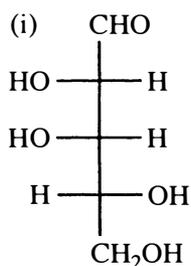
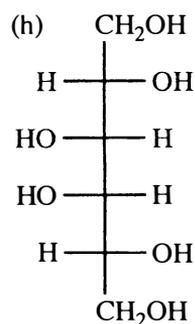
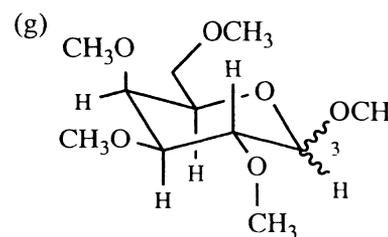
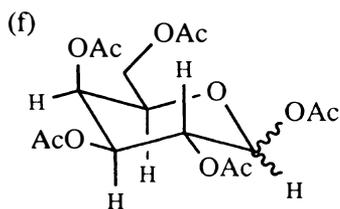
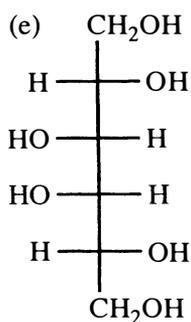
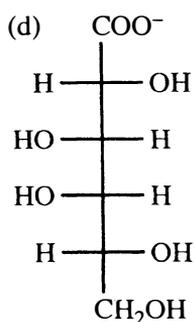
23-62 These are reducing sugars and would undergo mutarotation:

- in problem 23-59: (b) and (c);
 —in problem 23-60: (a) and (c);
 —in problem 23-61: (b), (c), and (d)

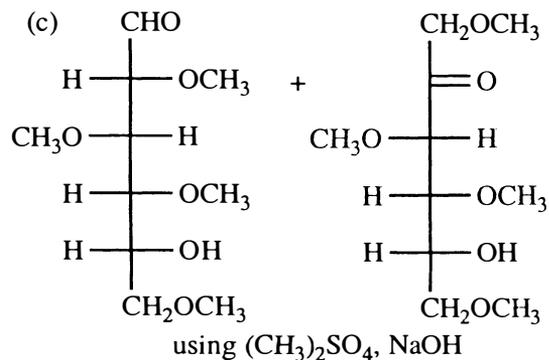
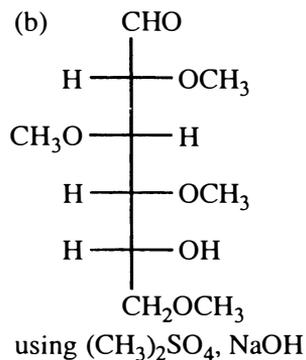
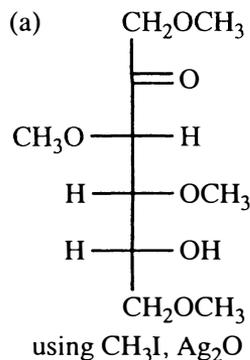
23-63



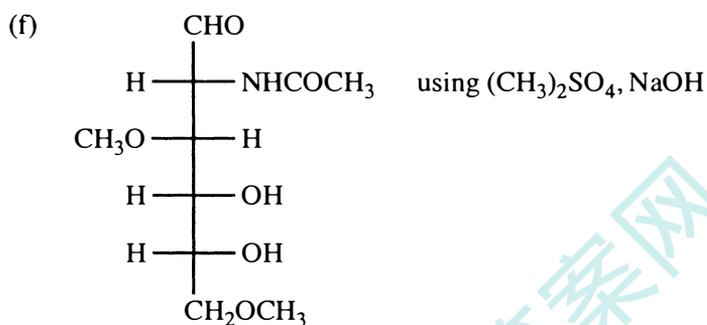
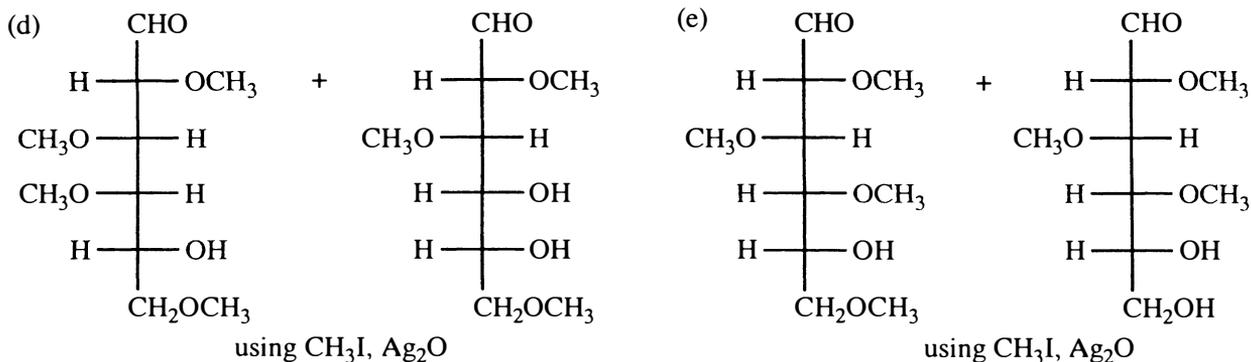
23-63 continued



23-64 Use the milder reagent, $\text{CH}_3\text{I}/\text{Ag}_2\text{O}$, when the sugar is in the hemiacetal form; the mild conditions prevent isomerization. When the carbohydrate is present as an acetal (a glycoside), use the more basic reagent, $\text{NaOH}/(\text{CH}_3)_2\text{SO}_4$; an acetal is stable to basic conditions.

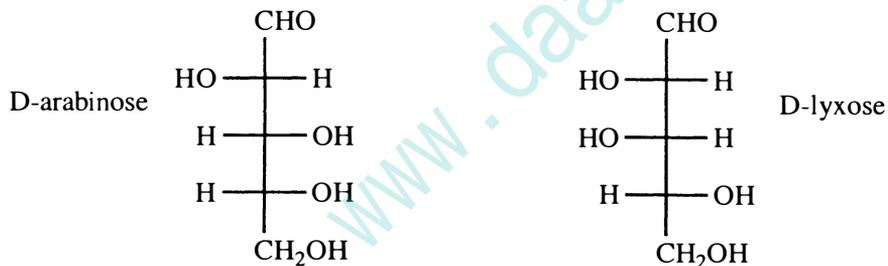


23-64 continued

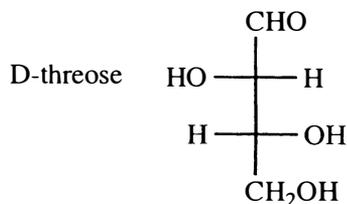


23-65

(a) These D-aldopentoses will give optically active aldaric acids.

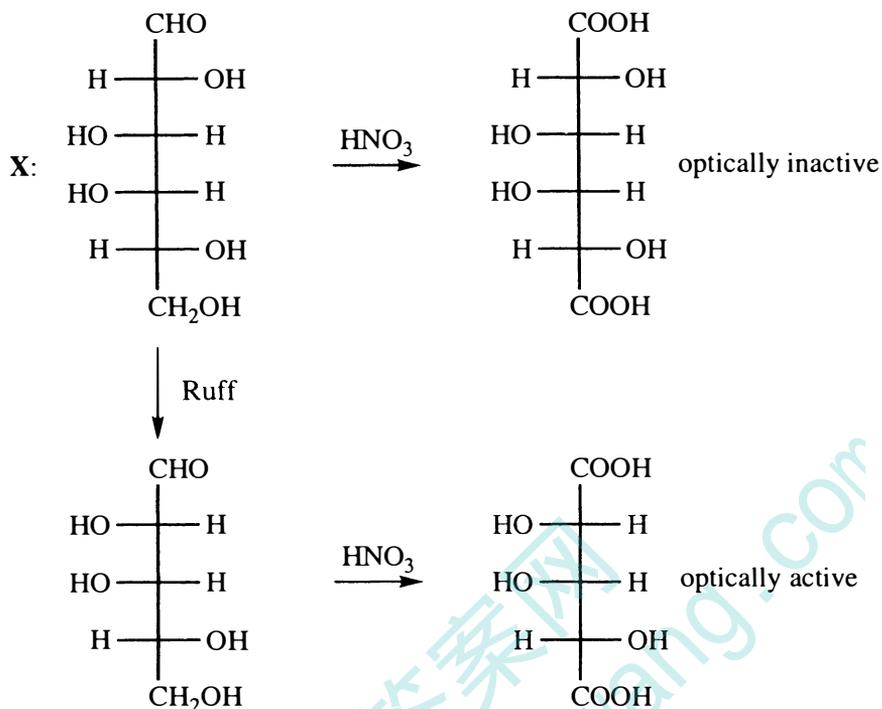


(b) Only D-threose (of the aldotetroses) will give an optically active aldaric acid.



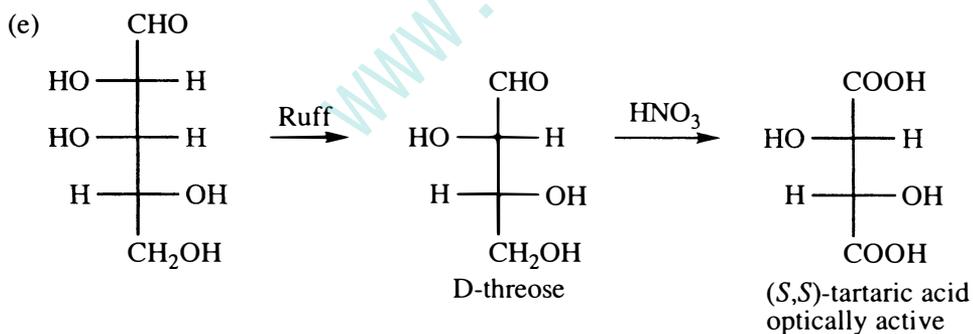
23-65 continued

(c) X is D-galactose.



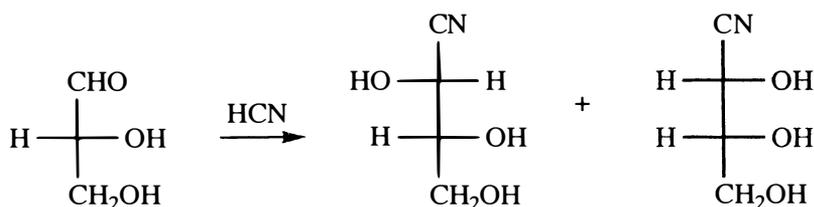
The other aldohexose that gives an optically inactive aldaric acid is D-allose, with all OH groups on the right side of the Fischer projection. Ruff degradation followed by nitric acid gives an optically *inactive* aldaric acid, however, so X cannot be D-allose.

(d) The optically active, five-carbon aldaric acid comes from the optically active pentose, not from the optically inactive, six-carbon aldaric acid. The principle is not violated.



23-66

(a)

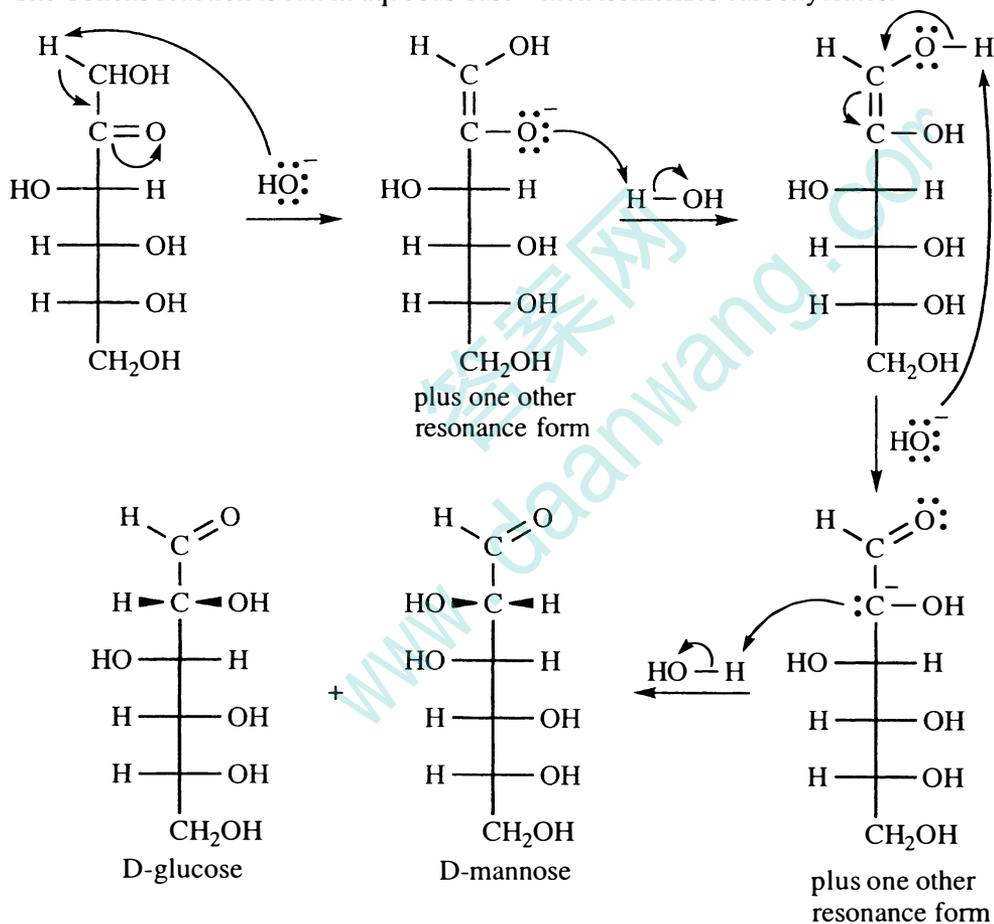


(b) The products are diastereomers with different physical properties. They could be separated by crystallization, distillation, or chromatography.

(c) Both products are optically active. Each has two chiral centers and no plane of symmetry.

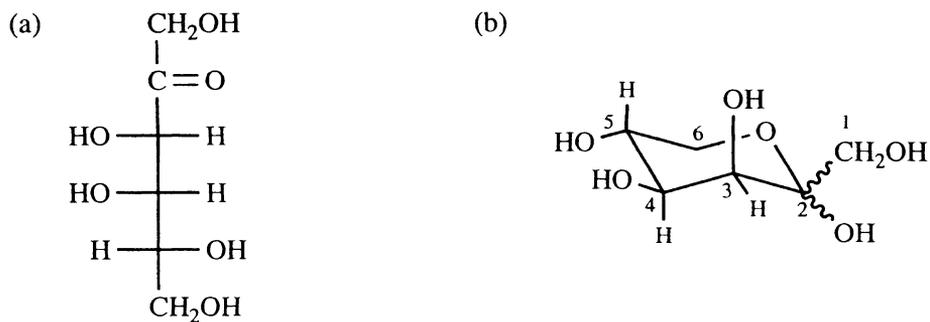
23-67

(a) The Tollens reaction is run in aqueous base which isomerizes carbohydrates.

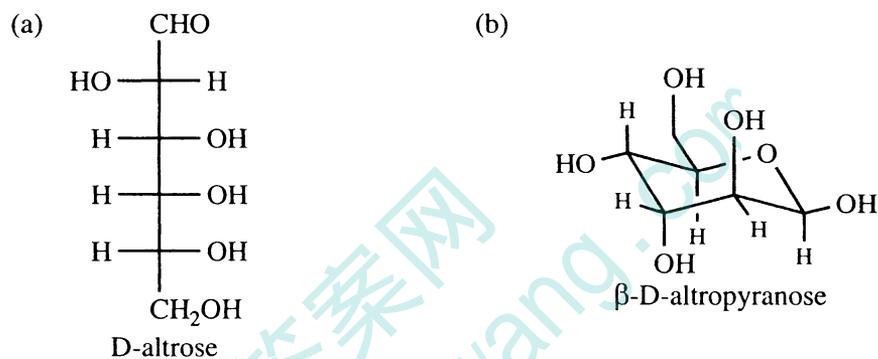


(b) Bromine water is acidic, not basic like the Tollens reagent. Carbohydrates isomerize quickly in base, but only very slowly in acid, so bromine water can oxidize without isomerization.

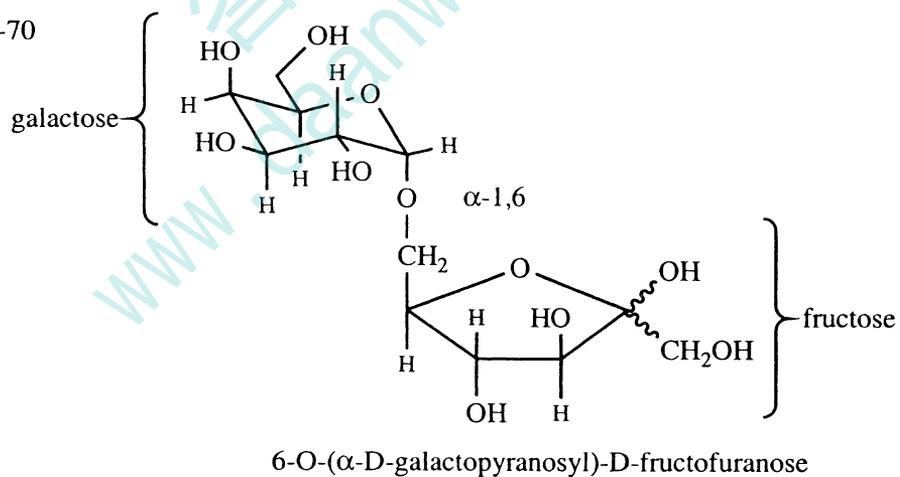
23-68 Tagatose is a monosaccharide, a ketohexose, that is found in the pyranose form.

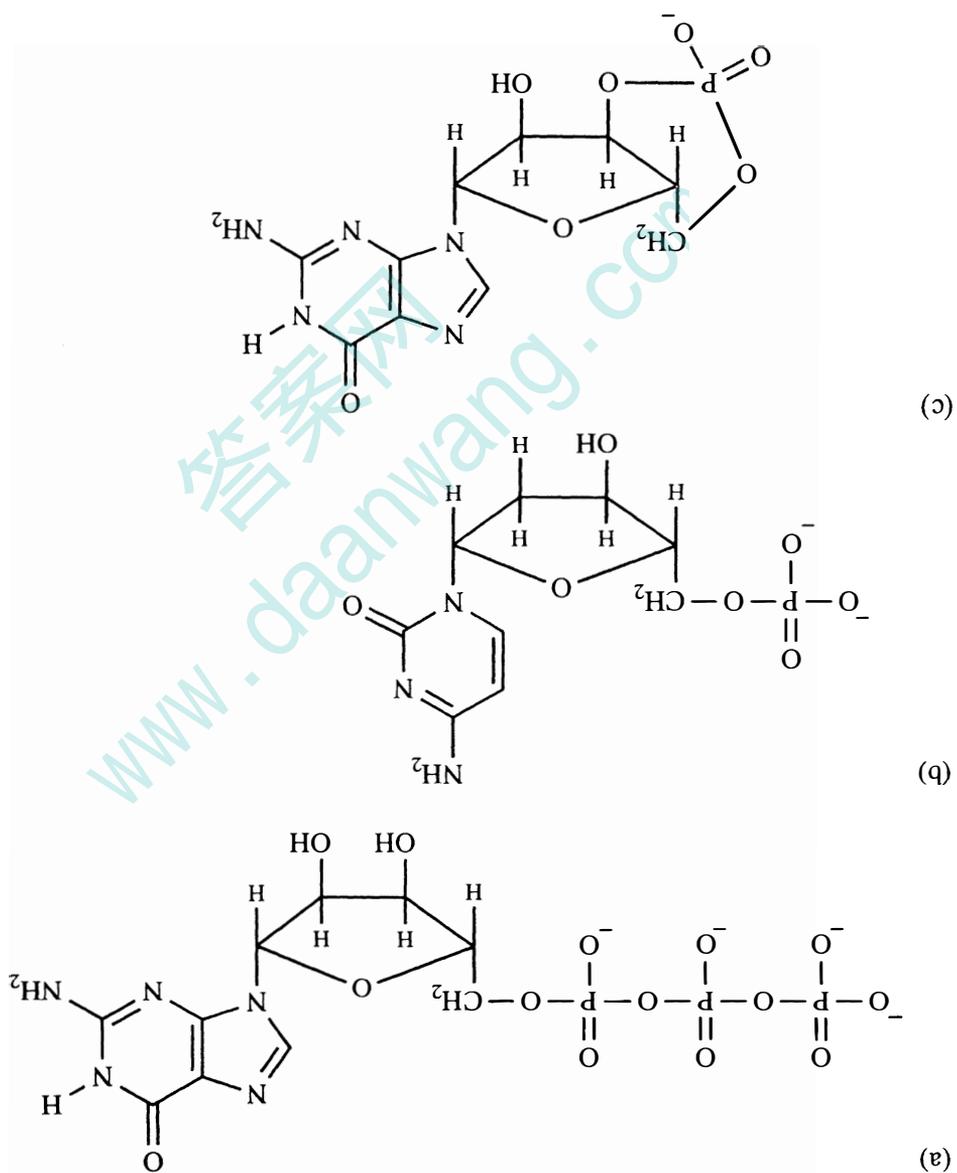


23-69

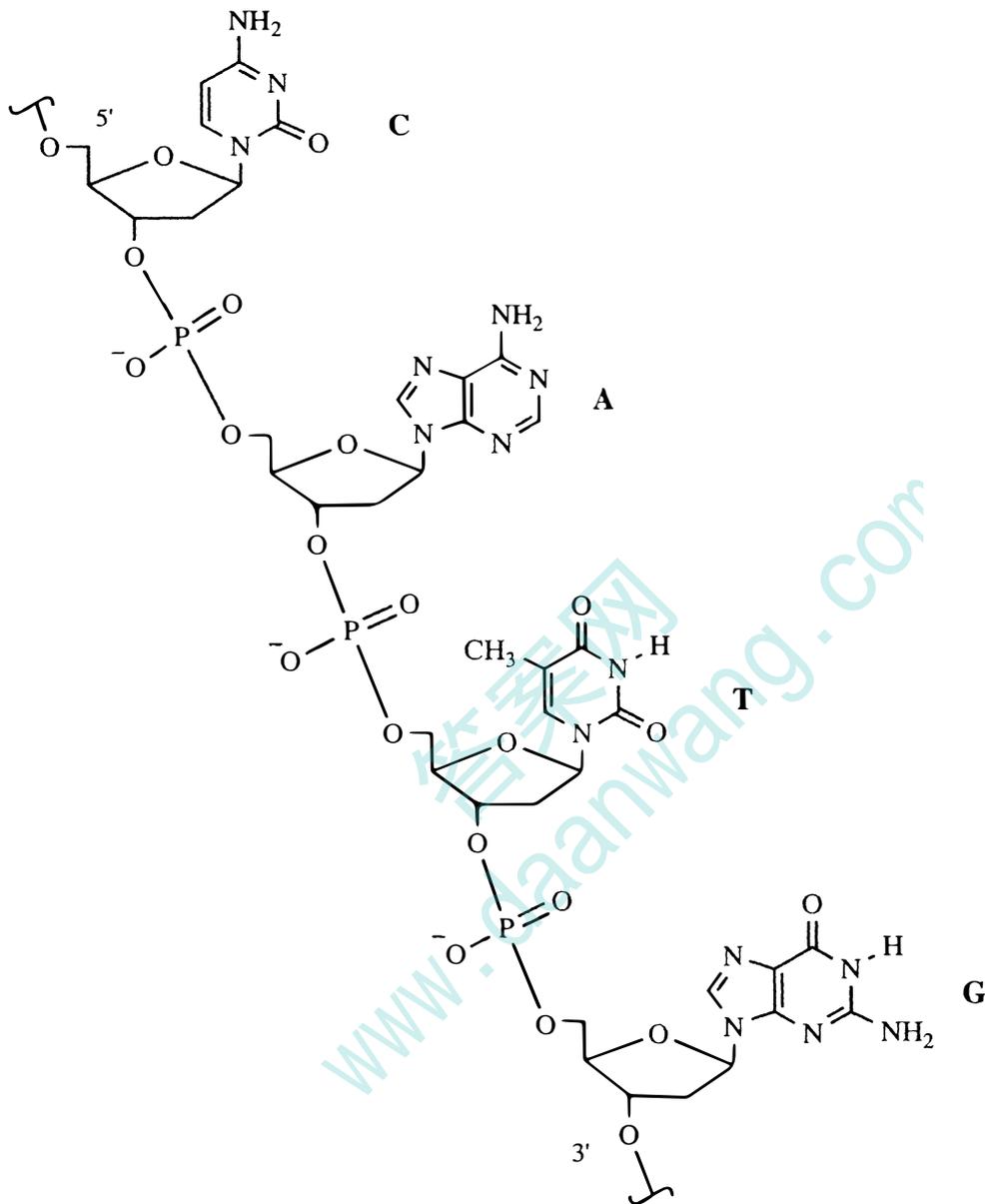


23-70





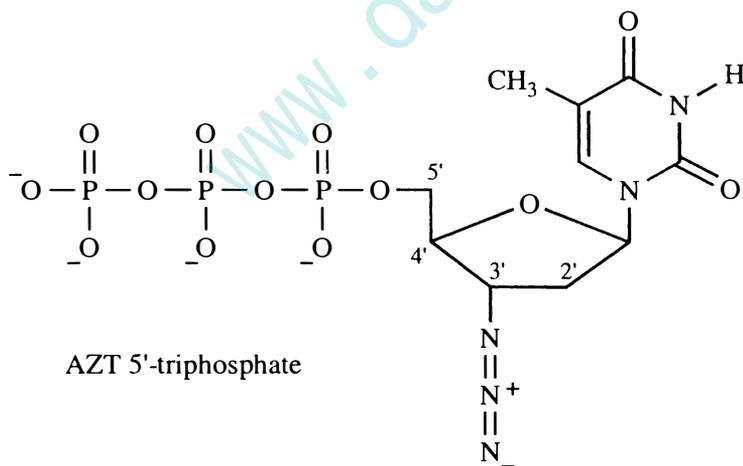
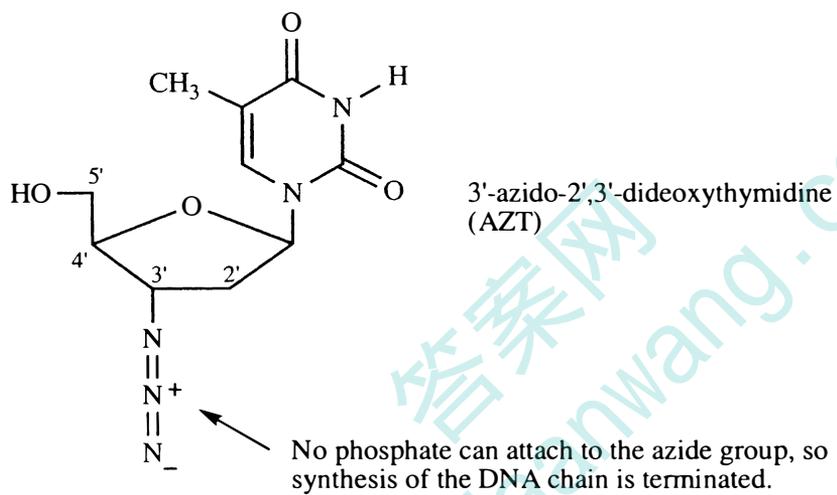
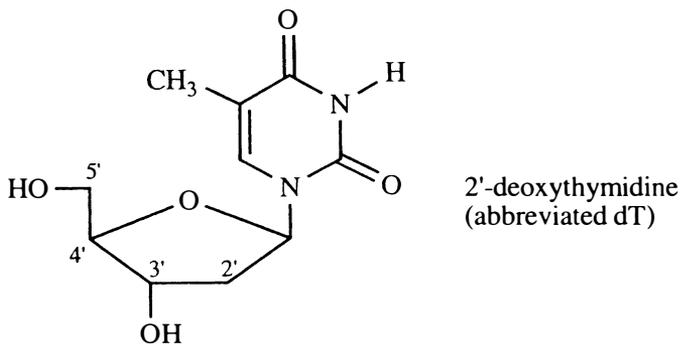
23-72 Bonds from C to H are omitted for simplicity.



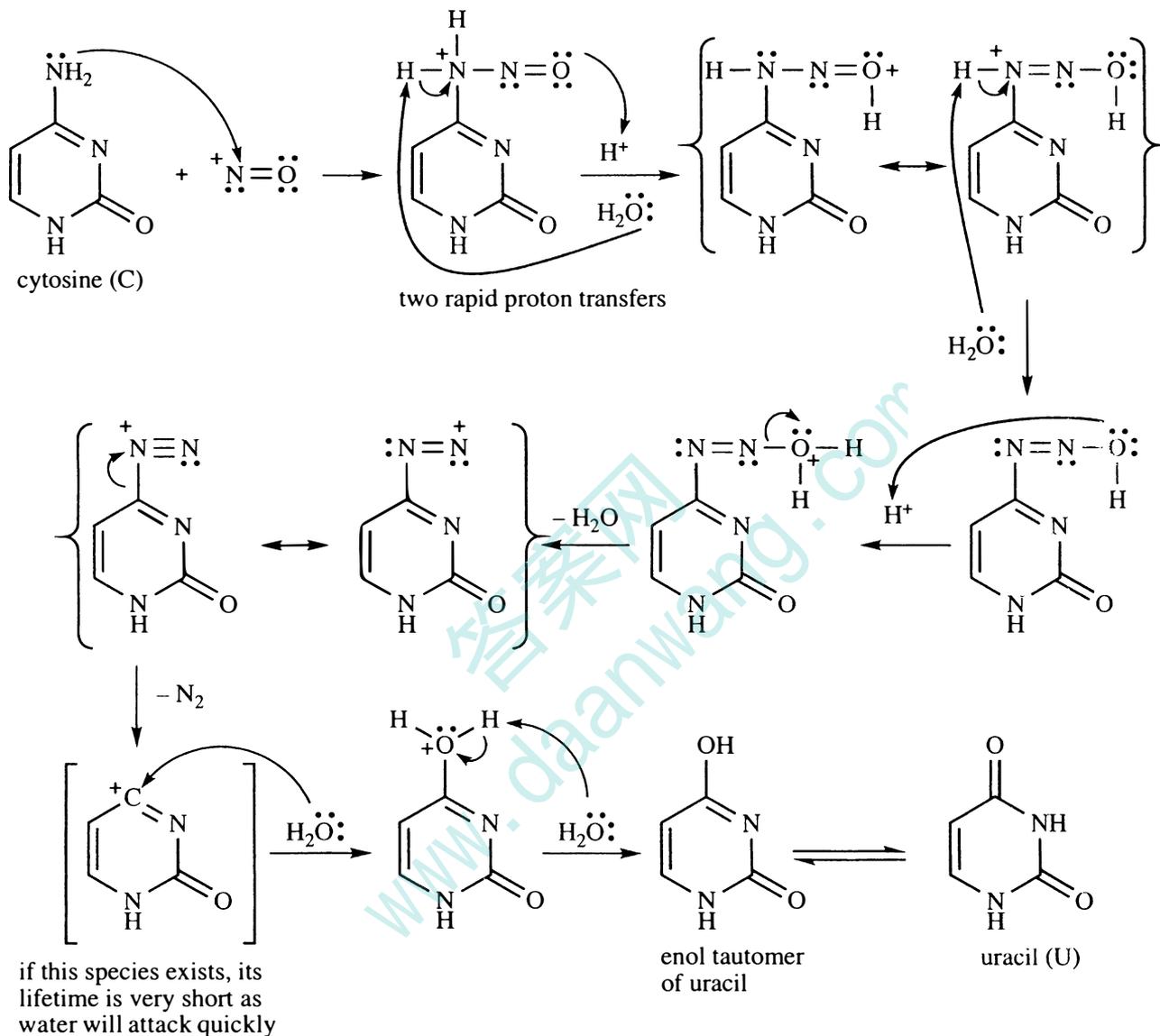
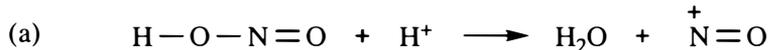
23-73

- (a) No, there is no relation between the amount of G and A.
- (b) Yes, this must be true mathematically.
- (c) Chargaff's rule must apply only to double-stranded DNA. For each G in one strand, there is a complementary C in the opposing strand, but there is no correlation between G and C *in the same strand*.

23-74 Bonds from C to H are omitted for simplicity.



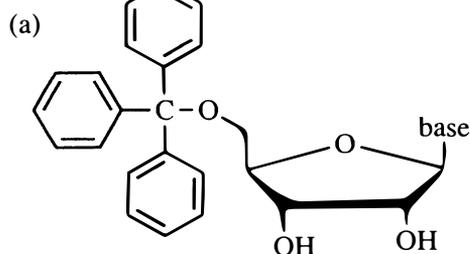
23-75 Recall from section 19-17 that nitrous acid is unstable, generating nitrosonium ion.



(b) In base pairing, cytosine pairs with guanine. If cytosine is converted to uracil, however, each replication will not carry the complement of cytosine (guanine) but instead will carry the complement of uracil (adenine). This is the definition of a mutation, where the wrong base is inserted in a nucleic acid chain.

(c) In RNA, the transformation of cytosine (C) to uracil (U) is not detected as a problem because U is a base normally found in RNA so it goes unrepaired. In DNA, however, thymine (with an extra methyl group) is used instead of uracil. If cytosine is diazotized to uracil, the DNA repair enzymes detect it as a mutation and correct it.

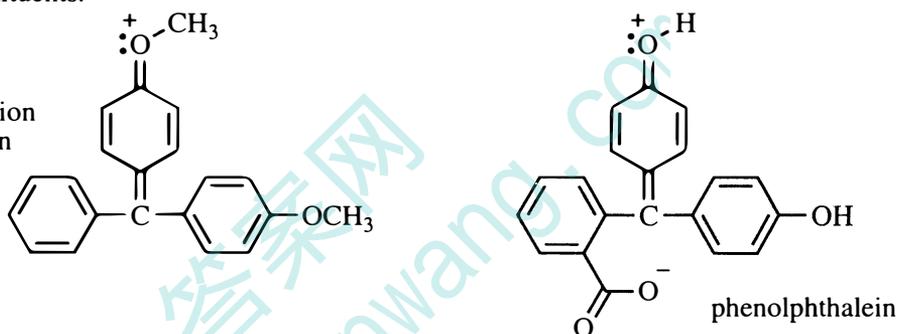
23-76



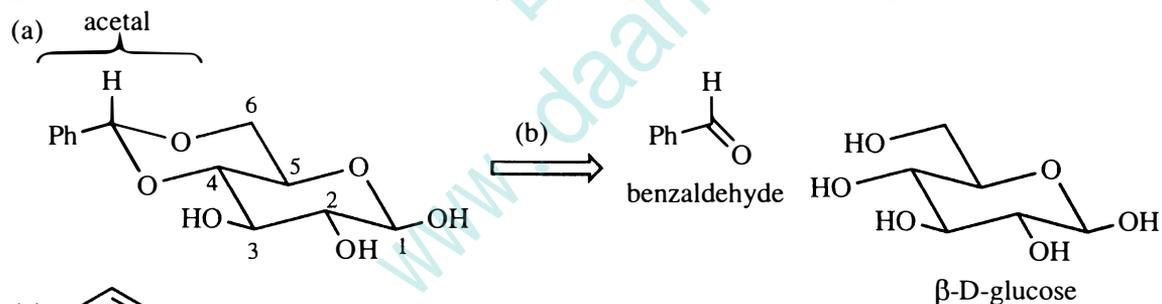
(b) Trityl groups are specific for 1° alcohols for steric reasons: the trityl group is so big that even a 2° alcohol is too crowded to react at the central carbon. It is possible for a trityl to go on a 2° alcohol, but the reaction is exceedingly slow and in the presence of a 1° alcohol, the reaction is done at the 1° alcohol long before the 2° alcohol gets started.

(c) Reactions happen faster when the product or intermediate is stabilized. Each OCH₃ group stabilizes the carbocation by resonance as shown here; two OCH₃ groups stabilize more than just one, increasing the rate of removal. The color comes from the extended conjugation through all three rings and out to the OCH₃ groups. Compare the DMT structure with that of phenolphthalein, the most common acid base indicator, that turns pink in its ring open form shown here. Phenolphthalein is simply another trityl group with different substituents.

one of the major resonance contributors showing the delocalization of the positive charge on the oxygen



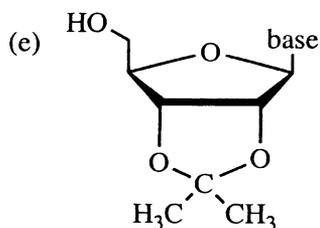
23-77



(c)

The 4- and 6-OH groups of glucose reacted with benzaldehyde to form the acetal.

(c) and (d) The chiral center is marked with (*). This stereoisomer is a diastereomer since only one chiral center is inverted. This diastereomer puts the phenyl group in an axial position, definitely less stable than the structure shown in part (a). Only the product shown in (a) will be isolated from this reaction.

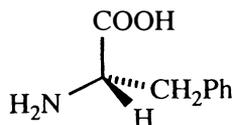


Only the 2'- and 3'-OH groups are close enough to form this cyclic acetal (ketal) from acetone, called an acetonide.

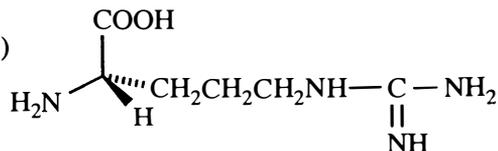
CHAPTER 24—AMINO ACIDS, PEPTIDES, AND PROTEINS

24-1

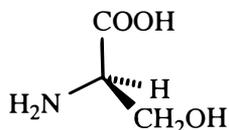
(a)



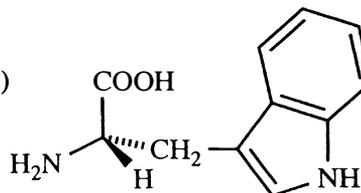
(b)



(c)



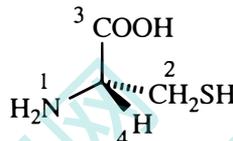
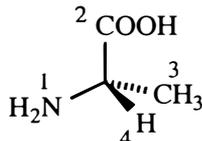
(d)



24-2

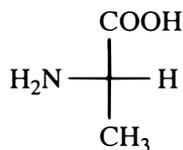
(a) The configurations around the asymmetric carbons of (*R*)-cysteine and (*S*)-alanine are the same. The designation of configuration changes because sulfur changes the priorities of the side chain and the COOH.

(*S*)-alanine with group priorities shown

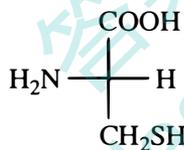


(*R*)-cysteine with group priorities shown; note that the COOH and the CH₂SH priorities are reversed compared with (*S*)-alanine

(b) Fischer projections show that both (*S*)-alanine and (*R*)-cysteine are L-amino acids.



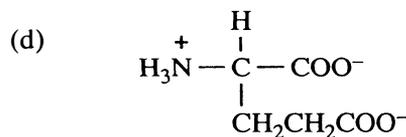
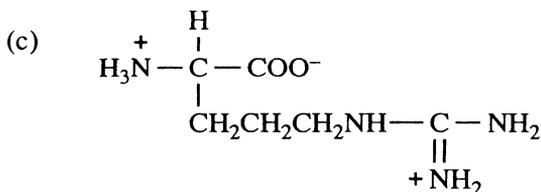
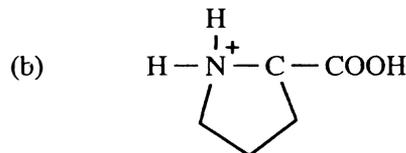
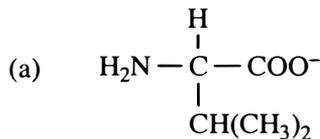
(*S*)-alanine
L-alanine



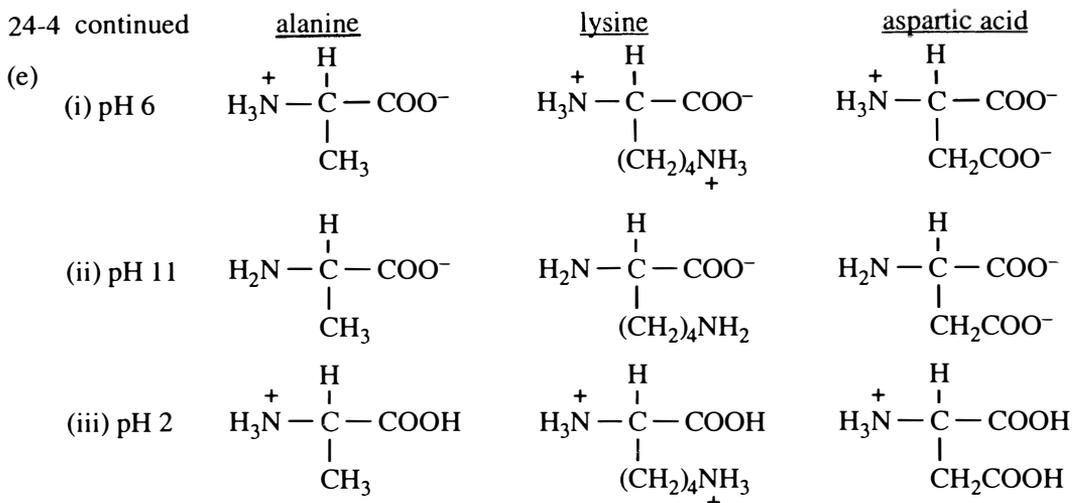
(*R*)-cysteine
L-cysteine

24-3 In their evolution, plants have needed to be more resourceful than animals in developing biochemical mechanisms for survival. Thus, plants make more of their own required compounds than animals do. The amino acid phenylalanine is produced by plants but required in the diet of mammals. To interfere with a plant's production of phenylalanine is fatal to the plant, but since humans do not produce phenylalanine, glyphosate is virtually non-toxic to us.

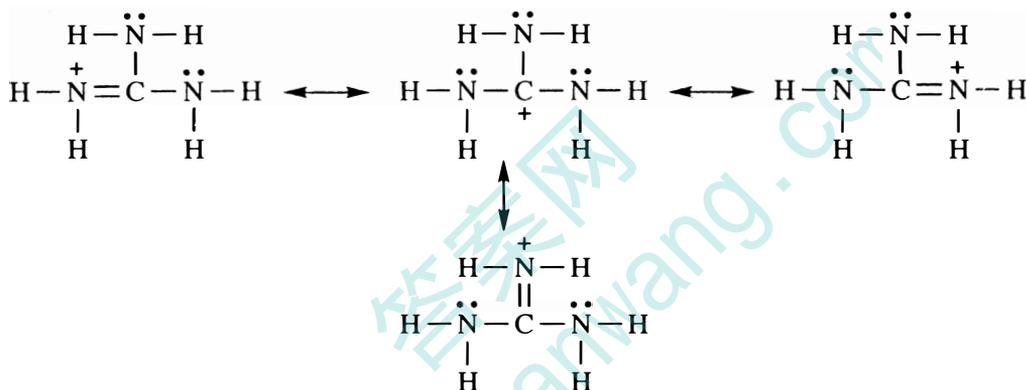
24-4 Here is a simple way of determining if a group will be protonated: at solution pH below the group's pK_a value, the group will be protonated; at pH higher than the group's pK_a value, it will not be protonated.



24-4 continued

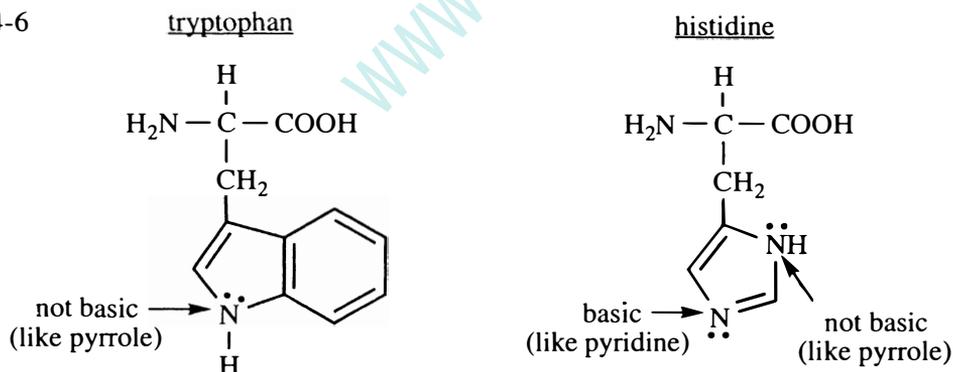


24-5



Protonation of the guanidino group gives a resonance-stabilized cation with all octets filled and the positive charge delocalized over three nitrogen atoms. Arginine's strongly basic isoelectric point reflects the unusual basicity of the guanidino group due to this resonance stabilization in the protonated form. (See Problems 1-39 and 19-49(a).)

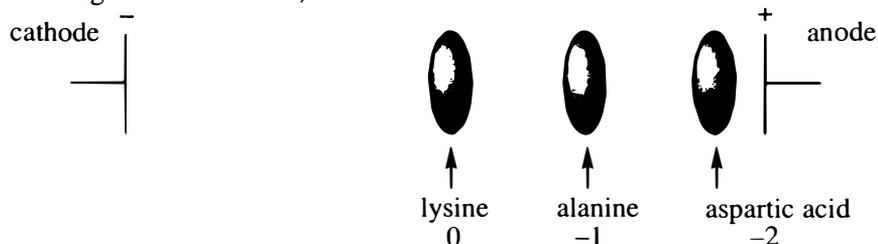
24-6



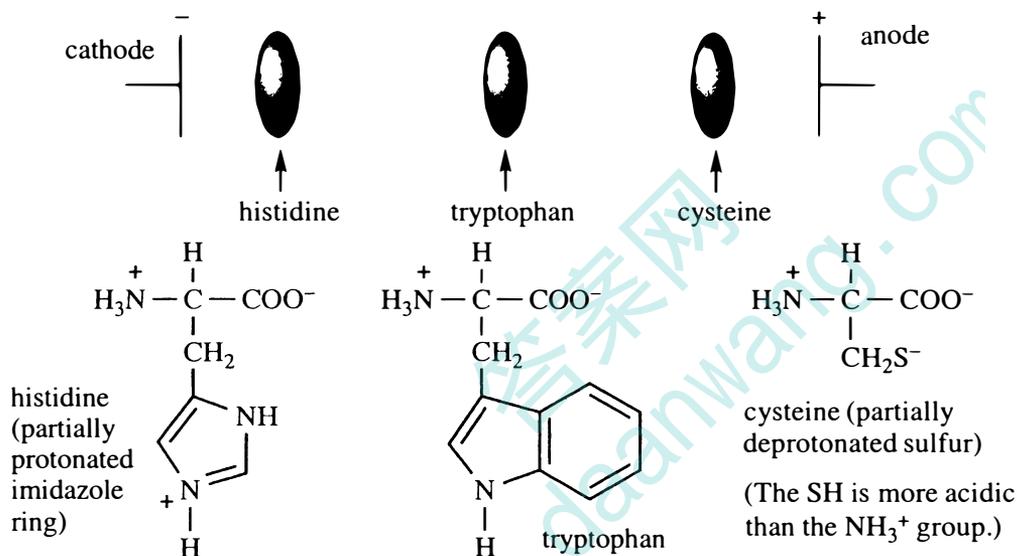
The basicity of any nitrogen depends on its electron pair's availability for bonding with a proton. In tryptophan, the nitrogen's electron pair is part of the aromatic π system; without this electron pair in the π system, the molecule would not be aromatic. Using this electron pair for bonding to a proton would therefore destroy the aromaticity—not a favorable process.

In the imidazole ring of histidine, the electron pair of one nitrogen is also part of the aromatic π system and is unavailable for bonding; this nitrogen is not basic. The electron pair on the other nitrogen, however, is in an sp^2 orbital available for bonding, and is about as basic as pyridine.

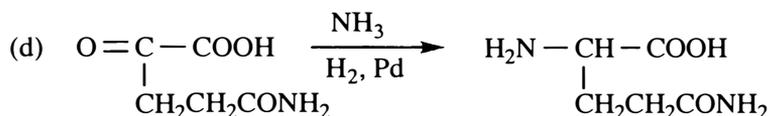
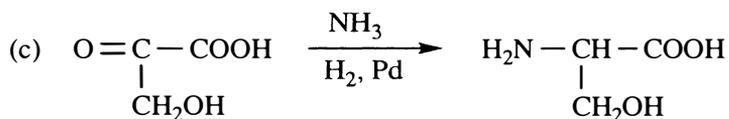
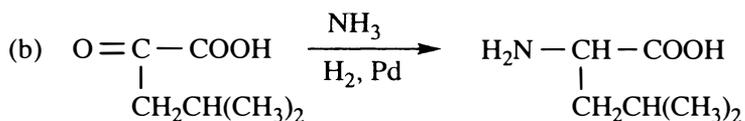
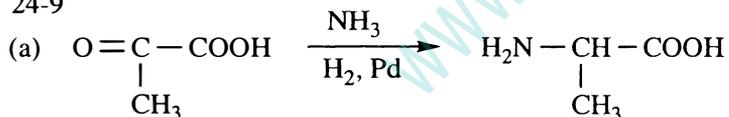
24-7 At pH 9.7, alanine (isoelectric point (IEP) 6.0) has a charge of -1 and will migrate to the anode. Lysine (IEP 9.7) is at its isoelectric point and will not move. Aspartic acid (IEP 2.8) has a charge of -2 and will also migrate to the anode, faster than alanine.



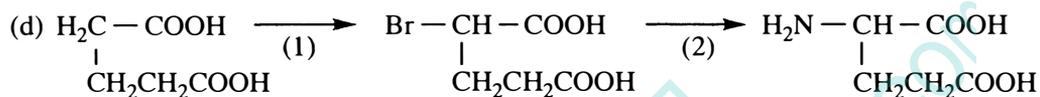
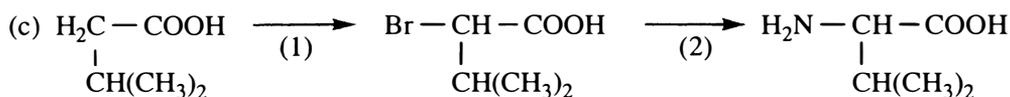
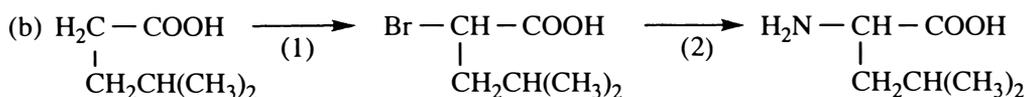
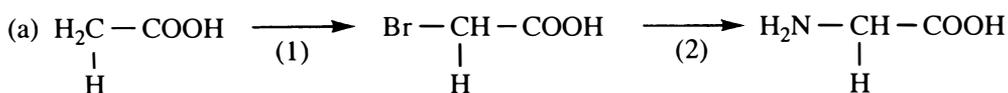
24-8 At pH 6.0, tryptophan (IEP 5.9) has a charge of zero and will not migrate. Cysteine (IEP 5.0) has a partial negative charge and will move toward the anode. Histidine (IEP 7.6) has a partial positive charge and will move toward the cathode.



24-9

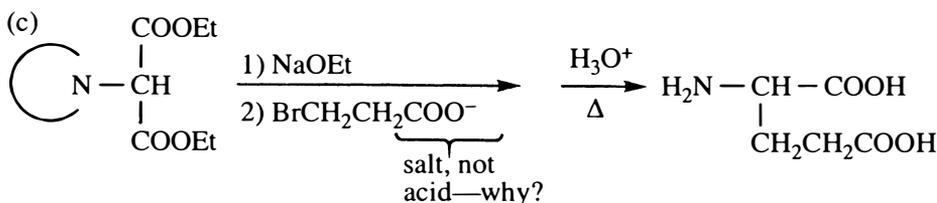
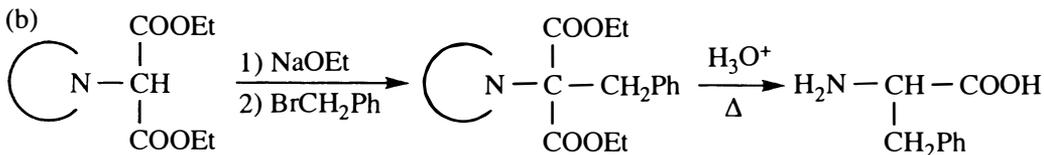
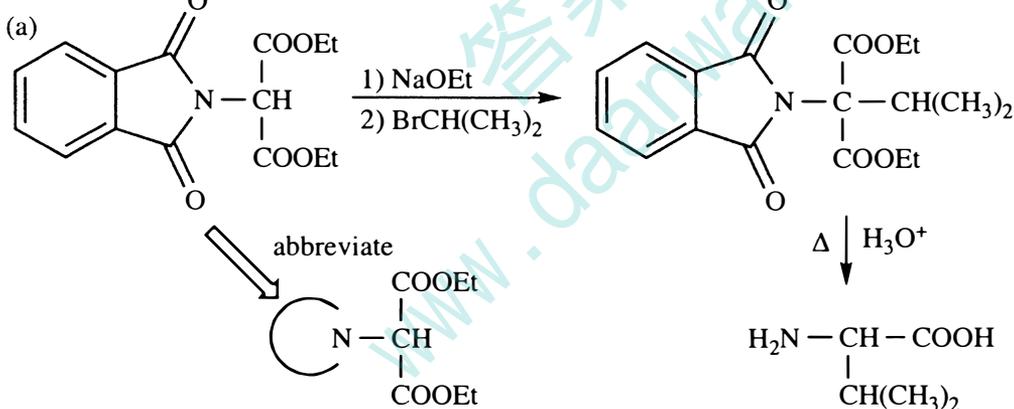


24-10 All of these reactions use: first arrow: (1) Br₂/PBr₃, followed by H₂O workup; second arrow: (2) excess NH₃, followed by neutralizing workup.

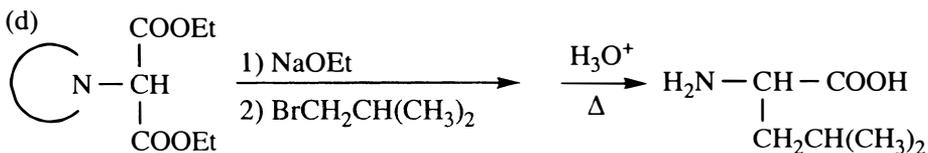


In part (d), care must be taken to avoid reaction α to the other COOH. In practice, this would be accomplished by using less than one-half mole of bromine per mole of the diacid.

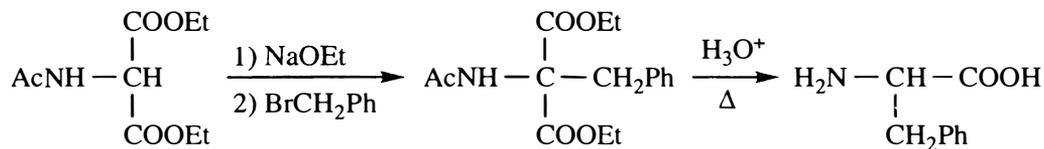
24-11



24-11 continued

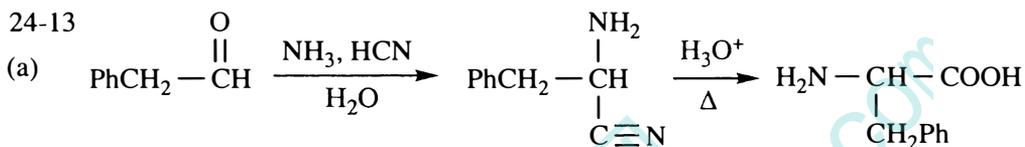


24-12

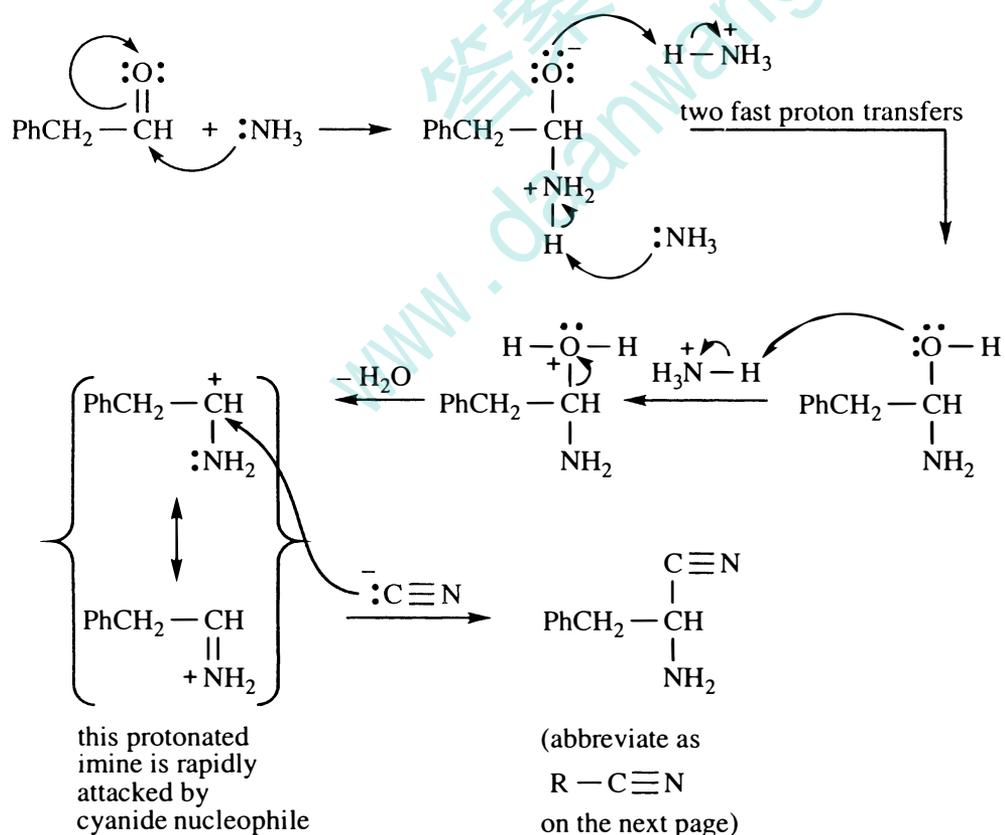


acetamidomalonic ester

24-13

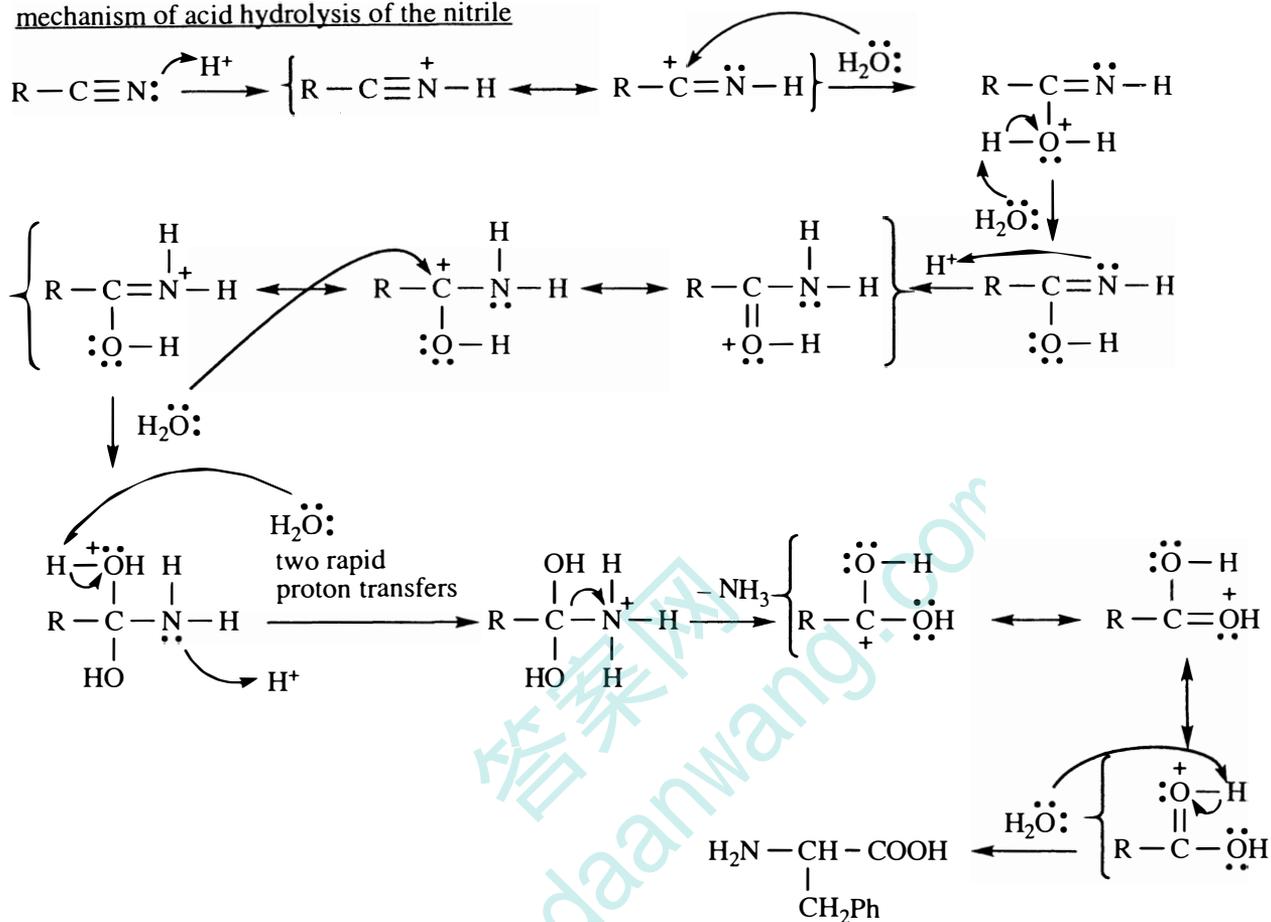


(b) While the solvent for the Strecker synthesis is water, the proton acceptor is ammonia and the proton donor is ammonium ion.

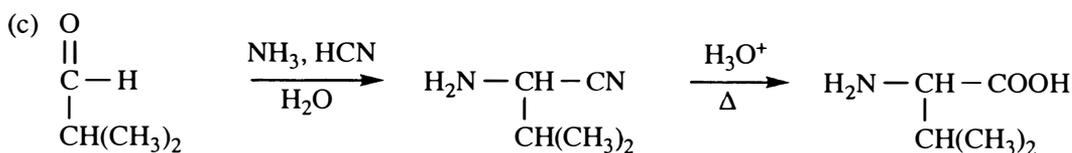
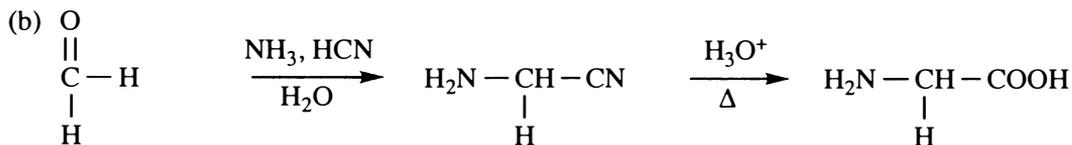
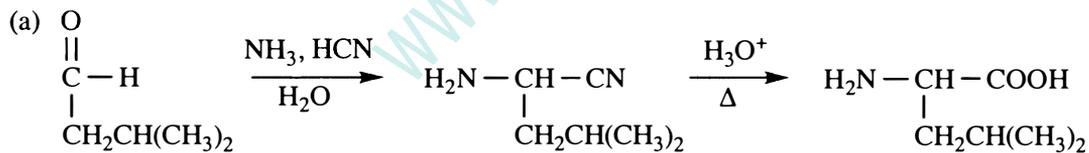


24-13 (b) continued

mechanism of acid hydrolysis of the nitrile

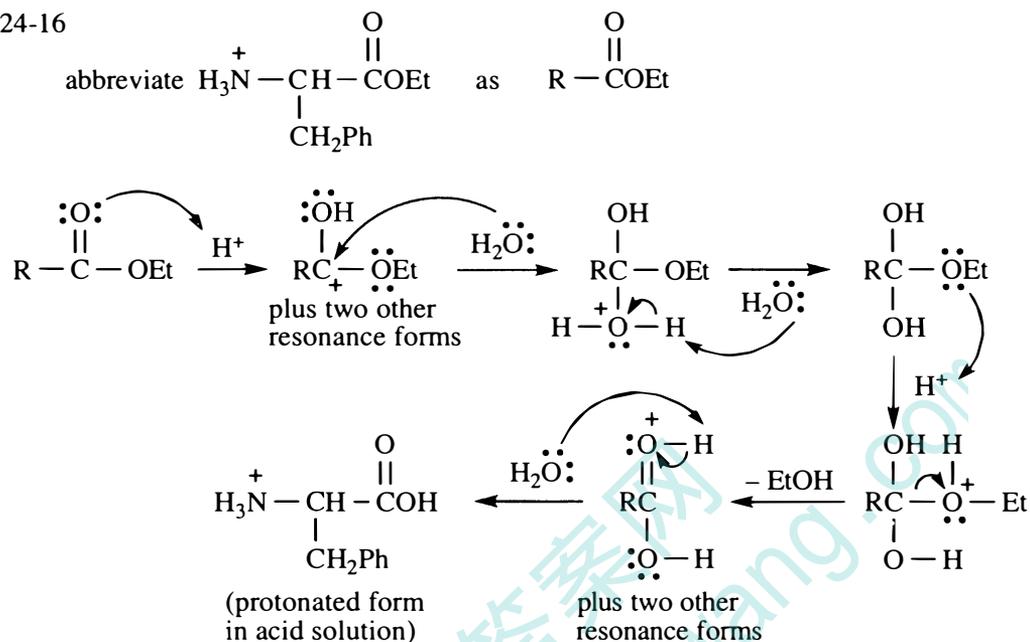


24-14

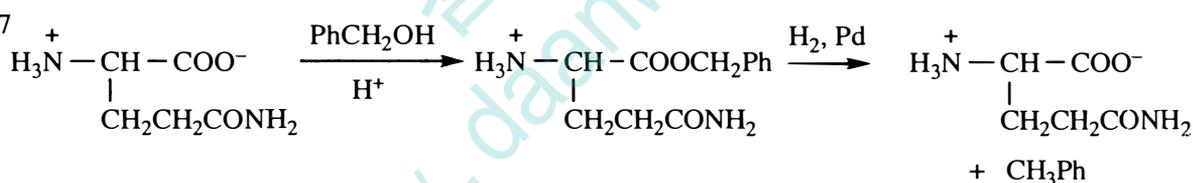


24-15 In acid solution, the free amino acid will be protonated, with a positive charge, and probably soluble in water as are other organic ions. The acylated amino acid, however, is not basic since the nitrogen is present as an amide. In acid solution, the acylated amino acid is neutral and not soluble in water. Water extraction or ion-exchange chromatography (Figure 24-11) would be practical techniques to separate these compounds.

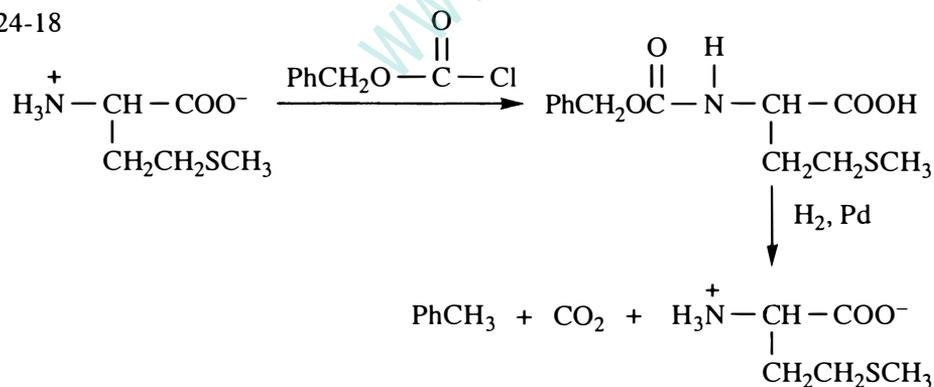
24-16



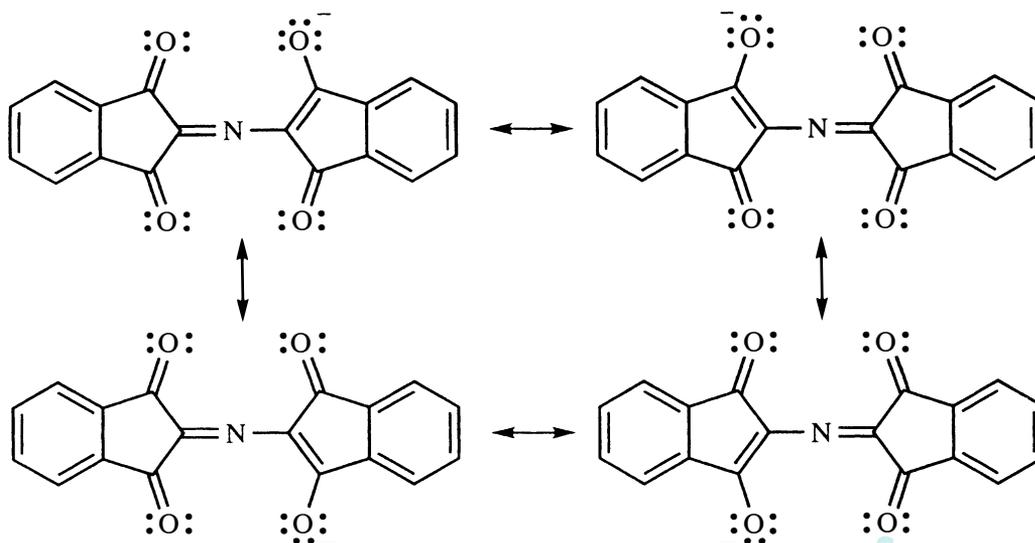
24-17



24-18

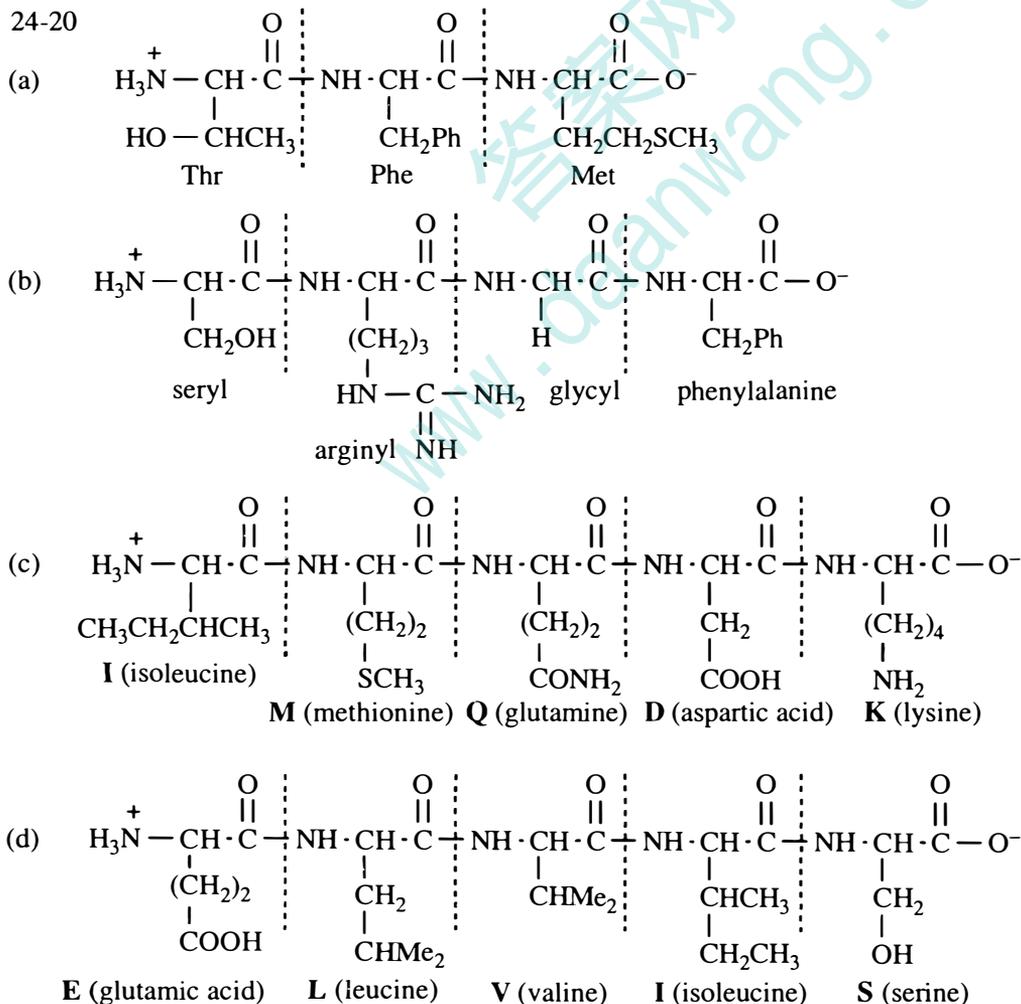


24-19

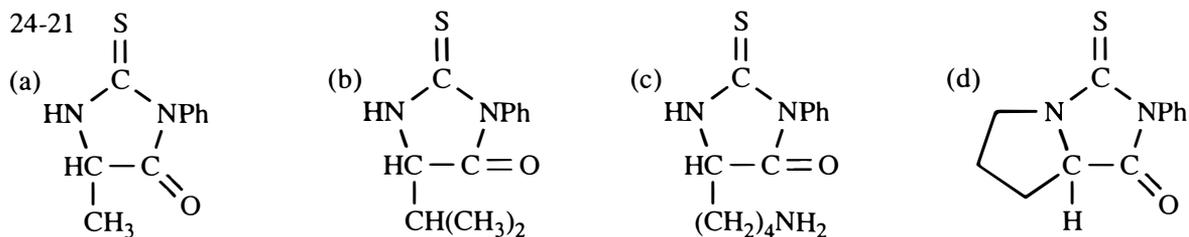


These are the most significant resonance contributors in which the electronegative oxygens carry the negative charge. There are also two other forms in which the negative charge is on the carbons bonded to the nitrogen, plus the usual resonance forms involving the alternate Kekulé structures of the benzene rings.

24-20

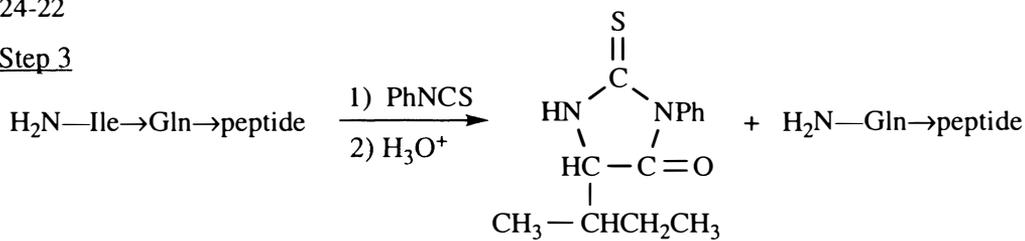


Try spelling your name in peptides!

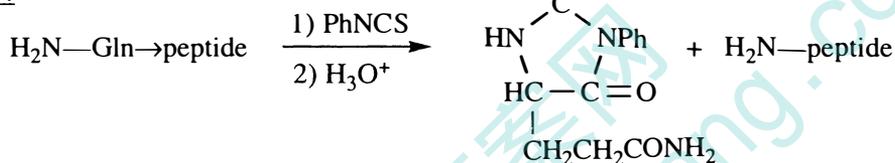


24-22

Step 3

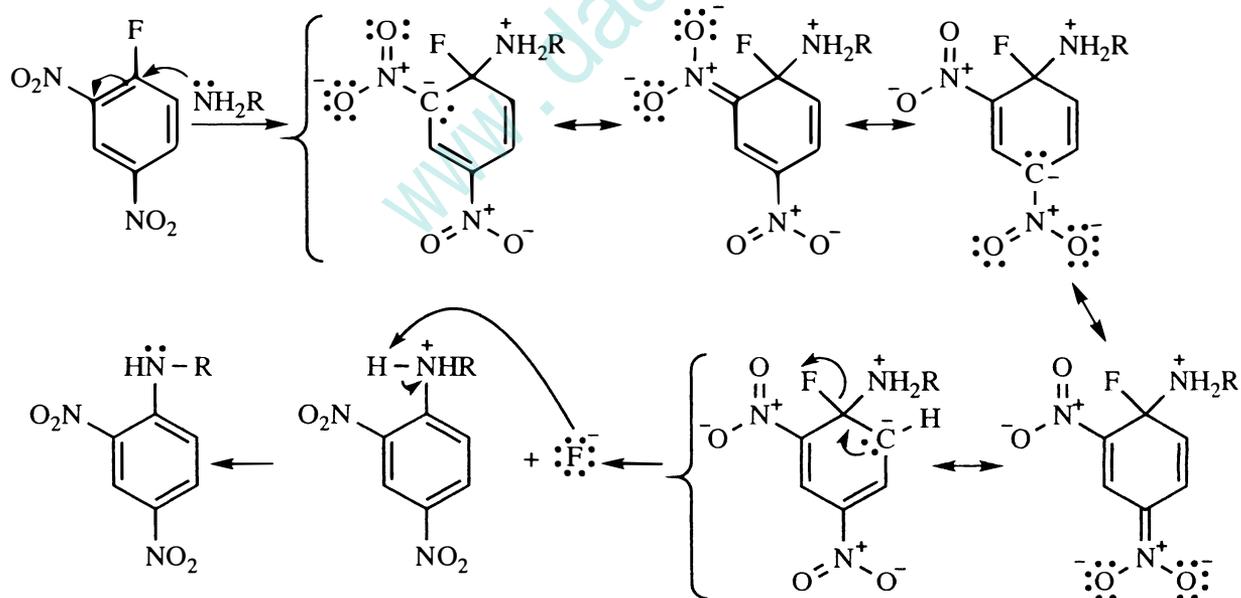


Step 4



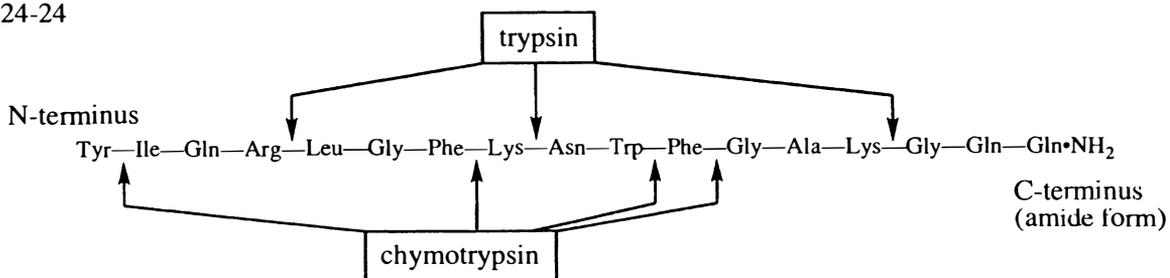
24-23 Abbreviate the N-terminus of the peptide chain as NH_2R .

(a) This is a nucleophilic aromatic substitution by the addition-elimination mechanism. The presence of two nitro groups makes this reaction feasible under mild conditions.

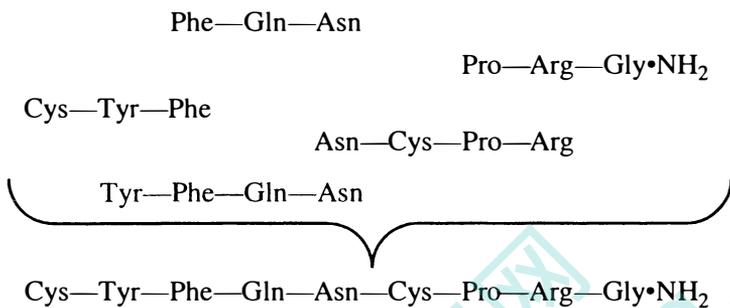


(b) The main drawback of the Sanger method is that only one amino acid is analyzed per sample of protein. The Edman degradation can usually analyze more than 20 amino acids per sample of protein.

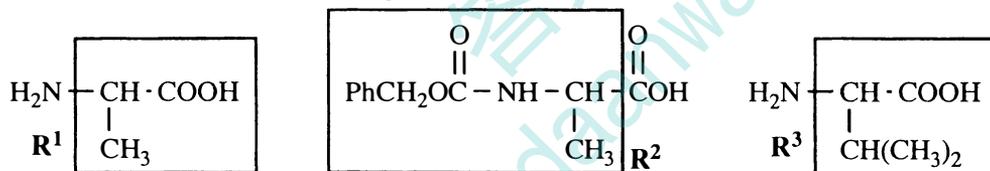
24-24



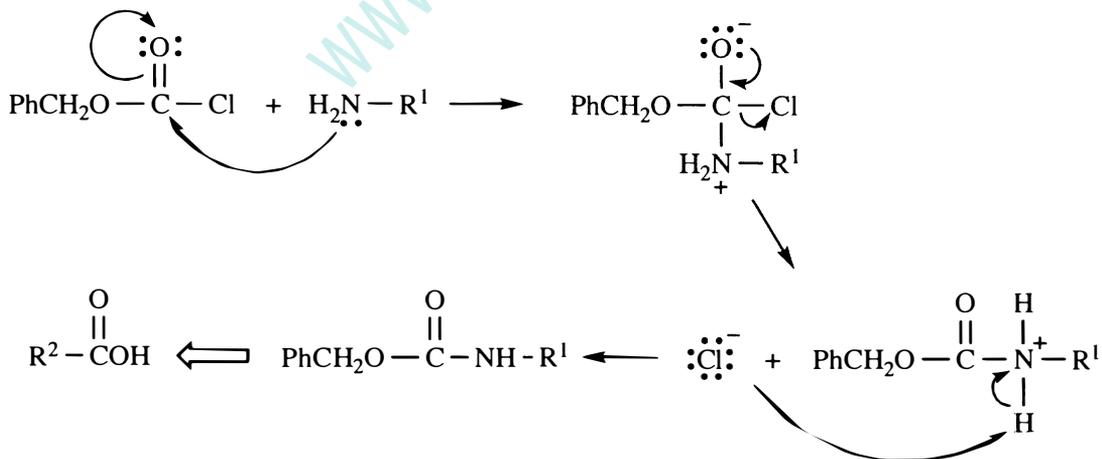
24-25



24-26 abbreviations used in this problem:



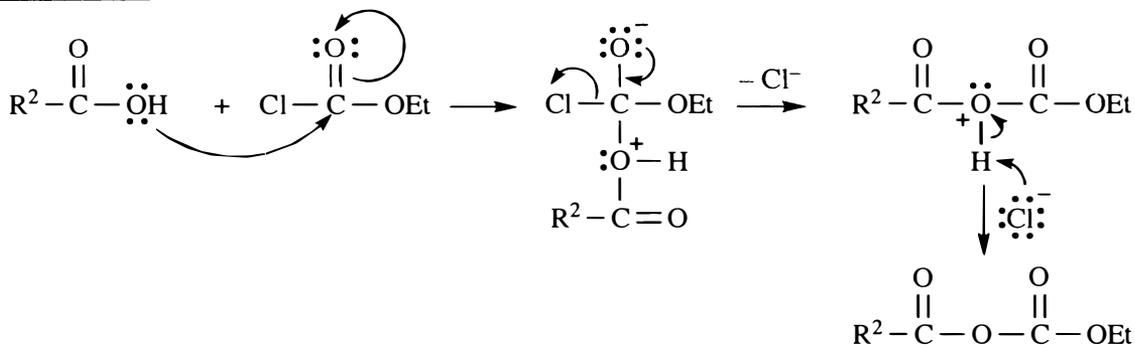
mechanism of formation of Z-Ala



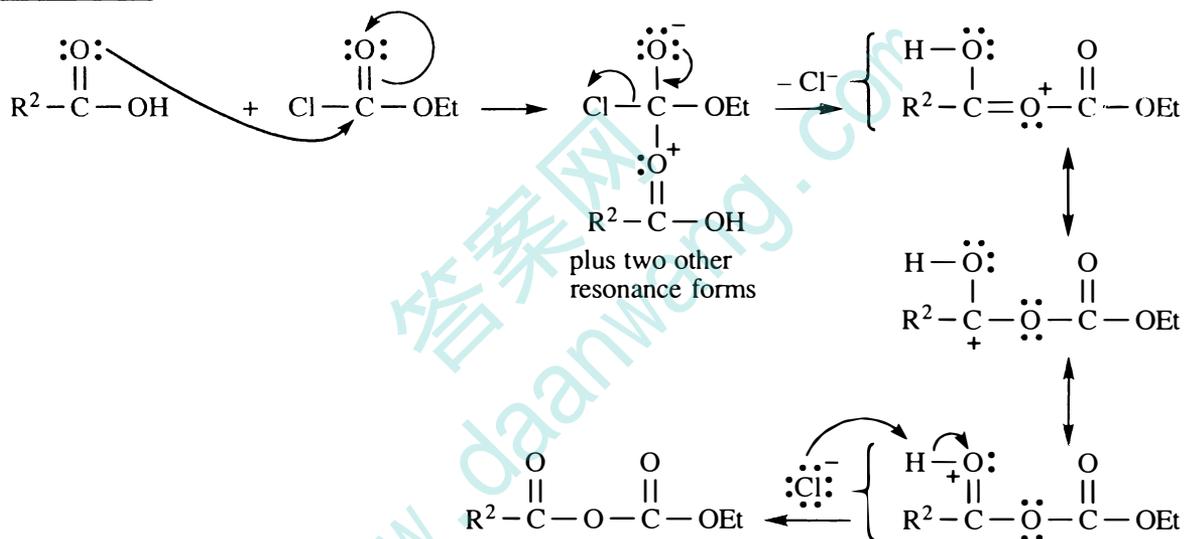
24-26 continued

two possible mechanisms of ethyl chloroformate activation

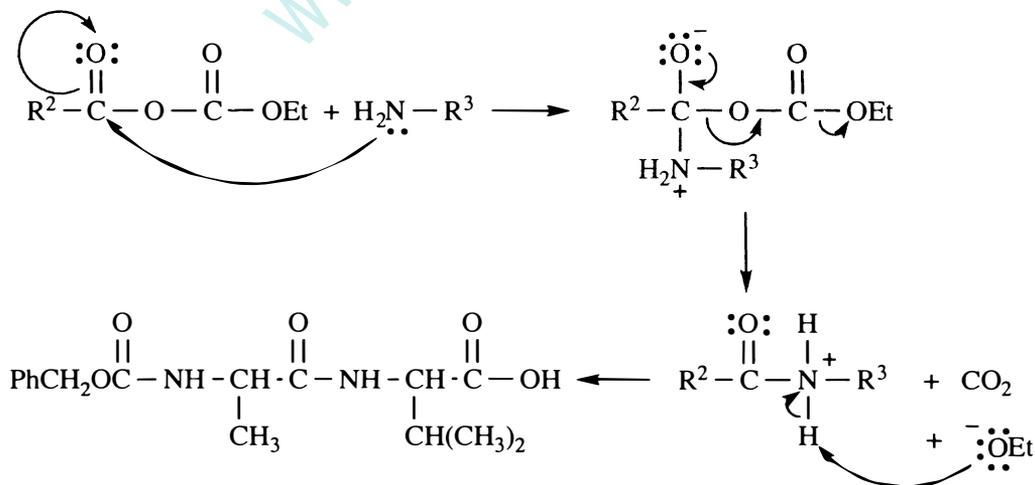
mechanism 1



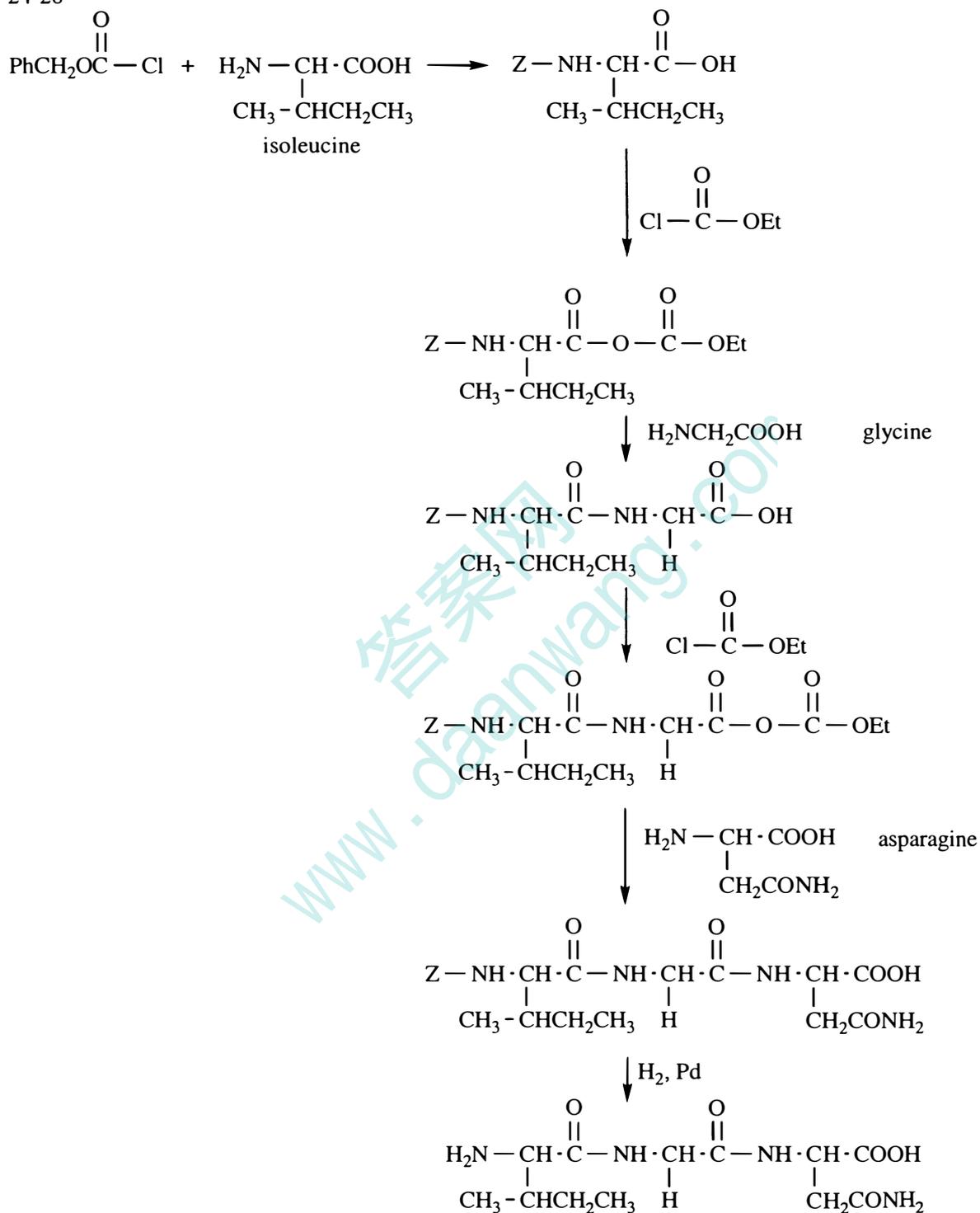
mechanism 2



mechanism of the coupling with valine



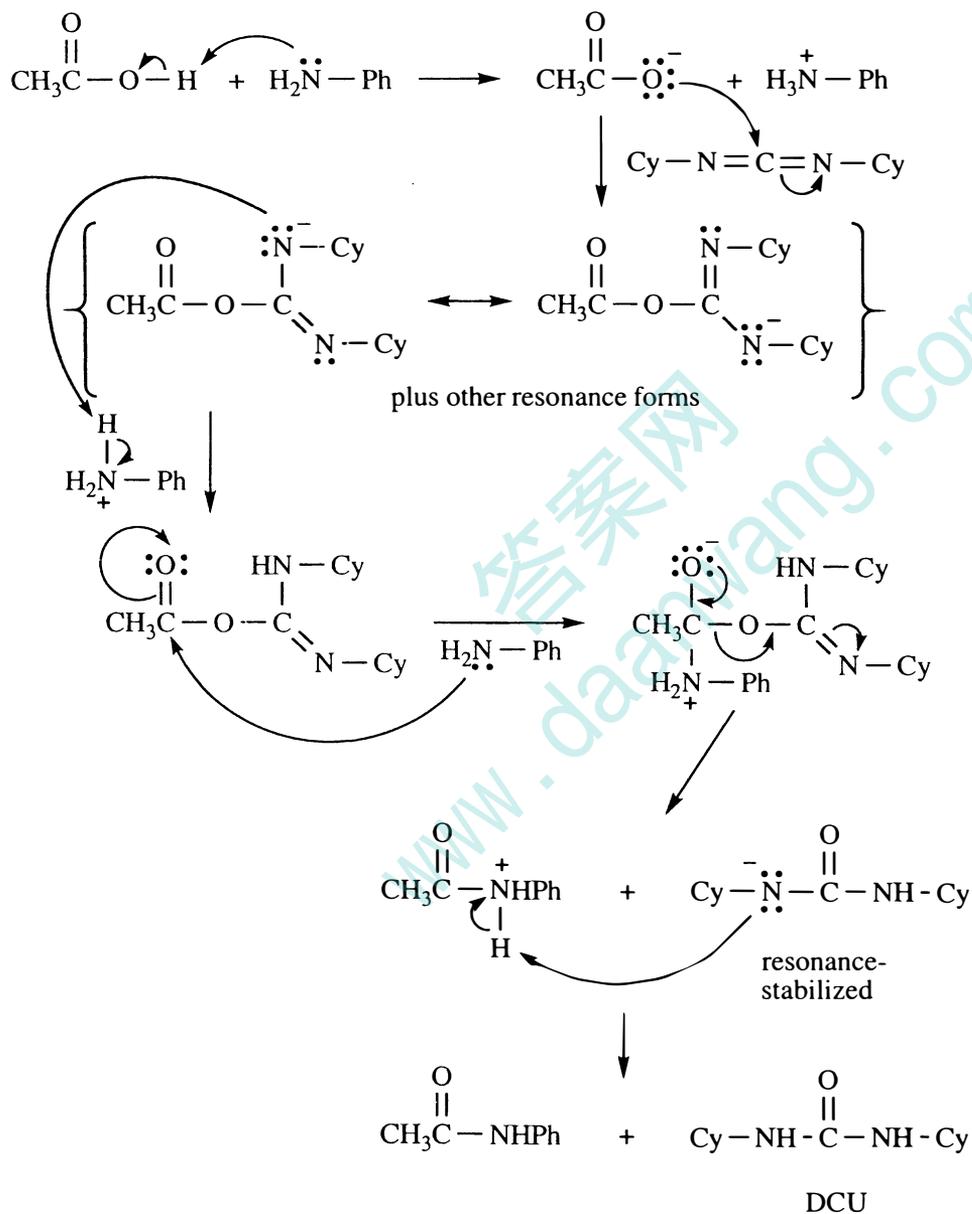
24-28



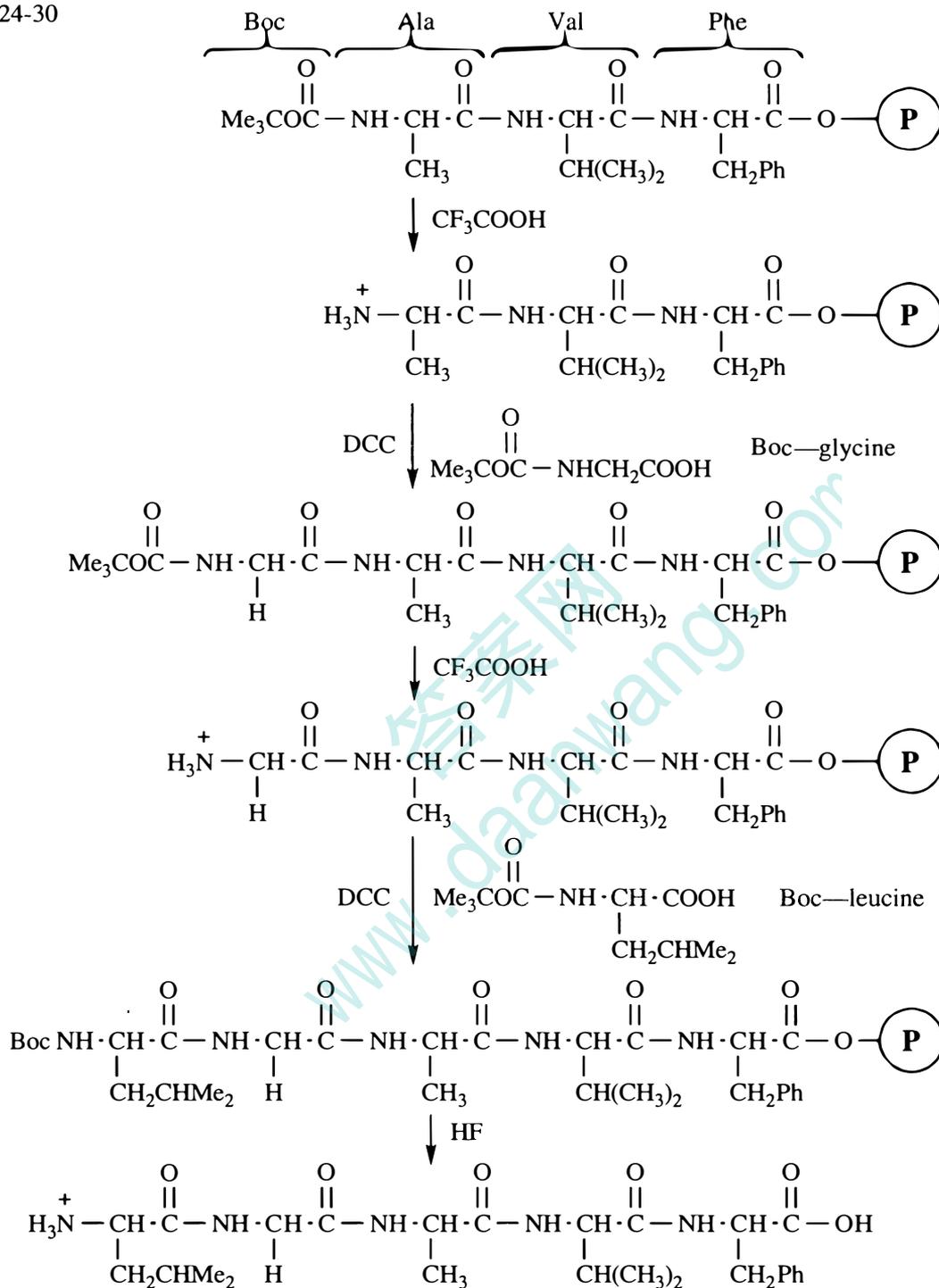
24-29 In this problem, "Cy" stands for "cyclohexyl".

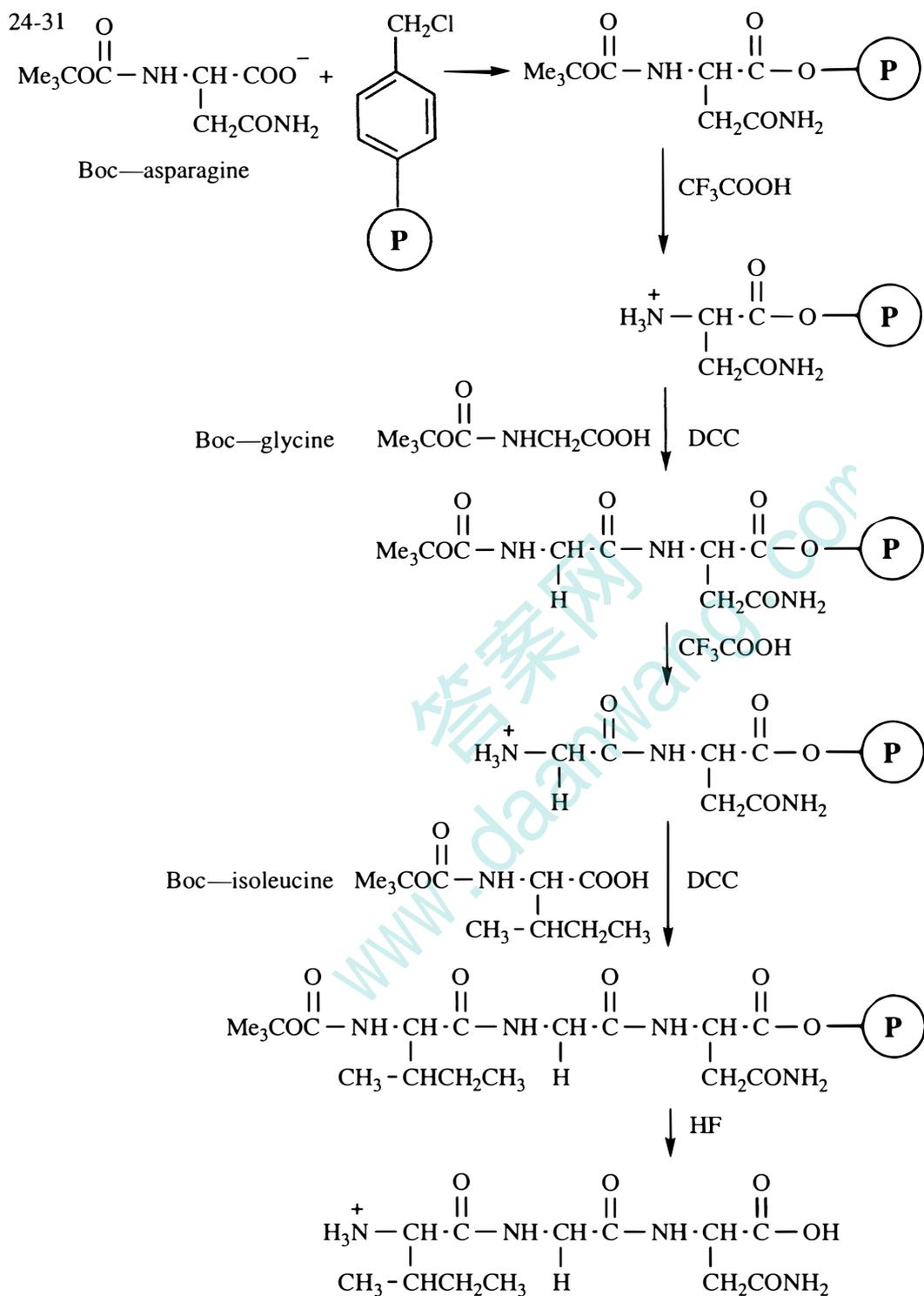


mechanism

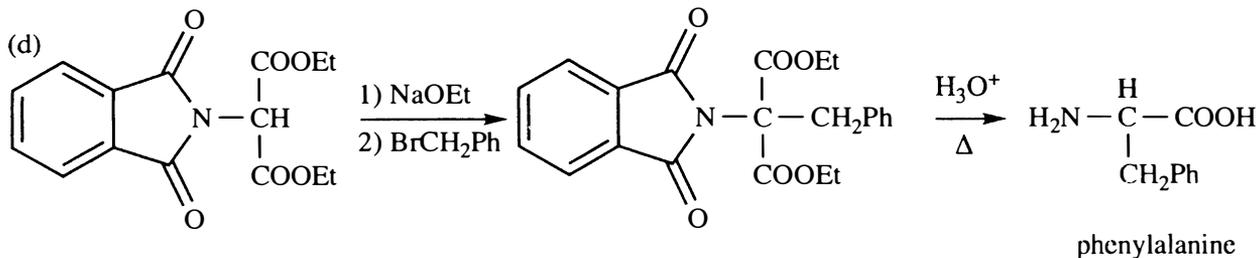
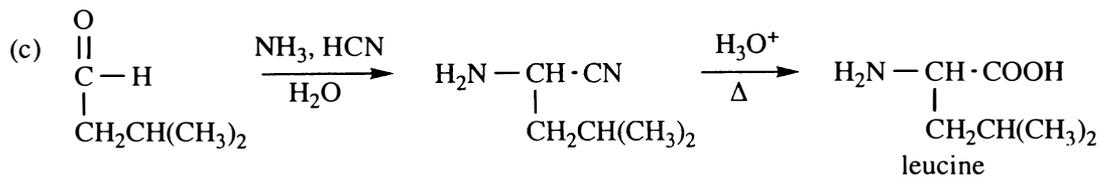


24-30

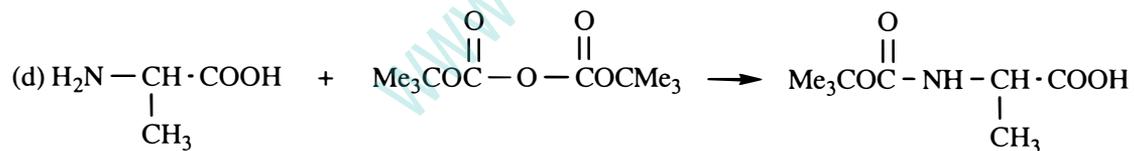
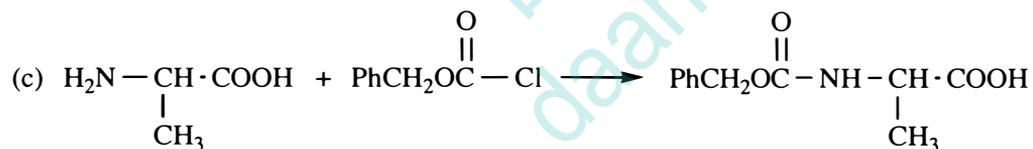
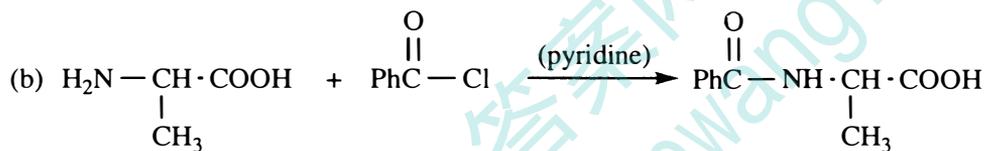
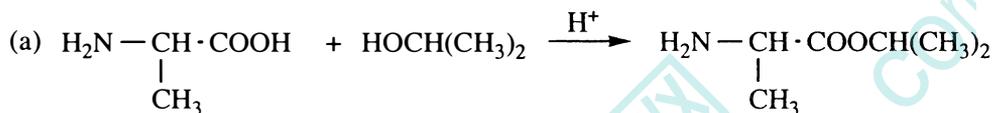




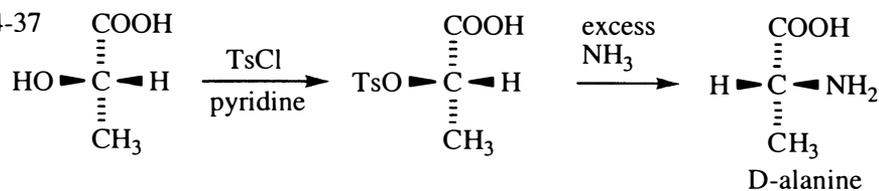
24-35 continued



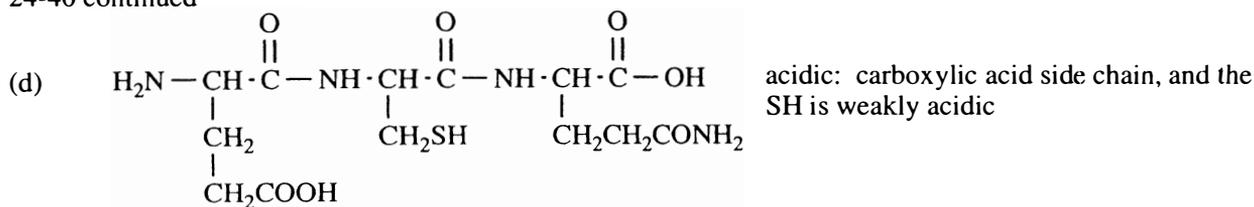
24-36



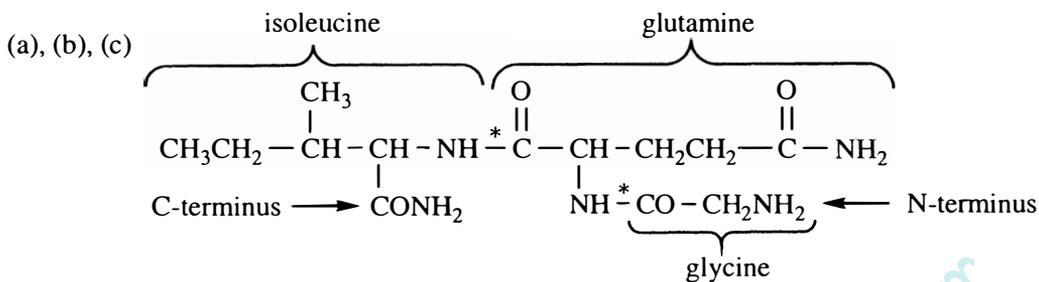
24-37



24-40 continued



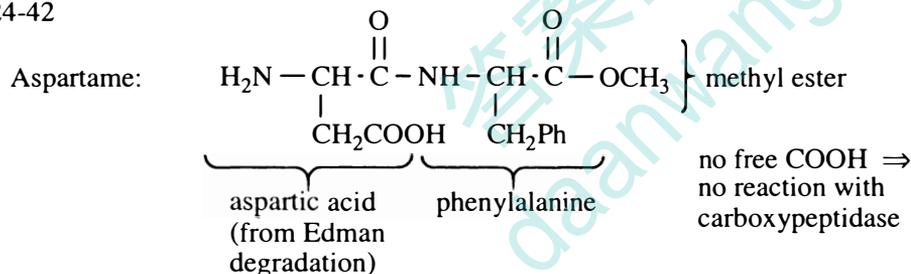
24-41



Peptide bonds are denoted with asterisks (*).

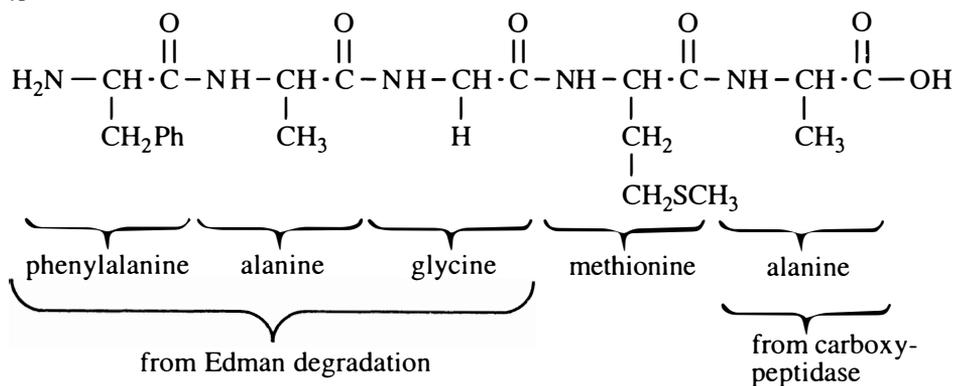
(d) glycyglutamylisoleucinamide; Gly—Gln—Ile • NH₂

24-42



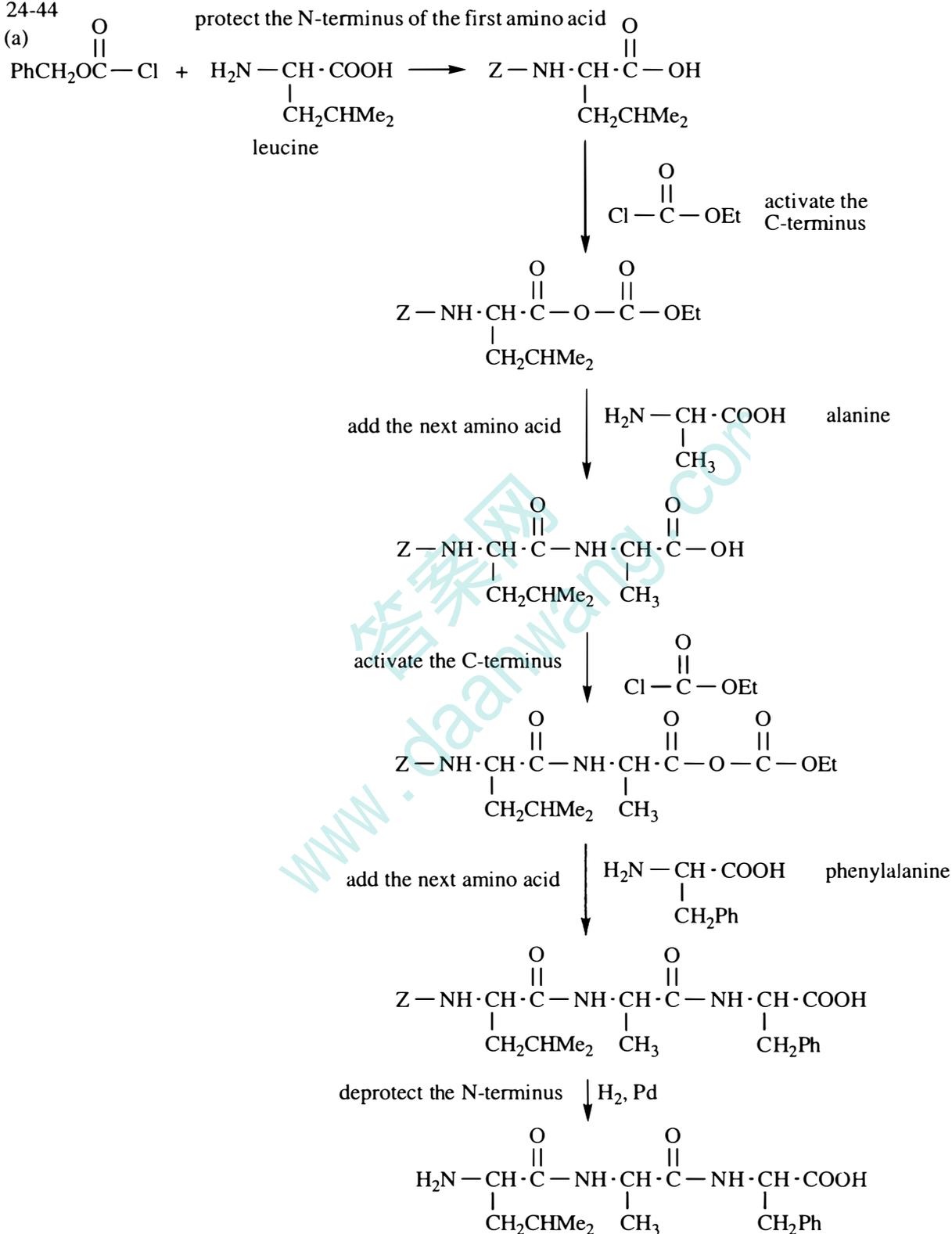
Aspartame is aspartylphenylalanine methyl ester.

24-43

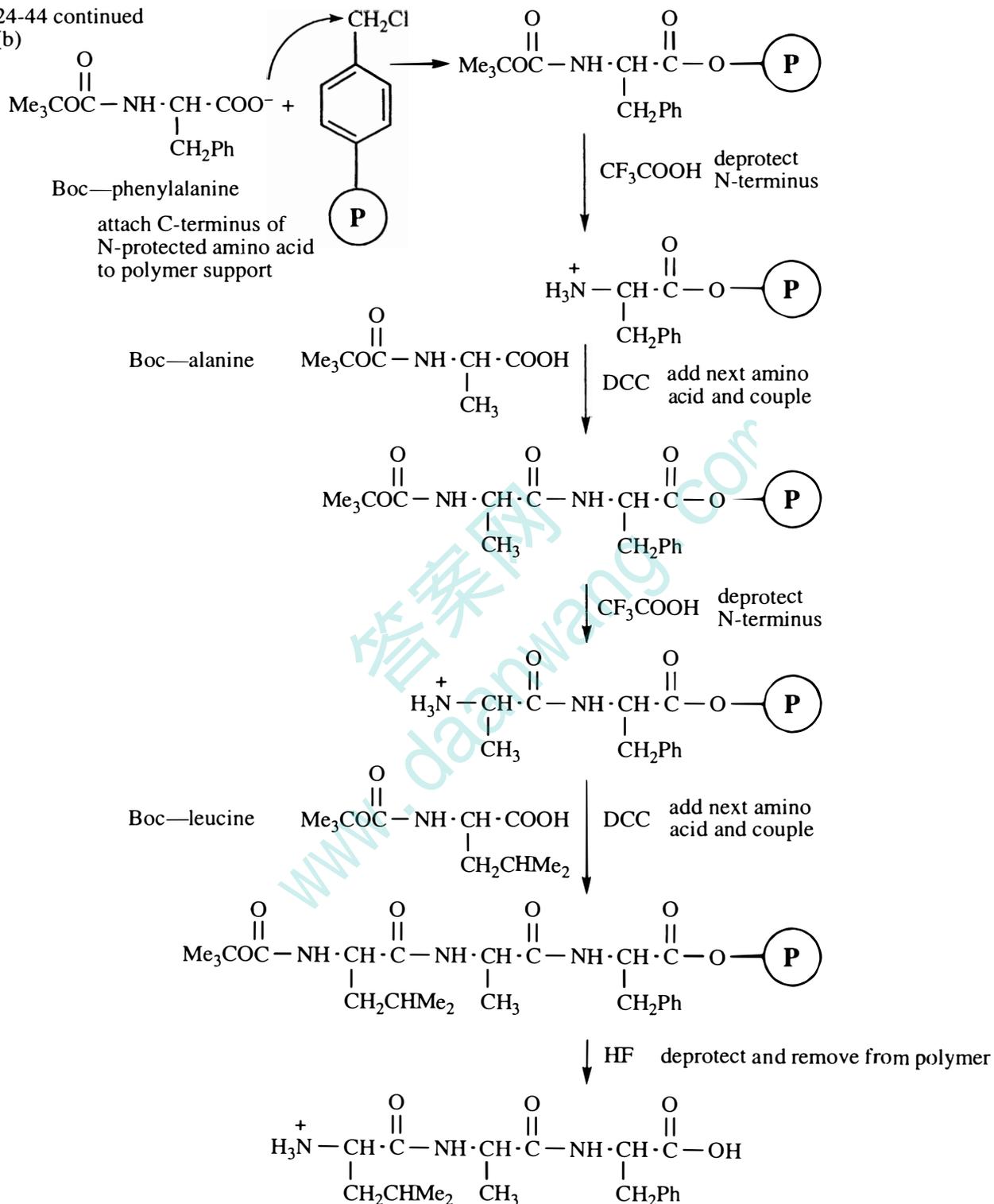


24-44

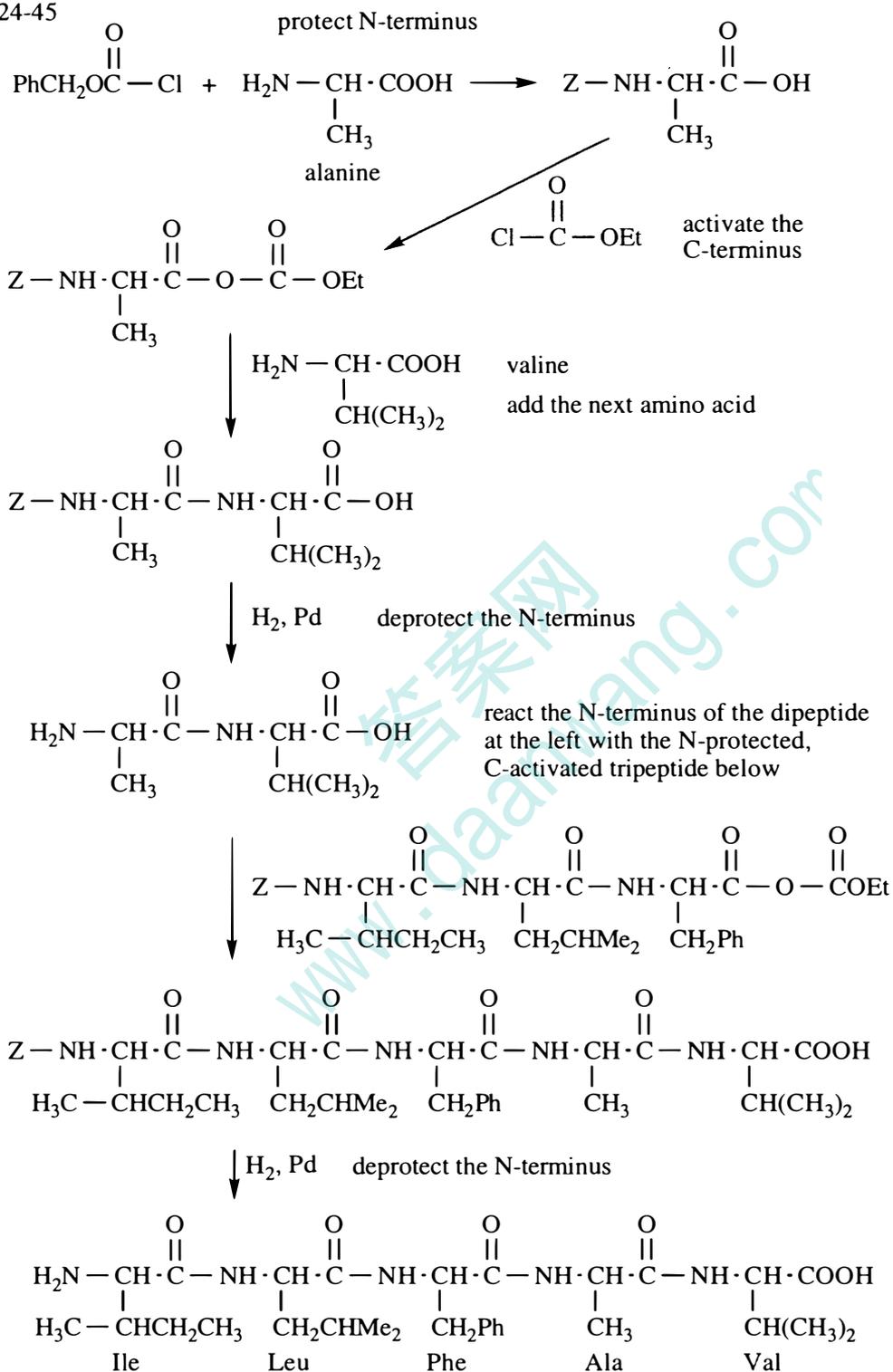
(a)



24-44 continued
(b)



24-45



24-46

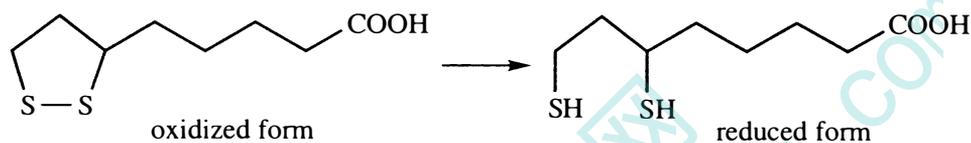
(a) There are two possible sources of ammonia in the hydrolysate. The C-terminus could have been present as the amide instead of the carboxyl, or the glutamic acid could have been present as its amide, glutamine.

(b) The C-terminus is present as the amide. The N-terminus is present as the lactam (cyclic amide) combining the amino group with the carboxyl group of the glutamic acid side chain.

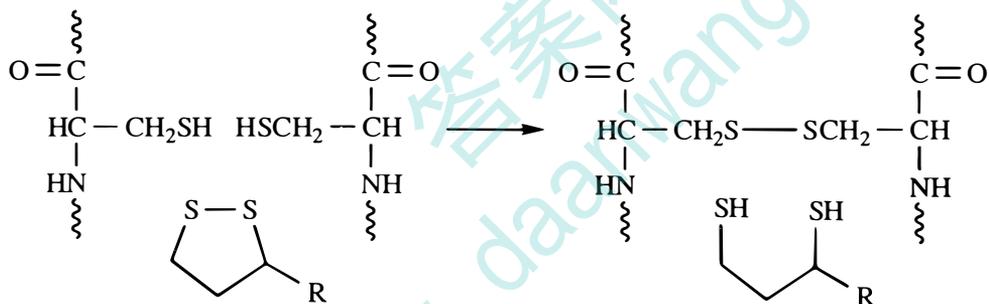
(c) The fact that hydrolysis does not release ammonia implies that the C-terminus is not an amide. Yet, carboxypeptidase treatment gives no reaction, showing that the C-terminus is not a free carboxyl group. Also, treatment with phenyl isothiocyanate gives no reaction, suggesting no free amine at the N-terminus. The most plausible explanation is that the N-terminus has reacted with the C-terminus to produce a cyclic amide, a lactam. (These large rings, called macrocycles, are often found in nature as hormones or antibiotics.)

24-47

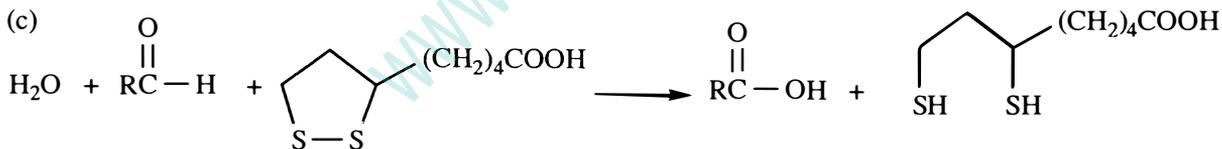
(a) Lipoic acid is a mild oxidizing agent. In the process of oxidizing another reactant, lipoic acid is reduced.



(b)

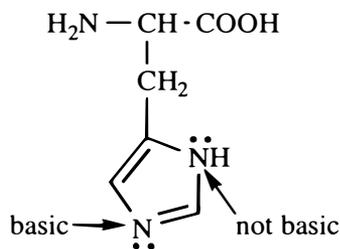


(c)

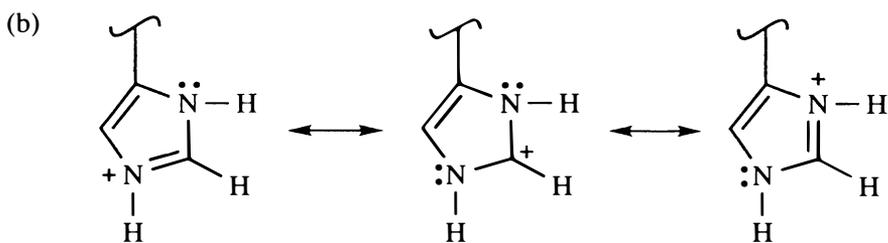


24-48

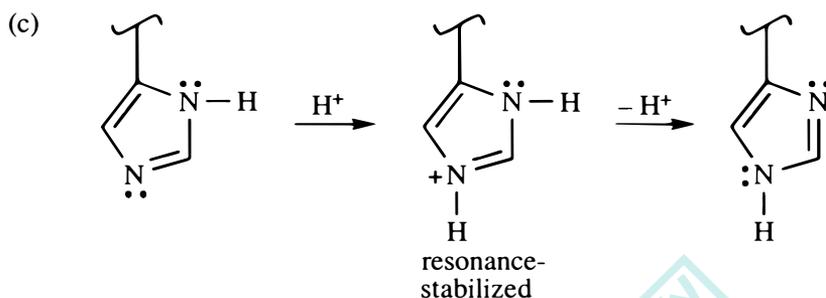
(a) histidine:



24-48 continued

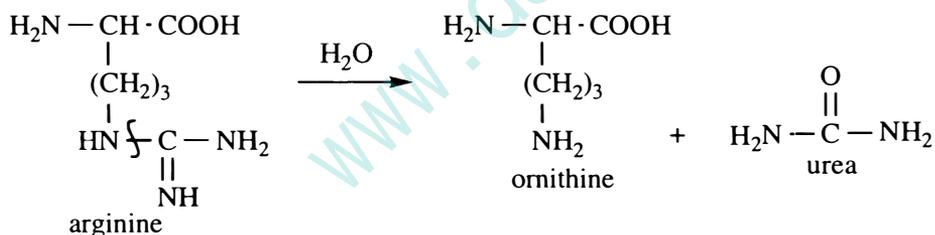


In the protonated imidazole, the two N's are similar in structure, and both NH groups are acidic.

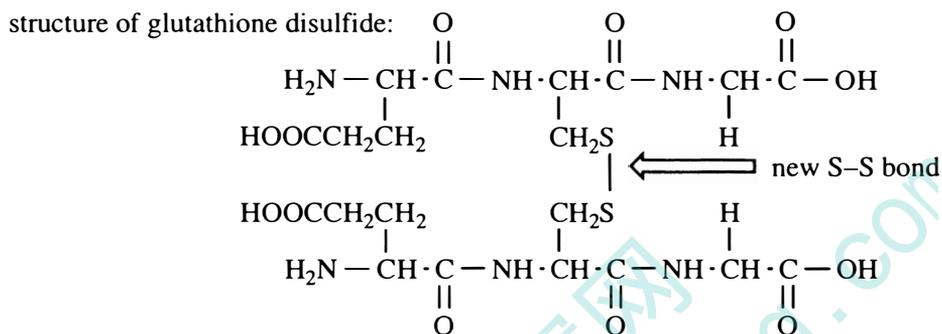
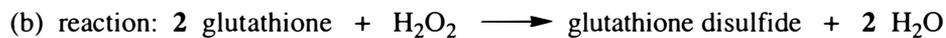
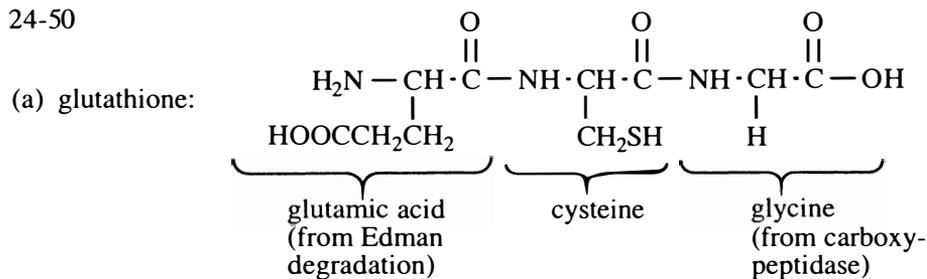


We usually think of protonation-deprotonation reactions occurring in solution where protons can move with solvent molecules. In an enzyme active-site, there is no "solvent", so there must be another mechanism for movement of protons. Often, conformational changes in the protein will move atoms closer or farther. Histidine serves the function of moving a proton toward or away from a particular site by using its different nitrogens in concert as a proton acceptor and a proton donor.

24-49 The high isoelectric point suggests a strongly basic side chain as in lysine. The N—CH₂ bond in the side chain of arginine is likely to have remained intact during the metabolism. (Can you propose a likely mechanism for this reaction?)

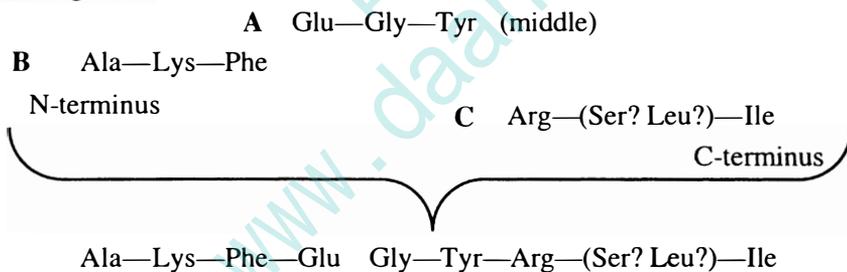


24-50

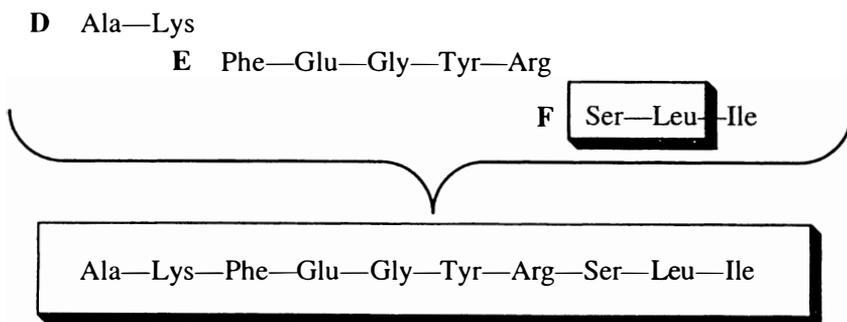


24-51

end groups: N-terminus Ala ————— Ile C-terminus
chymotrypsin fragments

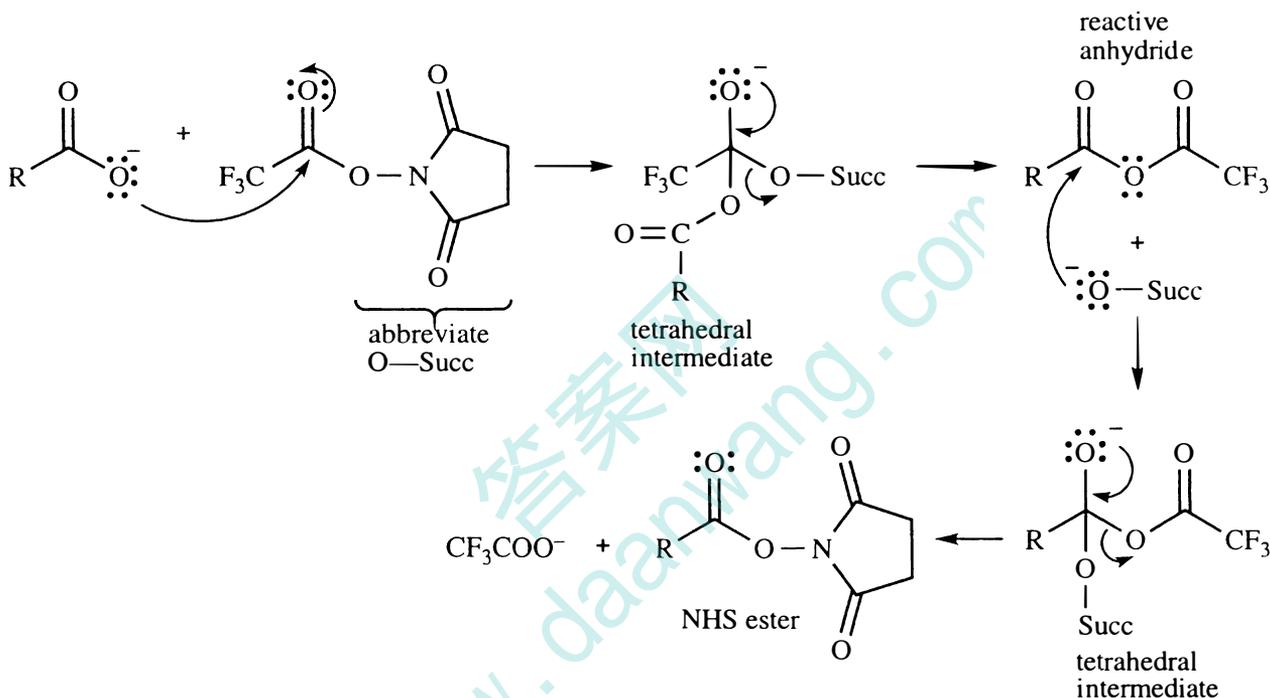
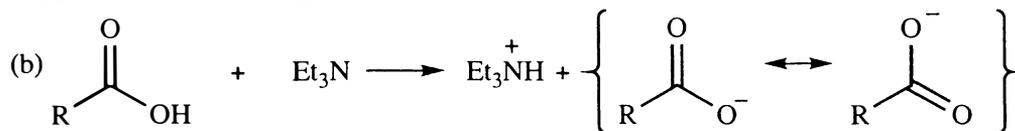


trypsin fragments

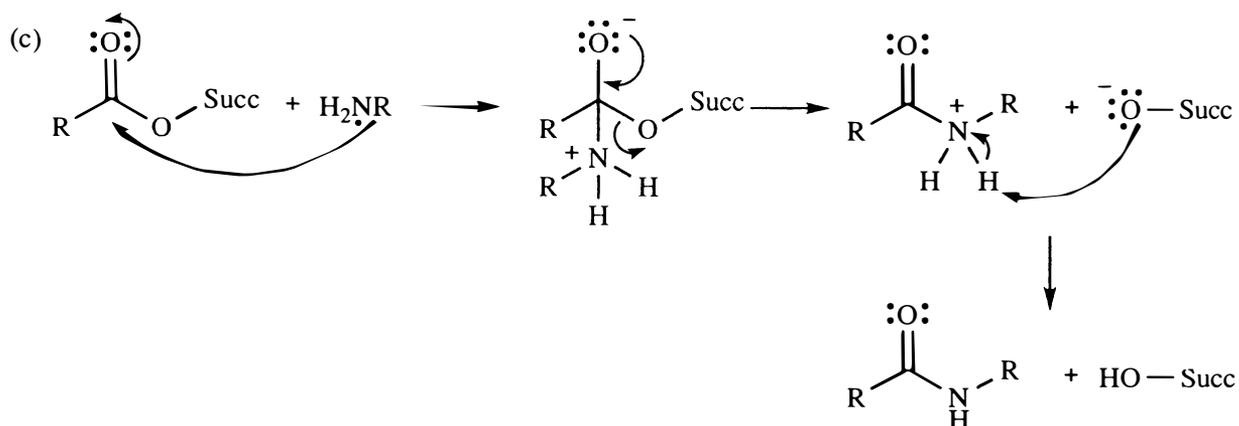


24-52

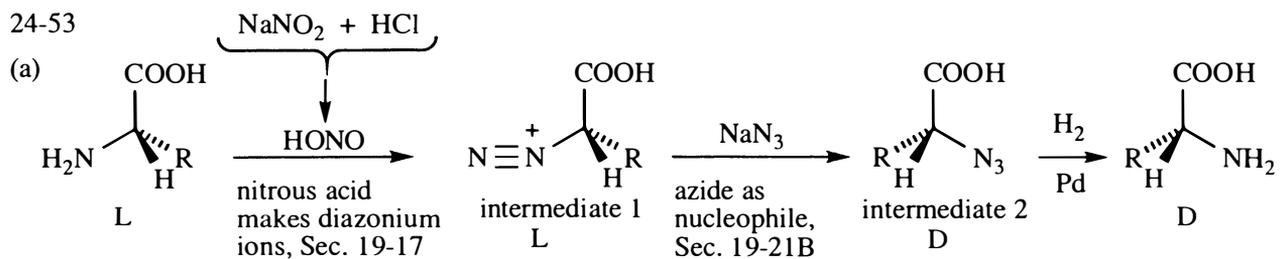
(a) One important factor in ester reactivity is the ability of the alkoxy group to leave, and the main factor in determining leaving group ability is the stabilization of the anion. An NHS ester is more reactive than an alkyl ester because the anion R_2NO^- has an electron-withdrawing group on the O^- , thereby distributing the negative charge over two atoms instead of just one. A simple alkyl ester has the full negative charge on the oxygen with nowhere to go, RO^- .



NHS trifluoroacetate is an amazing reagent. Not only does it activate the carboxylic acid through a mixed anhydride to form an ester under mild conditions, but the NHS leaving group is also the nucleophile that forms an ester that is both stable enough to work with, yet easily reactive when it needs to be. Perfect!



24-53

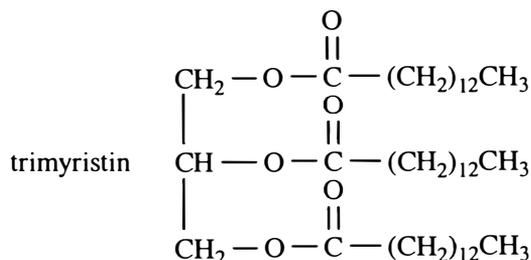


(b) The product has the opposite configuration from the starting because of the stereochemistry of the reactions. Diazotization does not break a bond to the chiral center so the L configuration is retained in Reaction 1. It is well documented that azide substitution is an S_N2 process that proceeds with inversion of configuration; this is why this process works. The third reaction does not break or form a bond to the chiral center, so the D configuration is retained.

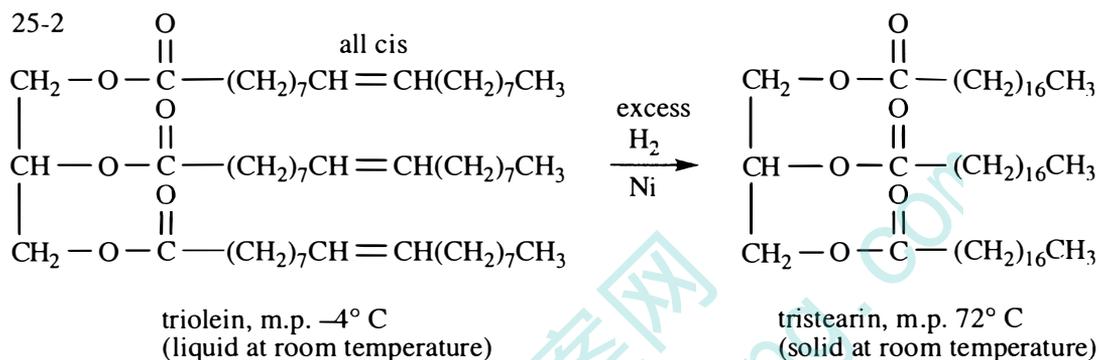
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CHAPTER 25—LIPIDS

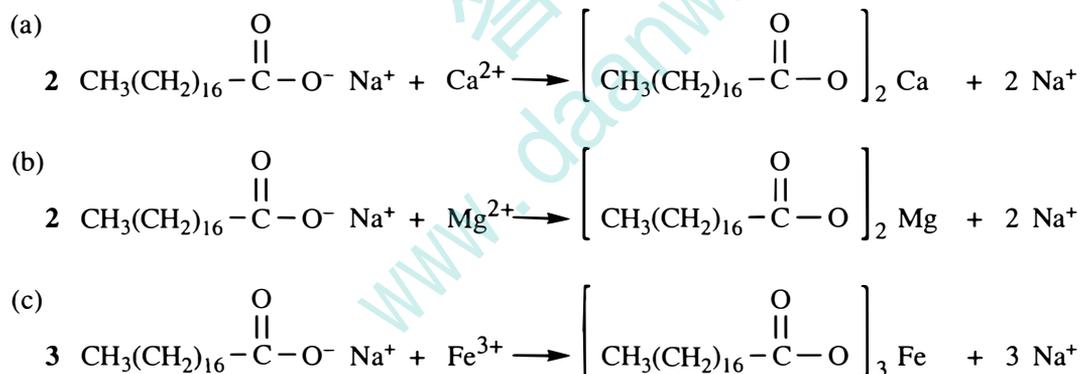
25-1



25-2



25-3



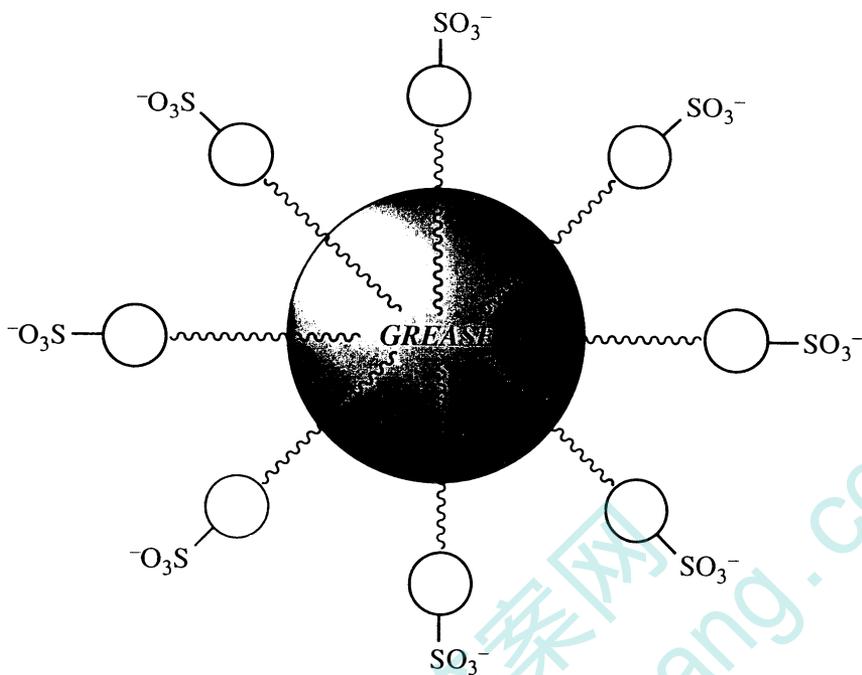
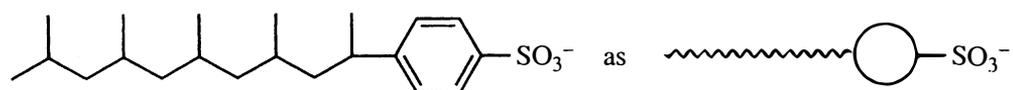
25-4

(a) Both sodium carbonate (its old name is "washing soda") and sodium phosphate will increase the pH above 6, so that the carboxyl group of the soap molecule will remain ionized, thus preventing precipitation.

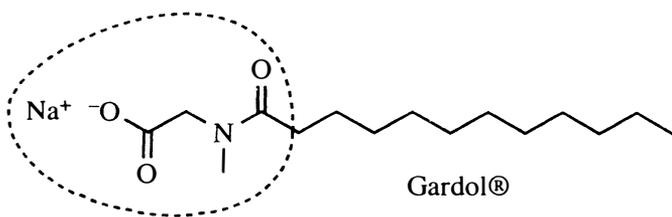
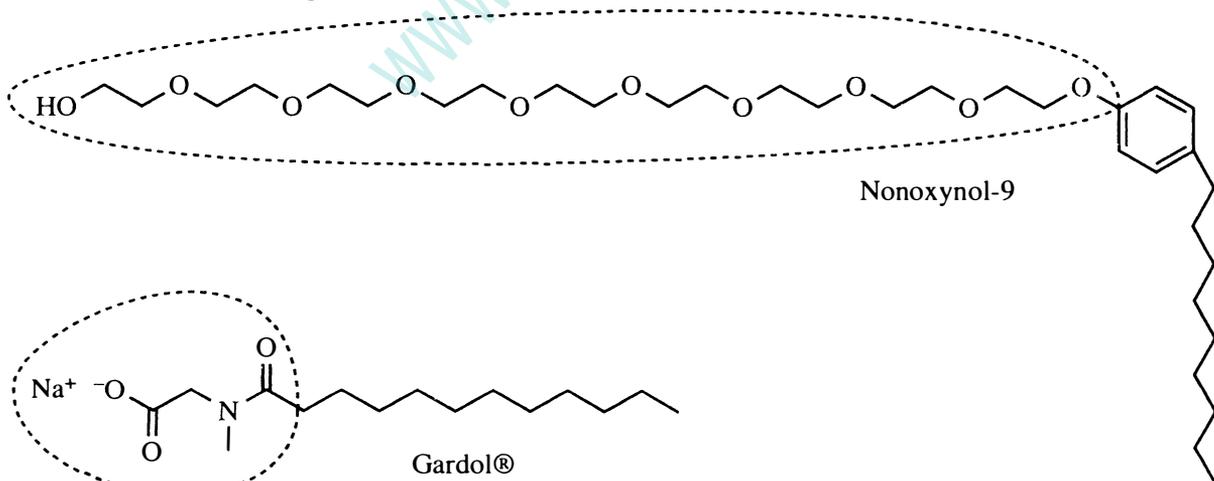
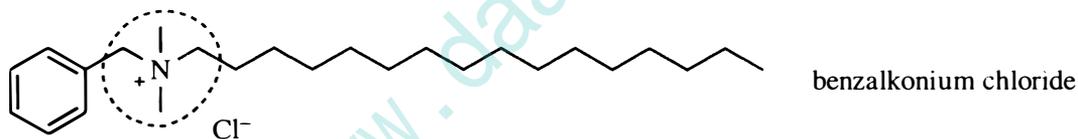
(b) In the presence of calcium, magnesium, and ferric ions, the carboxylate group of soap will form precipitates called "hard-water scum", or as scientists label it, "bathtub ring". Both carbonate and phosphate ions will form complexes or precipitates with these cations, thereby preventing precipitation of the soap from solution.

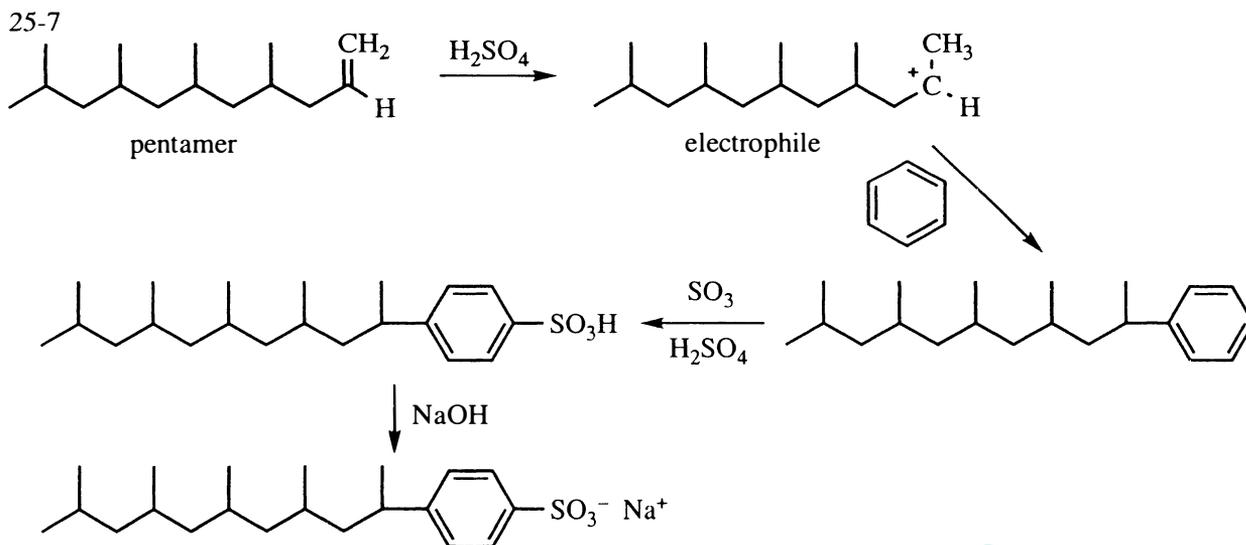
25-5

abbreviate

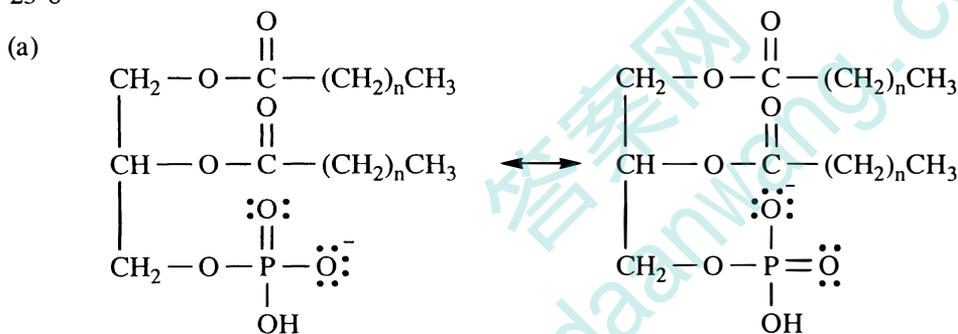


25-6 In each structure, the hydrophilic portion is circled. The uncircled part is hydrophobic.

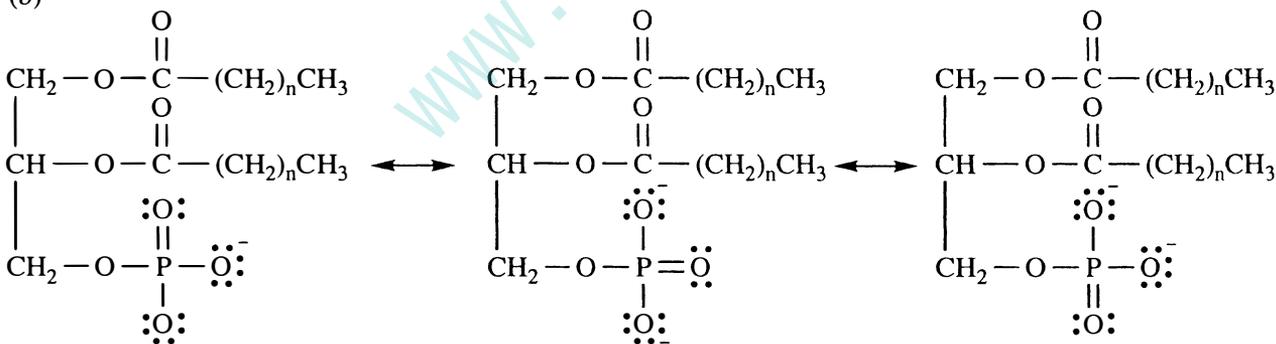




25-8

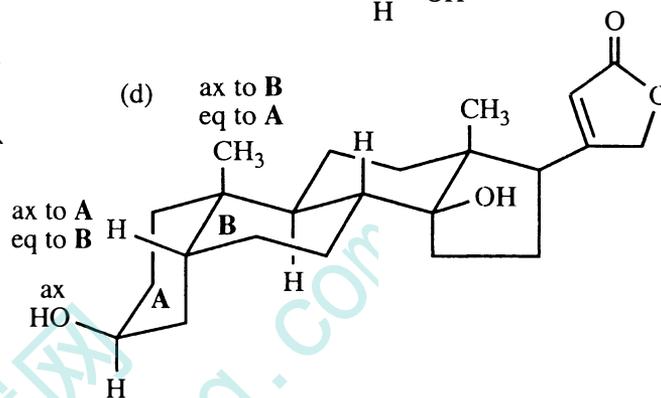
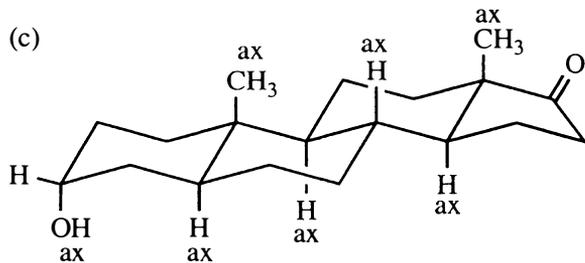
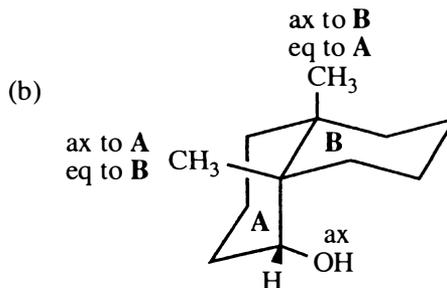
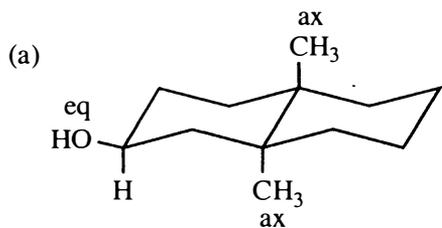


(b)

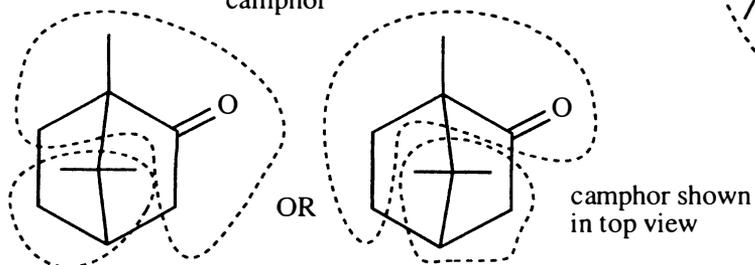
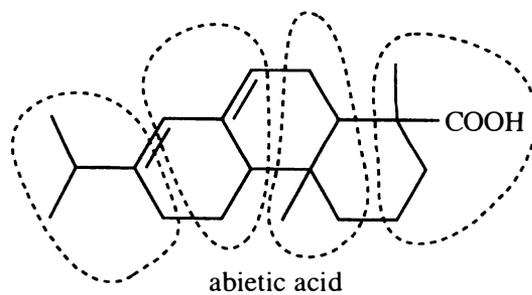
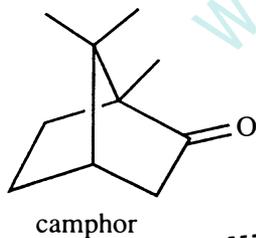
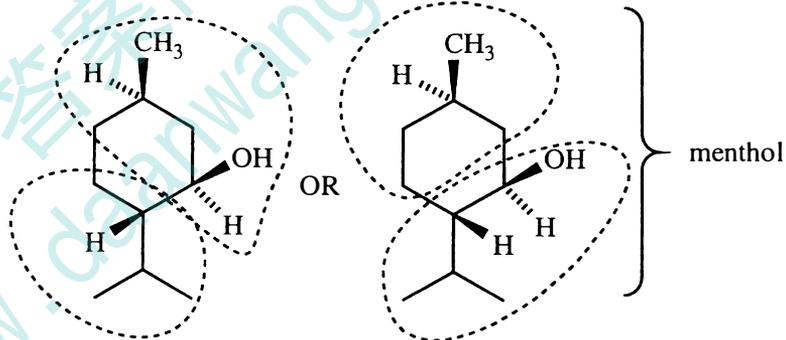
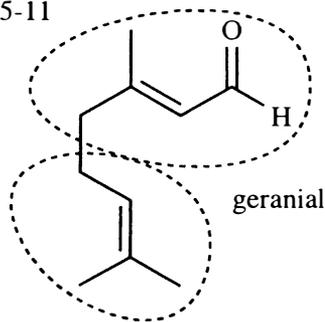


25-9 Estradiol is a phenol and can be ionized with aqueous NaOH. Testosterone does not have any hydrogens acidic enough to react with NaOH. Treatment of a solution of estradiol and testosterone in organic solvent with aqueous base will extract the phenoxide form of estradiol into the aqueous layer, leaving testosterone in the organic layer. Acidification of the aqueous base will precipitate estradiol which can be filtered. Evaporation of the organic solvent will leave testosterone.

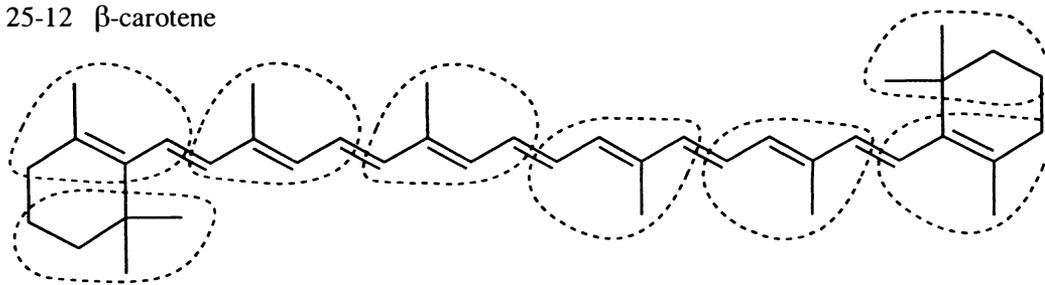
25-10 Models may help. Abbreviations: "ax" = axial; "eq" = equatorial. Note that substituents at *cis*-fused ring junctures are axial to one ring and equatorial to another.



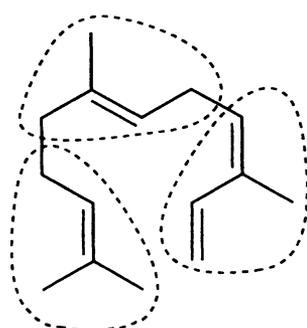
25-11



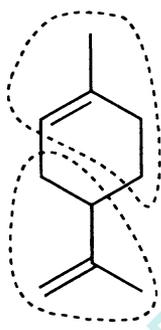
25-12 β -carotene



25-13

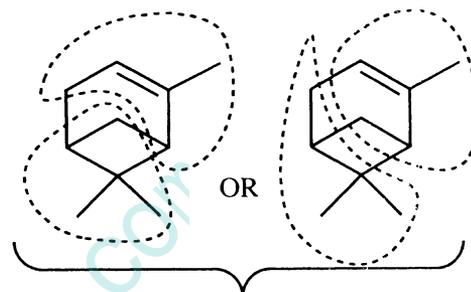


α -farnesene
sesquiterpene

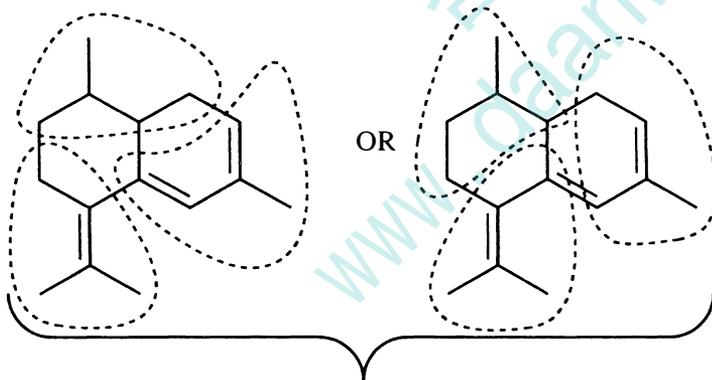


limonene
monoterpene

(Limonene can also be circled
in the other direction around
the ring—see menthol in 25-11.)



α -pinene
monoterpene



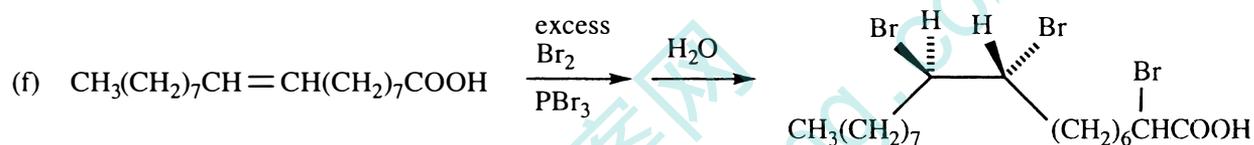
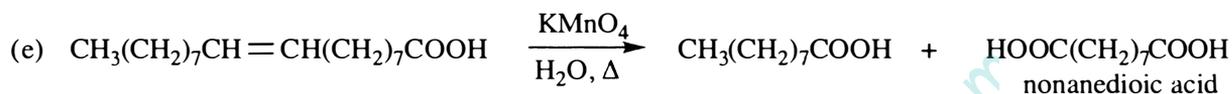
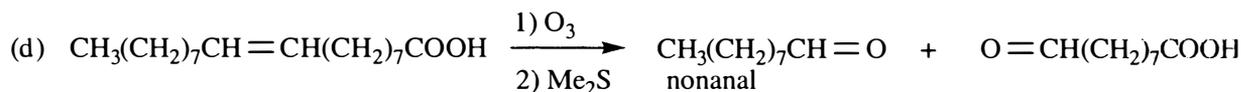
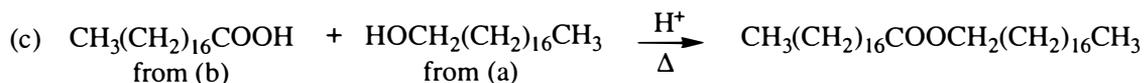
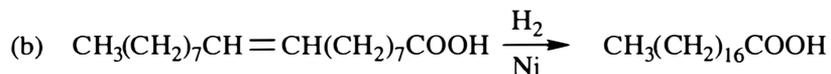
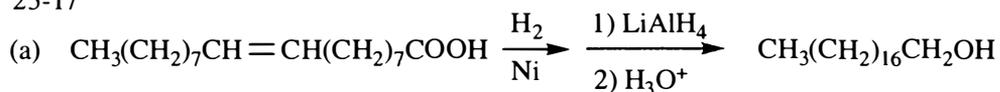
zingiberene
sesquiterpene

25-14 Please refer to problem 1-20, page 12 of this Solutions Manual.

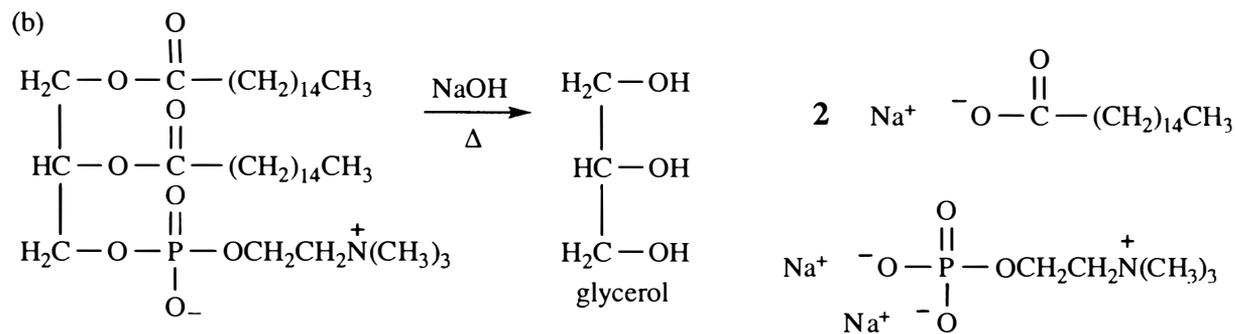
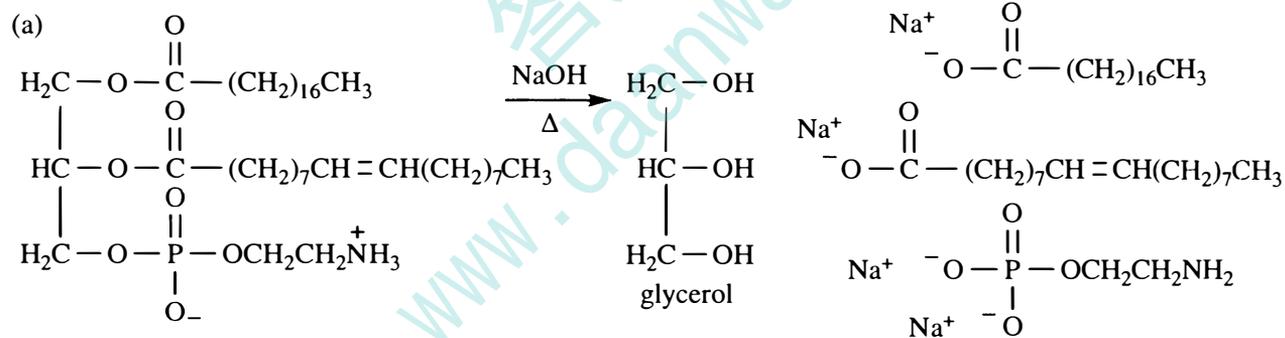
25-15

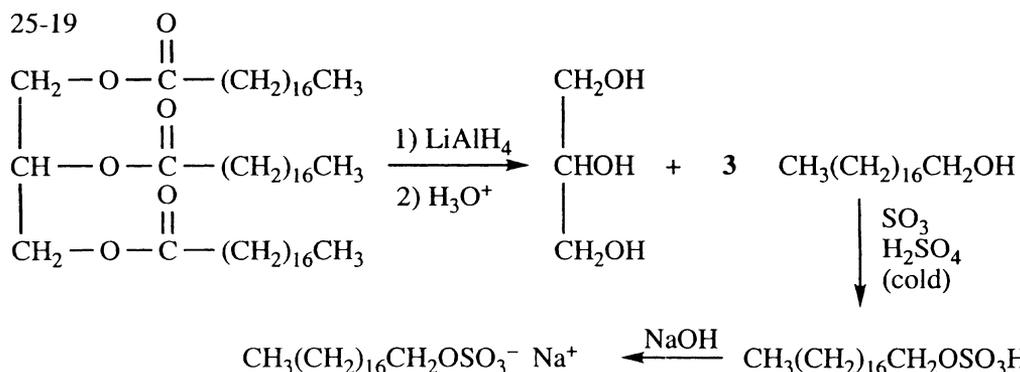
(a) triglyceride (b) synthetic detergent (c) wax (d) sesquiterpene (e) steroid

25-17



25-18





25-20 Reagents in parts (a), (b), and (d) would react with alkenes. If both samples contained alkenes, these reagents could not distinguish the samples. Saponification (part (c)), however, is a reaction of an ester, so only the vegetable oil would react, not the hydrocarbon oil mixture.

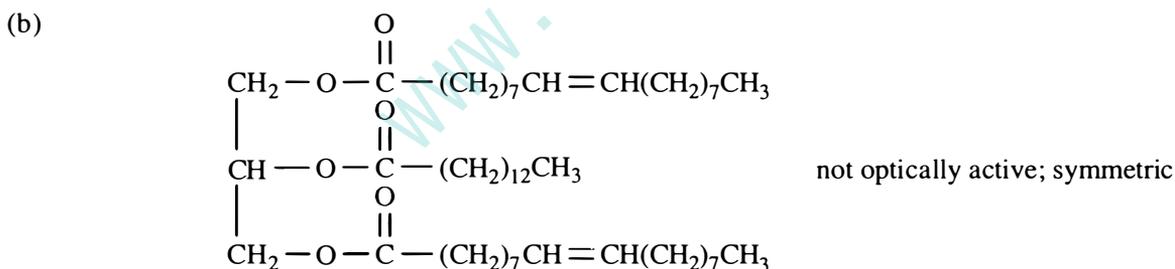
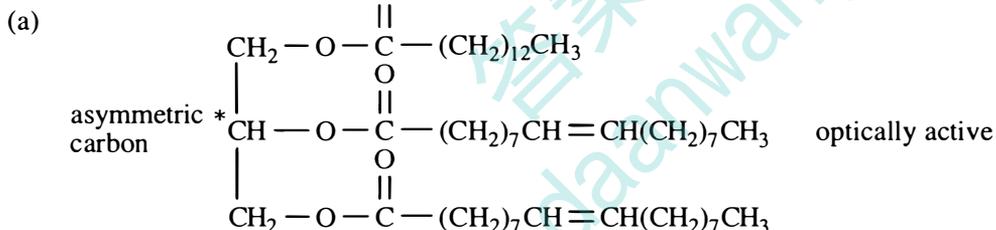
25-21 (a) Add an aqueous solution of calcium ion or magnesium ion. Sodium stearate will produce a precipitate, while the sulfonate will not precipitate.

(b) Beeswax, an ester, can be saponified with NaOH. Paraffin wax is a solid mixture of alkanes and will not react.

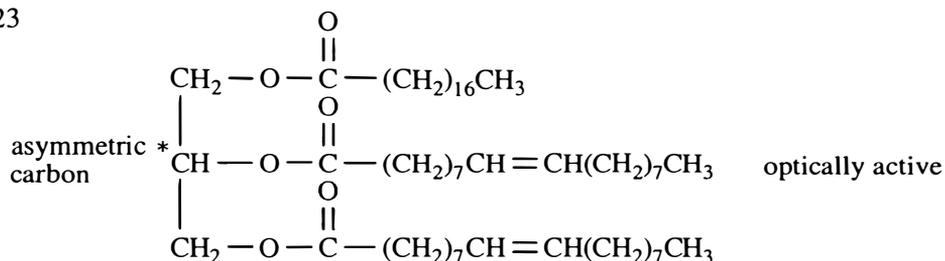
(c) Myristic acid will dissolve (or be emulsified) in dilute aqueous base. Trimyristin will remain unaffected.

(d) Triolein (an unsaturated oil) will decolorize bromine in CCl_4 , but trimyristin (a saturated fat) will not.

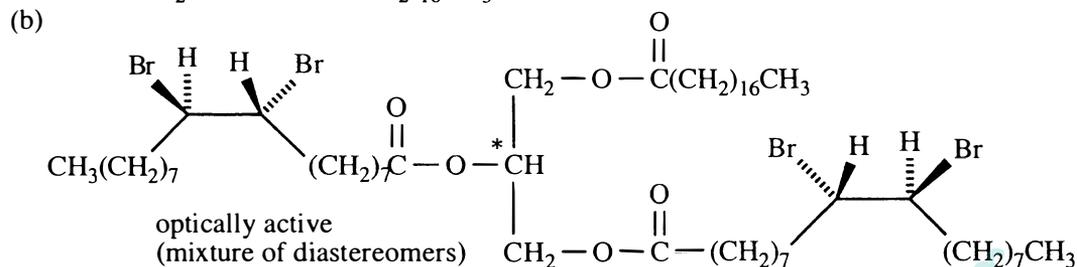
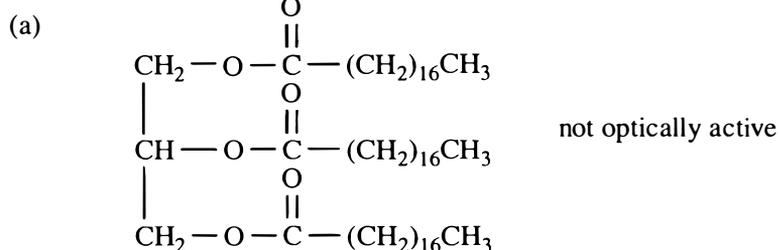
25-22



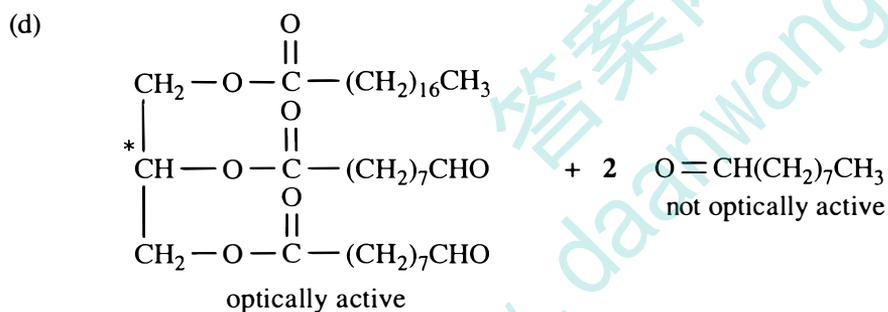
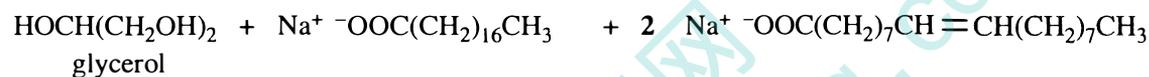
25-23



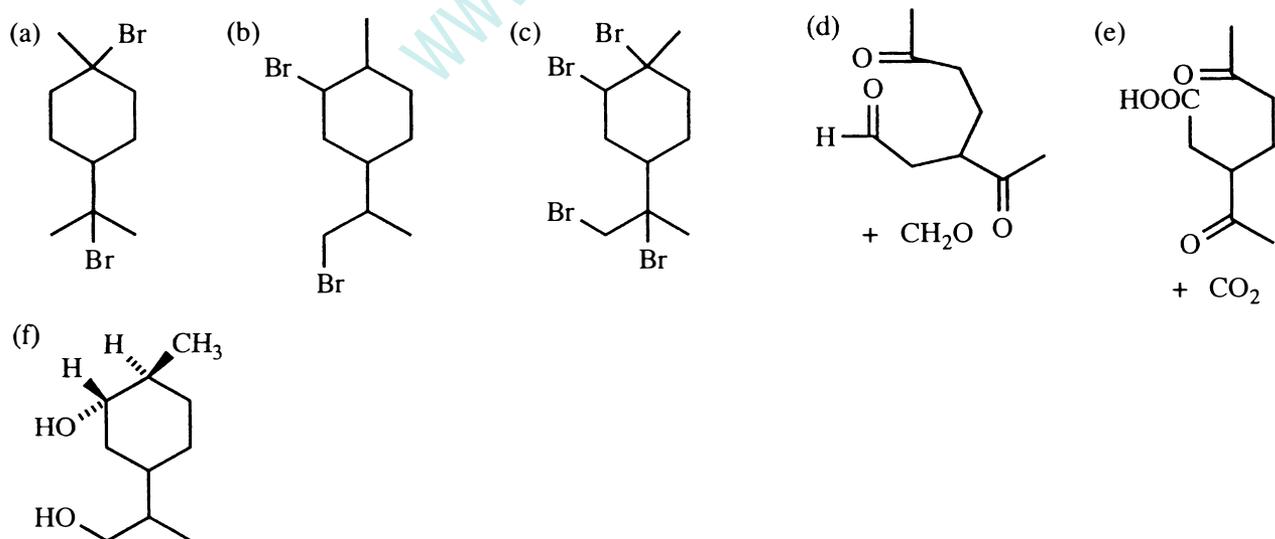
25-23 continued



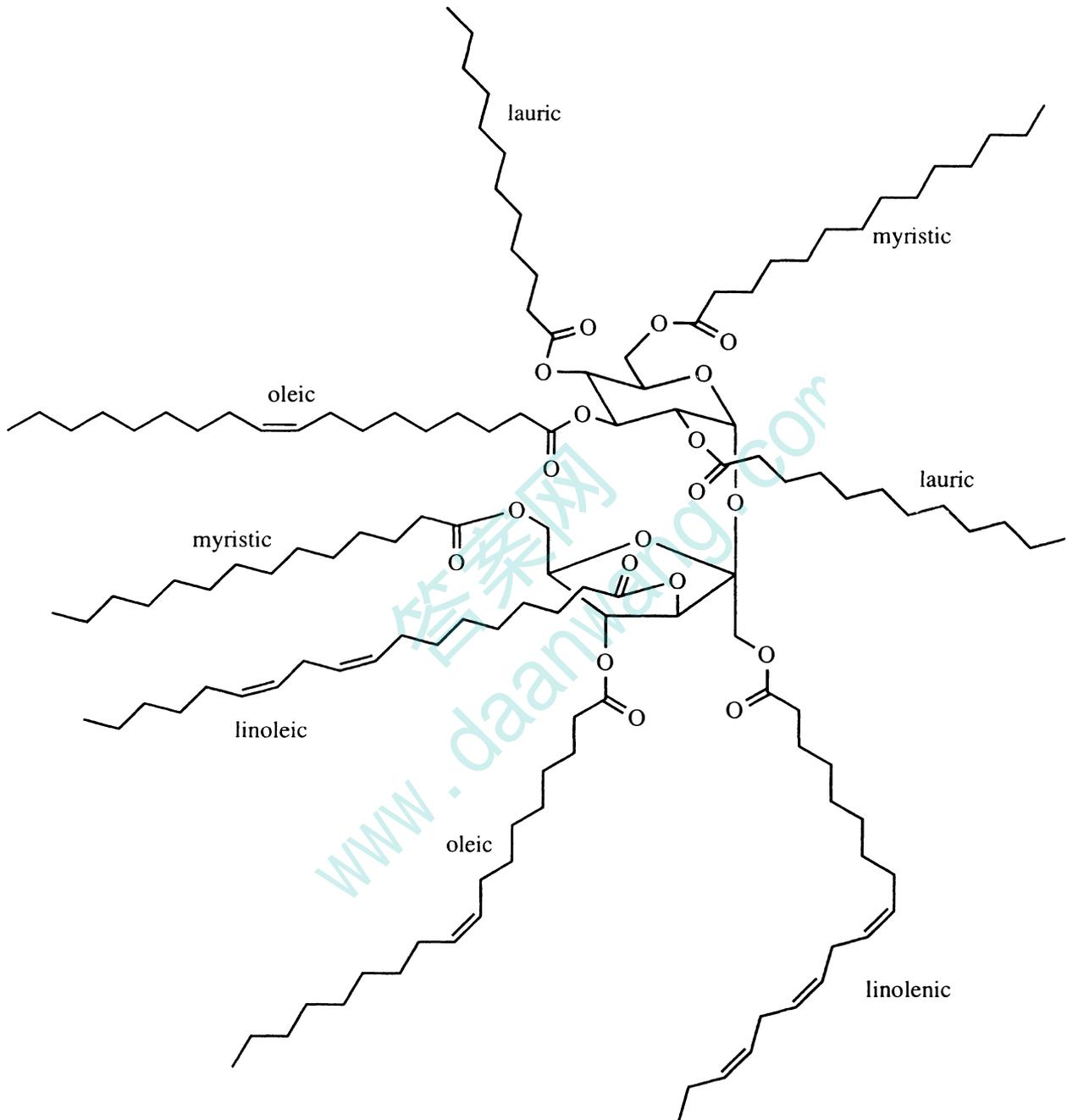
(c) products are not optically active



25-24 The products in (b), (c) and (f) are mixtures of stereoisomers.

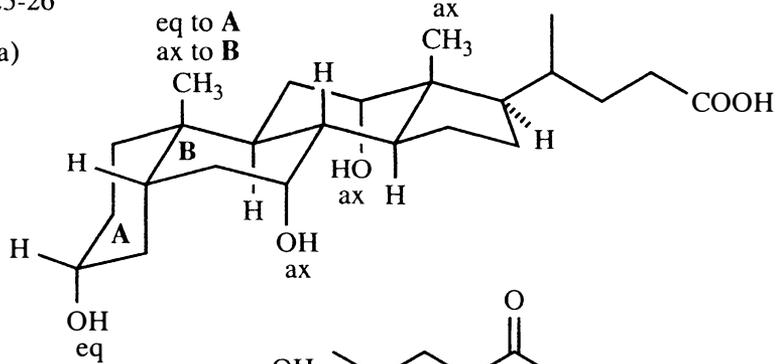


25-25 Is it any wonder that Olestra cannot be digested!

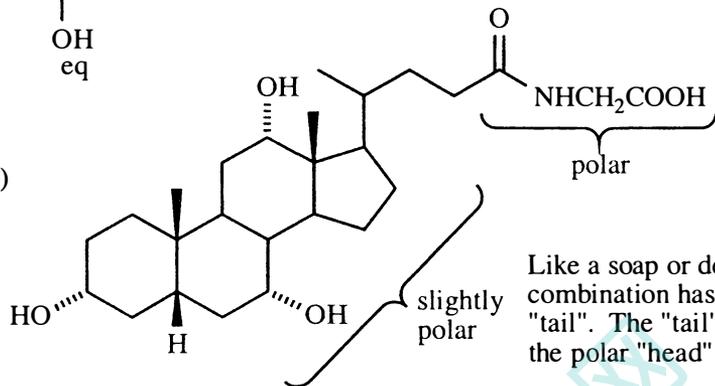


25-26

(a)



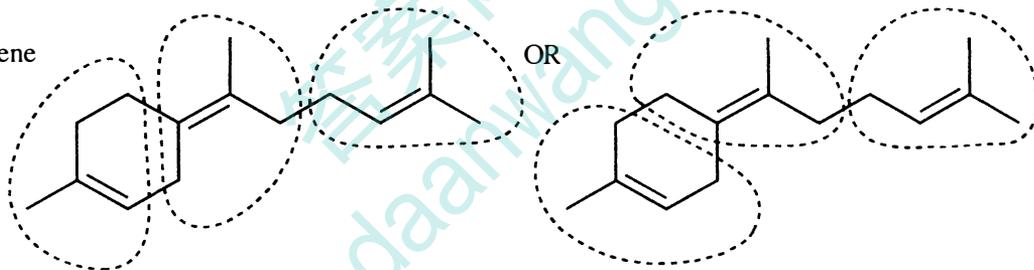
(b)



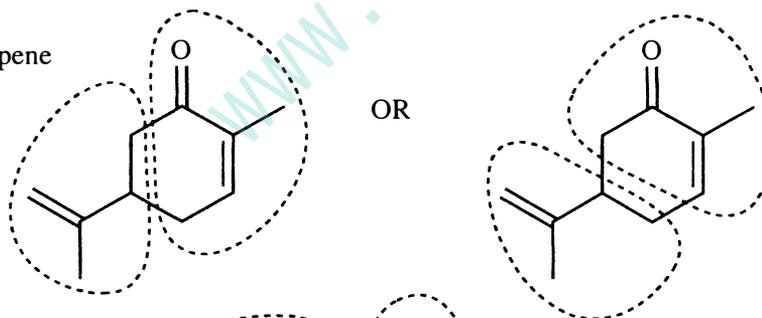
Like a soap or detergent, this cholic acid—glycine combination has a very polar "head" and a slightly polar "tail". The "tail" can dissolve non-polar molecules and the polar "head" can carry the complex into polar media.

25-27

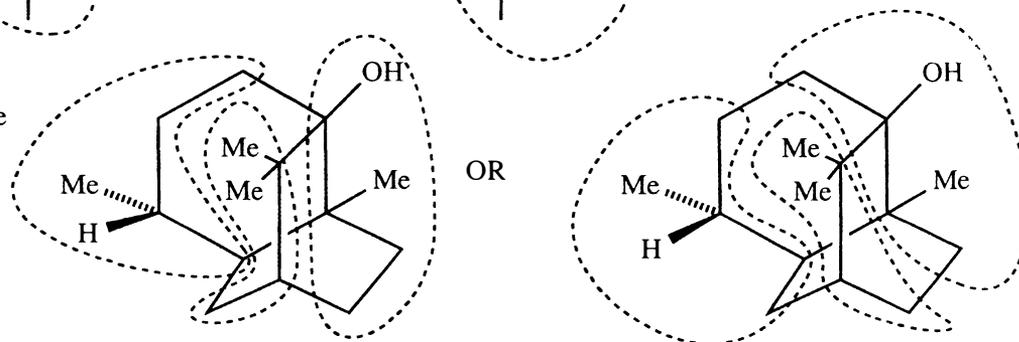
(a) sesquiterpene



(b) monoterpene

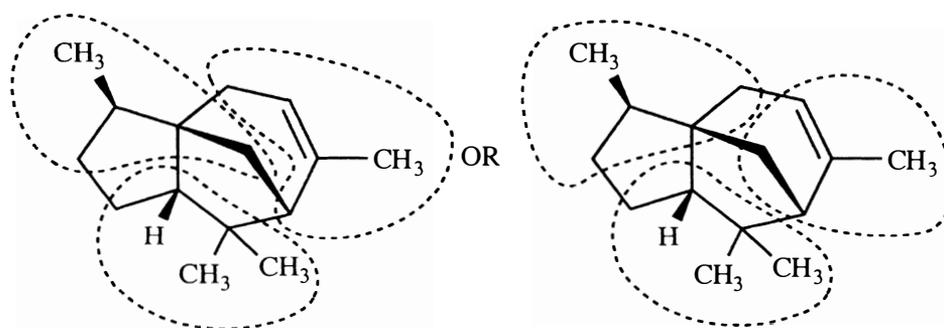


(c) sesquiterpene

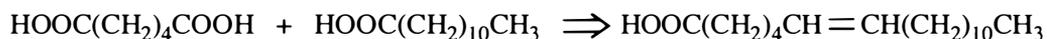


25-27

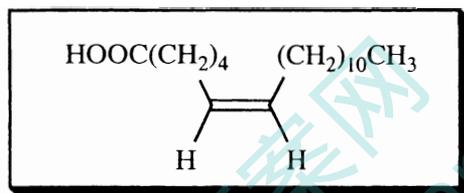
(d) sesquiterpene



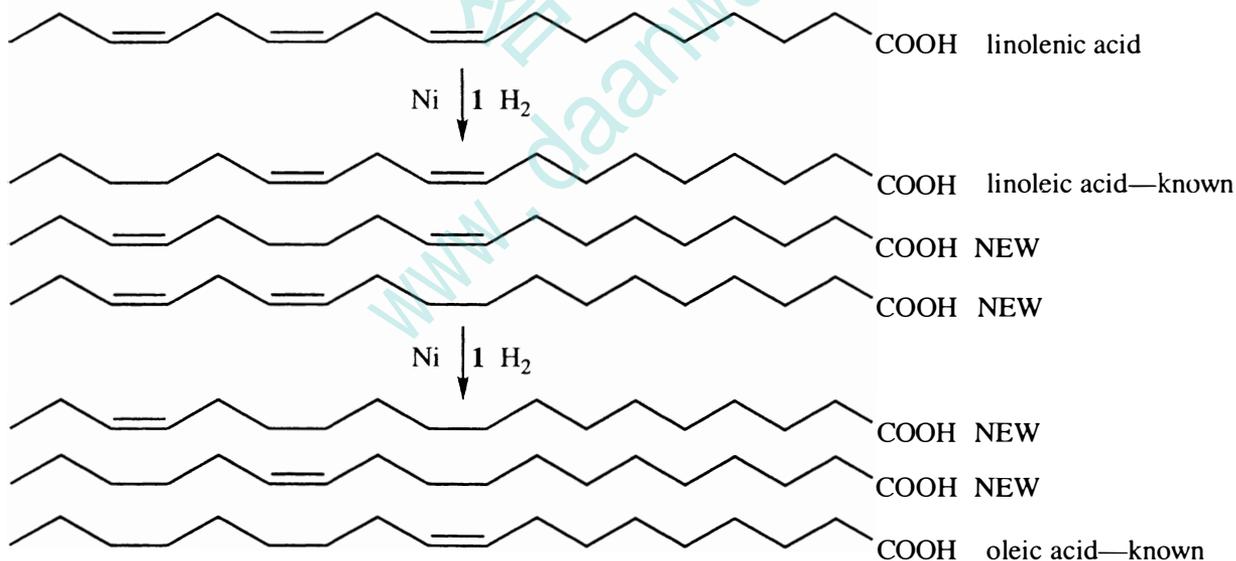
25-28 The formula $C_{18}H_{34}O_2$ has two elements of unsaturation; one is the carbonyl, so the other must be an alkene or a ring. Catalytic hydrogenation gives stearic acid, so the carbon cannot include a ring; it must contain an alkene. The products from $KMnO_4$ oxidation determine the location of the alkene:



If the alkene were *trans*, the coupling constant for the vinyl protons would be about 15 Hz; a 10 Hz coupling constant indicates a *cis* alkene. The 7 Hz coupling is from the vinyl H's to the neighboring CH_2 's.



25-29

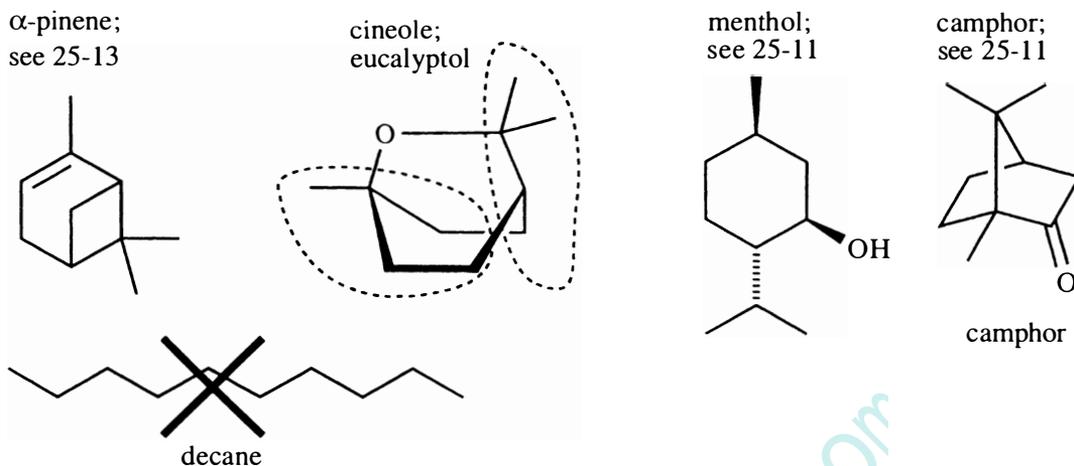


In addition to the new isomers with different positions of the double bonds, there has been growing concern over the *trans* fatty acids created by isomerizing the naturally occurring *cis* double bonds. More manufacturers are now listing the percent of "*trans* fat" on their food labels.

25-30 The cetyl glycoside would be a good emulsifying agent. It has a polar end (glucose) and a non-polar end (the hydrocarbon chain), so it can dissolve non-polar molecules, then carry them through polar media in micelles. This is found in Nature where non-polar molecules such as steroid hormones, antibiotics, and other physiologically-active compounds are carried through the bloodstream (aqueous) by attaching saccharides (usually mono, di, or tri), making the non-polar group water soluble.

25-31 (a) Four of these components in Vicks Vapo-Rub® are terpenes. The only one that is not is decane; it is not comprised of isoprene units despite having the correct number of carbons for a monoterpene.

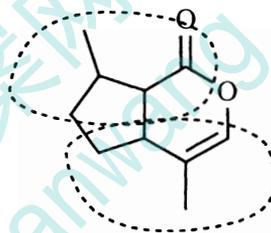
Three of the four terpenes have had their isoprene units indicated in previous problems; in each of those three, there are two possible ways to assign the isoprene units, so those pictures will not be duplicated here.



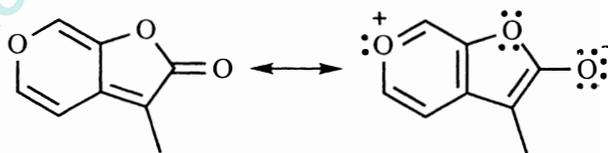
(b) Vicks Vapo-Rub® must be optically active as it contains four optically active terpenes.

25-32

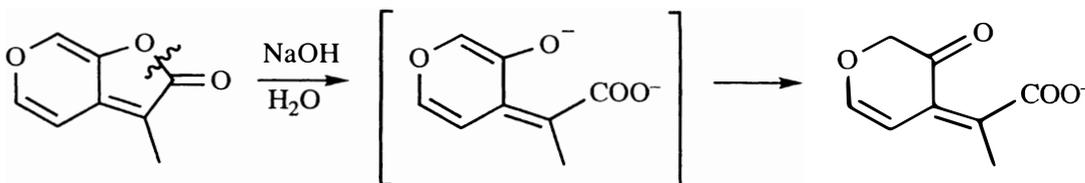
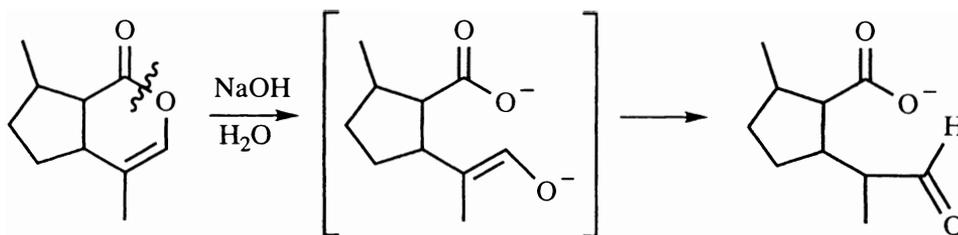
(a) Of the two, only nepetalactone is a terpene. The other has only 8 carbons and terpenes must be in multiples of 5 carbons.



(b) Of the two, only the second is aromatic as can be readily seen in one of the resonance forms.

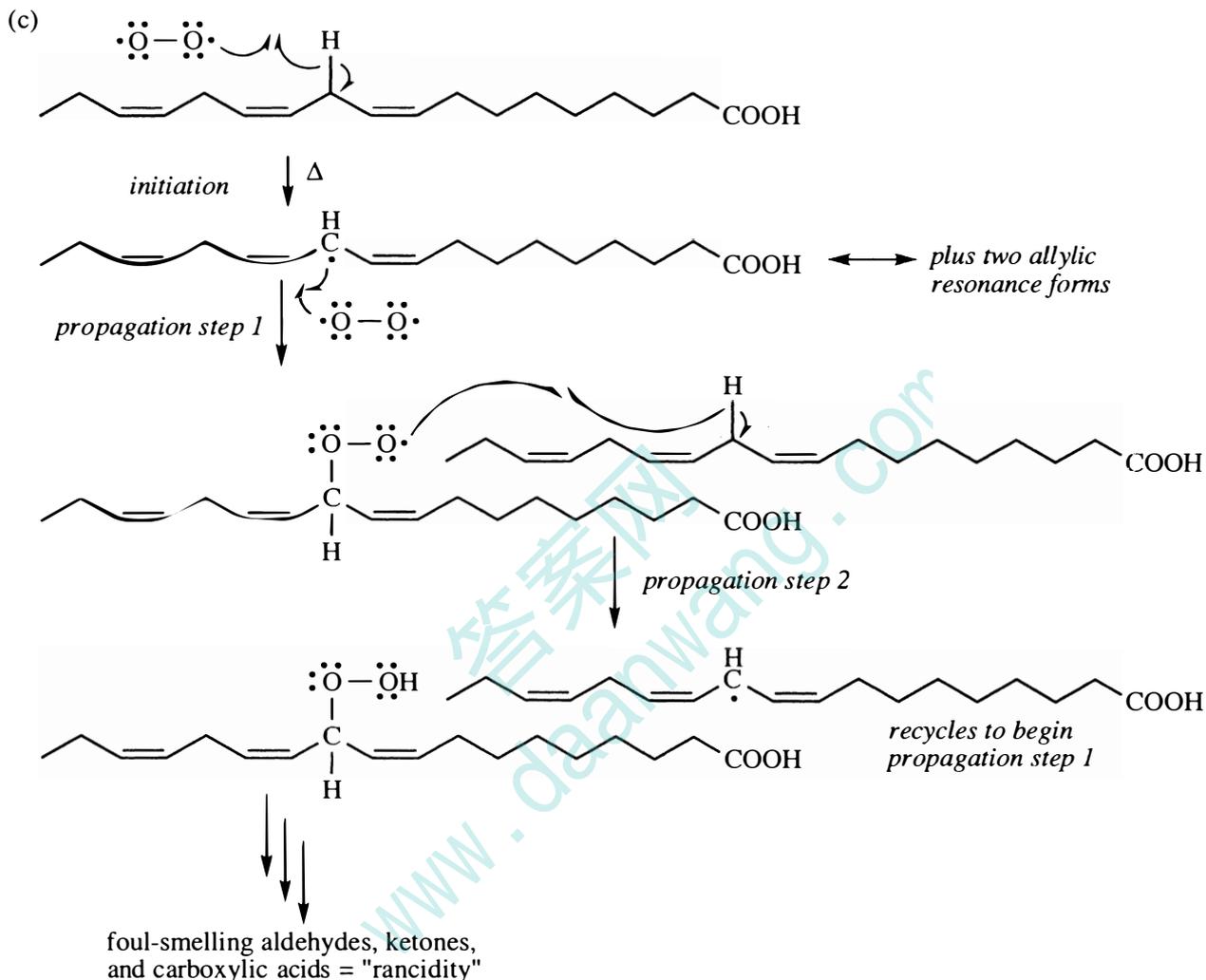


(c) Each compound is cleaved with NaOH (aq) to give an enolate that tautomerizes to the more stable keto form.

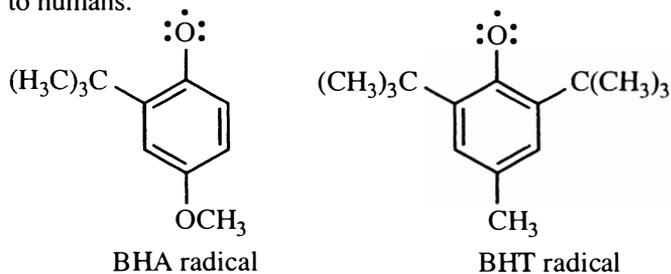


25-33

- (a) High temperature and the diradical O_2 molecule strongly suggest a radical mechanism.
 (b) Radical stability follows the order: benzylic > allylic > 3° > 2° > 1° . A radical at C-11 would be doubly allylic making it a prime site for radical reaction.



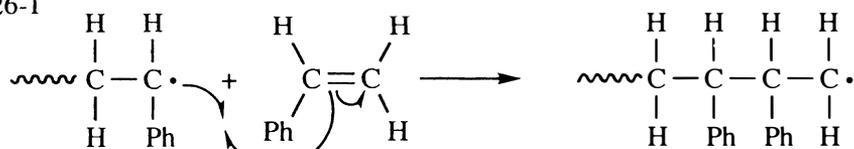
- (d) Antioxidants are molecules that stop the free radical chain mechanism. In each of the two cases here, abstraction of the phenolic H makes an oxygen radical that is highly stabilized by resonance, so stable that it does not continue the free radical chain process. It only takes a small amount of antioxidant to prevent the chain mechanism. Interestingly, in breakfast cereals, the antioxidant is usually put in the plastic bag that the cereal is packaged in, rather than in the food itself. BHA and BHT can also be used directly in food as there is no evidence that they are harmful to humans.



CHAPTER 26—SYNTHETIC POLYMERS

Note: In this chapter, the "wavy bond" symbol means the continuation of a polymer chain.

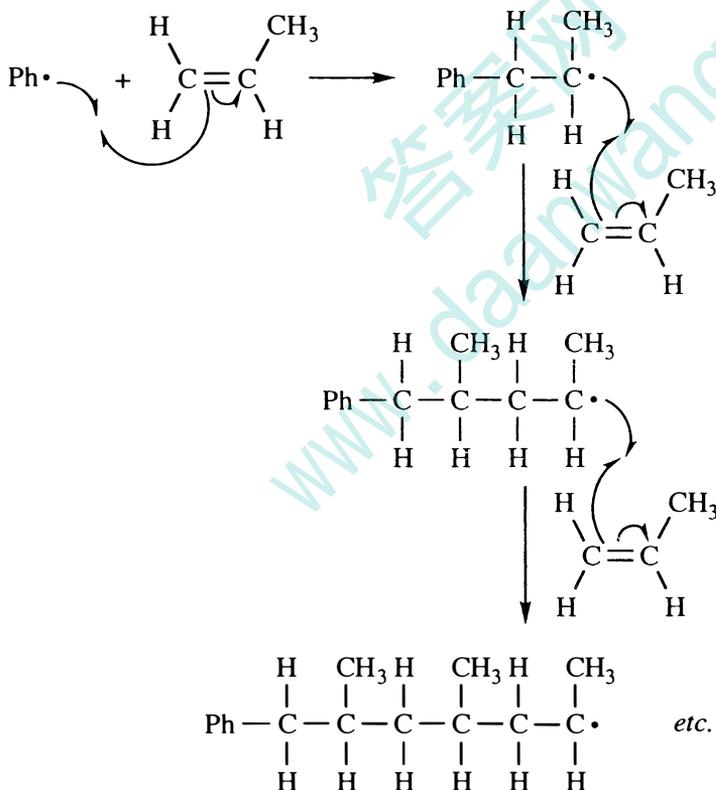
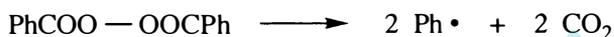
26-1



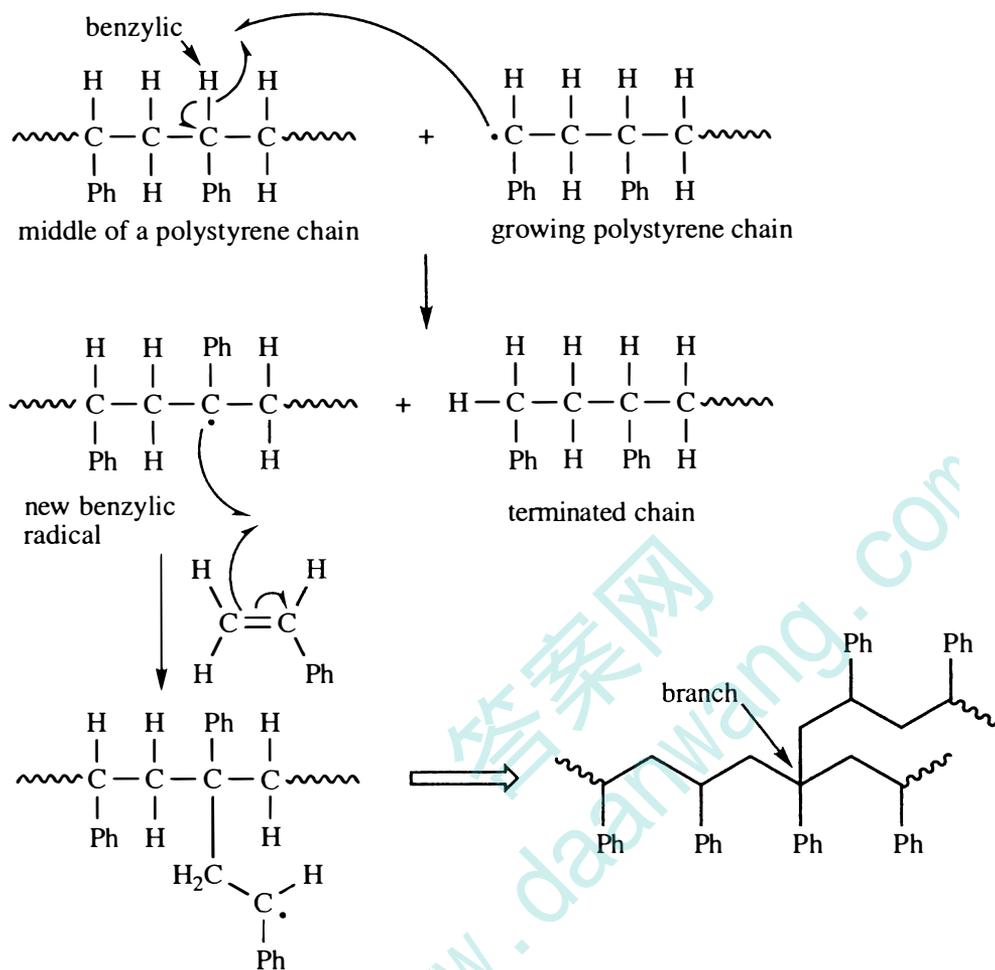
1° radical, and *not* resonance-stabilized—
this orientation is not observed

Orientation of addition always generates the more stable intermediate; the energy difference between a 1° radical (shown above) and a benzylic radical is huge. Moreover, this energy difference accumulates with each repetition of the propagation step. The phenyl substituents must necessarily be on alternating carbons because the orientation of attack is always the same—not a random process.

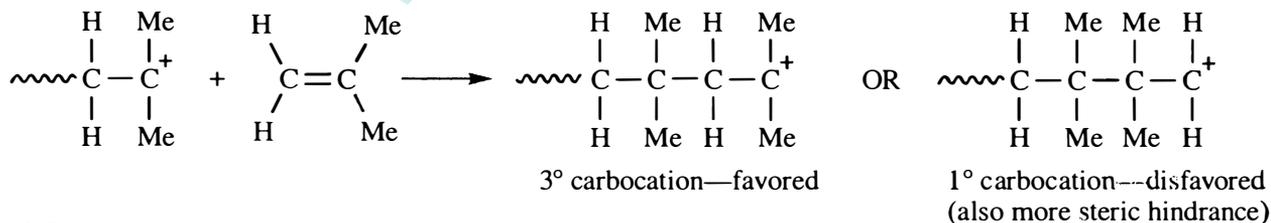
26-2



26-3 The benzylic hydrogen will be abstracted in preference to a 2° hydrogen because the benzylic radical is both 3° and resonance-stabilized, and the 2° radical is neither.

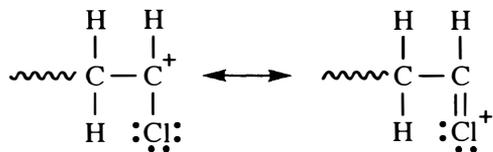


26-4 Addition occurs with the orientation giving the more stable intermediate. In the case of isobutylene, the growing chain will bond at the less substituted carbon to generate the more highly substituted carbocation.



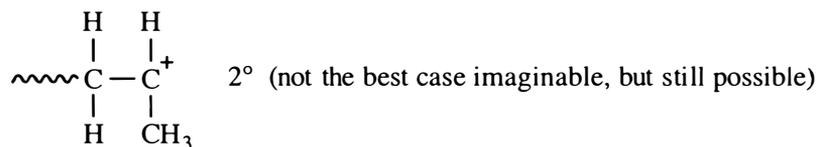
26-5

(a) chlorine can stabilize a carbocation intermediate by resonance

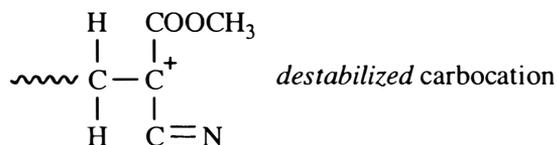


26-5 continued

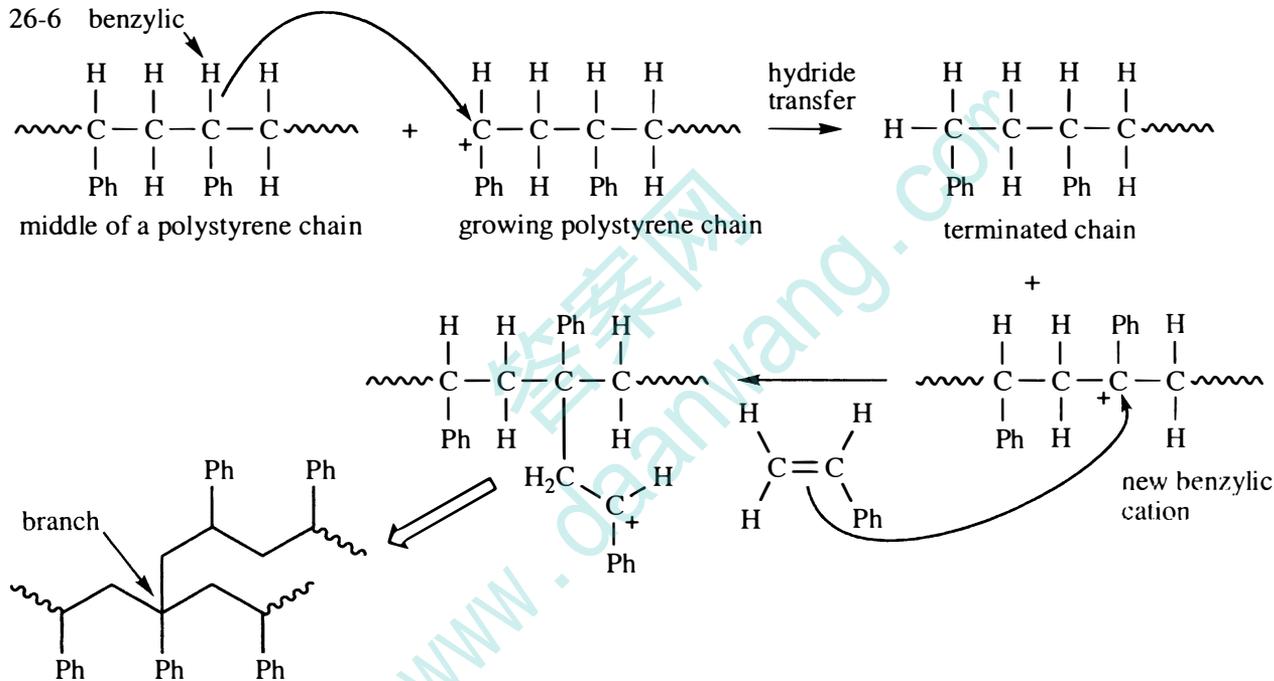
(b) CH₃ can stabilize the carbocation intermediate by induction



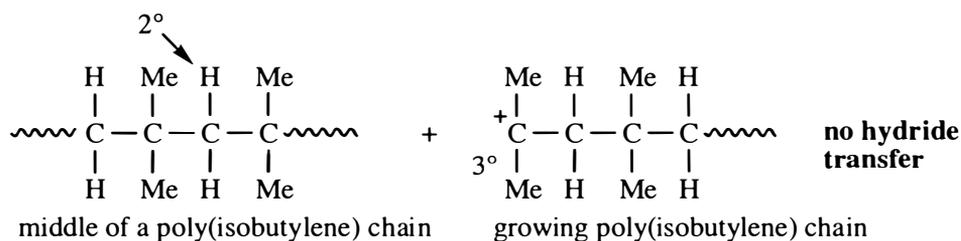
(c) terrible for cationic polymerization: both substituents are electron-withdrawing and would *destabilize* the carbocation intermediate



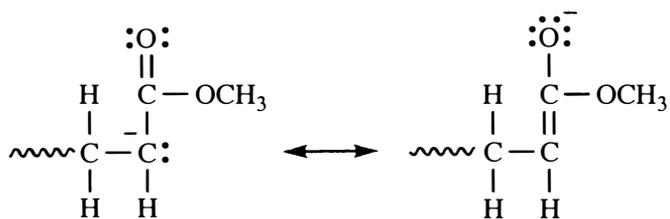
26-6 benzylic



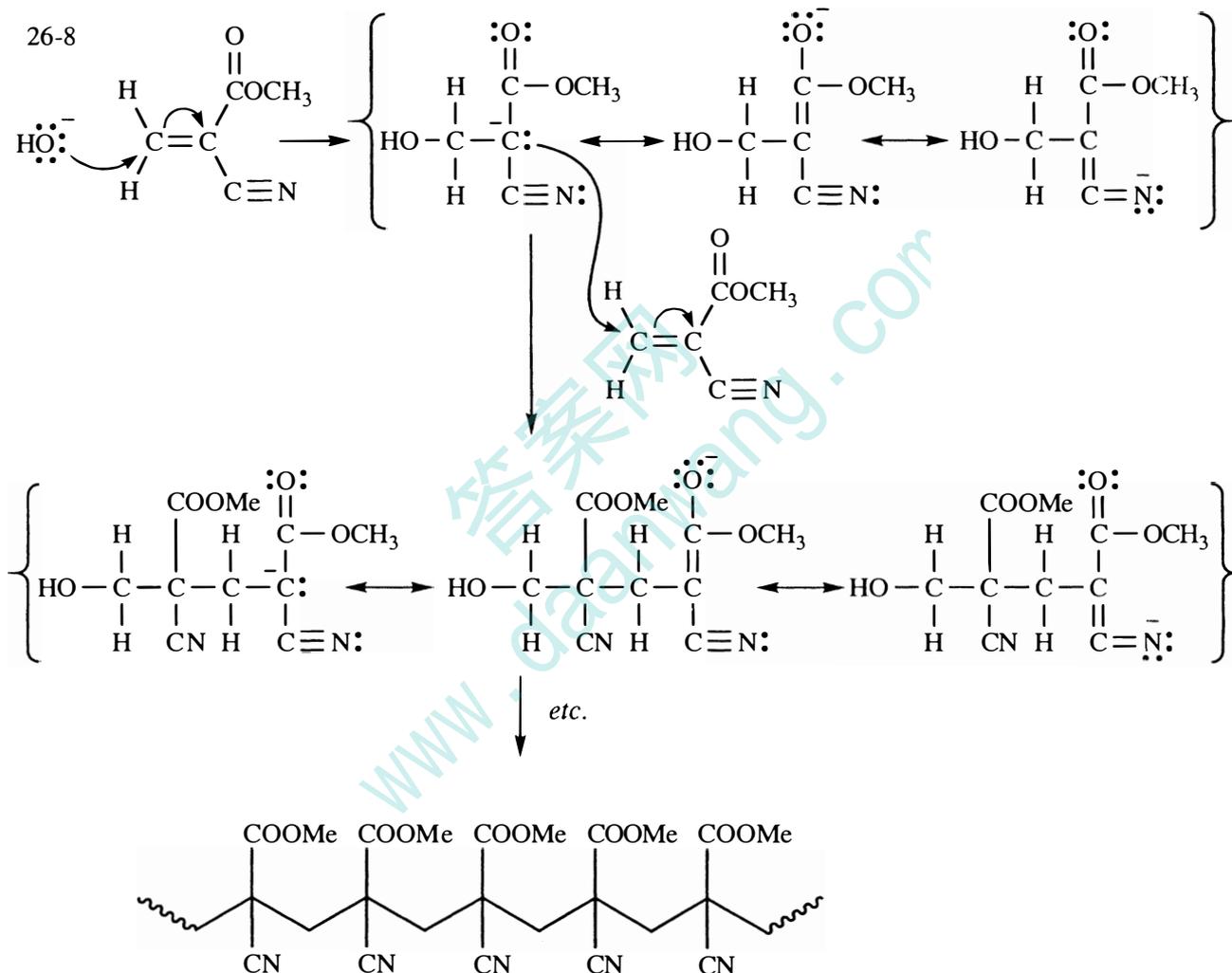
Polystyrene is particularly susceptible to branching because the 3° benzylic cation produced by a hydride transfer is so stable. In poly(isobutylene), there is no hydrogen on the carbon with the stabilizing substituents; any hydride transfer would generate a 2° carbocation at the expense of a 3° carbocation at the end of a growing chain—this is an increase in energy and therefore unfavorable.



26-7



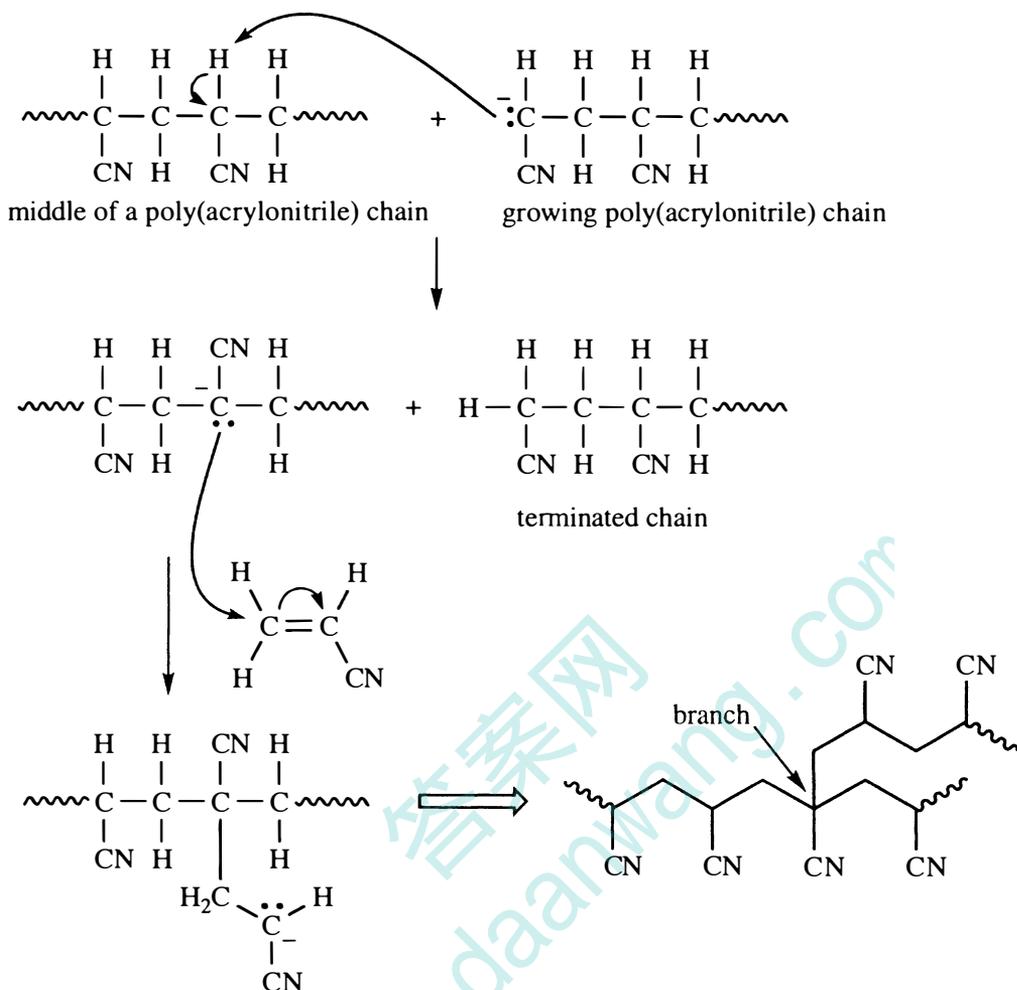
26-8



This polymerization goes so quickly because the anionic intermediate is highly resonance stabilized by the carbonyl and the cyano groups. A stable intermediate suggests a low activation energy which translates to a fast reaction.

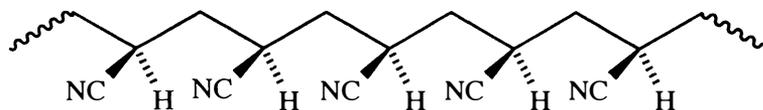
26-9

(a)

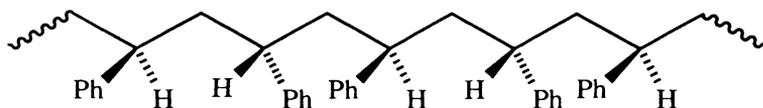


(b) The chain-branching hydride transfer (from a cationic mechanism) or proton transfer (from an anionic mechanism) ends a less-highly-substituted end of a chain and generates an intermediate on a more-highly-substituted middle of a chain (a 3° carbon in these mechanisms). This stabilizes a carbocation, but greater substitution *destabilizes* a carbanion. Branching can and does happen in anionic mechanisms, but it is less likely than in cationic mechanisms.

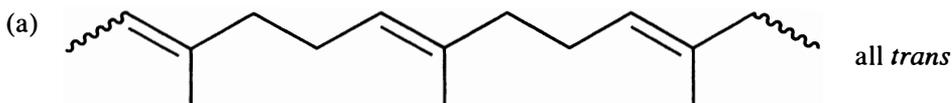
26-10 isotactic poly(acrylonitrile)



syndiotactic polystyrene

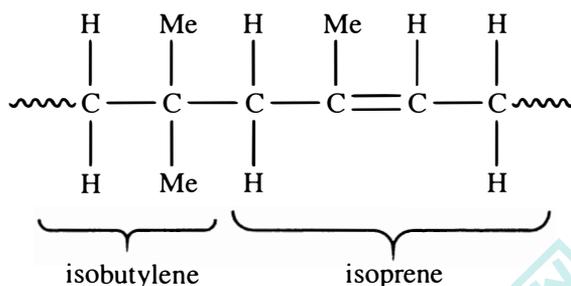


26-11



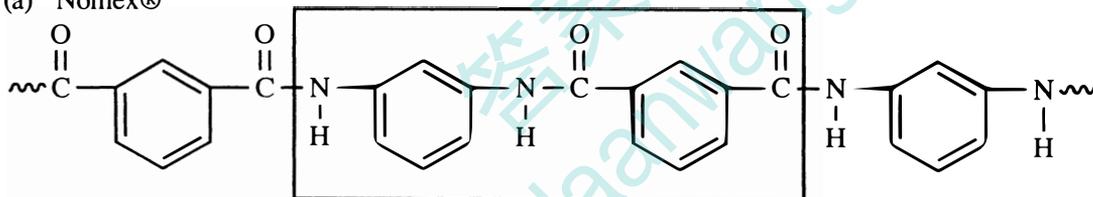
(b) The *trans* double bonds in gutta-percha allow for more ordered packing of the chains, that is, a higher degree of crystallinity. (Recall how *cis* double bonds in fats and oils lower the melting points because the *cis* orientation disrupts the ordering of the packing of the chains.) The more crystalline a polymer is, the less elastic it is.

26-12 Whether the alkene is *cis* or *trans* is not specified.

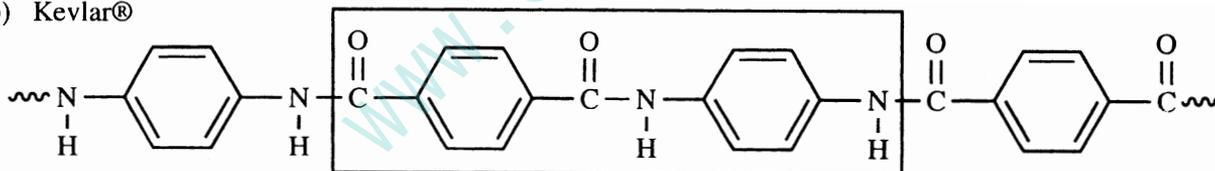


26-13 The repeating unit in each polymer is boxed.

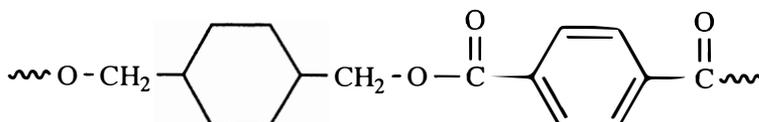
(a) Nomex®



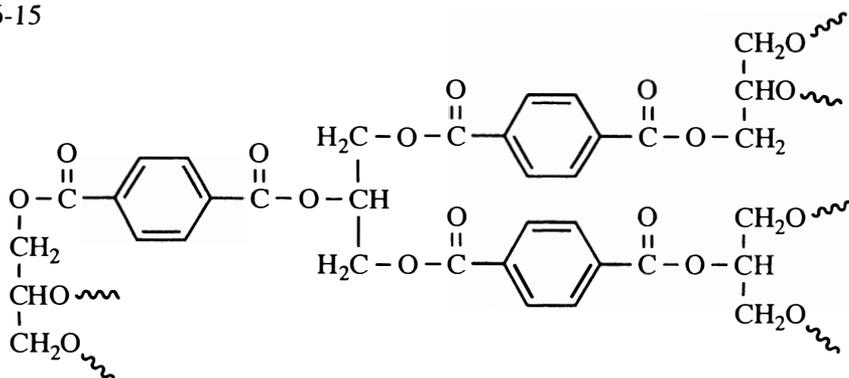
(b) Kevlar®



26-14 Kodel® polyester (only one repeating unit shown)

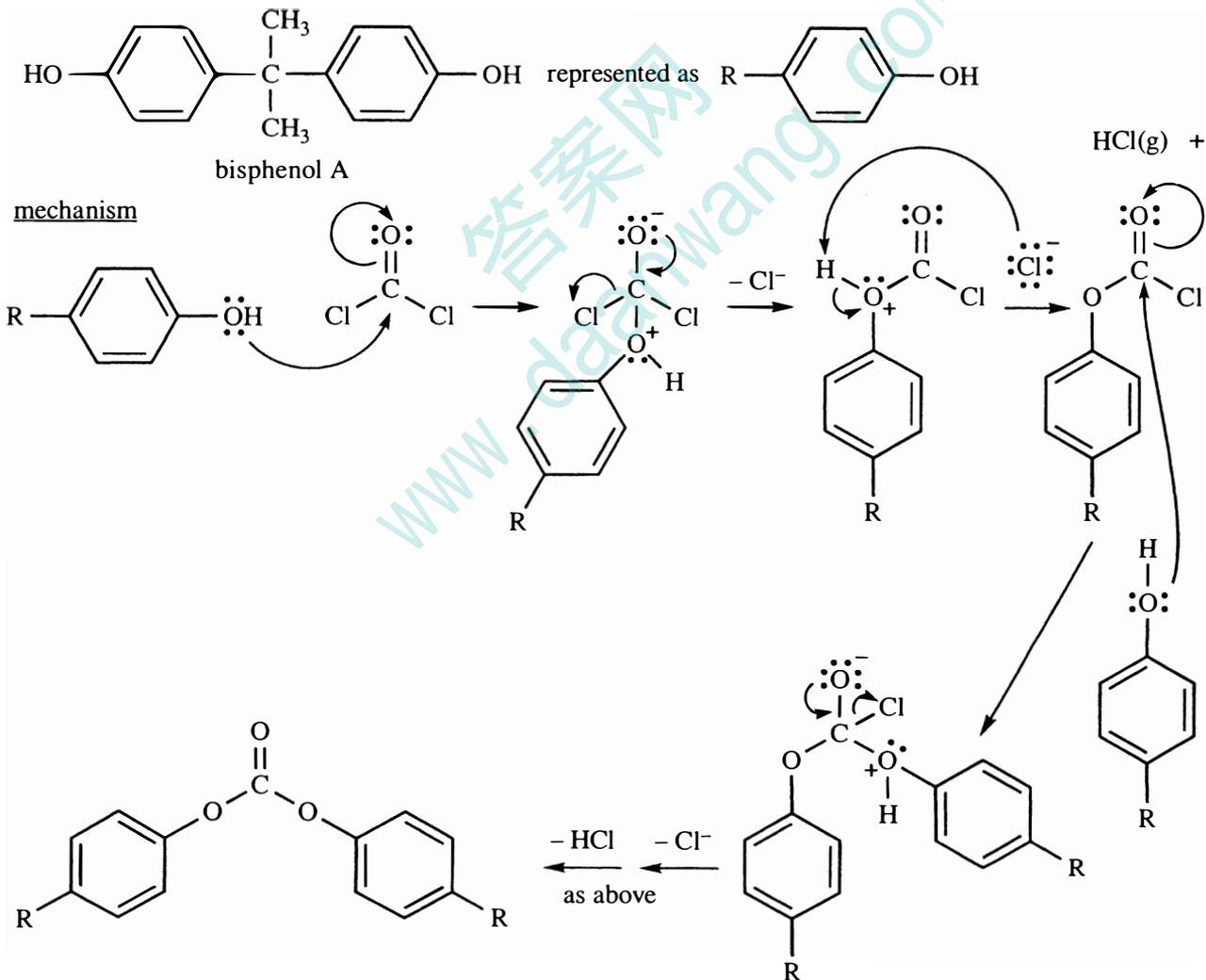


26-15

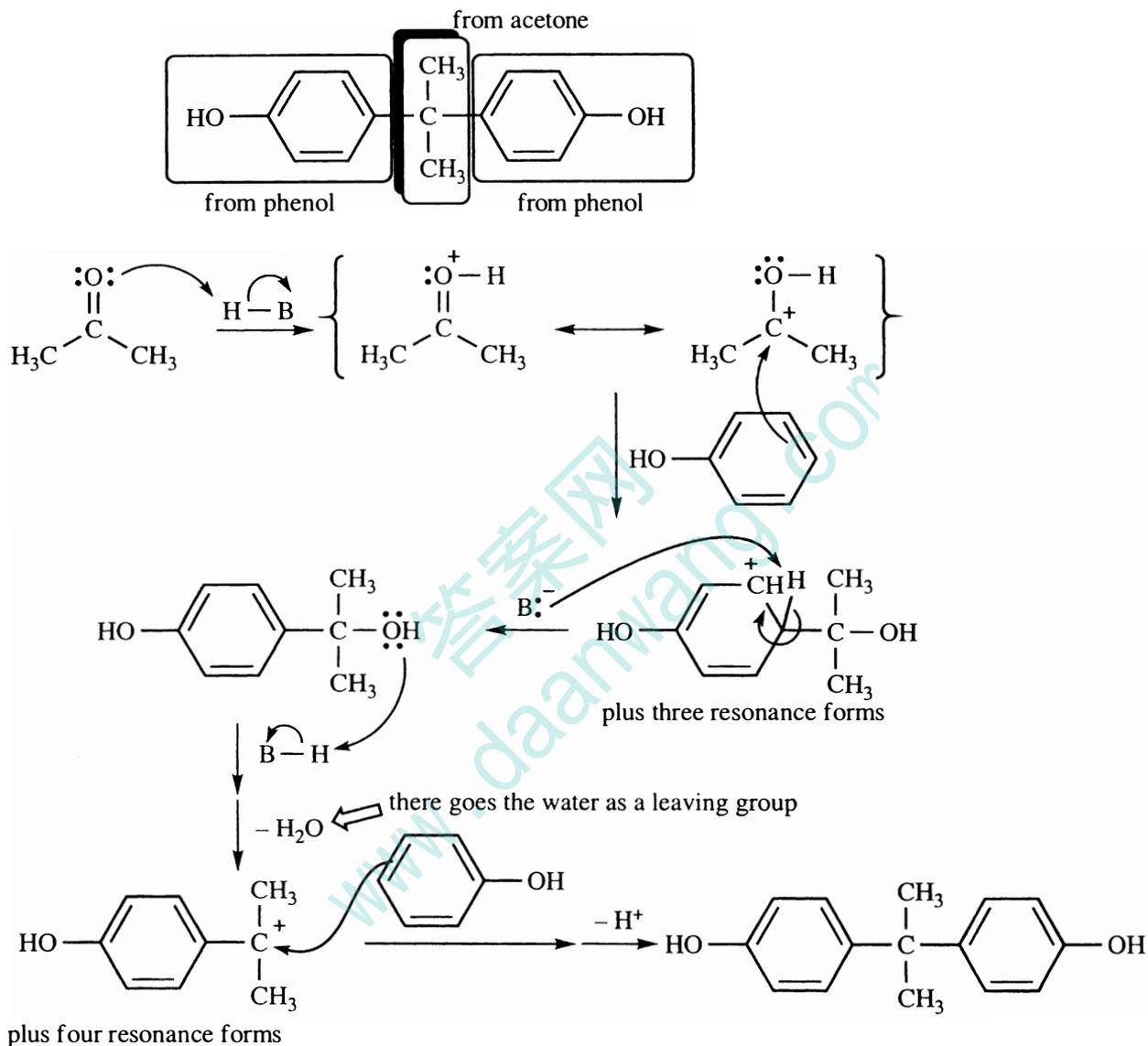


Glycerol is a trifunctional molecule, so not only does it grow in two directions to make a chain, it grows in three directions. All of its chains are cross-linked, forming a three-dimensional lattice with very little motion possible. The more cross-linked the polymer is, the more rigid it is.

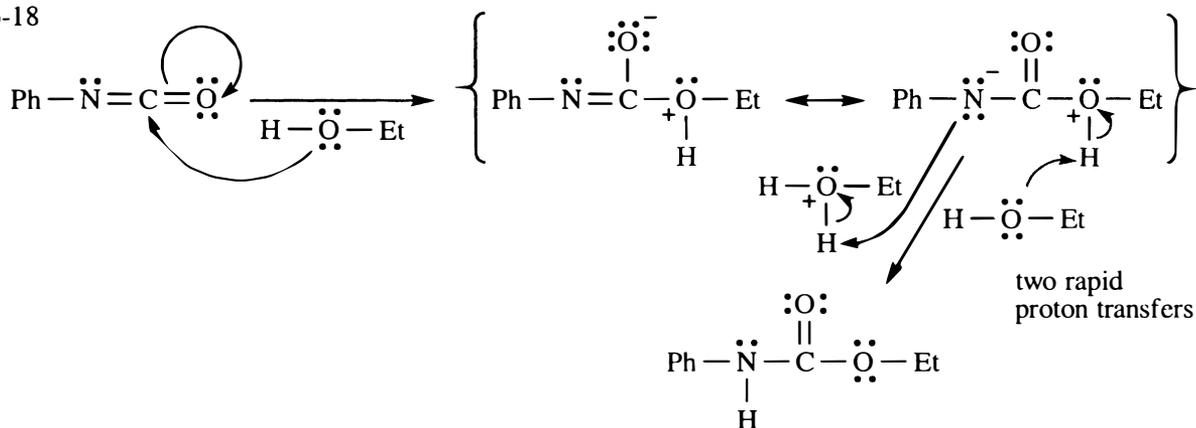
26-16 For simplicity in this problem, bisphenol A will be abbreviated as a substituted phenol.



26-17 Bisphenol A is made by condensing two molecules of phenol with one molecule of acetone, with loss of a molecule of water. This is an electrophilic aromatic substitution (more specifically, a Friedel-Crafts alkylation), and would require an acid catalyst to generate the carbocation. While a Lewis acid could be used, the mechanism below shows a protic acid.

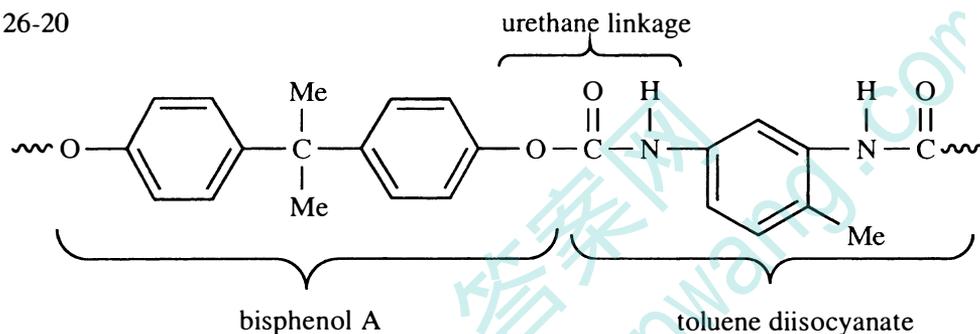


26-18



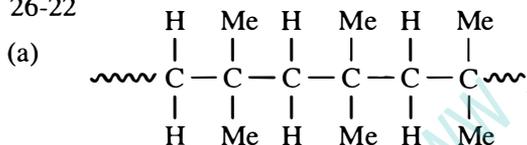
26-19 Glycerol is a trifunctional alcohol. It uses two of its OH groups in a growing chain. The third OH group cross-links with another chain. The more cross-linked a polymer, the more rigid it is.

26-20



26-21 Please refer to solution 1-20, page 12 of this Solutions Manual.

26-22



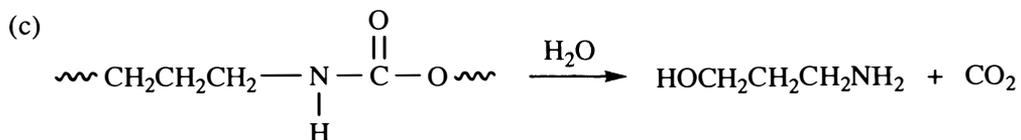
(b) Polyisobutylene is an addition polymer. No small molecule is lost, so this cannot be a condensation polymer.

(c) Either cationic polymerization or free-radical polymerization would be appropriate. The carbocation or free-radical intermediate would be 3° and therefore relatively stable. Anionic polymerization would be inappropriate as there is no electron-withdrawing group to stabilize the anion.

26-23

(a) It is a polyurethane.

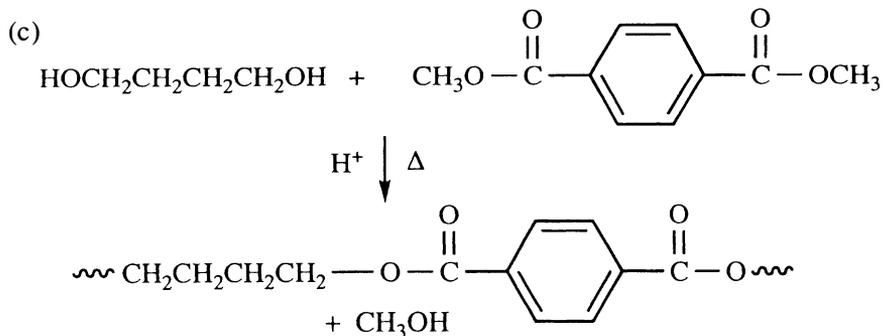
(b) As with all polyurethanes, it is a condensation polymer.



26-24

(a) It is a polyester.

(b) As with all polyesters, it is a condensation polymer.

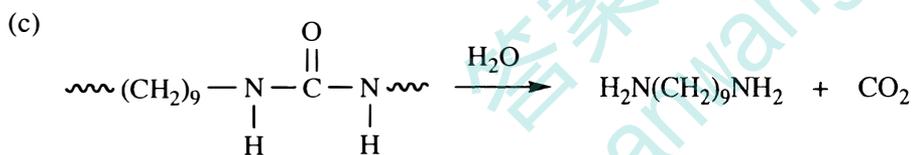


Using the dicarboxylic acid instead of the ester would produce water as the small neutral molecule lost in this condensation.

26-25

(a) Urylon® is a polyurea.

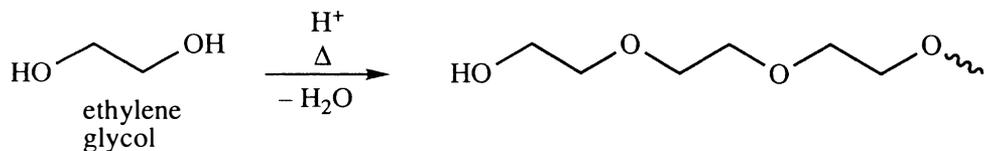
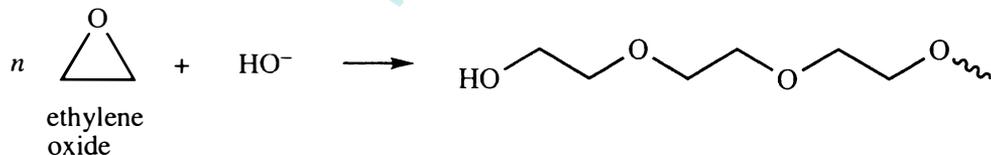
(b) A polyurea is a condensation polymer.



26-26

(a) Polyethylene glycol, abbreviated PEG, is a polyether.

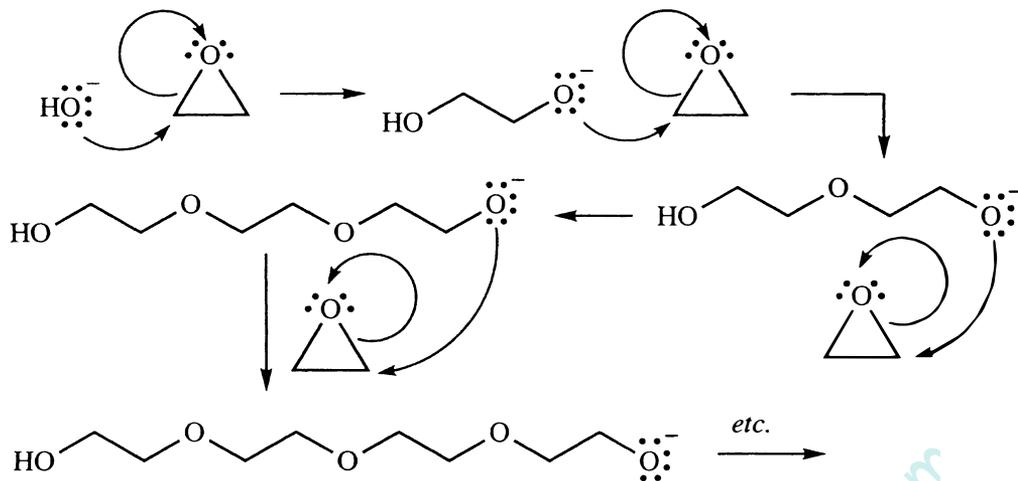
(b) PEG is usually made from ethylene oxide (first reaction shown). In theory, PEG could also be made by intermolecular dehydration of ethylene glycol (second reaction shown), but the yields are low and the chains are short.



(c) Basic catalysts are most likely as they open the epoxide to generate a new nucleophile. Acid catalysts are possible but they risk dehydration and ether cleavage.

26-26 continued

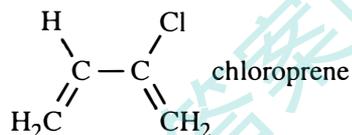
(d) Mechanism of ethylene oxide polymerization (showing hydroxide as the base):



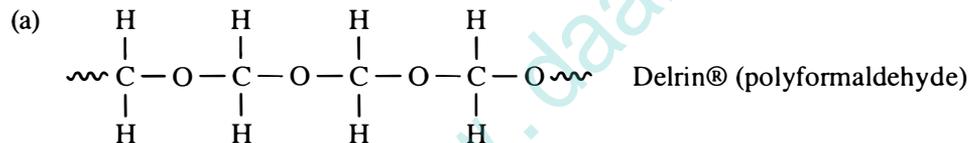
26-27

(a) Polychloroprene (Neoprene®) is an addition polymer.

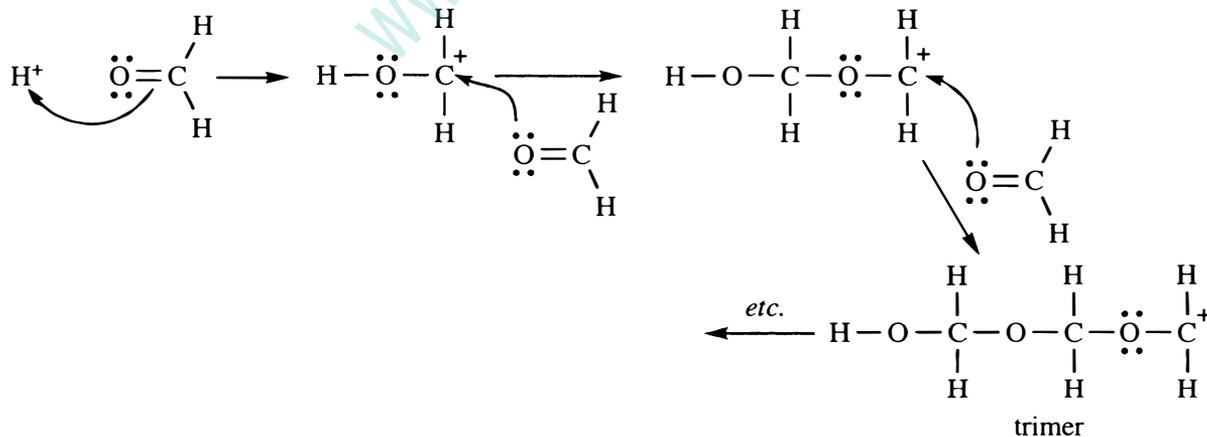
(b) Polychloroprene comes from the diene, chloroprene, just as natural rubber comes from isoprene:



26-28



(b) All of these intermediates are resonance-stabilized.



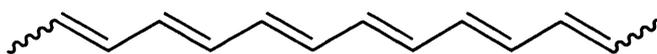
(c) Delrin® is an addition polymer; instead of adding across the double bond of an alkene, addition occurs across the double bond of a carbonyl group.

26-29

(a) *cis*



trans

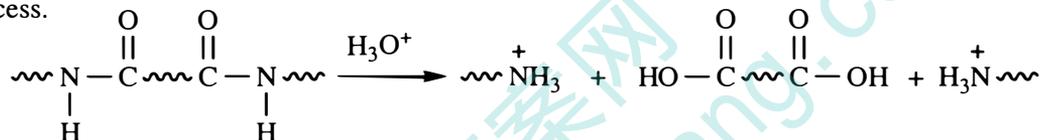


(b) Each structure has a fully conjugated chain. It is reasonable to expect electrons to be able to be transferred through the π system, just as resonance effects can work over long distances through conjugated systems.

(c) It is not surprising that the conductivity is directional. Electrons must flow along the π system of the chain, so if the chains were aligned, conductivity would be greater in the direction parallel to the polymer chains. (It is possible, though less likely, that electrons could pass from the π system of one chain to the π system of another, that is, perpendicular to the direction of the chain; we would expect reduced conductivity in that direction.)

26-30

(a) A Nylon is a polyamide. Amides can be hydrolyzed in aqueous acid, cleaving the polymer chain in the process.

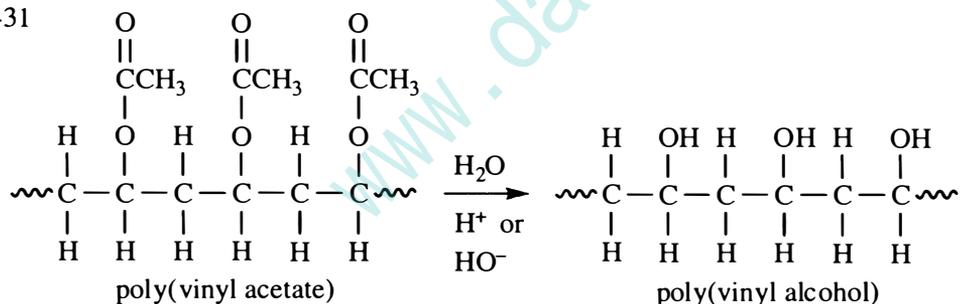


(b) A polyester can be saponified in aqueous base, cleaving the polymer chain in the process.



26-31

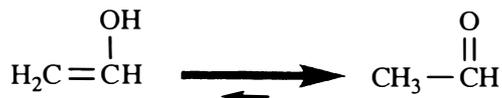
(a)

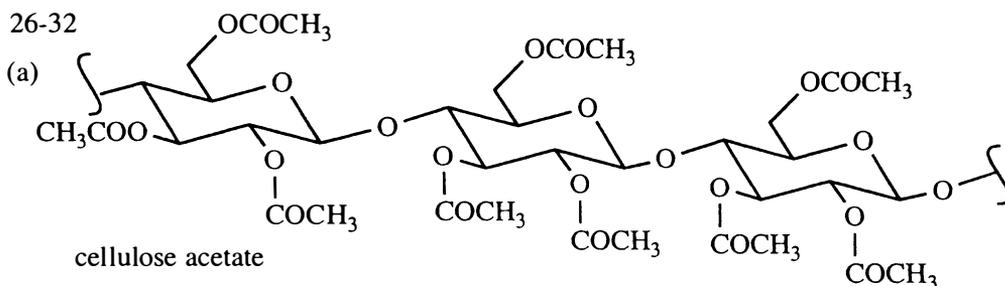


(b) A polyester is a condensation polymer in which monomer units are linked through ester groups as part of the polymer chain. Poly(vinyl acetate) is really a substituted polyethylene, an **addition** polymer, with only carbons in the chain; the ester groups are in the side chains, not in the polymer backbone.

(c) Hydrolysis of the esters in poly(vinyl acetate) does not affect the chain because the ester groups do not occur in the chain as they do in Dacron®.

(d) Vinyl alcohol cannot be polymerized because it is unstable, tautomerizing to acetaldehyde.

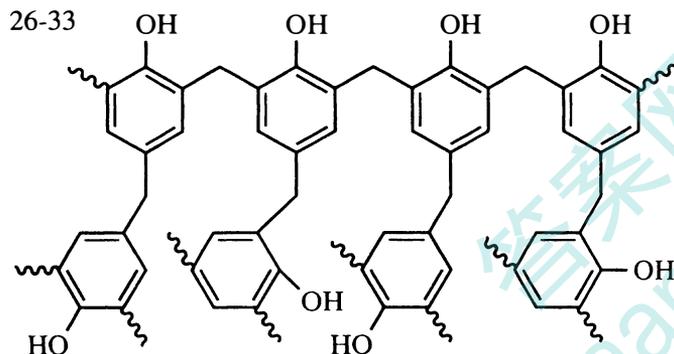




(b) Cellulose has three OH groups per glucose monomer, which form hydrogen bonds with other polar groups. Transforming these OH groups into acetates makes the polymer much less polar and therefore more soluble in organic solvents.

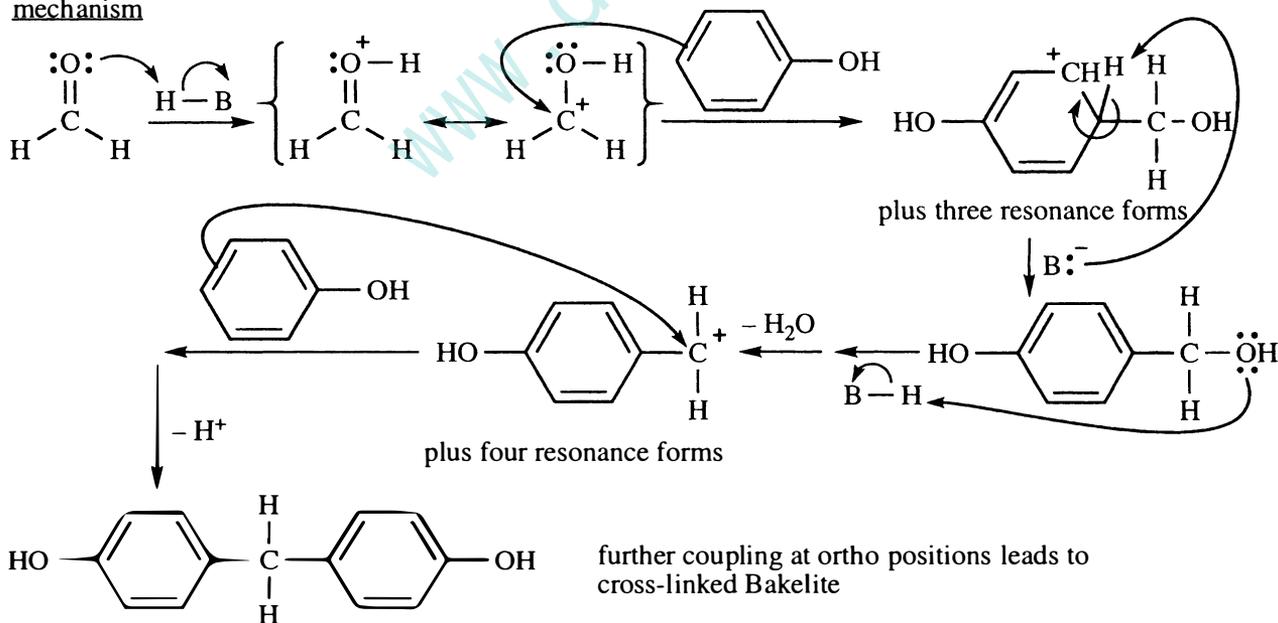
(c) The acetone dissolved the cellulose acetate in the fibers. As the acetone evaporated, the cellulose acetate remained but no longer had the fibrous, woven structure of cloth. It recrystallized as white fluff.

(d) Any article of clothing made from synthetic fibers is susceptible to the ravages of organic solvents. Solvent splashes leave dimples or blotches on Corfam shoes. (Yet, Corfam shoes could still provide protection for the toenail polish!)

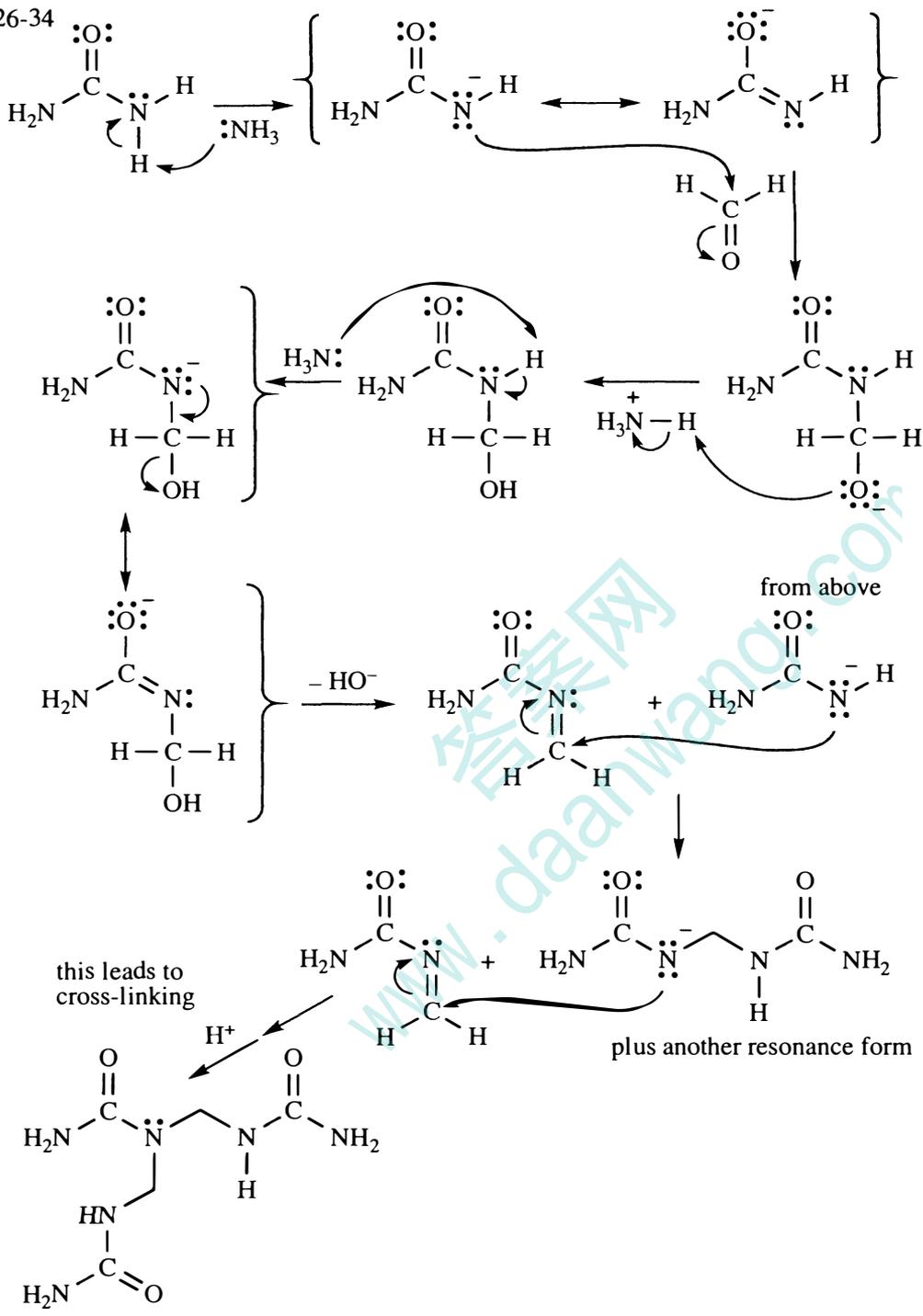


Bakelite is highly cross-linked through the ortho and para positions of phenol; each phenol can form a chain at two ring positions, then form a branch at the third position.

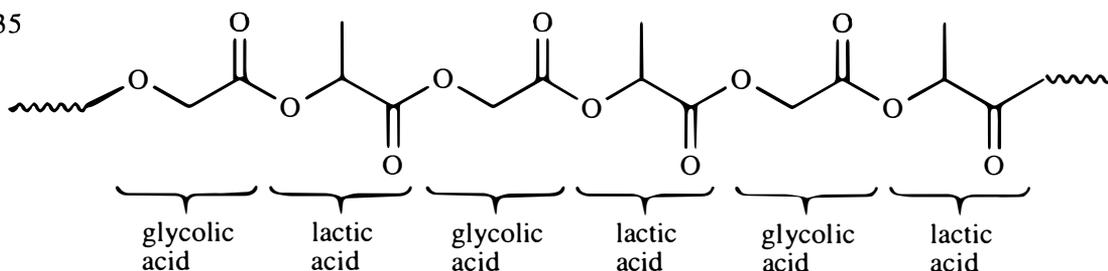
mechanism



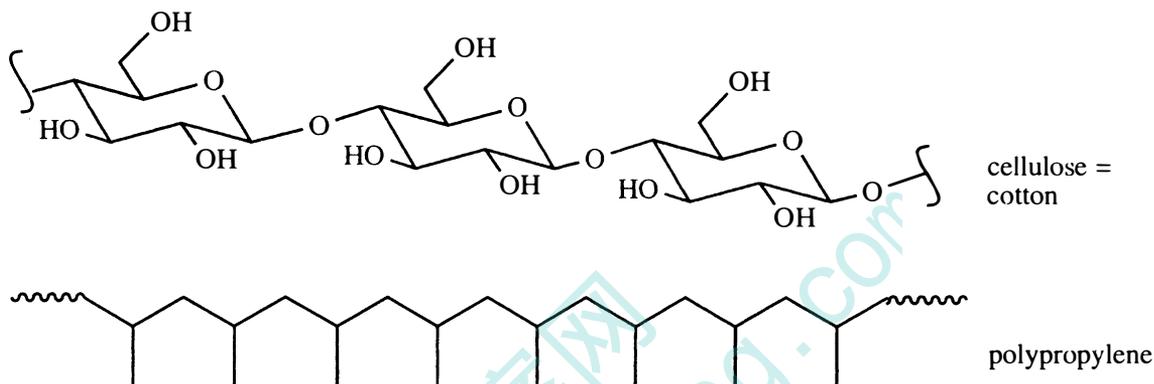
26-34



26-35



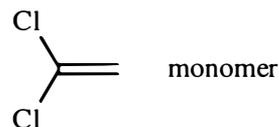
26-36



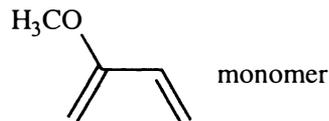
As we have seen repeatedly through this presentation of organic chemistry, physical and chemical behavior depend on *structure*. The structure of cotton, i.e. cellulose, has multiple oxygen atoms that form hydrogen bonds with water. When cotton gets wet, it holds onto the water tightly, as you have seen if you have put cotton clothes in a clothes dryer—it takes a long time to dry. Polypropylene is a hydrocarbon with no hydrogen bonding groups; the fiber feels dry because it cannot hold the water the way cotton can. Athletic garments are increasingly using polypropylene because they allow evaporation and cooling during periods of exertion; cotton is just the opposite.

26-37

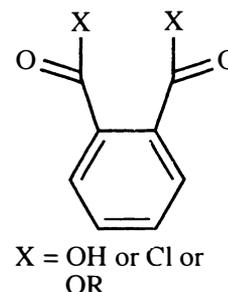
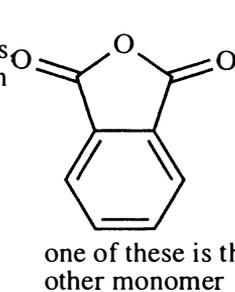
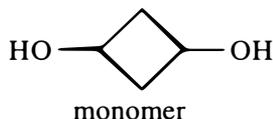
(a) This addition polymer is called polyvinylidene chloride, trade name Saran®. It could be made by any of the three mechanism types: radical, cationic, or anionic.



(b) When the substituent is on every fourth carbon, and one double bond in the chain in every 4-carbon unit, the polymer must come from addition across a diene, probably under cationic conditions.

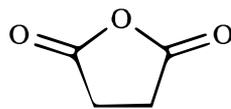


(c) This polyester is a condensation polymer of two monomers: a diol and a derivative of phthalic acid, either the anhydride, an ester, the acid chloride, or the acid itself. Heating the monomers will make the polymer; no catalyst is required if done at high temperature.

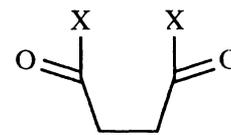


26-37 continued

(d) This polyamide (Nylon) is a condensation polymer made from two monomers, a diamine and a derivative of succinic acid, either the anhydride, an ester, the acid chloride, or the acid itself. Heating the monomers will make the polymer; no catalyst is required if done at high temperature.



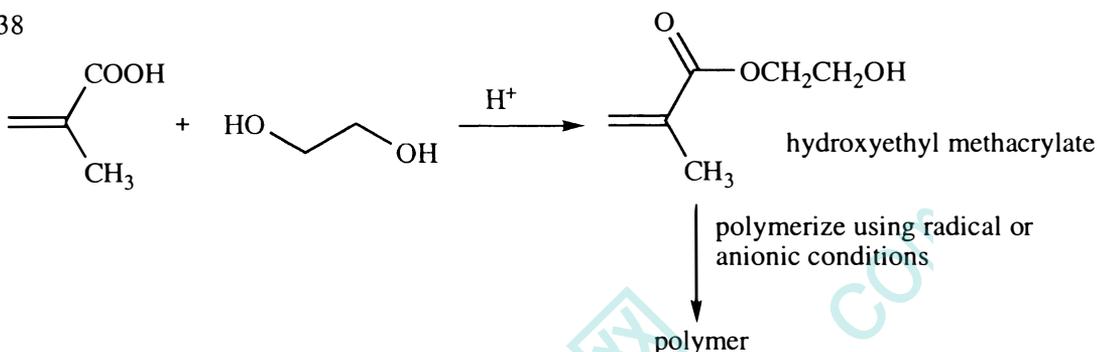
one of these is the other monomer



X = OH or Cl or OR

26-38

(a)



(b) This polymer has a few properties that make it useful as the material in soft, extended-wear contact lenses. First, carboxylic acids usually are crystalline solids with high melting points, but esters and alcohols are low melting, often liquids, so the polymer with this ester is softer than the carboxylic acid or even the methyl ester. (The methyl ester, polymethyl methacrylate or Plexiglas, was the first material used in the original hard contact lenses.) Second, the ability of the free OH to form hydrogen bonds with water makes the contact lens more fluid and less irritating to the cornea. Third, a hidden advantage but very important for ocular health: the fluidity of the contact lens also permits oxygen to go through the lens. Because the cornea does not have a large blood flow, it needs to absorb oxygen from the air to maintain its health, and this enhanced gas permeability permits the contact lens to be worn for days at a time without compromising the health of the cornea. Thanks, polymers!

Note to the student: BON VOYAGE!
I hope you have enjoyed your travels
through organic chemistry.
Jan Simek

Appendix 1—Summary of IUPAC Nomenclature of Organic Compounds

Introduction

The purpose of the IUPAC system of nomenclature is to establish an international standard of naming compounds to facilitate communication. The goal of the system is to give each structure a unique and unambiguous name, and to correlate each name with a unique and unambiguous structure.

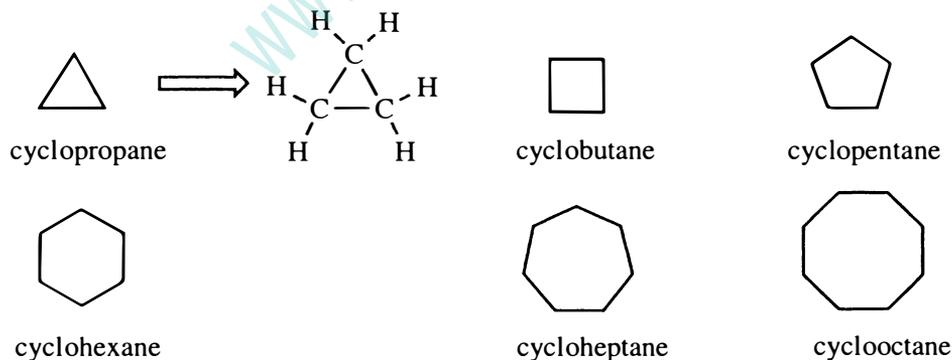
I. Fundamental Principle

IUPAC nomenclature is based on naming a molecule's longest chain of carbons connected by single bonds, whether in a continuous chain or in a ring. All deviations, either multiple bonds or atoms other than carbon and hydrogen, are indicated by prefixes or suffixes according to a specific set of priorities.

II. Alkanes and Cycloalkanes (also called "aliphatic" compounds)

Alkanes are the family of saturated hydrocarbons, that is, molecules containing carbon and hydrogen connected by single bonds only. These molecules can be in continuous chains (called linear or acyclic), or in rings (called cyclic or alicyclic). The names of alkanes and cycloalkanes are the root names of organic compounds. Beginning with the five-carbon alkane, the number of carbons in the chain is indicated by the Greek or Latin prefix. Rings are designated by the prefix "cyclo". (In the geometrical symbols for rings, each apex represents a carbon with the number of hydrogens required to fill its valence.)

C ₁	CH ₄	methane	C ₁₂	CH ₃ [CH ₂] ₁₀ CH ₃	dodecane
C ₂	CH ₃ CH ₃	ethane	C ₁₃	CH ₃ [CH ₂] ₁₁ CH ₃	tridecane
C ₃	CH ₃ CH ₂ CH ₃	propane	C ₁₄	CH ₃ [CH ₂] ₁₂ CH ₃	tetradecane
C ₄	CH ₃ [CH ₂] ₂ CH ₃	butane	C ₂₀	CH ₃ [CH ₂] ₁₈ CH ₃	icosane
C ₅	CH ₃ [CH ₂] ₃ CH ₃	pentane	C ₂₁	CH ₃ [CH ₂] ₁₉ CH ₃	hencicosane
C ₆	CH ₃ [CH ₂] ₄ CH ₃	hexane	C ₂₂	CH ₃ [CH ₂] ₂₀ CH ₃	docosane
C ₇	CH ₃ [CH ₂] ₅ CH ₃	heptane	C ₂₃	CH ₃ [CH ₂] ₂₁ CH ₃	tricosane
C ₈	CH ₃ [CH ₂] ₆ CH ₃	octane	C ₃₀	CH ₃ [CH ₂] ₂₈ CH ₃	triacontane
C ₉	CH ₃ [CH ₂] ₇ CH ₃	nonane	C ₃₁	CH ₃ [CH ₂] ₂₉ CH ₃	hentriacontane
C ₁₀	CH ₃ [CH ₂] ₈ CH ₃	decane	C ₄₀	CH ₃ [CH ₂] ₃₈ CH ₃	tetracontane
C ₁₁	CH ₃ [CH ₂] ₉ CH ₃	undecane	C ₅₀	CH ₃ [CH ₂] ₄₈ CH ₃	pentacontane



The IUPAC system of nomenclature is undergoing many changes, most notably in the placement of position numbers. The new system places the position number close to the functional group designation; however, you should be able to use and recognize names in either the old or the new style. Ask your instructor which system to use.

Appendix 1, Summary of IUPAC Nomenclature, continued

III. Nomenclature of Molecules Containing Substituents and Functional Groups

A. Priorities of Substituents and Functional Groups

LISTED HERE FROM HIGHEST TO LOWEST PRIORITY, except that the substituents within Group C have equivalent priority.

Group A—Functional Groups Named By Prefix Or Suffix

Functional Group	Structure	Prefix	Suffix
Carboxylic Acid	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{OH} \end{array}$	carboxy-	-oic acid (-carboxylic acid)
Aldehyde	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{H} \end{array}$	oxo- (formyl)	-al (carbaldehyde)
Ketone	$\begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{R} \end{array}$	oxo-	-one
Alcohol	$\text{R}-\text{O}-\text{H}$	hydroxy-	-ol
Amine	$\text{R}-\text{N} \begin{array}{l} / \\ \backslash \end{array}$	amino-	-amine

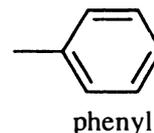
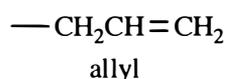
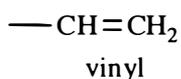
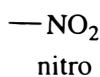
Group B—Functional Groups Named By Suffix Only

Functional Group	Structure	Prefix	Suffix
Alkene	$\begin{array}{c} \diagup \quad \diagdown \\ \text{C}=\text{C} \\ \diagdown \quad \diagup \end{array}$	-----	-ene
Alkyne	$-\text{C}\equiv\text{C}-$	-----	-yne

Group C—Substituent Groups Named By Prefix Only

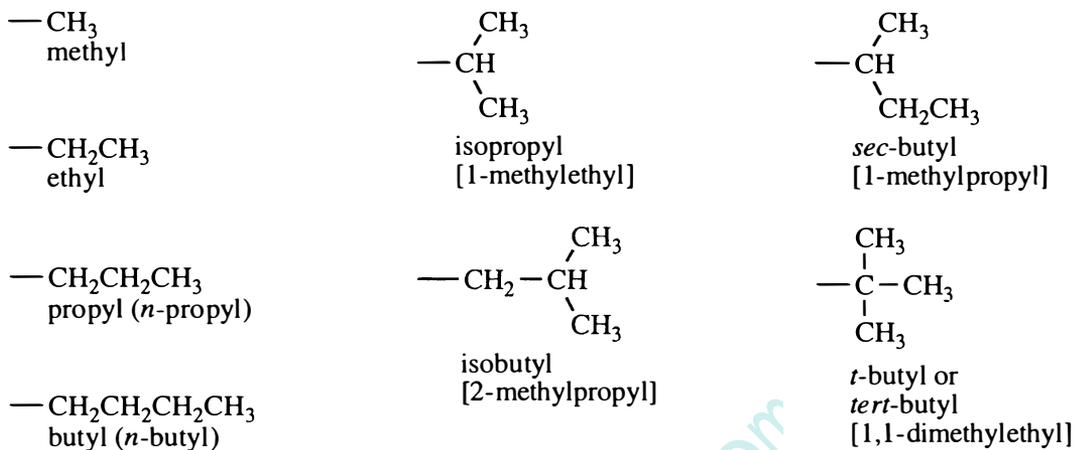
Substituent	Structure	Prefix	Suffix
Alkyl (see next page)	$\text{R}-$	alkyl-	-----
Alkoxy	$\text{R}-\text{O}-$	alkoxy-	-----
<i>(alkoxy groups take the name of the alkyl group, like methyl or ethyl, drop the "yl", and add "oxy"; CH₃O is methoxy; CH₃CH₂O is ethoxy)</i>			
Halogen	$\text{F}-$	fluoro-	-----
	$\text{Cl}-$	chloro-	-----
	$\text{Br}-$	bromo-	-----
	$\text{I}-$	iodo-	-----

Miscellaneous substituents and their prefixes



Appendix 1, Summary of IUPAC Nomenclature, continued

Common alkyl groups—replace "ane" ending of alkane name with "yl". Alternate names for complex substituents are given in brackets.



B. Naming Substituted Alkanes and Cycloalkanes—Group C Substituents Only

Organic compounds containing substituents from Group C are named following this sequence of steps, as indicated on the examples below:

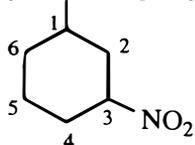
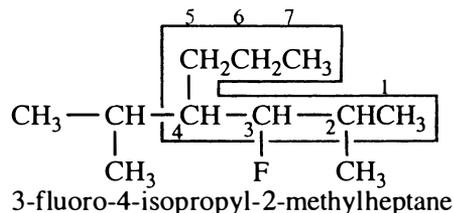
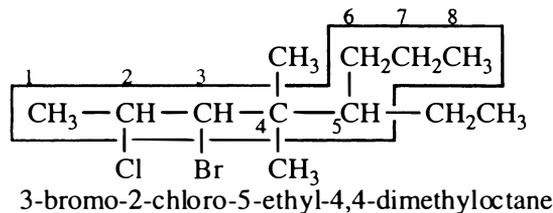
•Step 1. Find the longest continuous carbon chain. Determine the root name for this parent chain. In cyclic compounds, the ring is usually considered the parent chain, unless it is attached to a longer chain of carbons; indicate a ring with the prefix "cyclo" before the root name. (When there are two longest chains of equal length, use the chain with the greater number of substituents.)

•Step 2. Number the chain in the direction such that the position number of the first substituent is the smaller number. If the first substituents have the same number, then number so that the second substituent has the smaller number, *etc.*

•Step 3. Determine the name and position number of each substituent. (A substituent on a nitrogen is designated with an "N" instead of a number; see Section III.D.1. below.)

•Step 4. Indicate the number of identical groups by the prefixes di, tri, tetra, *etc.*

•Step 5. Place the position numbers and names of the substituent groups, in alphabetical order, before the root name. In alphabetizing, ignore prefixes like *sec*-, *tert*-, di, tri, *etc.*, but include iso and cyclo. Always include a position number for each substituent, regardless of redundancies.



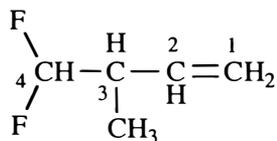
1-*sec*-butyl-3-nitrocyclohexane
(numbering determined by the alphabetical order of substituents, "b" comes before "n")

Appendix 1, Summary of IUPAC Nomenclature, continued

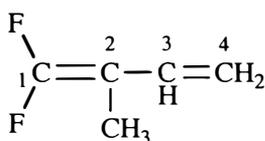
C. Naming Molecules Containing Functional Groups from Group B—Suffix Only

1. Alkenes—Follow the same steps as for alkanes, except:

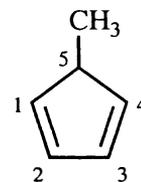
- Number the chain of carbons *that includes the C=C* so that the C=C has the lower position number, since it has a higher priority than any substituents;
- Change "ane" to "ene" and assign a position number to the first carbon of the C=C; place the position number just before the name of functional group(s);
- Designate geometrical isomers with a *cis,trans* or *E,Z* prefix.



4,4-difluoro-3-methylbut-1-ene

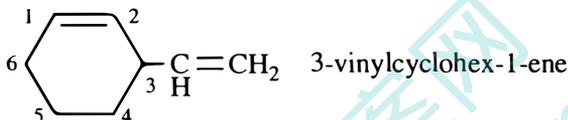


1,1-difluoro-2-methylbuta-1,3-diene



5-methylcyclopenta-1,3-diene

Special case: When the chain cannot include an alkene, a substituent name is used. See Section V.A.2.a.

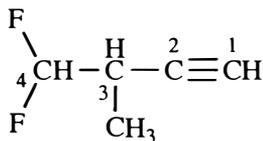


Numbering must be on EITHER a ring OR a chain, but not both.

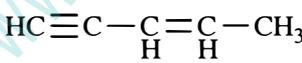
2. Alkynes—Follow the same steps as for alkanes, except:

- Number the chain of carbons *that includes the C≡C* so that the alkyne has the lower position number;
- Change "ane" to "yne" and assign a position number to the first carbon of the C≡C; place the position number just before the name of functional group(s).

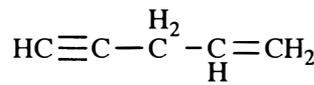
Note: The Group B functional groups (alkene and alkyne) are considered to have equal priority: in a molecule with both an ene and an yne, whichever is closer to the end of the chain determines the direction of numbering. In the case where each would have the same position number, the alkene takes the lower number. In the name, "ene" comes before "yne" because of alphabetization.



4,4-difluoro-3-methylbut-1-yne



pent-3-en-1-yne
("yne" closer to end of chain)



pent-1-en-4-yne
("ene" and "yne" have equal priority unless they have the same position number, when "ene" takes the lower number)

(Notes: 1. An "e" is dropped if the letter following it is a vowel: "pent-3-en-1-yne", not "pent-3-ene-1-yne". 2. An "a" is added if inclusion of di, tri, etc., would put two consonants together: "buta-1,3-diene", not "but-1,3-diene".)

D. Naming Molecules Containing Functional Groups from Group A—Prefix or Suffix

In naming molecules containing one or more of the functional groups in Group A, the group of highest priority is indicated by suffix; the others are indicated by prefix, with priority equivalent to any other substituents. The table in Section III.A. defines the priorities; they are discussed on the following pages in order of increasing priority.

Appendix 1, Summary of IUPAC Nomenclature, continued

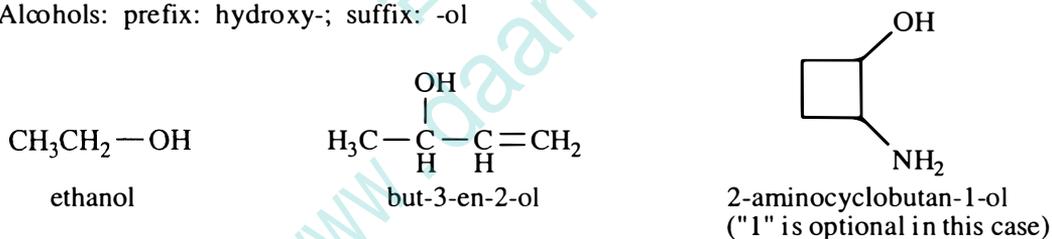
Now that the functional groups and substituents from Groups A, B, and C have been described, a modified set of steps for naming organic compounds can be applied to all simple structures:

- Step 1. Find the highest priority functional group. Determine and name the longest continuous carbon chain that includes this group.
- Step 2. Number the chain so that the highest priority functional group is assigned the lower number. (The number "1" is often omitted when there is no confusion about where the group must be. Aldehydes and carboxylic acids must be at the first carbon of a chain, so a "1" is rarely used with those functional groups.)
- Step 3. If the carbon chain includes multiple bonds (Group B), replace "ane" with "ene" for an alkene or "yne" for an alkyne. Designate the position of the multiple bond with the number of the first carbon of the multiple bond.
- Step 4. If the molecule includes Group A functional groups, replace the last "e" with the suffix of the highest priority functional group, and include its position number just before the name of the highest priority functional group.
- Step 5. Indicate all Group C substituents, and Group A functional groups of lower priority, with a prefix. Place the prefixes, with appropriate position numbers, in alphabetical order before the root name.

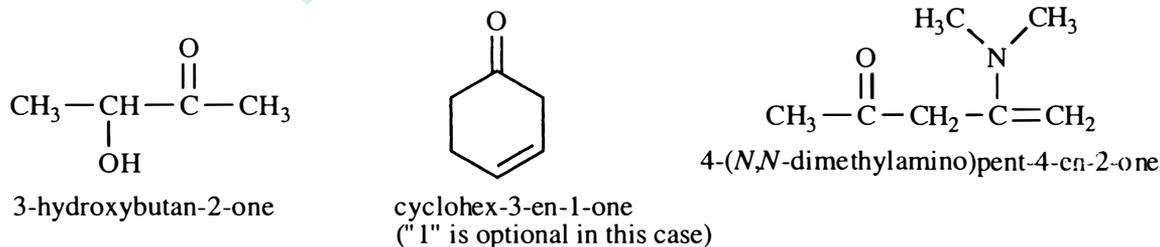
1. Amines: prefix: amino-; suffix: -amine—substituents on nitrogen denoted by "N"



2. Alcohols: prefix: hydroxy-; suffix: -ol

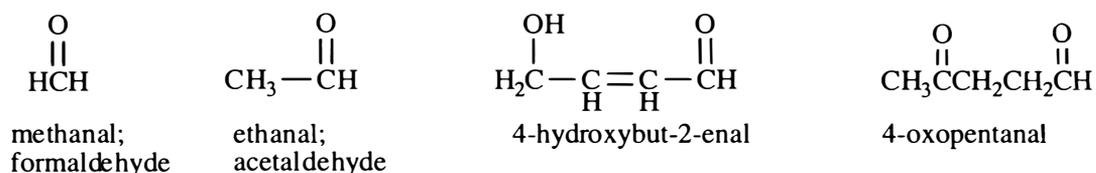


3. Ketones: prefix: oxo-; suffix: -one (pronounced "own")



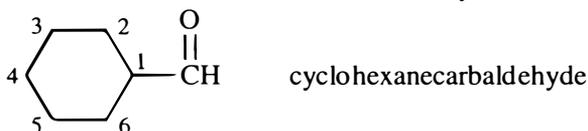
4. Aldehydes: prefix: oxo-, or formyl- (O=CH-); suffix: -al (abbreviation: —CHO)

An aldehyde can only be on carbon 1, so the "1" is generally omitted from the name.



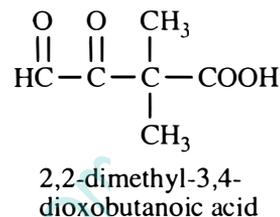
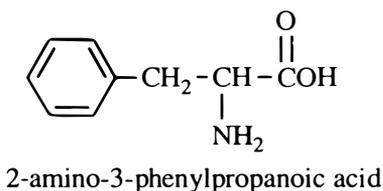
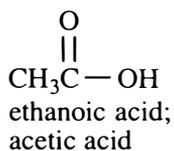
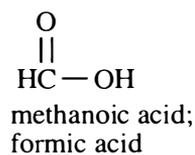
Appendix 1, Summary of IUPAC Nomenclature, continued

Special case: When the chain cannot include the carbon of the aldehyde, the suffix "carbaldehyde" is used:

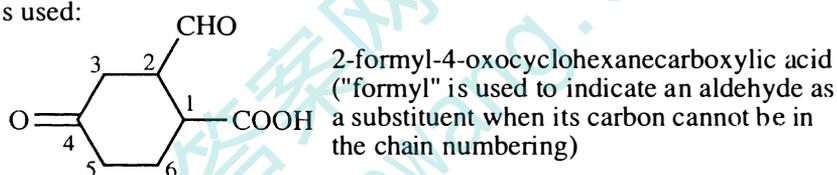


5. Carboxylic Acids: prefix: carboxy-; suffix: -oic acid (abbreviation: —COOH)

A carboxylic acid can only be on carbon 1, so the "1" is generally omitted from the name. (Note: Chemists traditionally use, and IUPAC accepts, the names "formic acid" and "acetic acid" in place of "methanoic acid" and "ethanoic acid".)



Special case: When the chain numbering cannot include the carbon of the carboxylic acid, the suffix "carboxylic acid" is used:



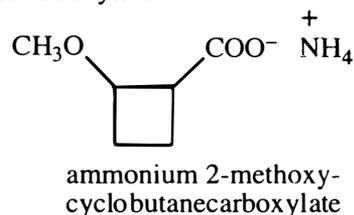
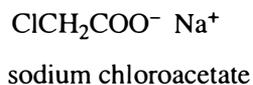
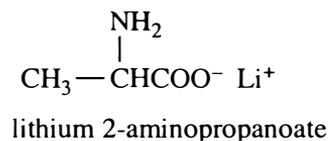
E. Naming Carboxylic Acid Derivatives

The six common groups derived from carboxylic acids are, in decreasing priority after carboxylic acids: salts, anhydrides, esters, acyl halides, amides, and nitriles.

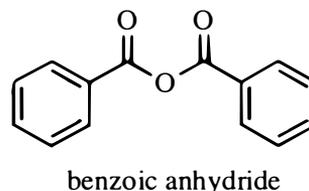
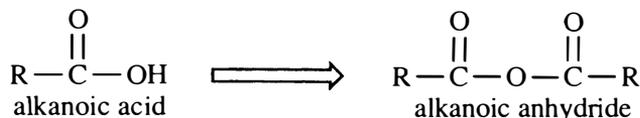
1. Salts of Carboxylic Acids

Salts are named with cation first, followed by the anion name of the carboxylic acid, where "ic acid" is replaced by "ate" :

acetic acid becomes acetate
butanoic acid becomes butanoate
cyclohexanecarboxylic acid becomes cyclohexanecarboxylate



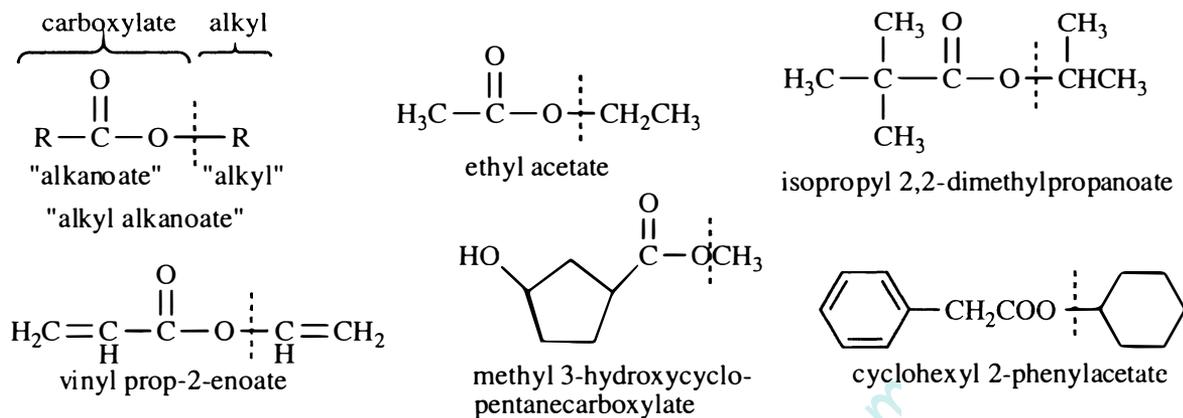
2. Anhydrides: "oic acid" is replaced by "oic anhydride"



Appendix 1, Summary of IUPAC Nomenclature, continued

3. Esters

Esters are named as "organic salts" that is, the alkyl name comes first, followed by the name of the carboxylate anion. (common abbreviation: —COOR)



4. Acyl Halides: "oic acid" is replaced by "oyl halide"



5. Amides: "oic acid" is replaced by "amide"



Amides are notable for their role in biochemistry, i.e., the special amide bond between two amino acids is called a peptide bond.

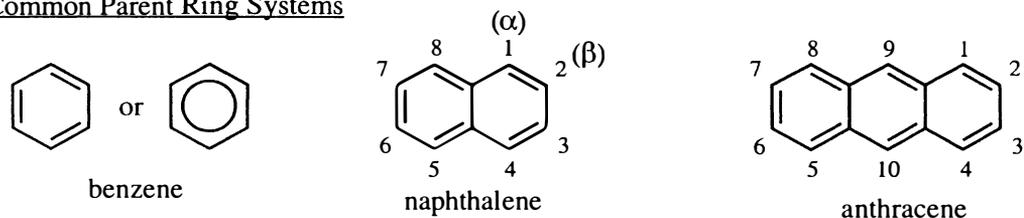
6. Nitriles: "oic acid" is replaced by "nitrile"



IV. Nomenclature of Aromatic Compounds

"Aromatic" compounds are those derived from benzene and similar ring systems. As with aliphatic nomenclature described above, the process is: determining the root name of the parent ring; determining priority, name, and position number of substituents; and assembling the name in alphabetical order. *Functional group priorities are the same in aliphatic and aromatic nomenclature.* See p. 676 for the list of priorities.

A. Common Parent Ring Systems



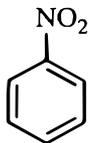
Appendix 1, Summary of IUPAC Nomenclature, continued

B. Monosubstituted Benzenes

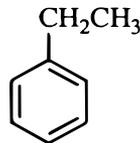
1. Most substituents keep their designation, followed by the word "benzene":



chlorobenzene

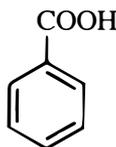


nitrobenzene

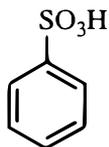


ethylbenzene

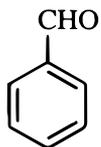
2. Some common substituents change the root name of the ring. IUPAC accepts these as root names, listed here in decreasing priority (same as Group A, p. 676):



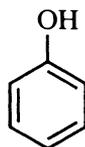
benzoic acid



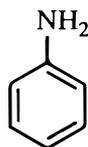
benzene-sulfonic acid



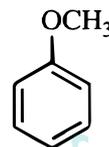
benzaldehyde



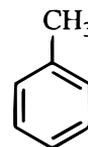
phenol



aniline



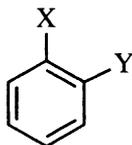
anisole



toluene

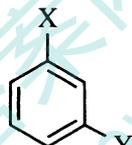
C. Disubstituted Benzenes

1. Designation of substitution—only three possibilities:

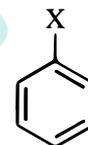


common:
IUPAC:

ortho- (*o-*)
1,2-



meta- (*m-*)
1,3-

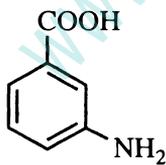


para- (*p-*)
1,4-

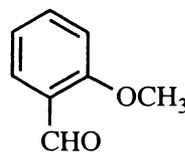
2. Naming disubstituted benzenes—Priorities from Group A, p. 676, determine root name and substituents



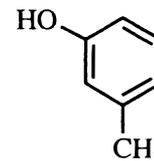
p-dibromobenzene
1,4-dibromobenzene



m-aminobenzoic acid
3-aminobenzoic acid

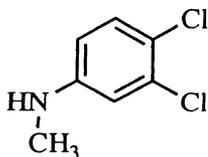


o-methoxybenzaldehyde
2-methoxybenzaldehyde

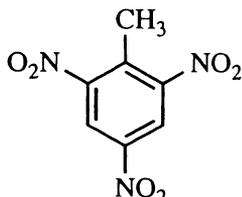


m-methylphenol
3-methylphenol

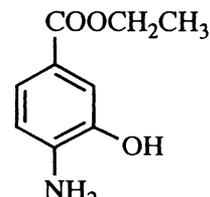
D. Polysubstituted Benzenes—must use numbers to indicate substituent position



3,4-dichloro-*N*-methylaniline



2,4,6-trinitrotoluene
(TNT)

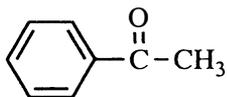


ethyl 4-amino-3-hydroxybenzoate

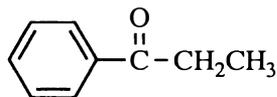
Appendix 1, Summary of IUPAC Nomenclature, continued

E. Aromatic Ketones

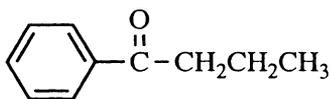
A special group of aromatic compounds are ketones where the carbonyl is attached to at least one benzene ring. Such compounds are named as "phenones", the prefix depending on the size and nature of the group on the other side of the carbonyl. These are the common examples:



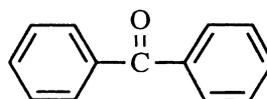
acetophenone



propiophenone



butyrophenone



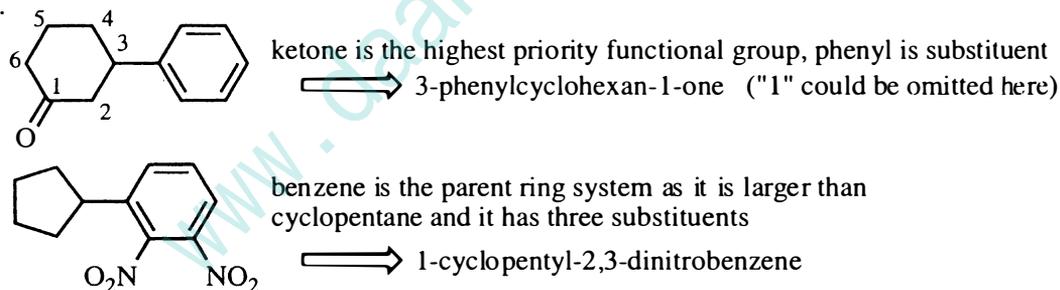
benzophenone

V. Nomenclature of Bicyclic Compounds

"Bicyclic" compounds are those that contain two rings. There are four possible arrangements of two rings that depend on how many atoms are shared by the two rings. The first arrangement in which the rings do not share any atoms does not use any special nomenclature, but the other types require a method to designate how the rings are put together. Once the ring system is named, then functional groups and substituents follow the standard rules described above.

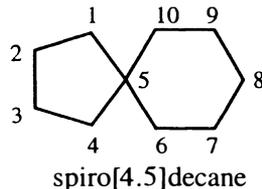
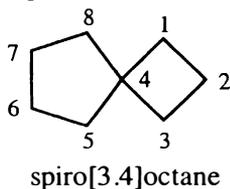
Type 1. Two rings with no common atoms

These follow the standard rules of choosing one parent ring system and describing the other ring as a substituent.



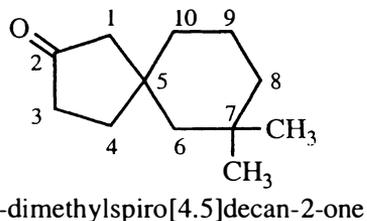
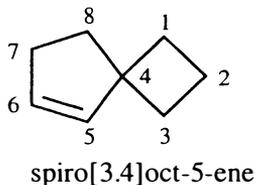
Type 2. Two rings with one common atom—spiro ring system

The ring system in spiro compounds is indicated by the word "spiro" (instead of "cyclo"), followed by brackets indicating how many atoms are contained in each path around the rings, ending with the alkane name describing how many carbons are in the ring systems including the spiro carbon. (If any atoms are not carbons, see section VI.) Numbering follows the smaller path first, passing through the spiro carbon and around the second ring.



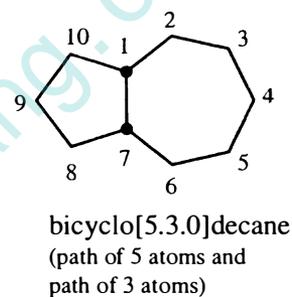
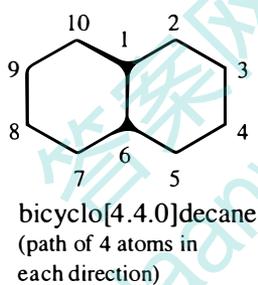
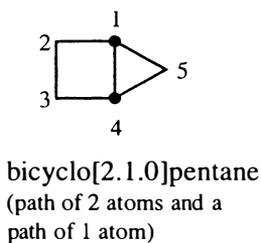
Appendix 1, Summary of IUPAC Nomenclature, continued

Substituents and functional groups are indicated in the usual ways. Spiro ring systems are always numbered smaller before larger, and numbered in such a way as to give the highest priority functional group the lower position number.



Type 3. Two rings with two common atom—fused ring system

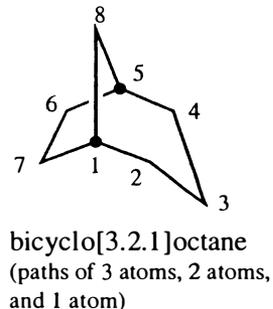
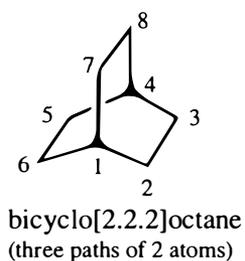
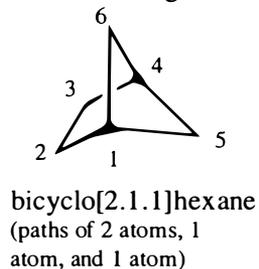
Two rings that share two common atoms are called fused rings. This ring system and the next type called bridged rings share the same designation of ring system. Each of the two common atoms is called a bridgehead atom, and there are three paths between the two bridgehead atoms. In contrast with naming the spiro rings, the *longer* path is counted first, then the shorter, then the shortest. In fused rings, the shortest path is always a zero, meaning zero atoms between the two bridgehead atoms. Numbering starts at a bridgehead, continues around the largest ring, through the other bridgehead and around the shorter ring. (In these structures, bridgeheads are marked with a dark circle for clarity.)



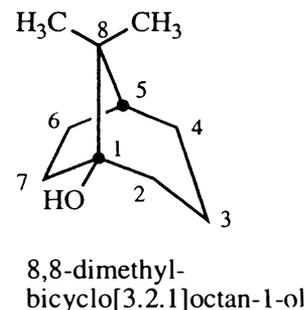
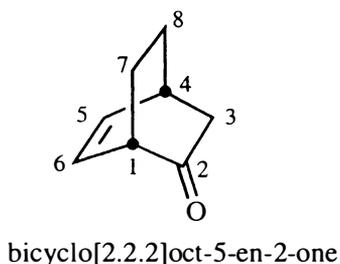
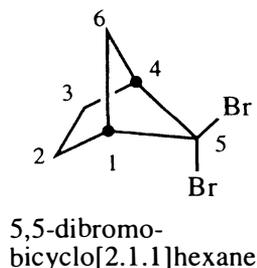
Substituents and functional groups are indicated in the usual ways. Fused rings systems are always numbered larger before smaller, and numbered in such a way as to give the highest priority functional group the lower position number.

Type 4. Two rings with more than two common atom—bridged ring system

Two rings that share more than two common atoms are called bridged rings. Bridged rings share the same designation of ring system as Type 3 in which there are three paths between the two bridgehead atoms. The longer path is counted first, then the medium, then the shortest. Numbering starts at a bridgehead, continues around the largest ring, through the other bridgehead and around the medium path, ending with the shortest path numbered from the original bridgehead atom. (In these structures, bridgeheads are marked with a dark circle for clarity.)



Appendix 1, Summary of IUPAC Nomenclature, continued



VI. Replacement Nomenclature of Heteroatoms

The term "heteroatom" applies to any atom other than carbon or hydrogen. It is common for heteroatoms to appear in locations that are inconvenient to name following basic rules, so a simple system called "replacement nomenclature" has been devised. The fundamental principle is to name a compound as if it contained only carbons in the skeleton, plus any functional groups or substituents, and then indicate which carbons are "replaced" by heteroatoms. The prefixes used to indicate these substitutions are listed here *in decreasing priority and listed in this order in the name*:

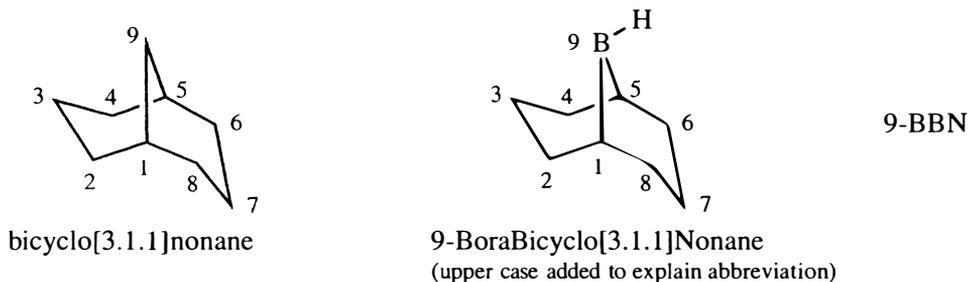
Element	Prefix	Example
O	oxa	
S	thia	
N	aza	
P	phospha	
Si	sila	
B	bora	

In the above example, note that the (imaginary) compound no longer has nine carbons, even though the name still includes "nonan". The heteroatoms have replaced carbons, but the compound is named as if it still had those carbons.

Where the replacement system is particularly useful is in polycyclic compounds. Shown below are three examples of commercially available and synthetically useful reagents that use this system.

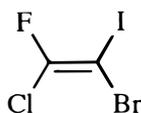
parent hydrocarbon	reagent	abbreviation
<p>bicyclo[2.2.2]octane</p>	<p>1,4-DiAzaBiCyclo[2.2.2]Octane (upper case added to explain abbreviation)</p>	DABCO
<p>bicyclo[5.4.0]undec-7-ene</p>	<p>1,8-DiazaBicyclo[5.4.0]Undec-7-ene (upper case added to explain abbreviation)</p>	DBU

Appendix 1, Summary of IUPAC Nomenclature, continued

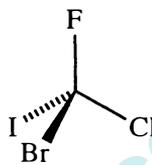


VII. Designation of Stereochemistry; Cahn-Ingold-Prelog system

Is this alkene cis or trans?

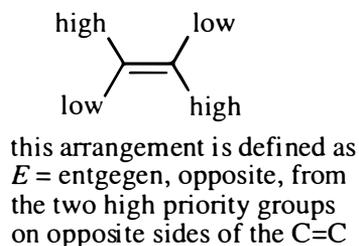
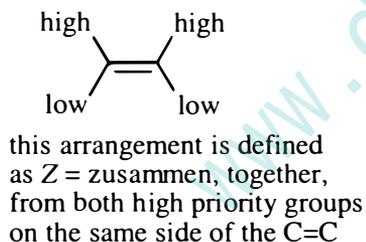


How can we distinguish this structure from its mirror image?

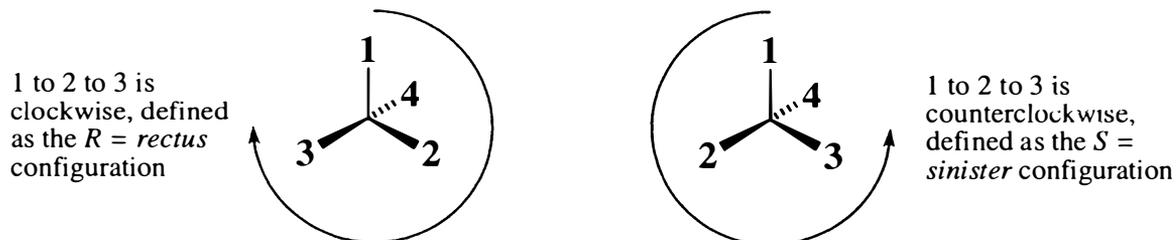


Compounds that exhibit stereoisomerism, whether geometric isomers around double bonds, substituent groups on rings, or molecules with asymmetric tetrahedral atoms (which are almost always carbons), require a system to designate relative and absolute orientation of the groups. The terms *cis/trans*, *D/L* in carbohydrates and amino acids, and *d/l* for optically active compounds, are limited and cannot be used generally, although each still is used in appropriate situations. For example, *cis/trans* still is used to indicate relative positions of substituents around a ring.

A system developed by chemists Cahn, Ingold, and Prelog, uses a series of steps to determine group priorities, and a definition of position based on the relative arrangement of the groups. In alkenes, the system is relatively simple:



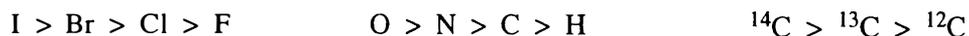
As with alkenes, the orientation around an asymmetric carbon can be only one of two choices. In three dimensions, clockwise and counterclockwise are the only two directions that are definite, and even that description requires a fixed reference point. To designate configuration, the lowest (fourth) priority group is always placed farthest away from the viewer (indicated by a dashed line), and the group priorities will follow 1 to 2 to 3 in either a clockwise or a counterclockwise direction.



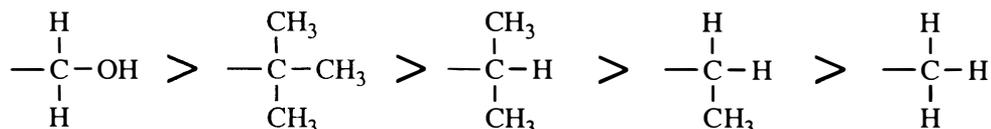
Appendix 1, Summary of IUPAC Nomenclature, continued

The only step remaining is to determine the priority of groups, for which there is a carefully defined set of rules.

Rule 1. Consider the first atom of the group, the point of attachment. Atoms with higher atomic number receive higher priority. Heavier isotopes have higher priority than lighter isotopes.

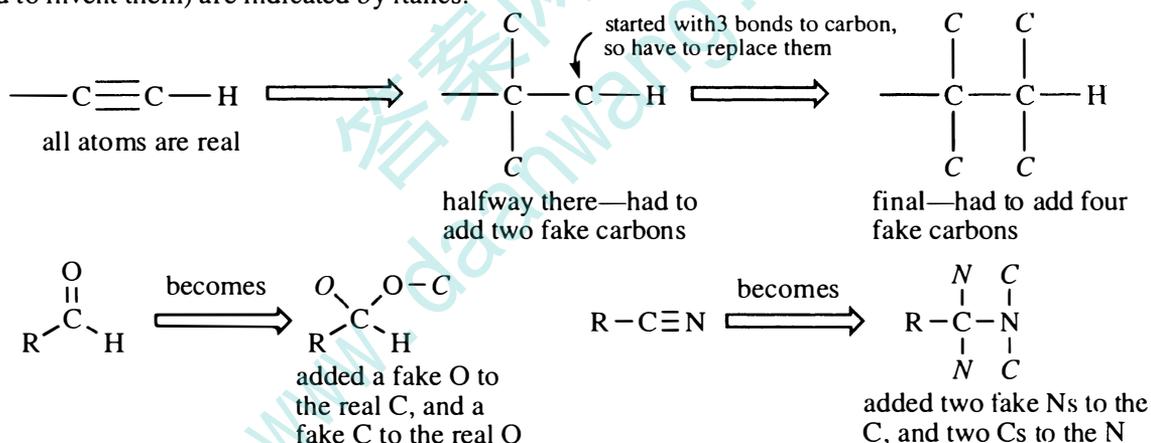


Rule 2. If the first atoms of two or more groups are the same, go out to the next atoms to break the tie. One high priority atom takes priority over any number of lower-priority atoms.

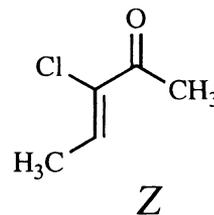
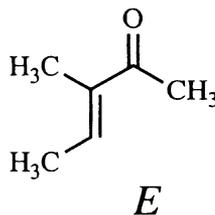
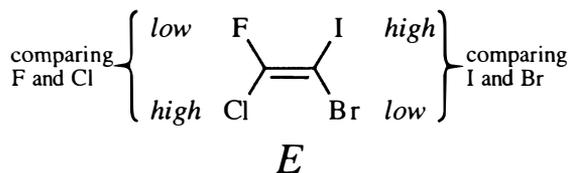


Rule 3. Treat multiple bonds as if they were all single bonds; one will be to the real atom, the others will be to imaginary atoms.

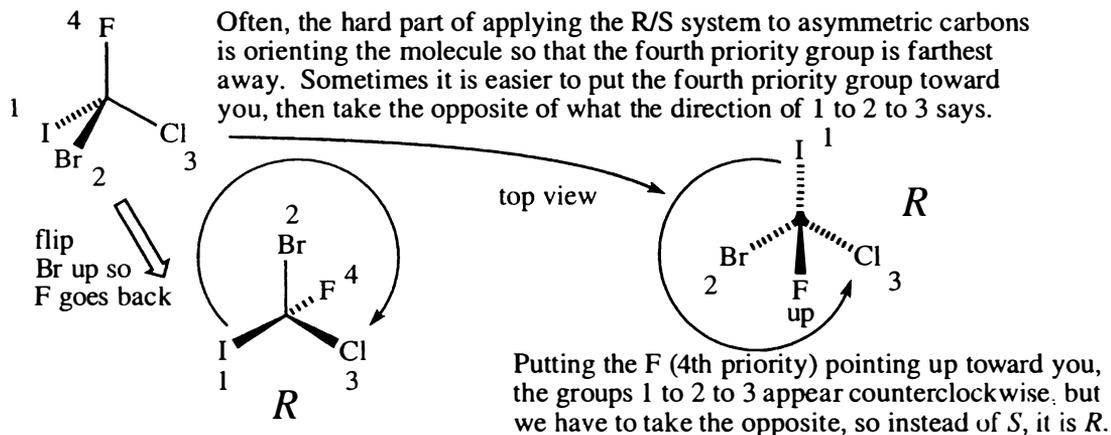
This is the hardest rule to put into practice. This example of an alkyne shows stepwise how to accomplish this. In the pictures, imaginary atoms (ones that did not start out in the structure, we had to invent them) are indicated by italics.



Examples applying the Cahn-Ingold-Prelog system



Appendix 1, Summary of IUPAC Nomenclature, continued

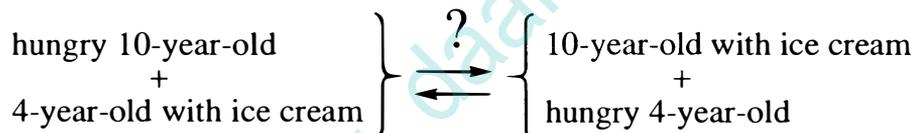


Appendix 2: Summary of Acidity and Basicity

Imagine that you are at a family reunion where you can observe the competition for ice cream cones among your nieces and nephews. Pretty soon, you formulate a generalization: the older kids can hold onto their ice cream cones more strongly than the younger ones. Another way of saying it is that the older ones are less likely to give up their cones. You could even represent this information in a table showing a series of equilibria between the child with ice cream, and the free ice cream plus the hungry child. The differences in strength could also be quantitated: the larger the hunger factor, pK_H , the less likely the child will give up the ice cream.

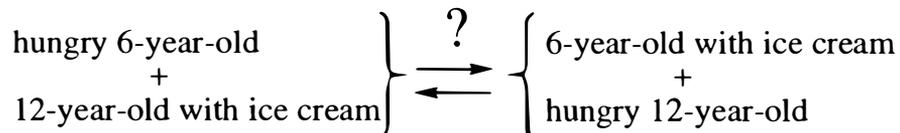
<u>pK_H</u>	<u>Approximate pK_H Values of Children</u>		
12	12-year-old with ice cream	\rightleftharpoons	ice cream + hungry 12-year-old
10	10-year-old with ice cream	\rightleftharpoons	ice cream + hungry 10-year-old
8	8-year-old with ice cream	\rightleftharpoons	ice cream + hungry 8-year-old
6	6-year-old with ice cream	\rightleftharpoons	ice cream + hungry 6-year-old
4	4-year-old with ice cream	\rightleftharpoons	ice cream + hungry 4-year-old

What good is this table? It allows anyone to make predictions about what will happen when kids with ice cream are mixed with hungry kids.



If the hungry 10-year-old was left unattended in a room with the 4-year-old with ice cream, which side of this equilibrium would be favored when you came back in a few minutes: "reactants" or "products"? More likely than not, there would be an ice cream transfer in your absence; "products" would be favored. You could have predicted this from the table, and you could generalize: the hungry 10-year-old will be strong enough to rip the ice cream away from any kid lower on the table than the 10-year-old him/herself.

Let's predict the results of another equilibrium:



Is the hungry 6-year-old strong enough to pull the ice cream away from the 12-year-old? Not in most families. The table shows that the only chance for the hungry 6-year-old is to find a 4-year-old with ice cream. The 12-year-old with ice cream is pretty safe as long as the hunger table doesn't go to higher ages.

If you understand this analogy and can make predictions of ice cream transfer using the table, then you can understand how to predict the direction of equilibrium in acid-base reactions. Turn the page.

Appendix 2 continued, Summary of Acidity and Basicity

To set the stage

A few generalizations:

A) This Appendix deals with protic acids and bases, called Bronsted-Lowry acids. Similar statements can be made about Lewis acids but they are not the focus of this discussion.

B) Values of pK_a are measures of equilibrium constants, described further below. Values between 0 and 15.7 are measured by titration in water solution and are known accurately, to within 0.1 pK unit and sometimes better. Values outside of this range cannot be measured in water because of the leveling effect of water, and there is no universally accepted method for measuring these pK_a values. This lack of a single standard of measurement means that the values below 0 and above 15.7 should be considered relative, not absolute. If your instructor says the pK_a of methane is 46 and this book says it is 50, those should be considered the same value within experimental variation.

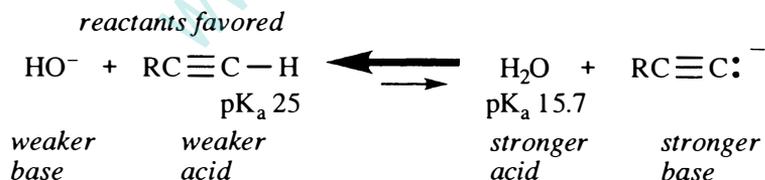
C) Acidity is a thermodynamic property, and the acid equilibrium constant, K_a , is a measure of the relative concentrations of species in the protonated and unprotonated form. As most organic acids are weak acids, meaning they are present mostly in the protonated form at equilibrium, the $K_a < 1$. Since the $pK_a = -\log K_a$, the pK_a values will be greater than 0, with the larger pK_a representing a weaker acid. If this is not clear, review text section 1-13.

D) Acids do not spontaneously spit out a proton! Despite our way of writing ionization equilibria as shown on the next page, acids do not give up a proton unless a base comes by to take the proton away. The reactions as drawn in the table should be considered half-reactions, just as the reactions in the electromotive series were half-reactions for balancing oxidation-reduction reactions in general chemistry.

I. Predicting equilibrium position

Look at the table on p. 691 and notice how it looks just like the "children-with-ice-cream" table. We can use this table to make predictions about equilibrium position in acid-base reactions just as we did for the children with ice cream.

1) *A base will deprotonate any acid stronger than its conjugate acid.* This is the most important principle of predicting acid-base reactions. On the table, this means that any base, hydroxide for example, can react with any acid more acidic than the conjugate acid of itself, water in our example. So hydroxide is a strong enough base to pull the proton from any of these: bicarbonate ion, a phenol, carbonic acid, a carboxylic acid, or a sulfonic acid. We can also predict that hydroxide is NOT a strong enough base to react with any acid above water on the table; for example, a mixture of hydroxide with an alkyne will favor the reactants at equilibrium, with only a small amount of products.



2) Another way of predicting the position of an equilibrium is to assign "stronger" and "weaker" to the acid and base on each side of the equation, using the table to determine which is stronger and which is weaker. *Equilibrium will always favor the weaker acid and base.* This method will always give the same answer as the principle in #1 above.

To lead into the next section, look again at the table on p. 691 and notice two things: a) with only a couple of exceptions, all the acidic protons are on either oxygen or carbon; and b) generalizations can be made about the acidity of functional groups. Learning to correlate acidity with functional group is important in predicting reactivity of the functional group.

Appendix 2 continued, Summary of Acidity and Basicity

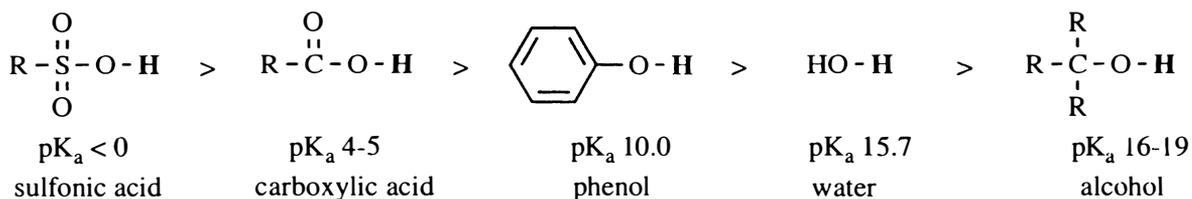
Approximate pKa Values of Organic Compounds

		pKa				
<i>weaker acid</i>	alkane	≈ 50	$\text{R}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{R}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}:^-$	<i>stronger base</i>
	alkene	≈ 45	$=\overset{\text{\'{/}}}{\underset{\text{H}}{\text{C}}}$	\rightleftharpoons	$\text{H}^+ + =\overset{\text{\'{/}}}{\underset{\text{\'{/}}}{\text{C}}}:^-$	
	amine	35-40	$-\overset{\text{..}}{\underset{\text{ }}{\text{N}}}-\text{H}$	\rightleftharpoons	$\text{H}^+ + -\overset{\text{..}}{\underset{\text{ }}{\text{N}}}:^-$	
		≈ 35	$\text{H}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{H}:^-$	
	alkyne	≈ 25	$\text{RC}\equiv\text{C}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{RC}\equiv\text{C}:^-$	
	ketone and ester	20-25	$-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}-\text{H}$	\rightleftharpoons	$\text{H}^+ + -\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{ }}{\underset{\text{ }}{\text{C}}}:^-$	
	alcohol	≈ 18	$\text{R}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{R}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	
		≈ 17	$\text{R}-\overset{\text{H}}{\underset{\text{R}}{\text{C}}}-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{R}-\overset{\text{H}}{\underset{\text{R}}{\text{C}}}-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	
		≈ 16	$\text{R}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{R}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	
↑ cannot be measured in water solution						
		15.7	H_2O	\rightleftharpoons	$\text{H}^+ + \text{HO}^-$	
↓ measured in water solution						
		10.3	HCO_3^-	\rightleftharpoons	$\text{H}^+ + \text{CO}_3^{2-}$	
	phenol	≈ 10	$\text{Ar}-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{Ar}-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	
		6.4	H_2CO_3	\rightleftharpoons	$\text{H}^+ + \text{HCO}_3^-$	
	carboxylic acid	4-5	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	
<i>stronger acid</i>	sulfonic acid	< 0	$\text{RSO}_2-\text{O}-\text{H}$	\rightleftharpoons	$\text{H}^+ + \text{RSO}_2-\overset{\text{..}}{\underset{\text{..}}{\text{O}}}:^-$	<i>weaker base</i>

Appendix 2 continued, Summary of Acidity and Basicity

II. Correlation of Acidity with Functional Group

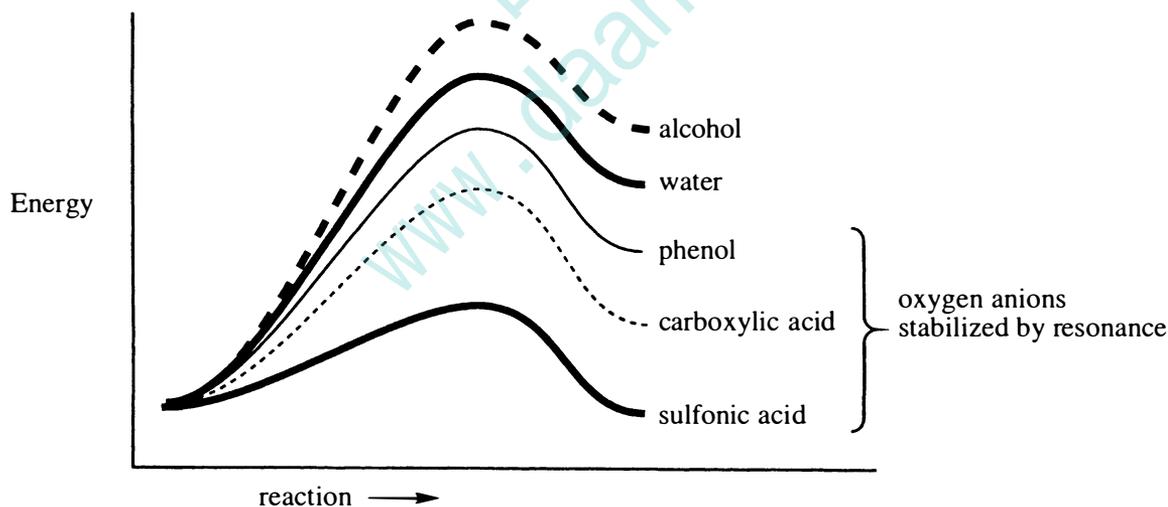
A. Oxygen Acids



Sulfonic acids are the strongest of the oxygen acids but are not common in organic chemistry. Carboxylic acids, however, are everywhere and are considered the strongest of the common organic oxygen acids. (Note that "strong" and "weak" are relative terms: acetic acid, pK_a 4.74, was a "weak" acid in general chemistry in comparison to sulfuric and hydrochloric acids, but acetic acid is a "strong" acid in organic chemistry relative to the other oxygen acids.) Phenols having OH groups on benzene or other aromatic rings are still stronger acids than water.

Why are phenols, carboxylic acids, and sulfonic acids stronger acids than water? Because their anions are stabilized by resonance. (Refer to text sections 1-13, 10-6, and 20-4, especially Figure 20-1.) Let's look at that statement in more detail.

Remember that acidity is a thermodynamic property; that is, acidity equilibrium depends on the difference in energy between the reactants and products. The more the anion is stabilized by resonance, the lower in energy it is, and the less positive the ΔG , as shown on the reaction energy diagram:



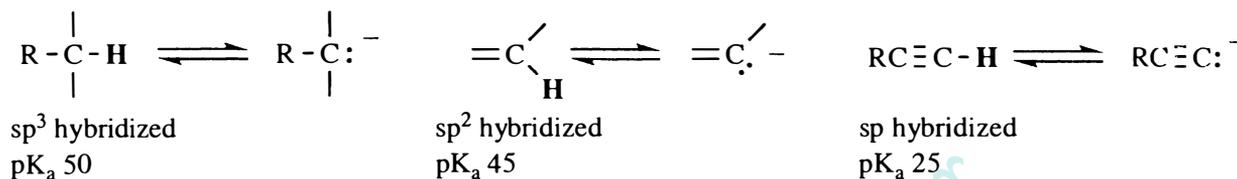
Why are alcohols weaker acids than water? There are two effects that contribute, both of which are consistent with the trend that 1° alcohols (pK_a 16) are slightly stronger than 2° alcohols (pK_a 17) which are slightly stronger than 3° alcohols (pK_a 18). Alkyl groups are mildly electron-donating in their inductive effect (more about this later) and destabilize the anion, as shown in the energy diagram above. Second, the more crowded the anion is, the less it can be stabilized by hydrogen bonding with the solvent.

Appendix 2 continued, Summary of Acidity and Basicity

B. Carbon Acids

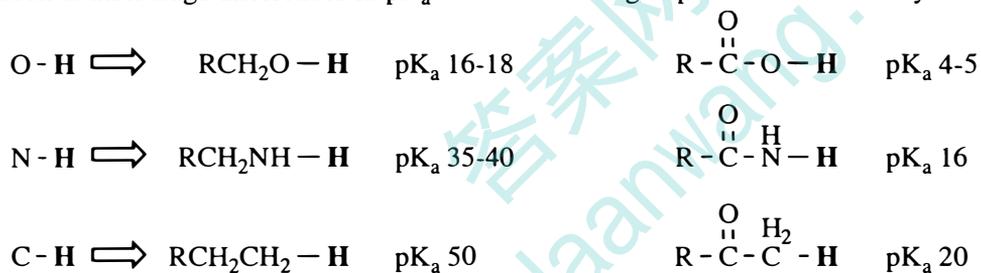
When we think of "acids", we do not usually think of protons on carbon, yet carbon acids and the carbanions that come from them are of tremendous importance in organic chemistry.

"Unstabilized" carbon acids are those that do not have any substituent to stabilize the anion. Alkanes, with only sp^3 carbons are the weakest acids with pK_a around 50. The vinyl carbon in a carbon-carbon double bond is sp^2 hybridized with the electrons of the anion slightly closer to the positive nucleus, leading to some stabilization of the anion. This type of stabilization is particularly important in alkynes with sp hybridized carbons.



C. Carbon Acids Alpha to Carbonyl (This topic is described in detail in text section 22-2B.)

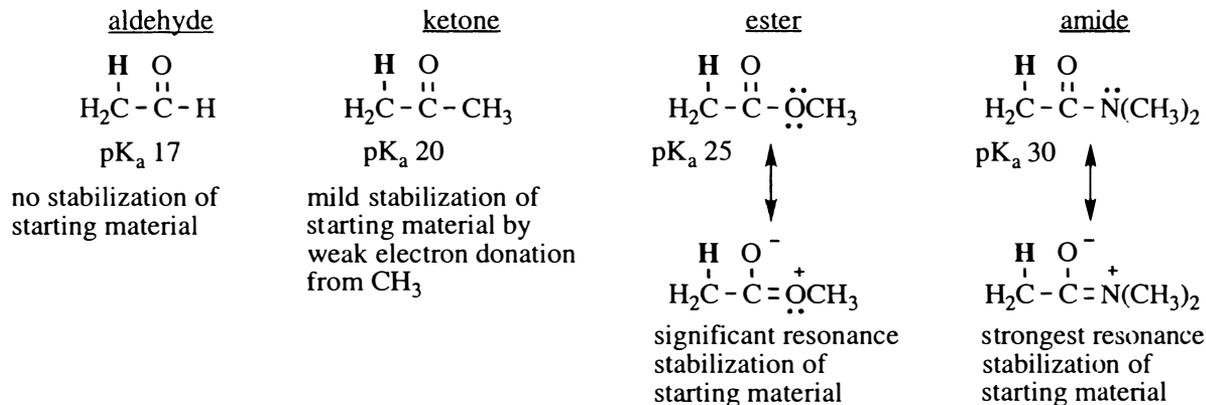
Look at these huge differences in pK_a when the acidic group is next to a carbonyl.



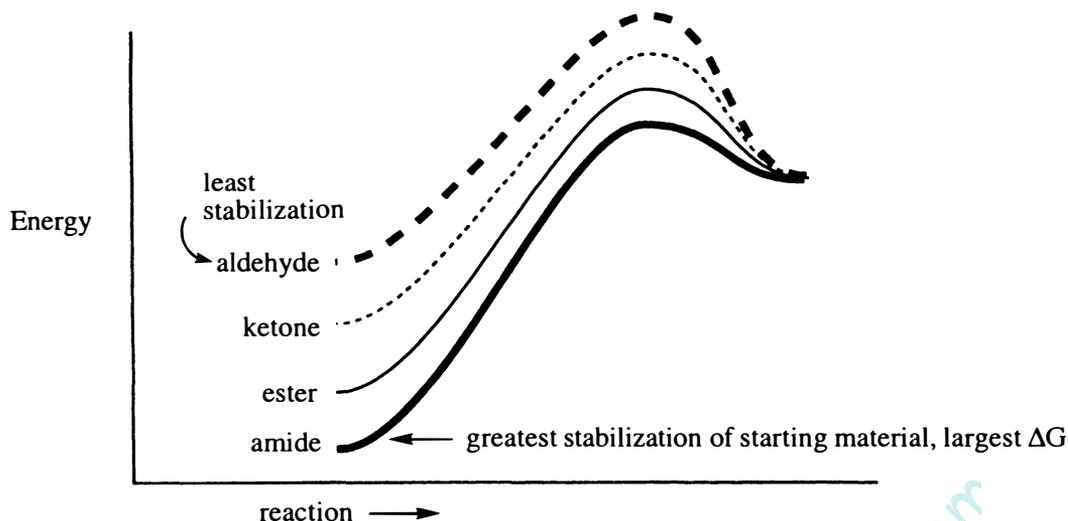
Hydrogens alpha to carbonyl are unusually acidic because of resonance stabilization of the anionic conjugate base.

D. Acidities of Acyl Functional Groups

In addition to the significant variation in the acidity of alpha hydrogens depending on which atom the H is bonded to, what is on the other side of the carbonyl also has a dramatic influence. In this case, the stabilization is more important on the starting material, not on the conjugate base. See the energy diagram on p. 694.

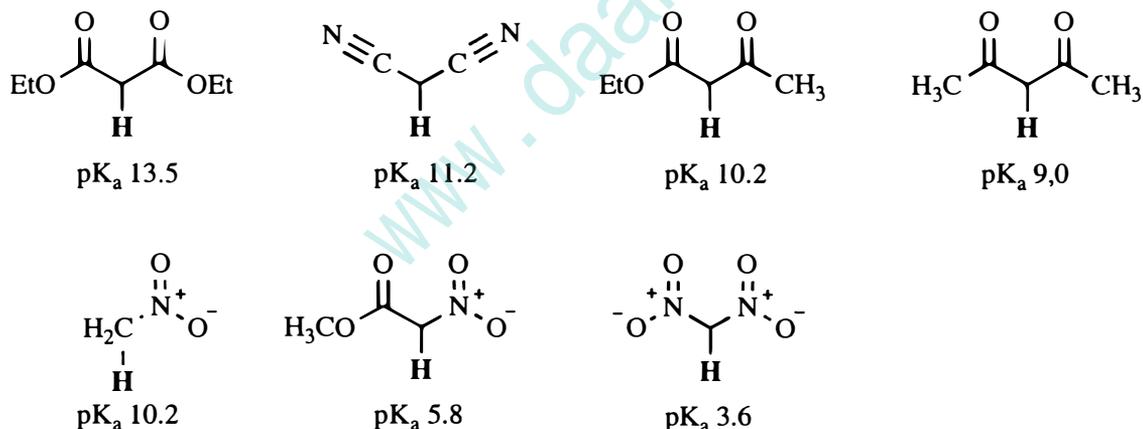


Appendix 2 continued, Summary of Acidity and Basicity



E. Carbon Acids Between Two Carbonyls (This topic is described in detail in text section 22-15.)

While a hydrogen alpha to one carbonyl moves into the pK_a 20-25 range for ketones and esters respectively, a hydrogen between two carbonyls (cyano and nitro are similar to carbonyl electronically) is more acidic than water. The increased resonance stabilization of the conjugate base is largely responsible, but there are subtle variations depending on the type of functional group as noted at the bottom of p. 693. Look at the enormous influence of the nitro group.



III. Correlation of Basicity with Functional Group

The bulk of this Appendix is on acidity because many more functional groups are acidic than are basic. Basically (oooh, sorry), only one functional group is basic: amines. There is variation among aliphatic, aromatic, and heteroaromatic amines; these are covered thoroughly in text sections 19-5 and 19-6. One point in the text, just before Table 19-3, deserves emphasis: for any conjugate acid-base pair:

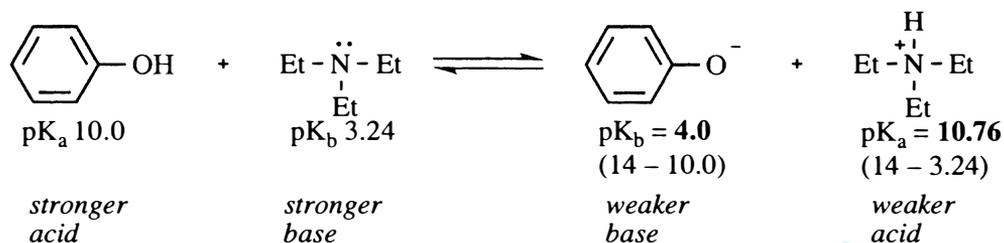
$$pK_a + pK_b = 14$$

Appendix 2 continued, Summary of Acidity and Basicity

This simple algebraic relationship is very useful:

Sample problem. Is triethylamine (pK_b 3.24) a strong enough base to deprotonate phenol (pK_a 10.0)?

We need to calculate either the pK_a of the conjugate acid of triethylamine or the pK_b of the conjugate base of phenol to see which is stronger and weaker. Then we can say with certainty which side of the equilibrium will be favored.



Aha! Products are favored at equilibrium, so the correct answer to the question is "Yes, triethylamine is a strong enough base to deprotonate phenol."

Try this for fun: How weak must a base be before it does NOT deprotonate phenol? What algebraic rule can you formulate to predict whether any combination of acid and base will favor products or reactants?

IV. Substituent Effects on Acidity

So far, we have focused on acidities of different functional groups. Let's turn to more minor, more subtle, structural changes to see what effect substituents will have on the acidity of a group. Primarily, we imply *electronic* effects as opposed to *steric* effects, but this Appendix will conclude with a discussion of how steric and electronic effects can work together.

A. Classification of Substituents—Induction and Resonance

Substituent groups can exert an electronic effect on an acidic functional group in two different ways: through sigma bonds, where this is called an *inductive effect*, or through p orbitals and pi bonds which is called a *resonance effect*. Groups can also be electron-donating or electron-withdrawing by either of the mechanisms, so there are four possible categories for groups. Note that a group can appear in more than one category, even in conflicting groups!

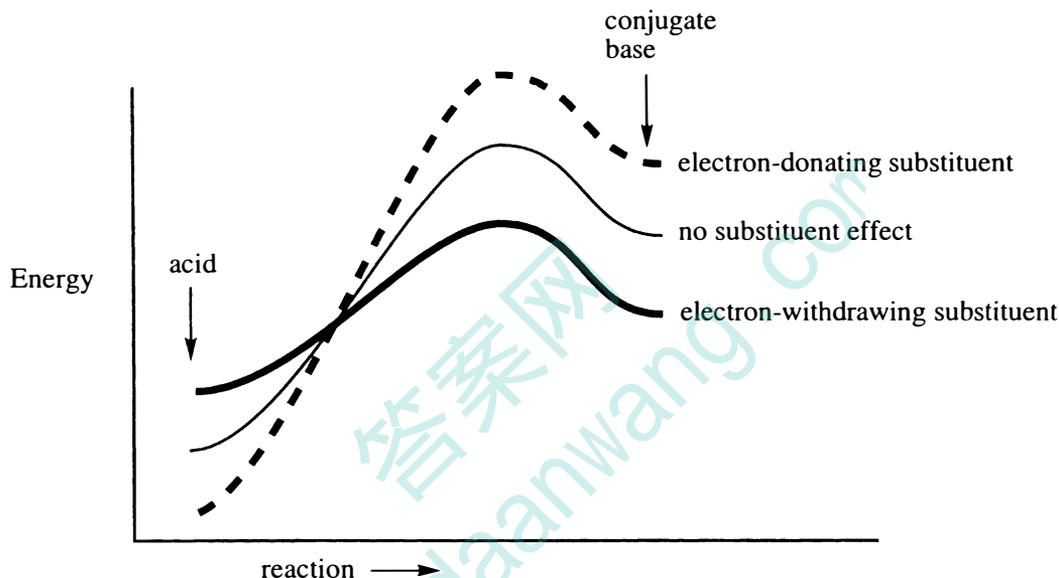
- a) Electron-donating by induction: only alkyl groups (abbreviated R) have electrons to share by induction;
- b) Electron-withdrawing by induction: every group that has a more electronegative atom than carbon is in this category; some examples: F, Cl, Br, I, OH, OR, NH_2 , NHR, NR_2 , NO_2 , C=O, CN, SO_3H , CX_3 where X is halogen;
- c) Electron-donating by resonance: groups that have electron pairs to share: F, Cl, Br, I, OH, OR, NH_2 , NHR, NR_2 ;
- d) Electron-withdrawing by resonance: NO_2 , C=O, CN, SO_3H .

Appendix 2 continued, Summary of Acidity and Basicity

B. Generalizations on Electronic Effects on Acidity (refer to text section 20-4B)

Electric charge is the key to understanding substituent effects. An acid is always more positive than its conjugate base; in other words, the conjugate base is always more negative than the acid. Electron-donating and electron-withdrawing groups will have opposite effects on the acid-base conjugate pair.

Electron-donating groups stabilize the more positive acid form and destabilize the more negative conjugate base. From the diagram, it is apparent that electron-donating groups widen the energy gap between reactants and products, making ΔG more positive, favoring reactants more than products. In essence, this weakens the acid strength.



Electron-withdrawing groups destabilize the more positive acid form and stabilize the more negative conjugate base, narrowing the energy gap between reactants and products, making ΔG less positive. Products are increased in concentration at equilibrium which we define as a stronger acid.

Electron-withdrawing groups increase acid strength; electron-donating groups decrease acid strength.

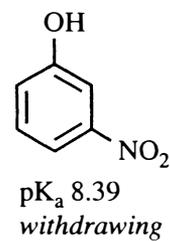
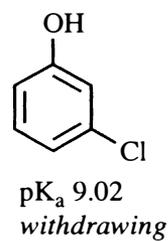
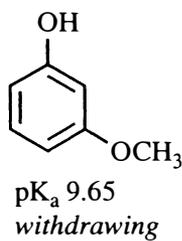
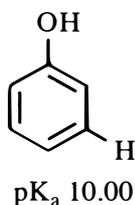
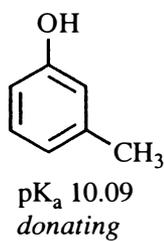
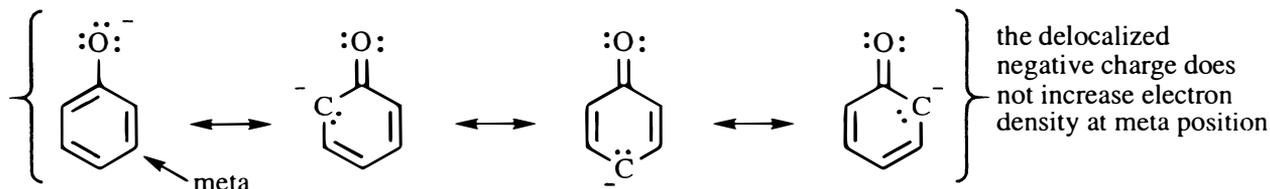
C. Inductive Effects on Acidity

Text section 20-4B gives a thorough explanation of the inductive effect of electron-withdrawing groups on simple carboxylic acids, from which three generalizations arise:

- A) Acidity increases with stronger electron-withdrawing groups. (See problem 20-33.)
- B) Acidity increases with greater number of electron-withdrawing groups.
- C) Acidity increases with closer proximity of the electron-withdrawing group to the acidic group.

We don't usually look to aromatic systems for examples of inductive effects, because the pi system of electrons is ripe for resonance effects. However, in analyzing the resonance forms of phenoxide on the next page, it becomes apparent that the negative charge is never distributed on the meta carbons. Meta substituents cannot exert any resonance stabilization or destabilization; at the meta position, substituents can exert only an inductive effect. The series of phenols demonstrates this phenomenon, consistent with aliphatic carboxylic acids.

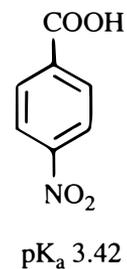
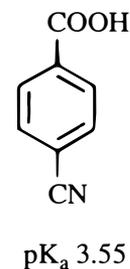
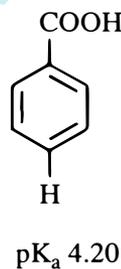
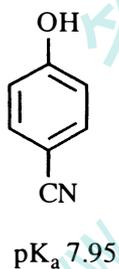
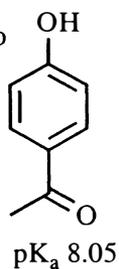
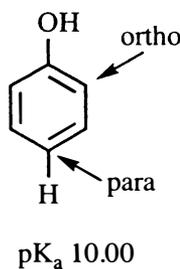
Appendix 2 continued, Summary of Acidity and Basicity



D. Resonance Effects on Acidity—benzoic acids and phenols (review the solution to problem 20-45)

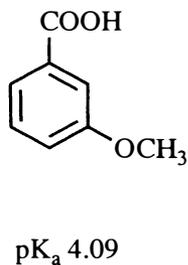
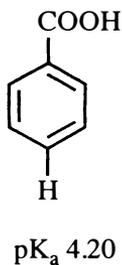
Resonance effects can be expressed with placement of substituents at ortho or para positions, but ortho has the complication of steric effects, so just para substitution is shown here.

Electron-withdrawing substituents increase the acidity of benzoic acids and phenols:



Electron-donating by resonance but electron-withdrawing by induction:

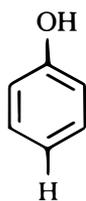
There is a group of substituents that donate by resonance but withdraw by induction: alkoxy groups and halogens are the most notable examples, and the acidity data provide an insight into which effect is stronger.



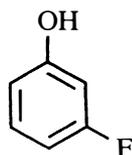
meta-Methoxybenzoic acid is stronger than benzoic acid, consistent with electron-withdrawing by induction which is expressed at the meta position. But the para isomer is weaker than benzoic acid; electron donation by resonance has not only compensated for the inductive effect (which is still operative at the para position) but has decreased the acidity even further. Thus, the donating effect by resonance must be stronger than the withdrawing effect by induction for the methoxy group.

See another example on the next page.

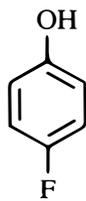
Appendix 2 continued, Summary of Acidity and Basicity



pK_a 10.00



pK_a 9.28



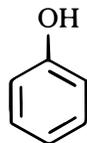
pK_a 9.81

meta-Fluorophenol is stronger than phenol, consistent with electron-withdrawing by induction which is expressed at the meta position. The para isomer is still stronger than phenol; electron donation by resonance has not compensated for the inductive effect (which is still operative at the para position). Thus, the donating effect by resonance must be weaker than the withdrawing effect by induction for the fluoro group.

Studying substituent effects on acidity is the standard method of determining whether a group is donating or withdrawing by induction and resonance.

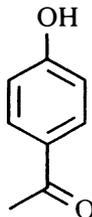
E. Proximity Effects of Substituents

pK_a 10.0



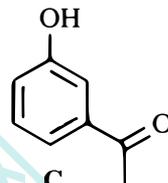
A

pK_a 8.05



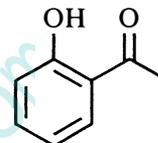
B

pK_a 9.19



C

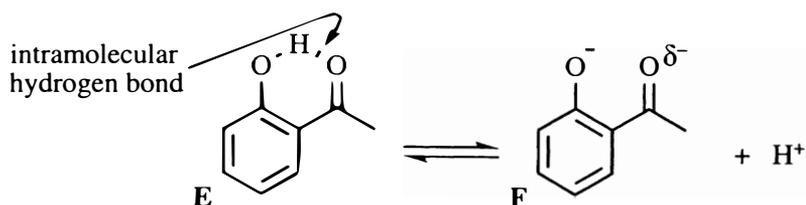
pK_a 9.90



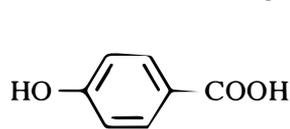
D

Three effects influence the pK_a values of these substituted phenols. In C, the acetyl group at the meta position is electron-withdrawing by induction only. In B, the acetyl group at the para position exerts both resonance and inductive effects, both of which are electron-withdrawing, making the acid stronger. In theory, substituents at the ortho position should be like para, exerting both resonance and inductive effects; in fact, the inductive effect should be stronger because of closer proximity to the acidic group. So we would predict D to be a stronger acid than B, yet it is not. What other effect is operating?

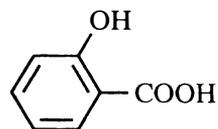
Structure E shows that because of the proximity of the acetyl group to the OH, *intramolecular hydrogen bonding* is possible. Hydrogen bonding stabilizes the starting material, lowering the energy of the starting material and making ΔG more positive. Intuitively, it should be apparent that a hydrogen held between two oxygens will be more difficult to remove by a base. Also, after the proton has left as shown in structure F, the negative charge on the phenolic oxygen is close to the partial negative charge on the oxygen of the carbonyl, destabilizing product F, raising its energy, also making ΔG more positive. The proximity of the acetyl group influences both sides of the equation to make the acid weaker.



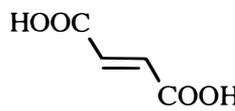
Here are two more examples where intramolecular hydrogen-bonding influences acidity.



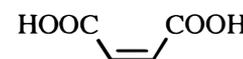
pK₁ 4.6; pK₂ 9.3



pK₁ 2.75; pK₂ 13.4



pK₁ 3.02; pK₂ 4.38



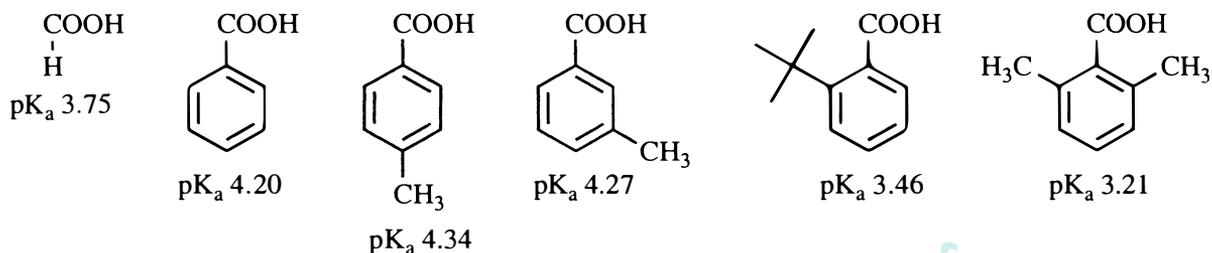
pK₁ 1.94; pK₂ 6.23

Appendix 2 continued, Summary of Acidity and Basicity

F. Steric Inhibition of Resonance

Another type of proximity effect arises when the placement of a substituent interferes with the orbital overlap required for resonance stabilization. This can be seen clearly in the acidity of substituted benzoic acids and in the basicity of substituted anilines.

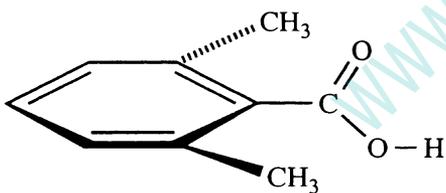
Let's analyze this series of carboxylic acids.



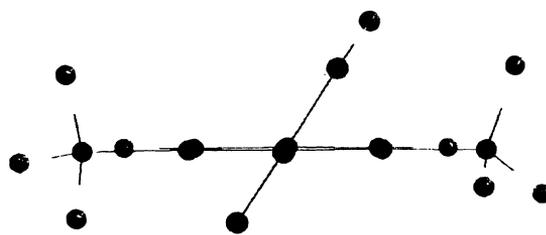
Formic acid, pK_a 3.75, serves as the reference carboxylic acid. Benzoic acid is weaker because the phenyl group is electron-donating by resonance, stabilizing the protonated form. Methyl substituents are known to be electron-donating by induction, strengthening the electron-donating effect, making the meta- and para-substituted acids weaker than benzoic acid.

Then come the anomalies. Alkyl groups are electron-donating by induction and should weaken the acids, but the ortho-t-butyl and the 2,6-dimethylbenzoic acids are not only stronger than benzoic acid, they are stronger than formic acid! Something has happened to turn the phenyl group into an electron-withdrawing group.

Phenyl is electron-donating by resonance but electron-withdrawing by induction, so what has happened is that the ortho substituents have forced the COOH out of the plane of the benzene ring so that there is no resonance overlap between the benzene ring and the COOH orbitals. The COOH "feels" the benzene ring as simply an inductive substituent. Resonance has been "inhibited" because of the steric effect of the substituent.

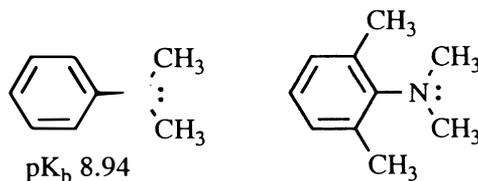


COOH group is not parallel with the plane of the benzene ring—no resonance interaction.



this three-dimensional view down the C-C bond between the COOH and the benzene ring shows that COOH is twisted out of the benzene plane

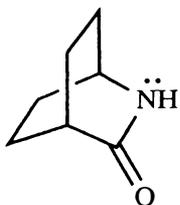
The same phenomenon is observed in substituted anilines. Anilines are usually much weaker bases than aliphatic amines because of resonance overlap of the nitrogen's lone pair of electrons with the pi system of benzene. When that resonance is disrupted, the aniline becomes closer in basicity to an aliphatic amine. (See problem 19-49(c).)



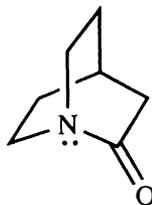
More examples on the next page.

Appendix 2 continued, Summary of Acidity and Basicity

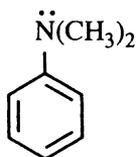
Examples of steric inhibition of resonance:



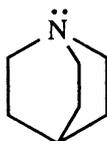
amide—not basic because of resonance sharing of N lone pair with carbonyl



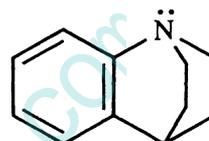
strong base similar to aliphatic amine; geometry of bridged ring prevents overlap of N lone pair with carbonyl



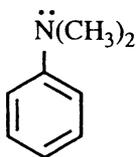
pK_b 8.9
3° aromatic amine



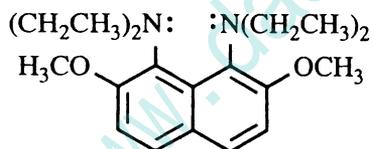
pK_b 3.4
3° aliphatic amine



pK_b 6.2
3° amine, and the N is bonded to a benzene, but the bridged ring system prevents overlap of N lone pair with benzene



pK_b 8.9



pK_b - 2.3 (yes, negative!)

Not only is steric inhibition of resonance important in this example, but so is intramolecular hydrogen-bonding in the protonated form. Draw a picture.