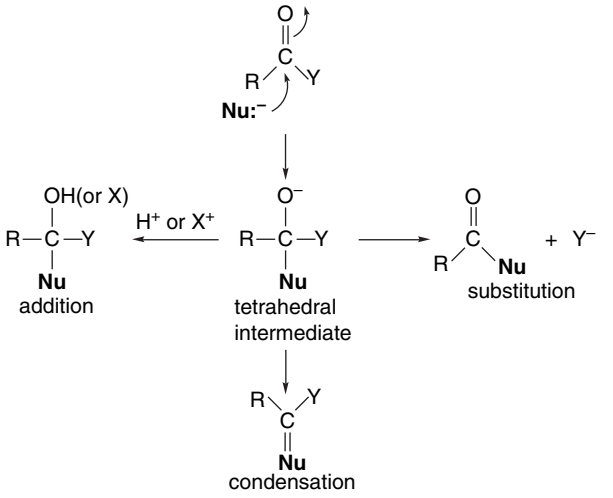
7

Addition, Condensation and Substitution Reactions of Carbonyl Compounds

Introduction

The carbonyl group is one of the most prevalent of the functional groups and is involved in many synthetically important reactions. Reactions involving carbonyl groups are also particularly important in biological processes. Most of the reactions of aldehydes, ketones, esters, carboxamides, and the other carboxylic acid derivatives directly involve the carbonyl group. We discussed properties of enols and enolates derived from carbonyl compounds in Chapter 6. In the present chapter, the primary topic is the mechanisms of addition, condensation and substitution reactions at carbonyl centers. We deal with the use of carbonyl compounds to form carbon-carbon bonds in synthesis in Chapters 1 and 2 of Part B.

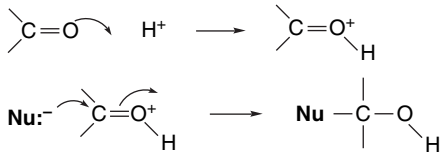
In many reactions at carbonyl groups, a key step is the addition of a nucleophile, which generates a tetracoordinate carbon atom. The overall course of the reaction is then determined by the fate of this tetrahedral intermediate. *Addition* occurs when the tetrahedral intermediate goes directly on to product. *Condensation* occurs if the carbonyl oxygen is eliminated and a double bond is formed. *Substitution* results when one of the groups is eliminated from the tetrahedral intermediate to re-form a carbonyl group.



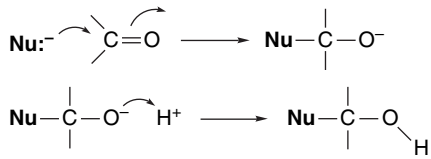
The reaction patterns of the specific classes of carbonyl compounds are related by the decisive importance of tetrahedral intermediates, and differences in reactivity can often be traced to structural features present in those intermediates. In Section 3.4.4, we considered some of the fundamental substituent effects on the stability of both carbonyl compounds and tetrahedral intermediates. These relationships will be important as we discuss the reactions in this chapter.

In broad terms, there are three possible mechanisms for addition of a nucleophile and a proton to give a tetrahedral intermediate in a carbonyl addition reaction.

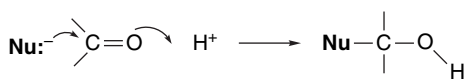
(a) Protonation followed by nucleophilic attack on the protonated carbonyl group:



(b) Nucleophilic addition at the carbonyl group followed by protonation:



(c) Concerted proton transfer and nucleophilic attack:

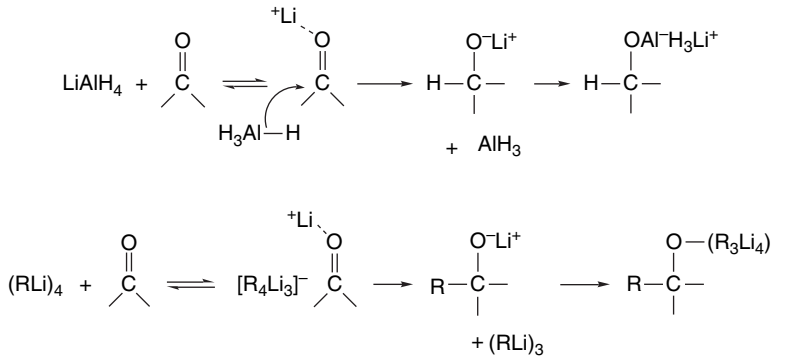


The nucleophile is shown as an anion, but can also be a neutral species, in which case a proton is subsequently lost.

There are carbonyl addition reactions that are examples of each of the general mechanisms, and a two-dimensional potential energy diagram provides a useful framework within which to consider specific addition reactions. The breakdown of a tetrahedral intermediate involves the same processes but operates in the opposite direction, so the principles that are developed also apply to the reactions of the tetrahedral intermediates. Let us examine the three general mechanistic cases in relation to the energy diagram in Figure 7.1.

Case (a) is favored for weak nucleophiles. The protonated carbonyl compound is more reactive toward such nucleophiles. The nucleophile may be neutral or a weakly basic anion. This mechanism is most likely to operate in relatively acidic conditions. Case (b) is favored for strongly basic nucleophiles. For example, carbanions cannot generally exist under acidic conditions, so carbanion additions occur under strongly basic conditions. These nucleophiles are more basic than carbonyl oxygens and are protonated in preference to the carbonyl group. In such systems, proton donors diminish the overall reaction rate by decreasing the amount of anionic nucleophile that is available for reaction. The concerted mechanism, case (c), is observed for less basic nucleophiles. The simultaneous transfer of the proton at the carbonyl oxygen facilitates addition by species that are not sufficiently nucleophilic to react by mechanism (b). The general pattern is that the weaker and less basic the nucleophile, the more important the partial or complete protonation of the carbonyl group. If we consider the reverse process, the same general relationships will hold. Good leaving groups (which are poor nucleophiles) can be expected to follow path (a); poor leaving groups will follow path (b); and intermediate cases are likely to react by the concerted mechanism (c).

Metal cations and other Lewis acids can replace protons as reagents/catalysts for carbonyl addition reactions. Metal cations, for example, are involved in hydride and organometallic addition reactions. Metal cations and Lewis acids are also key reagents in the aldol-type reactions that are considered in Section 7.7.



It is useful to recognize that the dissociation of tetrahedral intermediates in carbonyl chemistry is closely related to the generation of carbocations by ionization processes. The protonated carbonyl compounds or iminium ions that

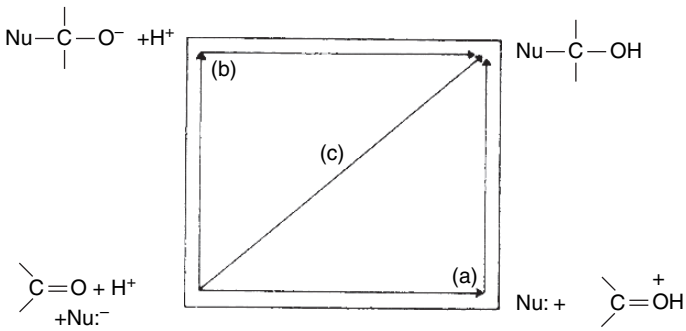
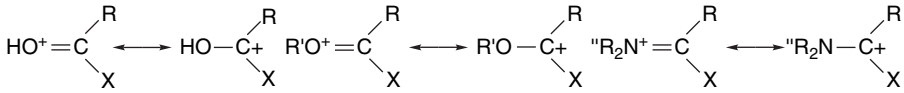


Fig. 7.1. Two-dimensional potential energy diagram for addition of a proton and nucleophile to a carbonyl group. (a) Proton transfer complete before nucleophilic addition begins; (b) nucleophilic addition complete before proton transfer begins; (c) concerted proton transfer and nucleophilic addition.

are generated by breakdown of tetrahedral intermediates are resonance-stabilized carbocations.



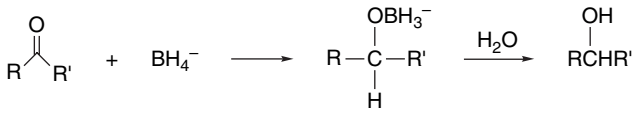
The question of which substituent on a tetrahedral intermediate is the best leaving group is similar to comparing S_N1 reactants on the basis of leaving-group ability. Poorer leaving groups such as alkoxides can function as leaving groups in the case of tetrahedral intermediates because of the assistance provided by the remaining oxygen or nitrogen substituents. Keeping these relationships in mind should be helpful in understanding the reactivity of tetrahedral intermediates.

7.1. Reactivity of Carbonyl Compounds toward Addition

At this point we consider some general relationships concerning the reactivity of carbonyl compounds toward addition of nucleophiles. Several factors influence the overall rate of a reaction under various conditions. Among the crucial factors are: (1) structural features of the carbonyl compound; (2) the role of protons or other Lewis acids in activating the carbonyl group toward nucleophilic attack; (3) the reactivity of the nucleophilic species and its influence on subsequent steps; and (4) the stability of the tetrahedral intermediate and the extent to which it proceeds to product rather than reverting to starting material.

We focus first on the inherent reactivity of the carbonyl compound itself. An irreversible process in which the addition product is stable is the most direct means of comparing the reactivity of carbonyl compounds. In these circumstances, the relative rate of reaction of different carbonyl compounds can be directly compared. One such reaction is hydride reduction. In particular, reductions by sodium borohydride in protic

solvents are fast, irreversible reactions that provide a convenient basis for comparing the reactivity of different carbonyl compounds.[1]



The reaction is second-order overall, with the rate equal to $k[R_2C{=}O][NaBH_4]$. The interpretation of the rates is complicated somewhat by the fact that the alkoxyborohydrides produced by the first addition can also function as reducing agents by successive hydride transfers, but this has little apparent effect on the relative reactivity of the carbonyl compounds. Table 7.1 presents some of the rate data obtained from these studies.

Reductions by $NaBH_4$ are characterized by low enthalpies of activation (8 to 13 kcal/mol) and large negative entropies of activation (−28 to −40 eu). These data suggest an early TS with considerable organization. Aldehydes are substantially more reactive than ketones, as can be seen by comparing benzaldehyde and acetophenone. This relative reactivity is characteristic of nearly all carbonyl addition reactions. The lower reactivity of ketones is due primarily to steric effects. Not only does the additional substituent increase the steric restrictions to approach of the nucleophile, but it also causes greater steric interaction in the tetrahedral adduct as the hybridization changes from trigonal to tetrahedral. Alkyl substituents also act as electron donors toward carbonyl groups by hyperconjugation (see Section 2.2.1).

Among the cyclic ketones shown in Table 7.1, the reactivity of cyclobutanone is enhanced because of the strain of the four-membered ring, which is decreased on going from sp^2 to sp^3 hybridization. The higher reactivity of cyclohexanone compared to cyclopentanone is quite general for carbonyl addition reactions. The major factor responsible for the difference in this case is the change in torsional strain as addition occurs. As the hybridization goes from sp^2 to sp^3, the torsional strain is *increased* in cyclopentanone. The opposite is true for cyclohexanone. The

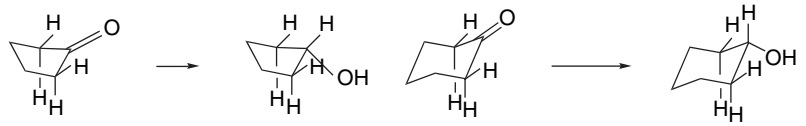
Table 7.1. Rates of Reduction of Aldehydes and Ketones by Sodium Borohydride

Carbonyl compound	$k \times 10^4\ M^{-1}s^{-1}$[a]
Benzaldehyde	12,400[b]
Benzophenone	1.9
Acetophenone	2.0
Acetone	15.1
Cyclobutanone	264
Cyclopentanone	7
Cyclohexanone	161

a. In isopropanol at 0°C.
b. Extrapolated from data at lower temperatures.

1. H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957); H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

equatorial hydrogens are nearly eclipsed with the carbonyl oxygen in cyclohexanone, but the chair structure of cyclohexanol allows all bonds to attain staggered arrangements.



The borohydride reduction rate data are paralleled by many other carbonyl addition reactions. In fact, for a series of ketones, most of which are cyclic, a linear free-energy correlation of the form

$$\log k = A \log k_0 + B$$

exists for nucleophiles such as NH_2OH, CN^-, $HOCH_2CH_2S^-$, and HSO_3^-.[2] These nucleophiles span a wide range of reactivity and include nitrogen, carbon, and sulfur nucleophiles. This free-energy relationship implies that in this series of ketones the same structural features govern reactivity toward each of the nucleophiles. To a good approximation the parameter $A = 1$, which reduces the correlation to

$$\log (k/k_0) = B$$

This equation implies that the *relative reactivity is independent of the specific nucleophile* and is insensitive to changes in position of the transition state. Table 7.2 lists some of the B values for some representative ketones. The parameter B indicates relative reactivity on a log scale. Cyclohexanone is seen to be a particularly reactive ketone, being almost as reactive as cyclobutanone and more than ten times as reactive as acetone.

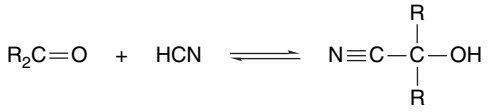
The same structural factors come into play in determining the position of equilibria in reversible additions to carbonyl compounds. An example of such equilibrium processes is the addition of cyanide to give cyanohydrins.

Table 7.2. Relative Reactivity of Some Ketones toward Addition of Nucleophiles

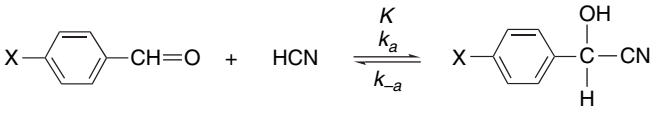
Ketone	B[a]
Cyclobutanone	0.09
Cyclohexanone	0.00
4-*t*-Butylcyclohexanone	−0.008
Adamantanone	−0.46
Cycloheptanone	−0.95
Cyclopentanone	−1.18
Acetone	−1.19
Norbornan-2-one	−1.48
3,3,5,5-Tetramethylcyclohexanone	−1.92

a. A. Finiels and P. Geneste, *J. Org. Chem.*, **44**, 1577 (1979); reactivity relative to cyclohexanone.

2. A. Finiels and P. Geneste, *J. Org. Chem.*, **44**, 1577 (1979).



The equilibrium constants in Table 7.3 illustrate some of the broad trends in carbonyl group reactivity. Alkyl substitution decreases the extent of addition. Aromatic carbonyl compounds are somewhat less reactive toward addition than similar alkyl compounds because the carbonyl group is stabilized by conjugation with the aromatic ring. Strong electron-attracting groups, such as trifluoromethyl, favor addition by enhancing the electrophilicity of the carbonyl group. For cyclopentanone, cyclohexanone, and cycloheptanone the K's for addition of CN^- are 48, 1000, and 8 M^{-1}, respectively.[3] For aromatic aldehydes, the equilibria are affected by the electronic nature of the aryl substituent. Electron donors disfavor addition by stabilizing the aldehyde, whereas electron-accepting substituents have the opposite effect. The Hammett correlation with σ^+ gives $\rho = +1.01$.



Ref. 4

There are large differences in the reactivity of the various carboxylic acid derivatives, such as amides, esters, and acyl chlorides. One important factor is the resonance stabilization provided by the heteroatom substituent, which is in the order N > O > Cl. Electron delocalization reduces the electrophilicity of the carbonyl group and the corresponding stabilization is lost in the tetrahedral intermediate.

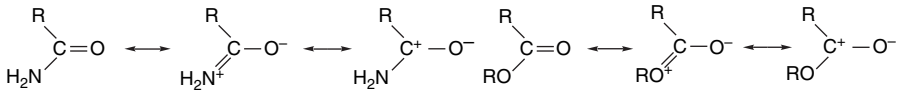


Table 7.3. Equilibrium Constants for Cyanohydrin Formation[a]

$R_2C=O$	log K
$CH_2=O$	7.48
$CH_3CH=O$	2.29
$(CH_3)_2C=O$	−1.84
$PhCH=O$	0.74[b]
$PhCOCF_3$	3.98[c]

a. Except where otherwise noted the data are from G. Schlesinger and S. L. Miller, *J. Am. Chem. Soc.*, **85**, 3729 (1973).
b. W. M. Ching and R. G. Kallen, *J. Am. Chem. Soc.*, **100**, 6119 (1978).
c. C. D. Ritchie, *J. Am. Chem. Soc.*,**106**, 7087 (1984).

3. V. Prelog and M. Kobelt, *Helv. Chim. Acta*, **32**, 1187 (1949).
4. W.-M. Ching and R. G. Kallen, *J. Am. Chem. Soc.*, **100**, 6119 (1978); V. Gold and W. N. Wassef, *J. Chem. Soc., Perkin Trans. 2*, 1431 (1984).

The high reactivity of the acyl chlorides also reflects the polar electron-withdrawing effect of the chlorine, which more than outweighs its small π-donor effect. Another factor that strongly affects the reactivity of these carboxylic acid derivatives is the leaving-group ability of the substituents. The order is $Cl > OAr > OR > NR_2 > O^-$ so that not only is it easier to form the tetrahedral intermediate in the order $Cl > OAr > OR > NR_2 > O^-$, but the tendency for subsequent elimination to occur is also in the same order. As the two factors work together, there are large differences in reactivity toward the nucleophiles. (See Scheme 3.3 for some specific data.)

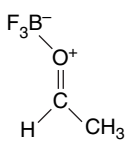
Approximate Relative Reactivity toward Hydrolysis

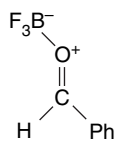
RCOCl	10^{11}
RCO_2R'	1
$RCONR'_2$	10^{-3}
RCO_2^-	$<< 1$

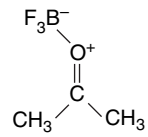
Many carbonyl addition and substitution reactions are carried out under acidic conditions or in the presence of Lewis acids. Qualitatively, protonation or complexation increases the electrophilicity of the carbonyl group. The structural effects of protonation have been examined for formaldehyde, acetaldehyde, acetone, formamide, and formyl fluoride. These effects should correspond to those in more complex carbonyl compounds. Protonation results in a substantial lengthening of the C=O bond.[5] The calculated [B3LYP/ 6-31++G(*d*, *p*)] gas phase proton affinities reflect the trend of increasing basicity with donor groups (CH_3, NH_2) and decreased basicity for fluorine.

	$CH_2{=}O$	$CH_3CH{=}O$	$(CH_3)_2C{=}O$	$H_2NCH{=}O$	$FCH{=}O$
$r_{C=O}$	1.209	1.214	1.219	1.219	1.186
$r_{C=OH^+}$	$CH_2{=}O^+H$	$CH_3CH{=}O^+H$	$(CH_3)_2C{=}O^+H$	$H_2NCH{=}O^+H$	$FCH{=}O^+H$
	1.252	1.270	1.282	1.294	1.252
PA in kcal/mol	168.9	184.4	195.7	198.0	156.2

The effect of Lewis acids has also been examined computationally. In agreement with crystal structure determinations,[6] Lewis acids such as BF_3 normally adopt an *anti* structure for aldehydes. Despite the unfavorable steric effect in acetone, the calculated (MP2/6-31G) energy of complexation with BF_3 is nearly as high as for acetaldehyde, presumably owing to the additional electron donation by the methyl groups.[7]



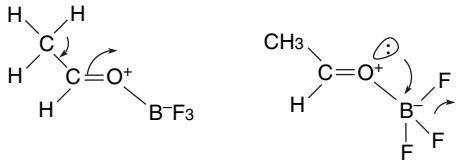




ΔE −11.9 −13.0 −10.3

5. A. K. Chandra, M. T. Nguyen, and T. Zeegers-Huyskens, *Chem. Phys.*, **255**, 149 (2000).
6. M. T. Reetz, M. Hullmann, W. Massa, S. Berger, P. Rademacher, and P. Heymanns, *J. Am. Chem. Soc.*, **108**, 2405 (1986).
7. B. W. Gung and M. A. Wolf, *J. Org. Chem.*, **57**, 1370 (1992).

It is believed that two significant hyperconjugative effects result from complexation with a Lewis acid. The donor effect of alkyl substituents is enhanced by the greater electrophilicity of the carbonyl oxygen. There is also believed to be an interaction of the remaining unshared oxygen electrons with the σ^* orbital of the B−F bond. The interaction lowers the energy of both the π and π^* orbitals and enhances the reactivity toward nucleophiles, as indicated in Figure 7.2.[8]



Several factors, then, are important in assessing relative reactivity of carbonyl compounds. Electronegative substituents enhance reactivity by a polar effect, but if they are also π donors, there is a resonance effect in the opposite direction. Alkyl and aryl substituents decrease reactivity relative to hydrogen by a combination of steric and electronic effects. Protonation or complexation with a Lewis acid at the carbonyl oxygen enhances reactivity.

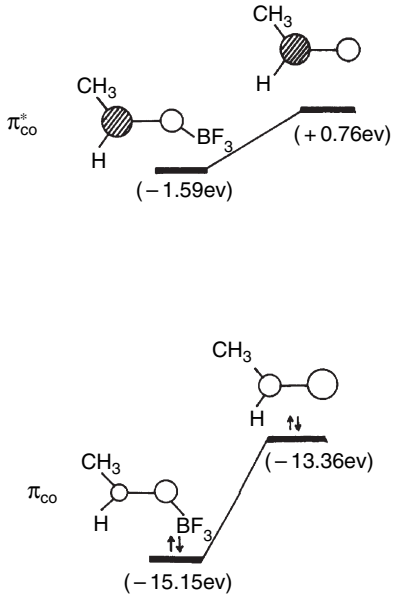


Fig. 7.2. Effect of BF_3 complexation of HOMO and LUMO in acetaldehyde. From MNDO calculations, *J. Am. Chem. Soc.*, **108**, 2405 (1986).

8. K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).

7.2. Hydration and Addition of Alcohols to Aldehydes and Ketones

The reactivity of carbonyl compounds toward hydration parallels the order indicated in Section 7.1. For most carbonyl compounds, the equilibrium constant for addition of water to the carbonyl group is unfavorable.

Formaldehyde is an exception and is nearly completely hydrated in aqueous solution. Unhindered aliphatic aldehydes are approximately 50% hydrated in water. Aryl groups disfavor hydration by conjugative stabilization of the carbonyl group. Ketones are much less extensively hydrated than aldehydes. Aldehydes and ketones with highly electronegative substituents such as trichloroacetaldehyde and hexafluoroacetone are extensively hydrated. α-Dicarbonyl compounds, such as biacetyl and ethyl pyruvate, are also significantly hydrated. Table 7.4 gives the K_{hydr} for a number of carbonyl compounds. Data on other compounds are available in Table 3.23.

Although the equilibrium constant for hydration is usually unfavorable, the equilibrium between an aldehyde or ketone and its hydrate is established rapidly and can be detected by isotopic exchange, using water labeled with ^{17}O, for example.[9] For

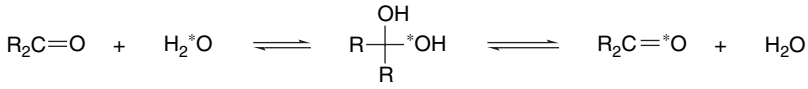
Table 7.4. Equilibrium Constants for Hydration of Carbonyl Compounds

Carbonyl compound	K (in water, 25°C)[a]
CH_2O	2.28×10^{3} [b]
CH_3CHO	1.06[b]
CH_3CH_2CHO	0.85[b]
$(CH_3)_2CHCHO$	0.61[b]
$(CH_3)_3CCCHO$	0.23[b]
CF_3CHO	2.9×10^{4} [b]
C_6H_5CHO	8×10^{-3}[c]
CH_3COCH_3	1.4×10^{-3} [b]
FCH_2COCH_3	0.11[c]
$ClCH_2COCH_3$	0.11[b]
CF_3COCH_3	35[b]
CF_3COCF_3	1.2×10^{6} [b]
$C_6H_5COCH_3$	9.3×10^{-6} [c]
$C_6H_5COCF_3$	78[b]
$CH_3COCOCH_3$	0.6[d]
$CH_3COCO_2CH_3$	0.8[d]

a. K = [hydrate]/[carbonyl] = $K_{eq}[H_2O] = 55.5\,K_{eq}$
b. J. P. Guthrie, *Can. J. Chem.*, **53**, 898 (1975).
c. J. P. Guthrie, *Can. J. Chem.*, **56**, 962 (1978).
d. T. J. Burkey and R. C. Fahey, *J. Am. Chem. Soc.*, **105**, 868 (1983).

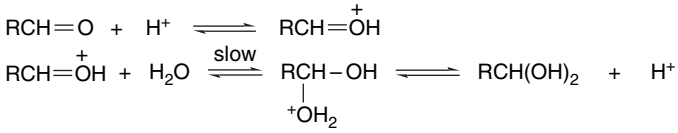
9. P. Greenzaid, Z. Luz, and D. Samuel, *Trans. Faraday Soc.*, **64**, 2780, 2787 (1968).

acetaldehyde, the half-life of the exchange reaction is on the order of 1 min under neutral conditions, but is considerably faster in acidic or basic solution. The second-order rate constant for acid-catalyzed hydration of acetaldehyde is about 500 $M^{-1}s^{-1}$.[10]

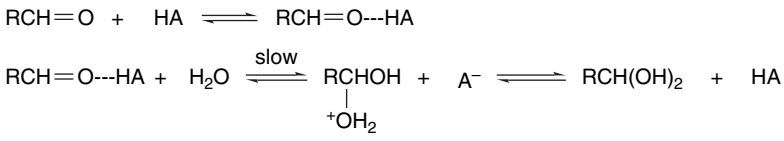


The hydration reaction is the mechanistic prototype for many reactions at carbonyl centers that involve more complex molecules.[11] Acid catalysis involves either protonation or hydrogen-bonding at the carbonyl oxygen. Both specific and general acid catalysis can be observed.[12] (Review Section 3.7.1.1 for the discussion of specific and general acid catalysis.)

Specific acid–catalyzed mechanism

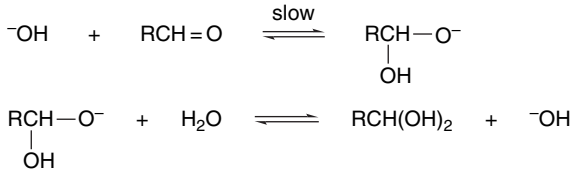


General acid–catalyzed hydration

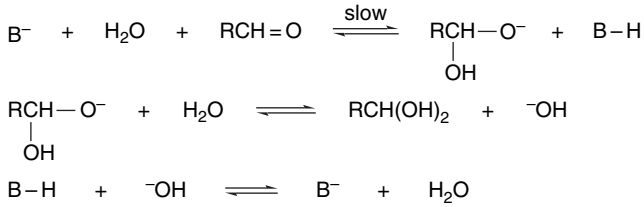


Hydroxide ion addition results in specific base-catalyzed hydration. General base catalysts function by deprotonating water to give the more nucleophilic hydroxide ion.

Specific base–catalyzed hydration

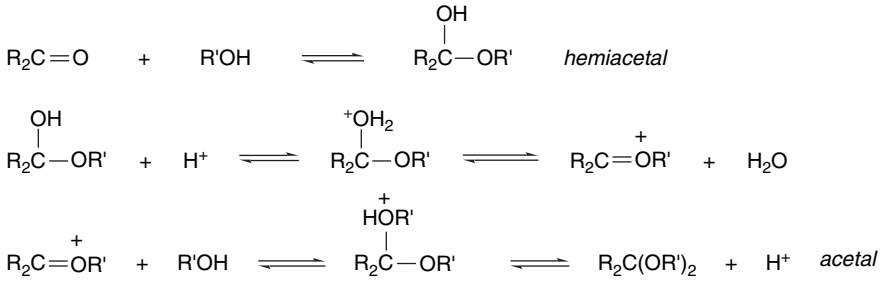


General base–catalyzed hydration



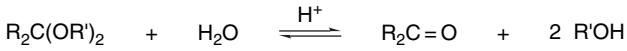
[10] P. Greenzaid, Z. Luz, and D. Samuel, *J. Am. Chem. Soc.*, **89**, 756 (1967).
[11] R. P. Bell, *Adv. Phys. Org. Chem.*, **4**, 1 (1966); W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
[12] L. H. Funderburk, L. Aldwin, and W. P. Jencks, *J. Am. Chem. Soc.*, **100**, 5444 (1978); R. A. McClelland and M. Coe, *J. Am. Chem. Soc.*, **105**, 2718 (1983).

Aldehydes and ketones undergo reversible addition reactions with alcohols. The product of addition of one molecule of alcohol to an aldehyde or ketone is referred to as a *hemiacetal*. Dehydration followed by addition of a second molecule of alcohol gives an *acetal*.[13] This second phase of the process can be catalyzed only by acids because a necessary step is elimination of hydroxide (as water) from the tetrahedral intermediate. There is no low-energy mechanism for base assistance of this elimination step, so acetals are stable toward hydrolysis in alkaline aqueous solution but are hydrolyzed rapidly in acidic solution.



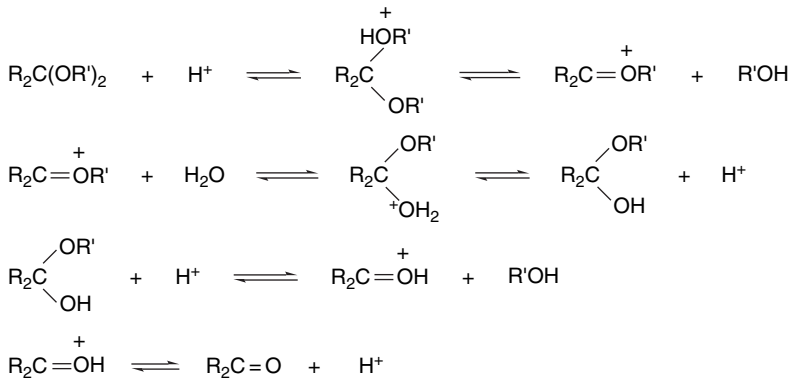
The equilibrium constants for addition of alcohols to carbonyl compounds to give hemiacetals show the same response to structural features as the hydration reaction. Equilibrium constants for addition of methanol to acetaldehyde in both water and chloroform solution are near $0.8\,M^{-1}$. The structural effects of the alcohol group have been examined.[14] Steric effects result in an order of $CH_3 \sim C_2H_5 > (CH_3)_2CH > (CH_3)_3C$ for acetaldehyde hemiacetals. EWG substituents in the alcohol disfavor hemiacetal formation and this trend is believed to reflect the decreasing $n \rightarrow \sigma^*$ hyperconjugation (anomeric effect, see Topic 1.2) as the substituents become more electron withdrawing.

The overall equilibrium constant for formation of the dimethyl acetal of acetaldehyde is $1.58\,M^{-1}$. The comparable value for the addition of water is about $0.02\,M^{-1}$.[15] Because the position of the equilibrium does not strongly favor product, the synthesis of acetals is carried out in such a way as to drive the reaction to completion. One approach is to use a dehydrating reagent or azeotropic distillation so that the water that is formed is irreversibly removed from the system. Because of the unfavorable equilibrium constant and the relative facility of the hydrolysis, acetals are rapidly converted back to aldehydes and ketones in acidic aqueous solution. The facile hydrolysis makes acetals useful carbonyl protecting groups (see Part B, Section 3.5.3).



13. Sometimes these derivatives of ketones are called hemiketals and ketals, respectively.
14. Y.-H. Fan and J. Haseltine, *Tetrahedron Lett.*, **37**, 9279 (1996).
15. R. Bone, P. Cullis, and R. Wolfenden, *J. Am. Chem. Soc.*, **105**, 1339 (1983).

The mechanism of this hydrolysis reaction has been studied in great detail.[16] The mechanism is the reverse of that for acetal formation. Acetal protonation is followed by elimination of an alcohol molecule. The resulting intermediate is a stabilized carbocation. Addition of water and a second acid-catalyzed elimination lead to the product.



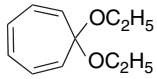
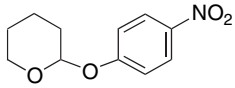
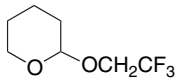
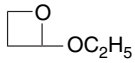
Some of the evidence that has helped to establish the general mechanism is as follows:

1. Isotopic-labeling experiments have established that C−O bond rupture occurs between the carbonyl carbon and oxygen; substitution at the alcohol C−O bond is not involved.
2. For most acetals, the reaction is *specific acid catalyzed*, which is consistent with the existence of a preequilibrium in which the acetal is protonated. The proton assists the departure of the alkoxy group by converting it to a better leaving group. In essence, this cleavage step is an S_N1 reaction with the remaining alkoxy group stabilizing the carbocation formed by ionization.
3. Hammett treatments show good correlations with large negative ρ values for the hydrolysis of acetals of aromatic aldehydes, which is consistent with the development of a positive charge at the carbonyl center in the rate-determining step.
4. Solvent isotope effects are usually in the range $k_{D_2O}/k_{H_2O} = 2$–3. These values reflect the greater equilibrium acidity of deuterated acids (see Section 3.7.1.1) and indicate that the initial protonation is a fast preequilibrium.

Acetal hydrolyses usually exhibit specific acid catalysis, in agreement with a mechanism involving rate-determining cleavage of the conjugate acid of the reactant. However, general acid catalysis is observed in certain acetals and ketals in which special structural features reduce the energy required for C−O bond cleavage.[17] Thus, hydrolysis of each of the acetals shown in Scheme 7.1 exhibits general acid catalysis, and each acetal has a structural feature that facilitates C−O bond heterolysis. Reducing the energy requirement for C−O bond cleavage permits the proton transfer step to become partially rate determining and results in the observation of general acid catalysis.

16. E. H. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581 (1974).
17. T. H. Fife, *Acc. Chem. Res.*, **5**, 264 (1972).

Scheme 7.1. Acetals that Exhibit General Acid Catalysis in Hydrolysis

	Acetal	Structural feature promoting hydrolysis
1[a]		Very stable oxonium ion intermediate; stabilized by aromaticity.
2[b]		Resonance–stabilized phenolic leaving group.
3[c]		Especially acidic alcohol is good leaving group.
4[d]		Ring strain is relieved in bond–breaking step
5[e]	$(Ar)_2C(OC_2H_5)_2$	Aryl substituents stabilize oxonium ion.
6[f]	$PhCH[OC(CH_3)_3]_2$	Aryl stabilization of oxonium ion and relief of steric strain.

a. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **91**, 7163 (1969).
b. T. H. Fife and L. H. Brod, *J. Am. Chem. Soc.*, **92**, 1681 (1970).
c. J. L. Jensen and W. B. Wuhrman, *J. Org. Chem.*, **48**, 4686 (1983).
d. R. F. Atkinson and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 819 (1974).
e. R. H. DeWolfe, K. M. Ivanetich, and N. F. Perry, *J. Org. Chem.*, **34**, 848 (1969).
f. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **93**, 1701 (1971).

Two-dimensional potential energy diagrams can be used to evaluate structural effects on the reactivity of carbonyl compounds and the tetrahedral intermediates. These reactions involve the formation or breaking of two separate bonds. This is the case in the first stage of acetal hydrolysis, which involves both a proton transfer and breaking of a C−O bond. The overall reaction might take place in several ways, but there are two stepwise mechanistic extremes.

1. The proton can be completely transferred and then the departing alcohol molecule can leave to form a carbocation in a distinct second step. This is the specific acid-catalyzed mechanism.
2. The acetal can undergo ionization with formation of an alkoxide ion and a carbocation. The alkoxide is protonated in a second step. This mechanism is very unlikely, because an alkoxide ion is a poor leaving group.
3. An alternative mechanism involves general acid catalysis, in which the proton transfer and the C−O bond rupture occur as a *concerted process*. The concerted process need not be perfectly synchronous; that is, proton transfer might be

more complete at the TS than C−O rupture, or vice-versa. These ideas are represented in the two-dimensional energy diagram in Figure 7.3.

The two paths around the edge of the diagram represent the stepwise processes described as the mechanistic extremes 1 and 2. We know that Process 2 represented by path (a) is a high-energy process so the upper-left corner of the diagram would have a very high energy. The lines designated (b) and (c) indicate concerted but nonsynchronous mechanisms in which there is both partial proton transfer and partial C−O bond rupture at the transition state. In path (b) C−O cleavage is more complete than proton transfer at the transition state, whereas the reverse is true for path (c). Both these paths represent concerted, general acid-catalyzed processes. Path (d) represents the specific acid-catalyzed process in which proton transfer precedes C−O cleavage.

If it is possible to estimate or calculate the energy of the reacting system at various stages, the energy dimension can be added as in Figure 7.4 and can be shown as contours. The actual mechanism is the process that proceeds over the lowest energy barrier. The diagram in Figure 7.4 shows the initial ionization to an alkoxide and carbocation as very high in energy. The stepwise path of protonation followed by ionization is shown with smaller barriers with the protonated ketal as an intermediate. The lowest energy path is shown as a concerted process represented by the dashed line. The TS, which lies at the highest energy point on this line, would exhibit more complete proton transfer than C−O cleavage.

Structural and substituent effects can be discussed by considering how they affect the position of the TS on the potential energy surface. The stepwise path via the protonated acetal is preferred in the case of alcohols that are poor leaving groups. If the alcohol is more acidic, its conjugate base is a better leaving group and the TS shifts to a point where C−O bond breaking begins before proton transfer is complete. This means that the mechanism is concerted, although the TS still has much of the character of a carbocation. Two-dimensional reaction energy diagrams can be used to describe how structural changes affect the nature of the TS. Just as potential energy diagrams give

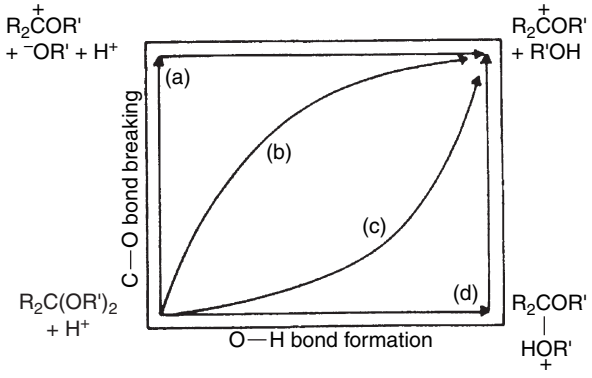


Fig. 7.3. Representation of mechanism for the first stage of acetal hydrolysis: (a) stepwise mechanism with initial C−O bond breaking; (b) concerted mechanism with C−O bond breaking leading O−H bond formation; (c) concerted mechanism with proton transfer leading C−O bond breaking; and (d) stepwise mechanism with initial proton transfer.

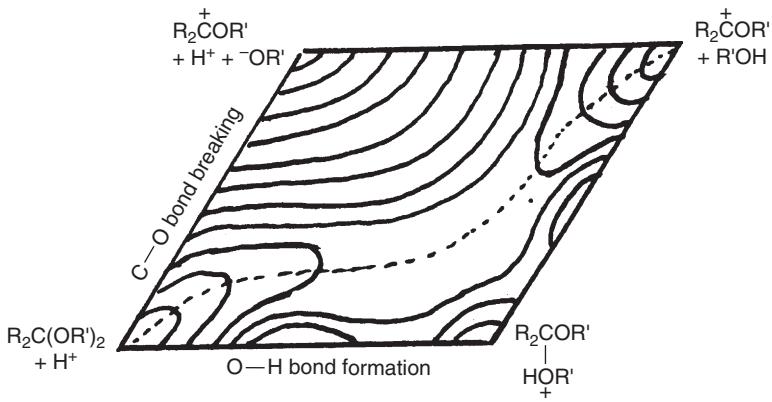
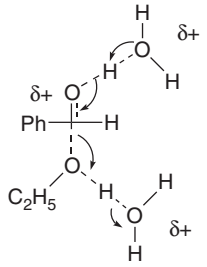


Fig. 7.4. Contour plot showing a favored concerted mechanism for the first step in acetal hydrolysis, with proton transfer more advanced at the transition state than C−O bond breaking.

meaning to such phrases as an "early" or a "late" TS, the two-dimensional diagrams are illustrative of statements such as "C−O cleavage is more advanced than proton transfer."

Consideration of the types of acetals shown in Scheme 7.1, which exhibit general acid catalysis, indicates why the concerted mechanism operates in these molecules. The developing aromatic character of the cation formed in the case of Entry 1 lowers the energy requirement for C−O bond rupture. The bond can begin to break before protonation is complete. Entries 2 and 3 are cases where a better leaving group reduces the energy requirement for C−O bond cleavage. In Entry 4, the four-membered ring is broken in the reaction. Cleavage in this case is facilitated by release of strain energy. Entries 5 and 6 are similar to Entry 1 because the aryl groups provide stabilization for developing cationic character.

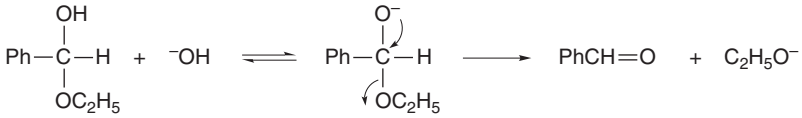
The second step in acetal hydrolysis is conversion of the hemiacetal to the carbonyl compound. The mechanism of this step is similar to that of the first step. Usually the second step is faster than the initial one.[18] Hammett σ−ρ plots and solvent isotope effects both indicate that the TS has less cationic character than is the case for the first step. These features of the mechanism suggest that a concerted removal of the proton at the hydroxy group occurs as the alcohol is eliminated.



[18] Y. Chiang and A. J. Kresge, *J. Org. Chem.*, **50**, 5038 (1985); R. A. McClelland, K. M. Engell, T. S. Larsen, and P. O. Sorensen, *J. Chem. Soc., Perkin Trans. 2*, 2199 (1994).

The positive charge is dispersed over several atoms and this diminishes the sensitivity of the reaction to substituent effects. The ρ values that are observed are consistent with this interpretation. Whereas ρ is −3.25 for hydrolysis of aryl acetals, it is only −1.9 for hemiacetal hydrolysis.[19]

In contrast to acetals, which are base stable, hemiacetals undergo base-catalyzed hydrolysis. In the alkaline pH range the mechanism shifts toward a base-catalyzed elimination.



There are two opposing substituent effects on this reaction. Electron-attracting aryl substituents favor the deprotonation but disfavor the elimination step. The observed substituent effects are small, and under some conditions the Hammett plots are nonlinear.[20]

7.3. Condensation Reactions of Aldehydes and Ketones with Nitrogen Nucleophiles

The mechanistic pattern of hydration and alcohol addition reactions of ketones and aldehydes is followed in reactions of carbonyl compounds with amines and related nitrogen nucleophiles. These reactions involve addition and elimination steps proceeding through tetrahedral intermediates. These steps can be either acid catalyzed or base catalyzed. The rates of the reactions are determined by the energy and reactivity of the tetrahedral intermediates. With primary amines, C=N bond formation ultimately occurs. These reactions are reversible and the position of the overall equilibrium depends on the nitrogen substituents and the structure of the carbonyl compound.

Scheme 7.2 lists some familiar types of such reactions. In general, these reactions are reversible and mechanistic information can be obtained by study of either the forward or the reverse process.

[19] T. J. Przystas and T. H. Fife, *J. Am. Chem. Soc.*, **103**, 4884 (1981).
[20] R. L. Finley, D. G. Kubler, and R. A. McClelland, *J. Org. Chem.*, **45**, 644 (1980).

Scheme 7.2. Addition-Elimination Reactions of Aldehydes and Ketones

$R_2C{=}O + R'NH_2 \rightleftharpoons$	$R_2C{=}NR'$	imine, also called Schiff base, especially when the amine is an aniline derivative
$R_2C{=}O + NH_2OH \rightleftharpoons$	$R_2C{=}NOH$	oxime
$R_2C{=}O + H_2NNHR' \rightleftharpoons$	$R_2C{=}NNHR'$	hydrazone
$R_2C{=}O + H_2NNHC(=O)NH_2 \rightleftharpoons$	$R_2C{=}NNHC(=O)NH_2$	semicarbazone

For simple alkyl amines, the K for imine formation in aqueous solution is defined as

$$K = \frac{[\text{imine}][H_2O]}{[\text{aldehyde}][\text{amine}]}$$

The value of K has been measured for several amines with 2-methylpropanal.[21] The effect of the structure of the alkyl group is quite small, although the trifluoroethyl group significantly reduces imine stability.

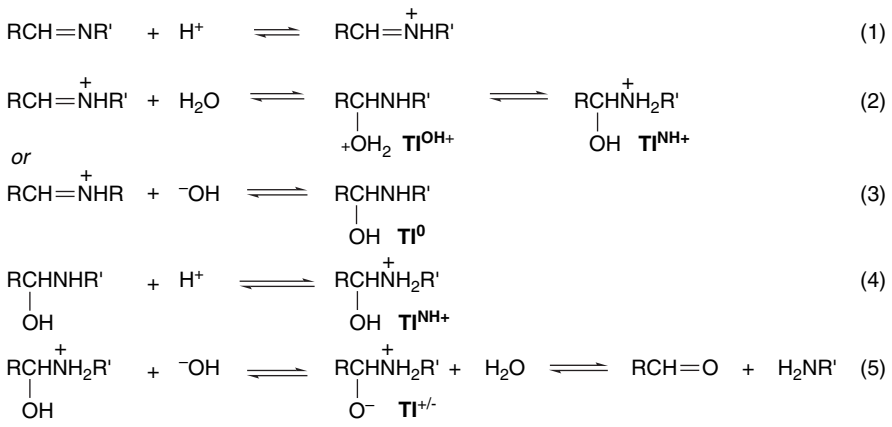
Equilibrium Constants for Imines Formation with 2-Methylpropanal

Amine	K
CH_3NH_2	4.98×10^3
$CH_3CH_2NH_2$	3.49×10^3
$CH_3CH_2CH_2NH_2$	4.18×10^3
$(CH_3)_2CHNH_2$	1.84×10^3
$PhCH_2NH_2$	2.50×10^3
$CF_3CH_2NH_2$	2.38×10^2
$CH_3OCH_2CH_2NH_2$	2.06×10^3

The hydrolysis of simple imines occurs readily in aqueous acid, and has been studied in detail by kinetic methods. The precise mechanism is a function of the reactant structure and the pH of the solution. The overall mechanism consists of an addition of water to the C=N bond, followed by expulsion of the amine from a tetrahedral intermediate.[22] There are at least four variants of the tetrahedral intermediate that differ in the extent and site of protonation. In the general mechanism below, the neutral intermediate is labeled $\mathbf{TI}^0$ and the zwitterionic form is labeled $\mathbf{TI}^{+/-}$. There are two possible monoprotonated forms, one protonated on oxygen ($\mathbf{TI}^{\mathbf{OH}+}$) and one protonated on nitrogen ($\mathbf{TI}^{\mathbf{NH}+}$).

[21] J. Hine and C. Y. Yeh, *J. Am. Chem. Soc.*, **89**, 2669 (1967); J. Hine, C. Y. Yeh, and F. C. Schmalstieg, *J. Org. Chem.*, **35**, 340 (1970).

[22] (a) J. Hine, J. C. Craig, Jr., J. G. Underwood, II, and F. A. Via, *J. Am. Chem. Soc.*, **92**, 5194 (1970); (b) E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **85**, 2843 (1963).



The rates of the various steps are a function of the pH of the solution, the basicity of the imine, and the reactivity of the aldehyde. Imine protonation enhances reactivity toward either water or hydroxide ion as nucleophiles. *N*-Protonation in the tetrahedral intermediate makes the amine a better leaving group. The zwitterionic intermediate $\mathbf{TI}^{+/-}$ is more reactive toward elimination of the amine than $\mathbf{TI}^{\mathbf{NH}+}$ because of the assistance of the anionic oxygen. In the alkaline range, the rate-determining step is usually nucleophilic attack by hydroxide ion on the protonated C=N bond (Step 3). At intermediate pH values, water replaces hydroxide as the dominant nucleophile (Step 2). In acidic solution, the rate-determining step is the breakdown of the tetrahedral intermediate (Step 5). A mechanism of this sort, in which the observed rate is sensitive to pH, can be usefully studied by constructing a pH-rate profile, which is a plot of the observed rate constants versus pH. (See Section 3.7.1.4 to review pH-rate profiles.) Figure 7.5 is an example of the pH-rate profile for hydrolysis of a series of imines derived from substituted aromatic aldehydes and *t*-butylamine. The form of pH-rate profiles can be predicted on the basis of the detailed mechanism of the reaction. The value of the observed rates can be calculated as a function of pH if a sufficient number of the individual rate constants and the acid dissociation constants of the participating species are known. Agreement between the calculated and observed pH-rate profiles serves as a sensitive test of the adequacy of the postulated mechanism. Alternatively, one may begin with the experimental pH-rate profile and deduce details of the mechanism from it.

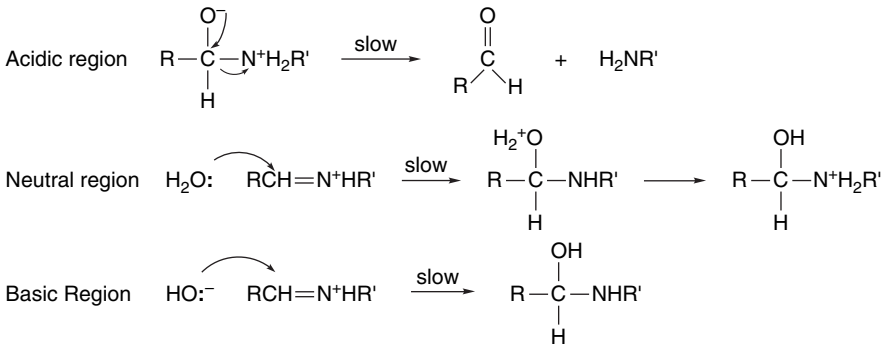
Complete understanding of the shape of the curves in Figure 7.5 requires a kinetic expression somewhat more complicated than we wish to deal with here. However, the nature of the extremities of the curve can be understood on the basis of qualitative arguments. The rate decreases with pH in the acidic region because formation of the zwitterionic tetrahedral intermediate $\mathbf{TI}^{+/-}$ is required for expulsion of the amine (Step 5). The concentration of the zwitterionic species decreases with increasing acidity, since its concentration is governed by an acid-base equilibrium.

$$K = \frac{[\mathrm{H}^+][\mathbf{TI}^{+/-}]}{[\mathbf{TI}^{\mathbf{NH}+}]}$$

Note also that in the acidic region, EWG substituents accelerate the reaction, owing to a more favorable equilibrium for the hydration step. In the alkaline region, the rate is pH independent. In this region, the rate-controlling step is attack of the

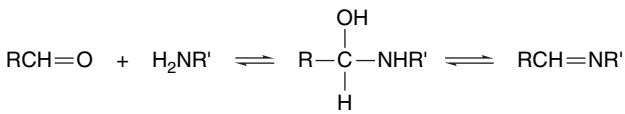
hydroxide ion on the protonated imine (Step 3). The concentration of both of these species is pH dependent, but in opposite, compensating, ways. The overall rate is therefore pH independent in the alkaline range. (Work problem 7.26 to establish that this is so.) Note that in this region the substituent effect is considerably smaller and is in the opposite sense from the acidic portion of the profile. This is due to the enhanced basicity of the ERG-substituted imines. At any given pH, more of the protonated imine is present for the ERG substituents.

The pH-rate profile for the hydrolysis of the *N*-methylimine of 2-methylpropanal is shown in Figure 7.6. The curve is similar to that for aromatic ketones with EWG substituents. The rate increases in the pH range 0–4.5, where decomposition of the zwitterionic intermediate is rate controlling. In the pH range 4.5–8, the rate decreases and then levels off. This corresponds to the transformation of the protonated imine to the less reactive neutral form. Above pH 8, the rate is again constant, as the increase in $[^{-}OH]$ is compensated by the decrease in the amount of protonated imine.



G2 computations have been used to model the formation of the imine between methylamine and formaldehyde and to study the effect of water on the process.[23] The computations lead to the TS structures and energy profiles shown in Figure 7.7. The results point to the importance of the proton transfer steps in the overall energy requirement of the reaction. The inclusion of one or two water molecules leads to cyclic TS for proton transfer. This corresponds to concerted addition and elimination of water through six- and eight-membered cyclic hydrogen-bonded structures. The addition of water molecules substantially lowers the energy of the TS for each step of the reaction, while having relatively modest effects on the energy of the products. This is because the TSs involve considerably more charge separation than the products.

The formation of imines takes place by a mechanism that is the reverse of hydrolysis. Preparative procedures often ensure completion of the reaction by removing water by azeotropic distillation or by the use of an irreversible dehydrating agent.



The other C=N systems included in Scheme 7.2 are more stable to aqueous hydrolysis than the imines. The equilibrium constants for oxime formation are high, even in

[23] N. E. Hall and B. I. Smith, *J. Phys. Chem. A*, **102**, 4930 (1998).

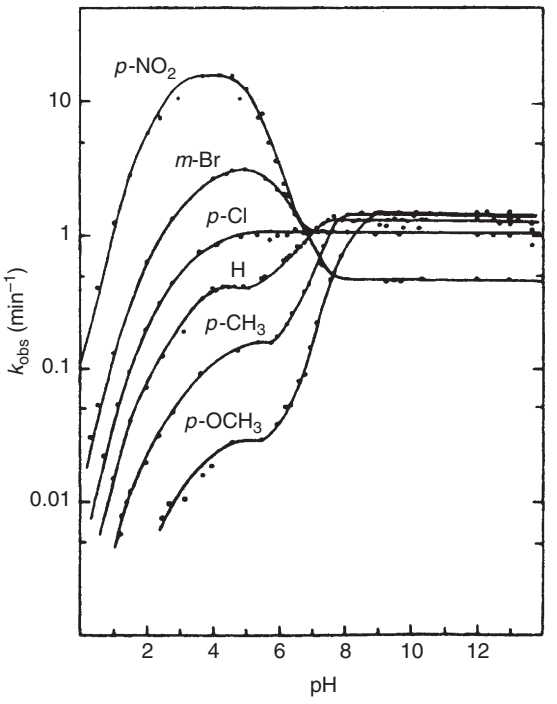


Fig. 7.5. pH-Rate profile for the hydrolysis of substituted benzylidene-1,1-dimethylethylamines. Reproduced from *J. Am. Chem. Soc.*, **85**, 2843 (1963), by permission of the American Chemical Society.

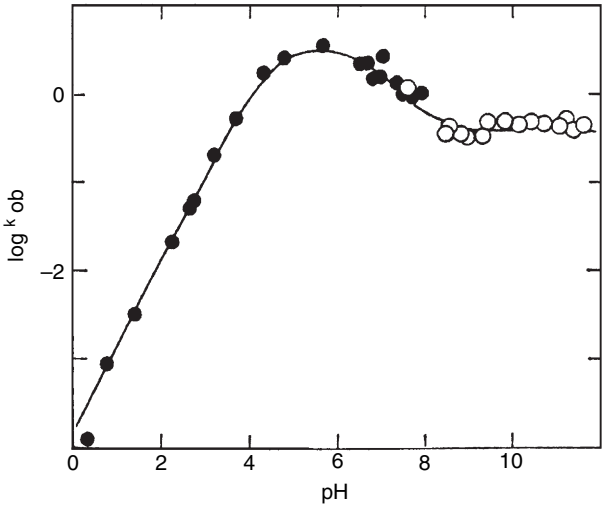


Fig. 7.6. pH-Rate profile for hydrolysis of *N*-methyl-2-methylpropanimine in water at 35°C. Solid points are from the hydrolysis reaction and open points are from the formation of the imine. Reproduced from *J. Am. Chem. Soc.*, **92**, 5194 (1970), by permission of the American Chemical Society.

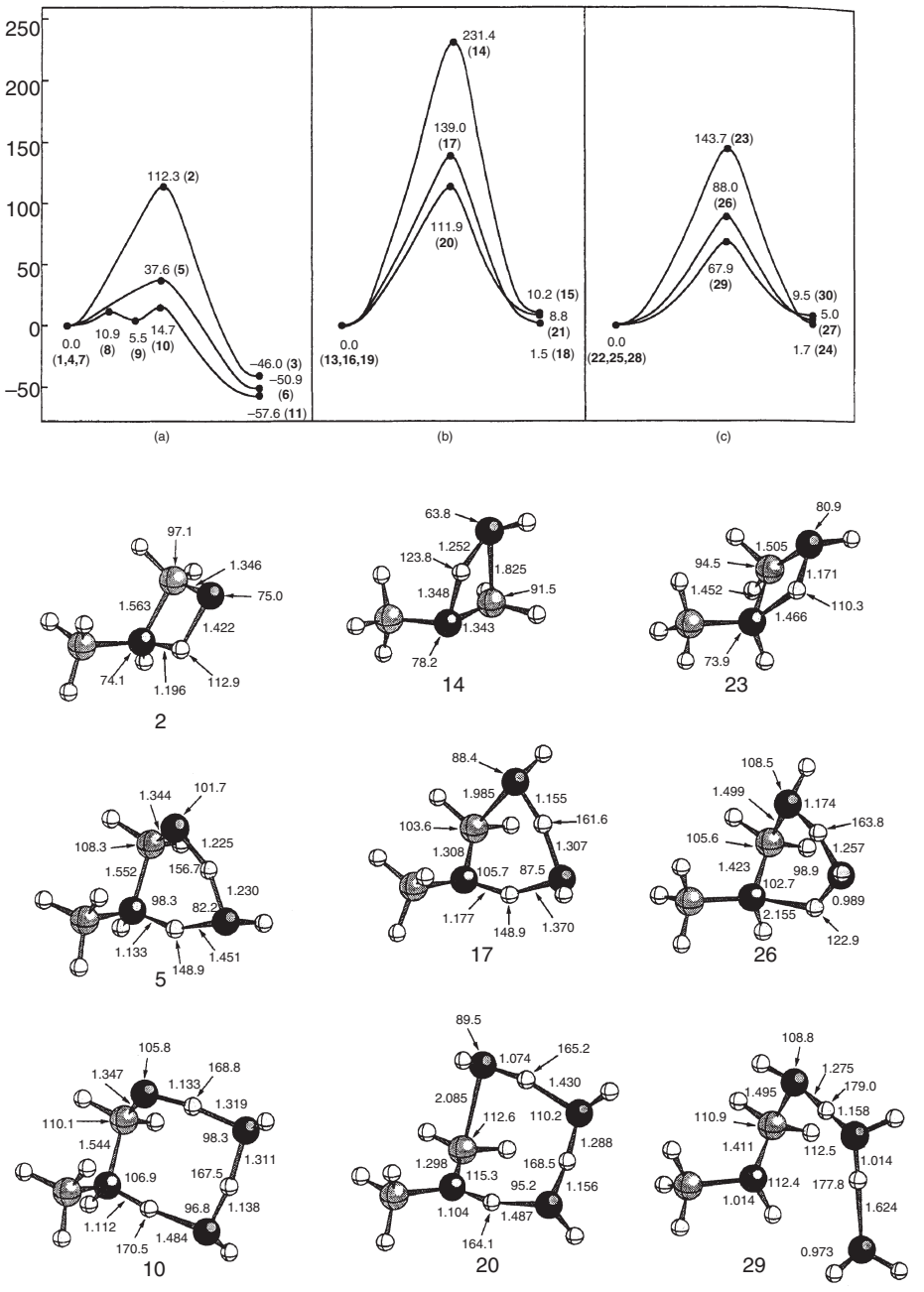
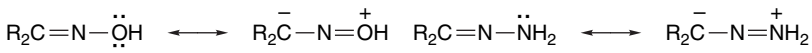


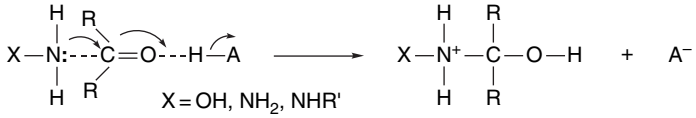
Fig. 7.7. Upper panel: Energy profiles in kJ/mol from G2 computations for: (a) carbinolamine formation, (b) imine formation, and (c) iminium ion formation with zero, one, and two water molecules. Lower panel: Transition structures for carbinolamine, imine, and iminium ion formation with zero, one, and two water molecules and showing selected bond lengths and angles. Reproduced from *J. Phys. Chem. A*, **102**, 4930 (1998), by permission of the American Chemical Society.

aqueous solution. For example, the values for acetone ($4.7 \times 10^5\ M^{-1}$), 3-pentanone ($7.7 \times 10^4\ M^{-1}$), and cyclopentanone ($4.0 \times 10^5\ M^{-1}$) have been measured.[24] Traditionally, the additional stability was attributed to the participation of the atom adjacent to the nitrogen in delocalized bonding.

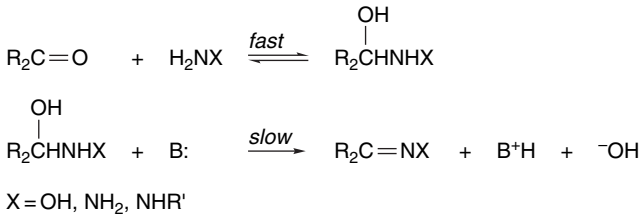


However, analysis based on HF/6-31G* computations suggests that reduction of the lone pair repulsions that are present in hydroxylamine and hydrazine reactants may be more important.[25]

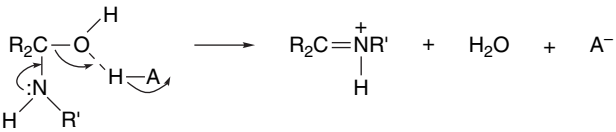
The formation of oximes and hydrazones is usually catalyzed by both general acids and general bases. The acid-catalyzed addition step can be depicted as concerted proton transfer and nucleophilic addition.[26]



General base catalysis of dehydration of the tetrahedral intermediate involves nitrogen deprotonation concerted with elimination of hydroxide ion.[27]



General acid catalysis of the breakdown of the carbinolamine intermediate occurs by assistance of the expulsion of water.



As with imines, the identity of the rate-limiting step changes with solution pH. As the pH decreases, the rate of addition decreases because protonation of the amino compound reduces the concentration of the nucleophilic unprotonated form. Thus, while the dehydration step is normally rate determining in neutral and basic solutions, addition becomes rate determining in acidic solutions. Figure 7.8 shows the pH-rate profiles for oximation of benzaldeyhyde and acetone. The acetone profile shows a region from pH 8 to 10 that is pH independent and corresponds to catalysis by water. The profile for benzaldehyde shows only a very slight contribution from a pH-independent reaction.

24. J. Hine, J. P. Zeigler, and M. Johnston, *J. Org. Chem.*, **44**, 3540 (1979).
25. K. B. Wiberg and R. Glaser, *J. Am. Chem. Soc.*, **114**, 841 (1992).
26. C. G. Swain and J. C. Worosz, *Tetrahedron Lett.*, 3199 (1965).
27. W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964); J. M. Sayer, M. Peskin, and W. P. Jencks, *J. Am. Chem. Soc.*, **95**, 4277 (1973).

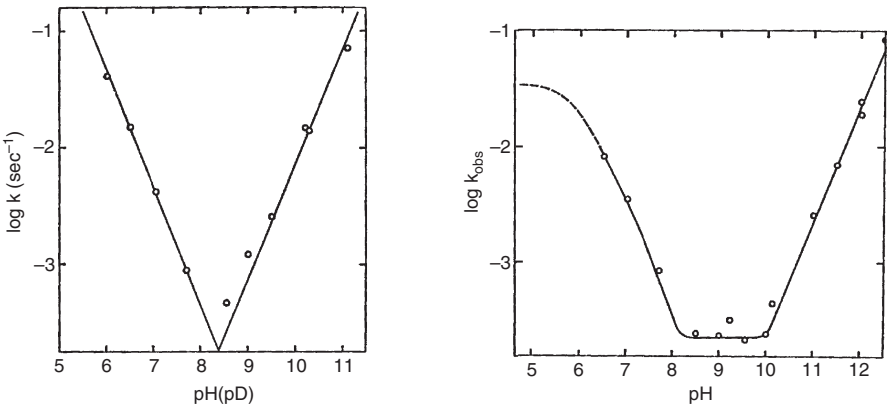


Fig. 7.8. pH-Rate profiles for formation of oximes of benzaldehyde (left) and acetone (right). The solid lines are the theoretical lines of slope −1, 0, and +1. Reproduced from *J. Am. Chem. Soc.*, **88**, 2508 (1966), by permission of the American Chemical Society.

The ρ values for both the addition and elimination steps in oxime formation of aromatic aldehydes have been determined.[28] For addition, ρ is +1.21 (and the best correlation is with σ^+). This is due to the decreased reactivity of aldehydes having direct conjugation with donor substituents. For the dehydration step, ρ is −0.85, which is the result of stabilization of the developing C=N bond by conjugation with donor substituents.

The mechanism of semicarbazone formation is similar to that for oximes.[29] The rate-limiting step at neutral pH is acid-catalyzed dehydration of the tetrahedral intermediate. Comparison of the semicarbazone and oxime formation reactions with those for imines has shown that there are differences in the details, such as the pH ranges associated with the different steps. The less basic amines, including aromatic amines and semicarbazide, undergo the addition step through concerted general acid catalysis. That is, the activation of the carbonyl group by simultaneous interaction with a proton donor is important.[30] For the more nucleophilic primary amines and hydroxylamine, the proton transfer associated with the addition step can be accomplished by the solvent, without an external proton source. Note that this relationship between amine nucleophilicity and the nature of proton transfer are consistent with the broad concepts indicated in Figure 7.1.

Certain reactions between carbonyl compounds and nucleophiles are catalyzed by amines. Some of these reactions are of importance for forming carbon-carbon bonds and these are discussed in Section 2.2.3 of Part B. The mechanistic principle can be illustrated by considering the catalysis of the reaction between ketones and hydroxylamine by aniline derivatives.[31]

$$\mathrm{ArCH{=}O} + \mathrm{H_2NOH} \xrightarrow{\mathrm{ArNH_2}} \mathrm{ArCH{=}NOH} + \mathrm{H_2O}$$

[28] M. Calzadilla, A. Malpica, and T. Cordova, *J. Phys. Org. Chem.*, **12**, 708 (1999).

[29] W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959); B. M. Anderson and W. P. Jencks, *J. Am. Chem. Soc.*, **82**, 1773 (1960).

[30] R. B. Martin, *J. Phys. Chem.*, **68**, 1369 (1964).

[31] E. H. Cordes and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 826 (1962); J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.*, **42**, 1593 (1977).

Analysis of the kinetics of this catalysis points to the protonated imine as the key reactant.

$$ArCH{=}O + Ar'NH_2 + H^+ \xrightarrow{slow} ArCH{=}N^+HAr' + H_2O$$
$$ArCH{=}N^+HAr' + H_2NOH \xrightarrow{fast} ArCH{=}NOH + Ar'NH_2$$

Because the imine nitrogen is much more basic than the carbonyl oxygen, it is more extensively protonated than the aldehyde at any given pH. The protonated imine is also more reactive as an electrophile than the neutral aldehyde. There are four possible electrophiles in the system.

$$ArCH{=}O^+H > ArCH{=}N^+HAr' > ArCH{=}O > ArCH{=}NAr'$$

The protonated imine is the dominant reactive form. Although the protonated aldehyde is more reactive, its concentration is very low, because it is much less basic than the imine or the reactant hydroxylamine. On the other hand, even though the aldehyde may be present in a greater concentration than the protonated imine, its reactivity is sufficiently less that the iminium ion is the major reactant.

Secondary amines cannot form imines, and dehydration proceeds to give a carbon-carbon double bond bearing an amino substituent (enamine). Enamines were mentioned in Chapter 6 as examples of nucleophilic carbon species, and their synthetic utility is discussed in Section 1.3 of Part B. The equilibrium for the reaction between secondary amines and carbonyl compounds ordinarily lies to the left in aqueous solution, but the reaction can be driven forward by dehydration methods.

$$R''_2NH + RCH_2\overset{O}{\overset{\|}{C}}R' \rightleftharpoons RCH_2\underset{NR''_2}{\overset{OH}{\overset{|}{\underset{|}{C}}}}R' \rightleftharpoons RCH{=}\underset{NR''_2}{\overset{}{\underset{|}{C}}}R' + H_2O$$

The mechanism of hydrolysis of enamines has been studied kinetically over a range of pH. In alkaline solution, rate-determining C-protonation is followed by attack of hydroxide ion on the resulting iminium ion. The carbinolamine intermediate then breaks down as in imine hydrolysis. In the neutral and weakly acidic pH range, water attack on the C-protonated enamine becomes rate limiting. As in imine hydrolysis, decomposition of the tetrahedral intermediate becomes rate limiting in strongly acidic solutions.[32]

$$RCH{=}\underset{NR''_2}{\overset{}{\underset{|}{C}}}R' + H^+ \longrightarrow RCH_2\underset{R'}{\overset{+}{\underset{|}{C}}}{=}NR''_2$$

$$RCH_2\underset{R'}{\overset{+}{\underset{|}{C}}}{=}NR''_2 + {}^-OH \longrightarrow RCH_2\underset{R'}{\overset{OH}{\overset{|}{\underset{|}{C}}}}{-}NR''_2 \longrightarrow RCH_2\overset{O}{\overset{\|}{C}}R' + H_2NR''_2$$

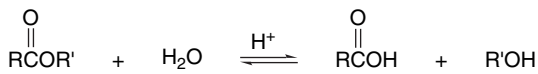
[32] P. Y. Sollenberger and R. B. Martin, *J. Am. Chem. Soc.*, **92**, 4261 (1970); W. Maas, M. J. Janssen, E. J. Stamhuis, and H. Wynberg, *J. Org. Chem.*, **32**, 1111 (1967); E. J. Stamhuis and W. Maas, *J. Org. Chem.*, **30,** 2156 (1965).

7.4. Substitution Reactions of Carboxylic Acid Derivatives

Substitution reactions of carboxylic acid derivatives are among the most fundamental reactions in organic chemistry. The most common derivatives include acyl halides, anhydrides, esters, and carboxamides. Both synthesis and hydrolysis of esters and amides are examples of these substitution reactions. Most of these substitution reactions involve the formation and breakdown of a tetrahedral intermediate. The structural features of the carboxylic acid derivatives and related tetrahedral intermediates are discussed in Section 3.4.4. The fundamental difference in the chemistry of the carboxylic acid derivatives, as compared to ketones and aldehydes, is the presence of a potential leaving group at the carbonyl carbon. The order of reactivity as leaving groups is Cl,Br $>$ O_2CR $>$ OR $>$ NHR $>$ O^- $>$ N^-R. The broad reactivity trends among the carboxylic acid derivatives can be recognized by taking account of the *effect of the substituents on the stability of the carbonyl center and the ability of the various substituents to act as leaving groups from the tetrahedral intermediate*. The detailed mechanisms of these reactions also depend on the site and extent of protonation in the tetrahedral intermediate.

7.4.1. Ester Hydrolysis and Exchange

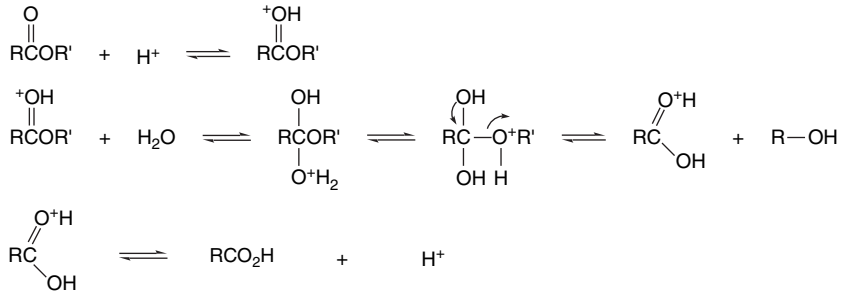
Esters can be hydrolyzed in either basic or acidic solution. In acidic solution, the reaction is reversible. The position of the equilibrium depends on the relative concentration of water and the alcohol. In aqueous solution, hydrolysis occurs. In alcoholic solution, the equilibrium is shifted in favor of the ester.



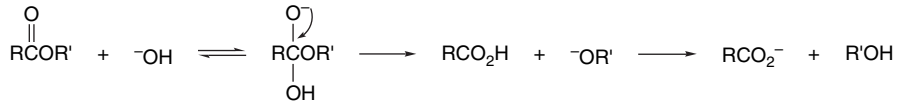
In alkaline aqueous solution, ester hydrolysis is essentially irreversible.

The carboxylic acid is converted to its anion under these conditions, and the position of the equilibrium lies far to the right. The mechanistic designations $A_{AC}2$ and $B_{AC}2$ are given to the acid- and base-catalyzed hydrolysis mechanisms, respectively. The A denotes acid catalysis and B indicates base catalysis. The subscript AC designation indicates that acyl-oxygen bond cleavage occurs. The digit 2 has its usual significance, indicating the bimolecular nature of the rate-determining step.

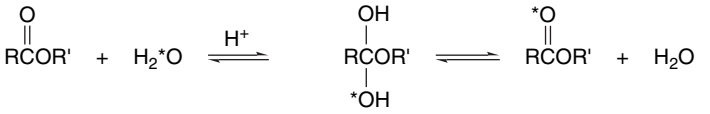
$A_{AC}2$ mechanism



$B_{AC}2$ mechanism



Esters without special structural features can hydrolyze by either of these mechanisms. Among the evidence supporting these mechanisms are kinetic studies that show the expected dependence on hydrogen ion or hydroxide ion concentration and isotopic-labeling studies that prove it is the acyl-oxygen bond, not the alkyl-oxygen bond, that is cleaved during hydrolysis.[33] Acid-catalyzed hydrolysis of esters is accompanied by some exchange of oxygen from water into the carbonyl group. This exchange occurs by way of the tetrahedral intermediate because loss of water is competitive with expulsion of the alcohol.



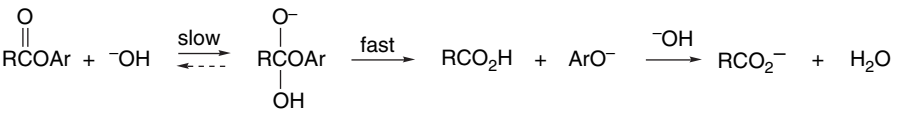
Alkyl benzoate esters give only a small amount of exchange under basic hydrolysis conditions. This means that reversal of the hydroxide addition must be slow relative to the forward breakdown of the tetrahedral intermediate.[34]

Substituent effects come into play at several points in the ester hydrolysis mechanism. In the base-catalyzed reaction, EWG substituents in either the acyl or alkoxy group facilitate hydrolysis. If the carbonyl group is conjugated with an ERG, reactivity is decreased by ground state stabilization. Since the rate-determining tetrahedral intermediate is negatively charged, the corresponding TS is stabilized by an EWG. The partitioning of the tetrahedral intermediate between reversion to starting material by loss of hydroxide ion and formation of product by expulsion of the alkoxide is strongly affected by substituents in the alkoxy group. An EWG on the alkoxy group shifts the partitioning to favor loss of the alkoxide and accelerates hydrolysis. For this reason, exchange of carbonyl oxygen with solvent does not occur in basic hydrolyses when the alkoxy group is a good leaving group. This has been demonstrated, for example, for esters of phenols. As phenols are stronger acids than alcohols,

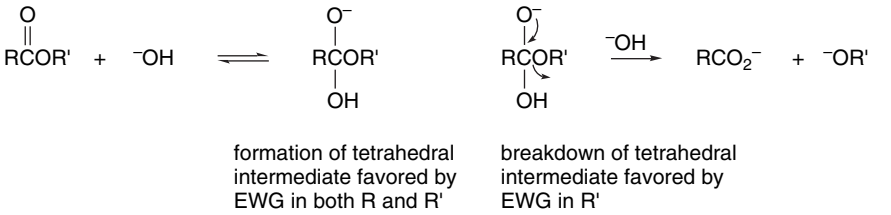
[33] M. I. Bender, *Chem. Rev.*, **60**, 53 (1960); S. L. Johnson, *Adv. Phys. Org. Chem.*, **5**, 237 (1967); D. P. N. Satchell and R. S. Satchell, in *Chemistry of Carboxylic Acid Derivatives*, Vol. 2, Part 1, S. Patai, ed., Wiley, New York, 1992, pp. 747–802.

[34] R. A. McClelland, *J. Am. Chem. Soc.*, **106**, 7579 (1984).

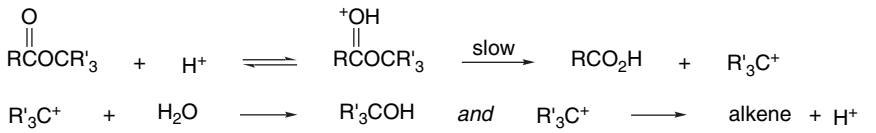
their conjugate bases are better leaving groups than alkoxide ions. Aryl esters are hydrolyzed faster than alkyl esters, without observable exchange of carbonyl oxygen with solvent.



These substituent effects can be summarized for the $B_{AC}2$ mechanism by noting the effect of substituents on each step of the mechanism.



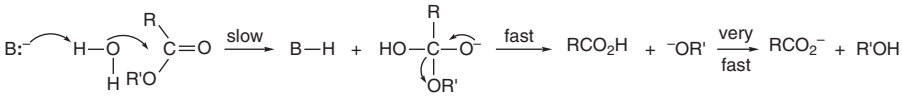
Structural changes in the reactant can shift ester hydrolysis away from the usual $A_{AC}2$ or $B_{AC}2$ mechanisms. When the ester is derived from a tertiary alcohol, acid-catalyzed hydrolysis often occurs by a mechanism involving *alkyl oxygen fission*. The change in mechanism is due to the stability of the tertiary carbocation that can be formed by alkyl-oxygen cleavage.[35] When this mechanism occurs, alkenes as well as alcohols are produced, because the carbocation can react by either substitution or elimination. This mechanism is referred to as $A_{AL}1$, indicating the cleavage of the alkyl-oxygen bond and the unimolecular character of the rate-determining step.



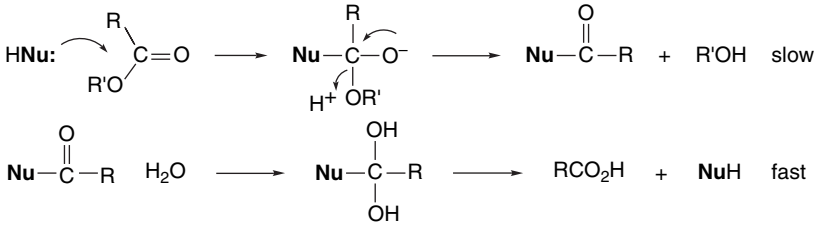
The facile $A_{AL}1$ mechanism of tertiary alkyl esters is valuable in synthetic methodology because it permits tertiary esters to be hydrolyzed selectively. The usual situation involves the use of *t*-butyl esters, which can be cleaved to carboxylic acids by the action of acids such as *p*-toluenesulfonic acid or trifluoroacetic acid under anhydrous conditions where other esters are stable.

The ester hydrolysis mechanisms discussed in the preceding paragraphs pertains to aqueous solutions of strong acids and strong bases, in which specific acid or base catalysis is dominant. In media where other acids or bases are present, general acid-catalyzed and general base-catalyzed hydrolysis can occur. General base catalysis has been observed in the case of esters in which the acyl group carries EWG substituents.[36] The TS for esters undergoing hydrolysis by a general base-catalyzed mechanism involves partial proton transfer from the attacking water molecule to the general base during formation of the tetrahedral intermediate.

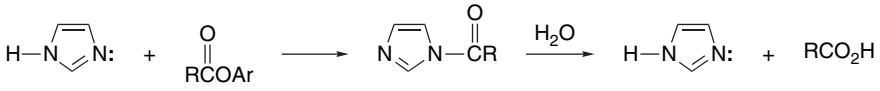
35. A. G. Davies and J. Kenyon, *Q. Rev. Chem. Soc.*, **9**, 203 (1955).
36. W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961); D. Stefanidis and W. P. Jencks, *J. Am. Chem. Soc.*, **115**, 6045 (1993).



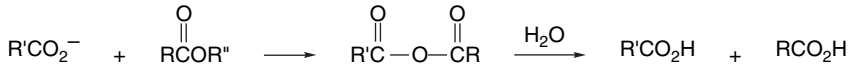
Ester hydrolysis can also occur by *nucleophilic catalysis*. If a component of the reaction system is a more effective nucleophile toward the carbonyl group than water under a given set of conditions, an acyl transfer reaction can take place to form the acyl derivative of the catalytic nucleophile. If this acyl intermediate, in turn, is more rapidly attacked by water than the original ester, the overall reaction will be faster in the presence of the nucleophile than in its absence. These are the requisite conditions for nucleophilic catalysis.



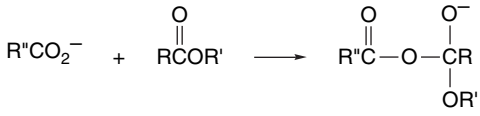
Esters of relatively acidic alcohols (in particular phenols) are hydrolyzed by the nucleophilic catalysis mechanism in the presence of imidazole.[37] The acylimidazolides are inherently quite reactive and protonation of the second nitrogen can facilitate the hydrolysis.



Carboxylate anions can also serve as nucleophilic catalysts.[38] In this case, an anhydride is the reactive intermediate.



The nucleophilic catalysis mechanism only operates when the alkoxy group being hydrolyzed is not substantially more basic than the nucleophilic catalyst. This requirement can be understood by considering the tetrahedral intermediate generated by attack of the potential catalyst on the ester.

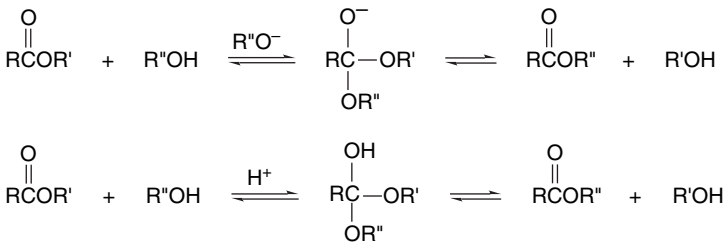


The relative leaving-group abilities of $R'O^-$ and $R''CO_2^-$ are strongly correlated with the basicity of the two anions. If $R''CO_2^-$ is a much better leaving group than $R'O^-$, it will be eliminated preferentially from the tetrahedral intermediate and no catalysis will occur.

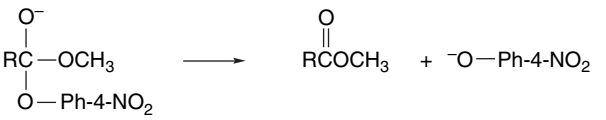
37. T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, **79**, 1663 (1967); M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, **79**, 1652, 1656 (1957); P. Menegheli, J. P. S. Farah, and O. A. El Seoud, *Ber. Bunsenges. Phys. Chem.*, **95**, 1610 (1991).
38. V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc., Perkin Trans. B*, 515 (1968).

The preceding discussion has touched on the most fundamental aspects of ester hydrolysis mechanisms. Much effort has been devoted to establishing some of the finer details, particularly concerning proton transfers during the formation and breakdown of the tetrahedral intermediates. These studies have been undertaken in part because of the importance of hydrolytic reactions in biological systems, which are catalyzed by enzymes. The detailed mechanistic studies of ester hydrolysis laid the groundwork for understanding the catalytic mechanisms of the hydrolytic enzymes. Discussions of the biological mechanisms and their relationship to the fundamental mechanistic studies are available in several books that discuss enzyme catalysis in terms of molecular mechanisms.[39]

Esters react with alcohols in either acidic or basic solution to exchange alkoxy groups (ester interchange) by a mechanism that parallels hydrolysis. The alcohol or alkoxide acts as the nucleophile.



As in the case of hydrolysis, there has been a good deal of study of substituent effects, solvent effects, isotopic exchange, kinetics, and the catalysis of these processes.[40] In contrast to hydrolysis, the alcoholysis reaction is reversible in both acidic and basic solutions. The key intermediate is the tetrahedral adduct. Its fate is determined mainly by the relative basicity of the two alkoxy groups. A tetrahedral intermediate generated by addition of methoxide ion to a *p*-nitrophenyl ester, for example, breaks down exclusively by elimination of the much less basic *p*-nitrophenoxide ion.



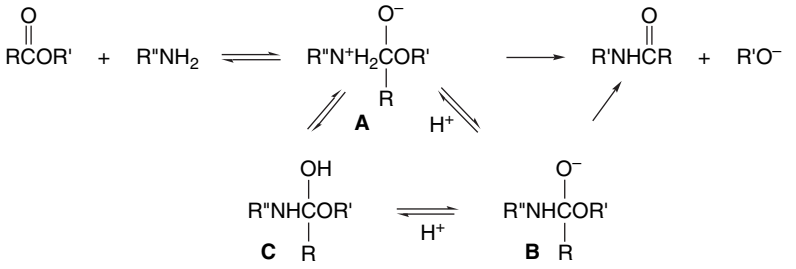
In general, the equilibrium in a base-catalyzed alcohol exchange reaction lies in the direction of incorporation of the less acidic alcohol in the ester. This is a reflection both of the kinetic factor, the more acidic alcohol being a better leaving group, and the greater stabilization provided to the carbonyl group by the more electron-rich alkoxy substituent.

39. T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*, Vol. 1, W. A. Benjamin, New York, 1966, pp. 1–258; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969; M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley-Interscience, New York, 1971; C. Walsh, *Enzymatic Reaction Mechanisms*, W. H. Freeman, San Francisco, 1979; A. Fersht, *Enzyme Structure and Mechanism*, 2nd Edition, W. H. Freeman, New York, 1985.

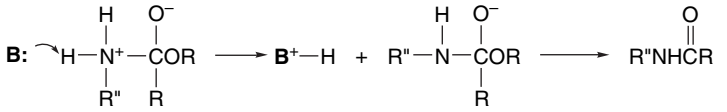
40. C. G. Mitton, R. L. Schowen, M. Gresser, and J. Shapely, *J. Am. Chem. Soc.*, **91**, 2036 (1969); C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Am. Chem. Soc.*, **91**, 2045 (1969).

7.4.2. Aminolysis of Esters

Esters react with ammonia and amines to give amides. The mechanism involves nucleophilic attack of the amine at the carbonyl group, followed by expulsion of the alkoxy group from the tetrahedral intermediate. The identity of the rate-determining step depends primarily on the leaving-group ability of the alkoxy group.[41] With relatively good leaving groups such as phenols or trifluoroethanol, the slow step is expulsion of the oxygen leaving group from a zwitterionic tetrahedral intermediate **A**. With poorer leaving groups, breakdown of the tetrahedral intermediate occurs only after formation of the anionic species **B**.

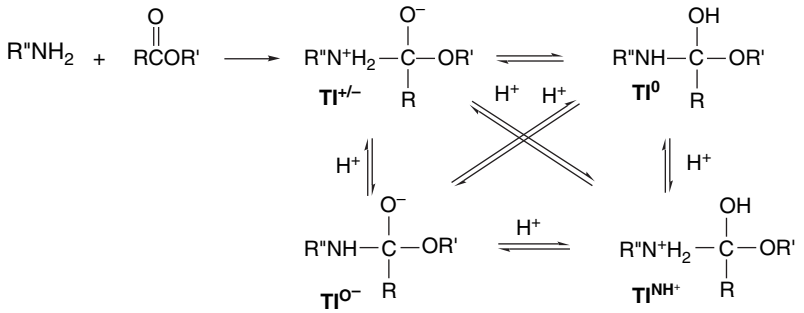


Aminolysis of esters often exhibits general base catalysis in the form of reaction rate terms that are second order in the amine. The amine is believed to assist deprotonation of the zwitterionic tetrahedral intermediate.[42] Deprotonation of the nitrogen facilitates breakdown of the tetrahedral intermediate because the increased electron density at nitrogen favors expulsion of an alkoxide ion.

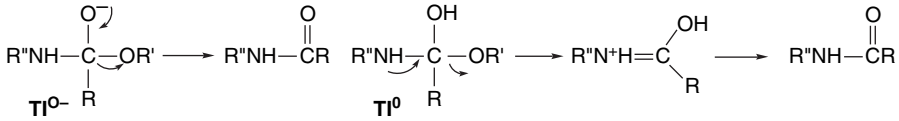


Detailed mechanistic studies have been carried out on aminolysis of substituted aryl acetates and aryl carbonates.[43] Aryl esters are considerably more reactive than alkyl esters because phenoxide ions are better leaving groups than alkoxide ions. The tetrahedral intermediate formed in aminolysis can exist in several forms that differ in the extent and the site of protonation.

41. F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972); A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974).
42. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 104 (1966); J. F. Kirsch and A. Kline, *J. Am. Chem. Soc.*, **91**, 1841 (1969); A. S. Shawali and S. S. Biechler, *J. Am. Chem. Soc.*, **89**, 3020 (1967); J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1961).
43. W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968); A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974); A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7031 (1974); M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 6970 (1977).

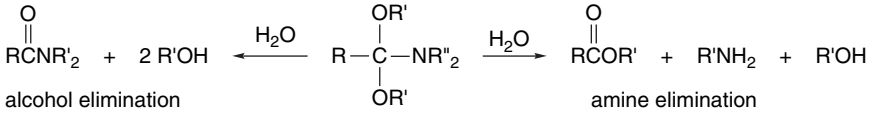


In $\mathbf{TI}^{+/-}$ and $\mathbf{TI}^{\mathbf{NH}+}$, the best leaving group is the neutral amine, whereas in $\mathbf{TI}^{\mathbf{O}-}$ and $\mathbf{TI}^{\mathbf{0}}$ the group $R'O^-$ is a better leaving group than $R''NH^-$. Furthermore, in $\mathbf{TI}^{\mathbf{O}-}$ and $\mathbf{TI}^{\mathbf{0}}$ the unshared pair on nitrogen can assist in elimination. In $\mathbf{TI}^{+/-}$ the negatively charged oxygen also has increased capacity to "push" out the leaving group, with reformation of the carbonyl group. Precisely how the intermediate proceeds to product depends upon pH and the identity of the groups $R''NH_2$ and $R'O^-$. When $R'O^-$ is a relatively poor leaving group, as in the case for alkyl esters, reaction usually occurs through $\mathbf{TI}^{\mathbf{O}-}$ or $\mathbf{TI}^{\mathbf{0}}$.

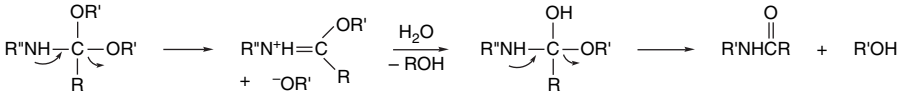


When the leaving group is better, breakdown can occur directly from $\mathbf{TI}^{+/-}$. This is the case when $R'O^-$ is a phenolate anion. The mechanism also depends upon the pH and the presence of general acids and bases because the position of the equilibria among the tetrahedral intermediates and rates of breakdown are determined by these factors.

Insight into the factors that govern breakdown of tetrahedral intermediates has been gained by studying the hydrolysis of amide acetals. If the amine is expelled, an ester is formed, whereas elimination of an alcohol gives an amide.

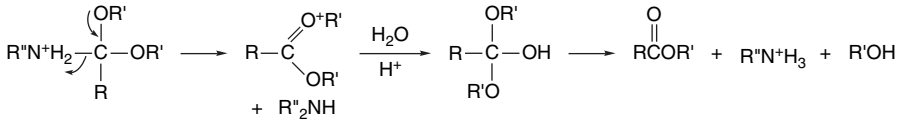


The pH of the solution is of overwhelming importance in determining the course of these hydrolyses.[44] In basic solution, oxygen elimination is dominant, because the unprotonated nitrogen substituent is a very poor leaving group and is also more effective at facilitating the alkoxide elimination by electron donation.



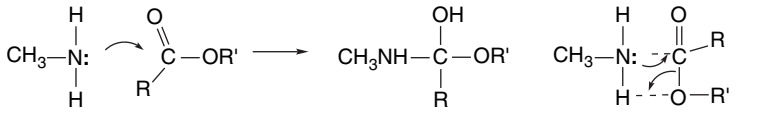
[44.] R. A. McClelland, *J. Am. Chem. Soc.*, **100**, 1844 (1978).

In acidic solution, the protonated nitrogen is a better leaving group, and also loses its ability to assist in the elimination of the alkoxide. Under these circumstances, nitrogen elimination is favored.



In analyzing the behavior of these types of tetrahedral intermediates, it should be kept in mind that proton transfer reactions are usually fast relative to other steps. This circumstance permits the possibility that a minor species in equilibrium with the major species may be the kinetically dominant intermediate. Detailed studies of kinetics, solvent isotope effects, and catalysis are the best tools for investigating the various possibilities.

Recent computational work has suggested the existence of a mechanism for aminolysis that bypasses the tetrahedral intermediates. Transition structures corresponding to both stepwise addition-elimination through a tetrahedral intermediate and direct substitution were found for the reaction of methylamine with methyl acetate and phenyl acetate.[45] There is considerable development of charge separation in the direct displacement mechanism because proton transfer lags rupture of the C−O bond.



Addition-elimination Direct Substitution

The direct substitution reaction becomes progressively more favorable as the alcohol becomes a better leaving group. According to the computations, the two mechanisms are closely competitive for alkyl esters, but the direct substitution mechanism is favored for aryl esters. These results refer to the gas phase.

Computed Activation Energy (kcal/mol)

	Addition-elimination	Direct substitution
$CH_3CO_2CH_3$	35.5	36.2
$CH_3CO_2C_6H_5$	32.1	26.6
$CH_3CO_2C_6H_4NO_2$		~1.7

A direct substitution mechanism was indicated for the 2-pyridone catalysis of aminolysis of methyl acetate by methylamine.[46] This mechanism is represented in Figure 7.9. It avoids a tetrahedral intermediate and describes a concerted displacement process that is facilitated by proton transfer involving 2-pyridone. Two very closely related TSs involving either the 2-hydroxypyridine or 2-pyridone tautomers were found. These TSs show extensive cleavage of the C−O bond (2.0–2.2 Å) and formation

45. H. Zipse, L.-h. Wang, and K. N. Houk, *Liebigs Ann.*, 1511 (1996).
46. L.-h. Wang and H. Zipse, *Liebigs Ann.*, 1501 (1996).

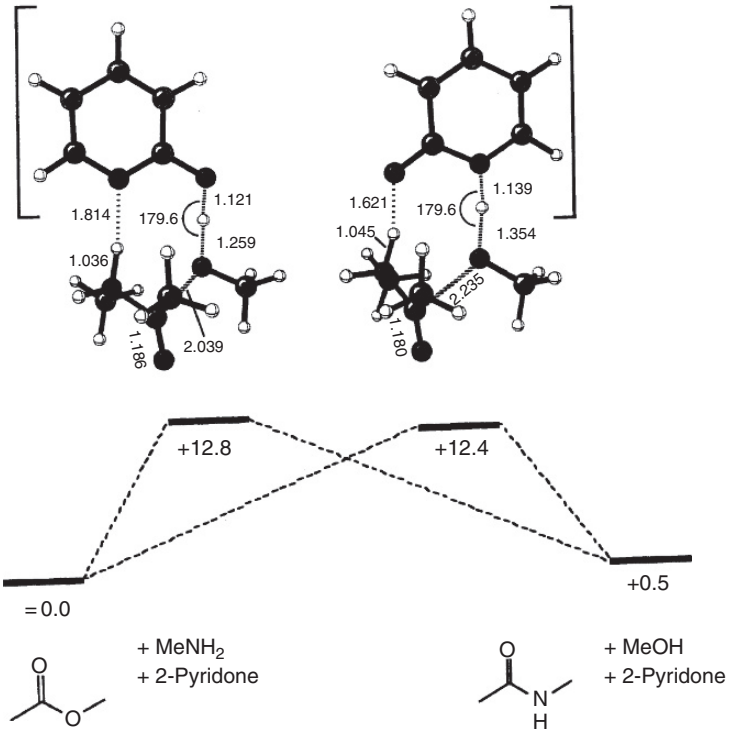
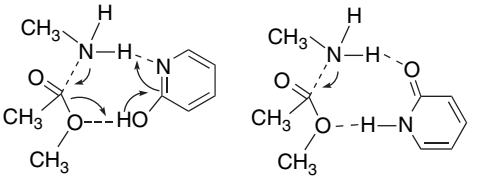


Fig. 7.9. Concerted mechanism for 2-pyridone-catalyzed reaction of methylamine with methyl acetate. TS energies (kcal/mol) are from B3LYP/6-31G** calculations. Reproduced from *Liebigs Ann.*, 1501 (1996), by permission of Wiley-VCM.

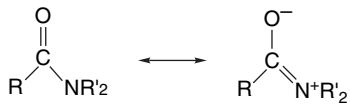
of the C−N bond. O-Protonation is also advanced, but N-deprotonation is minimal. Experimentally, it was found that catalytic efficiency could be improved by a factor of about 2500 by use of the more acidic 4-cyano-2-pyridone.



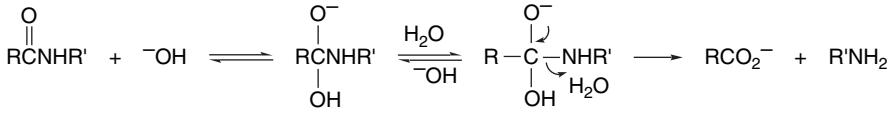
7.4.3. Amide Hydrolysis

The hydrolysis of amides to carboxylic acids and amines requires considerably more vigorous conditions than ester hydrolysis.[47] The reason is that the electron-releasing nitrogen imparts a very significant ground state stabilization that is lost in the TS leading to the tetrahedral intermediate.

[47] C. O'Connor, *Q. Rev. Chem. Soc.*, **24**, 553 (1970).

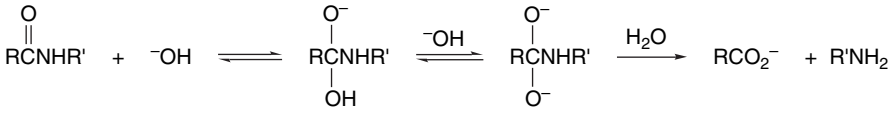


In basic solution, a $B_{AC}2$ mechanism similar to the that for ester hydrolysis is believed to operate.[48]



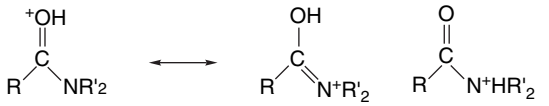
The principal difference lies in the poorer ability of amide anions to act as leaving groups, compared to alkoxides. As a result, protonation at nitrogen is required for dissociation of the tetrahedral intermediate. Exchange between the carbonyl oxygen and water is extensive because reversal of the tetrahedral intermediate to reactants is faster than decomposition to products.

In some amide hydrolyses, the rupture of the tetrahedral intermediate in the forward direction requires formation of a dianion.[49]



This variation from the ester hydrolysis mechanism also reflects the poorer leaving ability of amide ions, as compared to alkoxide ions. The evidence for the involvement of the dianion comes from kinetic studies and from solvent isotope effects that suggest that a rate-limiting proton transfer is involved.[50] The reaction is also higher than first order in hydroxide ion under these circumstances, which is consistent with the dianion mechanism.

The mechanism for acid-catalyzed hydrolysis of amides involves attack by water on the protonated amide. Amides are weak bases with pK_a values in the range from 0 to -2.[51] An important feature of the chemistry of amides is that the most basic site is the carbonyl oxygen. Very little of the N-protonated form is present.[52] The major factor that favors the O-protonated form is the retention of π-electron delocalization over the O−C−N system. No such delocalization is possible in the N-protonated form.



[48] M. L. Bender and R. J. Thomas, *J. Am. Chem. Soc.*, **83**, 4183 (1961); R. S. Brown, A. J. Bennet, and H. Slebocka-Tilk, *Acc. Chem. Res.*, **25**, 481 (1992).

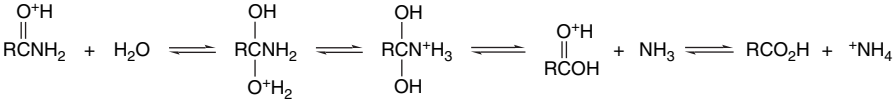
[49] R. M. Pollack and M. L. Bender, *J. Am. Chem. Soc.*, **92**, 7190 (1970).

[50] R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *J. Am. Chem. Soc.*, **88**, 4008 (1966).

[51] R. A. Cox, L. M. Druet, A. E. Klausner, T. A. Modro, P. Wan, and K. Yates, *Can. J. Chem.*, **59**, 1568 (1981); A. Bagno, G. Lovato, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 1091 (1993).

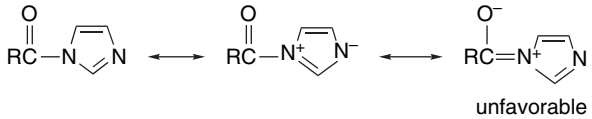
[52] R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148, 2642 (1963); A. R. Fersht, *J. Am. Chem. Soc.*, **93**, 3504 (1971); R. B. Martin, *J. Chem. Soc., Chem. Commun.*, 793 (1972); A. J. Kresge, P. H. Fitzgerald, and Y. Chiang, *J. Am. Chem. Soc.*, **96**, 4698 (1974).

The usual hydrolysis mechanism in strongly acidic solutions involves addition of water to the O-protonated amide followed by dissociation of the tetrahedral intermediate.



There is almost no exchange of oxygen with water during acid-catalyzed hydrolysis of amides.[53] Since a tetrahedral intermediate is involved, the lack of exchange means that it must react exclusively by elimination of the nitrogen substituent. This result is reasonable, because the amino group is the most basic site and is the preferred site of protonation in the tetrahedral intermediate. The protonated amine is a much better leaving group than the hydroxide ion.

Acylimidazoles and related amides in which the nitrogen atom is part of an aromatic ring hydrolyze much more rapidly than aliphatic amides. A major factor is the decreased resonance stabilization of the carbonyl group, which is opposed by the participation of the nitrogen lone pair in the aromatic sextet.

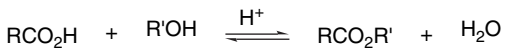


The acid-catalyzed hydrolysis of imidazolides is accelerated by protonation of N(3), which increases the leaving-group ability of the ring,[54] and accumulation of additional nitrogens in the ring (triazoles, tetrazoles) further increased that ability.[55]

7.4.4. Acylation of Nucleophilic Oxygen and Nitrogen Groups

The conversion of alcohols to esters by O-acylation and of amines to amides by N-acylation are fundamental organic reactions that are the reverse of the hydrolyses discussed in the preceding sections. In Section 3.4 of Part B we discuss these reactions from the point of view of synthetic applications and methods.

Although the previous two sections of this chapter emphasized hydrolytic processes, two mechanism that led to O or N-acylation were considered. In the discussion of acid-catalyzed ester hydrolysis, it was pointed out that this reaction is reversible (p. 654). Thus it is possible to acylate alcohols by acid-catalyzed reaction with a carboxylic acid. This is called the *Fischer esterification* method. To drive the reaction forward, the alcohol is usually used in large excess, and it may also be necessary to remove water as it is formed. This can be done by azeotropic distillation in some cases.



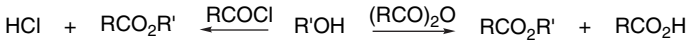
[53] R. A. McClelland, *J. Am. Chem. Soc.*, **97**, 5281 (1975); For cases in which some exchange does occur, see H. Slebocka-Tilk, R. S. Brown, and J. Olekszyk, *J. Am. Chem. Soc.*, **109**, 4620 (1987); A. J. Bennet, H. Slebocka-Tilk, R. S. Brown, J. P. Guthrie, and A. J. Jodhan, *J. Am. Chem. Soc.*, **112**, 8497 (1990).

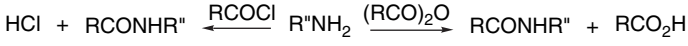
[54] T. H. Fife, *Acc. Chem. Res.*, **26**, 325 (1993).

[55] J. F. Patterson, W. P. Huskey, and J. L. Hoggs, *J. Org. Chem.*, **45**, 4675 (1980); B. S. Jursic and Z. Zdravkovski, *Theochem*, **109**, 177 (1994).

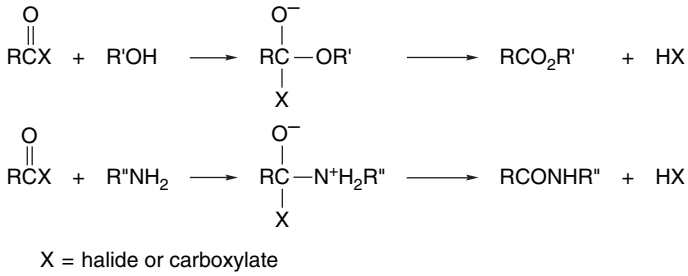
The second reaction that should be recalled is the aminolysis of esters (p. 659), which leads to the formation of amides by N-acylation. The equilibrium constant for this reaction is ordinarily favorable, but the reactions are rather slow.

The most common O- and N-acylation procedures use acylating agents that are more reactive than carboxylic acids or their esters. Acyl chlorides and anhydrides react rapidly with most unhindered alcohols and amines to give esters and amides, respectively.

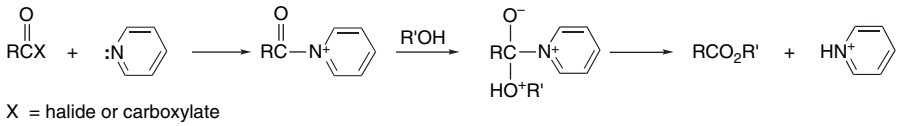




The general features of the mechanisms are well established.[56] The nucleophilic species undergoes addition at the carbonyl group, followed by elimination of the halide or carboxylate group. Acyl halides and anhydrides are reactive acylating reagents because of a combination of the polar effect of the halogen or oxygen substituent, which enhances the reactivity of the carbonyl group, and the ease with which the tetrahedral intermediate can expel these relatively good leaving groups.



Acylation of alcohols is often performed in the presence of an organic base such as pyridine. The base serves two purposes: it neutralizes the protons generated in the reaction and prevents the development of high acid concentrations. Pyridine also becomes directly involved in the reaction as a *nucleophilic catalyst* (see p. 657).

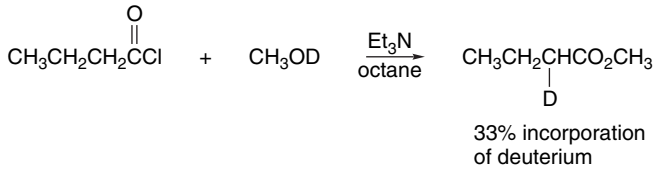


Pyridine is more nucleophilic than an alcohol toward the carbonyl center of an acyl chloride. The product that results, an acylpyridinium ion, is, in turn, more reactive toward an alcohol than the original acyl chloride. The conditions required for nucleophilic catalysis therefore exist, and acylation of the alcohol by acid chloride is faster in the presence of pyridine than in its absence. Among the evidence that supports this

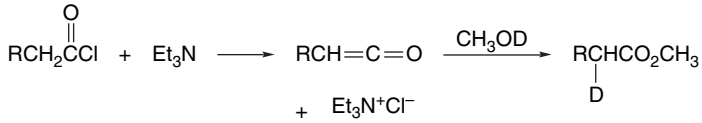
[56] D. P. N. Satchell, *Q. Rev. Chem. Soc.*, **17**, 160 (1963).

mechanism is spectroscopic observation of the acetylpyridinium ion intermediate.[57] An even more effective catalyst is 4-dimethylaminopyridine (DMAP), which functions in the same way, but is more reactive because of the ERG dimethylamino substituent.[58]

With more strongly basic tertiary amines such as triethylamine, another mechanism can come into play. It has been found that when methanol deuterated on oxygen reacts with acyl chlorides in the presence of triethylamine, some deuterium is introduced α to the carbonyl group in the ester.

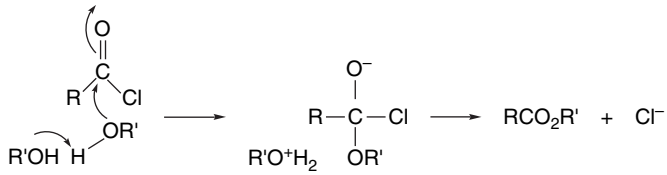


This finding suggests that some of the ester is formed via a ketene intermediate.[59]



Ketenes undergo rapid addition by nucleophilic attack at the *sp*-carbon atom. The reaction of tertiary amines and acyl halides in the absence of nucleophiles is a general preparation for ketenes for other purposes.[60]

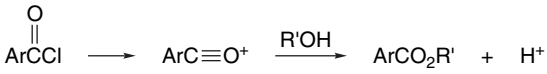
Kinetic studies of the reaction of alcohols with acyl chlorides in polar solvents in the absence of basic catalysts generally reveal terms of both first and second order in alcohol.[61] Transition structures in which the second alcohol molecule acts as a proton acceptor have been proposed.



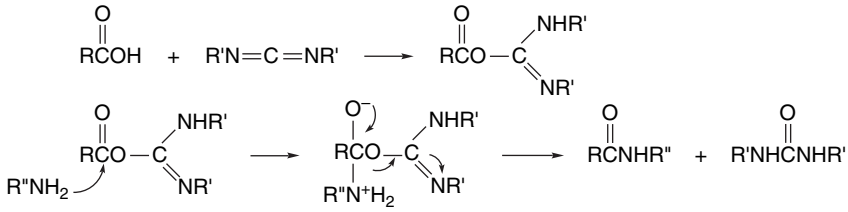
There is an alternative to the addition-elimination mechanism for nucleophilic substitution of acyl chlorides. Certain acyl chlorides react with alcohols by a dissociative mechanism in which *acylium ions* are intermediates. This mechanism is observed with aroyl halides having ERG substituents.[62] Other acyl halides show

57. A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432, 5442 (1970).
58. E. F. V. Scriven, *Chem. Soc. Rev.*, **12**, 129 (1983).
59. W. E. Truce and P. S. Bailey, *J. Org. Chem.*, **34**, 1341 (1969).
60. R. N. Lacey, in *The Chemistry of Alkenes*, S. Patai, ed., Interscience Publishers, New York, 1964, pp. 1168–1170; W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 108 (1947).
61. D. N. Kevill and F. D. Foss, *J. Am. Chem. Soc.*, **91**, 5054 (1969); S. D. Ross, *J. Am. Chem. Soc.*, **92**, 5998 (1970).
62. M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, **85**, 30 (1963); T. W. Bentley, H. C. Harris, and I. S. Koo, *J. Chem. Soc., Perkin Trans. 2*, 783 (1988); B. D. Song and W. P. Jencks, *J. Am. Chem. Soc.*, **111**, 8470 (1989).

reactivity indicative of mixed or borderline mechanisms.[63] The existence of the S_N1-like dissociative mechanism reflects the relative stability of acylium ions.

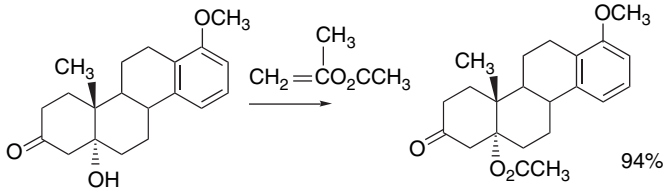


In addition to acyl chlorides and acid anhydrides, there are a number of other types of compounds that are reactive acylating agents. Many have been developed to facilitate the synthesis of polypeptides, for which mild conditions and high selectivity are required (see Part B, Section 3.4). The carbodiimides, such as dicyclohexylcarbodiimide, make up an important group of reagents for converting carboxylic acids to active acylating agents. The mechanism for carbodiimide-promoted amide bond formation is shown below.



The first step is addition of the carboxylic acid to the C=N bond of the carbodiimide, which generates an O-acylated urea derivative. This is a reactive acylating agent because there is a strong driving force for elimination of the very stable urea carbonyl group.[64] The amine reacts with the active acylating agent. In the absence of an amine, the acid is converted to the anhydride, with a second molecule of the carboxylic acid serving as the nucleophile.

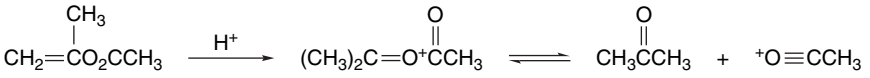
Enol esters are another type of acylating agent. The acetate of the enol form of acetone, isopropenyl acetate, is the most commonly used example. In the presence of an acid catalyst, they act as acylating agents and are reactive toward weak nucleophiles such as hindered hydroxy groups.



Ref. 65

The active acylating agent is presumably the C-protonated enol ester. This species is highly reactive owing to the presence of a positively charged oxygen. An alternative possibility is that the protonated enol ester dissociates to acetone and the acetylium ion, which then acts as the acylating agent.

63. T. W. Bentley, I. S. Koo, and S. J. Norman, *J. Org. Chem.*, **56**, 1604 (1991); T. W. Bentley and B. S. Shim, *J. Chem. Soc., Perkin Trans. 2*, 1659 (1993).
64. D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013, 1020 (1966).
65. W. S. Johnson, J. Ackerman, J. F. Eastham, and H. A. DeWalt, Jr., *J. Am. Chem. Soc.*, **78**, 6302 (1956).

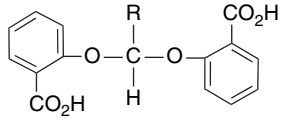


Other examples of synthetically useful acylating reagents are given in Section 3.4 of Part B.

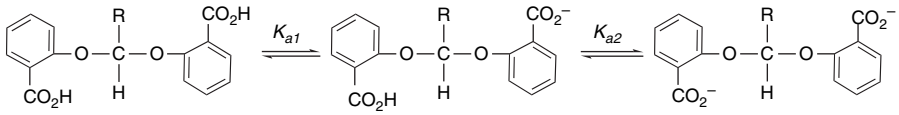
7.5. Intramolecular Catalysis of Carbonyl Substitution Reactions

The reactions of carbonyl compounds have provided an important testing ground for developing an understanding of *intramolecular catalysis*, which is a neighboring-group interaction that accelerates a reaction. Studies in intramolecular catalysis have been designed to determine how much more efficiently a given functional group can act as a catalyst when it is part of the reacting molecule and located in a position that enables an encounter between the catalytic group and the reaction center. These studies are relevant to understanding biological mechanisms, because enzymes achieve exceedingly efficient catalysis by bringing together at the "active site" combinations of basic, acidic, and nucleophilic groups in a geometry that is particularly favorable for reaction. The present section illustrates some of the facts that have emerged from these studies and the mechanistic conclusions that have been drawn.

It was pointed out in the mechanistic discussion concerning acetal hydrolysis that general acid catalysis occurs only for acetals having special structural features (see p. 641) Usually, specific acid catalysis operates. The question of whether general acid catalysis can be observed in intramolecular reactions has been of interest because intramolecular general acid catalysis is thought to play a part in the mechanism of action of the enzyme lysozyme, which hydrolyzes the acetal linkage present in certain polysaccharides. One group of molecules that has been examined as a model system are acetals derived from *o*-hydroxybenzoic acid (salicylic acid).[66]



The pH-rate profile for hydrolysis of the benzaldehyde acetal (see Figure 7.10) indicates that of the species that are available, the *monoanion* of the acetal is the most reactive. The reaction is fastest in the pH range where the concentration of the monoanion is at a maximum. The neutral molecule decreases in concentration with increasing pH and the converse is true for the dianion.



66. E. Anderson and T. H. Fife, *J. Am. Chem. Soc.*, **95**, 6437 (1973).

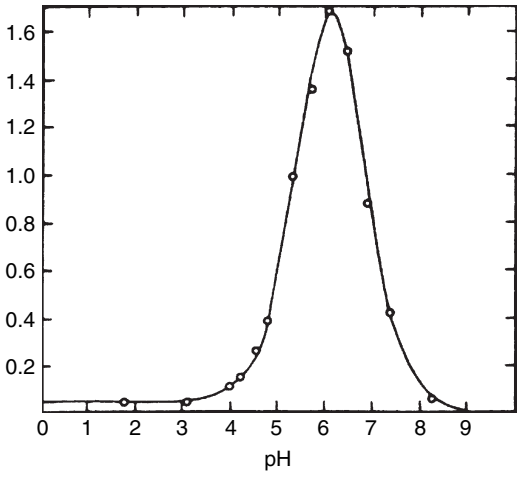
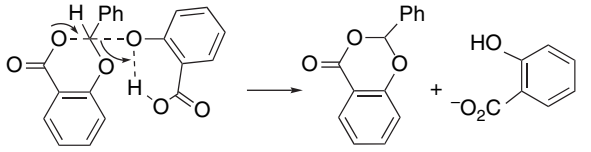
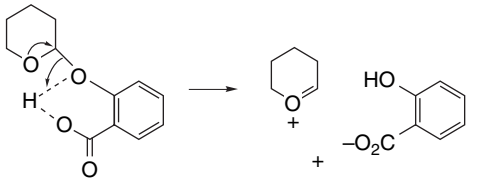


Fig. 7.10. pH-Rate profile for release of salicylic acid from benzaldehyde disalicyl acetal. Reproduced from *J. Am. Chem. Soc.*, **95**, 6437 (1973), by permission of the American Chemical Society.

The TS for the rapid hydrolysis of the monoanion is depicted as involving an intramolecular general acid catalysis by the carboxylic acid group, with participation by the anionic carboxylate group, which becomes bound at the developing electrophilic center. The un-ionized carboxylic acid group acts as a *general acid catalyst* and the carboxylate as a *nucleophilic catalyst*.



A mixed acetal of benzaldehyde, tetrahydropyranol, and salicylic acid has also been studied.[67] It, too, shows a marked rate enhancement attributable to intramolecular general acid catalysis. In this case the pH-rate profile (Figure 7.11) shows a plateau in the region pH 2–5. As the carboxy group becomes protonated below pH 6, it provides an increment owing to intramolecular general acid catalysis.



The case of intramolecular carboxylate participation in ester hydrolysis has been extensively studied using acetylsalicylic acid (aspirin) and its derivatives. The kinetic data show that the anion is hydrolyzed more rapidly than the neutral species, indicating

67. T. H. Fife and E. Anderson, *J. Am. Chem. Soc.*, **93**, 6610 (1971).

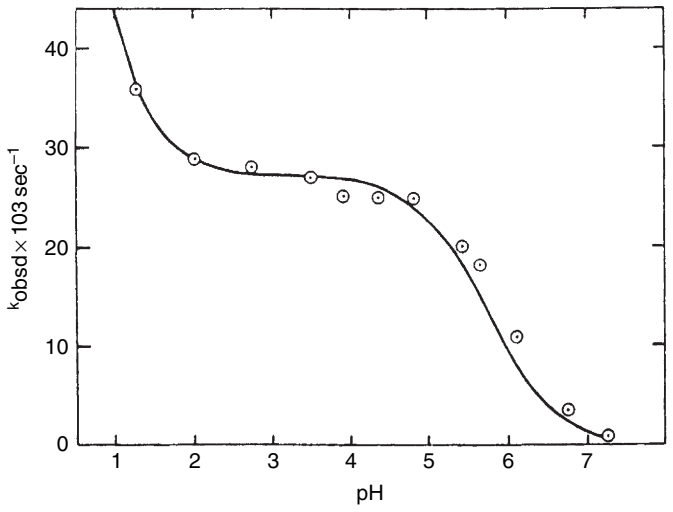
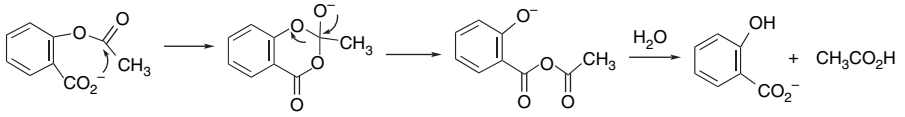


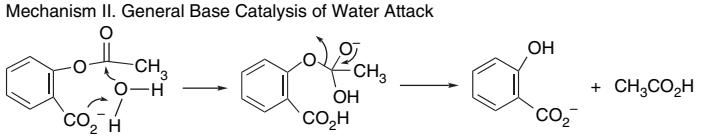
Fig. 7.11. pH-Rate profile for hydrolysis of 2-(*o*-carboxyphenoxy)tetrahydropyran in 50% dioxane-water at 15°C. Reproduced from *J. Am. Chem. Soc.*, **93**, 6610 (1971), by permission of the American Chemical Society.

that the carboxylate group becomes involved in the reaction in some way. Three mechanisms can be considered.

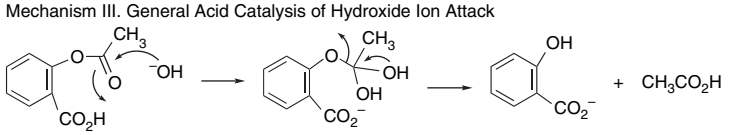
Mechanism I. Nucleophilic Catalysis



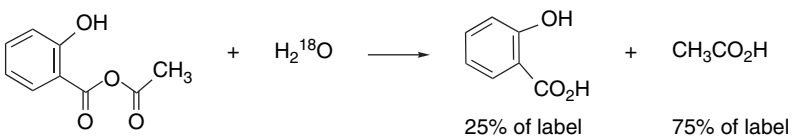
Mechanism II. General Base Catalysis of Water Attack



Mechanism III. General Acid Catalysis of Hydroxide Ion Attack



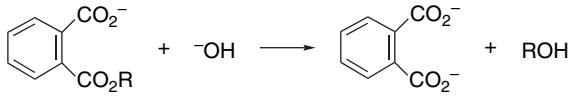
Mechanism I was ruled out by an isotopic-labeling experiment. The mixed anhydride of salicylic acid and acetic acid is an intermediate if nucleophilic catalysis occurs by Mechanism I. This molecule, which can be prepared independently, hydrolyzes in water with about 25% incorporation of solvent water into the salicylic acid.



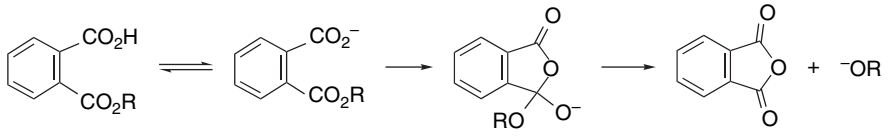
Hydrolysis of aspirin in $H_2{}^{18}O$ does not lead to incorporation of ^{18}O into the product salicylic acid, ruling out the anhydride as an intermediate and thereby excluding

Mechanism I.[68] Mechanism III cannot be distinguished from the first two on the basis of kinetics alone, because the reactive species shown is in rapid equilibrium with the anion and therefore equivalent to it in terms of reaction kinetics. The general acid catalysis of Mechanism III can be eliminated on the basis of failure of other nucleophiles to show evidence for general acid catalysis by the neighboring carboxylic acid group. Since there is no reason to believe hydroxide should be special in this way, Mechanism III is ruled out. Thus Mechanism II, general base catalysis of water attack, is believed to be the correct description of the hydrolysis of aspirin.

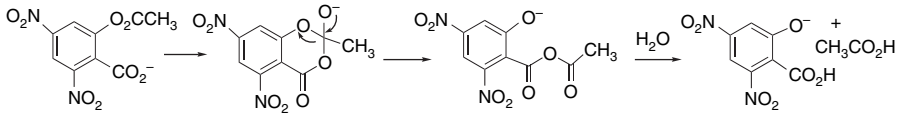
The extent to which intramolecular nucleophilic catalysis of the type depicted in Mechanism I is important is a function of the leaving ability of the alkoxy group. This has been demonstrated by the study of the hydrolysis of a series of monoesters of phthalic acid.



Nucleophilic participation is important only for esters of alcohols that have $pK_a < 13$. Specifically, phenyl and trifluoroethyl esters exhibit nucleophilic catalysis, but methyl and 2-chloroethyl esters do not.[69] This result reflects the fate of the tetrahedral intermediate that results from nucleophilic participation. For relatively acidic alcohols, the alkoxide group can be eliminated, leading to hydrolysis via nucleophilic catalysis.



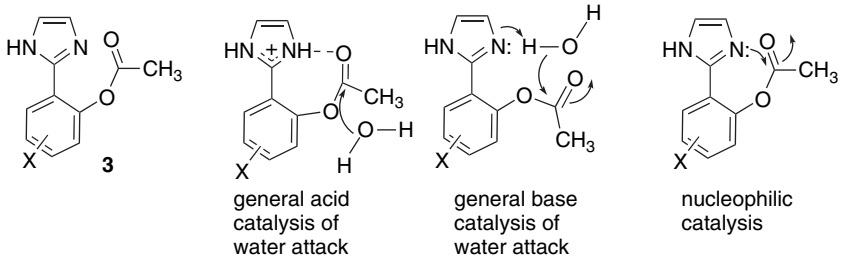
For less acidic alcohols, nucleophilic participation is ineffective because of the low tendency of such alcohols to function as leaving groups. The tetrahedral intermediate formed by intramolecular addition simply returns to starting material because the carboxylate is a much better leaving group than the alkoxide. A similar observation is made for salicylate esters. In contrast to aspirin itself, acetyl salicylates with EWG groups (*o*- and *p*-nitro analogs) hydrolyze via the nucleophilic catalysis mechanism in which the phenolates act as leaving groups from the cyclic intermediate.[70] The difference, in comparison with aspirin, is the improved leaving group capacity of the phenolate.



Intramolecular catalysis of ester hydrolysis by nitrogen nucleophiles is also important. The role of imidazole rings in intramolecular catalysis has received particularly close scrutiny. There are two reasons for this. One is that the imidazole ring of

[68] A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 4857 (1967).
[69] J. W. Thanassi and T. C. Bruice, *J. Am. Chem. Soc.*, **88**, 747 (1966).
[70] A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, **89**, 5960 (1967); *J. Am. Chem. Soc.*, **90**, 5818 (1968).

the histidine residue in proteins is involved in enzyme-catalyzed hydrolyses. Secondly, the imidazole ring has several possible catalytic functions, which include acting as a general acid in the protonated form, acting as a general base, or acting as a nucleophile in the neutral form. A study of a number of derivatives of Structure **3** was undertaken to distinguish between these various possible mechanisms as a function of pH.[71]



The relative importance of the potential catalytic mechanisms depends on pH, which also determines the concentration of the other participating species such as water, hydronium ion, and hydroxide ion. The change in mechanism with pH gives rise to the pH-rate profile shown in Figure 7.12.

The rates at the extremities pH < 2 and pH > 9 are proportional to $[H^+]$ and $[^-OH]$, respectively, and represent the specific proton-catalyzed and hydroxide-catalyzed mechanisms. In the absence of an intramolecular catalytic mechanisms, the H^+- and ^-OH-catalyzed reactions would decrease in proportion to the concentration of the catalytic species and intersect at a minimum value representing the "uncatalyzed water hydrolysis." An estimate of the effectiveness of the intramolecular mechanisms can be made by extrapolating the lines that are proportional to $[H^+]$ and $[^-OH]$. The extent to which the actual rate lies above these extrapolated lines in the pH range 2–8 represents the contribution from the intramolecular catalysis. The region at pH 2–4 is the area where intramolecular general acid catalysis operates. Comparison with similar systems where intramolecular proton transfer is not available suggests a 25–100 fold rate enhancement. At pH 6–8 the intramolecular general base catalysis mechanism is

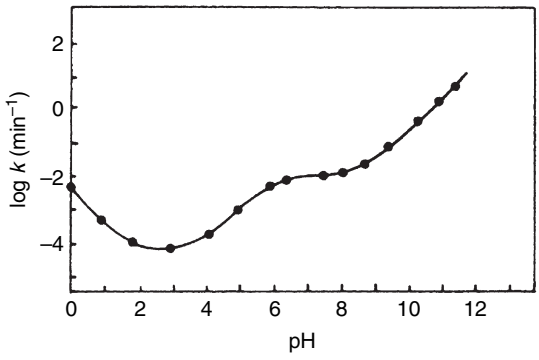
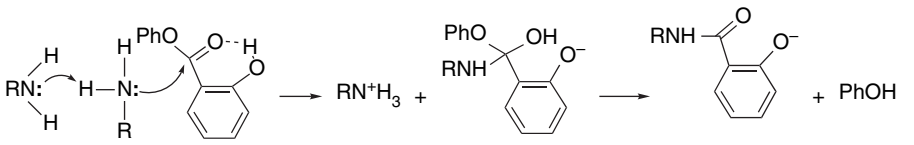


Fig. 7.12. pH-rate profile for hydrolysis of Compound **3**. Reproduced from *J. Am. Chem. Soc.*, **96**, 2463 (1974), by permission of the American Chemical Society.

[71] G. A. Rogers and T. C. Bruice, *J. Am. Chem. Soc.*, **96**, 2463 (1974).

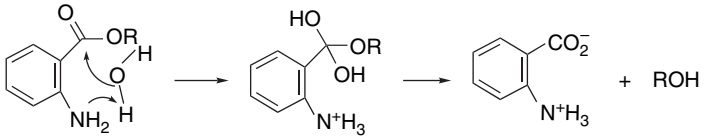
dominant. Analysis of the kinetic data indicates an acceleration of about 10^4. Although the nucleophilic catalysis mechanism was not observed in the parent compound, it did occur in certain substituted derivatives.

Intramolecular participation of the *o*-hydroxy group in aminolysis of phenyl salicylate has been established by showing that such compounds are more reactive than analogs lacking the hydroxy substituent. This reaction exhibits overall third-order kinetics, second order in the reacting amine. Similar kinetics are observed in the aminolysis of simple esters (see p. 659) Both intermolecular general base catalysis (by the second amine molecule) and intramolecular general acid catalysis (by the hydroxyl group) apparently occur.[72]

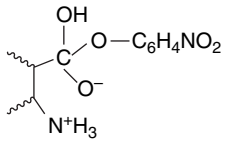


This mechanism can reduce the overall activation energy of the reaction in at least two ways. The partial transfer of a proton to the carbonyl oxygen increases its electrophilicity. Likewise, partial deprotonation of the amino group increases its nucleophilicity.

Intramolecular general base-catalyzed water attack has also been observed for phenyl 2-aminobenzoate.[73]



Similar results have been obtained with β-aminoalkyl 4-nitrophenolates, with observed rate enhancements of $\sim 10^4$.[74] Besides the general base-catalyzed mechanism, it has been suggested that the kinetically equivalent electrostatic stabilization of the tetrahedral intermediate by the protonated amino group might be involved.



Neither of these systems is likely to react by direct nucleophilic catalysis, because that would require formation of a four-membered ring. The pH-rate profiles for these reactions are shown in Figure 7.13. Note that the plateau region for the aromatic amines occurs at lower pH than for the alkylamines, reflecting the difference in the basicity of the two types of amino groups.

Certain molecules that can permit concerted proton transfers are efficient catalysts for reaction at carbonyl centers. An example is the catalytic effect that 2-pyridone

[72] F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **91**, 5346 (1969).
[73] T. H. Fife, R. Singh, and R. Bembi, *J. Org. Chem.*, **67**, 3179 (2002).
[74] M. I. Page, D. Pender, and G. Bernath, *J. Chem. Soc., Perkin Trans. 2*, 867 (1986).

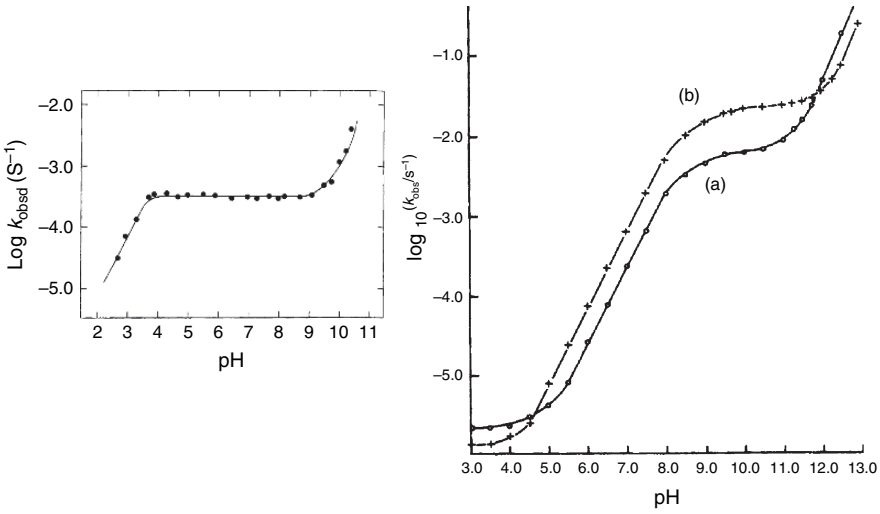
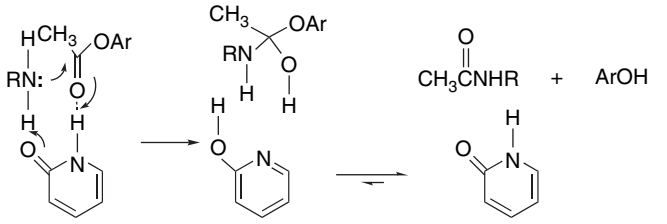
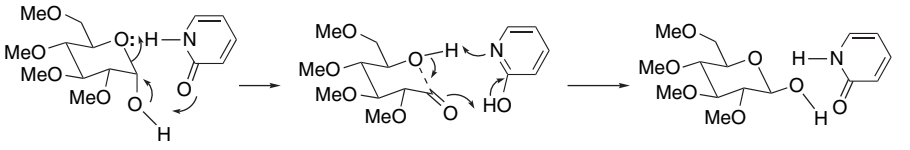


Fig. 7.13. pH-Rate profiles for phenyl *o*-aminobenzoates (left, 50°C) and β-aminoalkyl 4-nitrophenolates (right, 30°C). Reproduced from *J. Org. Chem.*, **67**, 3179 (2002) and *J. Chem. Soc., Perkin Trans.*, **2**, 867 (1986), respectively, by permission of the American Chemical Society and the Royal Society of Chemistry.

has on the aminolysis of esters (see also p. 661–662). Although neither a strong base ($pK_{aH+} = 0.75$) nor a strong acid ($pK_a = 11.6$), 2-pyridone is an effective catalyst of the reaction of *n*-butylamine with 4-nitrophenyl acetate.[75] The overall rate is more than 500 times greater when 2-pyridone acts as the catalyst than when a second molecule of butylamine (acting as a general base) is present in the TS. 2-Pyridone has been called a *tautomeric catalyst* to emphasize its role in proton transfer. Such molecules are also called *bifunctional catalysts*, since two atoms in the molecule are involved in the proton transfer process.



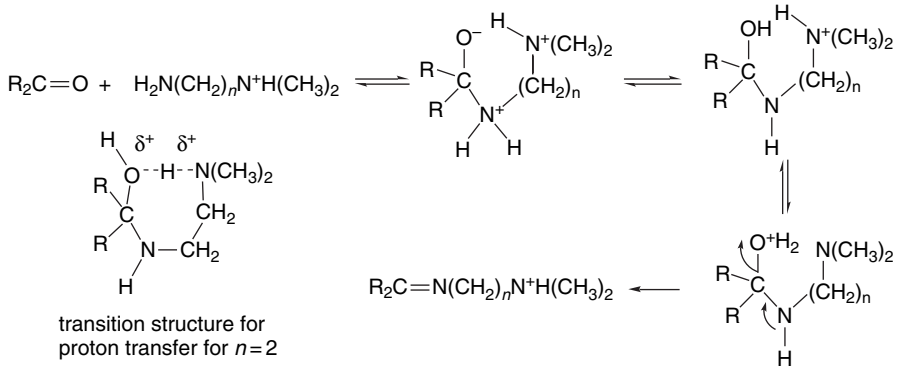
2-Pyridone also catalyzes epimerization of the anomeric position of the tetramethyl ether of glucose. The mechanism involves two double-proton transfers. The first leads to a ring-opened intermediate and the second results in ring closure to the isomerized product.



[75] P. R. Rony, *J. Am. Chem. Soc.*, **91**, 6090 (1969).

Other compounds such as benzoic acid and pyrazole, which can effect similar concerted proton transfer and avoid charged species, also catalyze this and related reactions.[76]

Another type of bifunctional catalysis has been noted with α, ω-diamines in which one of the amino groups is primary and the other tertiary. These substituted diamines are from several times to as much as 1000 times more reactive toward imine formation than monofunctional amines.[77] This is attributed to a catalytic intramolecular proton transfer.



The rate enhancement is greatest for $n = 2$ (1000) but still significant for $n = 3$ (a factor of 10). As the chain is lengthened to $n = 4$ and $n = 5$, the rate enhancement, if any, is minor. This relationship reflects the fact that when $n = 4$ or 5, the TS for the intramolecular proton transfer would have to involve rings of nine and ten atoms, respectively, which is not structurally advantageous. The particularly rapid reaction when $n = 2$ corresponds to the possibility of a proton transfer via a seven-membered cyclic TS. If the assumption is that the proton is transferred in a colinear fashion through a hydrogen bond, this represents a favorable TS geometry.

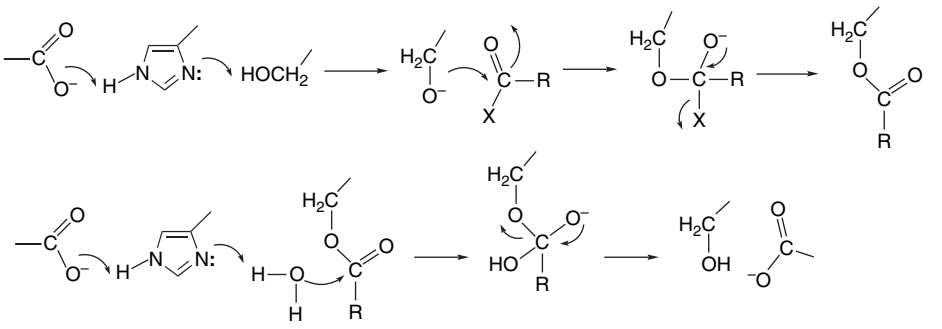
These examples serve to illustrate the concept of intramolecular catalysis and the idea that favorable juxtaposition of acidic, basic, or nucleophilic sites can markedly accelerate some of the common reactions of carbonyl compounds. Nature has used optimal placement of functional groups to achieve the catalytic activity of enzymes. The functional groups employed to accomplish this are those present on the amino acid residues found in proteins. The acidic sites available include phenolic (tyrosine) or carboxylic acid groups (glutamic acid and aspartic acid). Basic sites include the imidazole ring (histidine) and the ϵ-amino group of lysine. This latter group and the guanidine group in arginine are normally protonated at physiological pH and can stabilize nearby anionic centers by electrostatic effects. Thiol (cysteine) and hydroxy (threonine and serine) groups and the deprotonated carboxy groups of glutamic and aspartic acids are potential nucleophilic sites.

A good example of an enzyme active site is the "catalytic triad" found in various hydrolytic enzymes. The active sites of these enzymes contain a hydroxy group (from serine), a carboxylate group (from glutamic or aspartic acid), and an imidazole ring (from histidine). The three groups are aligned in such a way that the carboxylate group assists a proton transfer from the serine hydroxy to the imidazole. This enhances the nucleophilicity of the serine toward the carbonyl group of the substrate undergoing

[76] P. R. Rony, *J. Am. Chem. Soc.*, **90**, 2824 (1968).

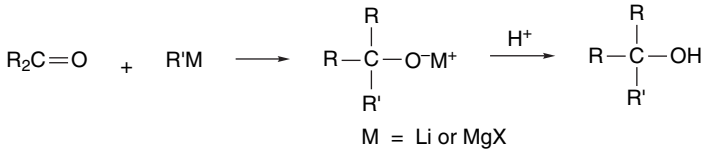
[77] J. Hine, R. C. Dempsey, R. A. Evangelista, E. T. Jarvi, and J. M. Wilson, *J. Org. Chem.*, **42**, 1593 (1977); J. Hine and Y. Chou, *J. Org. Chem.*, **46**, 649 (1981).

hydrolysis. The acyl group is transferred to the serine through a tetrahedral intermediate. Breakdown of the tetrahedral intermediate is accompanied by transfer of a proton back to the leaving group. Subsequently, a water molecule is activated by the same mechanism to cleave the acyl enzyme intermediate.[78]

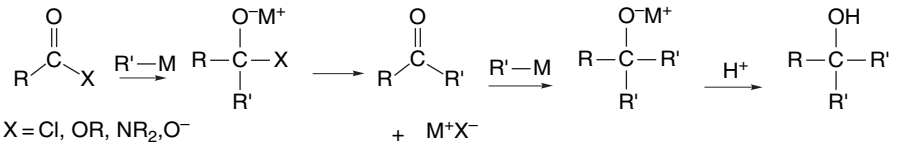


7.6. Addition of Organometallic Reagents to Carbonyl Groups

The addition of carbon nucleophiles, such as organometallic compounds, to carbonyl groups is one of the main methods of formation of carbon-carbon bonds. Such reactions are extremely important in synthesis and are discussed extensively in Chapter 7 of Part B. Here, we examine some of the fundamental mechanistic aspects of the addition of organometallic reagents to carbonyl groups. Organolithium and organomagnesium reagents are highly reactive toward most carbonyl compounds. With aldehydes and ketones, the tetrahedral adduct is stable and alcohols are isolated after protonation of the adduct.



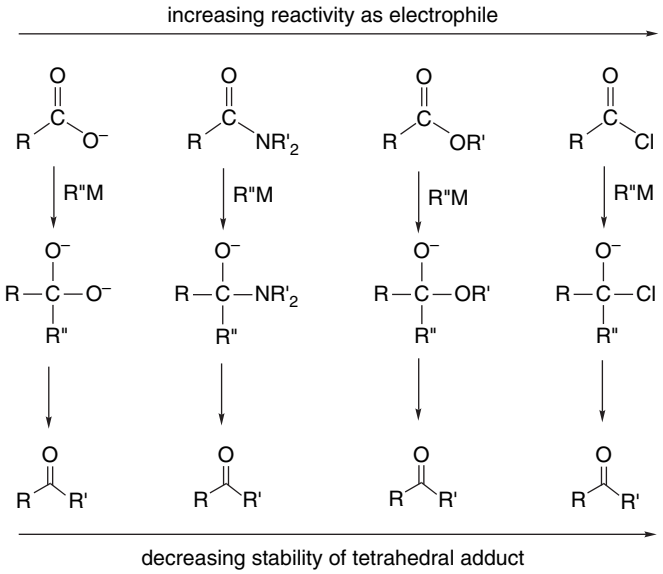
For acyl chlorides, anhydrides, esters, carboxamides, and carboxylate anions, the tetrahedral adduct can undergo elimination. The elimination forms a ketone, permitting a second addition step to occur.



The rate at which dissociation of the tetrahedral adduct occurs depends on the reactivity of the heteroatom substituent as a leaving group. The order of stability of the tetrahedral

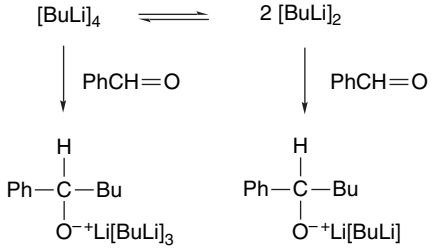
[78] D. M. Blow, *Acc. Chem. Res.*, **9**, 145 (1976); R. M. Garavito, M. G. Rossman, P. Argos, and W. Eventoff, *Biochemistry*, **16**, 5065 (1977); M. L. Bender, R. J. Bergeron, and M. Komiyama, *The Bioorganic Chemistry of Enzymatic Catalysis*, Wiley, New York, 1984, pp. 121–123; C.-H. Hu, T. Brinck, and K. Hult, *Int. J. Quantum Chem.*, **69**, 89 (1998).

adducts is shown in the diagram below. In some cases, the product can be controlled by the choice of reaction conditions. Ketones are isolated under conditions where the tetrahedral intermediate is stable until hydrolyzed, whereas tertiary alcohols are formed when the tetrahedral intermediate decomposes while unreacted organometallic reagent remains. Ketones can also be obtained with certain organometallic reagents that react only with acyl halides.



7.6.1. Kinetics of Organometallic Addition Reactions

The reactions of organolithium reagents with simple carbonyl compounds are very fast and there is relatively little direct kinetic evidence concerning the details of the reaction. It is expected that one important factor in determining reactivity is the degree of aggregation of the organolithium reagent (see p. 588). It is possible to follow the reaction of benzaldehyde with *n*-butyllithium at −85°C, using NMR techniques that are capable of monitoring fast reactions. The reaction occurs over a period of 50–300 ms. It has been concluded that the dimer of *n*-butyllithium is more reactive than the tetramer by a factor of about 10. As the reaction proceeds, the product alkoxide ion is incorporated into butyllithium aggregates, which gives rise to additional species with different reactivities.[79]



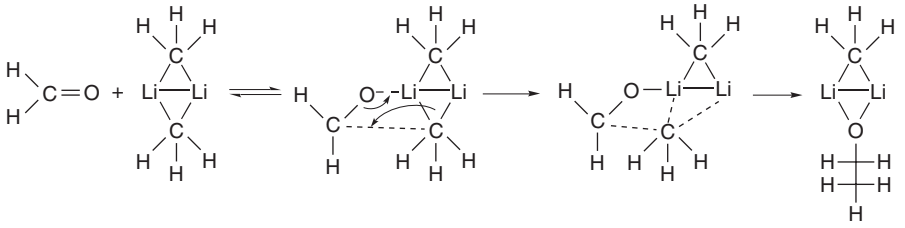
[79] J. F. McGarrity, C. A. Ogle, Z. Brich, and H.-R. Loosli, *J. Am. Chem. Soc.*, **107**, 1810 (1985).

The rates for the reaction of several aromatic ketones with alkyllithium reagents have been examined. The reaction of 2,4-dimethyl-4'-(methylthio)benzophenone with methyl lithium in ether exhibits the rate expression

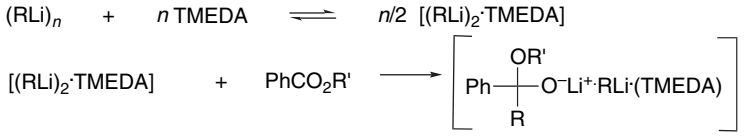
$$\text{Rate} = k[\text{MeLi}]^{1/4}\ [\text{ketone}]$$

This is consistent with a mechanism in which monomeric methyllithium, in equilibrium with the tetramer, is the reactive nucleophile.[80] Most other studies have indicated considerably more complex behavior. The rate data for reaction of 3-methyl-1-phenyl-1-butanone with *s*-butyllithium and *n*-butyllithium in cyclohexane can be fit to a mechanism involving product formation both through a complex of the ketone with alkyllithium aggregate and by reaction with dissociated alkyllithium.[81] Initial formation of a complex is indicated by a shift in the carbonyl absorption band in the infrared spectrum. Complex formation presumably involves a Lewis acid-base interaction between the lithium ions and carbonyl oxygen in the alkyllithium cluster. In general terms, it appears likely that alkyllithium reagents have the possibility of reacting through any of several aggregated forms.

MO modeling (HF/3-21G) of the reaction of organolithium compounds with carbonyl groups has examined the interaction of formaldehyde with the dimer of methyllithium. The reaction is predicted to proceed by initial complexation of the carbonyl group at lithium, followed by a rate-determining formation of the new carbon-carbon bond. The cluster then reorganizes to incorporate the newly formed alkoxide ion.[82] The TS is reached very early in the second step with only slight formation of the C−C bond. This feature is consistent with the fast and exothermic nature of the addition step.

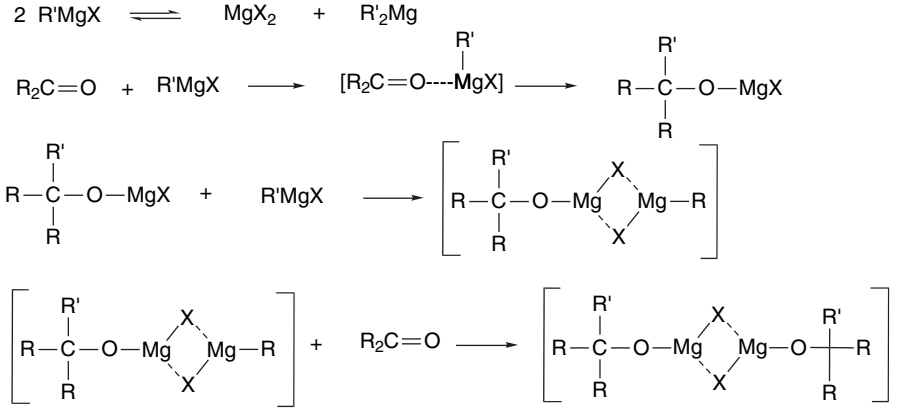


The kinetics of addition of alkyllithium reagents to esters has been studied using a series of ethyl benzoates.[83] The rates show a rather complex dependence on both alkyllithium concentration and the nature of aryl substituents. The rapid formation of an initial ester-alkyllithium complex can be demonstrated. It is believed that product can be formed by reaction with aggregated or monomeric alkyllithium reagent. *N,N,N,N*-Tetramethylethylenediamine greatly accelerates the reaction, presumably by dissociating the organometallic aggregate (see Section 6.1).

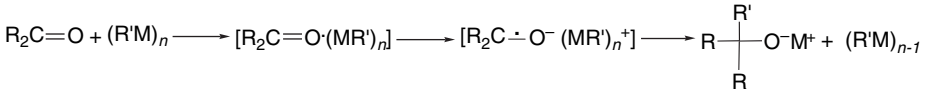


[80] S. G. Smith, L. F. Charbonneau, D. P. Novak, and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 7059 (1972).
[81] M. A. Al-Aseer and S. G. Smith, *J. Org. Chem.*, **49**, 2608 (1984).
[82] E. Kaufmann, P. v. R. Schleyer, K. N. Houk, and Y.-D. Wu, *J. Am. Chem. Soc.*, **107**, 5560 (1985).
[83] M. A. Al-Aseer, B. D. Allison, and S. G. Smith, *J. Org. Chem.*, **50**, 2715 (1985).

The kinetics of reaction of Grignard reagents with ketones is also subject to a number of complications. The purity of the magnesium metal used in the preparation of the Grignard reagent is crucial since trace transition metal impurities have a major effect on the observed reaction rates. One of the most thorough studies available involves the reaction of methylmagnesium bromide with 2-methylbenzophenone in diethyl ether.[84] The results suggest a mechanism similar to that discussed for alkyllithium reactions. There is initial complexation between the ketone and Grignard reagent. The main Grignard species, CH_3MgBr, is in equilibrium with $(CH_3)_2Mg$, which can contribute to the overall rate. The product alkoxide forms a complex with the Grignard reagent to give yet another reactive species. The general mechanistic scheme is outlined below.



There is another possible mechanism for addition of organometallic reagents to carbonyl compounds, which involves a discrete electron transfer step.[85]

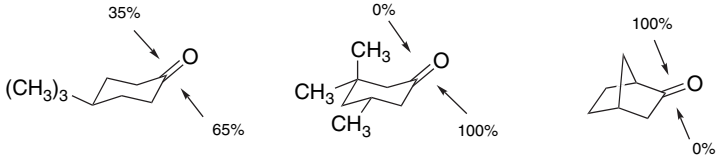


The distinguishing feature of this mechanism is the second step, in which an electron is transferred from the organometallic reagent to the carbonyl compound to give the radical anion of the carbonyl compound. Subsequent collapse of the radical ion pair with transfer of an alkyl group to carbon gives the same product that is formed by the direct nucleophilic addition mechanism. The electron transfer mechanism would be expected to be favored by structural features that stabilize the radical anion intermediate. Aryl ketones and diones fulfill this requirement and evidence for the electron transfer mechanism has been accumulated for such ketones. In several cases it is possible to observe a radical anion intermediate by ESR spectroscopy.[86] (See Section 11.1.3 for a discussion of some of the limits of this methodology.) The relative importance of the electron transfer mechanisms also depends on the ease of oxidation of the organometallic reagent. Allyllithium is particularly likely to react by the electron transfer mechanism because of its ease of oxidation.[87]

84. E. C. Ashby, J. Laemmle, and H. M. Neumann, *J. Am. Chem. Soc.*, **94**, 5421 (1972).
85. E. C. Ashby, *Pure Appl. Chem.*, **52**, 545 (1980); E. C. Ashby, J. Laemmle, and H. M. Neuman, *Acc. Chem. Res.*, **7**, 272 (1974).
86. K. Maruyama and T. Katagiri, *J. Am. Chem. Soc.*, **108**, 6263 (1986); E. C. Ashby and A. B. Goel, *J. Am. Chem. Soc.*, **103**, 4983 (1981); T. Lund, M. L. Pedersen, and L. A. Frandsen, *Tetrahedron Lett.*, **35**, 9225 (1994).
87. J. J. Gajewski, W. Bocian, N. J. Harris, L. P. Olson, and J. P. Gajewski, *J. Am. Chem. Soc.*, **121**, 326 (1999).

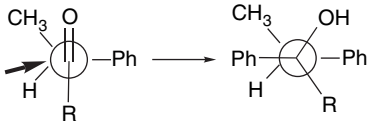
7.6.2. Stereoselectivity of Organometallic Addition Reactions

The stereochemistry of organometallic additions with carbonyl compounds fits into the general pattern for nucleophilic attack discussed in Chapter 2. With 4-*t*-butylcyclohexanone there is a preference for equatorial approach, but the selectivity is low. Enhanced steric factors promote stereoselective addition.



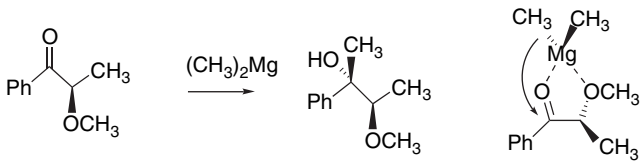
Ref. 88

The stereochemistry of organometallic additions in acyclic carbonyl compounds has also been examined. Additions of Grignard reagents to ketones and aldehydes was one of the reactions that led to the formulation of Cram's rule (see p. 179).[89] Many ketones and aldehydes have subsequently been subjected to studies to determine the degree of stereoselectivity. Cram's rule is obeyed when no special complexing functional groups are present near the reaction site. One series of studies is summarized in Table 7.5. These data show consistent agreement with Cram's rule and the Felkin TS, as discussed in Section 2.4.1.2.



Felkin Transition Structure Model

The role of chelation has been investigated both experimentally and computationally. In experimental studies, it was found that an α-methoxy group increases the rate of addition of dimethylmagnesium to propiophenone approximately 2000-fold.[90] The rate acceleration indicates that chelation not only controls stereochemistry but also facilitates the addition step. The methyl group adds from the less hindered face of the chelate. The reaction gives a greater than 99:1 preference for chelation-controlled addition.



[88] E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).

[89] D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); D. J. Cram and J. D. Knight, *J. Am. Chem. Soc.*, **74**, 5835 (1952); F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **74**, 5846 (1952).

[90] S. V. Frye, E. L. Eliel, and R. Cloux, *J. Am. Chem. Soc.*, **109**, 1862 (1987); X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **112**, 6130 (1990).

Table 7.5. Stereoselectivity in Addition of Organometallic Reagents to Some Chiral Aldehydes and Ketones[a]

R	L	M	S	R'M	Percent of major product
H	Ph	CH_3	H	CH_3MgBr	71
H	Ph	CH_3	H	PhMgBr	78
H	*t*-C_4H_9	CH_3	H	PhMgBr	98
CH_3	Ph	CH_3	H	C_2H_5Li	93
CH_3	Ph	CH_3	H	C_2H_5MgBr	88
CH_3	Ph	CH_3	H	*t*-C_4H_9MgBr	96
C_2H_5	Ph	CH_3	H	CH_3MgBr	86
C_2H_5	Ph	CH_3	H	CH_3Li	94
C_2H_5	Ph	CH_3	H	PhLi	85
i-C_3H_7	Ph	CH_3	H	CH_3MgBr	90
i-C_3H_7	Ph	CH_3	H	CH_3Li	96
i-C_3H_7	Ph	CH_3	H	PhLi	96
t-C_4H_9	Ph	CH_3	H	CH_3MgBr	96
t-C_4H_9	Ph	CH_3	H	CH_3Li	97
t-C_4H_9	Ph	CH_3	H	PhLi	98
Ph	Ph	CH_3	H	CH_3MgBr	87
Ph	Ph	CH_3	H	CH_3Li	97
Ph	Ph	CH_3	H	*t*-C_4H_9MgBr	96

a. Data from O. Arjona, R. Perez-Ossorio, A. Perez-Rubalcaba, and M. L. Quroga, *J. Chem. Soc., Perkin Trans. 2*, 587 (1981); C. Alvarez-Ibarra, P. Perz-Ossorio, A. Perez-Rubalcaba, M. L. Quiroga, and M. J Santesmases, *J. Chem. Soc. Perkin Trans. 2*, 1645 (1983).

An α-benzyloxy group was found to cause rate acceleration of more than 100, relative to a nonchelating α-trimethylsiloxy group. On the other hand, a 4-benzyloxy group in 2-butanone (β-substitution) caused only a 20% rate increase.

Computational studies were carried out on the addition reaction of dimethylmagnesium to several α- and β-substituted carbonyl compounds, including methoxyacetaldehyde, methoxyacetone, and 3-methoxypropanal. MP2/6-31+G* energies were computed for structures minimized with HF/3-31G calculations.[91] Some of the salient features of this study are summarized in Figure 7.14, which compares relative energy of reactants, prereaction complexes, TS, and products. In Panel A, the energies of acetone (A) , methoxyacetone (B), and methoxyacetaldehyde (C) are shown. Both of the chelated TSs have lower ΔH than for acetone, in agreement with the experimental finding of rate acceleration by an α-methoxy substituent. The structures of the TS for the chelated reactants also indicate an earlier TS than for acetone. Furthermore, IRC analysis indicates that chelation is maintained throughout the course of the reaction. Use of a continuum solvent model ($\varepsilon = 7.58$) resulted in only small changes in the computed $\Delta H^{\ddagger}$. These results are all consistent with chelation control of reagent approach for α-methoxy substituents.

The results for the β-methoxy substituents in 3-methoxypropanal (**D**) and 4-methoxy-2-butanone (**E**) are less clear. There are two chelated TSs of comparable energy, and only the chairlike TS suggests strong diastereoselectivity. There is also a qualitative difference in regard to the experimental kinetic studies. The

91. S. Mori, M. Nakamura, E. Nakamura, N. Koga, and K. Morokuma, *J. Am. Chem. Soc.*, **117**, 5055 (1995).

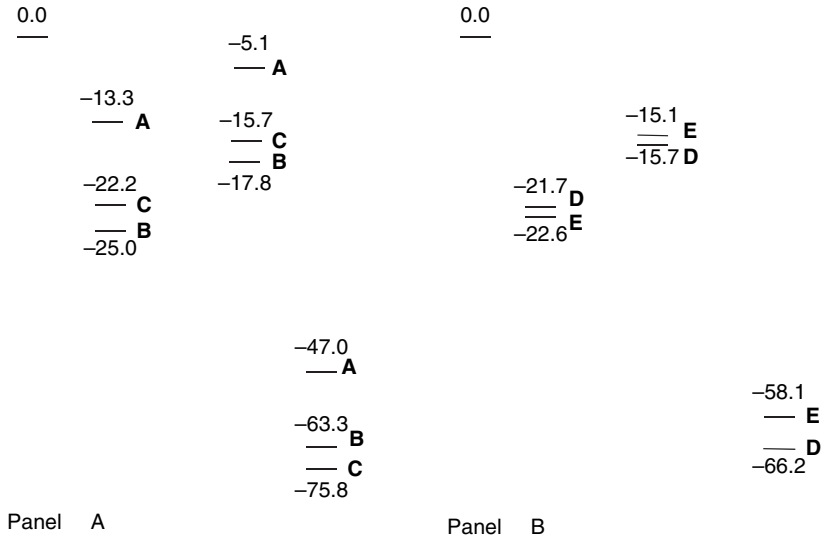
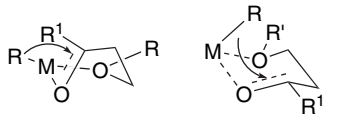


Fig. 7.14. Panel A: Relative ΔH of reactant complex, transition structure, and products at 0°C (including ZPE correction) for acetone (**A**), methoxyacetone (**B**), and methoxyacetaldehyde (**C**). Panel B: Relative ΔH at 0°C (including ZPE correction) for 3-methoxypropanal (**D**) and 4-methoxy-2-butanone (**E**). Data from *J. Am. Chem. Soc.*, **117**, 5055 (1995).

calculated activation barriers for β-methoxy groups are similar to those for α-methoxy substituents, whereas the experimental kinetic studies indicate that β-substituents are much less activating.

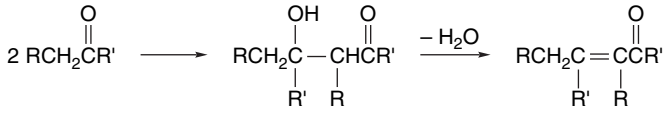


7.7. Addition of Enolates and Enols to Carbonyl Compounds: The Aldol Addition and Condensation Reactions

7.7.1. The General Mechanisms

The prototypical *aldol addition reaction* is the acid- or base-catalyzed dimerization of a ketone or aldehyde.[92] Under certain conditions, the reaction product may undergo dehydration leading to an α,β-unsaturated aldehyde or ketone. This variant can be called the *aldol condensation*.

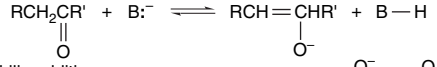
[92] A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); R. L. Reeves, in *Chemistry of the Carbonyl Group*, S. Patai, ed., Interscience, New York, 1966, pp. 580–593; H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin, Menlo Park, CA, 1972, pp. 629–682; C. H. Heathcock, in *Asymmetric Synthesis*, Vol 2, J. D. Morrison, ed., 1984; C. H. Heathcock, in *Comprehensive Carbanion Chemistry*, E. Buncel and T. Durst, eds., Elsevier, Amsterdam, 1984, Chap. 6.



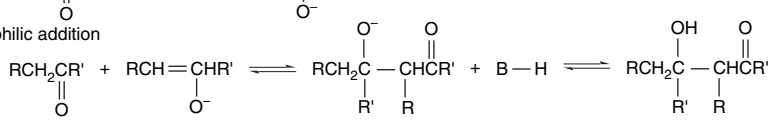
R' = H, alkyl or aryl

The mechanism of the base-catalyzed reaction involves equilibrium formation of the enolate ion, followed by addition of the enolate to the carbonyl group of the aldehyde or ketone. These reactions of aldehydes occur in dilute basic solution at or below room temperature. Under somewhat more vigorous conditions, such as higher temperature or increased base concentration, the elimination step occurs.

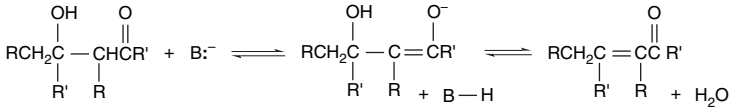
1. Addition phase
   a. Enolate formation



   b. Nucleophilic addition



2. Dehydration phase

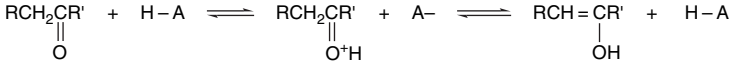


It is also possible to carry out the aldol condensation under acidic conditions. The mechanism was established in detail for acetaldehyde.[93] Under conditions of acid catalysis, it is the enol form of the aldehyde or ketone that functions as the nucleophile. The carbonyl group is activated toward nucleophilic attack by O-protonation.

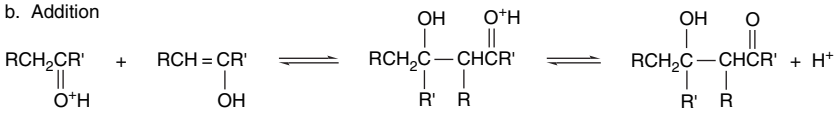
Acid – Catalyzed Mechanism

1. Addition phase

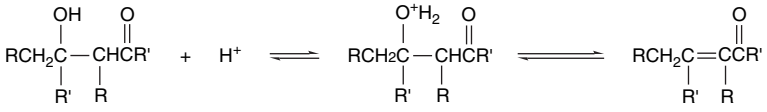
a. Enolization



b. Addition



2. Dehydration phase

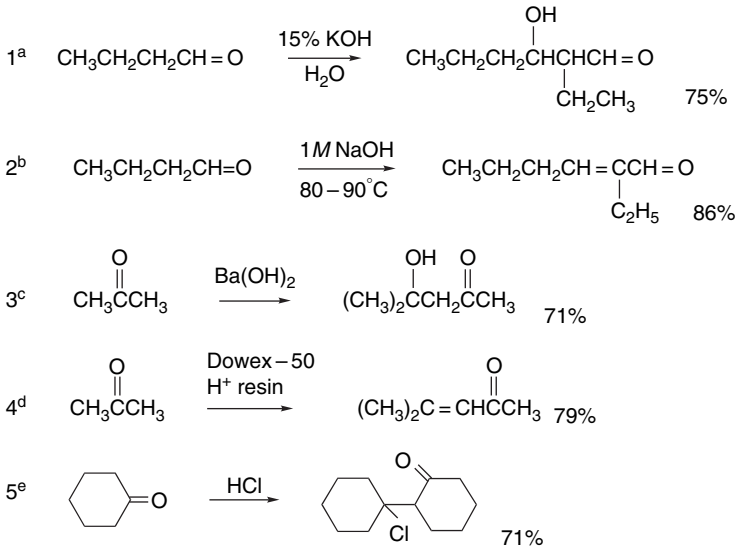


[93] L. M. Baigrie, R. A. Cox, H. Slebocka-Tilk, M. Tencer, and T. T. Tidwell, *J. Am. Chem. Soc.*, **107**, 3640 (1985).

In general, the reactions in the addition phase of both the base- and acid-catalyzed mechanisms are reversible. The equilibrium constant for addition is usually unfavorable for ketones. The equilibrium constant for the dehydration phase is usually favorable because of the conjugated α,ß-unsaturated carbonyl system that is formed. When the reaction conditions are sufficiently vigorous to cause dehydration, the overall reaction can go to completion, even if the equilibrium constant for the addition step is unfavorable.

Several examples of aldol addition and condensation are given in Scheme 7.3. Entries 1 and 2 are typical aldol reactions of aldehydes, with and without dehydration. The reaction in Entry 1 was done with 15% KOH in aqueous solution at room temperature. The condensation reaction in Entry 2 was carried out at 80°–90°C with 1 *M* NaOH. Entries 3 and 4 show addition and condensation reactions of acetone. Entry 3 features a clever way of overcoming the unfavorable equilibrium of the addition step. The basic catalyst is contained in a separate compartment of a Soxhlet extractor. Acetone is repeatedly passed over the basic catalyst by distillation and the condensate returns to the flask. Since there is no catalyst present in the flask, the adduct remains stable. The concentration of the addition product builds up as the more volatile acetone distills preferentially. The acid-catalyzed condensation in Entry 4 is carried out similarly. The acetone is continuously passed over the acidic resin, and the reaction is driven forward by the stability of the conjugated condensation product. In Entry 5, the final product is a β-chloroketone, presumably formed by addition of HCl to a dehydrated intermediate.

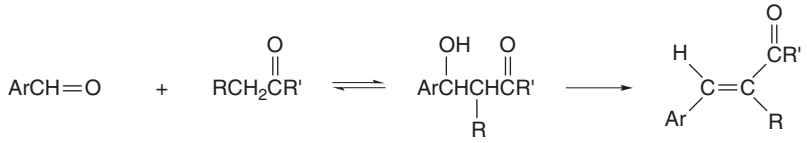
Scheme 7.3. Examples of Aldol Addition and Condensation Reactions



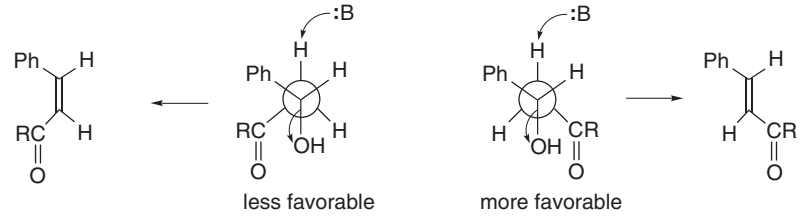
a. V. Grignard and A. Vesterman, *Bull. Chim. Soc. Fr.*,**37**, 425 (1925); *Chem. Abstr.*, **19**, 1852 (1925).
b. M. Hausemann, *Helv. Chim. Acta*, **34**, 1482 (1951).
c. J. B. Conant and N. Tuttle, *Org. Synth.*, **I**, 199 (1941).
d. N. B. Lorette, *J. Org. Chem.*, **22**, 346 (1957).
e. O. Wallach, *Berichte*, **40**, 70 (1907); E. Wenkert, S. K. Bhattacharya, and E. M. Wilson, *J. Chem. Soc.*, 5617 (1964).

7.7.2. Mixed Aldol Condensations with Aromatic Aldehydes

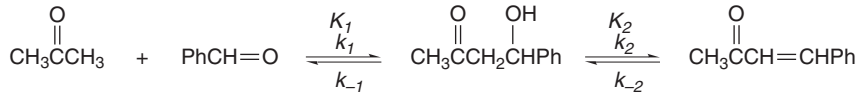
Aldol addition and condensation reactions involving two different carbonyl compounds are called *mixed aldol reactions*. To be useful as a method for synthesis there must be some basis for controlling which carbonyl component serves as the electrophile and which acts as the enolate precursor. One of the most general mixed aldol condensations involves the use of aromatic aldehydes with alkyl ketones or aldehydes. There are numerous examples of both acid- and base-catalyzed mixed aldol condensations involving aromatic aldehydes. The reaction is sometimes referred to as the *Claisen-Schmidt condensation*. Aromatic aldehydes are incapable of enolization and cannot function as the nucleophilic component. Furthermore, dehydration is especially favorable because the resulting enone is conjugated with the aromatic ring.



There is a pronounced preference for the formation of a *trans* double bond in the Claisen-Schmidt condensation of methyl ketones. This stereoselectivity arises in the dehydration step. In the TS for elimination to a *cis* double bond, an unfavorable steric interaction develops between the substituent (R) and the phenyl group. This interaction is absent in the TS for elimination to the *trans* double bond.



The dehydration reactions require somewhat higher activation energies than the addition step. Detailed studies have provided rate and equilibrium constants for the individual steps in a few cases. The results for the acetone-benzaldehyde system in the presence of hydroxide ion are given below. Note that K_2 is sufficiently large to drive the first equilibrium forward.



$K_1 = 0.083\ M^{-1}$ $\quad K_2 = 24$

$k_1 = 0.17\ M^{-1}\ s^{-1}$ $\quad k_2 = 7.5 \times 10^{-3}\ s^{-1}$

$k_{-1} = 1.4\ s^{-1}$ $\quad k_{-2} = 3.2 \times 10^{-4}\ s^{-1}$

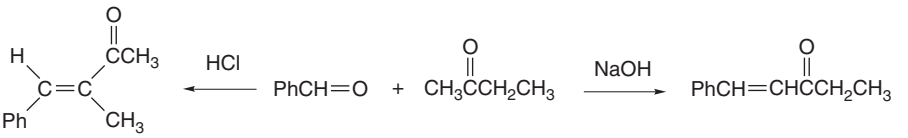
Ref. 94

Additional insight into the factors affecting product structure was obtained by study of the condensation of 2-butanone with benzaldehyde.[95] When catalyzed by base,

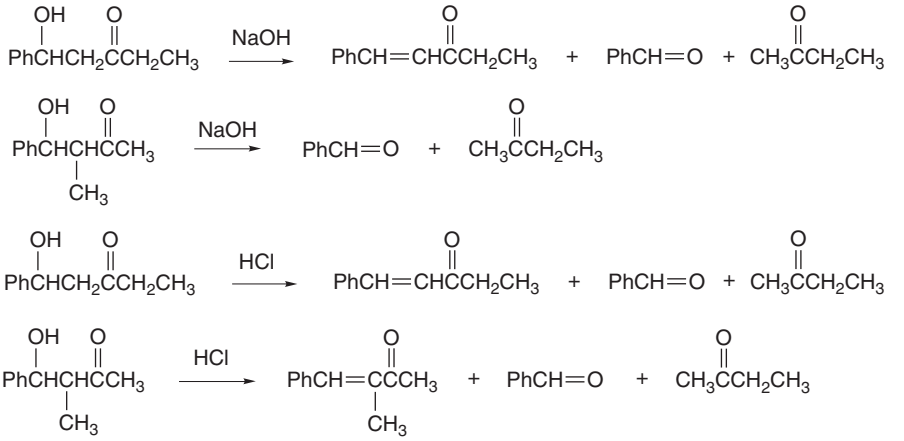
94. J. P. Guthrie, J. Cossar, and K. F. Taylor, *Can. J. Chem.*, **62**, 1958 (1984).

95. M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.*, **81**, 628 (1959); D. S. Noyce and W. A. Pryor, **81**, 618 (1959); D. S. Noyce and L. R. Snyder, **81**, 620 (1959); D. S. Noyce and W. L. Reed, *J. Am. Chem. Soc.*, **81**, 624 (1959).

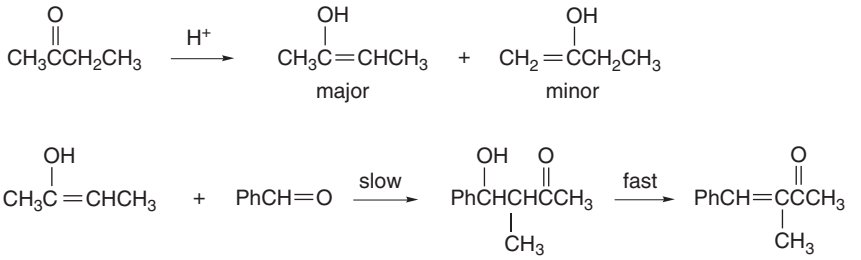
2-butanone reacts with benzaldehyde at the methyl group to give 1-phenylpent-1-en-3-one. Under acid-catalyzed conditions the product is the result of condensation at the methylene group, namely 3-methyl-4-phenylbut-3-en-2-one.



The results indicate that the product ratio is determined by the competition among the various reaction steps. Under the reaction conditions used, it is not possible to isolate the intermediate ketols because the addition step is rate limiting. These intermediates can be prepared by alternative methods and they behave as shown in the following equations.



These results establish that the base-catalyzed dehydration is slow relative to the reverse of the addition step for the branched-chain isomer. The reason for selective formation of the straight-chain product under conditions of base catalysis is then apparent. In base, the straight-chain ketol is the only intermediate that is dehydrated. The branched-chain ketol reverts to starting material. Under acid conditions, both intermediates are dehydrated. However, under acid-catalyzed conditions the branched-chain ketol is formed most rapidly because of the preference for acid-catalyzed enolization to give the more-substituted enol (see Section 6.3).



In general, the product ratio of a mixed aldol condensation depends upon the individual reaction rates in the equilibrium process. Most methyl ketones show a pattern similar

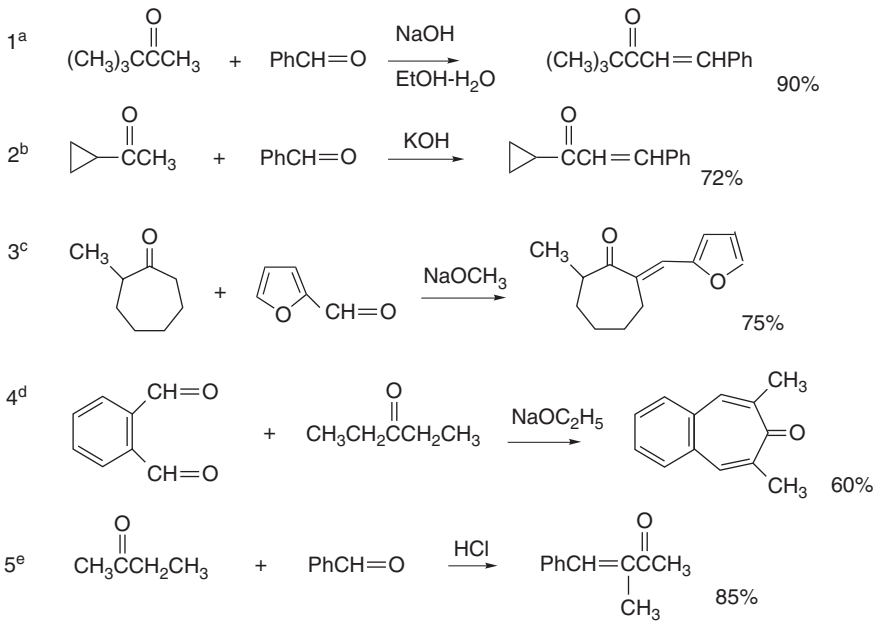
to 2-butanone in reactions with aromatic aldehydes. Base catalysis favors reaction at a methyl position over a methylene group, whereas acid catalysis gives the opposite preference.

Scheme 7.4 presents some representative examples of Claisen-Schmidt reactions. Entries 1 and 2 are typical base-catalyzed condensations at methyl groups. Entry 3 illustrates the use of a cyclic ketone, and reaction occurs at the methylene group, where dehydration is possible. The stereochemistry presumably places the furan ring *trans* to the carbonyl group for maximum conjugation. Entry 4 shows the use of phthalaldehyde to effect a cyclization. Entry 5 illustrates the preference for condensation at the more-substituted position under acidic conditions.

7.7.3. Control of Regiochemistry and Stereochemistry of Aldol Reactions of Ketones

The wide synthetic applicability of the aldol reaction depends on the ability to achieve both versatility in reactants and control of regiochemistry and stereochemistry. The term *directed aldol addition*[96] is applied to reaction conditions that are designed to achieve specific regio- and stereochemical outcomes. Control of product structure requires that one reactant act exclusively as the electrophile and the other exclusively

Scheme 7.4. Mixed Aldol Condensation Reactions of Ketones and Aromatic Aldehydes

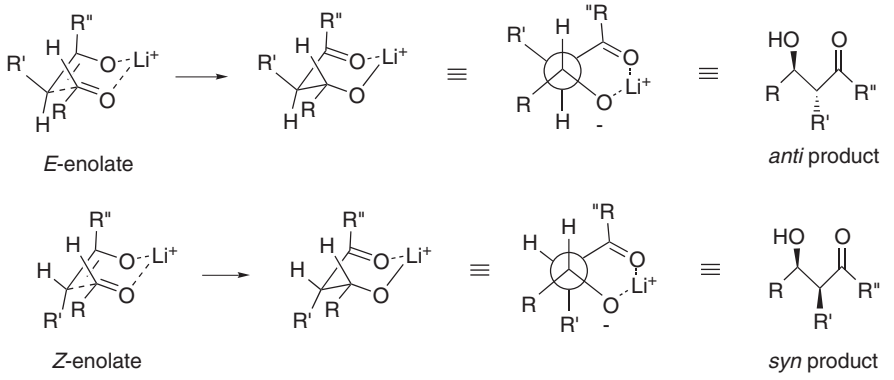


a. G. A. Hill and G. Bramann, *Org. Synth.*, **I**, 81 (1941).
b. S. C. Bunce, H. J. Dorsman, and F. D. Popp, *J. Chem. Soc.*, 303 (1963).
c. A. M. Islam and M. T. Zenaity, *J. Am. Chem. Soc.*, **79**, 6023 (1957).
d. D. Meuche, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **41**, 2220 (1958).
e. M. E. Kronenberg and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **84**, 17 (1965).

96. T. Mukaiyama, *Org. React.*, **28**, 203 (1982).

as the nucleophile. This can be achieved by preforming the reactive nucleophilic enolate and ensuring that the addition step is fast relative to proton exchange between the nucleophilic and electrophilic reactants. These reactions are under *kinetic control*, both at the stage of forming the enolate and at the addition step. The enolate that is to serve as the nucleophile is generated stoichiometrically, usually with lithium as the counterion in an aprotic solvent. Under these conditions enolates do not equilibrate with the other regio- or stereoisomeric enolates that can be formed from the ketone (see Section 6.3). The electrophilic carbonyl compound is then added. The structure of the reaction product is determined primarily by two factors: (1) the *E*- or *Z*-configuration of the initial enolate and (2) the structure of the TS for addition to the electrophilic carbonyl group.

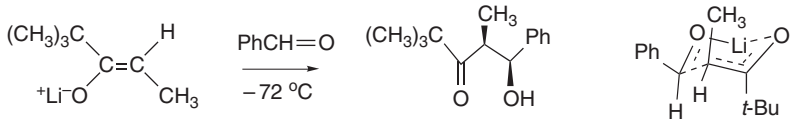
The fundamental mechanistic concept for stereochemical control of an aldol reaction under conditions of kinetic control is based on a cyclic TS in which both the carbonyl and enolate oxygen are coordinated to a Lewis acid.[97] This Lewis acid promotes reaction by enhancing the carbonyl group electrophilicity and by bringing the reactants together in the TS. It is further assumed that the structure of this TS is sufficiently similar to that of chair cyclohexane that the conformational concepts for cyclohexane derivatives can be applied. We use the Li^+ cation in our initial discussion, but other metal cations and electrophilic atoms can play the same role. We discuss reactions of boron, titanium, and tin enolates shortly. In the structures below, the reacting aldehyde is shown with R rather than H in the equatorial-like position. The orientation of the aldehyde substituent establishes the degree of facial selectivity. A consequence of the cyclic TS is that the reaction is *stereospecific* with respect to the *E*- or *Z*-configuration of the enolate. The *E*-enolate will give the *anti*-aldol product whereas the *Z*-enolate will give the *syn*-aldol.



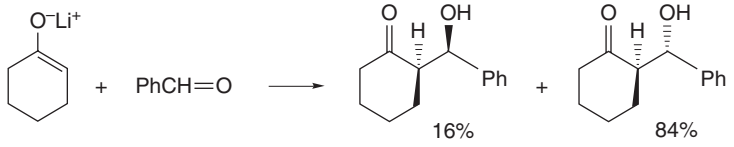
Owing to the dependence of the product stereochemistry on enolate configuration, control of the stereochemistry of enolate formation is important. For ketones with one relatively bulky group, the *Z*-enolate is favored, resulting in formation of the *syn*-aldol product. This is the case, for example, in the reaction of 2,2-dimethyl-3-pentanone and

[97] H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957); C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

benzaldehyde.[97] The product stereochemistry is correctly predicted if the aldehyde is in a conformation with the phenyl substituent in an equatorial position in the cyclic TS.



The enolates derived from cyclic ketones are necessarily *E*-isomers. The enolate of cyclohexanone reacts with benzaldehyde to give both possible stereoisomeric products under kinetically controlled conditions. The stereoselectivity is about 6:1 in favor of the *anti* isomer under optimum conditions.[98]



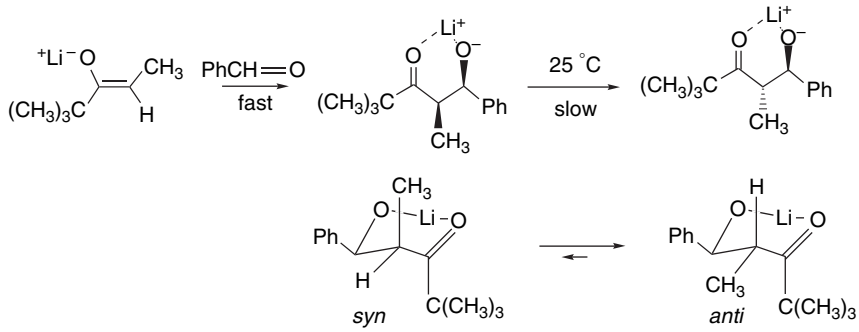
While ketones with one tertiary alkyl substituent give mainly the *Z*-enolate, less highly substituted ketones usually give mixtures of *E*- and *Z*-enolates.[99] Therefore efforts aimed at expanding the scope of stereoselective aldol condensations have been directed at two facets of the problem: (1) control of enolate stereochemistry, and (2) enhancement of the degree of stereoselectivity in the addition step. The *E*:*Z* ratio can be modified by the precise conditions for formation of the enolate. For example, the *E*:*Z* ratio for 3-pentanone and 2-methyl-3-pentanone can be increased by use of a 1:1 lithium tetramethylpiperidide-LiBr mixture for kinetic enolization.[100] The precise mechanism of this effect is not clear, but it is probably due to an aggregate species containing bromide acting as the base.[101] Relatively weakly basic lithium anilides, specifically lithium 2,4,5-trichloroanilide and lithium diphenylamide, give high *Z*:*E* ratios.[102] On the other hand, lithium *N*-trimethylsilyl-*iso*-propylamide and lithium *N*-trimethylsilyl-*tert*-butylamide give selectivity for the *E*-enolate.[103]

	E : *Z* Stereoselectivity					
R	LDA	LiHMDS	LiTMP	LiTMP-LiBr	LiTMSN*t*Bu	LiNHAr
Ethyl	77:33	34:66	83:17	98:2	92:8	11:89
Isopropyl	63:37	2:98	66:34	95:5	94:6	2:98
t-Butyl	1:99	>2:98	<5:>95	<5:95	11:89	0:100

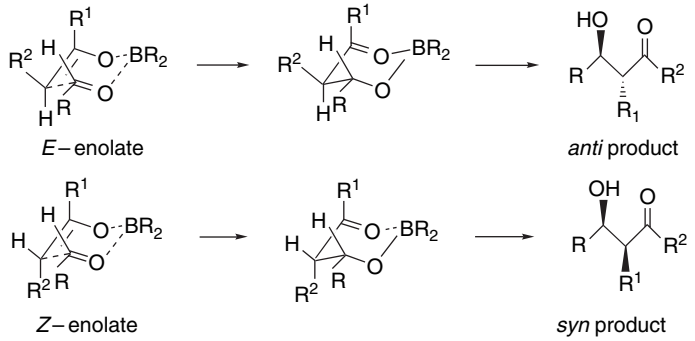
98. M. Majewski and D. M. Gleave, *Tetrahedron Lett.*, **30**, 5681 (1989).
99. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).
100. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).
101. F. S. Mair, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 3388 (1993).
102. L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).
103. L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997).

Under other reaction conditions, the product can result from *thermodynamic control*. Aldol reactions can be effected for many compounds using less than a stoichiometric amount of base. In these circumstances, the aldol reaction is reversible and the product ratio is determined by the relative stability of the various possible products. Thermodynamic conditions also permit equilibration among all the enolates of the nucleophile. The conditions that lead to equilibration include higher reaction temperatures, the presence of protic or dissociating polar solvents, and the use of less tightly coordinating cations.

When the aldol addition reaction is carried out under thermodynamic conditions, the difference in stability of the stereoisomeric *anti* and *syn* products determines the product composition. In the case of lithium enolates, the adducts can be equilibrated by keeping the reaction mixture at room temperature. This has been done, for example, for the product from the reaction of the enolate of ethyl *t*-butyl ketone and benzaldehyde. The greater stability of the *anti* isomer is attributed to the pseudoequatorial position of the methyl group in the chairlike product chelate. With larger substituent groups, the thermodynamic preference for the *anti* isomer is still greater.[104]



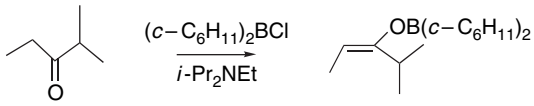
Another important version of the aldol reaction involves the use of boron enolates.[105] A cyclic TS similar to that for lithium enolates is involved and the same relationship exists between enolate geometry and product stereochemistry. In general, the stereoselectivity is higher than for lithium enolates. The O−B bond distances are shorter than those in lithium enolates, and this leads to a more compact TS and magnifies the steric interactions that control facial stereoselectivity. As with lithium enolates, the enolate stereochemistry controls diastereoselectivity.



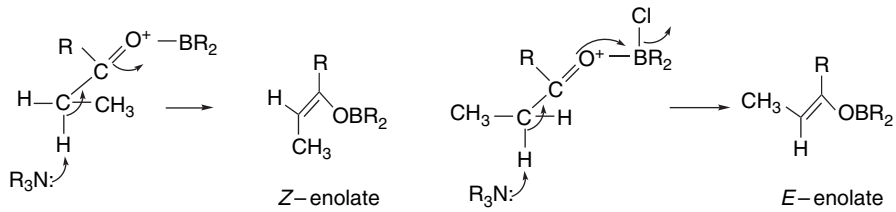
104. C. H. Heathcock and J. Lampe, *J. Org. Chem.*, **48**, 4330 (1983).

105. C. J. Cowden and I. A. Paterson, *Org. React.*, **51**, 1 (1997); E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *Adv. Carbanion Chem.*, **2,** 111 (1996).

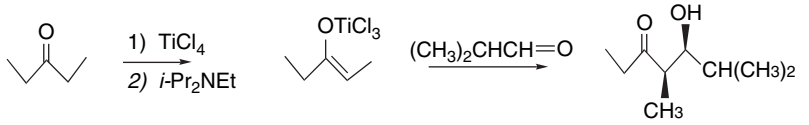
Boron enolates can be prepared by reaction of the ketone with a dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine.[106] Use of boron triflates with a hindered amine favors the *Z*-enolate. The resulting aldol products are predominantly the *syn* stereoisomers. The *E*-boron enolates of some ketones can be preferentially obtained by using dialkylboron chlorides.[107]



The contrasting stereoselectivity of the boron triflates and chlorides has been discussed in terms of reactant conformation and the stereoelectronic requirement for perpendicular alignment of the hydrogen with the carbonyl group π orbital.[108] The distinction between the two types of borylation reagents seems to lie in the extent of dissociation of the leaving group. The triflate is likely present as an ion pair, whereas with the less reactive chloride, the deprotonation may be a concerted (E2-like) process. The difference between trigonal and tetrahedral coordination of boron affects the steric interactions and reactant conformation. The two proposed TSs are shown below.



Titanium enolates can be prepared from lithium enolates by reaction with a trialkoxytitanium(IV) chloride, such as tri-(isopropoxy)titanium chloride.[109] Titanium enolates can also be prepared directly from ketones by reaction with $TiCl_4$ and a tertiary amine.[110]



106. D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).

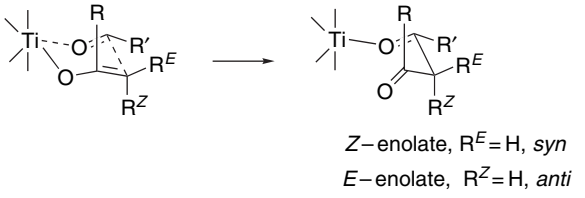
107. H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and B. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, R. K. Dhar, K. Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 499 (1992); H. C. Brown, R. K. Dhar, K.Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 2716 (1992); H. C. Brown, K. Ganesan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993); K. Ganesan and H. C. Brown, *J. Org. Chem.*, **58**, 7162 (1993).

108. J. M. Goodman and I. Paterson, *Tetrahedron Lett.*, **33**, 7223 (1992); E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).

109. C. Siegel and E. R. Thornton, *J. Am. Chem. Soc.*, **111**, 5722 (1989).

110. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

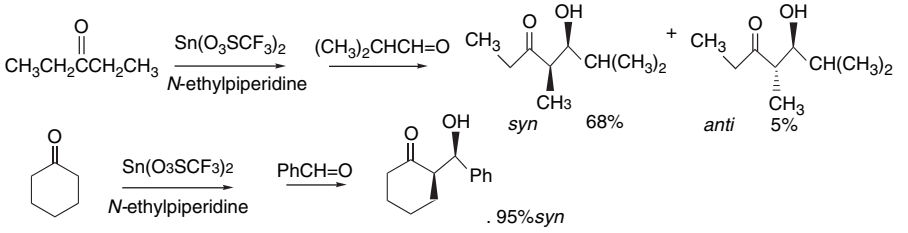
Under these conditions, the *Z*-enolate is formed and the aldol adducts have *syn* stereochemistry. The addition proceeds through a cyclic TS assembled around titanium.



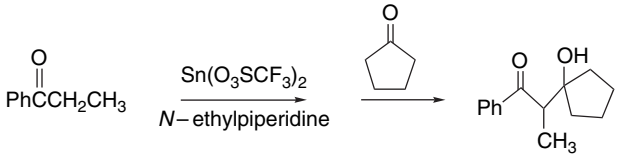
Z–enolate, R^E = H, *syn*

E–enolate, R^Z = H, *anti*

Tin enolates can be generated from ketones and $Sn(II)(O_3SCF_3)_2$ in the presence of tertiary amines.[111] The subsequent aldol addition is *syn* selective.[112]



Tin(II) enolates prepared in this way also show good reactivity toward ketones as the carbonyl component.



Ref. 113

7.7.4. Aldol Reactions of Other Carbonyl Compounds

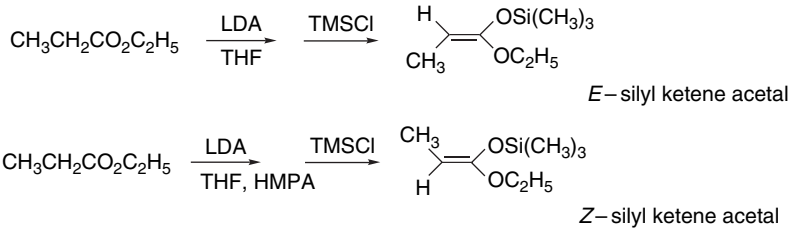
The enolates of other carbonyl compounds can be used in mixed aldol condensations. Extensive use has been made of the enolates of esters, thioesters, and amides. Of particular importance are several modified amides, such as those derived from oxazolidinones, that can be used as chiral auxiliaries. The methods for formation of these enolates are similar to those for ketones. Lithium, boron, tin, and titanium derivatives have all been used. Because of their usefulness in aldol additions and other synthetic methods (see especially Section 6.4.2.3, Part B), there has been a good deal of interest in the factors that control the stereoselectivity of enolate formation from esters. For simple esters such as ethyl propanoate, the *E*-enolate is preferred under kinetic conditions using a strong base such as LDA in THF solution. Inclusion of a

[111] T. Mukaiyama, N. Isawa, R. W. Stevens, and T. Haga, *Tetrahedron,* **40**, 1381 (1984); T. Mukaiyama and S. Kobayahi, *Org. React.*, **46**, 1 (1994); I Shibata and A. Babu, *Org. Prep. Proc. Int.*, **26**, 85 (1994).

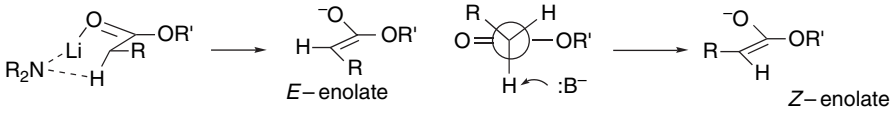
[112] T. Mukaiyama, R. W. Stevens, and N. Iwasawa, *Chem. Lett.*, 353 (1982).

[113] R. W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1459 (1982).

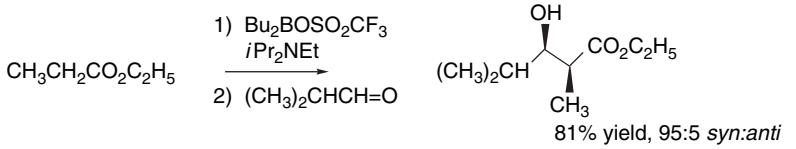
strong cation-solvating cosolvent, such as HMPA or DMPU favors the *Z*-enolate.[114] The enolates are often trapped as the corresponding silyl ethers, which are called *silyl ketene acetals*.



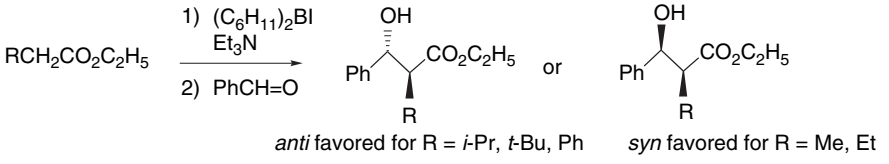
These observations are explained in terms of a cyclic TS for the LDA/THF conditions and a more open TS in the presence of an aprotic dipolar solvent.



Boron enolates can also be obtained from esters[115] and amides[116] and undergo aldol addition reactions. Various combinations of borylating reagents and amines have been used and the *E*:*Z* ratios are dependent on the reagents and conditions. In most cases esters give *Z*-enolates, which lead to *syn* adducts, but there are exceptions. For example, branched-chained esters give mainly *anti* adducts when the enolates are formed using dicyclohexyliodoborane.



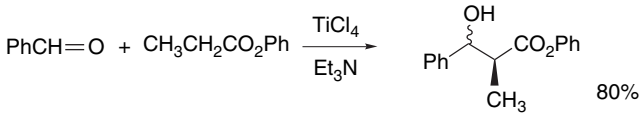
Ref. 117

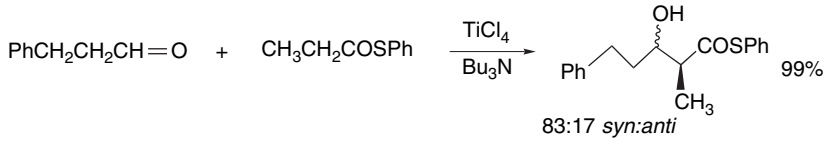


Ref. 115

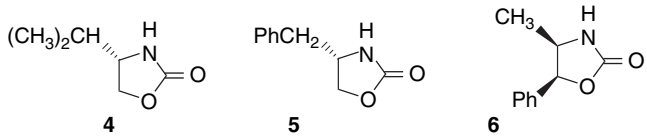
114. R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).
115. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 2336 (1994).
116. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).
117. A. Abiko, J.-F. Liu, and S. Masamune, *J. Org. Chem.*, **61**, 2590 (1996).

Phenyl and phenylthio esters have proven to be advantageous in $TiCl_4$-mediated additions, perhaps because they are slightly more acidic than the alkyl analogs. The reactions show *syn* diastereoselectivity.[118]



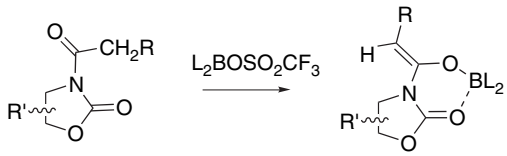


The methods that we have just discussed can be used to control the ratio of *syn* and *anti* diastereomeric products. It is often desired to also control the reaction to provide a *specific enantiomer*. Nearby stereocenters in either the carbonyl compound or the enolate can impose facial selectivity. Chiral auxiliaries can achieve the same effect. Finally, use of chiral Lewis acids as catalysts can also achieve enantioselectivity. Much effort has also been devoted to the use of chiral auxiliaries and chiral catalysts to effect enantioselective aldol reactions.[119] A very useful approach for enantioselective aldol additions is based on the oxazolidinones **4**,**5**, and **6**.



4 **5** **6**

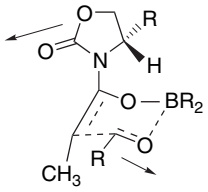
These compounds are readily available in enantiomerically pure form. They can be acylated and converted to the lithium or boron enolates by the same methods applicable to ketones and esters. When they are converted to boron enolates using di-*n*-butylboron triflate and triethylamine, the enolates are the *Z*-stereoisomers.[120] The carbonyl oxygen of the oxazolidinone ring is bonded to the boron.



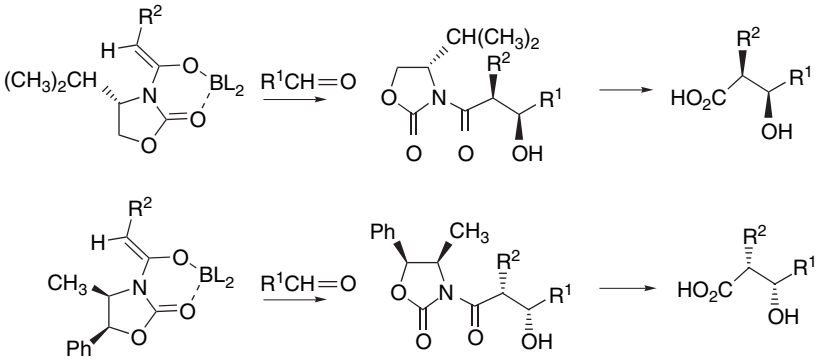
Reaction occurs through a cyclic TS in which the aldehyde displaces the oxazolidinone oxygen as a boron ligand. The oxazolinone substituents direct the approach of the aldehyde. The conformation of the addition TS for boron enolates is believed to have

118. Y. Tanabe, N. Matsumoto, S. Funakoshi, and N. Mantra, *Synlett*, 1959 (2001).
119. M. Braun and H. Sacha, *J. prakt. Chem.*, **335**, 653 (1993); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998); E. Carreira, in *Catalytic Asymmetric Synthesis,* 2nd Edition, I. Ojima, ed., Wiley-VCH, 2000, pp. 513–541.
120. D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).

the oxazolidinone ring oriented with opposed dipoles of the ring and the aldehyde carbonyl groups.

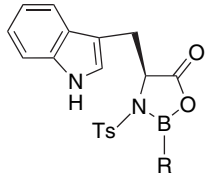


Because of the opposite steric encumbrance provided by **4** and **6**, the products, both of which are *syn*, result from opposite facial selectivity and have opposite absolute configuration. The acyl oxazolidinones are solvolyzed in water or alcohols to give the enantiomeric ß-hydroxy acid or ester. Alternatively, they can be reduced to aldehydes or alcohols.



We discuss other chiral auxiliaries and other strategies for controlling facial selectivity in Section 2.1.3 of Part B.

There are also several catalysts that can effect enantioselective aldol addition. The reactions generally involve enolate equivalents, such as silyl enol ethers, that are unreactive toward the carbonyl component alone, but can react when activated by a Lewis acid. The tryptophan-based oxaborazolidinone **7** has proven to be a useful catalyst[121] that induces preferential *re* facial attack on simple aldehydes.



7

The enantioselectivity appears to involve the shielding of the *si* face by the indole ring, through a π-stacking interaction, as indicated in Fig. 7.15.[122]

121. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992).

122. The model is from S. G. Nelson, *Tetrahedron: Asymmetry,* **9**, 357 (1998).

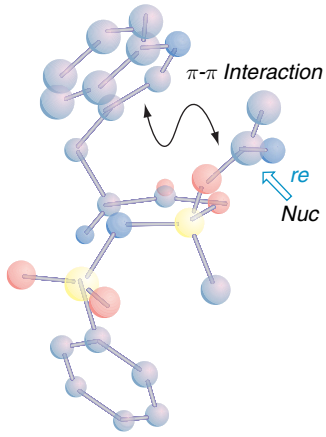
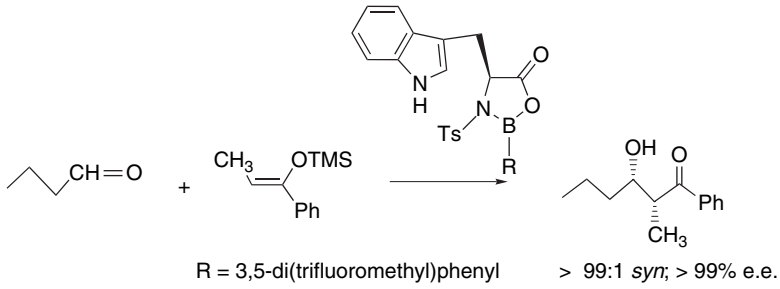
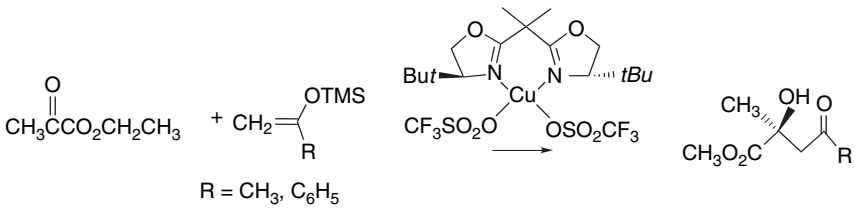


Fig. 7.15. Facial selectivity of 3-indolylmethyloxaborazolidinone catalyst. Reproduced from *Tetrahedron Asymmetry,* **9**, 357 (1998), by permission of Elsevier. (See also color insert.)

The *B*-3,5-di(trifluoromethyl)phenyl derivative was found to be a very effective catalyst.[123]



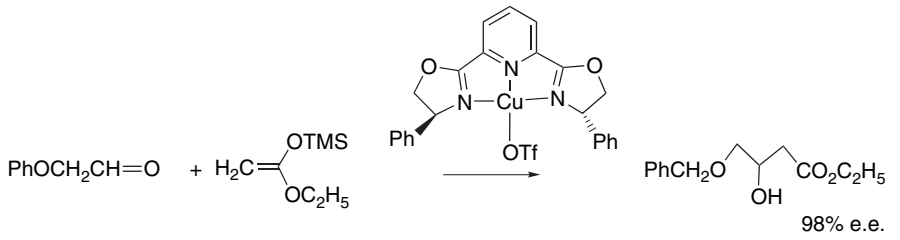
Another effective group of catalysts is made up of the copper *bis*-oxazolines.[124]



[123] K. Ishihara, S. Kondo, and H. Yamamoto, *J. Org. Chem.*, **65**, 9125 (2000).

[124] D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996).

These and similar catalysts are effective with silyl ketene acetals and silyl ketene thioacetals.[125]



These catalysts function as Lewis acids at the carbonyl oxygen. The chiral ligands promote facial selectivity.[126] Figure 7.16 shows a representation of the reactant complex.

In summary, several factors determine the stereochemical outcome of aldol addition reactions. The diastereochemical preference of the *syn* or *anti* isomer is determined by the configuration of the enolate and the orientation of the aldehyde within the TS. Chirality in either reactant introduces another stereochemical influence. The use of chiral auxiliaries can promote high facial selectivity in the approach of the aldehyde and thus permit the preparation of enantiomerically enriched products. The same outcome can be achieved using chiral Lewis acids as reaction catalysts.

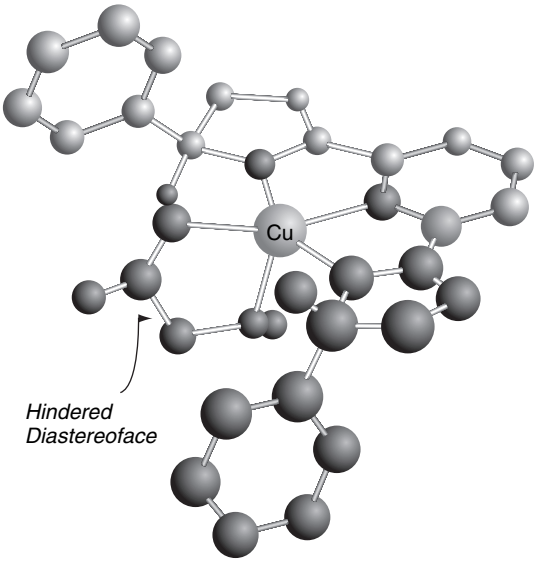


Fig. 7.16. Facial selectivity of diphenyl pyridine-*bis*-oxazoline catalysts. Reproduced from *Tetrahedron Asymmentry*, **9**, 357 (1998), by permission of Elsevier.

125. D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997); D. A. Evans, M. C. Kozlowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997).

126. The model is from S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998).

General References

M. L. Bender, *Mechanisms of Homogeneous Catalysis from Protons to Proteins*, Wiley-Interscience, New York, 1971.

T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms*, W. A. Benjamin, New York, 1966.

H. Dugas and C. Penney, *Bioorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd Edition, Springer-Verlag, New York, 1996.

W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969.

A. J. Kirby and A. R. Fersht, *Progress in Bioorganic Chemistry,* Vol. 1, E. T. Kaiser and R. J. Kezdy, eds., Wiley-Interscience, New York, 1971, pp. 1–82.

S. Patai, ed., *The Chemistry of Acid Derivatives*, Suppl. B, Vol. 2, Wiley, New York, 1992.

S. Patai, ed., *The Chemistry of the Carbonyl Group*, Wiley-Interscience, New York, 1969.

S. Patai, ed., *The Chemistry of Carboxylic Acids and Esters*, Wiley-Interscience, New York, 1969.

J. E. Zabricky,ed., *The Chemistry of Amides*, Wiley- Interscience, New York, 1970.

Problems

(*References for these problems will be found on page 1162.*)

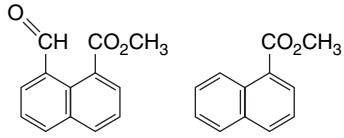
7.1. The hydrates of aldehydes and ketones are considerably more acidic than alcohols (p*K* 16–19). Some values are shown below. How do you account for this enhanced acidity? Explain the relative order of acidity for the compounds in the list.

Hydrate	p*K*
$CH_2(OH)_2$	13.3
$CH_3CH(OH)_2$	13.6
$Cl_3CCH(OH)_2$	10.0
$PhC(CF_3)(OH)_2$	10.0
$3\text{-}NO_2PhC(CF_3)(OH)_2$	9.2

7.2. Suggest explanations for each of the following observations:

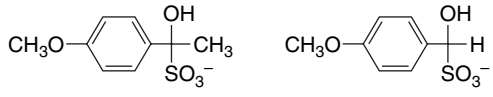
a. The equilibrium constant for cyanohydrin formation for 3,3-dimethyl-2-butanone (pinacolone) is 40 times larger than for acetophenone.

b. The ester **2-A** undergoes alkaline hydrolysis 8300 faster than the unsubstituted analog **2-B**.



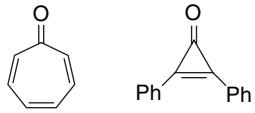
2-A **2-B**

c. Under comparable conditions, the general base-catalyzed elimination of bisulfite ion from **2-C** is about 10 times faster than for **2-D**.



2-C **2-D**

d. The rates of isotopic exchange of the carbonyl oxygen in tropone (**2-E**) and 2,3-diphenyl-cyclopropenone (**2-F**) are much less than for acetophenone.



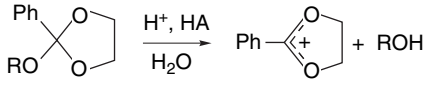
2-E **2-F**

7.3. Arrange each series of compounds in order of decreasing rate of acid-catalyzed hydrolysis of the corresponding diethyl acetals. Explain your reasoning.

a. acetaldehyde, chloroacetaldehyde, buten-2-al
b. acetaldehyde, formaldehyde, acetone
c. cyclopentanone, cyclohexanone, camphor
d. acetone, 3,3-dimethyl-2-butanone, 4,4-dimethyl-2-butanone
e. benzaldehyde, 4-methoxybenzaldehyde, butanal

7.4 The acid-catalyzed hydrolysis of 2-alkoxy-2-phenyl-1,3-dioxolane exhibits general acid catalysis of the initial rate-determining cleavage under some circumstances, as is indicated by the rate law:

$$k_{obs} = k_{H+}[H^+] + k_{H2O}[H_2O] + k_{HA}[HA]$$



The Brønsted relationship (see Section 3.7.1.2 to review the Brønsted catalysis law) shows a correlation with the identity of the alkoxy group. The alkoxy groups derived from more acidic alcohols have lower Brønsted coefficients α.

Alcohol	pK	α
Cl_2CHCH_2OH	12.9	0.69
$ClCH_2CH_2OH$	14.3	0.80
$CH_3OCH_2CH_2OH$	14.8	0.85
CH_3OH	15.7	0.90

What information about the reaction mechanism does this correlation provide? Interpret the results in terms of a More O'Ferrall-Jencks two-dimensional potential energy diagram.

7.5 Each of the following molecules is capable of some form of intramolecular catalysis of ester hydrolysis. For each reactant, indicate one or more possible mechanisms for intramolecular catalysis. Indicate the relationship that you would expect to exist between the catalytic mechanism and the pH. Determine if that relationship is consistent with the experimental pH-rate profile shown in Fig. 7.P5. Depict a mechanism showing the proposed catalysis.

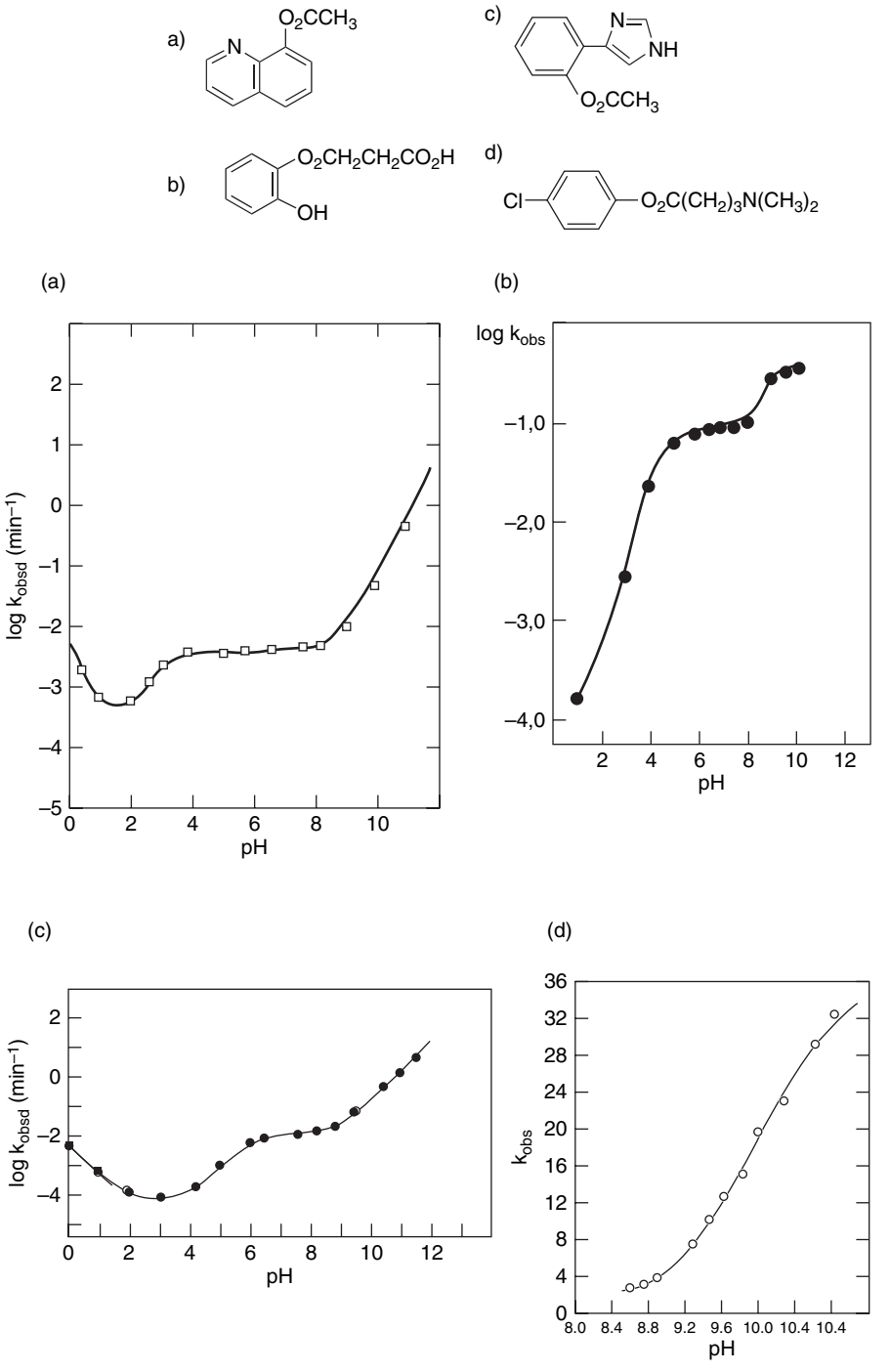
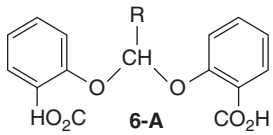


Fig. 7.P5. Reproduced from problem references 5 a–d by permission of the American Chemical Society.

7.6 Derive the general expression for the observed rate of hydrolysis of compound **6-A** as a function of pH. Assume that intramolecular general acid catalysis outweighs specific acid catalysis in the region between pH 3 and pH 9.

Does the form of the rate expression agree with the shape of the pH-rate profile in Figure 7.10?

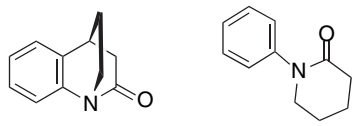


6-A

7.7. Enantiomerically pure dipeptide is obtained when the 4-nitrophenyl ester of *N*-benzoyl-L-leucine is coupled with ethyl glycinate in ethyl acetate. If, however, the leucine ester is treated with 1-methylpiperidine in chloroform for 30 min prior to coupling, the dipeptide in nearly completely racemized. Treatment of the leucine ester with 1-methylpiperidine leads to formation of a crystalline material of composition $C_{13}H_{15}NO_2$, which has strong IR bands at 1832 and 1664 cm^{-1}. Explain how racemization occurs and suggest a reasonable structure for the crystalline material.

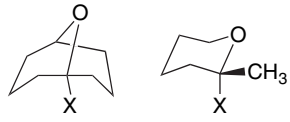
7.8 Provide an explanation in terms of structure and mechanism for the following observations:

a. The bicyclic lactam **8-A** hydrolyzes 10^7 times faster than the related monocyclic compound **8-B**



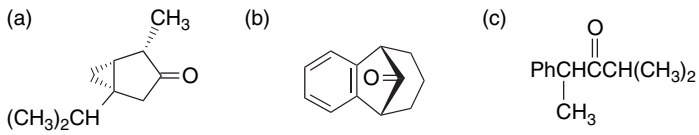
8-A **8-B**

b. Leaving groups X solvolyze from the bicyclic structure **8-C** at a rate that is 10^{-13} less than for the monocyclic analog **8-D**.



8-C **8-D**

7.9. Analyze the factors that determine the stereoselectivity of the addition of organometallic compounds to the following ketones. Predict the stereochemistry of the major product.



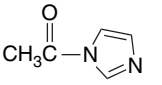
7.10. Indicate which of the compounds of each of the following pairs will have the more negative free-energy change for hydrolysis at pH 7. Explain your reasoning.

(a) $CH_3CO_2CH_3$ or $CH_3C(=O)SCH_3$

(b) $CH_3CO_2CH_3$ or $CH_3C(=O)OPO_3H_2$

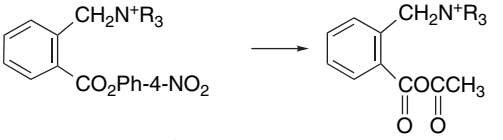
(c) $CH_3CO_2CH_3$ or $H_2NCH_2CO_2CH_3$

(d) $CH_3CO_2CH_3$ or $CH_3C(=O)CH_2CO_2CH_3$

(e) $CH_3CO_2CH_3$ or 

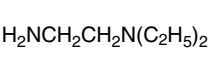
(f) $CH_3CO_2CH_3$ or $CH_3CON(CH_3)_2$

7.11. Sodium acetate reacts with 4-nitrophenyl benzoates to give mixed anhydrides when the reaction is conducted in a polar aprotic solvent in the presence of a crown ether. The reaction is strongly accelerated by a quaternary nitrogen substituent in the *ortho* position. Suggest an explanation for this substituent effect.

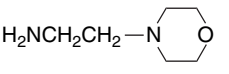


introduction of $^+NR_3$ substituent accelerates the reaction by $> 10^3$.

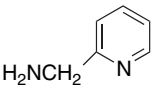
7.12. The kinetics of the hydrolysis of a series of imines derived from benzophenone and primary amines reveals a normal dependence of mechanism on pH with rate-determining nucleophilic attack at high pH and rate-determining decomposition of the tetrahedral intermediate at low pH. The primary amines show a linear correlation between the rate of nucleophilic addition and the basicity of the amine. Several diamines, in particular **12-A**, **12-B**, and **12-C,** all showed positive (more reactive) deviation from the correlation line for other primary amines. Why might these amines be more reactive than predicted on the basis of their basicity?



12-A



12-B



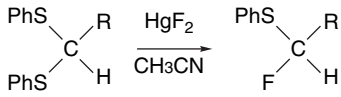
12-C

7.13. The following data give the dissociation constants and rate of acetaldehyde hydration catalysis by each acid. Treat the data according to the Brønsted equation and discuss the mechanistic significance of the results.

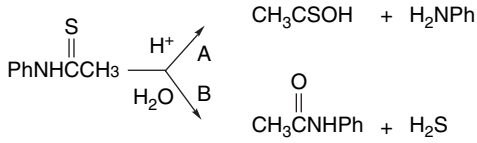
Acid	K_a	k_{hydr} $mol^{-1}s^{-1}$
Formic	1.77×10^{-4}	1.74
Phenylacetic	4.9×10^{-5}	0.91
Acetic	1.75×10^{-5}	0.47
Pivalic	9.4×10^{-6}	0.33

7.14. 1,1-(Diphenylthio)alkanes react with mercuric fluoride to give 1-fluoro-1-(phenylthio)alkanes. Provide a likely mechanism for this reaction. Consider

such questions as: (1) is the reaction an S_N1 or S_N2 process? Would NaF cause the same reaction? Why is only one of the phenylthio groups replaced?



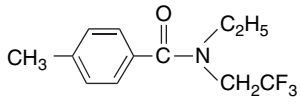
7.15. The acid-catalyzed hydrolysis of thioacetanilide can follow two different courses.



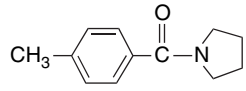
The product composition is a function of acid concentration, as shown below. Provide a mechanism that accounts for the change in product composition as a function of acid concentration.

H_2SO_4 (% by weight)	1.1	3.2	6.1	12	18	36	48
% formed by path A	20	50	55	65	75	96	100

7.16. A comparison of the kinetics of hydrolysis and isotopic exchange of amides **16-A** and **16-B** gave the data below for reactions conducted in 0.1–1.0 *M* [$^-$OH]. An interesting observation is that there is more C=O exchange for **16-A** than for **16-B**. From this information and the other data given, propose a stepwise mechanism for hydrolysis of each amide. Make a qualitative comparison of the behavior of the substituent effects on the various steps in the mechanisms.



16-A



16-B

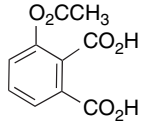
		16-A	**16-B**
$k_{ex/hydrol}$	(1.0 *M* $^-$OD in D_2O)	35.6	0.04
k_{ex}	(100 °C; 1.0 *M* $^-$OD in D_2O)	$1.09\times10^{-3}s^{-1}$	$1.53\times10^{-5}s^{-1}$
k_{hydrol}	(100 °C; 1.0 *M* $^-$OD in D_2O)	$3.06\times10^{-5}s^{-1}$	$3.85\times10^{-4}s^{-1}$
$\Delta G^{\ddagger}_{ex}$	(100 °C)	26.5 kcal/mol	27.1 kcal/mol
$\Delta G^{\ddagger}_{hydrol}$	(100 °C)	29.6 kcal/mol	24.4 kcal/mol

7.17. Data pertaining to substituent effects on the acid-catalyzed hydrolysis of mixed aryl-methyl acetals of benzaldehyde are given below. The reactions exhibited general acid catalysis, and the Brønsted α values are tabulated for a series of substituents in both the benzaldehyde ring and the phenoxy group. Discuss the information that these data provide about the nature of the TS for the first hydrolysis step, making reference to a three-dimensional energy diagram.

Series I, substituent in Ar			Series II, substituent in Ar′		
X	k_{cat} [a]	α	X	k_{cat} [a]	α
m-NO_2	2.7×10^{-4}	1.05	*m*-NO_2	8.85×10^{-2}	0.49
m-F	2.2×10^{-3}	0.92	*m*-Br	4.7×10^{-2}	0.65
m-CH_3O	9.6×10^{-3}	0.78	*m*-F	2.45×10^{-2}	0.67
H	1.3×10^{-2}	0.77	*m*-CH_3O	2.55×10^{-2}	0.71
p-CH_3	1.1×10^{-1}	0.72	H	1.3×10^{-2}	0.77
p-CH_3O	2.8×10^{-1}	0.68	*p*-CH_3	1.3×10^{-2}	0.88
			p-CH_3O	1.65×10^{-2}	0.96

a. Rate constant in s^{-1} for catalysis by acetic acid.

7.18. The introduction of an additional carboxy function into the structure of aspirin results in a significant rate enhancement of hydrolysis. The hydrolysis is 6300 times faster than for the monoanion of aspirin. 3-Hydroxyphthalic anhydride is an observable intermediate. The pH-rate profile is shown in Figure 7.P18. Suggest a mechanism to account for the accelerated hydrolysis involving both of the carboxy derivatives.



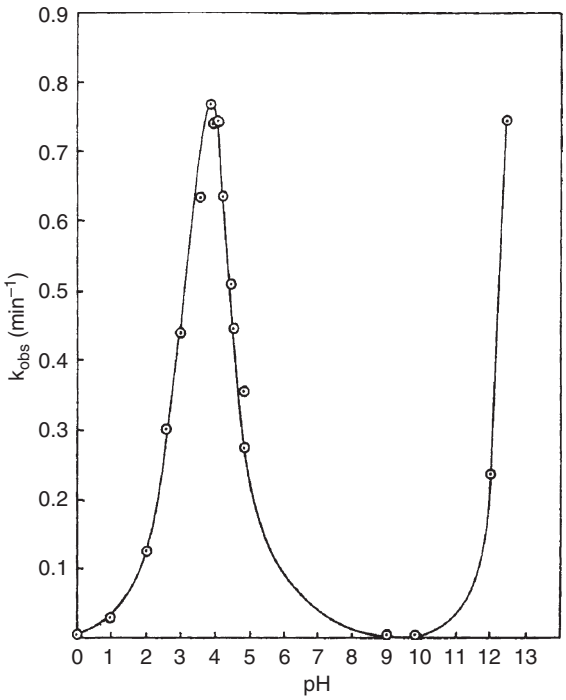
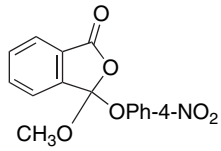


Fig. 7.P18. pH-Rate profile for hydrolysis of 3-acetoxyphthalic acid. Reproduced from *J. Am. Chem. Soc.*, **90**, 5833 (1968), by permission of the American Chemical Society.

7.19. The hydrolysis of the lactone **19-A** shows catalysis by acetate ion, with the rate expression being

$$k_{obs} = 1.6 \times 10^{-6} + 6.4 \times 10^{-4}[H^+] + 2.08 \times 10^{-5}[^-OAc] + 49[^-OH]\,s^{-1}$$

This expression results in a pH-rate profile shown in Figure 7.P19, with acetate catalysis being significant in the pH range 3–6. The reaction shows a solvent isotope effect of 2.65. Discuss how the catalysis by acetate might occur. What are the likely mechanisms for hydrolysis at pH < 1 and pH > 7, where the rates are linearly dependent on $[H^+]$ and $[^-OH]$, respectively?



19-A

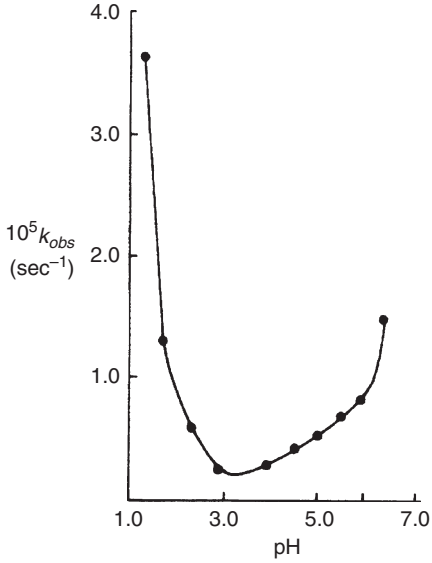
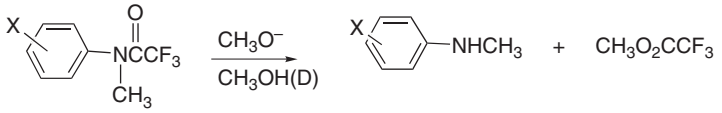


Fig. 7.P19. pH-Rate profile for hydrolysis of **19-A** in acetate buffer solution. Reproduced from *J. Am. Chem. Soc.*, **103**, 3555 (1981), by permission of the American Chemical Society.

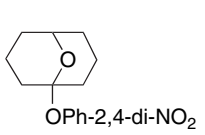
7.20. Some data on substituent effects for the reaction of trifluoroacetanilides with methoxide ion in methanol and methanol-OD are given below. Calculate the isotope effect for each reactant. Plot the rate data against appropriate Hammett substituent constants. What facets of the data are in specific agreement with the normal addition-intermediate mechanism proceeding through a tetrahedral intermediate? What facets of the data suggest other complications? Propose a mechanism that is consistent with the data given.



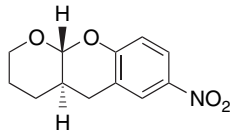
X	k_{CH_3OH}	k_{CH_3OD}
m-NO_2	5.75	8.13
m-Br	0.524	0.464
p-Cl	0.265	0.274
p-Br	0.349	0.346
m-Cl	0.513	0.430
m-OCH_3	0.110	0.101
H	0.104	0.0899
m-CH_3	0.0833	0.0595
p-CH_3	0.0729	0.0451
p-OCH_3	0.0564	0.0321

a. Second-order rate constants in M^{-1} s^{-1}.

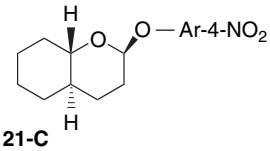
7.21. The order of the reactivity of the cyclic acetals toward hydrolysis is **21-A** << **21-B** << **21-C**. Offer an explanation for the large differences in reactivity of these acetals.



21-A



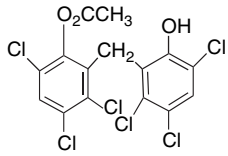
21-B



21-C

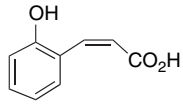
7.22. Examine the structure of the following reactants and the corresponding pH-rate profiles. Offer mechanisms for each reaction that is consistent with the pH-rate profile. Indicate the most likely mechanism corresponding to each feature of the profile.

(a)



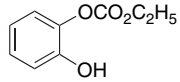
ester hydrolysis

(b)



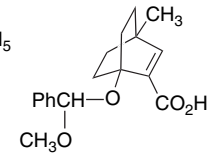
lactonization

(c)

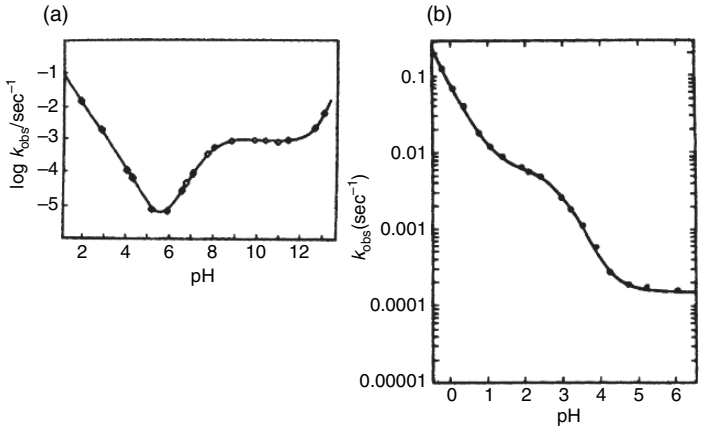


ester hydrolysis

(d)



acetal hydrolysis



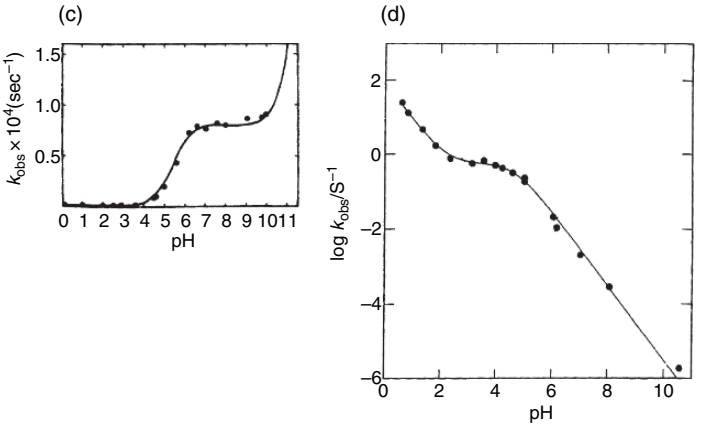
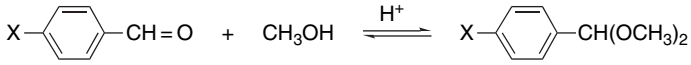


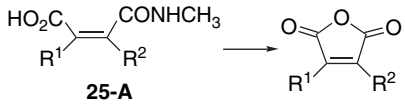
Fig. 7.P22. Reproduced from problem references 22a–c, by permission of the American Chemical Society and reference 22d by permission of the Royal Society of Chemistry.

7.23. The pH-rate profiles for 2-carboxy- and 4-carboxy benzylidene acetals of the *trans*-1,2-cyclohexanediol are shown in Figure 7.P23a (page 708). Figure 7.P23b is the pH-rate profile of 3-(*trans*-2-hydroxycyclohexyloxy) phthalide, an intermediate isolated from the 2-carboxy derivative. Interpret both the relative rates and the form of the pH-rate profiles.

7.24. The rates of both formation and hydrolysis of dimethyl acetals of *p*-substituted benzaldehydes are substituent dependent. Do you expect the rate of formation to increase or decrease with the increasing EWG strength of the substituent? How do you expect the rate of hydrolysis to respond to the nature of the substituent? The equilibrium constant for acetal formation is determined by these two rates. How do you expect K to vary with substitution?



7.25. Figure 7.P25 (page 709) gives the pH-rate profile for conversion of the acid **25-A** to the anhydride in aqueous solution. Note that the rate of the reaction increases with the size of the alkyl substituent, and, although not shown, the compound with both R^1 and $R^2 = CH_3$ is still more reactive. Suggest a mechanism for the reaction, including the structure of any intermediate. How do you account for the effect of the alkyl substituents on the reaction rate?



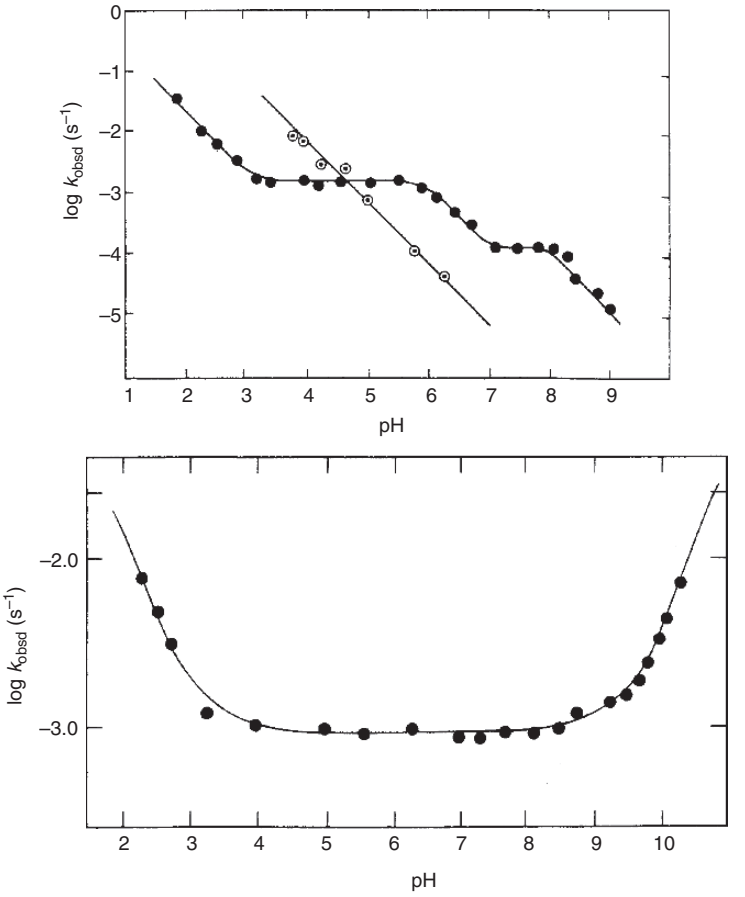


Fig. 7.P23. (a) pH-Rate profile for hydrolysis of 2-carboxy (solid circles) and 4-carboxy (open circles) benzylidene acetals of *trans*-1,2-cyclohexanediol. (b) pH-Rate profile for 3-(*trans*-2-hydroxycyclohexyloxy)phthalide, an intermediate isolated from the 2-carboxy derivative. Reproduced from *J. Am. Chem. Soc.*, **118**, 12956 (1996), by permission of the American Chemical Society.

7.26. Assume that the general mechanism for imine hydrolysis described on p. 647–648 is operative. Assume that a steady state approximation can be applied to the tetrahedral intermediate. Derive the kinetic expression for the observed rate of imine hydrolysis. What variables have to be determined to construct the pH-rate profile? What simplifying assumptions can be justified at very high and very low pH values? What are the kinetic expressions that result from these assumptions?

7.27. Give the expected structure, including stereochemistry if appropriate, for the products of the following reactions:

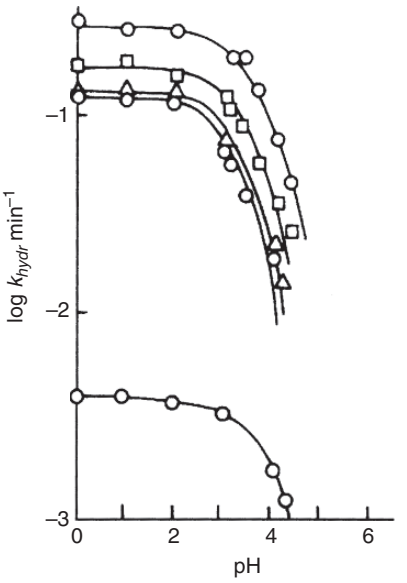
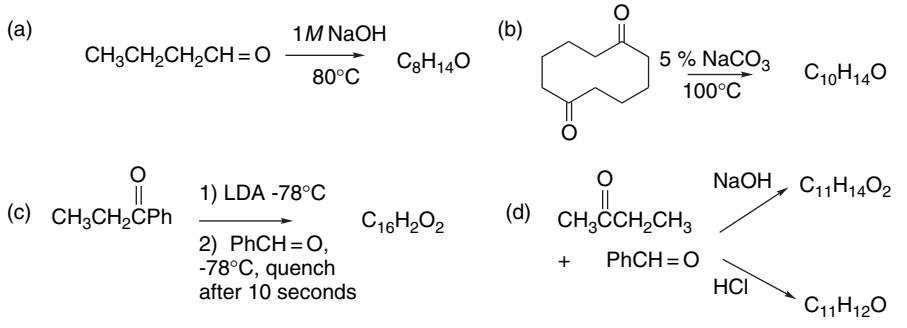
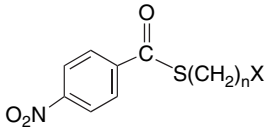


Fig. 7.P25. pH-Rate profile for the hydrolysis of alkyl *N*-methylmaleamic acids at 39°C. The order of increasing reactivity is $R^1 = H <$ Me < Et < *i*-Pr << *t*-Bu. Reproduced from *J. Chem. Soc.*, *Perkin Trans. 2*, 1206 (1972), by permission of the Royal Society of Chemistry.



7.28. Figure 7.P28 (page 710) gives the pH-rate profile for the hydrolysis of thioesters **28-A**–**D** and indicates differing dependence on pH, depending on the thiol substituents. Propose a mechanism that would account for the observed pH dependence in each case.



28

	n	X
A	1	$CO_2C_2H_5$
B	1	CO_2H
C	2	$N(CH_3)_2$
D	2	$N^+(CH_3)_3$

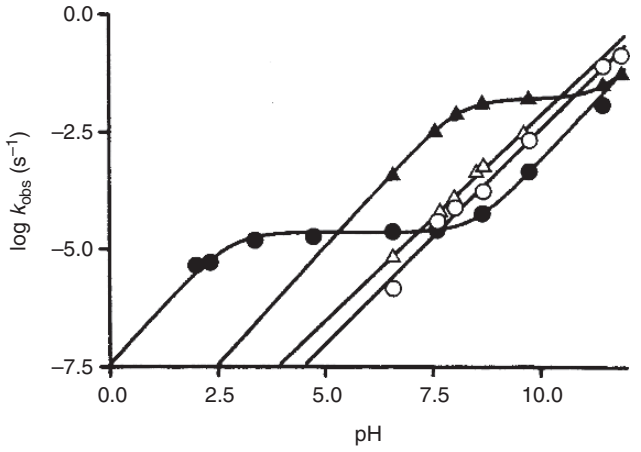


Fig. 7.P28. pH-Rate plots for thioesters **28-A** (○),**28-B** (●),**28-C**(▲) and **28-D**(△). Reproduced from *J. Org. Chem.*, **62**, 4816 (1997), by permission of the American Chemical Society.

7.29. Figure 7.P29 gives the pH-rate profile for alkaline hydrolysis of two substituted salicylate amides, as compared with benzamide. Consider whether the pH-rate profiles for the salicylamides are more consistent with mechanism (A), intramolecular basic catalysis of water attack, or (B), intramolecular acid catalysis of hydroxide ion attack.

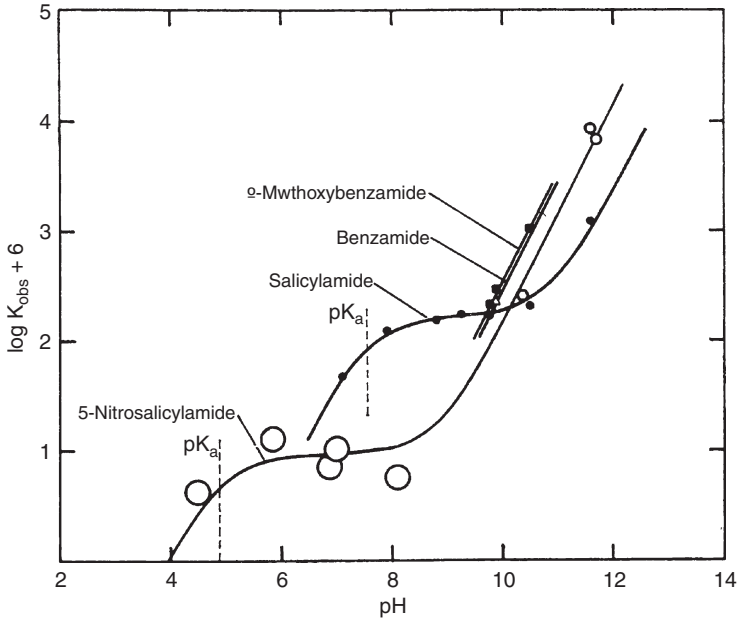
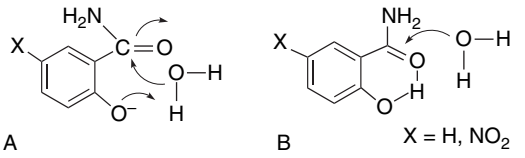


Fig. 7.P29. pH-Rate profiles for substituted salicylamides compared to benzamide in water at 100°C. The rate constants are in min^{-1}. Reproduced from *J. Org. Chem.*. **30**, 1668 (1965), by permission of the American Chemical Society.



7.30. The hydrolysis of the ester group in 2-acetoxybenzaldehyde is accelerated by about 10^4, relative to the 4-isomer. The rate of hydrolysis in the pH range 6.0–8.5 follows the rate expression

$$\text{Rate} = k_0 + k[^-\text{OH}]$$

Both the k_0 and $k[^-\text{OH}]$ terms are larger than for the 4-isomer. When the hydrolysis is carried out in ^{18}O-labeled water, the acetic acid contains 50% ^{18}O. Suggest a mechanism that is consistent with these observations.

7.31. The pH-rate profile for the hydrolysis of 4-nitrophenyl 2-aminobenzoate is given in Figure 7.13 (p. 674). The reaction exhibits a solvent isotope effect of ~ 0.5 in D_2O. Suggest possible mechanisms for the reaction, based on the shape of the pH-rate profile and chemical structure considerations. Derive the kinetic expression for the most likely mechanism.