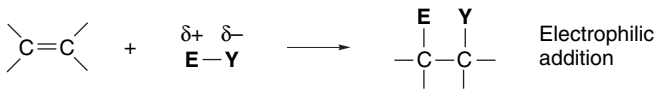
5

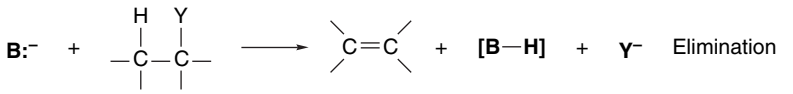
Polar Addition and Elimination Reactions

Introduction

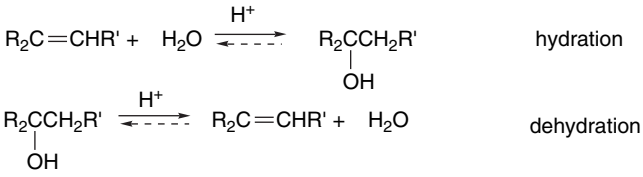
In this chapter, we discuss reactions that either add adjacent (*vicinal*) groups to a carbon-carbon double bond (*addition*) or remove two adjacent groups to form a new double bond (*elimination*). The discussion focuses on addition reactions that proceed by electrophilic polar (*heterolytic*) mechanisms. In subsequent chapters we discuss addition reactions that proceed by *radical* (*homolytic*), *nucleophilic*, and *concerted* mechanisms. The electrophiles discussed include protic acids, halogens, sulfenyl and selenenyl reagents, epoxidation reagents, and mercuric and related metal cations, as well as diborane and alkylboranes. We emphasize the relationship between the regio- and stereoselectivity of addition reactions and the reaction mechanism.



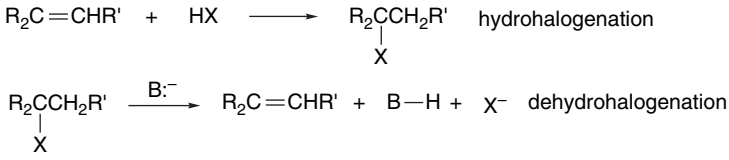
The discussion of elimination reactions considers the classical E2, E1, and E1cb eliminations that involve removal of a hydrogen and a leaving group. We focus on the kinetic and stereochemical characteristics of elimination reactions as key indicators of the reaction mechanism and examine how substituents influence the mechanism and product composition of the reactions, paying particular attention to the nature of transition structures in order to discern how substituent effects influence reactivity. We also briefly consider reactions involving trisubstituted silyl or stannyl groups. Thermal and concerted eliminations are discussed elsewhere.



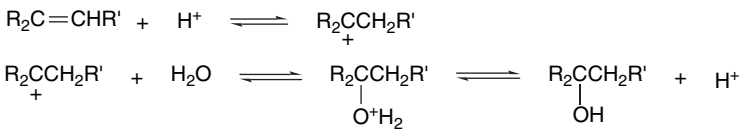
Addition and elimination processes are the formal reverse of one another, and in some cases the reaction can occur in either direction. For example, acid-catalyzed hydration of alkenes and dehydration of alcohols are both familiar reactions that constitute an addition-elimination pair.



Another familiar pair of addition-elimination reactions is hydrohalogenation and dehydrohalogenation, although these reactions are not reversible under normal conditions, because the addition occurs in acidic solution, whereas the elimination requires a base.



When reversible addition and elimination reactions are carried out under similar conditions, they follow the same mechanistic path, but in opposite directions. The *principle of microscopic reversibility* states that the mechanism of a reversible reaction is the same in the forward and reverse directions. The intermediates and transition structures involved in the addition process are the same as in the elimination reaction. Under these circumstances, mechanistic conclusions about the addition reaction are applicable to the elimination reaction and vice versa. The reversible acid-catalyzed reaction of alkenes with water is a good example. Two intermediates are involved: a carbocation and a protonated alcohol. The direction of the reaction is controlled by the conditions, which can be adjusted to favor either side of the equilibrium. Addition is favored in aqueous solution, whereas elimination can be driven forward by distilling the alkene from the reaction solution. The reaction energy diagram is show in Figure 5.1.



Several limiting general mechanisms can be written for polar additions. Mechanism A involves prior dissociation of the electrophile and implies that a carbocation is generated that is free of the counterion $\mathbf{Y}^-$ at its formation. Mechanism B also involves a carbocation intermediate, but it is generated in the presence of an anion and exists initially as an ion pair. Depending on the mutual reactivity of the two ions, they might or might not become free of one another before combining to give product. Mechanism C leads to a bridged intermediate that undergoes addition by a second step in which the ring is opened by a nucleophile. Mechanism C implies stereospecific *anti* addition. Mechanisms A, B, and C are all Ad_E2 reactions; that

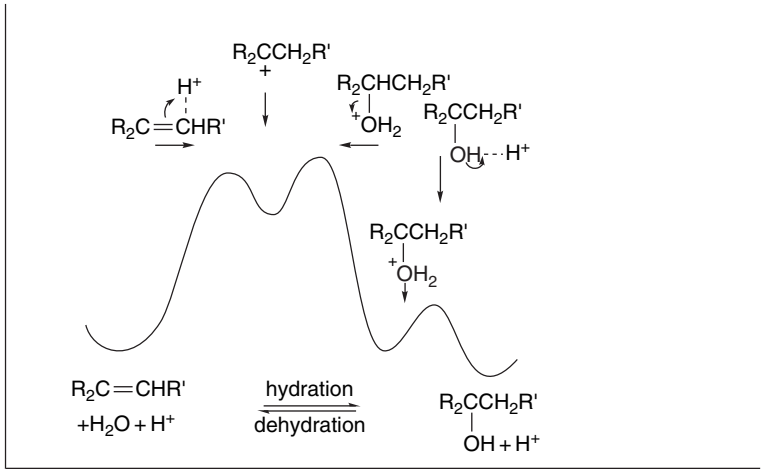
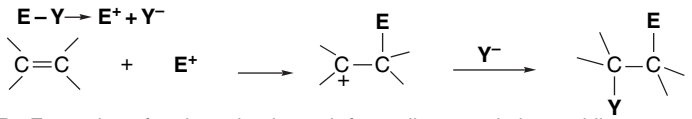


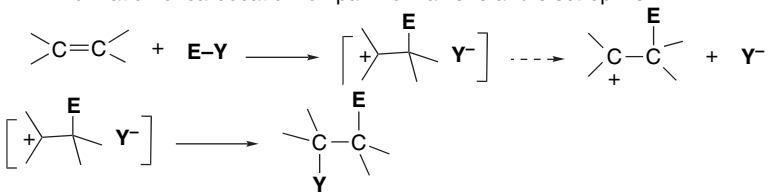
Fig. 5.1. Conceptual representation of the reversible reaction path for the hydration-dehydration reaction pair.

is, they are *bimolecular electrophilic additions*. Mechanism D is a process that has been observed for several electrophilic additions and implies concerted transfer of the electrophilic and nucleophilic components of the reagent from two separate molecules. It is a *termolecular electrophilic addition*, Ad_E3, a mechanism that implies formation of a complex between one molecule of the reagent and the reactant and also is expected to result in *anti* addition. Each mechanism has two basic parts, the electrophilic interaction of the reagent with the alkene and a step involving reaction with a nucleophile. Either formation of the bond to the electrophile or nucleophilic capture of the cationic intermediate can be rate controlling. In mechanism D, the two stages are concurrent.

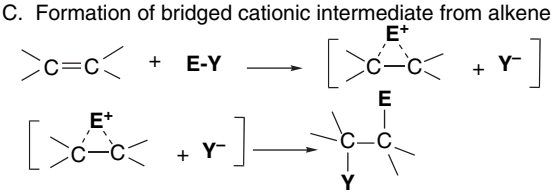
A. Prior dissociation of electrophile and formation of carbocation intermediate



B. Formation of carbocation ion pair from alkene and electrophile



C. Formation of bridged cationic intermediate from alkene and electrophile



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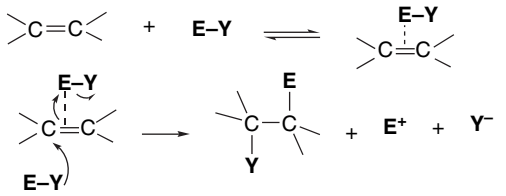
D. Concerted addition of electrophile and nucleophile in a termolecular reaction



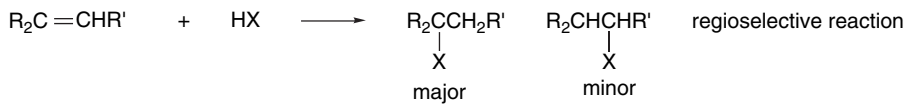
All of these mechanisms are related in that they involve electrophilic attack on the π bond of the alkene. Based on the electron distribution and electrostatic potential maps of alkenes (Section 1.4.5), the initial attack is expected to be perpendicular to the plane of the double bond and near the midpoint of the π bond. The mechanisms differ in the relative stability of the carbocation or bridged intermediates and in the timing of the bonding to the nucleophile. Mechanism A involves a prior dissociation of the electrophile, as would be the case in protonation by a strong acid. Mechanism B can occur if the carbocation is fairly stable and $\mathbf{E}^+$ is a poor bridging group. The lifetime of the carbocation may be very short, in which case the ion pair would react faster than it dissociates. Mechanism C is an important general mechanism that involves bonding of $\mathbf{E}^+$ to *both carbons of the alkene* and depends on the ability of the electrophile to function as a bridging group. Mechanism D avoids a cationic intermediate by concerted formation of the C−**E** and C−**Y** bonds.

The nature of the electrophilic reagent and the relative stabilities of the intermediates determine which mechanism operates. Because it is the hardest electrophile and has no free electrons for bridging, the proton is most likely to react via a carbocation mechanism. Similarly, reactions in which $\mathbf{E}^+$ is the equivalent of F^+ are unlikely to proceed through bridged intermediates. Bridged intermediates become more important as the electrophile becomes softer (more polarizable). We will see, for example, that bridged halonium ions are involved in many bromination and chlorination reactions. Bridged intermediates are also important with sulfur and selenium electrophiles. Productive termolecular collisions are improbable, and mechanism D involves a prior complex of the alkene and electrophilic reagent. Examples of each of these mechanistic types will be encountered as specific reactions are considered in the sections that follow. The discussion focuses on a few reactions that have received the most detailed mechanistic study. Our goal is to see the common mechanistic features of electrophilic additions and recognize some of the specific characteristics of particular reagents.

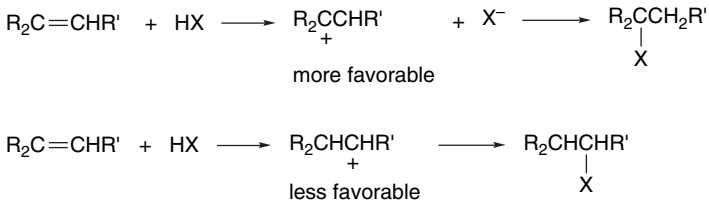
5.1. Addition of Hydrogen Halides to Alkenes

The addition of hydrogen halides to alkenes has been studied from a mechanistic perspective for many years. One of the first aspects of the mechanism to be established was its regioselectivity, that is, the direction of addition. A reaction is described as *regioselective* if an unsymmetrical alkene gives a predominance of one of the two isomeric addition products.[1]

[1] A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).



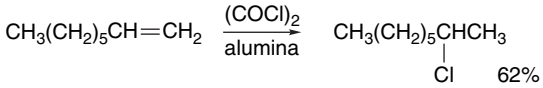
In the addition of hydrogen halides to alkenes, it is usually found that the nucleophilic halide ion becomes attached to the more-substituted carbon atom. This general observation is called *Markovnikov's rule*. The basis for this regioselectivity lies in the relative ability of the carbon atoms to accept positive charge. The addition of hydrogen halide is initiated by protonation of the alkene. The new C−H bond is formed from the π electrons of the carbon-carbon double bond. It is easy to see that if a carbocation is formed as an intermediate, the halide will be added to the more-substituted carbon, since protonation at the less-substituted carbon atom provides the more stable carbocation intermediate.



As is indicated when the mechanism is discussed in more detail, discrete carbocations are not always formed. Unsymmetrical alkenes nevertheless follow the Markovnikov rule, because the partial positive charge that develops is located predominantly at the carbon that is better able to accommodate an electron deficiency, which is the more-substituted one.

The regioselectivity of addition of hydrogen bromide to alkenes can be complicated if a free-radical chain addition occurs in competition with the ionic addition. The free-radical chain reaction is readily initiated by peroxidic impurities or by light and leads to the *anti* Markovnikov addition product. The mechanism of this reaction is considered more fully in Chapter 11. Conditions that minimize the competing radical addition include use of high-purity alkene and solvent, exclusion of light, and addition of a radical inhibitor.[2]

The order of reactivity of the hydrogen halides is HI > HBr > HCl, and reactions of simple alkenes with HCl are quite slow. The reaction occurs more readily in the presence of silica or alumina and convenient preparative methods that take advantage of this have been developed.[3] In the presence of these adsorbents, HBr undergoes exclusively ionic addition. In addition to the gaseous hydrogen halides, liquid sources of hydrogen halide such as $SOCl_2$, $(COCl)_2$, $(CH_3)_3SiCl$, $(CH_3)_3SiBr$, and $(CH_3)_3SiI$ can be used. The hydrogen halide is generated by reaction with water and/or hydroxy group on the adsorbent.

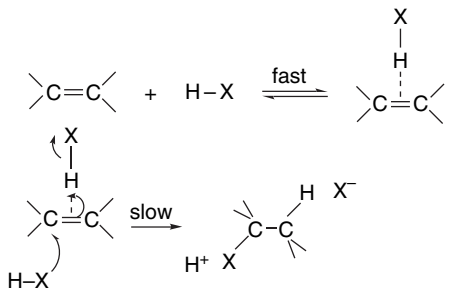


2. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.*, **96**, 1858 (1974).
3. P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. C. Craig, M. M. Baillargeon, and G. W. Breton, *J. Am. Chem. Soc.*, **115**, 3071 (1993).

Studies aimed at determining mechanistic details of hydrogen halide addition to alkenes have focused on the kinetics and stereochemistry of the reaction and on the effect of added nucleophiles. Kinetic studies often reveal rate expressions that indicate that more than one process contributes to the overall reaction rate. For addition of hydrogen bromide or hydrogen chloride to alkenes, an important contribution to the overall rate is often made by a third-order term.

$$\text{Rate} = k[\text{alkene}][\text{HX}]^2$$

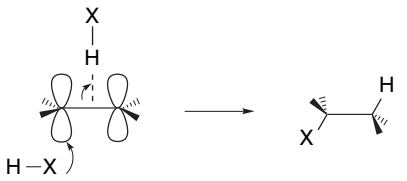
Among the cases in which this type of kinetics has been observed are the addition of HCl to 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene,[4] and cyclohexene.[5] The addition of HBr to cyclopentene also follows a third-order rate expression.[2] The TS associated with the third-order rate expression involves proton transfer to the alkene from one hydrogen halide molecule and capture of the halide ion from the second, and is an example of general mechanism D (Ad_E3). Reaction occurs through a complex formed by the alkene and hydrogen halide with the second hydrogen halide molecule.



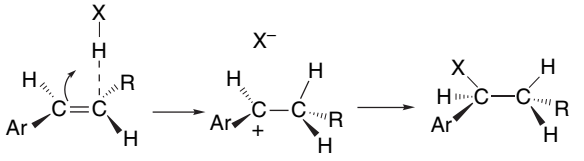
The stereochemistry of addition of hydrogen halides to unconjugated alkenes is usually *anti*. This is true for addition of HBr to 1,2-dimethylcyclohexene,[6] cyclohexene,[7] 1,2-dimethylcyclopentene,[8] cyclopentene,[2] *Z*- and *E*-2-butene,[2] and 3-hexene,[2] among others. *Anti* stereochemistry is also dominant for addition of hydrogen chloride to 1,2-dimethylcyclohexene[9] and 1-methylcyclopentene.[4] Temperature and solvent can modify the stereochemistry, however. For example, although the addition of HCl to 1,2-dimethylcyclohexene is *anti* near room temperature, *syn* addition dominates at $-78°$ C.[10]

Anti stereochemistry is consistent with a mechanism in which the alkene interacts simultaneously with a proton-donating hydrogen halide and a source of halide ion, either a second molecule of hydrogen halide or a free halide ion. The *anti* stereochemistry is consistent with the expectation that the attack of halide ion occurs from the opposite side of the π-bond to which the proton is delivered.

4. Y. Pocker, K. D. Stevens, and J. J. Champoux, *J. Am. Chem. Soc.*, **91**, 4199 (1969); Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.,* **91**, 4205 (1969).
5. R. C. Fahey, M. W. Monahan, and C. A. McPherson, *J. Am. Chem. Soc.*, **92**, 2810 (1970).
6. G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.*, **76**, 4121 (1954).
7. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.*, **86**, 5035 (1964); R. C. Fahey, C. A. McPherson, and R. A. Smith, *J. Am. Chem. Soc.*, **96**, 4534 (1974).
8. G. S. Hammond and C. H. Collins, *J. Am. Chem. Soc.*, **82**, 4323 (1960).
9. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **93**, 1445 (1971).
10. K. B. Becker and C. A. Grob, *Synthesis,* 789 (1973).

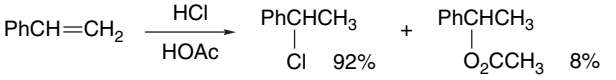


A change in the stereoselectivity is observed when the double bond is conjugated with a group that can stabilize a carbocation intermediate. Most of the specific cases involve an aryl substituent. Examples of alkenes that give primarily *syn* addition are *Z*- and *E*-1-phenylpropene,[11] *cis*- and *trans*-ß-*t*-butylstyrene,[12] 1-phenyl-4-*t*-butylcyclohexene,[13] and indene.[14] The mechanism proposed for these reactions features an ion pair as the key intermediate. Owing to the greater stability of the benzylic carbocations formed in these reactions, concerted attack by halide ion is not required for protonation. If the ion pair formed by alkene protonation collapses to product faster than rotation takes place, *syn* addition occurs because the proton and halide ion are initially on the same face of the molecule.



Kinetic studies of the addition of hydrogen chloride to styrene support the conclusion than an ion pair mechanism operates. The reaction is first order in hydrogen chloride, indicating that only one molecule of hydrogen chloride participates in the rate-determining step.[15]

There is a competing reaction with solvent when hydrogen halide additions to alkenes are carried out in nucleophilic solvents.



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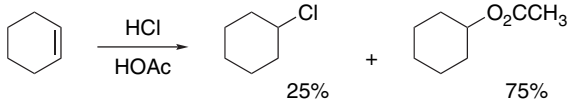

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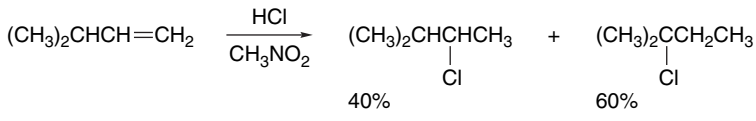
This result is consistent with the general mechanism for hydrogen halide additions. These products are formed because the solvent competes with halide ion as the nucleophilic component in the addition. Solvent addition can occur via a concerted mechanism or by capture of a carbocation intermediate. Addition of a halide salt increases the likelihood of capture of a carbocation intermediate by halide ion. The effect of added halide salt can be detected kinetically. For example, the presence of tetramethylammonium chloride increases the rate of addition of hydrogen chloride to cyclohexene.[9] Similarly, lithium bromide increases the rate of addition of hydrogen bromide to cyclopentene.[8]

11. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 3645 (1963).
12. R. J. Abraham and J. R. Monasterios, *J. Chem. Soc., Perkin Trans. 2*, 574 (1975).
13. K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *J. Chem. Soc., Chem. Commun.*, 1246 (1970).
14. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2248 (1963).
15. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **91**, 3865 (1969).

Skeletal rearrangements are possible in hydrogen halide additions if hydride or alkyl migration can give a more stable carbocation



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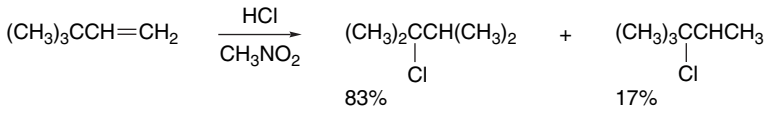

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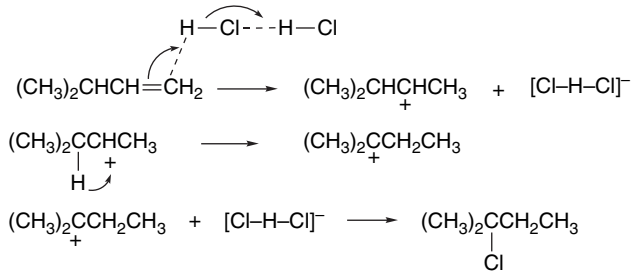
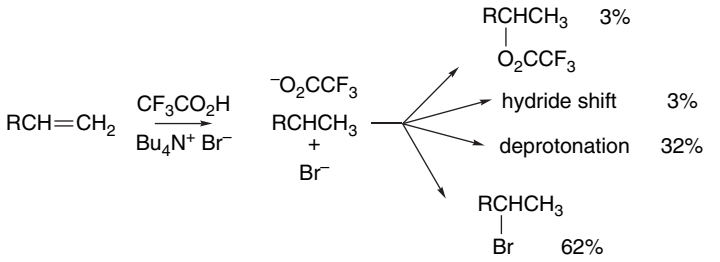
Even though the rearrangements suggest that discrete carbocation intermediates are involved, these reactions frequently show kinetics consistent with the presence of a least two hydrogen chloride molecules in the rate-determining step. A termolecular mechanism in which the second hydrogen chloride molecule assists in the ionization of the electrophile has been suggested to account for this observation.[4]



Another possible mechanism involves halide-assisted protonation.[16] The electrostatic effect of a halide anion can facilitate proton transfer. The key intermediate in this mechanism is an ion sandwich involving the acid anion and a halide ion. Bromide ion accelerates addition of HBr to 1- , 2- , and 4-octene in 20% TFA in CH_2Cl_2. In the same system, 3,3-dimethyl-1-butene shows substantial rearrangement, indicating formation of a carbocation intermediate. Even 1- and 2-octene show some evidence of rearrangement, as detected by hydride shifts. The fate of the 2-octyl cation under these conditions has been estimated.

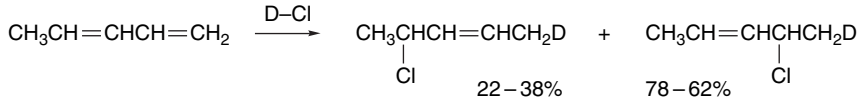


This behavior of the cationic intermediates generated by alkene protonation is consistent with the reactivity associated with carbocations generated by leaving-group

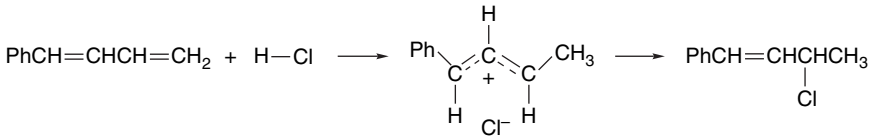
16. H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1517 (1998).

ionization, as discussed in Chapter 4. The prevalence of nucleophilic capture by Br^- over $CF_3CO_2^-$ reflects relative nucleophilicity and is also dependent on Br^- concentration. Competing elimination is also consistent with the pattern of the solvolytic reactions.

The addition of hydrogen halides to dienes can result in either 1,2- or 1,4-addition. The extra stability of the allylic cation formed by proton transfer to a diene makes the ion pair mechanism more favorable. Nevertheless, a polar reaction medium is required.[17] 1,3-Pentadiene, for example, gives a mixture of products favoring the 1,2-addition product by a ratio of from 1.5:1 to 3.4:1, depending on the temperature and solvent.[18]

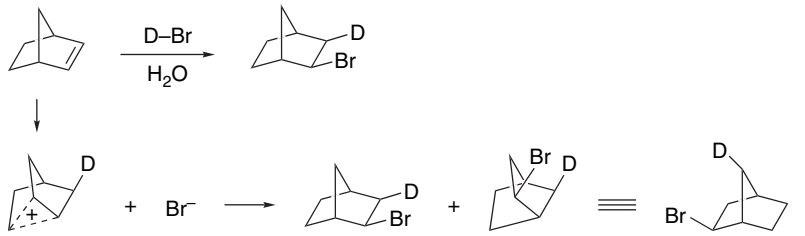


With 1-phenyl-1,3-butadiene, the addition of HCl is exclusively at the 3,4-double bond. This reflects the greater stability of this product, which retains styrene-type conjugation. Initial protonation at C(4) is favored by the fact that the resulting carbocation benefits from both allylic and benzylic stabilization.



The kinetics of this reaction are second order, as would be expected for the formation of a relatively stable carbocation by an Ad_E2 mechanism.[19]

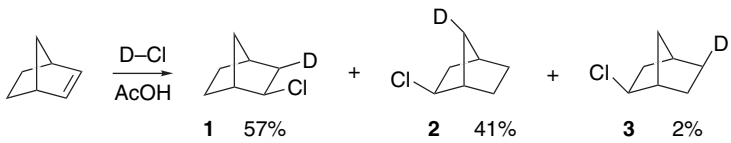
The additions of HCl or HBr to norbornene are interesting cases because such factors as the stability and facile rearrangement of the norbornyl cation come into consideration. (See Section 4.4.5 to review the properties of the 2-norbornyl cation.) Addition of deuterium bromide to norbornene gives *exo*-norbornyl bromide. Degradation to locate the deuterium atom shows that about half of the product is formed via the bridged norbornyl cation, which leads to deuterium at both the 3- and 7-positions.[20] The *exo* orientation of the bromine atom and the redistribution of the deuterium indicate the involvement of the bridged ion.



Similar studies have been carried out on the addition of HCl to norbornene.[21] Again, the chloride is almost exclusively the *exo* isomer. The distribution of deuterium

17. L. M. Mascavage, H. Chi, S. La, and D. R. Dalton, *J. Org. Chem.*, **56**, 595 (1991).
18. J. E. Nordlander, P. O. Owuor, and J. E. Haky, *J. Am. Chem. Soc.*, **101**, 1288 (1979).
19. K. Izawa, T. Okuyama, T. Sakagami, and T. Fueno, *J. Am. Chem. Soc.*, **95**, 6752 (1973).
20. H. Kwart and J. L. Nyce, *J. Am. Chem. Soc.*, **86**, 2601 (1964).
21. J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Am. Chem. Soc.*, **88**, 4922 (1966).

in the product was determined by NMR. The fact that **1** and **2** are formed in unequal amounts excludes the possibility that the symmetrical bridged ion is the only intermediate.[22]

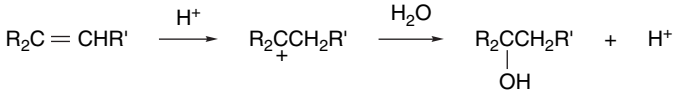


The excess of **1** over **2** indicates that some *syn* addition occurs by ion pair collapse before the bridged ion achieves symmetry with respect to the chloride ion. If the amount of **2** is taken as an indication of the extent of bridged ion involvement, one can conclude that 82% of the reaction proceeds through this intermediate, which must give equal amounts of **1** and **2**. Product **3** results from the C(6) → C(2) hydride shift that is known to occur in the 2-norbornyl cation with an activation energy of about 6 kcal/mol (see p. 450).

From these examples we see that the mechanistic and stereochemical details of hydrogen halide addition depend on the reactant structure. Alkenes that form relatively unstable carbocations are likely to react via a termolecular complex and exhibit *anti* stereospecificity. Alkenes that can form more stable cations can react via rate-determining protonation and the structure and stereochemistry of the product are determined by the specific properties of the cation.

5.2. Acid-Catalyzed Hydration and Related Addition Reactions

The formation of alcohols by acid-catalyzed addition of water to alkenes is a fundamental reaction in organic chemistry. At the most rudimentary mechanistic level, it can be viewed as involving a carbocation intermediate. The alkene is protonated and the carbocation then reacts with water.

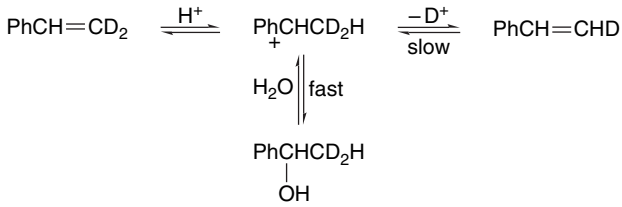


This mechanism explains the formation of the more highly substituted alcohol from unsymmetrical alkenes (Markovnikov's rule). A number of other points must be considered in order to provide a more complete picture of the mechanism. Is the protonation step reversible? Is there a discrete carbocation intermediate, or does the nucleophile become involved before proton transfer is complete? Can other reactions of the carbocation, such as rearrangement, compete with capture by water?

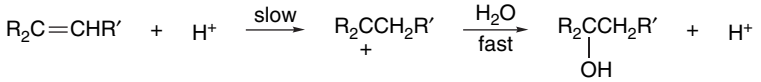
Much of the early mechanistic work on hydration reactions was done with conjugated alkenes, particularly styrenes. Owing to the stabilization provided by the phenyl group, this reaction involves a relatively stable carbocation. With styrenes, the rate of hydration is increased by ERG substituents and there is an excellent correlation

[22] H. C. Brown and K.-T. Liu, *J. Am. Chem. Soc.*, **97**, 600 (1975).

with σ^+.[23] A substantial solvent isotope effect k_{H2O}/k_{D2O} equal to 2 to 4 is observed. Both of these observations are in accord with a rate-determining protonation to give a carbocation intermediate. Capture of the resulting cation by water is usually fast relative to deprotonation. This has been demonstrated by showing that in the early stages of hydration of styrene deuterated at C(2), there is no loss of deuterium from the unreacted alkene that is recovered by quenching the reaction. The preference for nucleophilic capture over elimination is also consistent with the competitive rate measurements under solvolysis conditions, described on p. 438–439. The overall process is reversible, however, and some styrene remains in equilibrium with the alcohol, so isotopic exchange eventually occurs.



Alkenes lacking phenyl substituents appear to react by a similar mechanism. Both the observation of general acid catalysis[24] and solvent isotope effect[25] are consistent with rate-limiting protonation of alkenes such as 2-methylpropene and 2,3-dimethyl-2-butene.



Relative rate data in aqueous sulfuric acid for a series of alkenes reveal that the reaction is strongly accelerated by alkyl substituents. This is as expected because alkyl groups both increase the electron density of the double bond and stabilize the carbocation intermediate. Table 5.1 gives some representative data. The $1 : 10^7 : 10^{12}$ relative rates for ethene, propene, and 2-methylpropene illustrate the dramatic rate enhancement by alkyl substituents. Note that styrene is intermediate between monoalkyl and dialkyl alkenes. These same reactions show solvent isotope effects consistent with the reaction proceeding through a rate-determining protonation.[26] Strained alkenes show enhanced reactivity toward acid-catalyzed hydration. *trans*-Cyclooctene is about 2500 times as reactive as the *cis* isomer,[27] which reflects the higher ground state energy of the strained alkene.

Other nucleophilic solvents can add to alkenes in the presence of strong acid catalysts. The mechanism is analogous to that for hydration, with the solvent replacing water as the nucleophile. Strong acids catalyze the addition of alcohols

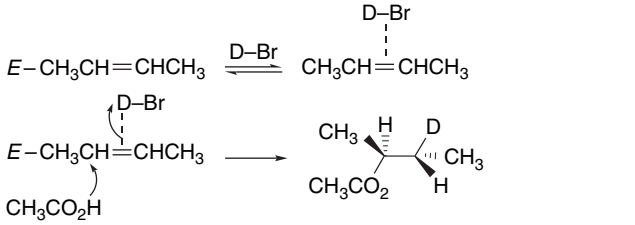
23. W. M. Schubert and J. R. Keefe, *J. Am. Chem. Soc.*, **94**, 559 (1972); W. M. Schubert and B. Lamm, *J. Am. Chem. Soc.*, **88**, 120 (1966); W. K. Chwang, P. Knittel, K. M. Koshy, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99,** 3395 (1977).
24. A. J. Kresge, Y. Chiang, P. H. Fitzgerald, R. S. McDonald, and G. H. Schmid, *J. Am. Chem. Soc.*, **93**, 4907 (1971); H. Slebocka-Tilk and R. S. Brown, *J. Org. Chem.*, **61**, 8079 (1998).
25. V. Gold and M. A. Kessick, *J. Chem. Soc.*, 6718 (1965).
26. V. J. Nowlan and T. T. Tidwell, *Acc. Chem. Res.*, **10**, 252 (1977).
27. Y. Chiang and A. J. Kresge, *J. Am. Chem. Soc.*, **107**, 6363 (1985).

Table 5.1. Rates of Alkene Hydration in Aqueous Sulfuric Acid[a]

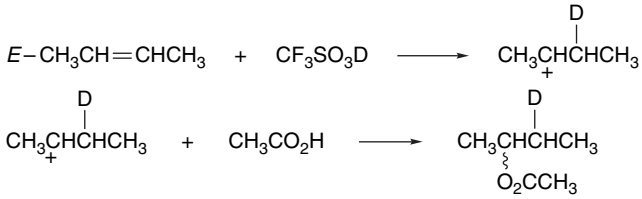
Alkene	$k_2(M^{-1}s^{-1})$	k_{rel}
$CH_2{=}CH_2$	1.56×10^{-15}	1
$CH_3CH{=}CH_2$	2.38×10^{-8}	1.6×10^7
$CH_3(CH_2)_3CH{=}CH_2$	4.32×10^{-8}	3.0×10^7
$(CH_3)_2C{=}CHCH_3$	2.14×10^{-3}	1.5×10^{12}
$(CH_3)_2C{=}CH_2$	3.71×10^{-3}	2.5×10^{12}
$PhCH{=}CH_2$	2.4×10^{-6}	1.6×10^9

a. W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 7233 (1977).

to alkenes to give ethers, and the mechanistic studies that have been done indicate that the reaction closely parallels the hydration process.[28] The strongest acid catalysts probably react via discrete carbocation intermediates, whereas weaker acids may involve reaction of the solvent with an alkene-acid complex. In the addition of acetic acid to *Z*- or *E*-2-butene, the use of DBr as the catalyst results in stereospecific *anti* addition, whereas the stronger acid CF_3SO_3H leads to loss of stereospecificity. This difference in stereochemistry can be explained by a stereospecific Ad_E3 mechanism in the case of DBr and an Ad_E2 mechanism in the case of CF_3SO_3D.[29] The dependence of stereochemistry on acid strength reflects the degree to which nucleophilic participation is required to complete proton transfer.



nucleophilic participation required: *anti* addition

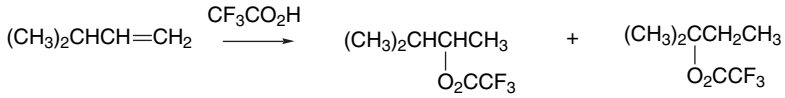


nucleophilic participation not required: nonstereospecific addition

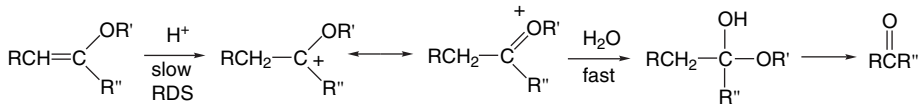
Trifluoroacetic acid adds to alkenes without the necessity of a stronger acid catalyst.[30] The mechanistic features of this reaction are similar to addition of water catalyzed by strong acids. For example, there is a substantial isotope effect when CF_3CO_2D is used ($k_H/k_D = 4.33$)[31] and the reaction rates of substituted styrenes are

28. N. C. Deno, F. A. Kish, and H. J. Peterson, *J. Am. Chem. Soc.*, **87**, 2157 (1965).
29. D. J. Pasto and J. F. Gadberry, *J. Am. Chem. Soc.*, **100**, 1469 (1978).
30. P. E. Peterson and G. Allen, *J. Am. Chem. Soc.*, **85**, 3608 (1963); A. D. Allen and T. T. Tidwell, *J. Am. Chem. Soc.*, **104,** 3145 (1982).
31. J. J. Dannenberg, B. J. Goldberg, J. K. Barton, K. Dill, D. M. Weinwurzel, and M. O. Longas, *J. Am. Chem. Soc.*, **103**, 7764 (1981).

correlated with σ^+.[32] 2-Methyl-1-butene and 2-methyl-2-butene appear to react via the 2-methylbutyl cation, and 3-methyl-1-butene gives the products expected for a carbocation mechanism, including rearrangement. These results are consistent with rate-determining protonation.[33]



The reactivity of carbon-carbon double bonds toward acid-catalyzed addition of water is greatly increased by ERG substituents. The reaction of vinyl ethers with water in acidic solution is an example that has been carefully studied. With these reactants, the initial addition products are unstable hemiacetals that decompose to a ketone and alcohol. Nevertheless, the protonation step is rate determining, and the kinetic results pertain to this step. The mechanistic features are similar to those for hydration of simple alkenes. Proton transfer is rate determining, as demonstrated by general acid catalysis and solvent isotope effect data.[34]



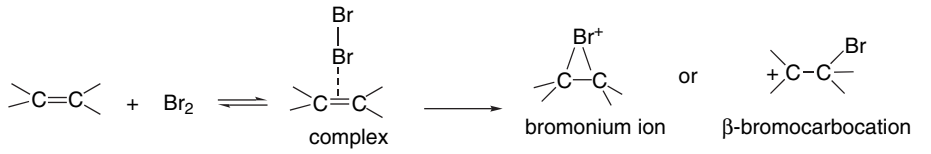
5.3. Addition of Halogens

Alkene chlorinations and brominations are very general reactions, and mechanistic study of these reactions provides additional insight into the electrophilic addition reactions of alkenes.[35] Most of the studies have involved brominations, but chlorinations have also been examined. Much less detail is known about fluorination and iodination. The order of reactivity is $F_2 > Cl_2 > Br_2 > I_2$. The differences between chlorination and bromination indicate the trends for all the halogens, but these differences are much more pronounced for fluorination and iodination. Fluorination is strongly exothermic and difficult to control, whereas for iodine the reaction is easily reversible.

The initial step in bromination is the formation of a complex between the alkene and Br_2. The existence of these relatively weak complexes has long been recognized. Their role as intermediates in the addition reaction has been established more recently.

32. A. D. Allen, M. Rosenbaum, N. O. L. Seto, and T. T. Tidwell, *J. Org. Chem.*, **47**, 4234 (1982).
33. D. Farcasiu, G. Marino, and C. S. Hsu, *J. Org. Chem.*, **59**, 163 (1994).
34. A. J. Kresge and H. J. Chen, *J. Am. Chem. Soc.*, **94**, 2818 (1972); A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Am. Chem. Soc.*, **99**, 7228 (1977).
35. Reviews: D. P. de la Mare and R. Bolton, in *Electrophilic Additions to Unsaturated Systems*, 2nd Edition, Elsevier, New York, 1982, pp. 136–197; G. H. Schmidt and D. G. Garratt, in *The Chemistry of Double Bonded Functional Groups*, Supplement A, Part 2, S. Patai, ed., Wiley-Interscience, New York, 1977, Chap. 9; M.-F. Ruasse, *Adv. Phys. Org. Chem.,* **28**, 207 (1993); M.-F. Ruasse, *Industrial Chem. Library*, **7**, 100 (1995); R. S. Brown, *Industrial Chem. Library*, **7**, 113 (1995); G. Bellucci and R. Bianchini, *Industrial Chem. Library*, **7**, 128 (1995); R. S. Brown, *Acc. Chem. Res.*, **30**, 131 (1997).

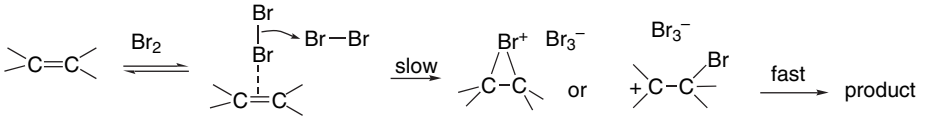
The formation of the complex can be observed spectroscopically, and they subsequently disappear at a rate corresponding to the formation of bromination product.[36,37] The second step in bromination involves formation of an ionic intermediate, which can be either a bridged bromonium ion or a β-bromocarbocation. Whether a bridged intermediate or a carbocation is formed depends on the stability of the potential cation. Aliphatic systems normally react through the bridged intermediate but styrenes are borderline cases. When the phenyl ring has an ERG substituent, there is sufficient stabilization to permit carbocation formation, whereas EWGs favor the bridged intermediate.[38] Because this step involves formation of charged intermediates, it is strongly solvent dependent. Even a change from CCl_4 to 1,2-dichloroethane accelerates the reaction (with cyclohexene) by a factor of 10^5.[39]



The kinetics of bromination reactions are often complex, with at least three terms making contributions under given conditions.

$$\text{Rate} = k_1[\text{alkene}][\text{Br}_2] + k_2[\text{alkene}][\text{Br}_2]^2 + k_3[\text{alkene}][\text{Br}_2][\text{Br}^-]$$

In methanol, pseudo-second-order kinetics are observed when a high concentration of Br^- is present.[40] Under these conditions, the dominant contribution to the overall rate comes from the third term of the general expression. In nonpolar solvents, the observed rate is frequently described as a sum of the first two terms in the general expression.[41] The mechanism of the third-order reaction is similar to the process that is first order in Br_2, but with a second Br_2 molecule replacing solvent in the rate-determining conversion of the complex to an ion pair.



There are strong similarities in the second- and third-order reaction in terms of magnitude of ρ values and product distribution.[41b] In fact, there is a quantitative correlation between the rate of the two reactions over a broad series of alkenes, which can be expressed as

$$\Delta G_3^{\ddagger} = \Delta G_2^{\ddagger} + \text{constant}$$

36. S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, **104**, 7599 (1982).
37. G. Bellucci, R. Bianchi, and R. Ambrosetti, *J. Am. Chem. Soc.*, **107**, 2464 (1985).
38. M.-F. Ruasse, A. Argile, and J. E. Dubois, *J. Am. Chem. Soc.*, **100**, 7645 (1978).
39. M.-F. Ruasse and S. Motallebi, *J. Phys. Org. Chem.*, **4**, 527 (1991).
40. J.-E. Dubois and G. Mouvier, *Tetrahedron Lett.*, 1325 (1963); *Bull. Soc. Chim. Fr.*, 1426 (1968).
41. (a) G. Bellucci, R. Bianchi, R. A. Ambrosetti, and G. Ingrosso, *J. Org. Chem.*, **50**, 3313 (1985); G. Bellucci, G. Berti, R. Bianchini, G. Ingrosso, and R. Ambrosetti, *J. Am. Chem. Soc.*, **102**, 7480 (1980); (b) K. Yates, R. S. McDonald, and S. Shapiro, *J. Org. Chem.*, **38**, 2460 (1973); K. Yates and R. S. McDonald, *J. Org. Chem.*, **38**, 2465 (1973); (c) S. Fukuzumi and J. K. Kochi, *Int. J. Chem. Kinetics,* **15**, 249 (1983).

Table 5.2. Relative Reactivity of Alkenes toward Halogenation

Alkene	Relative reactivity		
	Chlorination[a]	Bromination[b]	Bromination[c]
Ethene		0.01	0.0045
1-Butene	1.00	1.00	1.00
3,3-Dimethyl-1-butene	1.15	0.27	1.81
Z-2-Butene	63	27	173
E-2-Butene	50	17.5	159
2-Methylpropene	58	57	109
2-Methyl-2-butene	1.1×10^4	1.38×10^4	
2,3-Dimethyl-2-butene	4.3×10^5	19.0×10^4	

a. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965), in excess alkene.
b. J. E. Dubois and G. Mouvier, *Bull. Chim. Soc. Fr.*, 1426 (1968), in methanol.
c. A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.* **42**, 3673 (1977), in $ClCH_2CH_2Cl$.

where $\Delta G_3^{\ddagger}$ and $\Delta G_2^{\ddagger}$ are the free energies of activation for the third- and second-order processes, respectively.[41c] These correlations suggest that the two mechanisms must be very similar.

Observed bromination rates are very sensitive to common impurities such as HBr[42] and water, which can assist in formation of the bromonium ion.[43] It is likely that under normal preparative conditions, where these impurities are likely to be present, these catalytic mechanisms may dominate.

Chlorination generally exhibits second-order kinetics, first-order in both alkene and chlorine.[44] The relative reactivities of some alkenes toward chlorination and bromination are given in Table 5.2. The reaction rate increases with alkyl substitution, as would be expected for an electrophilic process. The magnitude of the rate increase is quite large, but not as large as for protonation. The relative reactivities are solvent dependent.[45] Quantitative interpretation of the solvent effect using the Winstein-Grunwald *Y* values indicates that the TS has a high degree of ionic character. The Hammett correlation for bromination of styrenes is best with σ^+ substituent constants, and gives $\rho = -4.8$.[46] All these features are in accord with an electrophilic mechanism.

Stereochemical studies provide additional information pertaining to the mechanism of halogenation. The results of numerous stereochemical studies can be generalized as follows: For brominations, *anti* addition is preferred for alkenes lacking substituent groups that can strongly stabilize a carbocation intermediate.[47] When the alkene is conjugated with an aryl group, the extent of *syn* addition increases and can become the dominant pathway. Chlorination is not as likely to be as stereospecific as bromination, but tends to follow the same pattern. Some specific results are given in Table 5.3.

42. C. J. A. Byrnell, R. G. Coombes, L. S. Hart, and M. C. Whiting, *J. Chem. Soc.*, *Perkin Trans. 2*, 1079 (1983); L. S. Hart and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1087 (1983).
43. V. V. Smirnov, A. N. Miroshnichenko, and M. I. Shilina, *Kinet. Catal.*, **31**, 482, 486 (1990).
44. G. H. Schmid, A. Modro, and K. Yates, *J. Org. Chem.*, **42**, 871 (1977).
45. F. Garnier and J -E. Dubois, *Bull. Soc. Chim. Fr.*, 3797 (1968); F. Garnier, R. H. Donnay, and J. -E. Dubois, *J. Chem. Soc., Chem. Commun.,* 829 (1971); M.-F. Ruasse and J. -E. Dubois, *J. Am. Chem. Soc*., **97**, 1977 (1975); A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.*, **42**, 3673 (1977).
46. K. Yates, R. S. McDonald, and S. A. Shapiro, *J. Org. Chem.*, **38**, 2460 (1973).
47. J. R. Chretien, J.-D. Coudert, and M.-F. Ruasse, *J. Org. Chem.*, **58**, 1917 (1993).

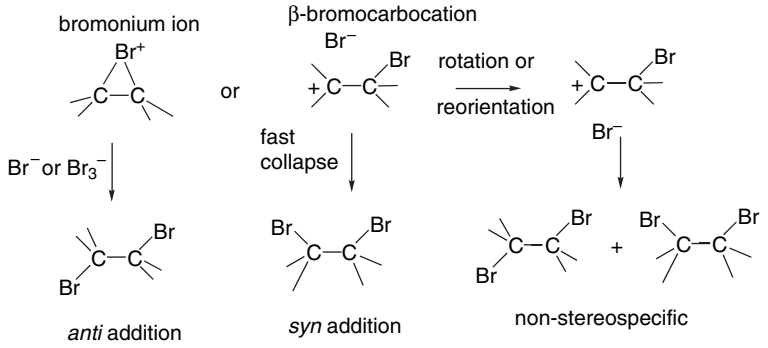
Table 5.3. Stereochemistry of Alkene Halogenation

Alkene	Solvent	Ratio *anti:syn*
A. Bromination		
Z-2-Butene[a]	CH_3CO_2H	> 100 : 1
E-2-Butene[a]	CH_3CO_2H	> 100 : 1
Cyclohexene[b]	CCl_4	Very large
Z-1-Phenylpropene[c]	CCl_4	83:17
E-1-Phenylpropene[c]	CCl_4	88:12
Z-2-Phenylbutene[a]	CH_3CO_2H	68:32
E-2-Phenylbutene[a]	CH_3CO_2H	63:37
cis-Stilbene[d]	CCl_4	> 10 : 1
	CH_3NO_2[d]	1:9
B. Chlorination		
Z-2-Butene[e]	None	> 100 : 1
	CH_3CO_2H[f]	> 100 : 1
E-2-Butene[e]	None	> 100 : 1
	CH_3CO_2H[f]	> 100 : 1
Cyclohexene[g]	None	> 100 : 1
E-1-Phenylpropene[f]	CCl_4	45:55
	CH_3CO_2H[f]	41:59
Z-1-Phenylpropene[f]	CCl_4	32:68
	CH_3CO_2H[f]	22:78
Cis-Stilbene[h]	$ClCH_2CH_2Cl$	8:92
Trans-Stilbene[h]	$ClCH_2CH_2Cl$	35:65

a. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469, 1477 (1969).
b. S. Winstein, *J. Am. Chem. Soc.*, **64**, 2792 (1942).
c. R. C. Fahey and H.-J. Schneider, *J. Am. Chem. Soc.*, **90**, 4429 (1968).
d. R. E. Buckles, J. M. Bader, and R. L. Thurmaier, *J. Org. Chem.*, **27**, 4523 (1962).
e. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2172 (1965).
f. R. C. Fahey and C. Schubert, *J. Am. Chem. Soc.*, **87**, 5172 (1965).
g. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2161 (1965).
h. R. E. Buckles and D. F. Knaack, *J. Org. Chem.,* **25**, 20 (1960).

Interpretation of reaction stereochemistry has focused attention on the role played by bridged halonium ions. When the reaction with Br_2 involves a bromonium ion, the *anti* stereochemistry can be readily explained. Nucleophilic ring opening occurs by back-side attack at carbon, with rupture of one of the C−Br bonds, giving overall *anti* addition. On the other hand, a freely rotating open β-bromo carbocation can give both the *syn* and *anti* addition products. If the principal intermediate is an ion pair that collapses faster than rotation occurs about the C−C bond, *syn* addition can predominate. Other investigations, including kinetic isotope effect studies, are consistent with the bromonium ion mechanism for unconjugated alkenes, such as ethene,[48] 1-pentene,[49] and cyclohexene.[50]

48. T. Koerner, R. S. Brown, J. L. Gainsforth, and M. Klobukowski, *J. Am. Chem. Soc.*, **120**, 5628 (1998).
49. S. R. Merrigan and D. A. Singleton, *Org. Lett.*, **1**, 327 (1999).
50. H. Slebocka-Tilk, A Neverov, S. Motallebi, R. S. Brown, O. Donini, J. L. Gainsforth, and M. Klobukowski, *J. Am. Chem. Soc.*, **120**, 2578 (1998).

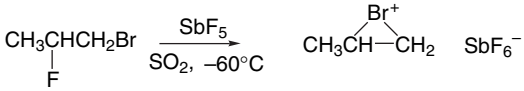


Substituent effects on stilbenes provide examples of the role of bridged ions versus nonbridged carbocation intermediates. In aprotic solvents, stilbene gives clean *anti* addition, but 4, 4′-dimethoxystilbene gives a mixture of the *syn* and *anti* addition products indicating a carbocation intermediate.[51]

Nucleophilic solvents compete with bromide, but *anti* stereoselectivity is still observed, except when ERG substituents are present. It is proposed that *anti* stereoselectivity can result not only from a bridged ion intermediate, but also from very fast capture of a carbocation intermediate.[52] Interpretation of the ratio of capture by competing nucleophiles has led to the estimate that the bromonium ion derived from cyclohexene has a lifetime on the order of 10^{-10} s in methanol, which is about 100 times longer than for secondary carbocations.[53]

The stereochemistry of chlorination also can be explained in terms of bridged versus open cations as intermediates. Chlorine is a somewhat poorer bridging group than bromine because it is less polarizable and more resistant to becoming positively charged. Comparison of the data for *E*- and *Z*-1-phenylpropene in bromination and chlorination confirms this trend (see Table 5.3). Although *anti* addition is dominant for bromination, *syn* addition is slightly preferred for chlorination. Styrenes generally appear to react with chlorine via ion pair intermediates.[54]

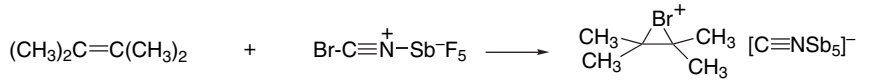
There is direct evidence for the existence of bromonium ions. The bromonium ion related to propene can be observed by NMR when 1-bromo-2-fluoropropane is subjected to superacid conditions.



Ref. 55

A bromonium ion also is formed by electrophilic attack on 2,3-dimethyl-2-butene by a species that can generate a positive bromine.

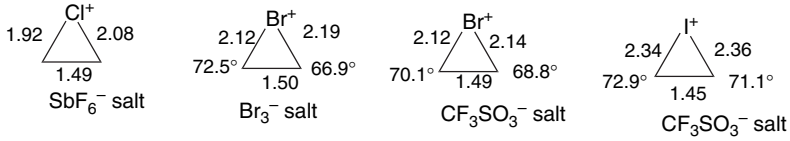
51. G. Bellucci, C. Chiappe, and G. Lo Moro, *J. Org. Chem.*, **62**, 3176 (1997).
52. M.-F. Ruasse, G. Lo Moro, B. Galland, R. Bianchini, C. Chiappe, and G. Bellucci, *J. Am. Chem. Soc.*, **119**, 12492 (1997).
53. R. W. Nagorski and R. S. Brown, *J. Am. Chem. Soc.*, **114**, 7773 (1992).
54. K. Yates and H. W. Leung, *J. Org. Chem.*, **45**, 1401 (1980).
55. G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Am. Chem. Soc.*, **90**, 2587 (1968).



Ref. 56

The highly hindered alkene adamantylideneadamantane forms a bromonium ion that crystallizes as a tribromide salt. This particular bromonium ion does not react further because of extreme steric hindrance to back-side approach by bromide ion.[57] Other very hindered alkenes allow observation of both the initial complex with Br_2 and the bromonium ion.[58] An X-ray crystal structure has confirmed the cyclic nature of the bromonium ion species (Figure 5.2).[59]

Crystal structures have also been obtained for the corresponding chloronium and iodonium ions and for the bromonium ion with a triflate counterion.[60] Each of these structures is somewhat unsymmetrical, as shown by the dimensions below. The significance of this asymmetry is not entirely clear. It has been suggested that the bromonium ion geometry is affected by the counterion and it can be noted that the triflate salt is more symmetrical than the tribromide. On the other hand, the dimensions of the unsymmetrical chloronium ion, where the difference is considerably larger, has been taken as evidence that the bridging is inherently unsymmetrical.[61] Note that the C− C bond lengthens considerably from the double-bond distance of 1.35 Å.



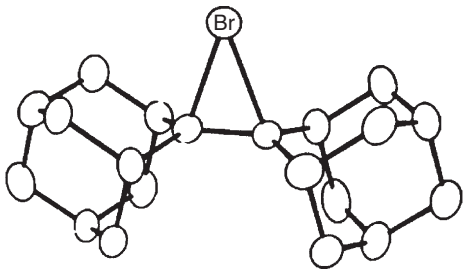
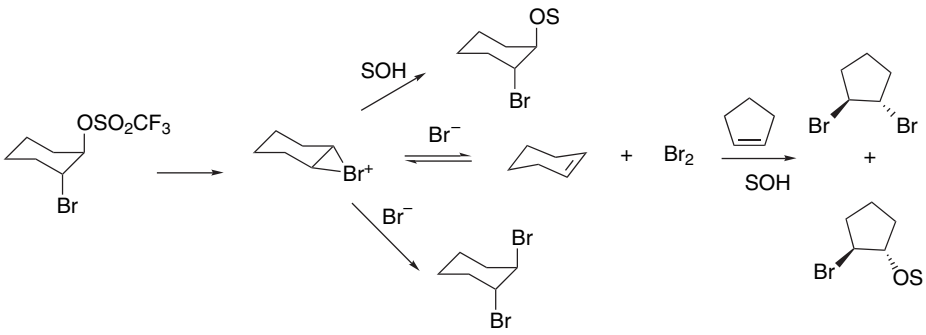


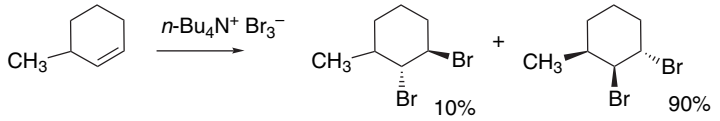
Fig. 5.2. X-ray crystal structure of the bromonium ion from adamantylideneadamantane. Reproduced from *J. Am. Chem. Soc*., **107**, 4504 (1985), by permission of the American Chemical Society.

56. G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 3581 (1974).
57. R. S. Brown, *Acc. Chem. Res*, **30**, 131 (1997).
58. G. Bellucci, R. Bianichini, C. Chiappe, F. Marioni, R. Ambrosetti, R. S. Brown, and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, **111**, 2640 (1989); G. Bellucci, C. Chiappe, R. Bianchini, D. Lenoir, and R. Herges, *J. Am. Chem. Soc.*, **117**, 12001 (1995).
59. H. Slebocka-Tilk, R. G. Ball, and R. S. Brown, *J. Am. Chem. Soc.*, **107**, 4504 (1985).
60. R. S. Brown, R. W. Nagorski, A. J. Bennet, R. E. D. McClung, G. H. M. Aarts, M. Klobukowski, R. McDonald, and B. D. Santarisiero, *J. Am. Chem. Soc.*, **116**, 2448 (1994).
61. T. Mori, R. Rathore, S. V. Lindeman, and J. K. Kochi, *Chem. Commun.*, 1238 (1998); T. Mori and R. Rathore, *Chem. Commun*., 927 (1998).

Another aspect of the mechanism is the reversibility of formation of the bromonium ion. Reversibility has been demonstrated for highly hindered alkenes,[62] and attributed to a relatively slow rate of nucleophilic capture. However, even the bromonium ion from cyclohexene appears to be able to release Br_2 on reaction with Br^-. The bromonium ion can be generated by neighboring-group participation by solvolysis of *trans*-2-bromocyclohexyl triflate. If cyclopentene, which is more reactive than cyclohexene, is included in the reaction mixture, bromination products from cyclopentene are formed. This indicates that free Br_2 is generated by reversal of bromonium ion formation.[63] Other examples of reversible bromonium ion formation have been found.[64]

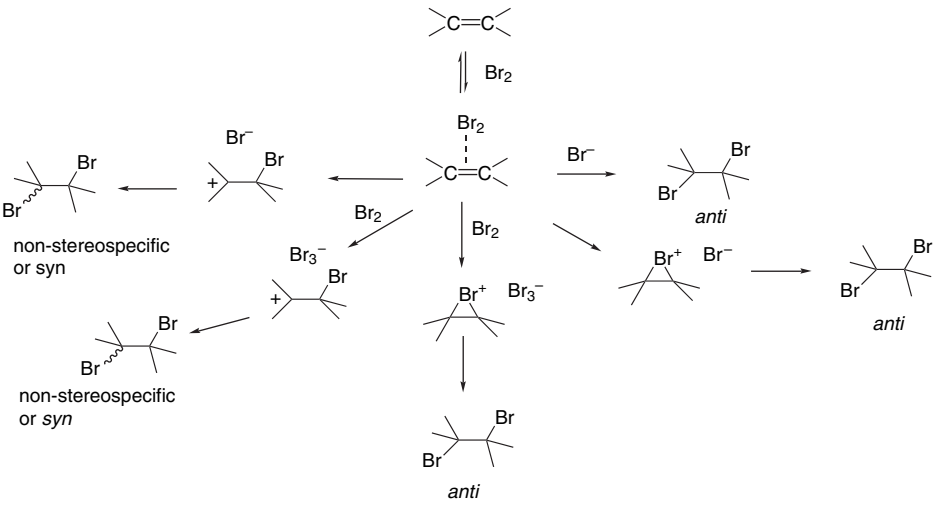


Bromination also can be carried out with reagents that supply bromine in the form of the Br_3^- anion. One such reagent is pyridinium bromide tribromide. Another is tetrabutylammonium tribromide.[65] These reagents are believed to react via the Br_2-alkene complex and have a strong preference for *anti* addition.

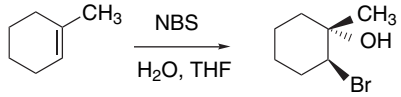


In summary, it appears that bromination usually involves a complex that collapses to an ion pair intermediate. The ionization generates charge separation and is assisted by solvent, acids, or a second molecule of bromine. The cation can be a β-carbocation, as in the case of styrenes, or a bromonium ion. Reactions that proceed through bromonium ions are stereospecific *anti* additions. Reactions that proceed through open carbocations can be *syn* selective or nonstereospecific.

62. R. S. Brown, H. Slebocka-Tilk, A. J. Bennet, G. Belluci, R. Bianchini, and R. Ambrosetti, *J. Am. Chem. Soc.*, **112**, 6310 (1990); G. Bellucci, R. Bianchini, C. Chiappe, F. Marioni, R. Ambrosetti, R. S. Brown, and H. Slebocka-Tilk, *J. Am. Chem. Soc.*, **111**, 2640 (1989).
63. C. Y. Zheng, H. Slebocka-Tilk, R. W. Nagorski, L. Alvarado, and R. S. Brown, *J. Org. Chem.*, **58**, 2122 (1993).
64. R. Rodebaugh and B. Fraser-Reid, *Tetrahedron*, **52**, 7663 (1996).
65. J. Berthelot and M. Founier, *J. Chem. Educ.*, **63**, 1011 (1986); J. Berthelot, Y. Benammar, and C. Lange, *Tetrahedron Lett.*, **32**, 4135 (1991).

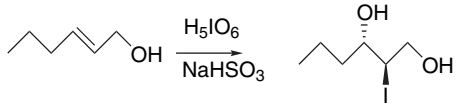


The cationic intermediates also can be captured by solvent. Halogenation with solvent capture is a synthetically important reaction, especially for the preparation of chlorohydrins and bromohydrins.[66] Chlorohydrins can be prepared using various sources of electrophilic chlorine. Chloroamine T is a convenient reagent for chlorohydrin formation.[67] Bromohydrins are prepared using NBS and an aqueous solvent mixture with acetone or THF. DMSO has also been recommended as a solvent.[68] These reactions are regioselective, with the nucleophile water introduced at the more-substituted position.



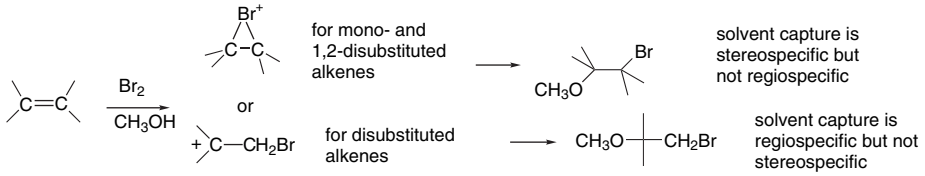
Ref. 69

Iodohydrins can be prepared using iodine or phenyliodonium di-trifluoroacetate.[70] Iodohydrins can be prepared in generally good yield and high *anti* stereoselectivity using H_5IO_6 and $NaHSO_3$.[71] These reaction conditions generate hypoiodous acid. In the example shown below, the hydroxy group exerts a specific directing effect, favoring introduction of the hydroxyl at the more remote carbon.

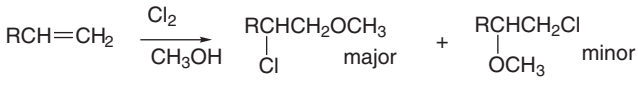


66. J. Rodriguez and J. P. Dulcere, *Synthesis*, 1177 (1993).
67. B. Damin, J. Garapon, and B. Sillion, *Synthesis*, 362 (1981).
68. J. N. Kim, M. R. Kim, and E. K. Ryu, *Synth. Commun.*, **22**, 2521 (1992); V. L. Heasley, R. A. Skidgel, G. E. Heasley, and D. Strickland, *J. Org. Chem.*, **39**, 3953 (1974); D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1988).
69. D. J. Porter, A. T. Stewart, and C. T. Wigal, *J. Chem. Educ.*, **72**, 1039 (1995).
70. A. R. De Corso, B. Panunzi, and M. Tingoli, *Tetrahedron Lett.*, **42**, 7245 (2001).
71. H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama, and Y. Ishii, *J. Org. Chem.*, **59**, 5550 (1994).

A study of several substituted alkenes in methanol developed some generalizations pertaining to the capture of bromonium ions by methanol.[72] For both *E*- and *Z*-disubstituted alkenes, the addition of both methanol and Br^- was completely *anti* stereospecific. The reactions were also completely regioselective, in accordance with Markovnikov's rule, for disubstituted alkenes, *but not for monosubstituted alkenes*. The lack of high regioselectivity of the addition to monosubstituted alkenes can be interpreted as competitive addition of solvent at both the mono- and unsubstituted carbons of the bromonium ion. This competition reflects conflicting steric and electronic effects. Steric factors promote addition of the nucleophile at the unsubstituted position, whereas electronic factors have the opposite effect.

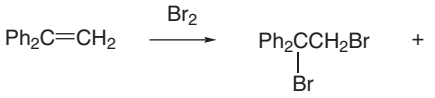


Similar results were obtained for chlorination of several of alkenes in methanol.[73] Whereas styrene gave only the Markovnikov product, propene, hexene, and similar alkenes gave more of the *anti* Markovnikov product. This result is indicative of strong bridging in the chloronium ion.



We say more about the regioselectivity of opening of halonium ions in Section 5.8, where we compare halonium ions with other intermediates in electrophilic addition reactions.

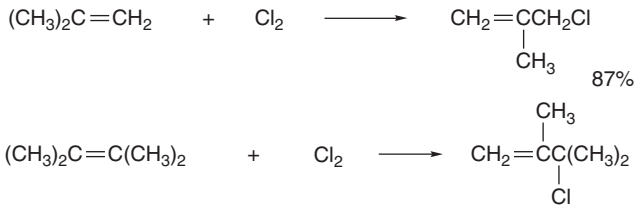
Some alkenes react with halogens to give substitution rather than addition. For example, with 1,1-diphenylethene, substitution is the main reaction at low bromine concentration. Substitution occurs when loss of a proton is faster than capture by bromide.



$[Br_2]$	Ratio
$10^{-2}\,M$	>99:1
$10^{-3}\,M$	90:10
$10^{-4}\,M$	<1:99

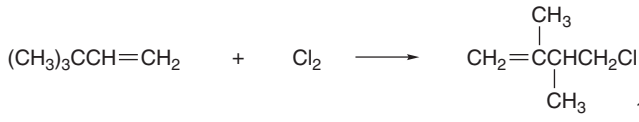
Similarly, in chlorination, loss of a proton can be a competitive reaction of the cationic intermediate. 2-Methylpropene and 2,3-dimethyl-2-butene give products of this type.

72. J. R. Chretien, J.-D. Coudert, and M.-F. Ruasse, *J. Org. Chem.*, **58**, 1917 (1993).
73. K. Shinoda and K. Yasuda, *Bull. Chem. Soc. Jpn.*, **61**, 4393 (1988).

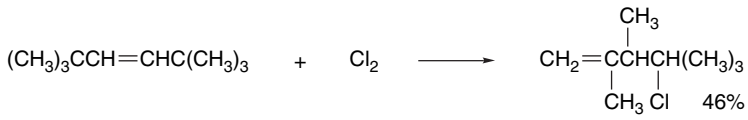


Ref. 74

Alkyl migrations can also occur.



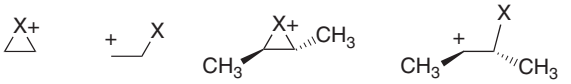
Ref. 74



Ref. 75

These reactions are characteristic of carbocation intermediates. Both proton loss and rearrangement are more likely in chlorination than in bromination because of the weaker bridging by chlorine.

There have been several computational investigations of bromonium and other halonium ions. These are gas phase studies and so do not account for the effect of solvent or counterions. In the gas phase, formation of the charged halonium ions from halogen and alkene is energetically prohibitive, and halonium ions are not usually found to be stable by these calculations. In an early study using PM3 and HF/3-21G calculations, bromonium ions were found to be unsymmetrical, with weaker bridging to the more stabilized carbocation.[76] Reynolds compared open and bridged $[CH_2CH_2X]^+$ and $[CH_3CHCHXCH_3]^+$ ions.[77] At the MP2/6-31G** level, the bridged haloethyl ion was favored slightly for X= F and strongly for X= Cl and Br. For the 3-halo-2-butyl ions, open structures were favored for F and Cl, but the bridged structure remained slightly favored for Br. The relative stabilities, as measured by hydride affinity are given below.

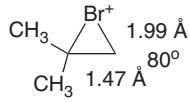


X				
F	274.3	278.6	249.9	227.6
Cl	253.4	277.8	233.8	230.6
Br	239.9	270.8	221.6	225.0

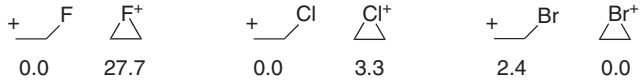
Hydride affinity in kcal/mol

74. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965).
75. R. C. Fahey, *J. Am. Chem. Soc.*, **88**, 4681 (1966).
76. S. Yamabe and T. Minato, *Bull. Chem. Soc. Jpn.*, **66**, 3339 (1993).
77. C. H. Reynolds, *J. Am. Chem. Soc.*, **114**, 8676 (1992).

The computed structure of bromonium ions from alkenes such as 2-methylpropene are highly dependent on the computational method used and inclusion of correlation is essential.[78] CISD/DZV calculations gave the following structural characteristics.

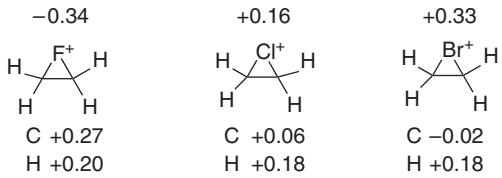


Another study gives some basis for comparison of the halogens.[79] QCISD(T)/6-311(*d*, *p*) calculations found the open carbocation to be the most stable for $[C_2H_4F]^+$ and $[C_2H_4Cl]^+$ but the bridged ion was more stable for $[C_2H_4Br]^+$. The differences were small for Cl and Br.

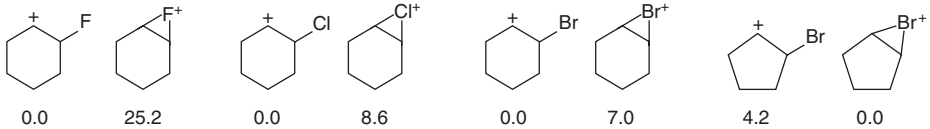


Relative energy in kcal/mol of open and bridged $[C_2H_4X]^+$ ions

AIM charges for the bridged ions were as follows (MP2/6-311G(*d*, *p*)). Note the very different net charge for the different halogens.



MP2/6-311G(*d*, *p*) calculations favored open carbocations for the ions derived from cyclohexene. On the other hand, the bridged bromonium ion from cyclopentene was found to be stable relative to the open cation.



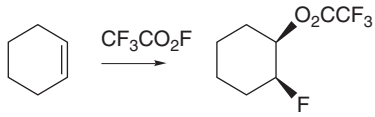
Relative stability of open and bridged cations in kcal/mol

Ref. 79

This result is in qualitative agreement with an NMR study under stable ion conditions that found that the bromonium ion from cyclopentene could be detected, but not the one from cyclohexene.[80] Broadly speaking, the computational results agree with the F < Cl < Br order in terms of bridging, but seem to underestimate the stability of the bridged ions, at least as compared to solution behavior.

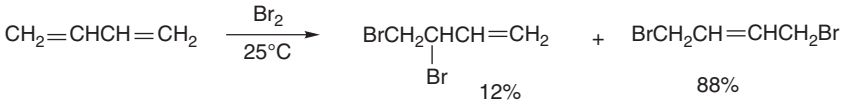
78. M. Klobukowski and R. S. Brown, *J. Org. Chem.*, **59**, 7156 (1994).
79. R. Damrauer, M. D. Leavell, and C. M. Hadad, *J. Org. Chem.*, **63**, 9476 (1998).
80. G. K. S. Prakash, R. Aniszefeld, T. Hashimoto, J. W. Bausch, and G. A. Olah, *J. Am. Chem. Soc.*, **111**, 8726 (1989).

Much less detail is available concerning the mechanism of fluorination and iodination of alkenes. Elemental fluorine reacts violently with alkenes giving mixtures including products resulting from degradation of the carbon chain. Electrophilic additions of fluorine to alkenes can be achieved with xenon difluoride,[81] electrophilic derivatives of fluorine,[82] or by use of highly dilute elemental fluorine at low temperature.[83] Under the last conditions, *syn* stereochemistry is observed. The reaction is believed to proceed by rapid formation and then collapse of an ß-fluorocarbocation-fluoride ion pair. Both from the stereochemical results and theoretical calculations,[84] it appears unlikely that a bridged fluoronium species is formed. Acetyl hypofluorite, which can be prepared by reaction of fluorine with sodium acetate at −75°C in halogenated solvents,[85] reacts with alkenes to give ß-acetoxyalkyl fluorides.[86] The reaction gives predominantly *syn* addition, which is also consistent with rapid collapse of a ß-fluorocarbocation-acetate ion pair.



There have been relatively few mechanistic studies of the addition of iodine. One significant feature of iodination is that it is easily reversible, even in the presence of excess alkene.[87] The addition is stereospecifically *anti* but it is not entirely clear whether a polar or a radical mechanism is involved.[88]

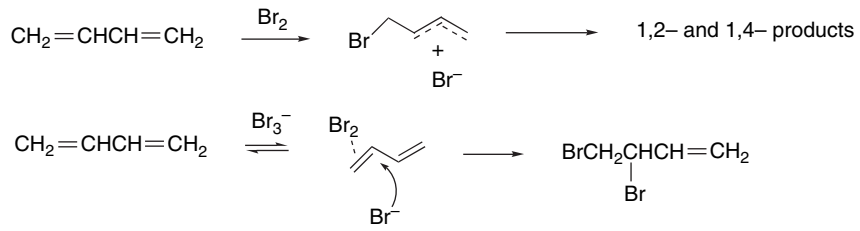
As with other electrophiles, halogenation can give 1,2- or 1,4-addition products from conjugated dienes. When molecular bromine is used as the brominating agent in chlorinated solvent, the 1,4-addition product dominates by ∼ 7:1 in the case of butadiene.[89]



The product distribution can be shifted to favor the 1,2-product by use of milder brominating agents such as the pyridine-bromine complex or the tribromide ion, Br_3^-. It is believed that molecular bromine reacts through a cationic intermediate, whereas

81. M. Zupan and A. Pollak, *J. Chem. Soc., Chem. Commun.*, 845 (1973); M. Zupan and A. Pollak, *Tetrahedron Lett.*, 1015 (1974).
82. For reviews of fluorinating agents, see A. Haas and M. Lieb, *Chimia*, **39**, 134 (1985); W. Dmowski, *J. Fluorine Chem.*, **32**, 255 (1986); H. Vyplel, *Chimia*, **39**, 134 (1985).
83. S. Rozen and M. Brand, *J. Org. Chem.*, **51**, 3607 (1986); S. Rozen, *Acc. Chem. Res.*, **29**, 243 (1996).
84. W. J. Hehre and P. C. Hiberty, *J. Am. Chem. Soc.*, **96**, 2665 (1974); T. Iwaoka, C. Kaneko, A. Shigihara, and H.Ichikawa, *J. Phys. Org. Chem.*, **6**, 195 (1993).
85. O. Lerman, Y. Tov, D. Hebel, and S. Rozen, *J. Org. Chem.*, **49**, 806 (1984).
86. S. Rozen, O. Lerman, M. Kol, and D. Hebel, *J. Org. Chem.*, **50**, 4753 (1985).
87. P. W. Robertson, J. B. Butchers, R. A. Durham, W. B. Healy, J. K. Heyes, J. K. Johannesson, and D. A. Tait, *J. Chem. Soc.*, 2191 (1950).
88. M. Zanger and J. L. Rabinowitz, *J. Org. Chem.*, **40**, 248 (1975); R. L. Ayres, C. J. Michejda, and E. P. Rack, *J. Am. Chem. Soc.*, **93**, 1389 (1971); P. S. Skell and R. R. Pavlis, *J. Am. Chem. Soc.*, **86**, 2956 (1964).
89. G. Bellucci, G. Berti, R. Bianchini, G. Ingrosso, and K. Yates, *J. Org. Chem.*, **46**, 2315 (1981).

the less reactive brominating agents involve a process more like the Ad_E3 *anti*-addition mechanism and do not form allylic cations.

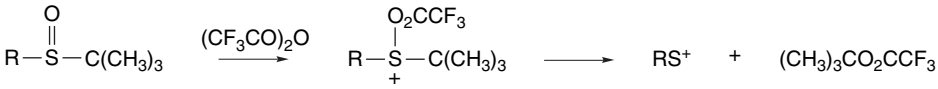


The stereochemistry of both chlorination and bromination of several cyclic and acyclic dienes has been determined. The results show that bromination is often stereospecifically *anti* for the 1,2-addition process, whereas *syn* addition is preferred for 1,4-addition. Comparable results for chlorination show much less stereospecificity.[90] It appears that chlorination proceeds primarily through ion pair intermediates, whereas in bromination a stereospecific *anti*-1,2-addition may compete with a process involving a carbocation intermediate. The latter can presumably give *syn* or *anti* product.

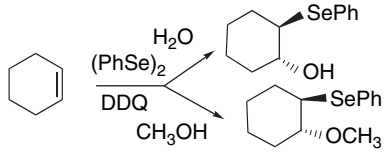
5.4. Sulfenylation and Selenenylation

Electrophilic derivatives of both sulfur and selenium can add to alkenes. A variety of such reagents have been developed and some are listed in Scheme 5.1. They are characterized by the formulas RS−X and RSe−X, where X is a group that is more electronegative than sulfur or selenium. The reactivity of these reagents is sensitive to the nature of both the R and the X group.

Entry 4 is a special type of sulfenylation agent. The sulfoxide fragments after O-acylation, generating a sulfenyl electrophile.



Entries 12 to 14 are examples of oxidative generation of selenenylation reagents from diphenyldiselenide. These reagents can be used to effect hydroxy- and methoxyselenenylation.



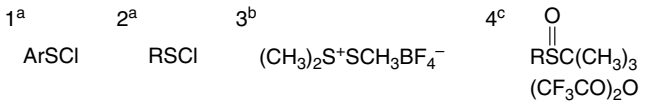
Ref. 91

Entry 15 shows *N*-(phenylselenyl)phthalimide, which is used frequently in synthetic processes.

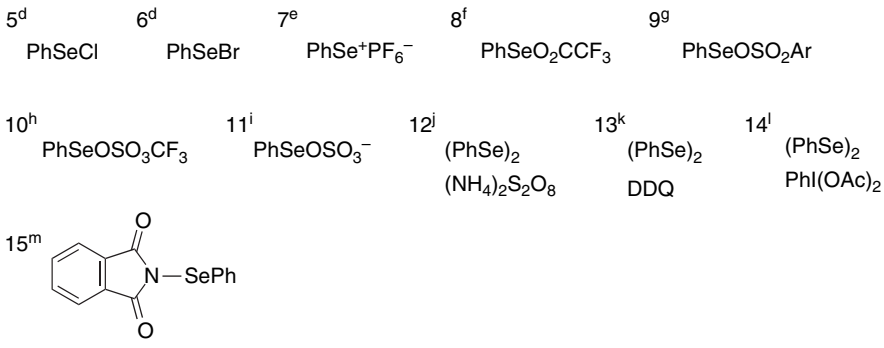
90. G. E. Heasley, D. C. Hayes, G. R. McClung, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold, and T. L. Ungermann, *J. Org. Chem.*, **41**, 334 (1976).
91. M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, and C. Santi, *Synlett*, 1767 (2001).

Scheme 5.1. Electrophilic Sulfur and Selenium Reagents

A. Sulfenylation Reagents



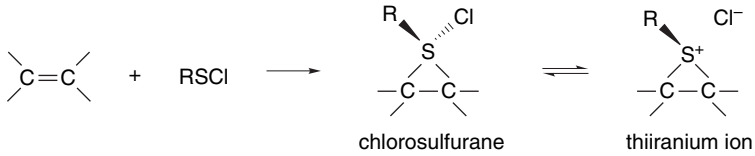
B. Selenenylation Reagents



a. G. Capozzi, G. Modena, and L. Pasquato, in *The Chemistry of Sulphenic Acids and Their Derivatives*, S. Patai, editor, Wiley, Chichester, 1990, Chap. 10.
b. B. M. Trost, T Shibata, and S. J. Martin, *J. Am. Chem. Soc.*, **104**, 3228 (1982).
c. M.-H.Brichard, M. Musick, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, **20**, 2379 (1990).
d. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).e. W. P. Jackson, S. V. Ley, and A. J. Whittle, *J. Chem. Soc., Chem. Commun.*, 1173 (1980).
f. H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974).
g. T. G. Back and K. R. Muralidharan, *J. Org. Chem.*, **58**, 2781 (1991).
h. S. Murata and T. Suzuki, *Tetrahedron Lett.*, **28**, 4297, 4415 (1987).
i. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and F. Marini, *J. Chem. Soc., Perkin Trans. 1*, 1989 (1993).
j. M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, and D. Bartoli, *Tetrahedron Lett.*, **30**, 1417 (1989).
k. M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, and C. Santi, *Synlett*, 1767 (2001).
l. M. Tingoli, M. Tiecco, L. Testaferri, and A. Temperini, *Synth. Commun.*, **28**, 1769 (1998).
m. K. C. Nicolaou, N. A. Petasis, and D. A. Claremon, *Tetrahedron*, **41**, 4835 (1985).

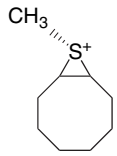
5.4.1. Sulfenylation

By analogy with halogenation, *thiiranium ions* can be intermediates in electrophilic sulfenylation. However, the corresponding tetravalent sulfur compounds, which are called *sulfuranes*, may also lie on the reaction path.[92]

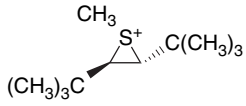


The sulfur atom is a stereogenic center in *both* the sulfurane and the thiiranium ion, and this may influence the stereochemistry of the reactions of stereoisomeric alkenes. Thiiranium ions can be prepared in various ways, and several have been characterized, such as the examples below.

92. M. Fachini, V. Lucchini, G. Modena, M. Pasi, and L. Pasquato, *J. Am. Chem. Soc.*, **121**, 3944 (1999).

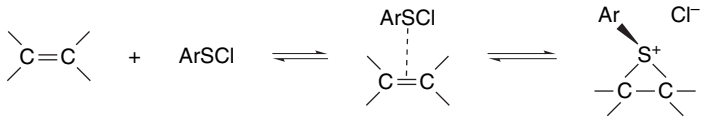


Ref. 93



Ref. 94

Perhaps the closest analog to the sulfenyl chlorides is chlorine, in the sense that both the electrophilic and nucleophilic component of the reagent are third-row elements. However, the sulfur is less electronegative and is a much better bridging element than chlorine. Although sulfenylation reagents are electrophilic in character, they are much less so than chlorine. The extent of rate acceleration from ethene to 2,3-dimethyl-2-butene is only 10^2, as compared to 10^6 for chlorination and 10^7 for bromination (see Table 5.2). The sulfur substituent can influence reactivity. The initial complexation is expected to be favored by EWGs, but if the rate-determining step is ionization to the thiiranium ion, ERGs are favored.



As sulfur is less electronegative and more polarizable than chlorine, a strongly bridged intermediate, rather than an open carbocation, is expected for alkenes without ERG stabilization. Consistent with this expectation, sulfenylation is weakly regioselective and often shows a preference for *anti-Markovnikov addition*[95] as the result of steric factors. When bridging is strong, nucleophilic attack occurs at the less-substituted position. Table 5.4 gives some data for methyl- and phenyl- sulfenyl chloride. For bridged intermediates, the stereochemistry of addition is *anti.* Loss of stereospecificity with strong regioselectivity is observed when highly stabilizing ERG substituents are present on the alkene, as in 4-methoxyphenylstyrene.[96]

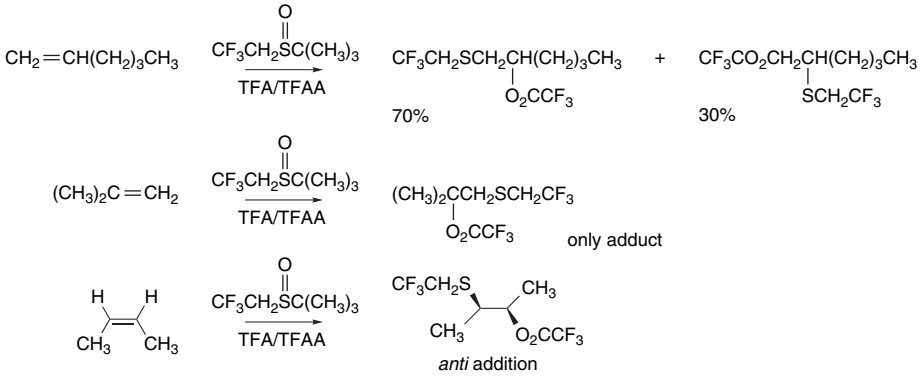
Similar results have been observed for other sulfenylating reagents. The somewhat more electrophilic trifluoroethylsulfenyl group shows a shift toward Markovnikov regioselectivity but retains *anti* stereospecificity, indicating a bridged intermediate.[97]

93. D. J. Pettit and G. K. Helmkamp, *J. Org. Chem.*, **28**, 2932 (1963).
94. V. Lucchini, G. Modena, and L. Pasquato, *J. Am. Chem. Soc.*, **113**, 6600 (1991); R. Destro, V. Lucchini, G. Modena, and L. Pasquato, *J. Org. Chem.*, **65**, 3367 (2000).
95. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **88**, 2866 (1966).
96. G. H. Schmid and V. J. Nowlan, *J. Org. Chem.*, **37**, 3086 (1972); I. V. Bodrikov, A. V. Borisov, W. A. Smit, and A. I. Lutsenko, *Tetrahedron Lett.*, **25**, 4983 (1984).
97. M. Redon, Z. Janousek, and H. G. Viehe, *Tetrahedron*, **53**, 15717 (1997).

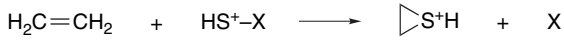
Table 5.4. Regiochemistry of Some Sulfenylation Reactions with Sulfenyl Chlorides

Alkene	Percent Markovnikov: *anti*-Markovnikov	
	CH_3SCl	PhSCl
Propene	18:82	32:68
3-Methylbutene	6:94	13:87
2-Methylpropene	20:80	
Styrene	98:2	

a. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2075 (1968).



G2 computations have been used to model the reaction of sulfenyl electrophiles with alkenes.[98] The reactions were modeled by $HS–X^+$, where X= FH, OH_2, NH_3, and ClH. The additions showed no gas phase barrier and the electrophile approaches the midpoint of the π bond. This is similar to halogenation. The overall exothermicity calculated for the reactions correlated with the leaving-group ability of HX.



X	$\triangle E$ (kcal/mol)
NH_3	–11.4
H_2O	–50.2
HF	–90.6
HCl	–61.9

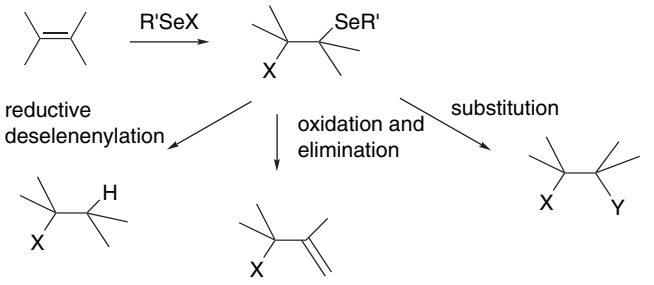
5.4.2. Selenenylation

Electrophilic selenenylation has important synthetic applications. Much of the research emphasis has been on the development of convenient reagents.[99] The selenides, per se, are not usually the desired final product. Selenenyl substituents can be removed both reductively and oxidatively. In some cases, the selenenyl substituent

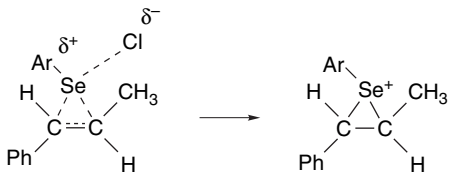
98. T. I. Solling and L. Radom, *Chem. Eur. J.*, 1516 (2001).

99. M. Tiecco, *Top. Curr. Chem.*, **208**, 7 (2000); T. G. Back, *Organoselenium Chemistry: A Practical Approach*, Oxford University Press, Oxford, 1999; C. Paulmier, *Selenium Reagents and Intermediates in Organic Chemistry*, Pergamon Press, Oxford, 1986; D. Liotta, *Organoselenium Chemistry*, Wiley, New York, 1987; S. Patai, ed., *The Chemistry of Organic Selenium and Tellurium Compounds*, Vols. 1 and 2, Wiley, New York, 1987.

can undergo substitution reactions. α-Selenenylation of carbonyl compounds has been particularly important and we consider this reaction in Section 4.7.2 of Part B.

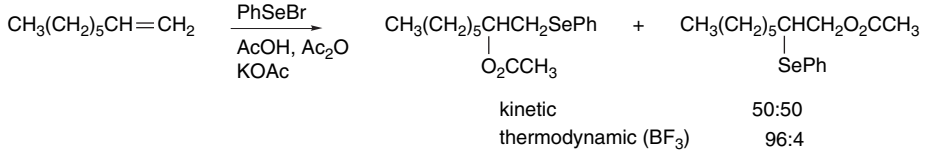


The various selenenylation reagents shown in Part B of Scheme 5.1 are characterized by an areneselenenyl group substituted by a leaving group. Some of the fundamental mechanistic aspects of selenenylation were established by studies of the reaction of *E*- and *Z*-1-phenylpropene with areneselenenyl chlorides.[100] The reaction is accelerated by an ERG in the arylselenenides. These data were interpreted in terms of a concerted addition, in which ionization of the Se−Cl bond leads C−Se bond formation. This accounts for the favorable effect of ERG substituents. Bridged seleniranium ions are considered to be intermediates.



As shown in Table 5.5, alkyl substitution enhances the reactivity of alkenes, but the effect is very small in comparison with halogenation (Table 5.2). Selenenylation seems to be particularly sensitive to steric effects. Note than a phenyl substituent is *rate retarding for selenenylation*. This may be due to both steric factors and alkene stabilization. The Hammett correlation with σ^+ gives a ρ value of −0.715, also indicating only modest electron demand at the TS.[101] Indeed, positive values of ρ have been observed in some cases.[102]

Terminal alkenes show anti-Markovnikov regioselectivity, but rearrangement is facile.[103] The Markovnikov product is thermodynamically more stable (see Section 3.1.2.2).



Ref. 104

100. G. H. Schmid and D. G. Garratt, *J. Org. Chem.*, **48**, 4169 (1983).
101. C. Brown and D. R. Hogg, *J. Chem. Soc. B*, 1262 (1968).
102. I. V. Bodrikov, A. V. Borisov, L. V. Chumakov, N. S. Zefirov, and W. A. Smit, *Tetrahedron Lett.*, **21**, 115 (1980).
103. D. Liotta and G. Zima, *Tetrahedron Lett.*, 4977 (1978); P. T. Ho and R. J. Holt, *Can. J. Chem.*, **60**, 663 (1982); S. Raucher, *J. Org. Chem.*, **42**, 2950 (1977).
104. L. Engman, *J. Org. Chem.*, **54**, 884 (1989).

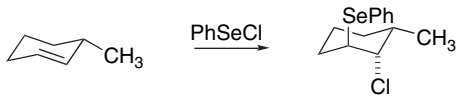
Table 5.5. Relative Reactivity of Some Alkenes toward 4-Chlorophenylsulfenyl Chloride and Phenylselenenyl Chloride[a]

Alkene	*p*-ClPhSCl k_{rel}	PhSeCl k_{rel}
Ethene	1.00	1.00
Propene	3.15	8.76
1-Butene	3.81	6.67
Z-2-Butene	20.6	3.75
E-2-Butene	6.67	2.08
Z-3-Hexene	54.8	5.24
E-3-Hexene	5.96	2.79
2-Methylpropene	8.46	6.76
2-Methyl-2-butene	46.5	3.76
2,3-Dimethyl-2-butene	119	2.46
Styrene	0.95	0.050
Z-1-Phenylpropene	0.66	0.010
E-1-Phenylpropene	1.82	0.016

a. G. H. Schmid and D. G. Garratt, in *The Chemistry of Double-Bonded Functional Groups, Supplement A, Part 2*, S. Patai, ed., Wiley, New York, 1977, Chap. 9.

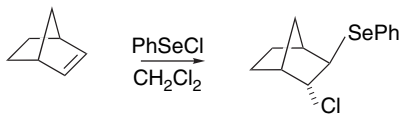
Styrene, on the other hand, is regioselective for the Markovnikov product, with the nucleophilic component bonding to the aryl-substituted carbon as the result of weakening of the bridging by the phenyl group.

Selenenylation is a stereospecific *anti* addition with acyclic alkenes.[105] Cyclohexenes undergo preferential diaxial addition.



Ref. 106

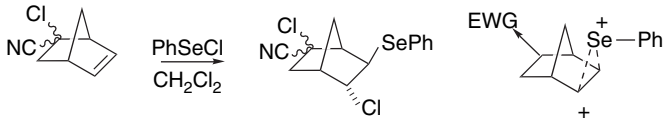
Norbornene gives highly stereoselective *exo-anti* addition, pointing to an *exo* bridged intermediate.



Ref. 107

The regiochemistry of addition to substituted norbornenes appears to be controlled by polar substituent effects.

105. H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974).
106. D. Liotta, G. Zima, and M. Saindane, *J. Org. Chem.*, **47**, 1258 (1982).
107. D. G. Garratt and A. Kabo, *Can. J. Chem.*, **58**, 1030 (1980).



Ref. 106

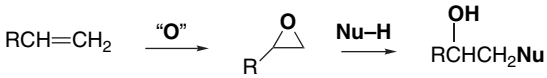
This regioselectivity is consistent with an unsymmetrically bridged seleniranium intermediate in which the more positive charge is remote from the EWG substituent. The directive effect is contrary to regiochemistry being dominated by the chloride ion approach, since chloride addition should be facilitated by the dipole of an EWG.

There has been some computational modeling of selenenylation reactions, particularly with regard to enantioselectivity of chiral reagents. The enantioselectivity is attributed to the relative ease of nucleophilic approach on the seleniranium ion intermediate, which is consistent with viewing the intermediate as being strongly bridged.[108] With styrene, a somewhat unsymmetrical bridging has been noted and the regiochemistry (Markovnikov) is attributed to the greater positive charge at C(1).[109]

Broadly comparing sulfur and selenium electrophiles to the halogens, we see that they are *less electrophilic* and characterized by *more strongly bridged intermediates.* This is consistent with reduced sensitivity to electronic effects in alkenes (e.g., alkyl or aryl substituents) and an increased tendency to anti-Markovnikov regiochemistry. The strongly bridged intermediates favor *anti* stereochemistry.

5.5. Addition Reactions Involving Epoxides

Epoxidation is an electrophilic addition. It is closely analogous to halogenation, sulfenylation, and selenenylation in that the electrophilic attack results in the formation of a three-membered ring. In contrast to these reactions, however, the resulting epoxides are neutral and stable and normally can be isolated. The epoxides are susceptible to nucleophilic ring opening so the overall pattern results in the addition of OH^+ and a nucleophile at the double bond. As the regiochemistry of the ring opening is usually controlled by the ease of nucleophilic approach, *the oxygen is introduced at the more-substituted carbon*. We concentrate on peroxidic epoxidation reagents in this chapter. Later, in Chapter 12 of Part B, transition metal–mediated epoxidations are also discussed.



5.5.1. Epoxides from Alkenes and Peroxidic Reagents

The most widely used reagents for conversion of alkenes to epoxides are peroxycarboxylic acids.[110] *m*-Chloroperoxybenzoic acid[111] (MCPBA) is a common reagent.

108. M. Spichty, G. Fragale, and T. Wirth, *J. Am. Chem. Soc.*, **122**, 10914 (2000); X. Wang, K. N. Houk, and M. Spichty, *J. Am. Chem. Soc.*, **121**, 8567 (1999).
109. T. Wirth, G. Fragale, and M. Spichty, *J. Am. Chem. Soc.*, **120**, 3376 (1998).
110. D. Swern, *Organic Peroxides*, Vol. II, Wiley-Interscience, New York, 1971, pp. 355–533; B. Plesnicar, in *Oxidation in Organic Chemistry*, Part C, W. Trahanovsky, ed., Academic Press, New York, 1978, pp. 211–253.
111. R. N. McDonald, R. N. Steppel, and J. E. Dorsey, *Org. Synth.*, **50**, 15 (1970).

The magnesium salt of monoperoxyphthalic acid is an alternative.[112] Peroxyacetic acid, peroxybenzoic acid, and peroxytrifluoroacetic acid also are used frequently for epoxidation. All of the peroxycarboxylic acids are potentially explosive materials and require careful handling. Potassium hydrogen peroxysulfate, which is sold commercially as Oxone®,[113] is a convenient reagent for epoxidations that can be done in aqueous solution.[114]

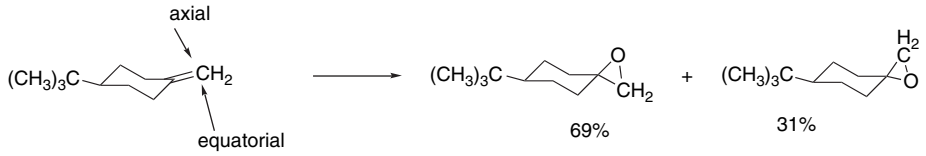
It has been demonstrated that no ionic intermediates are involved in the epoxidation of alkenes. The reaction rate is not very sensitive to solvent polarity.[115] Stereospecific *syn* addition is consistently observed. The oxidation is considered to be a concerted process, as represented by the TS shown below. The plane including the peroxide bond is approximately perpendicular to the plane of the developing epoxide ring, so the oxygen being transferred is in a *spiro* position.

The rate of epoxidation of alkenes is increased by alkyl groups and other ERG substituents, and the reactivity of the peroxy acids is increased by EWG substituents.[116] These structure-reactivity relationships demonstrate that the peroxy acid acts as an electrophile in the reaction. Low reactivity is exhibited by double bonds that are conjugated with strongly EWG substituents, and very reactive peroxy acids, such as trifluoroperoxyacetic acid, are required for oxidation of such compounds.[117] Strain increases the reactivity of alkenes toward epoxidation. Norbornene is about twice as reactive as cyclopentene toward peroxyacetic acid.[118] *trans*-Cyclooctene is 90 times more reactive than cyclohexene.[119] Shea and Kim found a good correlation between relief of strain, as determined by MM calculations, and the epoxidation rate.[120] There is also a correlation with ionization potentials of the alkenes.[121] Alkenes with aryl substituents are *less reactive* than unconjugated alkenes because of ground state stabilization and this is consistent with a lack of carbocation character in the TS.

The stereoselectivity of epoxidation with peroxycarboxylic acids has been studied extensively.[122] Addition of oxygen occurs preferentially from the less hindered side of nonpolar molecules. Norbornene, for example, gives a 96:4 *exo*:*endo* ratio.[123] In molecules where two potential modes of approach are not greatly different, a mixture

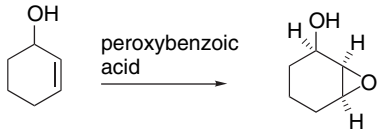
112. P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, and N. Thompson, *Synthesis*, 1015 (1987).
113. Oxone is a registered trademark of E.I. du Pont de Nemours and company.
114. R. Bloch, J. Abecassis, and D. Hassan, *J. Org. Chem.*, **50**, 1544 (1985).
115. N. N. Schwartz and J. N. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
116. B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
117. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).
118. J. Spanget-Larsen and R. Gleiter, *Tetrahedron Lett.*, **23**, 2435 (1982); C. Wipff and K. Morokuma, *Tetrahedron Lett.*, **21**, 4445 (1980).
119. K. J. Burgoine, S. G. Davies, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 2629 (1974).
120. K. J. Shea and J. -S. Kim, *J. Am. Chem. Soc.*, **114**, 3044 (1992).
121. C. Kim, T. G. Traylor, and C. L. Perrin, *J. Am. Chem. Soc.*, **120**, 9513 (1998).
122. V. G. Dryuk and V. G. Kartsev, *Russ. Chem. Rev.*, **68**, 183 (1999).
123. H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

of products is formed. For example, the unhindered exocyclic double bond in 4-*t*-butylmethylenecyclohexane gives both stereoisomeric products.[124]

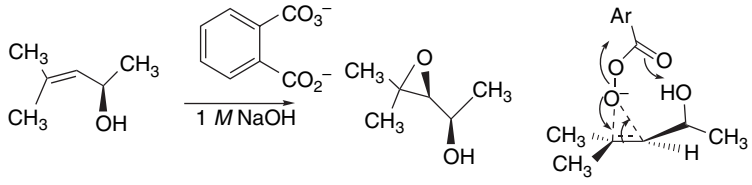


Several other conformationally biased methylenecyclohexanes have been examined and the small preference for axial attack is quite general, unless a substituent sterically encumbers one of the faces.[125]

Hydroxy groups exert a directive effect on epoxidation and favor approach from the side of the double bond closest to the hydroxy group.[126] Hydrogen bonding between the hydroxy group and the peroxidic reagent evidently stabilize the TS.

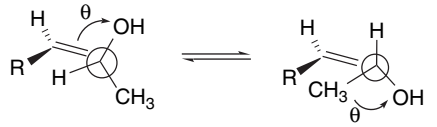


This is a strong directing effect that can exert stereochemical control even when steric effects are opposed. Other substituents capable of hydrogen bonding, in particular amides, also exert a *syn*-directing effect.[127] The hydroxy-directing effect also operates in alkaline epoxidation in aqueous solution.[128] Here the alcohol group can supply a hydrogen bond to assist the oxygen transfer.



The hydroxy-directing effect has been carefully studied with allylic alcohols.[129] The analysis begins with the reactant conformation, which is dominated by allylic strain.

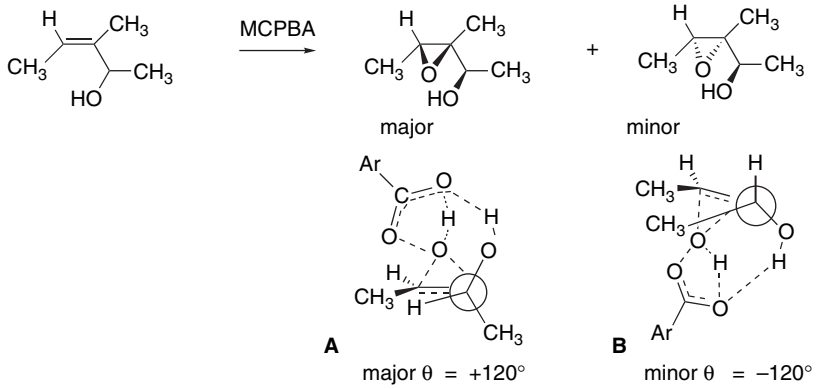
124. R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).
125. A. Sevin and J. -N. Cense, *Bull. Chim. Soc. Fr.*, 964 (1974); E. Vedejs, W. H. Dent, III, J. T. Kendall, and P. A. Oliver, *J. Am. Chem. Soc.*, **118**, 3556 (1996).
126. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
127. F. Mohamadi and M. M. Spees, *Tetrahedron Lett.*, **30**, 1309 (1989); P. G. M. Wuts, A. R. Ritter, and L. E. Pruitt, *J. Org. Chem.*, **57**, 6696 (1992); A. Jenmalm, W. Berts, K. Luthman, I. Csoregh, and U. Hacksell, *J. Org. Chem.*, **60**, 1026 (1995); P. Kocovsky and I. Stary, *J. Org. Chem.*, **55**, 3236 (1990); A. Armstrong, P. A. Barsanti, P. A. Clarke, and A. Wood, *J. Chem. Soc., Perkin Trans.*, *1*, 1373 (1996).
128. D. Ye, F. Finguelli, O. Piermatti, and F. Pizzo, *J. Org. Chem.*, **62**, 3748 (1997); I. Washington and K. N. Houk, *Org. Lett.*, **4**, 2661 (2002).
129. W. Adam and T. Wirth, *Acc. Chem. Res.*, **32**, 703 (1999).



θ = +120° θ = −120°

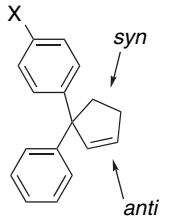
R = H	0.0 kcal/mol	0.7 kcal/mol
R = CH_3	0.0 kcal/mol	> 4.0 kcal/mol

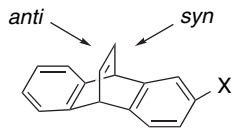
The epoxidation of goes through TS**A**, with 9:1 diastereoselectivity.[130]



The preference is the result of the CH_3–CH_3 steric interaction that is present in TS**B**. The same stereoselectivity is exhibited by other reagents influenced by hydroxy-directing effects.[131]

There has been considerable interest in finding and interpreting electronic effects in sterically unbiased systems. (See Topic 2.4 for the application of this kind of study to ketones.) The results of two such studies are shown below. Generally, EWGs are *syn* directing, whereas ERGs are *anti* directing, but the effects are not very large.





X	*syn:anti*
NO_2	73:27
Br	57:43
Cl	57:43
H	50:50
CH_3O	48:52

Ref. 132

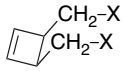
X	*syn:anti*
NO_2	77:23
F	58:42
H	50:50
CH_3O	48:52

Ref. 133

130. W. Adam and B. Nestler, *Tetrahedron Lett.*, **34**, 611 (1993).
131. W. Adam, H.-G. Degen, and C. R. Saha-Moller, *J. Org. Chem.*, **64**, 1274 (1999).
132. R. L. Halterman and M. A. McEvoy, *Tetrahedron Lett.*, **33**, 753 (1992).
133. T. Ohwada, I. Okamoto, N. Haga, and K. Shudo, *J. Org. Chem.*, **59**, 3975 (1994).

Whether these electronic effects have a stereoelectronic or an electrostatic origin is an open question. In either case, there would be a more favorable electronic environment *anti* to the ERG substituents and *syn* to the EWGs.

A related study of 3,4-disubstituted oxymethylcyclobutenes showed moderate *syn*-directive effects on MCPBA epoxidation.[134] In this case, the effect was attributed to interaction of the relatively electron-rich peroxide oxygens with the positively charged methylene hydrogens, but the electrostatic effect of the bond dipoles would be in the same direction.



X	*syn:anti*
H	55:45
OH	67:33
OCH_3	62:38
O_2CCH_3	72:28
OSO_2CH_3	79:21
OSO_2 (cyclic sulfite)	70:30

There have been several computational studies of the peroxy acid–alkene reaction. The proposed spiro TS has been supported in these studies for alkenes that do not present insurmountable steric barriers. The spiro TS has been found for ethene (B3LYP/6-31G*),[135] propene and 2-methylpropene (QCISD/6-31G*),[136] and 2,3-dimethylbutene and norbornene (B3LYP/6-311+G(d, p)).[137] These computational studies also correctly predict the effect of substituents on the E_a and account for these effects in terms of less synchronous bond formation. This is illustrated by the calculated geometries and E_a(B3LYP/6-31G*) of the TS for ethene, propene, methoxyethene, 1,3-butadiene, and cyanoethene, as shown in Figure 5.3. Note that the TSs become somewhat unsymmetrical with ERG substituents, as in propene, methoxyethene, and butadiene. The TS for acrylonitrile with an EWG substituent is even more unsymmetrical and has a considerably shorter C(3)– O bond, which reflects the electronic influence of the cyano group. In this asynchronous TS, the nucleophilic character of the peroxidic oxygen toward the β-carbon is important. Note also that the E_a is increased considerably by the EWG.

Visual images and additional information available at: springer.com/carysundberg

Another useful epoxidizing agent is dimethyldioxirane (DMDO).[138] This reagent is generated by an in situ reaction of acetone and peroxymonosulfate in buffered aqueous solution. Distillation gives an ~0.1 M solution of DMDO in acetone.[139]

134. M. Freccero, R. Gandolfi, and M. Sarzi-Amade, *Tetrahedron*, **55**, 11309 (1999).
135. K. N. Houk, J. Liu, N. C. DeMello, and K. R. Condroski, *J. Am. Chem. Soc.*, **119**, 10147 (1997).
136. R. D. Bach, M. N. Glukhovtsev, and C. Gonzalez, *J. Am. Chem. Soc.*, **120**, 9902 (1998).
137. M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *J. Org. Chem.*, **67**, 8519 (2002).
138. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989); W. Adam and L. P. Hadjiarapoglou, *Topics Current Chem.*, **164**, 45 (1993); W. Adam, A. K. Smerz, and C. G. Zhao, *J. Prakt. Chem., Chem. Zeit.,* **339**, 295 (1997).
139. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985); W. Adam, J. Bialas, and L. Hadjiarapaglou, *Chem. Ber.*, **124**, 2377 (1991).

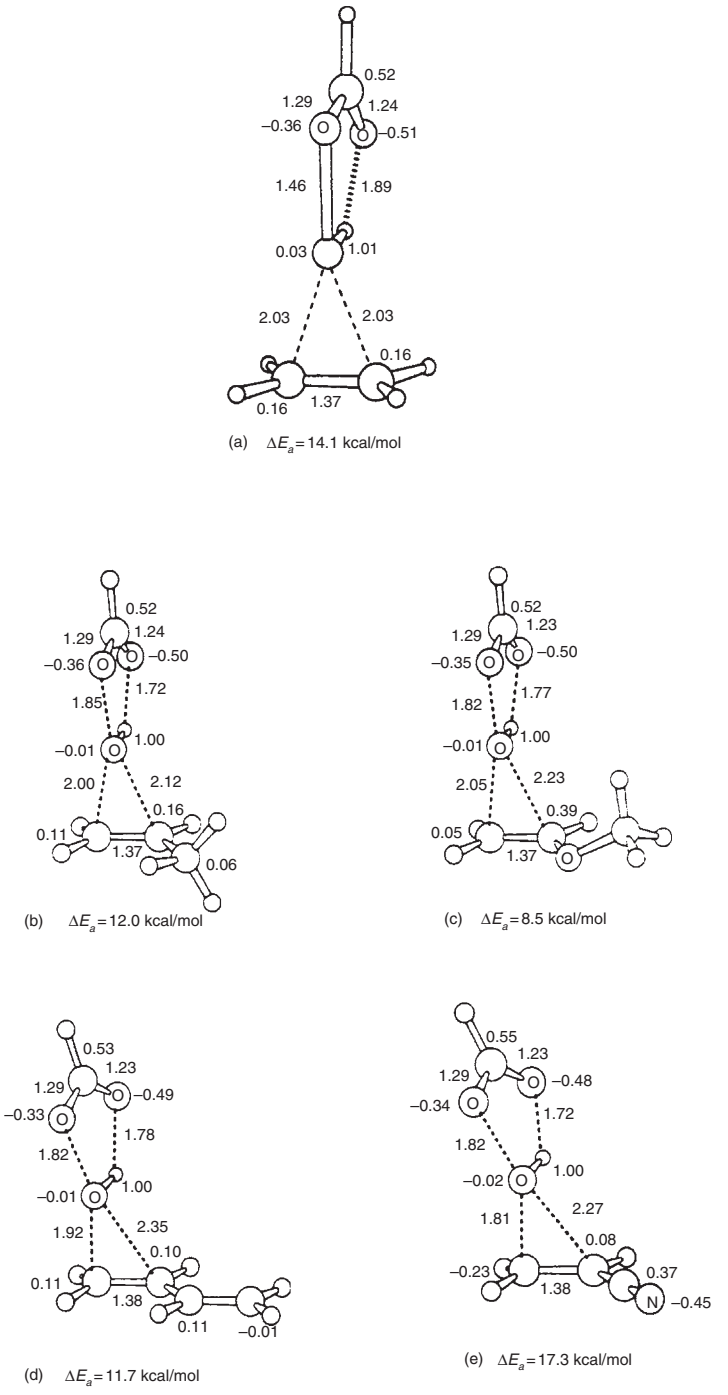
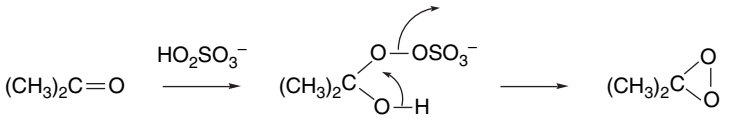
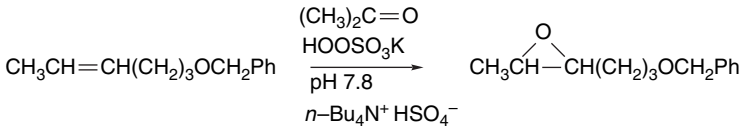


Fig. 5.3. Comparison of B3LYP/6-31G* TS structures and E_a for epoxidation by HCO_3H for: (a) ethene; (b) propene; (c) methoxyethene; (d) 1,3-butadiene, and (e) cyanoethene. Reproduced from *J. Am. Chem. Soc.*, **119**, 10147 (1997), by permission of the American Chemical Society.

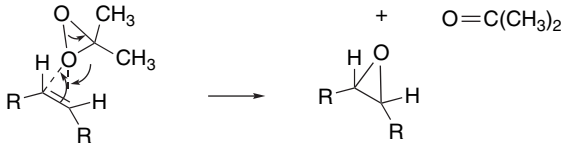


Higher concentrations of DMDO can be obtained by extraction of a 1:1 aqueous dilution of the distillate by CH_2Cl_2, $CHCl_3$, or CCl_4.[140] Other improvements in convenience have been described,[141] including in situ generation of DMDO under phase transfer conditions.[142]

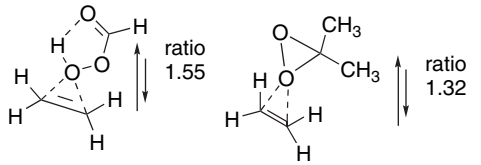


The yields and rates of oxidation by DMDO under these in situ conditions depend on pH and other reaction conditions.[143]

Various computational models of the TS show that the reaction occurs by a concerted mechanism that is quite similar to that for peroxy acids.[144] Kinetics and isotope effects are consistent with this mechanism.[145]

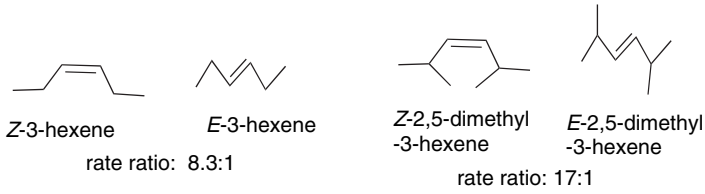


For example, the NPA charges for the DMDO and performic oxidations of ethene have been compared.[146] The ratio of the electrophilic interaction involving electron density transfer from the alkene to the O−O σ^* orbitals can be compared with the nucleophilic component involving back donation from the oxidant to the alkene π^* orbital. By this comparison, performic acid is somewhat more electrophilic.



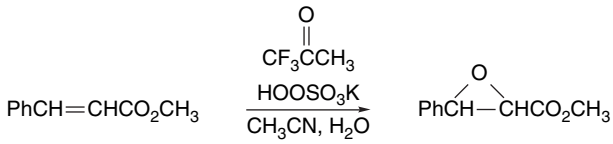
140. M. Gilbert, M. Ferrer, F. Sanchez-Baeza, and A. Messequer, *Tetrahedron*, **53**, 8643 (1997).
141. W. Adam, J. Bialoas, and L. Hadjiaropoglou, *Chem. Ber.*, **124**, 2377 (1991).
142. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).
143. M. Frohn, Z.-X. Wang, and Y. Shi, *J. Org. Chem.*, **63**, 6425 (1998); A. O'Connell, T. Smyth, and B. K. Hodnett, *J. Chem. Tech. Biotech.*, **72**, 60 (1998).
144. R. D. Bach, M. N. Glukhovtsev, C. Gonzalez, M. Marquez, C. M. Estevez, A. G. Baboul, and H. Schlegel, *J. Phys. Chem.*, **101**, 6092 (1997); M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *Tetrahedron*, **54**, 6123 (1998); J. Liu, K. N. Houk, A. Dinoi, C. Fusco, and R. Curci, *J. Org. Chem.*, **63**, 8565 (1998).
145. W. Adam, R. Paredes, A. K. Smerz, and L. A. Veloza, *Liebigs Ann. Chem.*, 547 (1997); A. L. Baumstark, E. Michalenabaez, A. M. Navarro, and H. D. Banks, *Heterocycl. Commun.*, **3**, 393 (1997); Y. Angelis, X. J. Zhang, and M. Orfanopoulos, *Tetrahedron Lett.*, **37**, 5991 (1996).
146. D. V. Deubel, G. Frenking, H. M. Senn, and J. Sundermeyer, *J. Chem. Soc., Chem. Commun.*, 2469 (2000).

It has been suggested that the TS for DMDO oxidation of electron-poor alkenes, such as acrylonitrile, has a dominant nucleophilic component.[147] DMDO oxidations have a fairly high sensitivity to steric effect. The *Z*-isomers of alkenes are usually more reactive than the *E*-isomers because in the former case the reagent can avoid the alkyl groups.[148] We say more about this in Section 5.8.



Similarly to peroxycarboxylic acids, DMDO is subject to *cis* or *syn* stereoselectivity by hydroxy and other hydrogen-bonding functional groups.[149] The effect is strongest in nonpolar solvents. For other substituents, both steric and polar factors seem to have an influence, and several complex reactants have shown good stereoselectivity, although the precise origin of the stereoselectivity is not always evident.[150]

Other ketones apart from acetone can be used for in situ generation of dioxiranes by reaction with peroxysulfate or another suitable peroxide. More electrophilic ketones give more reactive dioxiranes. 3-Methyl-3-trifluoromethyldioxirane is a more reactive analog of DMDO.[151] This reagent, which can be generated in situ from 1,1,1-trifluoroacetone, is capable of oxidizing less reactive compounds such as methyl cinnamate.

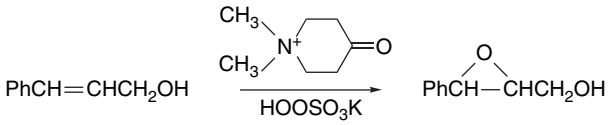


Ref. 152

Hexafluoroacetone and hydrogen peroxide in buffered aqueous solution epoxidizes alkenes and allylic alcohols.[153] Other fluoroketones also function as epoxidation catalysts.[154,155] *N*,*N*-dialkylpiperidin-4-one salts are also good catalysts for

147. D. V. Deubel, *J. Org. Chem.*, **66**, 3790 (2001).
148. A. L. Baumstark and C. J. McCloskey, *Tetrahedron Lett.*, **28**, 3311 (1987); A. L. Baumstark and P. C. Vasquez, *J. Org. Chem.*, **53**, 3437 (1988).
149. R. W. Murray, M. Singh, B. L. Williams, and H. M. Moncrieff, *J. Org. Chem.*, **61**, 1830 (1996); G. Asensio, C. Boix-Bernardini, C. Andreu, M. E. Gonzalez-Nunez, R. Mello, J. O. Edwards, and G. B. Carpenter, *J. Org. Chem.*, **64**, 4705 (1999).
150. R. C. Cambie, A. C. Grimsdale, P. S. Rutledge, M. F. Walker, and A. D. Woodgate, *Austr. J. Chem.*, **44**, 1553 (1991); P. Boricelli and P. Lupattelli, *J. Org. Chem.*, **59**, 4304 (1994); R. Curci, A. Detomaso, T. Prencipe, and G. B. Carpenter, *J. Am. Chem. Soc.*, **116**, 8112 (1994); T. C. Henninger, M. Sabat, and R. J. Sundberg, *Tetrahedron,* **52**, 14403 (1996).
151. R. Mello, M. Fiorentino, O. Sciacovelli, and R. Curci, *J. Org. Chem.*, **53**, 3890 (1988).
152. D. Yang, M.-K. Wong, and Y.-C. Yip, *J. Org. Chem.*, **60**, 3887 (1995).
153. R. P. Heggs and B. Ganem, *J. Am. Chem. Soc.*, **101**, 2484 (1979); A. J. Biloski, R. P. Hegge, and B. Ganem, *Synthesis*, 810 (1980); W. Adam, H.-G. Degen, and C. R. Saha-Moller, *J. Org. Chem.*, **64**, 1274 (1999).
154. E. L. Grocock, B.A. Marples, and R. C. Toon, *Tetrhahedron*, **56**, 989 (2000).
155. J. Legros, B. Crousse, J. Bourdon, D. Bonnet-Delpon, and J.-P. Begue, *Tetrahedron Lett.*, **42**, 4463 (2001).

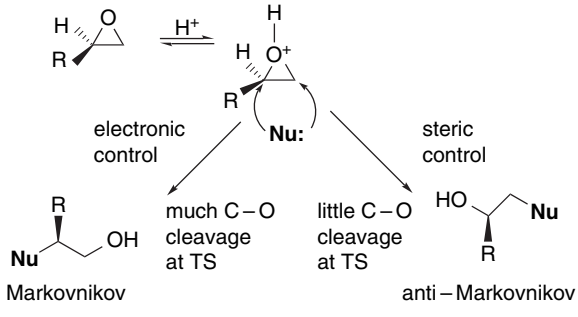
epoxidation.[156] The positively charged quaternary nitrogen enhances the reactivity of the carbonyl group toward nucleophilic addition and also makes the dioxirane intermediate more reactive.



5.5.2. Subsequent Transformations of Epoxides

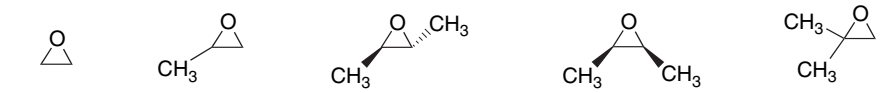
Epoxides are useful synthetic intermediates and the conversion of an alkene to an epoxide is often part of a more extensive overall transformation.[157] Advantage is taken of the reactivity of the epoxide ring to introduce additional functionality. As epoxide ring opening is usually stereospecific, such reactions can be used to establish stereochemical relationships between adjacent substituents. Such two- or three-step operations can achieve specific oxidative transformations of an alkene that might not be easily accomplished in a single step.

Ring opening of epoxides can be carried out under either acidic or basic conditions. The regiochemistry of the ring opening depends on whether steric or electronic factors are dominant. Base-catalyzed reactions in which the nucleophile provides the driving force for ring opening usually involve breaking the epoxide bond at the less-substituted carbon, since this is the position most accessible to nucleophilic attack (*steric factor dominates*).[158] The situation in acid-catalyzed reactions is more complicated. The bonding of a proton to the oxygen weakens the C−O bonds and facilitates rupture of the ring by weak nucleophiles. If the C−O bond is largely intact at the TS, the nucleophile will become attached to the less-substituted position for the same steric reasons that were cited for nucleophilic ring opening. If, on the other hand, C−O rupture is more complete when the TS is reached, the opposite orientation is observed. This results from the ability of the more-substituted carbon to stabilize the developing positive charge (*electronic factor dominates*). *Steric control corresponds to anti-Markovnikov regioselectivity, whereas electronic control leads to Markovnikov regioselectivity.*



156. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).
157. J. G. Smith, *Synthesis*, 629 (1984).
158. R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

These fundamental aspects of epoxide ring opening were established by kinetic and isotopic labeling studies.[159] The dominant role of bond cleavage in acidic hydrolysis is indicated by the increase in rates with additional substitution. Note in particular that the 2,2-dimethyl derivative is much more reactive than the *cis* and *trans* disubstituted derivative, as expected for an intermediate with carbocation character.



The pH-rate profiles of hydrolysis of 2-methyloxirane and 2,2-dimethyloxirane have been determined and interpreted.[160] The profile for 2,2-dimethyloxirane, shown in Figure 5.4, leads to the following rate constants for the acid-catalyzed, uncatalyzed, and base-catalyzed reactions.

$$k_{H^+} = 25.8 \pm 1.7\, M^{-1}\mathrm{s}^{-1}$$
$$k_{H_2O} = 2.19 \pm 10^{-6}\, M^{-1}\mathrm{s}^{-1}$$
$$k_{-OH} = 1.95 \pm 10^{-4}\, M^{-1}\mathrm{s}^{-1}$$

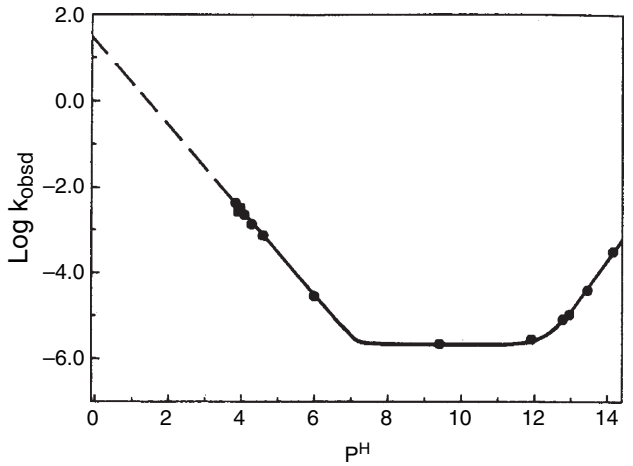


Fig. 5.4. pH-Rate profile for hydrolysis of 2,2-dimethyloxirane. Reproduced from *J. Am. Chem. Soc.*, **110**, 6492 (1988), by permission of the American Chemical Society.

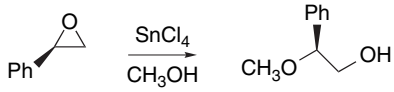
159. J. G. Pritchard and F. A. Long, *J. Am. Chem. Soc.*, **78**, 2667, 6008 (1956); F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).
160. Y. Pocker, B. P. Ronald, and K. W. Anderson, *J. Am. Chem. Soc.*, **110**, 6492 (1988).

Nucleophilic attack occurs at both the more-substituted and the less-substituted carbon, as determined by isotopic labeling.[161]

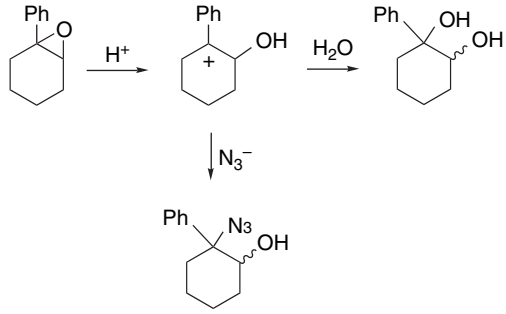
pH = 1	70	30	80–90	10–20
pH = 7	36	64	99	1

The opening of *cis*- and *trans*-2,3-dimethyloxirane in methanol or acetic acid is a stereospecific *anti* addition.[162]

The presence of an aryl substituent favors cleavage of the benzylic C−O bond. The case of styrene oxide hydrolysis has been carefully examined. Under acidic conditions the bond breaking is exclusively at the benzylic position (electronic control). Under basic conditions, ring opening occurs at both epoxide carbons.[163] Styrene also undergoes highly regioselective ring opening in the presence of Lewis acids. For example, methanolysis is catalyzed by $SnCl_4$; it occurs with more than a 95% attack at the benzyl carbon and with high *inversion of configuration*.[164] Similar results are observed with BF_3.[165] The stereospecificity indicates a concerted nucleophilic opening of the complexed epoxide, with bond-weakening factors (electronic control) determining the regiochemistry.

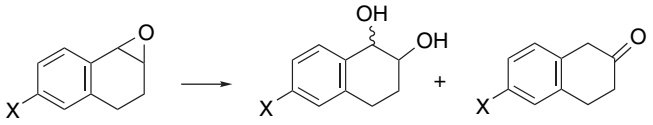


In the case of epoxides of 1-arylcyclohexene, there is direct evidence for a carbocation intermediate.[166] The hydrolysis product can be diverted by addition of azide ion as a competing nucleophile. As expected for a carbocation intermediate, both the *cis* and *trans* diols are formed.



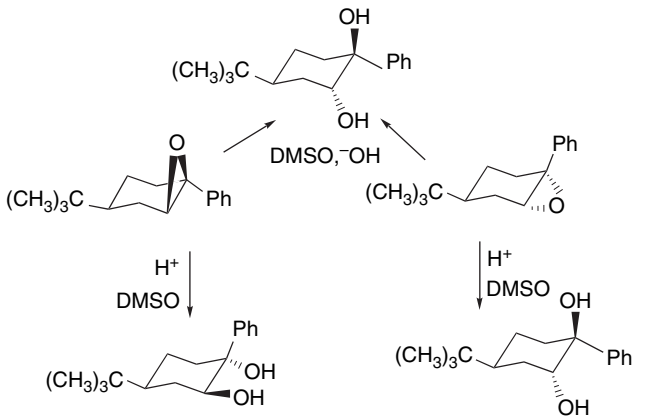
[161] F. A. Long and J. G. Pritchard, *J. Am. Chem. Soc.*, **78**, 2663, 2667 (1956); F. A. Long , J. G. Pritchard, and F. E. Stafford, *J. Am. Chem. Soc.*, **79**, 2362 (1957).
[162] V. F. Shvets, N. N. Lebedev, and O. A. Tyukova, *Zh. Org. Khim.*, **7**, 1851 (1971).
[163] B. Lin and D. L. Whalen, *J. Org. Chem.*, **59**, 1638 (1994); J. J. Blumenstein, V.C. Ukachukwu, R. S. Mohan, and D. L. Whalen, *J. Org. Chem.*, **58**, 924 (1993).
[164] C. Moberg, L. Rakos, and L. Tottie, *Tetrahedron Lett.*, **33**, 2191 (1992).
[165] Y. J. Liu, T. Y. Chu, and R. Engel, *Synth. Commun.*, **22**, 2367 (1992).
[166] L. Doan, K. Bradley, S. Gerdes, and D. L. Whalen, *J. Org. Chem.*, **64**, 6227 (1999).

Similarly, comparison of the epoxide of 1,2-dihydronaphthalene and its 6-methoxy analog provided interesting contrasts. The product was partitioned into the components formed by the acid-catalyzed and uncatalyzed mechanisms.[167] The unsubstituted compound gives the *trans* diol exclusively, indicating participation of the nucleophile in the ring opening. The 6-methoxy derivative gives a substantial amount of a rearrangement product and the diol is a mixture of the *cis* and *trans* stereoisomers. These differences indicate that the more stabilized carbocation has a significant lifetime.



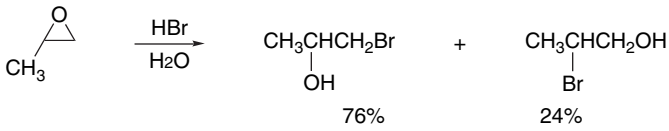
X	*cis*	*trans*	
H			
H^+ – catalyzed	6	94	0
uncatalyzed	0	100	0
CH_3O			
H^+ – catalyzed	81	19	<1
uncatalyzed	17	7	76

The conformationally biased *cis*- and *trans*-4-*t*-butyl derivatives were examined. The stereochemistry of both acid- and base-catalyzed reactions was investigated in 85:15 DMSO-H_2O. Under acidic conditions the epoxides give *anti* ring opening and the reaction is stereospecific. The base-catalyzed reactions involve *trans*-diaxial ring opening. The acid-catalyzed reactions occur by preferential opening of the benzylic bond with inversion.[168]



When saturated epoxides such as propylene oxide react with hydrogen halides, the dominant mode of reaction introduces halide at the less-substituted primary carbon (anti-Markovnikov).[169]

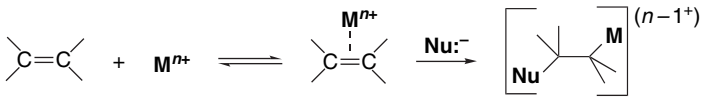
167. R. E. Gillilan, T. M. Pohl, and D. L. Whalen, *J. Am. Chem. Soc.*, **104**, 4481 (1982).
168. G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Lett.*, 3421 (1965).
169. C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).



Substituents that further stabilize a carbocation intermediate lead to reversal of the mode of addition.[170] To summarize, because they are stable compounds, both the stereochemistry and regiochemistry of epoxides can be controlled by the reaction conditions. Ring opening that is dominated by the nucleophilic reagent is determined by steric access. Ring opening that is electrophilic in character introduces the nucleophile at the position that has the largest cationic character.

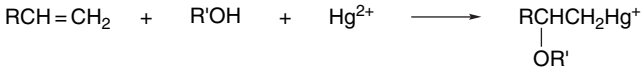
5.6. Electrophilic Additions Involving Metal Ions

Certain metal cations promote addition by electrophilic attack on alkenes. Addition is completed when a nucleophile adds to the alkene-cation complex. The nucleophile may be the solvent or a ligand from the metal ion's coordination sphere. The same process occurs for other transition metal cations, especially for Pd^{2+}, but the products often go on to react further. Synthetically important reactions involving Pd^{2+} are discussed in Section 8.2 of Part B. The mercuration products are stable, and this allows study of the addition reaction itself. We also consider reactions of the Ag^{+} ion, which give complexes, but usually do not proceed to adducts.



5.6.1. Solvomercuration

The best characterized of these reactions involve the mercuric ion, Hg^{2+}, as the cation.[171] The usual nucleophile is the solvent. The term *oxymercuration* is used to refer to reactions in which water or an alcohol acts as the nucleophile. The adducts can be isolated as halide salts, but in synthetic applications the mercury is often replaced by hydrogen (*oxymercuration reduction*; see below).



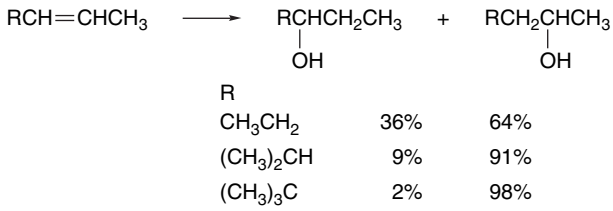
The reactivity of mercury salts is a function of both the solvent and the counterion.[172] Mercuric chloride, for example, is unreactive and mercuric acetate is the most commonly used reagent, but the trifluoroacetate, trifluoromethanesulfonate, nitrate, or perchlorate salts are preferable in some applications.

170. S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.*, **74**, 1160 (1952).
171. W. Kitching, *Organomet. Chem. Rev.*, **3**, 61 (1968); R. C. Larock, *Solvomercuration/Demercuration Reactions in Organic Synthesis*, Springer-Verlag, New York, 1986.
172. H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **49**, 2551 (1984).

The reactivity of different alkenes toward mercuration spans a considerable range and is governed by a combination of steric and electronic factors.[173] In contrast to protonation and halogenation reactions, the oxymercuration reaction is not always accelerated by alkyl substituents on the alkene. Dialkyl terminal alkenes are more reactive than monosubstituted ones, but internal disubstituted alkenes are less reactive. For example, 1-pentene is about ten times more reactive than *Z*-2-pentene and 40 times more reactive than *E*-2-pentene.[174] This reversal of reactivity is due to steric effects, which generally outweigh the normal electron-releasing effect of alkyl substituents.[175] The relative reactivity data for some pentene derivatives are given in Table 5.6.

As expected for an electrophilic reaction, the ρ values for oxymercuration of styrene (−3.16)[176] and α-methylstyrene (−3.12)[177] derivatives are negative. The positive deviation of the methoxy substituent, when treated by the Yukawa-Tsuno equation, is indicative of a modestly enhanced resonance component. The additional methyl substituent in α-methylstyrene is slightly activating and indicates that its electron-donating effect outweighs any adverse steric effect.

The addition of the nucleophile follows Markovnikov's rule and the regioselectivity of oxymercuration is ordinarily very high. Terminal alkenes are usually more than 99% regioselective and even disubstituted alkenes show significant regioselectivity, which is enhanced by steric effects.



Ref. 178

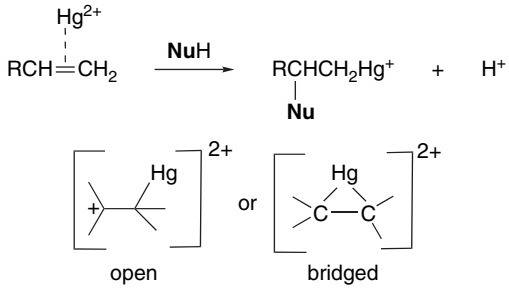
Table 5.6. Relative Reactivity of Some Alkenes in Oxymercuration

Alkene	Relative reactivity[a]
1-Pentene	6.6
2-Methyl-1-pentene	48
Z-2-Pentene	0.56
E-2-Pentene	0.17
2-Methyl-2-pentene	1.24
Cyclohexene	1.00

a. H. C. Brown and P. J. Geogheagan, Jr., *J. Org. Chem.*, **37**, 1937 (1972).

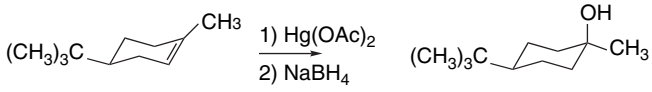
173. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972); H. C. Brown, P. J. Geoghegan, Jr., G. J. Lynch, and J. T. Kurek, *J. Org. Chem.*, **37**, 1941 (1972); H. C. Brown, P. J. Geoghegan, Jr., and J. T. Kurek, *J. Org. Chem.*, **46**, 3810 (1981).
174. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972).
175. S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, **103**, 2783 (1981).
176. A. Lewis and J. Azoro, *J. Org. Chem.*, **46**, 1764 (1981); A. Lewis, *J. Org. Chem.*, **49**, 4682 (1984).
177. I. S. Hendricks and A. Lewis, *J. Org. Chem.*, **64**, 7342 (1999).
178. H. C. Brown and J. P. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).

In analogy with other electrophilic additions, the mechanism of the oxymercuration reaction can be discussed in terms of a cationic intermediate.[179] The cationic intermediate can be bridged (*mercurinium ion*) or open, depending on the structure of the particular alkene. The intermediates can be detected by NMR in nonnucleophilic solvents.[180] The addition is completed by attack of a nucleophile at the more positive carbon.

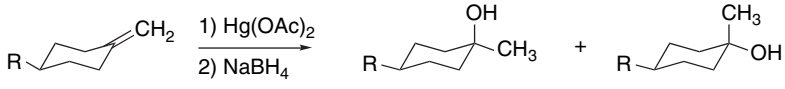


After the addition step is complete, the mercury is usually replaced by hydrogen, using a reducing agent. The net result is the addition of hydrogen and the nucleophile to the alkene, and the reaction is known as *oxymercuration reduction*. The regioselectivity is in the same sense as is observed for proton-initiated additions.[181]

Oxymercuration of unhindered alkenes is usually a stereospecific *anti* addition. This result is consistent with the involvement of a mercurinium ion intermediate that is opened by nucleophilic attack.[182] Conformationally biased cyclic alkenes such as 4-*t*-butylcyclohexene and 4-*t*-butyl-1-methycyclohexene give exclusively the product of *anti*-diaxial addition.[181,183]



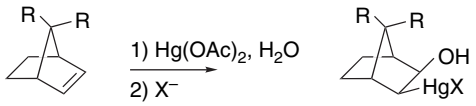
Methylenecyclohexenes are not very stereoselective, showing a small preference for the axial alcohol, which corresponds to mercuration from the equatorial face.[184]



R	
CH_3	68:32
$(CH_3)_3C$	71:29

179. S. J. Cristol, J. S. Perry, Jr., and R. S. Beckley, *J. Org. Chem.*, **41**, 1912 (1976); D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6902 (1971).
180. G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.*, **95**, 6067 (1973); G. A. Olah and S. H. Yu, *J. Org. Chem.,* **40**, 3638 (1975).
181. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **49**, 2511 (1984); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **50**, 1171 (1985).
182. H. B. Vardhan and R. D. Bach, *J. Org. Chem.*, **57**, 4948 (1992).
183. H. C. Brown, G. J. Lynch, W. J. Hammar, and L. C. Liu, *J. Org. Chem.*, **44**, 1910 (1979).
184. Y. Senda, S. Kamiyama, and S. Imaizumi, *J. Chem. Soc., Perkin Trans. 1*, 530 (1978).

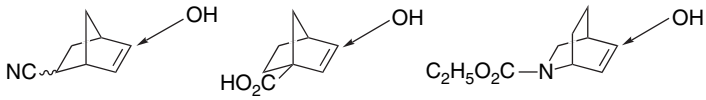
In contrast to the *anti* addition observed with acyclic and monocyclic alkenes, bicyclic alkenes frequently show *syn* addition. Norbornene gives exclusively *exo-syn* addition. Even 7,7-dimethylnorbornene gives the *exo-syn* product, in sharp contrast to the usual *endo*-directing effects of 7-substitution. These results are difficult to reconcile with a bridged mercurinium ion and suggest that intramolecular transfer of the nucleophile from mercury occurs. In norbornene derivatives, the competing *anti* addition is sterically restricted by the *endo* bridge.



R= H	Ref. 185
R= CH_3	Ref. 186

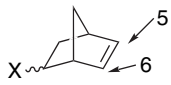
Other bicyclic alkenes have been observed to give largely or exclusively *syn* addition.[187]

Oxymercuration shows considerable sensitivity to polar substituents. Several early examples set the pattern, which is for the nucleophile to add at the carbon that is more remote from a polar EWG substituent.



Ref. 188 Ref. 188 Ref. 189

In considering the basis of this effect, Factor and Traylor[188] suggested that the EWGs "make the unsymmetrical TS having less positive charge near the substituted position the one of lowest energy." Mayo and colleagues carried out a systematic study of the effect, including comparison of *exo* and *endo* substituents.[190] Some of the results of that study are shown below. The directive effect was found for both *exo* and *endo* substituents, but was somewhat stronger for *exo* groups.



X	5:6 (*exo*)	5:6 (*endo*)
CH_2OTBS	1:1	1:1
CO_2CH_3	5:1	5:1
OH	6:1	3:1
OCH_2Ph	9:1	6:1
O_2CCH_3	14:1	9:1

185. T. G. Traylor and A. W. Baker, *J. Am. Chem. Soc.*, **85**, 2746 (1963).
186. H. C. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **95**, 8665 (1973).
187. T. N. Sokolova, V. R. Kartashov, O. V. Vasil'eva, and Y. K. Grishin, *Russ. Chem. Bull.*, **42**, 1583 (1993).
188. A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968).
189. G. Krow, R. Rodebaugh, M. Grippi, and R. Carmosin, *Synth. Commun.*, **2**, 211 (1972).
190. P. Mayo, G. Orlova, J. D. Goddard, and W. Tam, *J. Org. Chem.*, **66**, 5182 (2001).

These workers used B3PW91/LanL2DZ DFT calculations to probe the TS using $Hg(O_2CH)_2$ as the reagent. Using ethene as the reactant, they found a symmetrical bridged structure to be a stable prereaction complex. The TS for addition is very unsymmetrical with partial bonding by one of the formate ligands. The TS for addition to norbornenes was somewhat looser and the addition corresponded to a four-center *syn* mechanism. These gas phase computations may bias the ethene TS toward *syn* addition by virtue of the attachment of the nucleophile to Hg^{2+}. However, the results with both ethene and norbornene suggest that there is no strong prohibition against a *syn* addition, in agreement with the experimental results.

The regioselectivity in substituted norbornenes is the result of polarization of the double bond, with the Hg^{2+} attacking the more negative carbon. The NPA charges calculated for the TS show that this polarization becomes much larger as the C−Hg bond is formed and the TS is approached. The substituent effect results from an initial polarization of the double bond that is enhanced as the TS is approached. Figure 5.5 shows the TS for C(5) and C(6) for the *endo* hydroxyl reactant. The $\Delta E^{\ddagger}$ for the two TSs differ by 1.6 kcal and in the direction of the observed preferred addition of Hg at C(6).

Visual models, additional information and exercises on Oxymercuration can be found in the Digital Resource available at: Springer.com/carey-sundberg.

The effect of remote polar substituents was also probed with substituted 7-methylenenorbornanes.[191] The substituents are located in the *endo* position and cannot interact directly with the approaching reagent. Ester groups are strongly *syn*

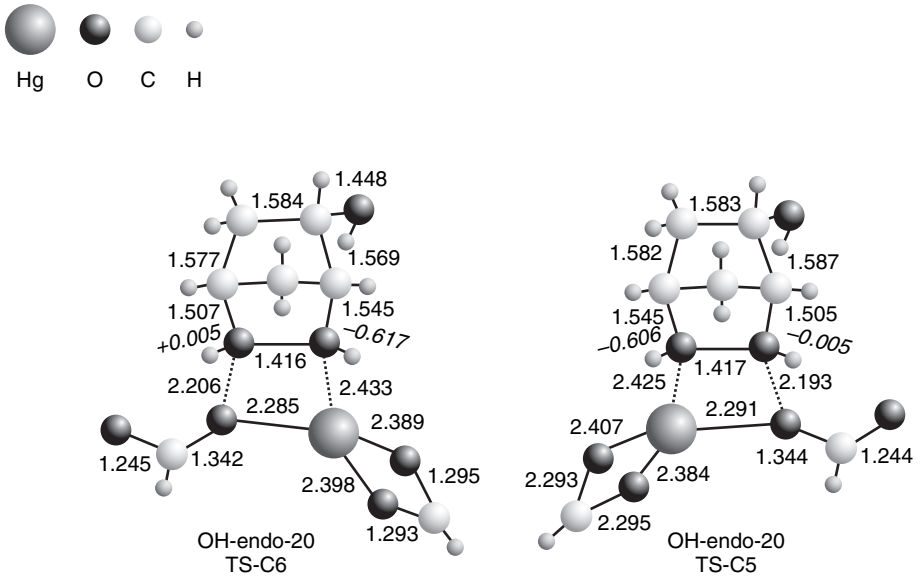
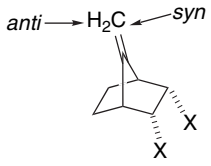


Fig. 5.5. Transition structures for C(6) and C(5) mercuration of the *endo* hydroxy derivative of norbornene. Italic numbers give the NPA charges at the reacting carbons. Reproduced from *J. Org. Chem.*, **66**, 5182 (2001), by permission of the American Chemical Society.

[191] G. Mehta and F. A. Khan, *J. Chem. Soc., Chem. Commun.*, 18 (1991).

directing, whereas ethyl groups are *anti* directing. These results were attributed to differential polarization of the faces of the π bond (see Section 2.4). Similar, but much weaker, directive effects are seen for epoxidation and hydroboration.

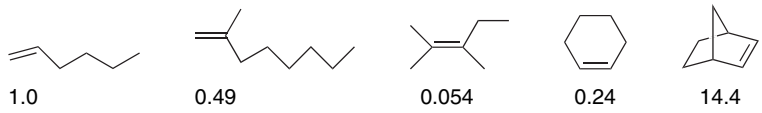


X	*syn*	*anti*
CO_2CH_3	>95	>5
CH_2OCH_3	40	60
CH_2CH_3	17	83

A broad mechanistic interpretation that can encompass most of these results suggests that the Hg^{2+} ion is rather loosely bound prior to the rate-determining nucleophilic addition. The bonding is weaker at the carbon best able to accommodate positive charge, resulting in Markovnikov regioselectivity. If there is little steric hindrance, *anti* addition of a nucleophile is preferred, but the *syn* mechanism is available. The *syn* mechanism, at least as modeled in the gas phase, seems to involve migration of a ligand from Hg^{2+} to carbon. It is *the nucleophilic capture that determines the regiochemistry and stereochemistry of the product*, since the mercuration step is reversible. It should also be noted that oxymercuration has a different electronic pattern from most of the other electrophilic additions in that the Hg-substituted carbon becomes *negatively charged* as bonding occurs (see Figure 5.5). This is also true in hydroboration, although less so, whereas halogenation, sulfenylation, and selenylation result in placing a more electronegative substituent on *both* carbons of the double bond.

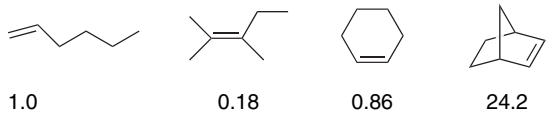
5.6.2. Argentation—the Formation of Silver Complexes

Several analytical and separation techniques are based on the reversible formation of complexes between alkenes and Ag^+ ions.[192] Analytical methods for terpenes, unsaturated acids and esters, and other unsaturated nonpolar compounds are based on the use of Ag^+-impregnated materials for thin-layer (TLC) and high-pressure (HPLC) as well as gas-liquid (GLC) chromatography. GLC measurements done some years ago suggest that the affinity decreases with additional substituents, but increases with strain.[193]



Relative affinity

An NMR study in methanol showed a similar trend in relative stability of the Ag(I) complexes.[194]



Relative affinity

192. G. Dobson, W. W. Christie, and B. Nikolovadamyanova, *J. Chromatogr. B,* **671**, 197 (1995); C. M. Williams and L. N. Mander, *Tetrahedron*, **57**, 425 (2001).
193. M. A. Muhs and F. T. Weiss, *J. Am. Chem. Soc.*, **84**, 4697 (1962).
194. H. B. Varhan and R. D. Bach, *J. Org. Chem.*, **57**, 4948 (1992).

In contrast to Hg(II), Ag(I) does not normally induce intermolecular nucleophilic addition to alkenes. However, internal nucleophiles can sometimes be captured, leading to cyclization reactions.

The structure and stability of alkene-Ag^+ complexes has also been examined by computation.[195] MP2/SBK(d) calculations indicate that three ethene molecules are accommodated at Ag^+ with ΔE of -30 ± 3 kcal/mol, but subsequent ethenes are less strongly bound. The computations find stronger complexation with alkyl-substituted alkenes in the gas phase, which is in contrast to the trend in the solution stabilities. This might be the result of the greater importance of solvation in the liquid phase, whereas polarization might be the dominant factor in the gas phase.

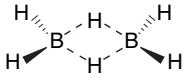
	Solution[a]	ΔE (gas phase)[b] kcal/mol
Ethene	1.32	−33.7
Propene	0.98	−36.6
Z-2-Butene	0.49	−38.0
E-2-Butene	0.27	−38.3
2-Methylpropene	0.16	−41.3
2,3-Dimethyl-2-butene	0.04	−43.5

a. T. A. van Beek and D. Suburtova, *Phytochem. Anal.*, **6**, 1 (1995). A solution relative affinity value based on chromatographic measurements.

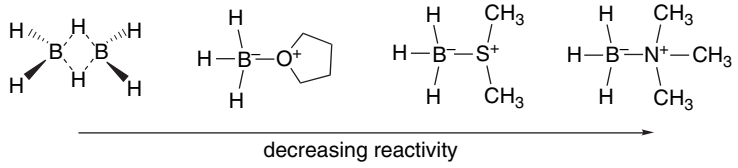
b. J. Kaneti, L. P. C. M. de Smet, R. Boom, H. Zuilhof, and E. J. R. Sudholter, *J. Phys. Chem. A*, **106**, 11197 (2002).

5.7. Synthesis and Reactions of Alkylboranes

Alkenes react with borane, BH_3, and a number of its derivatives to give synthetically useful alkylboranes. Borane is an electron-deficient molecule and in its pure form exists as a hydrogen-bridged dimer.



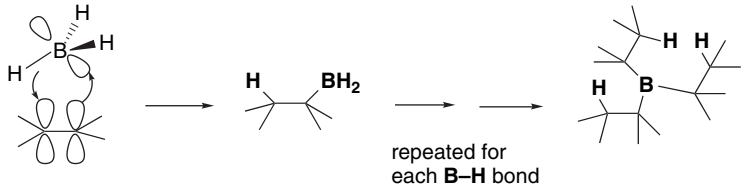
Borane reacts with electron pair donors to form Lewis acid-base complexes. The most common forms for use in synthesis are the THF and dimethyl sulfide complexes. Stronger bases, particularly amines, form less reactive adducts.



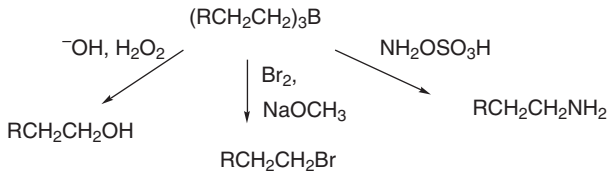
The addition of borane to alkenes is an electrophilic process, but it is concerted. The alkene donates electron density to the borane but a hydrogen shifts to carbon,

195. J. Kaneti, L. C. P. M. de Smet, R. Boom, H. Zuilhof, and E. J. R. Sudholter, *J. Phys. Chem. A,* **106**, 11197 (2002).

resulting in an overall *syn* addition. In MO terms, the addition is viewed as taking place by interaction of the alkene π orbital with the vacant *p* orbital on boron, accompanied by concerted C−H bond formation by interaction with the empty π* orbital.[196] Unhindered alkenes proceed to the trialkylborane stage by three successive additions.



As a result of a combination of steric and electronic factors, hydroboration is highly regioselective, with boron becoming bonded to the *less-substituted carbon.* The boron can eventually be replaced by hydroxy, carbonyl, amino, or halogen substituents. These reactions occur with retention of configuration. The overall transformations occur by *syn* addition with anti-Markovnikov regiochemistry.



5.7.1. Hydroboration

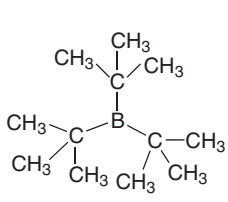
The synthetic applications of the hydroboration reaction are highly developed, largely through the work of H. C. Brown and his associates.[197] Hydroboration is one of the most widely applied of the alkene addition reactions for synthesis on a laboratory scale. Several aspects of the reaction are complementary to the reactions discussed earlier in this chapter. Hydroboration can be used to make alcohols and halides, and these reactions usually lead to the opposite (anti-Markovnikov) regiochemistry from reactions that proceed through cationic intermediates. Moreover, since there are no carbocation intermediates, there is no competition from rearrangement or elimination. The reactions are also stereospecific *syn* additions, as compared to the *anti* stereoselectivity for many reactions proceeding through cationic intermediates. On the basis of these contrasts, we might be inclined to think that hydroboration is fundamentally different from the other electrophilic addition reactions discussed in this chapter, but there are many similarities. At its outset, the hydroboration reaction involves an *electrophilic attack* on the π electrons of the alkene, just as is the case of the other reactions. The reaction is diverted to *syn* addition by the presence of the potentially

196. D. J. Pasto, B. Lepeska, and T.-C. Cheng, *J. Am. Chem. Soc.*, **94**, 6083 (1972); P. R. Jones, *J. Org. Chem.*, **37**, 1886 (1972); S. Nagase, K. N. Ray, and K. Morokuma, *J. Am. Chem. Soc.,* **102**, 4536 (1980); X. Wang, Y. Li, Y.-D. Wu, M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Org. Chem.*, **55**, 2601 (1990); N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

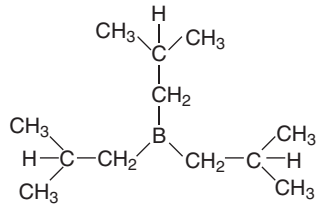
197. G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963); H. C. Brown, *Organic Synthesis via Boranes*, Wiley, New York, 1975; A. Pelter, K. Smith, and H. C. Brown, *Borane Reagents,* Academic Press, New York, 1988.

nucleophilic hydrogen on boron. As the electron-deficient boron bonds to one carbon, the hydrogen with two electrons shifts to the other carbon. The addition occurs through a four-center TS. Both the new C−B and C−H bonds are thus formed from the same side of the double bond.

Hydroboration is highly regioselective. The boron becomes bonded predominantly to the *less-substituted* carbon atom of the alkene. A *combination of steric and electronic effects* favors this orientation. Borane is an electrophilic reagent. The reaction with substituted styrenes exhibits a negative ρ value (−0.5).[198] Compared with bromination ($\rho^+ = -4.3$),[199] this is a weak substituent effect, but it does favor addition of the electrophilic boron at the more nucleophilic end of the double bond. In contrast to the case of addition of protic acids to alkenes, it is boron, not hydrogen, that is the more electrophilic atom. This electronic effect is reinforced by steric factors. Hydroboration is usually done under conditions in which the borane eventually reacts with three alkene molecules to give a trialkylborane. The second and third alkyl groups encounter severe steric repulsion if the boron is added at the internal carbon.



severe non-bonded repulsions



non-bonded repulsions reduced

Table 5.7 provides some data on the regioselectivity of the addition of diborane and several of its derivatives to representative alkenes.

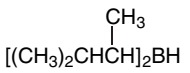
Table 5.7. Regioselectivity of Diborane and Derivatives toward Representative Alkenes

Hydroborating Reagent	Percent added at less-substituted carbon			
	1-Hexene	2-Methyl-1-Butene	4-Methyl-2-Pentene	Styrene
Diborane[a]	94	99	57	80
Chloroborane-dimethylsulfide[b]	99	99.5	—	98
Disiamylborane[a]	99	—	97	98
Thexylborane[c]	94	—	66	95
Chlorothexylborane-dimethylsulfide[d]	99	99	97	99
9-Borabicyclo[3.3.1]nonane (9-BBN)[e]	99.9	99.8[f]	99.8	98.5

a. G. Zweifel and H. C. Brown, *Org. React.*, **13,** 1 (1963).
b. H. C. Brown, N. Ravindran, and S. U. Kulkarni, *J. Org. Chem.*, **44**, 2417 (1969); H. C. Brown and U. S. Racherla, *J. Org. Chem.*, **51**, 895 (1986).
c. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4708 (1960).
d. H. C. Brown, J. A. Sikorski, S. U. Kulkarni, and H. D. Lee, *J. Org. Chem.* **45**, 4540 (1980).
e. H. C. Brown, E. F. Knight, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).
f. Data for 2-methyl-1-pentene.

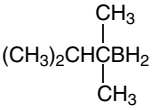
198. L. C. Vishwakarma and A. Fry, *J. Org. Chem.*, **45**, 5306 (1980).
199. J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

Table 5.7 includes data for some mono- and dialkylboranes that show even higher regioselectivity than diborane itself. These derivatives are widely used in synthesis and are frequently referred to by the shortened names shown with the structures.



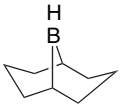
disiamylborane

bis-(1,2-dimethylpropyl)borane



thexylborane

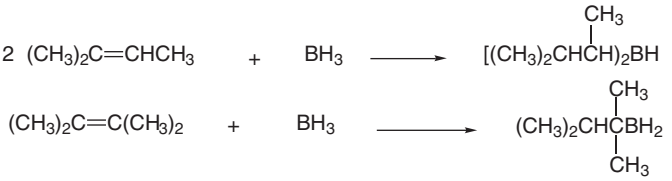
1,1,2-trimethylpropylborane



9-BBN

9-borabicyclo[3.3.1]nonane

These reagents are prepared by hydroboration of the appropriate alkene, using control of stoichiometry to achieve the desired degree of alkylation. 9-BBN is prepared from 1,4-cyclooctadiene



As is true for most addition reactions, there is a preference for approach of the borane from the less hindered face of the double bond. Since diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered molecules. Table 5.8 gives some data comparing the direction of approach for three cyclic alkenes. The products in all cases result from *syn* addition, but the mixtures result from both the low regioselectivity and from addition to both faces of the double bond. Even 7,7-dimethylnorbornene shows only a modest preference for *endo* addition with diborane. The selectivity is much enhanced with the bulkier reagent 9-BBN.

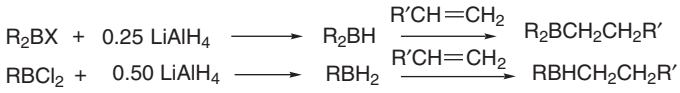
The haloboranes BH_2Cl, BH_2Br, $BHCl_2$, and $BHBr_2$ are also useful hydroborating reagents.[200] These compounds are somewhat more regioselective than borane itself, but otherwise show similar reactivity. The halogen(s) can be replaced by hydride and a second hydroboration step can then be carried out. This allows for preparation of unsymmetrically substituted boranes.

Table 5.8. Stereoselectivity of Hydroboration with Cyclic Alkenes[a]

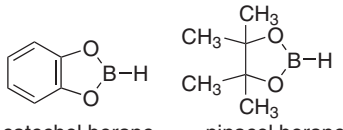
	Product composition[b]								
	3-Methyl-cyclopentene			3-Methyl-cyclohexene				7,7-Dimethyl norbornene	
Hydroboration Reagent	*trans*-2	*cis*-3	*trans*-3	*cis*-2	*trans*-2	*cis*-3	*trans*-3	*exo*	*endo*
Diborane	45		55	16	34	18	32	22[c]	78[c]
Disiamylborane	40		60	18	30	27	25	–	–
9-BBN	25	50	25	0	20	40	40	3	97

a. Data from H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.*, **99**, 3427 (1977), except where noted otherwise.
b. Product composition refers to the alcohols formed by subsequent oxidation.
c. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **95**, 2209 (1973).

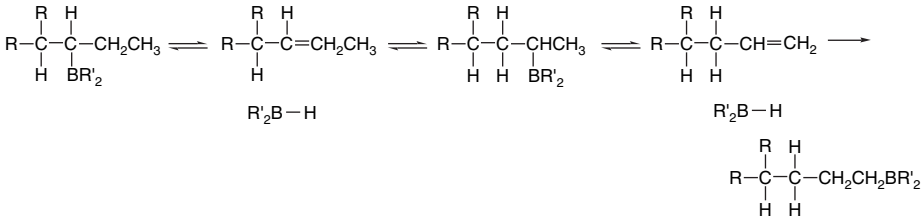
200. H. C. Brown and S. U. Kulkarni, *J. Organomet. Chem.*, **239**, 23 (1982).



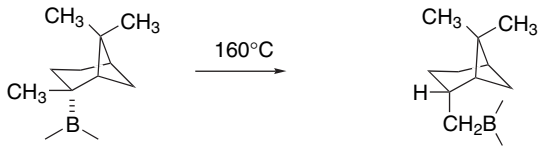
Catecholborane[201] and pinacolborane,[202] in which the boron has two oxygen substituents, are much less reactive hydroborating reagents than alkyl or haloboranes. The boron electron deficiency is attenuated by the oxygen atoms. Nevertheless, they are useful reagents for certain applications. The reactivity of catecholborane has been found to be substantially enhanced by addition of 10–20% of *N*, *N*-dimethylacetamide to CH_2Cl_2.[203]



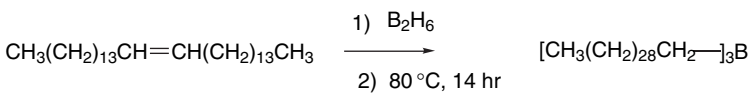
Hydroboration is thermally reversible. At 160 °C and above, B−H moieties are eliminated from alkylboranes, but the equilibrium is still in favor of the addition products. This provides a mechanism for migration of the boron group along the carbon chain by a series of eliminations and additions.



Migration cannot occur past a quaternary carbon, however, since the required elimination is blocked. At equilibrium, the major trialkylborane is the least-substituted terminal isomer that is accessible, because it is the one that minimizes unfavorable steric interactions. The availability of the isomerization provides a means for *thermodynamic control* of the hydroboration reaction.



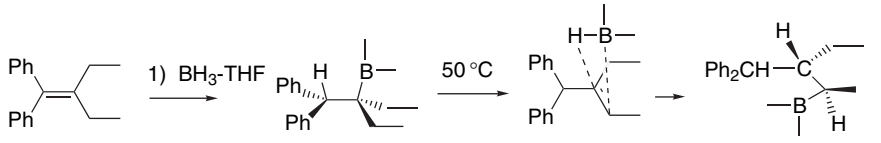
Ref. 204



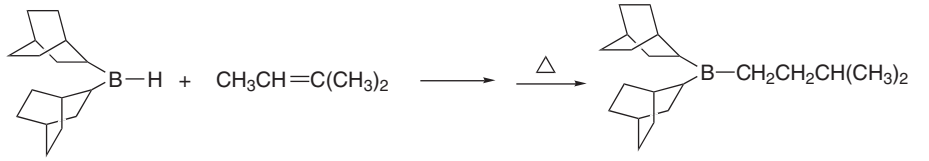
Ref. 205

201. H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **97**, 5249 (1975); H. C. Brown and J. Chandrasekharan, *J. Org. Chem.*, **48**, 5080 (1983).
202. C. E. Tucker, J. Davidson, and P. Knochel, *J. Org. Chem.*, **57**, 3482 (1992).
203. C. E. Garrett and G. C. Fu, *J. Org. Chem.*, **61**, 3224 (1996).
204. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, **86**, 393 (1964).
205. K. Maruyama, K. Terada, and Y. Yamamoto, *J. Org. Chem.*, **45**, 737 (1980).

Migrations are especially facile for *tetra*-substituted alkenes; they occur at 50–60°C and exhibit both regio- and stereoselectivity. The course of the reactions is dictated by the relative energy of the reversibly formed borane alkene complexes.[206]

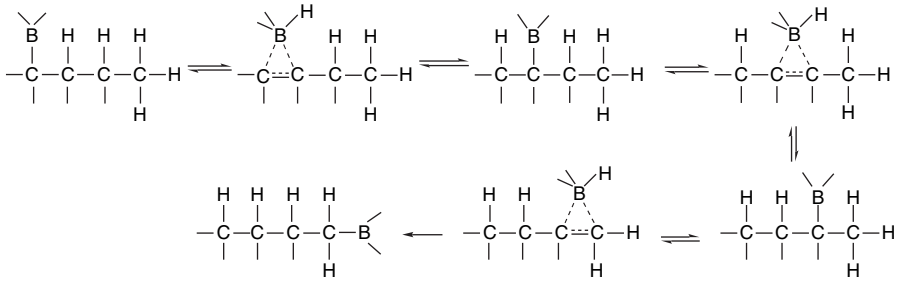


Unstrained bicyclic rings have little tendency to rearrange. *bis*-Bicyclo[2.2.2] octanylborane has been found to be particularly useful for formation and isomerization of monoalkyl derivatives.



Ref. 207

There is evidence that boron migration occurs *intramolecularly*.[208] A TS that describes this process has been located computationally (Figure 5.6).[209] It involves an electron-deficient π-complex about 20–25 kcal above the trialkylborane. These structures are analogous to the bridged carbocations in carbocation rearrangements. The boron can migrate to the end of the chain through a series of such structures.



5.7.2. Reactions of Organoboranes

Alkylboranes are very useful intermediates in organic synthesis. In this section we discuss methods by which the boron atom can be efficiently replaced by hydroxy,

206. L. O. Bromm, H. Laaziri, F. Lhermitte, K. Harms, and P. Knochel, *J. Am. Chem. Soc.*, **122**, 10218 (2000).
207. H. C. Brown and U. S. Racherla, *J. Am. Chem. Soc.*, **105**, 6506 (1983).
208. S. E. Wood and B. Rickborn, *J. Org. Chem.*, **48**, 555 (1983).
209. N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

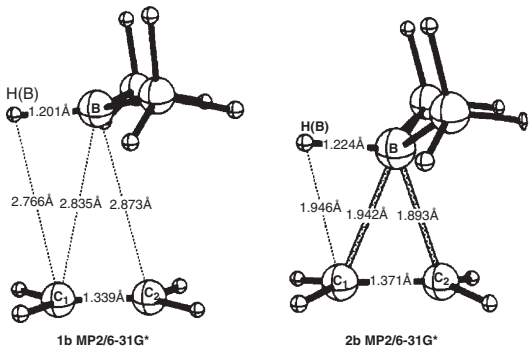
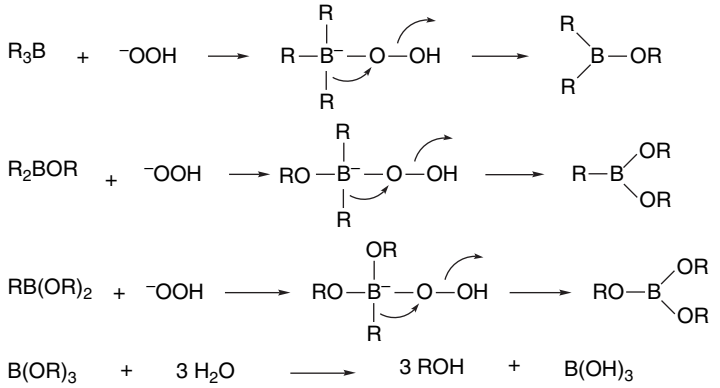


Fig. 5.6. Geometries (MP2/6-31G*) of (a) π complex and (b) transition state in reaction of ethene and dimethylborane. Reproduced from *J. Org. Chem.*, **56**, 4074 (1991), by permission of the American Chemical Society.

halogen, or amino groups. There are also important processes that use alkylboranes in the formation of new carbon-carbon bonds, and these reactions are discussed in Chapter 9 of Part B. The most widely used reaction of organoboranes is the oxidation to alcohols. Alkaline hydrogen peroxide is the reagent usually employed to effect the oxidation. The trialkylborane is converted to a trialkoxyborane (trialkyl borate) by a series of B → O migrations. The R−O−B bonds are hydrolyzed in the alkaline aqueous solution, generating the alcohol. The mechanism is outlined below.

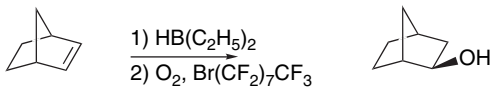


The stereochemical outcome is replacement of the C−B bond by a C−O bond with retention of configuration. In combination with the stereospecific *syn* hydroboration, this allows the structure and stereochemistry of the alcohols to be predicted with confidence. The preference for boronation at the less-substituted carbon of a double bond results in the alcohol being formed with regiochemistry that is complementary to that observed by direct hydration or oxymercuration, i.e., anti-Markovnikov.

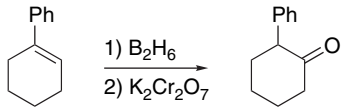
Conditions that permit oxidation of organoboranes to alcohols using other oxidants, including molecular oxygen,[210] sodium peroxycarbonate,[211] or amine

[210.] H. C. Brown, M. M. Midland, and G. W. Kabalka, *J. Am. Chem. Soc*. **93**, 1024 (1971).
[211.] G. W. Kabalka, P. P. Wadgaonkar, and T. M. Shoup, *Tetrahedron Lett.*, **30**, 5103 (1989).

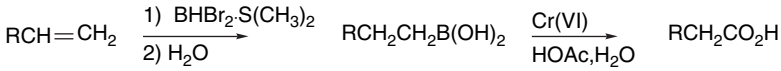
oxides[212] have been developed. Oxone® has been recommended for oxidations done on a large scale.[213] The reaction with molecular oxygen is particularly effective in perfluoroalkane solvents.[214]



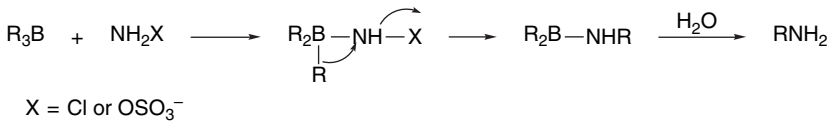
More vigorous oxidizing agents such as Cr(VI) reagents effect replacement of boron with oxidation to the carbonyl level.[215]



An alternative procedure for oxidation to ketones involves treatment of the alkylborane with a quaternary ammonium perruthenate salt and an amine oxide.[216] Use of dibromoborane-dimethyl sulfide for hydroboration of terminal alkenes followed by hydrolysis and Cr(VI) oxidation gives carboxylic acids.[217]



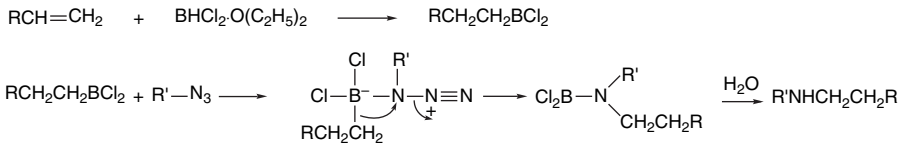
The boron atom can also be replaced by an amino group.[218] The reagents that effect this conversion are chloramine or hydroxylamine-*O*-sulfonic acid. The mechanisms of these reactions are very similar to that of the hydrogen peroxide oxidation of organoboranes. The nitrogen-containing reagent initially reacts as a nucleophile by adding at boron; then a B → N shift occurs with expulsion of chloride or sulfate. As in the oxidation, the migration step occurs with retention of configuration. The amine is freed from the borane by hydrolysis.



Secondary amines are formed by reaction of boranes with alkyl or aryl azides. The most efficient borane reagents are monoalkyldichloroboranes, which are generated by

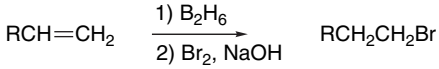
212. G. W. Kabalka and H. C. Hedgecock, Jr., *J. Org. Chem.*, **40**, 1776 (1975); R. Koster and Y. Monta, *Justus Liebigs Ann. Chem.*, **704**, 70 (1967).
213. D. H. B. Ripin, W. Cai, and S. T. Brenek, *Tetrahedron Lett.*, **41**, 5817 (2000).
214. I. Klement and P. Knochel, *Synlett*, 1004 (1996).
215. H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961); H. C. Brown, C. Rao, and S. Kulkarni, *J. Organomet. Chem.*, **172**, C20 (1979).
216. M. H. Yates, *Tetrahedron Lett.*, **38**, 2813 (1997).
217. H. C. Brown, S. V. Kulkarni, V. V. Khanna, V. D. Patil, and U. S. Racherla, *J. Org. Chem.*, **57**, 6173 (1992).
218. M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 2870 (1966); G. W. Kabalka, K. A. R. Sastry, G. W. McCollum, and H. Yoshioka, *J. Org. Chem.*, **46**, 4296 (1981).

the reaction of an alkene with $BHCl_2{\cdot}Et_2O$.[219] The entire sequence of steps and the mechanism of the final stages are summarized by the equation below.



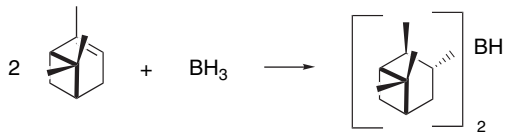
Secondary amines can also be made using the *N*-chloro derivatives of primary amines.[220]

Organoborane intermediates can also be used to synthesize alkyl halides. Replacement of boron by iodine is rapid in the presence of base.[221] The best yields are obtained using sodium methoxide in methanol.[222] If less basic conditions are desirable, the use of iodine monochloride and sodium acetate gives good yields.[223] As is the case in hydroboration-oxidation, the regioselectivity of hydroboration-halogenation is opposite to that observed with direct ionic addition of hydrogen halides to alkenes. Terminal alkenes give primary halides.



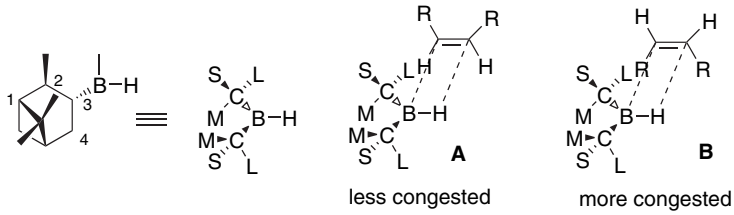
5.7.3. Enantioselective Hydroboration

Several alkylboranes are available in enantiomerically enriched or pure form and they can be used to prepare enantiomerically enriched alcohols and other compounds from organoborane intermediates.[224] The most thoroughly investigated of these boranes is *bis*-(isopinocampheyl)borane, $(Ipc)_2BH$, which can be prepared in 100% enantiomeric purity from the readily available terpene α-pinene.[225] Both enantiomers are available.



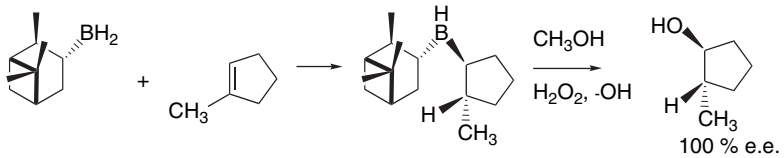
[219] H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **95**, 2394 (1973).
[220] G. W. Kabalka, G. W. McCollum, and S. A. Kunda, *J. Org. Chem.*, **49**, 1656 (1984).
[221] H. C. Brown, M. W. Rathke, and M. M. Rogic, *J. Am. Chem. Soc.*, **90**, 5038 (1968).
[222] N. R. De Lue and H. C. Brown, *Synthesis,* 114 (1976).
[223] G. W. Kabalka and E. E. Gooch, III, *J. Org. Chem.*, **45**, 3578 (1980).
[224] H. C. Brown and B. Singaram, *Acc. Chem. Res.*, **21**, 287 (1988); D. S. Matteson, *Acc. Chem. Res.*, **21**, 294 (1988).
[225] H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981); H. C. Brown and P. K. Jadhav, in *Asymmetric Synthesis*, Vol. 2, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 1.

$(Ipc)_2BH$ adopts a conformation that minimizes steric interactions. This conformation can be represented schematically, where the S, M, and L substituents are, respectively, the 3-H, 4-CH_2, and 2-$CHCH_3$ groups of the carbocyclic structure. The steric environment at boron in this conformation is such that *Z*-alkenes encounter less steric encumbrance in TS **A** than in **B**.

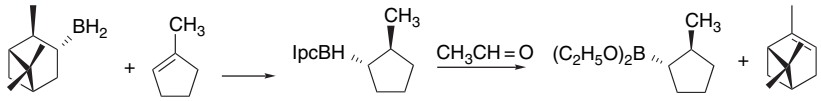


Z-2-Butene undergoes hydroboration with 98% enantioselectivity with $(Ipc)_2BH$.[226] Other *Z*-disubstituted alkenes give good enantioselectivity (75–90%) but *E*-alkenes and simple cycloalkenes give low enantioselectivity (5–30%).[227]

Monoisopinocampheylborane ($IpcBH_2$) can be prepared in enantiomerically pure form by purification of its TMEDA adduct.[228] When this monoalkylborane reacts with a prochiral alkene, one of the diastereomeric products is normally formed in excess and can be obtained in high enantiomeric purity by an appropriate separation.[229] Oxidation of the borane then provides the corresponding enantiomerically enriched alcohol.



As direct oxidation also converts the original chiral terpene–derived group to an alcohol, it is not directly reusable as a chiral auxiliary. Although this is not a problem with inexpensive materials, the overall efficiency of generation of enantiomerically pure product is improved by procedures that can regenerate the original terpene. This can be done by heating the dialkylborane intermediate with acetaldehyde. The α-pinene is released and a diethoxyborane is produced.[230] The usual oxidation conditions then convert this boronate ester to an alcohol.[231]



[226] H. C. Brown, M. C. Desai, and P. K. Jadhav, *J. Org. Chem.*, **47**, 5065 (1982).

[227] H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982).

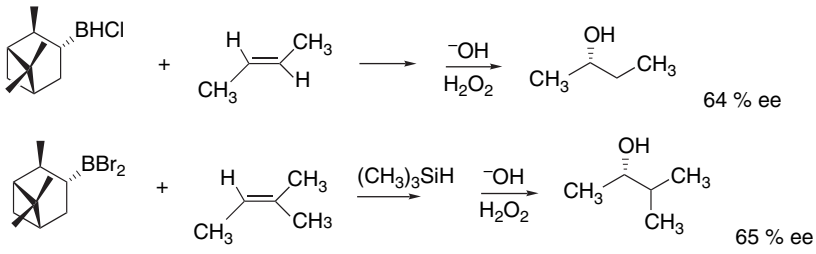
[228] H. C. Brown, J. R. Schwier, and B. Singaram, *J. Org. Chem.*, **43**, 4395 (1978); H. C. Brown, A. K. Mandal, N. M. Yoon, B. Singaram, J. R. Schwier, and P. K. Jadhav, *J. Org. Chem.*, **47**, 5069 (1982).

[229] H. C. Brown and B. Singaram, *J. Am. Chem. Soc.*, **106**, 1797 (1984); H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982).

[230] H. C. Brown, B. Singaram, and T. E. Cole, *J. Am. Chem. Soc.*, **107**, 460 (1985); H. C. Brown, T. Imai, M. C. Desai, and B. Singaram, *J. Am. Chem. Soc.*, **107**, 4980 (1985).

[231] D. S. Matteson and K. M. Sadhu, *J. Am. Chem. Soc.*, **105**, 2077 (1983).

The corresponding haloboranes are also useful for enantioselective hydroboration. Isopinocampheylchloroborane can achieve 45–80% e.e. with representative alkenes.[232] The corresponding bromoborane achieves 65–85% enantioselectivity with simple alkenes when used at −78 °C.[233]



5.8. Comparison of Electrophilic Addition Reactions

In this section, we make some broad comparisons among the electrophilic addition reactions that have been discussed. We have presented data on substituent effects, regioselectivity, and stereochemistry for protonation, halogenation, sulfenylation and selenenylation, epoxidation, mercuration, and hydroboration. What general trends and insights can be gained by comparing these reactions? There have been several efforts at elucidating correlations among the different reactions. Fukuzumi and Kochi showed that when steric effects are considered in a quantitative way, there is a strong correlation between bromination and mercuration rates.[234] Nelson and co-workers examined most of the reaction series and found correlations between the reactivity of various alkenes and the IP of the alkene. For some of these correlations, there were separate lines for mono- , di- , and trisubstituted alkenes, reflecting different steric environments.[235] We take a similar but less detailed look at relative reactivity of several representative alkenes. Figure 5.7 is a graph of the relative reactivity (with ethene as the standard) for the various reactions. The log of the relative reactivity, as shown in Table 5.9, is plotted against alkene IP. A separate symbol is used for each reaction. The alkenes are in order of decreasing IP.

We make comparisons based on these data in very broad terms. Looking first at protonation, represented in Figure 5.7 by circles, we see that reactivity rises sharply with substitution from ethene to propene to 2-methylpropene, but 2-methyl-2-butene and 2,3-dimethyl-2-butene have rates roughly similar to 2-methylpropene. *The degree of substitution at the more-substituted carbon is the major factor in reactivity*. We can surmise from this trend that *carbocation stability* is the major factor in determining the protonation rates. Note also that styrene is *more reactive* than propene, again consistent with carbocation stability as the major influence on reactivity. In terms of the Hammond postulate, the carbocation is a good model of the TS because the protonation step is substantially *endothermic* and the TS is late.

232. U. P. Dhokte, S. V. Kulkarni, and H. C. Brown, *J. Org. Chem.*, **61**, 5140 (1996).
233. U. P. Dhokte and H. C. Brown, *Tetrahedron Lett.*, **37**, 9021 (1996).
234. S. Fukuzumi and J. K. Kochi, *J. Am. Chem. Soc.*, **103**, 2783 (1981).
235. (a) D. J. Nelson and R. Soundararajan, *Tetrahedron Lett.*, **29**, 6207 (1988); (b) D. J. Nelson, P. J. Cooper, and R. Soundararajan, *J. Am. Chem. Soc.*, **111**, 1414 (1989); (c) D. J. Nelson, R. Li, and C. N. Brammer, *J. Org. Chem.*, **66**, 2422 (2001).

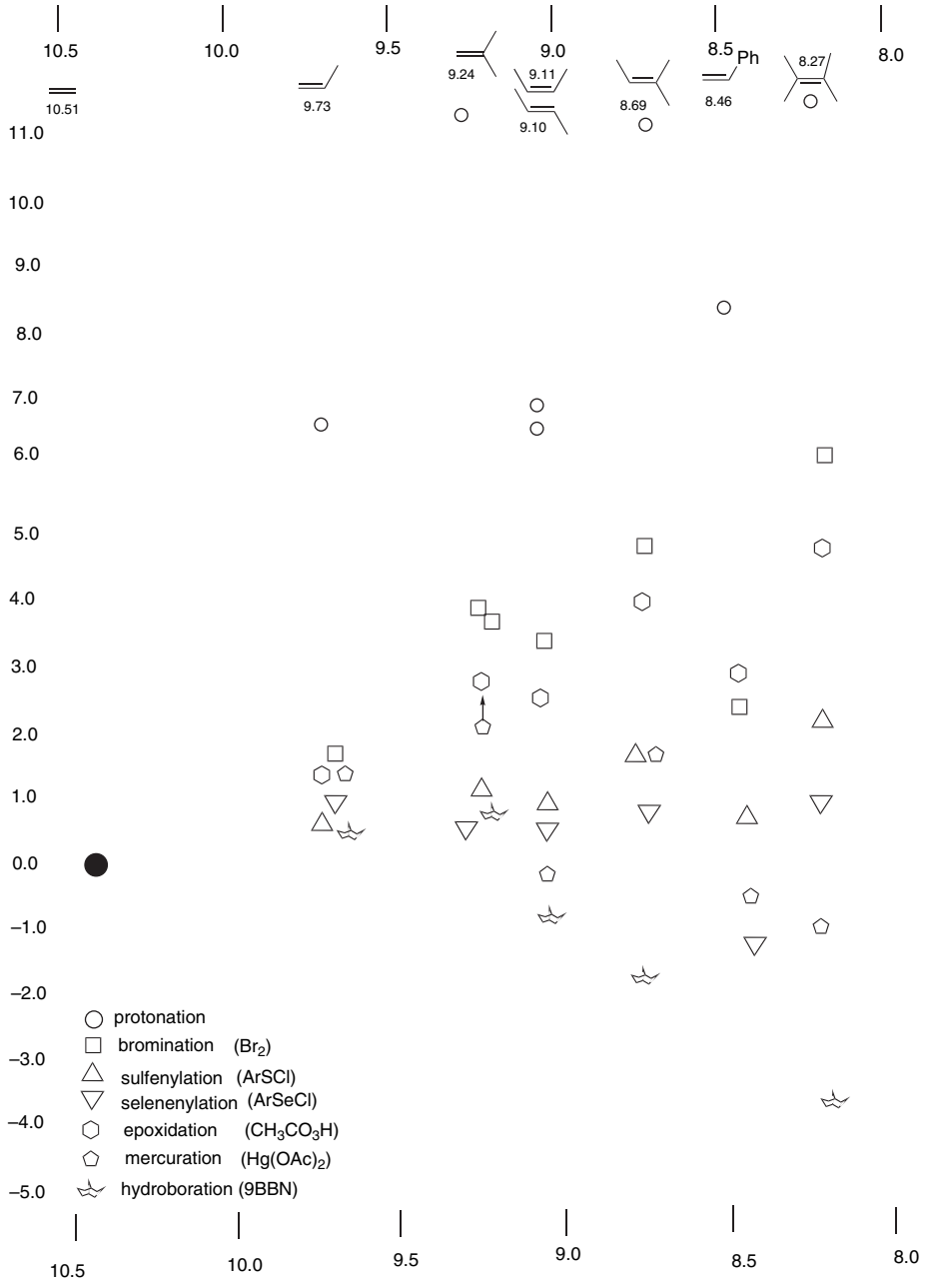


Fig. 5.7. Relationship between reactivity and IP for several alkenes.

Moving to bromination, represented by squares in the figure, we again see an increase of reactivity with alkyl substitution. Now, however, the *total number of substituents is important*. The rate continues to increase as substitution increases from ethene through 2,3-dimethyl-2-butene. This pattern is consistent with the more symmetrical (bridged) nature of the rate-determining TS. All of the substituents contribute to stabilization.

Table 5.9. Log of Relative Reactivity of Representative Alkenes.

Alkene	IP(ev)[a]	H^{+}[b]	Br_2[c]	ArSCl[d]	ArSeCl[d]	RCO_3H[e]	Hg^{2+}[f]	9-BBN[g]
Ethene	10.51	0	0	0	0	0	0	−−
Propene	9.73	6.2	1.8	0.50	0.94	1.3	1.3	0.3
2-Methylpropene	9.24	11.5	3.7	0.93	0.83	2.5	>2	0.6
Z-2-Butene	9.11	6.0	3.4	1.30	0.57	2.3	0.04	-1.0
E-2-Butene	9.10	6.4	3.2	0.82	0.32	2.3	−0.5	
Z-3-Hexene	9.0[h]							-1.2
E-3-Hexene	9.0[h]							-1.5
Cyclohexene	8.95	7.5				2.8	0.0	
2-Methyl-2-butene	8.69	11.2	5.1	1.6	0.57	3.8	1.6	-2.0
Styrene	8.46	8.2	2.4[i]	−0.03	−1.3	2.7	−0.6	
2,3-Dimethyl-2-butene	8.27	11.3	6.0	2.1	0.39	4.8	−1.2	-4.2

a. D. R. Lide, ed., *Handbook of Chemistry and Physics,* 83rd Edition, CRC Press, Boca Raton, FL, 2002, Sec. 10.
b. W. W. Chwang, V. J. Nowlan, and T. T. Tidwell, *J. Am. Chem. Soc.*, **99**, 7233 (1977); P. Knittel and T. T. Tidwell, *J. Am. Chem. Soc*. **99**, 3408 (1977)
c. J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1426 (1968).
d. G. H. Schmid and D. G. Garratt, in *The Chemistry of Double-Bonded Functional Groups*, Supplement A, Part 2, S. Patai, ed., Wiley, New York, 1977, Chap. 9.
e. M. H. Khalil and W. Pritzkow, *J. Prakt. Chem.*, **315**, 58 (1973); The 2-butene data is for *Z*- and *E*-2-pentene.
f. R. C. Larock, *Solvomercuration/Demercuration Reactions in Organic Synthesis*, Springer-Verlag, Berlin, 1986, pp. 86–87.
g. D. J. Nelson, P. J. Cooper, and R. Soundararajan, *J. Am. Chem. Soc.*, **111**, 1414 (1989). The relative rates for ethene, propene and 2-methylpropene are not available. The relative rate of propene was taken as equal to that of 1-hexene and estimated as 0.5. The value listed for 2-methylpropene is that given for 2-methyl-2-pentene.
h. Estimated from the tabulated value for the 2-hexene isomers.
i. M.-F. Ruasse, J. E. Dubois, and A. Argile, *J. Org. Chem.*, **44**, 1173 (1979).

The most noteworthy feature of the sulfenylation and selenenylation rates (represented by the triangles) is their much diminished sensitivity to substitution. This reflects both smaller electron demand in the TS and increased sensitivity to steric factors. The relatively low rate of styrene toward selenenylation is somewhat of an anomaly, and may reflect both ground state stabilization and steric factors in the TS. The epoxidation data (CH_3CO_3H, hexagons) show a trend similar to bromination, but with a reduced slope. There is no evidence of a rate-retarding steric component. One indicator of a strong steric component is decreased reactivity of the *E*-isomer in an *E*,*Z*−disubstituted alkene pair, but the rates for the 2-butene isomers toward epoxidation are very similar (Table 5.9).

Mercuration exhibits a carbocation-like pattern, but with the superposition of a large steric effect. For unsubstituted terminal carbons, the rate increases from ethene to propene to 2-methylpropene. This trend also holds for internal alkenes, as 2-methyl-2-butene is more reactive than 2-butene. However, steric effects become dominant for 2,3-dimethylbutene. This incursion of steric effects in oxymercuration has long been recognized and is exemplified by the results of Nelson and co-workers, who found separate correlation lines for mono- and disubstituted alkenes.[235b] Hydroboration by 9-BBN (structures) shows a different trend: steric effects are dominant and reactivity decreases with substitution. Similar trends apply to rates of addition of dibromoborane[236] and disiamylborane.[237] The importance of steric factors is no doubt due in part to the relatively bulky nature of these boranes. However, it also reflects a decreased electron demand in the hydroboration TS.

236. H. C. Brown and J. Chandrasekharan, *J. Org. Chem.*, **48**, 644 (1983).
237. J. Chandrasekharan and H. C. Brown, *J. Org. Chem.*, **50**, 518 (1985).

An overall perspective of the data in Table 5.9 and Figure 5.7 can be gained by simply comparing the relative rates of ethene and 2,3-dimethyl-2-butene. These go from very large for protonation ($10^{11.4}$) to small ($10^{-4.2}$) for hydroboration by 9-BBN as the dominance of carbocation stability effects for protonation is replaced by dominant steric effects for hydroboration by 9-BBN.

Another useful perspective from which to compare the electrophilic addition reactions is to focus on structure of the TS and intermediates. Figure 5.8 arranges the

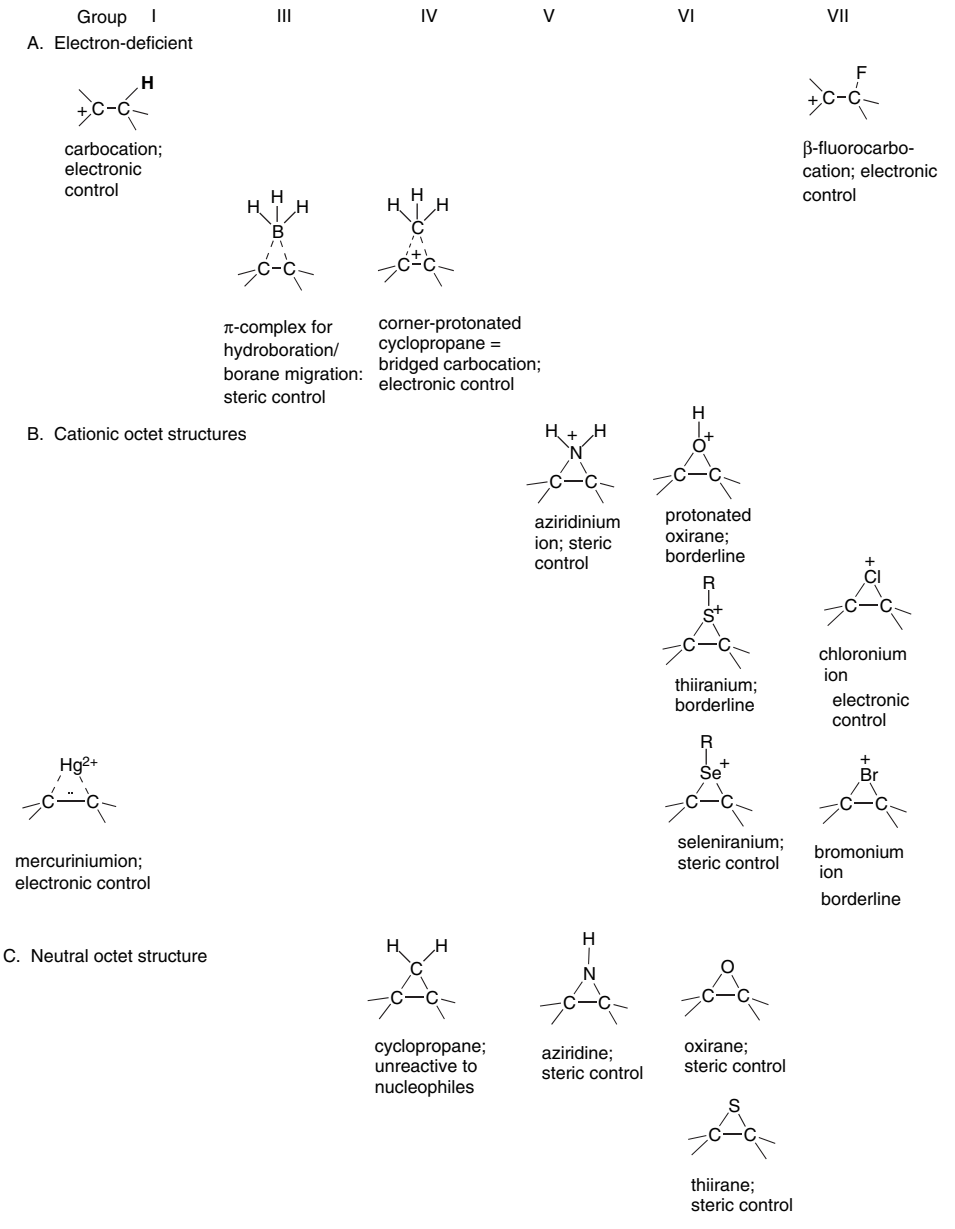
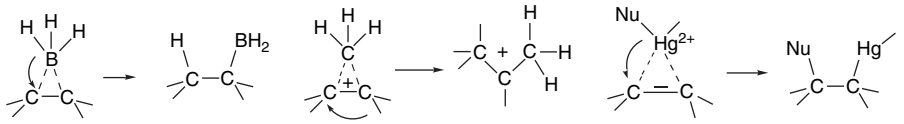


Fig. 5.8. Relationship between small ring structures and regiochemistry of addition reactions.

cationic and neutral species in relation to the periodic table. Some of these structures are stable products, others are reaction intermediates, and still other are transition structures. If the bridged and open versions of a species are comparable in energy, both are shown.

Taking the view that protonation of alkenes gives open carbocations, at least in solution, gives us a starting point for comparing the various addition reaction intermediates. From the discussion of carbocations in Chapter 4, we know the reactions that are characteristic of carbocations, namely nucleophilic capture, elimination of a proton, and rearrangement. These reactions are controlled by *electronic factors*, as illustrated by Markovnikov regioselectivity for nucleophile capture and Saytzeff regiochemistry for elimination. (see Section 4.4.3) The TSs for hydroboration and protonated cyclopropanes are related to open carbocations in being *electron deficient.* The hydroboration TS collapses by a hydride shift from boron to carbon that is driven by both electronegativity and steric factors. Corner-protonated cyclopropanes are converted to the carbocation best able to support positive charge. It is also clear from the mercuration reaction that a ligand transfer process is available when *anti*-nucleophilic addition is sterically hindered. The *syn* addition is similar to the hydride migration that occurs during hydroboration. The regiochemistry of the migration is dictated by electronic factors.



Moving to the right in the periodic table, aziridinium ions and protonated epoxides are no longer electron deficient, although they are electrophilic. Ring opening of aziridinium ions is normally controlled by *steric access*, because of the need for nucleophilic participation.[238] The regioselectivity of solvo-fluorination, by contrast, is subject to electronic control and strictly follows Markovnikov's rule because of the carbocationic character of the species (see p. 496). An O-protonated or Lewis acid–activated oxirane is borderline, with instances of both Markovnikov and anti-Markovnikov ring opening (see Section 5.5.2).

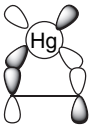
When we drop down to the next two rows of the periodic table, bridging becomes more important. For chloronium ions and bromonium ions (as in halohydrin formation; see p. 492), Markovnikov orientation (electronic control) usually prevails because the bridging bonds are relatively weak. However, the mixed regiochemistry of methoxybromination in methanol is an exception (see p. 493). For sulfenylation and selenenylation, the bridging bonds are stronger and anti-Markovnikov regiochemistry is frequently observed because nucleophilic engagement (steric access) is a critical feature for ring opening (see p. 499, 502). For the neutral small rings, cyclopropane is resistant to nucleophilic attack. Aziridines and epoxides are successively more reactive toward nucleophiles, but the regiochemistry is controlled by steric approach factors.

The proton that initiates acid-catalyzed addition processes is a hard acid and has no unshared electrons. It can form either a carbocation or a hydrogen-bridged cation. Both species are *electron deficient* and highly reactive. The formation of the cationic

238. C. M. Rayner, *Synlett*, 11 (1997).

intermediate is rate determining and nucleophilic capture is fast. The positive bromine in a bromonium ion intermediate is a softer electrophile and also has unshared electron pairs that permit a total of *four electrons* to participate in the bonding. The bromonium ion can be represented as having two covalent bonds to bromine and is *electrophilic* but not *electron deficient*. This results in a more strongly bridged and more stable species than is possible for the proton.

Where do mercuration reactions fit into this picture? A mercurinium ion has both similarities and differences, as compared with the intermediates that have been described for other electrophilic additions. The electrophile in oxymercuration reactions, ^{+}HgX or Hg^{2+}, is a soft Lewis acid and polarizes the π-electrons of an alkene to the extent that a three-center two-electron bond is formed between mercury and the two carbons of the double bond. However, there is also back bonding from Hg^{2+} *d* orbitals to the alkene π^* orbital. There is weaker bridging in the mercurinium ion than in the three-center four-electron bonding of the bromonium ion.



Cremer and Kraka have provided another perspective on the nature of some the cyclic structures represented in Figure 5.9 by focusing on the bond paths for the three-membered ring.[239] (See p. 63 to review the discussion of bond paths.) Neutral cyclopropane, aziridine, and oxirane rings are well described by the bent bond model, but the C−O bonds are somewhat less bent than those in cyclopropane. On the other hand, in protonated oxirane, the bonds begin to bend inward. For the bridged-fluorine species, there is no longer a ring; instead the structure is that of a π complex. (Remember, however, from p. 495 that a bridged fluoronium ion is unstable relative to the corresponding carbocation.) The differences in the nature of the bonds result from the relative ability of the bridging atom to donate electron density to the ring-forming orbitals, which is in the order $CH_2 > NH > O > O^{+}H > F^{+}$. These ideas are summarized in Figures 5.9.

5.9. Additions to Alkynes and Allenes

Reactions of alkynes with electrophiles are generally similar to those of alkenes. Since the HOMO of alkynes is also a π type orbital, it is not surprising that there is a good deal of similarity to the reactivity of alkenes.[240] The fundamental questions about additions to alkynes include the following: How reactive are alkynes in comparison with alkenes? What is the stereochemistry of additions to alkynes? What is the regiochemistry of additions to alkynes? The important role of bridged ions in addition reactions of alkenes raises the question of whether similar species are involved with alkynes, where the bridged intermediates includes a double bond and would be expected to be substantially more strained.

239. D. Cremer and E. Kraka, *J. Am. Chem. Soc.*, **107,** 3800 (1985).
240. G. H. Schmid, *The Chemistry of the Carbon-Carbon Triple Bond*, Part. 1, S. Patai, ed., Wiley, New York, 1978, Chap. 3.

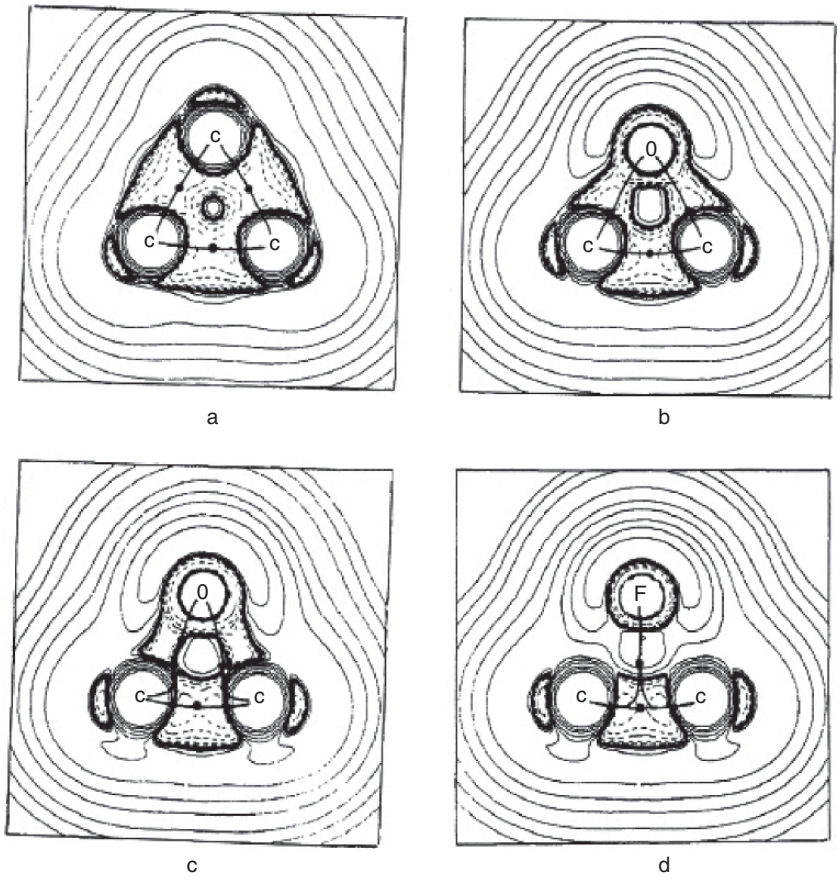
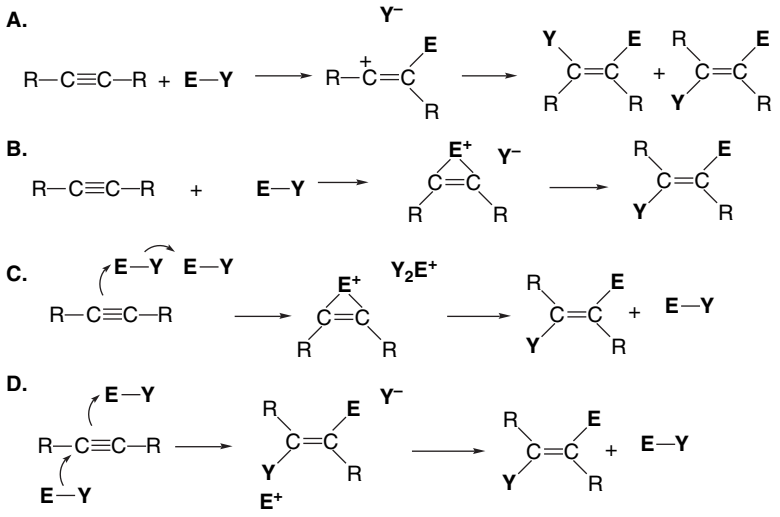


Fig. 5.9. Molecular graphs showing the Laplacian $-\nabla^2\rho(\mathbf{r})$ and bond paths. Bond paths are shown as solid lines and bond critical points as dots. Dashed contours show areas of electronic charge concentration and solid contours show regions of charge depletion. (a) cyclopropane, (b) oxirane, (c) protonated oxirane, and (d) fluorine-bridged cation. Reproduced from *J. Am. Chem. Soc.*, **107**, 3800 (1985), by permission of the American Chemical Society.

The basic mechanisms that are considered to be involved in electrophilic additions to alkynes are outlined below. The first, Mechanism A, involves a discrete vinyl cation. In general, this reaction will lead to a mixture of the two stereoisomeric addition products. Mechanisms **B** and **C** depict bridged intermediates formed without **(B)** or with **(C)** participation of a second electrophilic molecule. Mechanisms **B** and **C** should lead to *anti* addition. Mechanism **D** is a termolecular process that would be expected to be a stereospecific *anti* addition. Mechanisms **A** and **B** are of the Ad_E2 type, whereas **C** and **D** are classified as Ad_E3. Each of these mechanisms may involve a prior complex formation between the alkyne and an electrophile.



In general, alkynes are somewhat less reactive than alkenes toward many electrophiles. A major reason for this difference in reactivity is the substantially higher energy of the vinyl cation intermediate that is formed by an electrophilic attack on an alkyne. It is estimated that vinyl cations are about 10 kcal/mol less stable than an alkyl cation with similar substitution (see p. 300). For additions that proceed through bridged intermediates, the alkynes are also less reactive because of additional strain in the intermediate. The differences in the rate of addition between alkenes and alkynes depends upon the specific electrophile and the reaction conditions.[241] Table 5.10 summarizes some specific rate comparisons. These results show large differences for bromination and chlorination but relatively small differences for protonation. The presence of a carbocation-stabilizing phenyl group reduces the difference for bromination and chlorination.

5.9.1. Hydrohalogenation and Hydration of Alkynes

Hydrogen chloride adds to aryl alkynes in acetic acid to give mixtures of α–chlorostyrenes and the corresponding vinyl acetate.[242] A vinyl cation, which is stabilized by the aryl substituent, is believed to be an intermediate. The ion pair formed by

Table 5.10. Relative Reactivity of Alkenes and Alkynes[a]

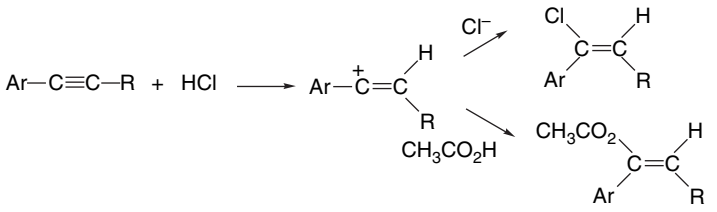
Alkene/alkyne pair	Bromination, HOAc	Chlorination, HOAc	Acid-catalyzed hydration
1-Hexene/1-hexyne	1.8×10^5	5.3×10^5	3.6
E-3-Hexene/3-hexyne	3.4×10^5	$\sim 1 \times 10^5$	16.6
Styrene/phenylethyne	2.6×10^3	7.2×10^2	0.65

a. From data tabulated in ref. 241.

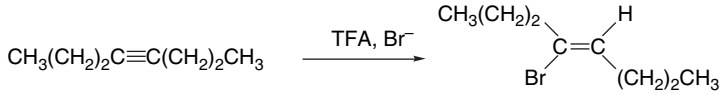
241. K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H.-W. Leung, and R. McDonald, *J. Am. Chem. Soc.*, **95**, 160 (1973).

242. R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.*, **90**, 2124 (1968).

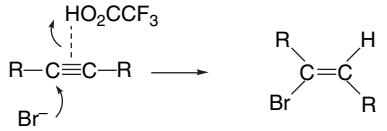
protonation can either collapse to give the vinyl halide or capture solvent to give the acetate. Aryl-substituted acetylenes give mainly the *syn* addition product.



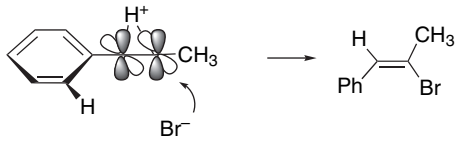
Alkyl-substituted acetylenes can react with HCl by either the Ad_E3 or the Ad_E2 mechanism. The Ad_E3 mechanism leads to *anti* addition. The preference for one or the other mechanism depends on the reactant structure and the reaction conditions. Added halide ion promotes the Ad_E3 mechanism and increases the overall rate of reaction.[243] Reaction of 4-octyne with TFA in CH_2Cl_2 containing 0.1–1.0 *M* Br^- leads mainly to *Z*-4-bromo-4-octene by an *anti* addition. The presence of Br^- greatly accelerates the reaction as compared to reaction with TFA alone, indicating the involvement of the Br^- in the rate-determining protonation step.[244]



1-Octyne and 2-octyne also give more than 95% *anti* addition under these conditions. The reactions are formulated as concerted Ad_E3 processes, involving bromide attack on an alkene-acid complex.



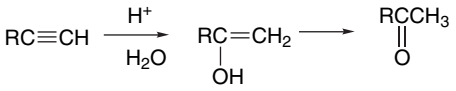
Under these conditions, 1-arylalkynes react by a mixture of Ad_E2 and Ad_E3 mechanisms with the proportion of Ad_E3 reaction increasing with increasing bromide concentration and decreasing effective acidity.[245] The Ad_E3 reaction of 1-phenylpropyne gives the anti-Markovnikov product. This is believed to be due to a steric effect of the phenyl group.



Compared to alkene additions carried out under similar conditions, there is less likely to be involvement of a cationic intermediate because of the higher energy of the vinyl cation (see Section 3.4.1).

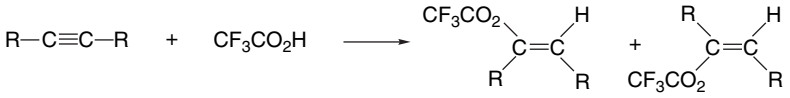
243. R. C. Fahey, M. T. Payne, and D.-J. Lee, *J. Org. Chem.*, **39**, 1124 (1974).
244. H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1523 (1998).
245. H. M. Weiss, K. M. Touchette, F. Andersen, and D. Iskhakov, *Org. Biomol. Chem.*, **1**, 2148 (2003); H. M. Weiss, K. M. Touchette, S. Angell, and J. Khan, *Org. Biomol. Chem.*, **1**, 2152 (2003).

Alkynes can be hydrated in concentrated aqueous acid solutions. The initial product is an enol, which isomerizes to the more stable ketone.



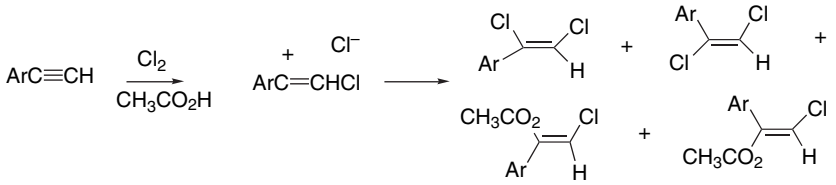
Alkynes are somewhat less reactive than alkenes. For example, 1-butene is 20 times more reactive than 1-butyne in 8.24 *M* H_2SO_4.[246] Alkyne reactivity increases with the addition of ERG substituents. Solvent isotope effects are indicative of a rate-determining protonation.[247] These reactions are believed to proceed by rate-determining proton transfer to give a vinyl cation. Reactions proceeding through a vinyl cation would not be expected to be stereospecific, since the cation will adopt *sp* hybridization (see Section 3.4.1).

Alkynes react when heated with TFA to give addition products. Mixtures of *syn* and *anti* addition products are obtained.[248] Similar addition reactions occur with trifluoromethanesulfonic acid.[249] These reactions are analogous to acid-catalyzed hydration and proceed through a vinyl cation intermediate.



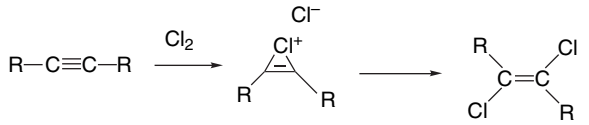
5.9.2. Halogenation of Alkynes

Alkynes undergo addition reactions with halogens. In the presence of excess halogen, tetrahaloalkanes are formed but mechanistic studies can be carried out with a limited amount of halogen so that the first addition step can be characterized. In general, halogenation of alkynes is slower than for the corresponding alkenes. We consider the reason for this later. The reaction shows typical characteristics of an electrophilic reaction. For example, the rates of chlorination of substituted phenylacetylenes are correlated by σ^+ with $\rho = -4.2$. In acetic acid, the reaction is overall second order, first order in both reactants. The addition is not very stereoselective and a considerable amount of solvent capture product is formed. All of these features are consistent with the reaction proceeding through a vinyl cation intermediate.[250]



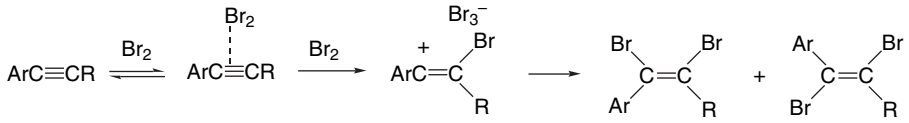
246. A. D. Allen, Y. Chiang, A. J. Kresge, and T. T. Tidwell, *J. Org. Chem.*, **47**, 775 (1982).
247. P. Cramer and T. T. Tidwell, *J. Org. Chem.*, **46**, 2683 (1981).
248. P. E. Peterson and J. E. Dudley, *J. Am. Chem. Soc.*, **88**, 4990 (1966); R. H. Summerville and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 1110 (1974).
249. P. J. Stang and R. H. Summerville, *J. Am. Chem. Soc.*, **91**, 4600 (1969); R. H. Summerville, C. A. Senkler, P. v. R. Schleyer, T. E. Dueber, and P. J. Stang, *J. Am. Chem. Soc.*, **96**, 100 (1974); R. H. Summerville and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 1110 (1974); G. I. Crisp and A. G. Meyer, *Synthesis*, 667 (1974).
250. K. Yates and T. A. Go, *J. Org. Chem.*, **45**, 2377, 2385 (1980).

For alkyl-substituted alkynes, there is a difference in stereochemistry between mono- and disubstituted derivatives. The former give *syn* addition, whereas the latter react by *anti* addition. The disubstituted (internal) compounds are considerably (~ 100 times) more reactive than the monosubstituted (terminal) ones. This result suggests that the TS of the rate-determining step is stabilized by *both* alkyl substituents and points to a bridged structure. This interpretation is consistent with the *anti* stereochemistry of the reaction for internal alkynes.

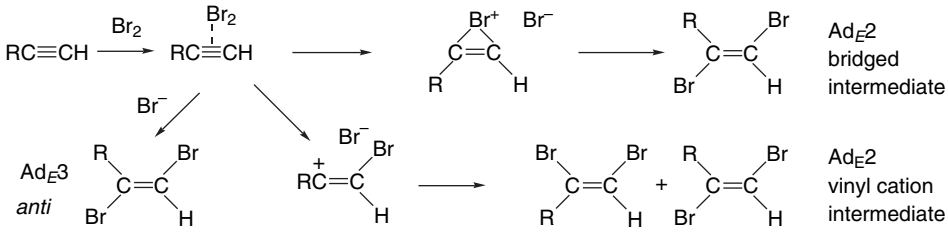


The monosubstituted intermediates do not seem to be effectively bridged, since *syn* addition predominates. A very short-lived vinyl cation appears to be the best description of the intermediate in this case.[251]

The stereochemistry of bromination is usually *anti* for alkyl-substituted alkynes.[252] A series of substituted arylalkynes has been examined in dichloroethane.[253] As with alkenes, a π-complex intermediate was observable. The ΔH for formation of the complex with 1-phenylpropyne is about -3.0 kcal/mol. The overall kinetics are third order, as for an Ad_E3 mechanism. The rate-determining step is the reaction of Br_2 with the π complex to form a vinyl cation, and both *syn* and *anti* addition products are formed.



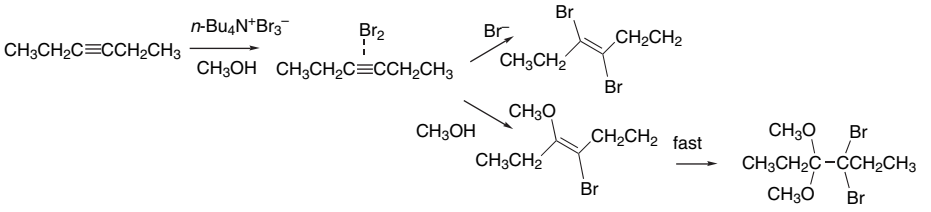
For the aryl-substituted alkynes, the reaction stereochemistry is sensitive to the aryl substitution. With EWG substituents (NO_2, CN) the reaction becomes stereospecifically *anti* and the same is true for 2-hexyne, reflecting the diminished stability of the vinyl cation in these cases. Aryl-substituted alkynes can be shifted toward *anti* addition by including a bromide salt in the reaction medium. Under these conditions, a species preceding the vinyl cation must be intercepted by a bromide ion. This intermediate is presumably the complex of molecular bromine with the alkyne. An overall mechanistic summary is shown in the following equations.



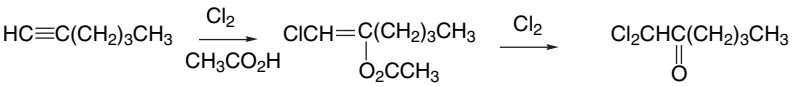
[251] K. Yates and T. A. Go, *J. Org. Chem.*, **45**, 2385 (1980).
[252] J. A. Pincock and K. Yates, *Can. J. Chem.,* **48**, 3332 (1970).
[253] R. Bianchini, C. Chiappe, G. Lo Moro, D. Lenoir, P. Lemmen, and N. Goldberg, *Chem. Eur. J.*, 1570 (1999).

This scheme shows an alkyne-bromine complex as an intermediate in all alkyne brominations, which is analogous to the case of alkenes. The complex may dissociate to a vinyl cation when the cation is sufficiently stable, as is the case when there is an aryl substituent. It may collapse to a bridged bromonium ion or undergo reaction with a nucleophile. The latter is the dominant reaction for alkyl-substituted alkynes and leads to stereospecific *anti* addition. Reactions proceeding through vinyl cations are nonstereospecific.

As for alkenes, the alkyne-Br_2 complex can be intercepted by nucleophilic solvent. Alkynes react with *n*-$Bu_4N^+Br_3^-$ in methanol to give a mixture of dimethoxydibromo and *E*-dibromo products. A key aspect of this reaction is the high reactivity of the methoxybromo intermediate, which is more reactive than the starting material. Evidently, the dibromo intermediate is unreactive toward Br_3^-.[254]



Chlorination of 1-hexyne in acetic acid gives mainly to 1,1-dichlorohexan-2-one via chlorination and deacetylation of the initial product, 2-acetoxy-1-chlorohexene.



The corresponding intermediate, *E*-3-acetoxy-4-chlorohexene can be isolated from 3-hexyne.[255]

The rates of bromination of a number of alkynes have been measured under conditions that permit comparison with the corresponding alkenes. The rate of bromination of styrene exceeds that of phenylacetylene by about 10^3.[256] For dialkylacetylene-disubstituted alkene comparisons, the ratios range from 10^3 to 10^7, being greatest in the least nucleophilic solvents.[257] Bromination of alkyl-substituted alkynes shows rate enhancement by both alkyl substituents, and this indicates that the TS has bridged character.[258] Remember (p. 512) that alkene bromination was similar in this respect. The lower reactivity of the alkynes is probably due to a combination of factors including greater strain in the bridged TS and reduced electron-donating capacity of alkynes. The IP of 2-butyne (9.6 eV), for example, is considerably higher than that of 2-butene (9.1 eV).

MP2/6-311+G** and B3LYP/6-311+G** computations have been used to compare the stability of the Br_2 complexes with ethene, ethyne, and allene. The computed

254. J. Berthelot, Y. Benammar, and B. Desmazieres, *Synth. Commun.*, **27**, 2865 (1997).

255. G. E. Heasley, C. Codding, J. Sheehy, K. Gering, V. L. Heasley, D. F. Shellhamer, and T. Rempel, *J. Org. Chem.*, **50**, 1773 (1985).

256. M.-F. Ruasse and J.-E. Dubois, *J. Org. Chem.*, **42**, 2689 (1977).

257. K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H.-W. Leung, and R. McDonald, *J. Am. Chem. Soc.*, **95**, 160 (1973); J. M. Kornprobst and J.-E. Dubois, *Tetrahedron Lett.*, 2203 (1974); G. Modena, F. Rivetti, and U. Tonellato, *J. Org. Chem.*, **43**, 1521 (1978).

258. G. H. Schmid, A. Modro, and K. Yates, *J. Org. Chem.*, **45**, 665 (1980).

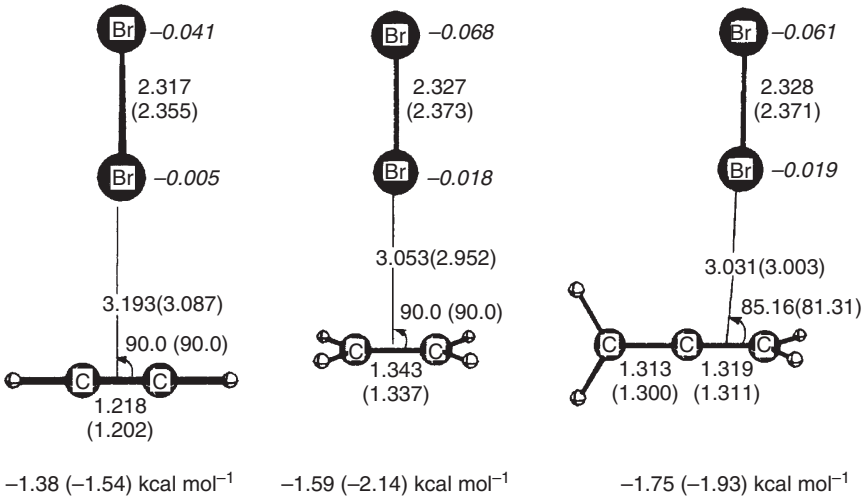
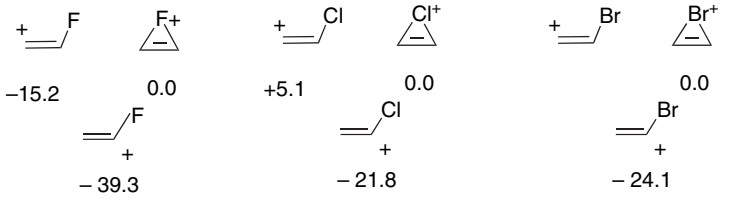


Fig. 5.10. Optimized structures and ΔE for formation of (a) ethyne-Br_2, (b) ethene-Br_2, and (c)allene-Br_2 complexes. Values of ΔE from MP2/6-311+G** and B3LYP/6-311G** (the latter in parentheses). Reproduced from *Chem. Eur. J.*, 967 (2002), by permission of Wiley-VCH.

structures and ΔE for formation of the complex are shown in Figure 5.10.[259] The structures and energies are quite similar. This indicates that it is the formation of the cationic intermediate that is more difficult for alkynes.

Calculations comparing the open β-halovinyl and bridged cations have been reported using MP2/6-311G++(3*df*,3*pd*)- and B3LYP/6-31+G(*d*)-level computations.[260] The bridged ions are found to be favored for chlorine and bromine but the open ion is favored for fluorine. The β-chloro and β-bromovinyl cations are found not to be minima. They rearrange to the much more stable α-halovinyl cations by a hydride shift. The bridged ions tend to be more strongly stabilized by solvation than the open ions. As was noted for the halonium ions derived from alkenes (p. 495), the charge on halogen is positive for Cl and Br, but negative for F.



When a methyl group is added, the vinyl cation is favored. The open cation was also favored for ions derived from 2-butyne.

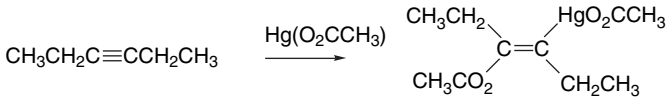
Computational studies have also explored the issue of how the π complex is converted to the intermediate and several potential mechanisms have been described.[261]

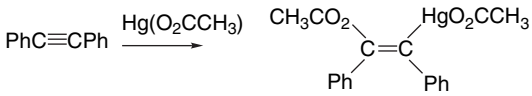
259. C. Chiappe, A. de Rubertis, H. Detert, D. Lenoir, C. S. Wannere, and P. v. R. Schleyer, *Chem. Eur. J.*, 967 (2002).
260. T. Okazaki and K. K. Laali, *J. Org. Chem.*, **70**, 9139 (2005).
261. R. Herges, A. Papafilippopoulos, K. Hess, C. Chiappe, D. Lenoir, and H. Detert, *Angew. Chem. Int. Ed.*, **44**, 1412 (2005); M. Zabalov, S. S. Karlov, D. A. Le menovskii, and G. S. Zaitseva, *J. Org. Chem.*, **70**, 9175 (2005).

A salient result of these studies is that ionization is energetically prohibitive, at least in the gas phase. This finding is consistent with experimental studies that indicate strong acceleration in polar solvents or in the presence of acids that can facilitate ionization.

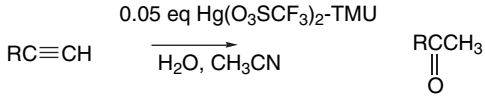
5.9.3. Mercuration of Alkynes

Alkynes react with mercuric acetate in acetic acid to give addition products. For 3-hexyne the product has *E*-stereochemistry but the *Z*-isomer is isolated from diphenylacetylene.[262] The kinetics of the addition reactions are first order in both alkyne and mercuric acetate.[263]





The most common synthetic application of mercury-catalyzed addition to alkynes is the conversion of alkynes to ketones. This reaction is carried out under aqueous conditions, where the addition intermediate undergoes protonation to regenerate Hg^{2+}. Mercuric triflate has been found to be a useful reagent for this reaction.[264]



5.9.4. Overview of Alkyne Additions

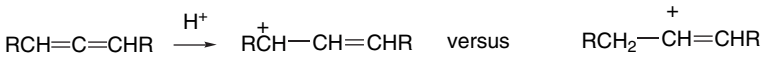
We can understand many of the general characteristics of electrophilic additions to alkynes by recognizing the possibility for both bridged ions and vinyl cations as intermediates. Reactions proceeding through vinyl cations are expected to be nonstereospecific, with the precise stereochemistry depending upon the lifetime of the vinyl cation and the identity and concentration of the potential nucleophiles. Stereospecific *anti* addition is expected from processes involving nucleophilic attack on either a bridged ion intermediate or an alkyne-electrophile complex. These general mechanisms also explain the relative reactivity of alkenes and alkynes in comparable addition processes. In general, reactions that proceed through vinyl cations, such as those involving rate-determining protonation, are only moderately slower for alkynes as compared to similar alkenes. This is attributed to the somewhat higher energy of vinyl cations compared to cations with sp^2 hybridization. It has been estimated that this difference for secondary ions is around 10–15 kcal/mol, a significant but not an

262. R. D. Bach, R. A. Woodard, T. J. Anderson, and M. D. Glick, *J. Org. Chem.*, **47**, 3707 (1982).
263. M. Bassetti and B. Floris, *J. Org. Chem.*, **51**, 4140 (1986).
264. M. Nishizawa, M. Skwarczynski, H. Imagawa, and T. Sugihara, *Chem. Lett.*, 12 (2002).

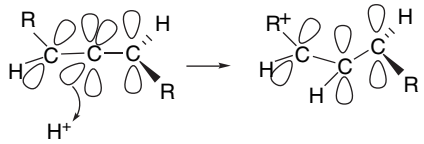
enormous difference,[265] which is partially compensated by the higher ground state energy of the alkynes. Reactions that proceed through TSs leading to bridged intermediates typically show much greater rate retardation for the alkyne addition. Bromination is the best studied example of this type. The lower rate reflects the greater strain of bridged species in the case of alkynes. Bridged intermediates derived from alkynes must incorporate a double bond in the three-membered ring.[266] The activation energies for additions to alkynes through bridged intermediates are thus substantially greater than for alkenes.

5.9.5. Additions to Allenes

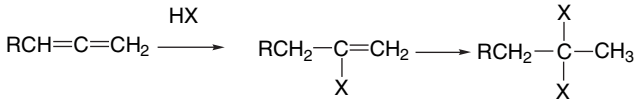
Electrophilic additions to allenes represent an interesting reaction type that is related to additions to both alkenes and alkynes.[267] An allene could, for example, conceivably be protonated at either a terminal sp^2 carbon or the central sp carbon.



The allylic carbocation resulting from protonation of the center carbon might seem the obvious choice but, in fact, the kinetically favored protonation at a sp^2 carbon leads to the vinyl cation intermediate. The reason for this is stereoelectronic. The allene structure is nonplanar, so that a protonation of the center carbon leads to a twisted structure that lacks of allylic conjugation. This twisted cation is calculated to be about 36–38 kcal/mol higher in energy than the cation formed by protonation at a terminal carbon.[268]



Consistent with this generalization, addition of hydrogen halides to terminal allenes initially gives the vinyl halide; if the second double bond reacts, a geminal dihalide is formed.[269] The regioselectivity of the second step is consistent with Markovnikov's rule because a halogen atom can stabilize a carbocation by resonance (see Section 3.4.1).



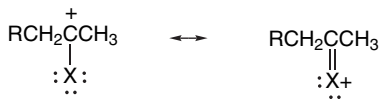
[265] Z. Rappoport, in *Reactive Intermediates*, Vol. 3, R. A. Abramovitch, ed., Plenum Press, New York, 1985, Chap. 7; Y. Apeloig and T. Muller, in *Dicoordinated Carbocations*, Z. Rappoport and P. J. Stang, eds., John Wiley & Sons, New York, 1997, Chap. 2.

[266] G. Melloni, G. Modena, and U. Tonellato, *Acc. Chem. Res.,* **8**, 227 (1981).

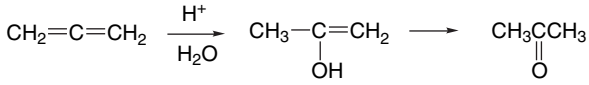
[267] For a review of electrophilic additions to allenes, see W. Smadja, *Chem. Rev.*, **83**, 263 (1983).

[268] K. B. Wiberg, C. M. Breneman, and T. J. Le Page, *J. Am. Chem. Soc.*, **112**, 61 (1990); A. Gobbi and G. Frenking, *J. Am. Chem. Soc.*, **116**, 9275 (1994).

[269] T. L. Jacobs and R. N. Johnson, *J. Am. Chem. Soc.*, **82**, 6397 (1960); R. S. Charleston, C. K. Dalton, and S. R. Schraeder, *Tetrahedron Lett.*, 5147 (1969); K. Griesbaum, W. Naegle, and G. G. Wanless, *J. Am. Chem. Soc.*, **87**, 3151 (1965).

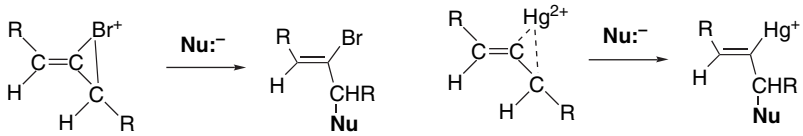


Strong acids in aqueous solution convert allenes to ketones via an enol intermediate. This process also involves protonation at a terminal carbon.



The kinetic features of this reaction, including the solvent isotope effect, are consistent with a rate-determining protonation to form a vinyl cation.[270]

Allenes react with other typical electrophiles such as the halogens and mercuric ion. In systems where bridged ion intermediates would be expected, nucleophilic capture generally occurs at the allylic position. This pattern is revealed, for example, in the products of solvent capture in halogen additions[271] and by the structures of mercuration products.[272]

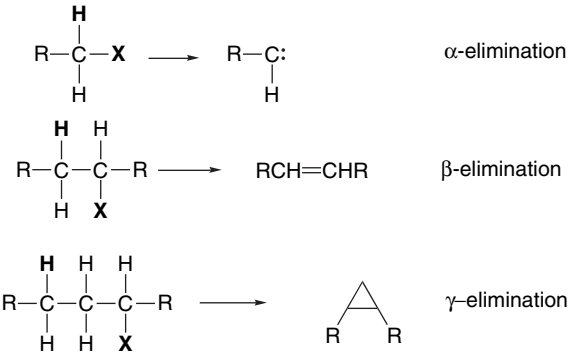


5.10. Elimination Reactions

Elimination reactions involve the removal of another molecule from a reactant. In this section we focus on polar elimination reactions involving heterolytic bond breaking. A fundamental example involves deprotonation in conjunction with expulsion of a good leaving group, such as dehydrohalogenation. Elimination reactions can be classified according to the structural relationship between the proton and the leaving group. The products of α eliminations are unstable divalent carbon species called carbenes, which are discussed in Chapter 10 of Part B. Here attention is focused on ß-elimination reactions that lead to formation of carbon-carbon double bonds.[273]

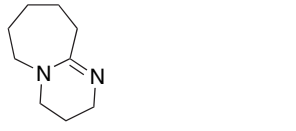
270. P. Cramer and T. T. Tidwell, *J. Org. Chem.*, **46**, 2683 (1981).
271. H. G. Peer, *Recl. Trav. Chim. Pays-Bas*, **81**, 113 (1962); W. R. Dolbier, Jr., and B. H. Al-Sader, *Tetrahedron Lett.*, 2159 (1975).
272. W. Waters and E. F. Kieter, *J. Am. Chem. Soc.*, **89**, 6261 (1967).
273. Reviews: J. R. Gandler, in *The Chemistry of Double-bonded Functional Groups*, S. Patai, ed., Wiley-Interscience, New York, 1989, Chap. 12; E. Baciocchi, in *Chemistry of Halides, Pseudo-Halides and Azides*, Part 2, S. Patai and Z. Rappoport, eds., Wiley-Interscience, New York, 1983, Chap. 23; W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley, New York, 1973; D. J. McLennan, *Tetrahedron*, **31**, 2999 (1975).

Eliminations of γ- and higher leaving groups result in *cyclization*; mechanistically they are intramolecular nucleophilic displacements.



Some representative examples of ß-elimination reactions are given in Scheme 5.2. Entry 1 is a typical dehydrohalogenation that involves no issue of regioselectivity or stereoselectivity. With primary reactants, the main competing reaction is substitution. The base used in Entry 1 ($K^+ \cdot^-$ O-*t*-Bu) favors elimination over substitution, as compared with less branched alkoxides. Entry 2 illustrates the issues of regiochemistry and stereochemistry that can arise, even with a relatively simple reactant and also shows that substitution can compete with elimination in unhindered systems. Entry 3 shows the use of a very hindered alkoxide to favor the less-substituted product. The strong organic bases DBU[274] and DBN[275] can also effect dehydrohalogenation, as illustrated by Entry 4. These bases are particularly effective for reactants that are easily ionized, such as tertiary halides.

DBN
1,3-diazabicyclo[3.2.0]nonene



DBU
1,3-diazabicyclo[4.3.0]undecene

Entry 5 is a case in which the carbanion-stabilizing effect of a carbonyl group facilitates elimination by a relatively weak base and controls regiochemistry by favoring deprotonation of the α-carbon. Entries 6 and 7 are tosylate eliminations. Generally speaking, tosylates give a higher proportion of substitution than do halides.[276] Entries 8 and 9 are examples of the *Hofmann elimination reaction*, which is a case where the relatively poor and bulky leaving group (trimethylamine) leads to a preference for formation of the less-substituted alkene (see Section 5.10.2).

In the sections that follow, we discuss the mechanisms of these and related reactions and explore the relationship between mechanism and regio-/stereoselectivity. We also look at some examples that illustrate how choice of reactant, reagent, and solvent can influence the outcome of the reaction.

274. H. Oediger and F. Moeller, *Angew. Chem. Int. Ed. Engl.*, **6**, 76 (1967); P. Wolkoff, *J. Org. Chem.*, **47**, 1944 (1982).
275. H. Oediger, H. J. Kabbe, F. Moeller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).
276. P. Veeravagu, R. T. Arnold, and E. W. Eigenmann, *J. Am. Chem. Soc.*, **86**, 3072 (1964).

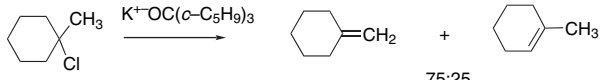
Scheme 5.2. Representative β-Elimination Reactions

A. Dehydrohalogenation

1[a] $CH_3(CH_2)_{15}CH_2CH_2Br \xrightarrow[(CH_3)_3COH]{K^+{}^-OC(CH_3)_3} CH_3(CH_2)_{15}CH{=}CH_2$ 85%

2[b] $CH_3(CH_2)_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[CH_3OH]{Na^+{}^-OCH_3} CH_3(CH_2)_4CH{=}CH_2 + CH_3CH_2CH_2CH{=}CHCH_3 + CH_3(CH_2)_2CH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_3$

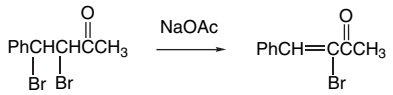
19% 55%; *E*:*Z* = 3.6 26%

3[c] 

75:25

4[d] $(CH_3)_2CH\underset{\displaystyle Br}{\underset{|}{C}}(CH_3)_2 \xrightarrow{DBU} (CH_3)_2C{=}C(CH_3)_2 + (CH_3)_2CHC(CH_3){=}CH_2$

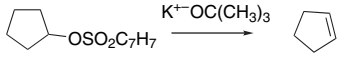
92:8

5[e] 

64–73%

B. Dehydrosulfonation

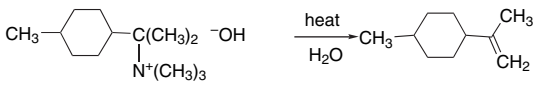
6[f] $Ph_2CHCH_2OSO_2C_7H_7 \xrightarrow{Na^+{}^-OCH_3} Ph_2C{=}CH_2$ 92%

7[g] 

76%

C. Eliminations of Quaternary Ammonium Hydroxides

8[h] $(CH_3)_3CCH_2CH_2N^+(CH_3)_3\ {}^-OH \xrightarrow{heat} (CH_3)_3CCH{=}CH_2$ 81%

9[i] 

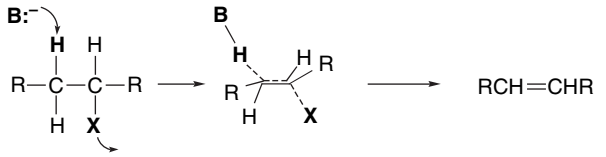
98%

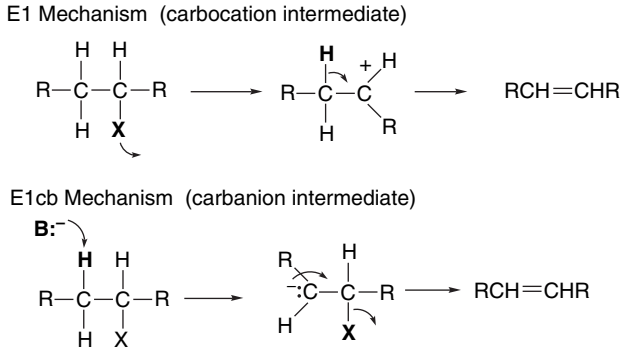
a. P. Veeragu, R. T. Arnold, and E. W. Eigemann, *J. Am. Chem. Soc.*, **86**, 3072 (1964).
b. R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.*, **90**, 408 (1968).
c. S. A. Acharya and H. C. Brown, *J. Chem. Soc., Chem. Commun.*, 305 (1968).
d. P. Wolkoff, *J. Org. Chem.*, **47**, 1944 (1982).
e. N. H. Cromwell, D. J. Cram, and C. E. Harris, *Org. Synth.*, **III**, 125 (1953).
f. P. J. Hamrick, Jr., and C. R. Hauser, *J. Org. Chem.*, **26**, 4199 (1961).
g. C. H. Snyder and A. R. Soto, *J. Org. Chem.*, **29**, 742 (1964).
h. A. C. Cope and D. L. Ross, *J. Am. Chem. Soc.*, **83**, 3854 (1961).
i. L. C. King, L. A. Subluskey, and E. W. Stern, *J. Org. Chem.*, **21**, 1232 (1956).

5.10.1. The E2, E1 and E1cb Mechanisms

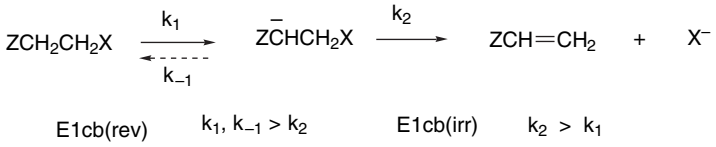
The ß-eliminations can be subdivided on the basis of the mechanisms involved. Three distinct limiting mechanisms are outlined below.

E2 Mechanism (concerted)





The E2 mechanism involves a bimolecular TS in which removal of a proton ß to the leaving group is concerted with departure of the leaving group. The rate-determining step in the E1 mechanism is the unimolecular ionization of the reactant to form a carbocation intermediate. This is the same process as the rate-determining step in the S_N1 mechanism. Elimination is completed by removal of a ß-proton. The E1cb mechanism, like the E1, involves two steps, but the order is reversed. Deprotonation, forming a carbanion intermediate, precedes expulsion of the leaving group. E1cb mechanisms can be subdivided into $E1cb_{(irr)}$ and $E1cb_{(rev)}$, depending on whether the formation of the carbanion intermediate is or is not rate determining. If the anion is formed reversibly it may be possible to detect proton exchange with the solvent ($E1cb_{(rev)}$). This is not the case if formation of the carbanion is the rate-determining step ($E1cb_{(irr)}$).



The correlation of many features of ß-elimination reactions is facilitated by recognition that these three mechanisms represent *variants of a continuum of mechanistic possibilities*. Many ß-elimination reactions occur via mechanisms that are intermediate between the limiting mechanistic types. This idea, called the *variable E2 transition state theory*, is outlined in Figure 5.11.

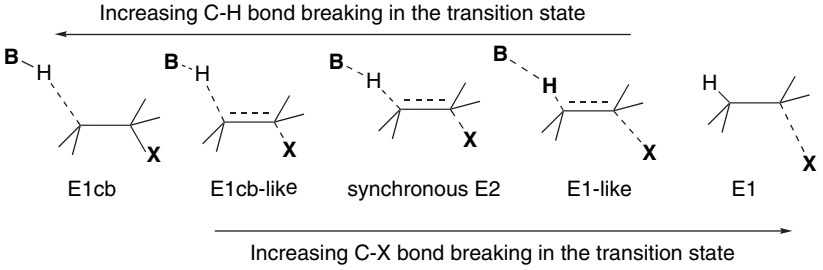
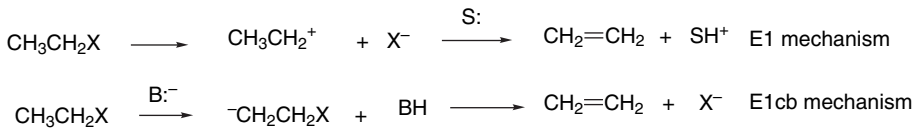


Fig. 5.11. Variable transition state theory of elimination reactions. J. F. Bunnett, *Angew. Chem. Int. Ed. Engl.*, **1**, 225 (1962); J. F. Bunnett, *Survey Prog. Chem.*, **5**, 53 (1969); W. H. Saunders, Jr., and A. F. Cockerill, *Mechanisms of Elimination Reactions*, John Wiley & Sons, New York, 1973, pp. 48–55; W. H. Saunders, Jr., *Acc. Chem. Res.*, **9**, 19 (1976).

The variable transition state theory allows discussion of reactions proceeding through TSs of intermediate character in terms of the limiting mechanistic types. These are called "E1cb-like" and "E1-like," as illustrated in Figure 5.11. The most important factors to be considered are: (1) the nature of the leaving group, (2) electronic and steric effect of substituents in the reactant molecule, (3) the nature of the base, and (4) solvent effects.

The ideas embodied in the variable transition state theory of elimination reactions can be depicted in a two-dimensional potential energy diagram.[277] If we consider the case of an ethyl halide, both stepwise reaction paths require the formation of high-energy intermediates. The E1 mechanism requires formation of a primary carbocation, whereas the E1cb proceeds via a carbanion intermediate.



In the absence of stabilizing substituent groups, both a primary carbocation and a primary carbanion are highly unstable intermediates. If we construct a reaction energy diagram in which progress of C−H bond breaking is one dimension, progress of C−X bond breaking is the second, and the energy of the reacting system is the third, we obtain a diagram such as the one in Figure 5.12. In Figure 5.12A only the two horizontal (bond-breaking) dimensions are shown. We see that the E1 mechanism corresponds to complete C−X cleavage before C−H cleavage begins, whereas the E1cb mechanism corresponds to complete C−H cleavage before C−X cleavage begins. In Figure 5.12B the energy dimension is added. The front-right and back-left corners correspond to the E1 and E1cb intermediates, respectively. Because of the high energy of both the E1 and E1cb intermediates, the lowest-energy path is the concerted E2 path, more or less diagonally across the energy surface. This pathway is of lower energy because the partially formed double bond provides some compensation for the energy required to break the C−H and C−X bonds and the high-energy intermediates are avoided.

The presence of a substituent on the ethyl group that stabilizes the carbocation intermediate lowers the right-front corner of the diagram, which corresponds

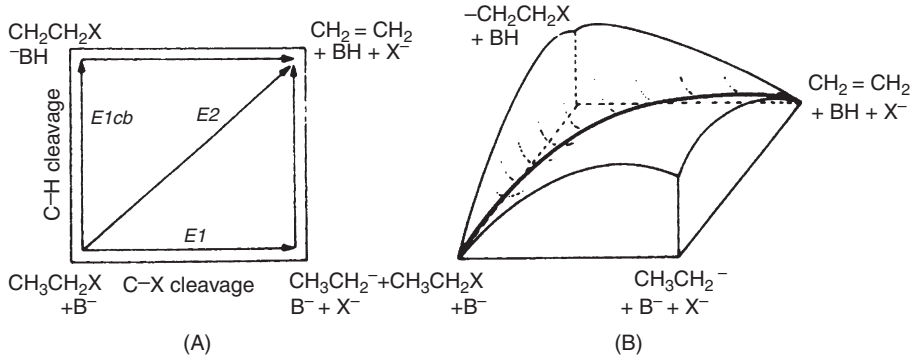
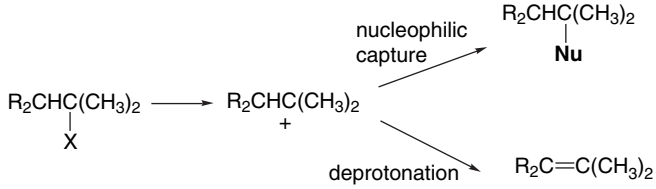


Fig. 5.12. Two-dimensional potential energy diagrams depicting E1, E2, and E1cb mechanisms.

277. R. A. More O'Ferrall, *J. Chem. Soc. B*, 274 (1970).

to the energy of the carbocation intermediate. Similarly, a substituent that stabilizes a carbanion intermediate lowers the back-left corner of the diagram. As a result, substituents that stabilize carbocation character move the E2 TS to a point that more closely resembles the E1 TS. A structural change that stabilizes carbanion character shifts the E2 TS to be more similar to the E1cb TS. In the E1-like TS, C−X bond cleavage is more advanced than C−H cleavage, whereas in the E1cb-like TS, the C−H bond breaking is more advanced. Figure 5.13 depicts these changes.

The variable transition state concept can be used to discuss specific structural effects that influence the possible mechanisms of elimination reactions. We have background that is pertinent to the structure-reactivity effects in E1 reactions from the discussion of S_N1 reactions in Chapter 4. Ionization is favored by: (1) electron-releasing groups that stabilize the positive charge in the carbocation intermediate; (2) readily ionized, i.e., "good," leaving groups; and (3) solvents that facilitate ionization. The base plays no role in the rate-determining step in the E1 mechanism, but its identity cannot be ignored. After ionization, the cationic intermediate is subject to two competing reactions: nucleophilic capture (S_N1) or proton removal (E1). Remember from Section 4.4.3 (p. 437) that there is an inherent preference for substitution. The reaction can be diverted to elimination by bases. Stronger and harder bases favor the E1 path over the S_N1 path.



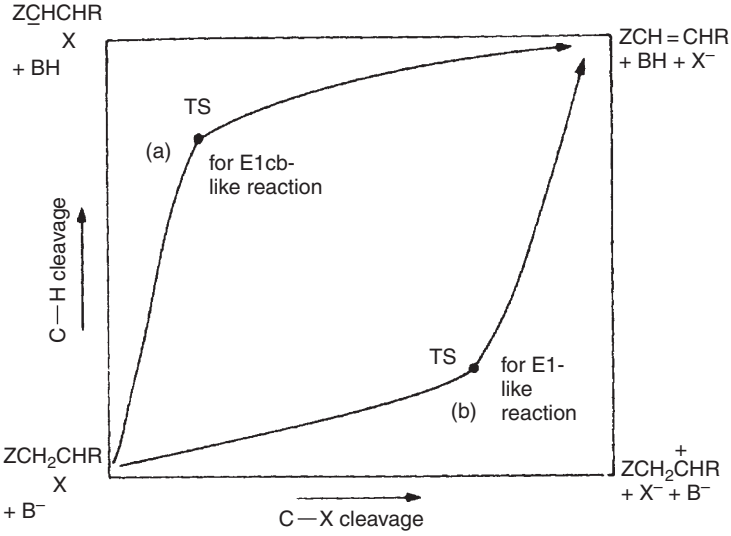


Fig. 5.13. Representation of changes in transition structure character in the E2 elimination reaction as a result of substituent effects: (a) substituent Z stabilizes carbanion character of E1cb-like TS; (b) substituent R stabilizes carbocation character of E1-like TS.

E2 reactions are distinguished from E1 reactions in that the base is present in the TS for the rate-determining step. The reactions therefore exhibit overall second-order kinetics. The precise nature of the TS is a function of variables such as the strength of the base, the identity of the leaving group, reactant structure, and the solvent. For example, an elimination reaction proceeding by an E2 TS will be moved in the E1cb direction by an increase in base strength or by a change to a poorer leaving group. On the other hand, a good leaving group in a highly ionizing solvent will result in an E2 TS that resembles an E1 process, with greater weakening of the bond to the leaving group. Reactions that proceed by the E1cb mechanism require substituents that can stabilize the carbanion intermediate. This mechanism is not observed with simple alkyl halides or sulfonates. It is more likely to be involved when the leaving group is ß to a carbonyl, nitro, cyano, sulfinyl, or other carbanion-stabilizing group. Poorer leaving groups move the E2 TS in the E1cb direction, since they require greater buildup of negative charge at the β-carbon. Scheme 5.3 summarizes some of the characteristic features of the E1, E2, and E1cb mechanisms.

Scheme 5.4 shows some examples of reactions for which the mechanisms have been characterized. From these data, we can conclude that E1cb reactions generally require *both* carbanion stabilization and a relatively poor leaving group. For example, simple 2-arylethyl halides and tosylates react by the E2 mechanism and only when a *p*-nitro group is present is there clear evidence of an E1cb mechanism (Entry 1). Entry 2 illustrates one of the distinguishing characteristics of E2 reactions. Both the α- and β-carbons show isotope effects because rehybridization occurs at both carbons. Entry 3 illustrates some of the kinetic features that characterize E2 reactions. In addition to second-order kinetics, the concerted mechanism results in kinetic isotope effects at both the β-hydrogen and the leaving group. The substantial Br > Cl ratio also

Scheme 5.3. Distinguishing Features of Elimination Mechanisms

A. E1 Mechanism
First Order Kinetics: rate = k[RX]
LFER indicate cationic character of the TS
Strong dependence on leaving group

B. E2 Mechanism
Second Order Kinetics: rate = k[RX][base]
Leaving group effect is normally I > Br > Cl >>F because bond-breaking occurs in RDS.
Kinetic isotope effect for both β-C-H and leaving group.
Kinetic isotope effect for both α- and β-carbons.

C. E1cb(rev)
Second Order Kinetics: rate = k[RX][base]
Exchange of β-H with protic solvent
LFER indicate anionic character in TS

D. Elcb(irr)
Second Order Kinetics: rate = k[RX][base]
Leaving group effect may be F > Cl > Br > I, since C-X bond-breaking is not involved in RDS.
LFER indicates anionic character in TS

Scheme 5.4. Examples of Systems Subjected to Mechanistic Characterization

1.[a] $ArCH_2CH_2X \xrightarrow[DMSO,\ H_2O]{^-OH \text{ and buffer anions}} ArCH{=}CH_2$

E2 for X = TsO^-, Br^-, and quinuclidinium, except for Ar = *p*-nitrophenyl and X = quinuclidinium: based on variation of sensitivity to base (Bronsted β) and LFER relationships.

2.[b] $ArCH_2CH_2N^+(CH_3)_3 \xrightarrow{NaOC_2H_5} ArCH{=}CH_2$

E2: based on $k^{12}C/k^{14}C$ isotope effects for both C(1) and C(2)

3.[c] $PhCH(CH_3)CH_2Cl \xrightarrow[EtOH,\ 75°C]{NaOC_2H_5} PhCH{=}CH_2$

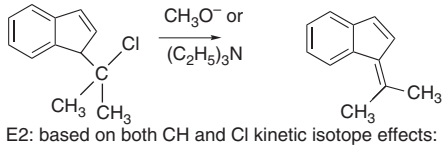
E2; based on $k^{35}Cl:k^{37}Cl = 1.0059$; $k_H/k_D = 5.37$, and $k_{Br}/k_{Cl} = 52$

4.[d] $O_2N{-}C_6H_4{-}CH_2CH_2{-}N^+(C_5H_5)X \xrightarrow{KOH} O_2N{-}C_6H_4{-}CH{=}CH_2$

E1cb: based on kinetics and Bronsted dependence on substituent X; shifts from E1cb(irr) to E1cb(rev) as X becomes ERG

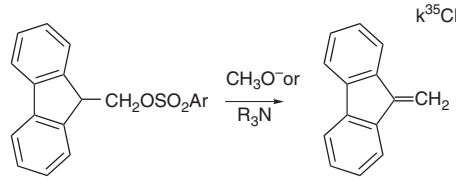
5.[e] $H{-}N^+(C_5H_5){-}CH_2CH_2{-}N^+(C_5H_5) \xrightarrow{buffer} H{-}N^+(C_5H_5){-}CH{=}CH_2$

E1cb(rev): based on observation of CH solvent exchange and solvent isotope effect

6.[f] 

E2: based on both CH and Cl kinetic isotope effects: k_H/k_D = 7.1 (CH_3O^-); 8.4 ($(C_2H_5)_3N$)

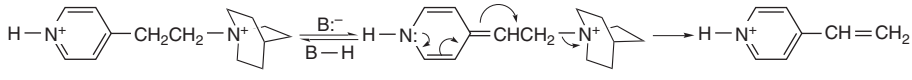
$k^{35}Cl:k^{37}Cl$ = 1.0086 (CH_3O^-); 1.0101 ($(C_2H_5)_3N$)

7.[g] 

E2 with transition to E1cb for ERG in Ar based on curved LFER (Hammett) relationships

a. J. R. Gandler and W. P. Jencks, *J. Am. Chem. Soc.*, **104**, 1937 (1982).
b. J. R. I. Eubanks, L. B. Sims, and A. Fry, *J. Am. Chem. Soc.*, **113**, 8821 (1991).
c. H. F. Koch, D. McLennan, J. G. Koch, W. Tumas, B. Dobson, and N. H. Koch, *J. Am. Chem. Soc.*, **105**, 1930 (1983).
d. J. W. Bunting and J. P. Kanter, *J. Am. Chem. Soc.*, **113**, 6950 (1991).
e. S. Alunni, A. Conti and R. P. Erico, *J. Chem. Soc., Perkin Trans.*, **2**, 453 (2000); S. Alunni, A. Conti, and R. P. Errico, *Res. Chem. Interm.*, **27**, 635 (2001).
f. J. S. Jia, J. Rudzinski, P. Paneth, and A. Thibblin, *J. Org. Chem.*, **67**, 177 (2002).
g. F. G. Larkin, R. A. More O'Ferrall, and D. G. Murphy, *Coll Czech. Chem. Commun.*, **64**, 1833 (1999).

shows that the bond to the leaving group is involved in the rate-determining step. The pyridinium system in Entry 5 is an interesting case. Kinetic studies have shown that the reaction occurs through the *conjugate acid* of the reactant. The protonation of the pyridine ring enhances the acidity of the C−H bond. The reaction occurs with exchange, indicating that the proton removal is reversible.



The indenyl (Entry 6) and fluorenyl (Entry 7) ring systems have been studied carefully. Note that these are cases where (aromatic) anionic stabilization could potentially stabilize an anionic intermediate. However, the elimination reactions show E2 characteristics. The reaction in Entry 7 shifts to an E1cb mechanism if the leaving group is made less reactive.

Because of their crucial role in the ionization step, solvents have a profound effect on the rates of E1 reactions. These rates for a number of tertiary halides have been determined in a variety of solvents. For *t*-butyl chloride there are huge differences in the rates in water ($\log k = -1.54$), ethanol ($\log k = -7.07$), and diethyl ether ($\log k = -12.74$).[278] Similarly, the rates of the E1 reaction of 1-methylcyclopentyl bromide range from $1 \times 10^{-3}\,s^{-1}$ in methanol to $2 \times 10^{-9}\,s^{-1}$ in hexane. Polar aprotic solvents such as DMSO ($k = 2 \times 10^{-4}\,s^{-1}$) and acetonitrile ($k = 9 \times 10^{-5}\,s^{-1}$) are also conducive for ionization.[279] The solvent properties that are most important are polarity and the ability to assist leaving group ionization. These, of course, are the same features that favor S_N1 reactions, as we discussed in Section 3.8.

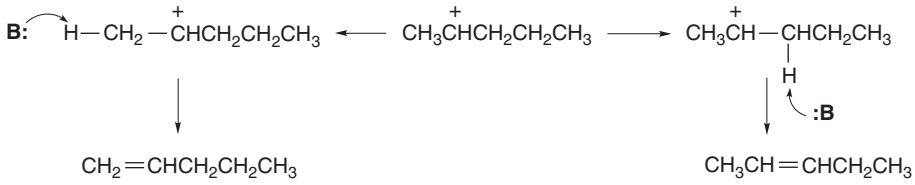
The details of the mechanism as well as the stereochemistry and regiochemistry also depend on the identity and degree of aggregation of the base. This is affected by variables such as the nature of the solvent, the cationic counterions, and the presence of coordinating ligands.[280] Under given reaction conditions, there may be an equilibrium involving a number of different species, which, in turn, have different rates for inducing elimination. The nature of the TS in elimination reactions also controls the regiochemistry of ß-elimination for compounds in which the double bond can be introduced at one of several positions. These effects are discussed in the next section.

5.10.2. Regiochemistry of Elimination Reactions

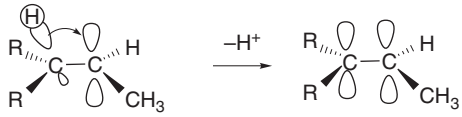
Useful generalizations and predictions regarding regioselectivity in elimination reactions can be drawn from the variable transition state theory. As we saw earlier in Figure 5.11, this theory proposes that the TSs in E2 reactions can vary over a mechanistic range between the E1 and E1cb extremes. When the base is present at the TS, the reaction will exhibit second-order kinetics and meet the other criteria of an E2 mechanism. There is no intermediate. The cleavage of the C−H and the C−X bonds is concerted, but not necessarily synchronous. The relative extent of the breaking of the two bonds at the TS may differ, depending on the nature of the leaving group X and the ease of removal of the β-hydrogen as a proton. If there are several nonequivalent β-hydrogens, competition among them determines which one is removed and the regiochemistry and stereochemistry of the reaction. If one compares E1 and E1cb eliminations, it is seen that quite different structural features govern the direction of elimination. The variable transition state theory suggests that E2 elimination proceeding through an "E1-like" TS will have the regiochemistry of E1 eliminations, whereas E2 eliminations proceeding through an "E1cb-like" TS will show regioselectivity similar to E1cb reactions. It is therefore instructive to consider these limiting mechanisms before discussing the E2 case.

278. M. H. Abraham, R. M. Doherty, M. J. Kamlet, J. M. Harris, and R. W. Taft, *J. Chem. Soc., Perkin Trans. 2*, 913 (1987).
279. E. A. Ponomareva, I. V. Koshchii, T. L. Pervishko, and G. F. Dvorko, *Russ. J. Gen. Chem.*, **70**, 907 (2000).
280. R. A. Bartsch and J. Zavada, *Chem. Rev.*, **80**, 453 (1980).

In the E1 mechanism, the leaving group is completely ionized before C−H bond breaking occurs. The direction of the elimination therefore depends on the structure of the carbocation and the identity of the base involved in the proton transfer that follows C−X heterolysis. Because of the high energy of the carbocation intermediate, quite weak bases can effect proton removal. The solvent can serve this function. The counterion formed in the ionization step can also act as the proton acceptor.



The product composition of the alkenes formed in E1 elimination reaction usually favors the more-substituted alkene, and therefore the more stable one. This indicates that the energies of the *product-determining TSs parallel those of the isomeric alkenes*. However, since the activation energy for proton removal from a carbocation is low, the TS should resemble the carbocation intermediate much more than the alkene product (Hammond postulate; Section 3.3.2.2). In the carbocation there is hyperconjugation involving each ß-hydrogen.[281] Since the hyperconjugation structures possess some double-bond character, the interaction with hydrogen is greatest at more highly substituted carbons; that is, there will be greater weakening of C−H bonds and more double-bond character at more highly substituted carbon atoms. This structural effect in the carbocation intermediate governs the direction of elimination and leads to the *preferential formation of the more highly substituted alkene*, as illustrated in Figure 5.14.



In the E1cb mechanism, the direction of elimination is governed by the *kinetic acidity* of the individual ß-protons, which in turn is determined by the polar and

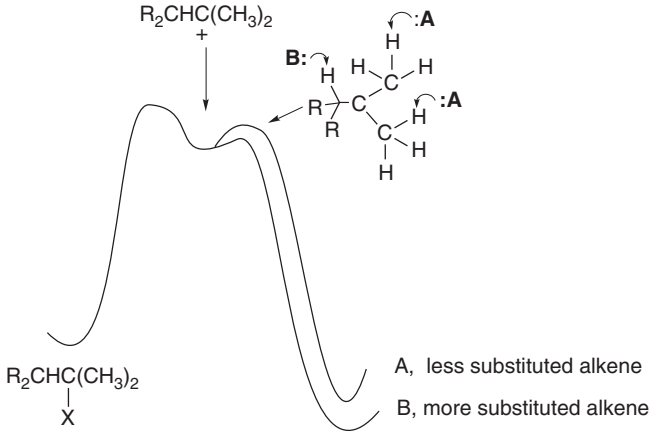


Fig. 5.14. Potential energy profile for product-determining step for E1 elimination.

281. P. B. D. de la Mare, *Pure Appl. Chem.*, **56**, 1755 (1984).

resonance effects of adjacent substituents, and by the degree of steric hindrance to approach of base to the proton. Alkyl substituents tend to retard proton abstraction both electronically and sterically. Preferential proton abstraction from less-substituted carbons leads to the formation of the less-substituted alkene. Carbanion-stabilizing substituents control the regiochemistry of E1cb eliminations by favoring deprotonation at the most acidic carbon.

The preferred direction of elimination via the E2 mechanism depends on the precise nature of the TS. The two extreme TSs for the E2 elimination resemble the E1 and E1cb mechanisms in their orientational effects. At the "E1cb-like" end of the E2 range, a highly developed bond is present between the proton and the base. The leaving group remains tightly bound to carbon, and there is relatively little development of the carbon-carbon double bond. *When the TS of an E2 reaction has E1cb character, the direction of the elimination is governed by the ease of proton removal*. In this case, the less-substituted alkene usually dominates. At the "E1-like" end of the E2 spectrum, the TS is characterized by well-advanced cleavage of the C−X bond and a largely intact C−H bonds. An "E1-like" TS for E2 reactions leads to formation of the more highly substituted of the possible alkenes. In a more synchronous E2 reaction, the new double bond is substantially formed at the TS with partial rupture of both the C−H and C−X bonds. E2 eliminations usually give mainly the more-substituted alkene. This is because the TSs leading to the isomeric alkenes reflect the partial double-bond character and the greater stability of the more-substituted double bond. Concerted E2 reactions are also subject to the stereoelectronic requirement that the reacting C−H and C−X bond be antiperiplanar. This requirement makes reactant conformation a factor in determining the outcome of the reaction.

Prior to development of the mechanistic ideas outlined above, it was recognized by experience that some types of elimination reactions give the more substituted alkene as the major product. Such eliminations are said to follow the *Saytzeff rule*. This behavior is characteristic of E1 reactions and E2 reactions involving relatively good leaving groups, such as halides and sulfonates. These are now recognized as reactions in which C−X cleavage is well advanced in the TS. E2 reactions involving poor leaving groups, particularly those with quaternary ammonium salts, are said to follow the *Hofmann rule* and give primarily the less-substituted alkene. We now recognize that such reactions proceed through TSs with E1cb character.

The data recorded in Table 5.11 for the 2-hexyl system illustrate two general trends that have been recognized in other systems as well. First, poorer leaving groups favor elimination according to the Hofmann rule, as shown, for example, by the increasing amount of terminal olefin in the halogen series as the leaving group is changed from iodide to fluoride. Poorer leaving groups move the TS in the E1cb direction. A higher negative charge must build up on the ß-carbon to induce loss of the leaving group. This charge increase is accomplished by more complete proton abstraction.

Comparison of the data for methoxide with those for *t*-butoxide in Table 5.11 illustrates a second general trend. Stronger bases favor formation of the less-substituted alkene.[282] A stronger base leads to an increase in the carbanion character at the TS and, thus, shifts it in the E1cb direction. A correlation between the strength of the

[282] (a) D. H. Froemsdorf and M. D. Robbins, *J. Am. Chem. Soc.*, **89**, 1737 (1967); I. N. Feit and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **92**, 5615 (1970); (b) R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.*, **95**, 3405 (1973); (c) R. A. Bartsch, K. E. Wiegers, and D. M. Guritz, *J. Am. Chem. Soc.*, **96**, 430 (1974).

Table 5.11. Product Ratios for Some Elimination Reactions of 2-Hexyl Systems

Leaving group	Base/solvent	Product Composition		
		1-Hexene	*E*-2-Hexene	*Z*-2-Hexene
I	MeO^-/MeOH	19	63	18
Cl	MeO^-/MeOH	33	50	17
F	MeO^-/MeOH	69	21	9
$OSO_2C_7H_7$	MeO^-/MeOH	33	44	23
I	*t*-BuO^-/*t*-BuOH	78	15	7
Cl	*t*-BuO^-/*t*-BuOH	91	5	4
F	*t*-BuO^-/*t*-BuOH	97	2	1
$OSO_2C_7H_7$	*t*-BuO^-/*t*-BuOH	83	4	14

a. R. A. Bartsch and J. F. Bunnett, *J. Am. Chem. Soc.*, **91**, 1376 (1967).

base and the difference in $\Delta G^{\ddagger}$ for the formation of 1-butene versus 2-butene has been established.[282b] Some of the data are given in Table 5.12.

The direction of elimination is also affected by steric effects, and if both the base and the reactant are highly branched, steric factors may lead to preferential removal of the less hindered hydrogen.[283] Thus, when 4-methyl-2-pentyl iodide reacts with very hindered bases such as potassium tricyclohexylmethoxide, there is preferential formation of the terminal alkene. In this case, potassium *t*-butoxide favors the internal alkene, although by a smaller ratio than for less branched alkoxides.

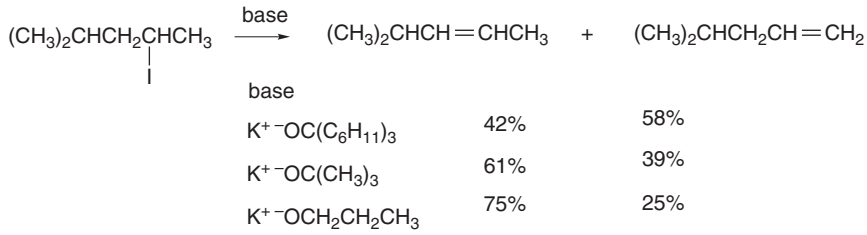


Table 5.12. Orientation of E2 Elimination as a Function of Base Strength

Base (K^+salt)	p*K*(DMSO)	Percent 1-butene	
		2-Iodobutane[a]	2-Butyl tosylate[b]
p-Nitrobenzoate	8.9	5.8	c
Benzoate	11.0	7.2	c
Acetate	11.6	7.4	c
Phenolate	16.4	11.4	30.6
Trifluoroethoxide	21.6	14.3	46.0
Methoxide	29.0	17.0	c
Ethoxide	29.8	17.1	56.0
t-Butoxide	32.2	20.7	58.5

a. R. A. Bartsch, G. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.*, **95**, 3405 (1973).
b. R. A. Bartsch, R. A. Read, D. T. Larsen, D. K. Roberts, K. J. Scott, and B. R. Cho, *J. Am. Chem. Soc.*, **101**, 1176 (1979).
c. Not reported.

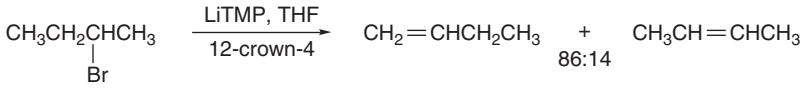
283. R. A. Bartsch, R. A. Read, D. T. Larsen, D. K. Roberts, K. J. Scott, and B. R. Cho, *J. Am. Chem. Soc*., **101**, 1176 (1979).

Table 5.13. Orientation of Elimination from 2-Butyl Systems under E2 Conditions

Leaving group	Base/solvent	1-Butene (%)	2-Butene (%)
I[a]	$PhCO_2^-$/DMSO	7	93
I[a]	$C_2H_5O^-$/DMSO	17	83
I[b]	t-$C_4H_9O^-$/DMSO	21	79
Br[b]	t-$C_4H_9O^-$/DMSO	33	67
Cl[b]	t-$C_4H_9O^-$/DMSO	43	57
Br[c]	$C_2H_5O^-$/DMSO	19	81
$OSO_2C_7H_7$[d]	$C_2H_5O^-$/DMSO	35	65
$OSO_2C_7H_7$[d]	t-$C_4H_9O^-$/DMSO	61	39
$S^+(CH_3)_2$[e]	$C_2H_5O^-$/DMSO	74	26
$N^+(CH_3)_3$[f]	OH^-	95	5

a. R. A. Bartsch, B. M. Pruss, B. A. Bushaw, and K. E. Wiegers, *J. Am. Chem. Soc.*, **95**, 3405 (1973).
b. D. L. Griffith, D. L. Meges, and H. C. Brown, *J. Chem. Soc. Chem. Commun.*, 90 (1968).
c. M. L. Dahr, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2058 (1948).
d. D. H. Froemsdorf and M. D. Robbins, *J. Am. Chem. Soc.*, **89**, 1737 (1967).
e. E. D. Hughes, C. K. Ingold, G. A. Maw, and L. I. Woolf, *J. Chem. Soc.*, 2077 (1948).
f. A. C. Cope, N. A. LeBel, H.-H. Lee, and W. R. Moore, *J. Am. Chem. Soc.*, **79**, 4720 (1957).

Branched amide bases can also control the regiochemistry of elimination on the basis of steric effects. For example LiTMP favors formation of 1-butene from 2-bromobutane.

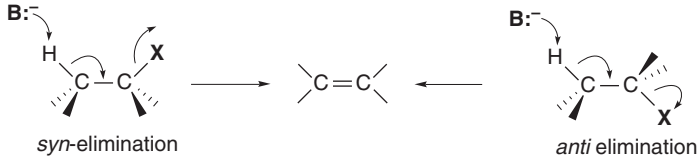


Ref. 284

The leaving group also affects the amount of internal versus terminal alkene that is formed. The poorer the leaving group, the more E1cb-like the TS. This trend is illustrated for the case of the 2-butyl system by the data in Table 5.13. Positively charged leaving groups, such as in dimethylsulfonium and trimethylammonium salts, may also favor a more E1cb-like TS because their inductive and field effects increase the acidity of the ß-protons.

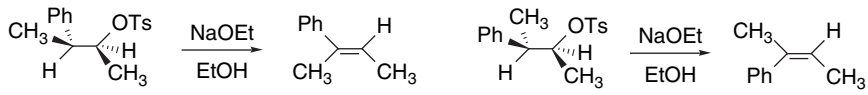
5.10.3. Stereochemistry of E2 Elimination Reactions

In this section we focus primarily on the stereochemistry of the concerted E2 mechanism. The most familiar examples are dehydrohalogenation and dehydrosulfonylation reactions effected by strong bases. In principle, elimination can proceed with either *syn* or *anti* stereochemistry. For acyclic systems, there is a preference for *anti* elimination, but this can be overridden if conformational factors favor a *syn* elimination. The *anti* TS maximizes orbital overlap and avoids the eclipsing that is present in the *syn* TS.

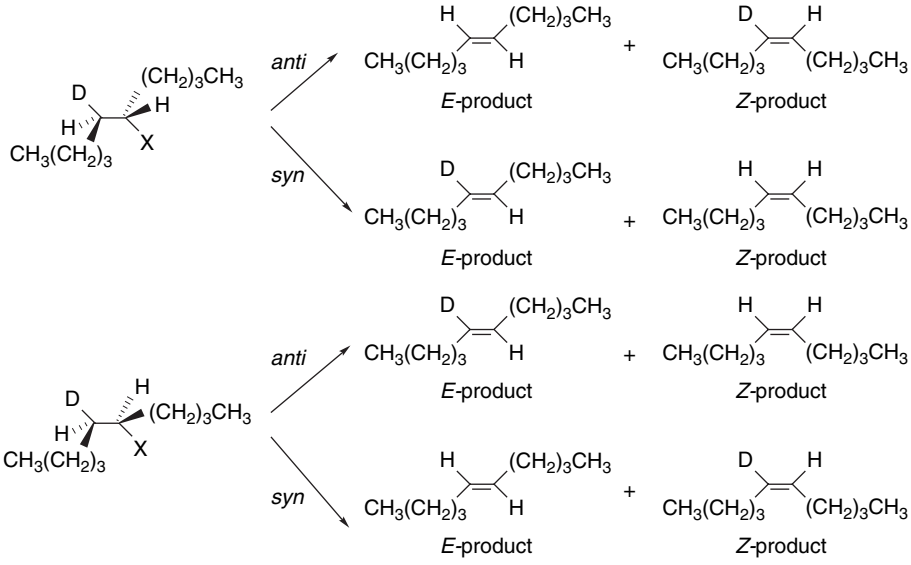


[284] I. E. Kopka, M. A. Nowak, and M. W. Rathke, *Synth. Commun.*, **16**, 27 (1986).

In acyclic systems, the extent of *anti* versus *syn* elimination can be determined by use of either stereospecifically deuterated reactants or diastereomeric reactants that give different products by *syn* and *anti* elimination. The latter approach showed that elimination from 3-phenyl-2-butyl tosylate is a stereospecific *anti* process.[285]



The extent of *syn* elimination in 5-decyl systems was measured using diastereomeric deuterium-labeled substrates. Stereospecifically deuterated 5-substituted decane derivatives were prepared and subjected to various elimination conditions. By comparison of the amount of deuterium in the *E*- and *Z*-isomers of the product, it is possible to determine the extent of *syn* and *anti* elimination.[286]



Data obtained for three different leaving groups are shown in Table 5.14. The results demonstrate that *syn* elimination is extensive for quaternary ammonium salts. With better leaving groups, the extent of *syn* elimination is small in the polar solvent DMSO but quite significant in benzene. The factors that promote *syn* elimination are discussed below. Table 5.15 summarizes some data on *syn* versus *anti* elimination in other acyclic systems.

The general trend revealed by these and other data is that *anti* stereochemistry is normally preferred for reactions involving good leaving groups such as bromide and tosylate. With poorer leaving groups (e.g., fluoride, trimethylamine), *syn* elimination becomes important. The amount of *syn* elimination is small in the 2-butyl system, but it becomes a major pathway with 3-hexyl compounds and longer chains.

In cyclic systems, the extent of *anti* and *syn* elimination depends on ring size, among other factors. Cyclohexyl systems have a very strong preference for *anti* elimination via

[285] W.-B. Chiao and W. H. Saunders, *J. Org. Chem.,* **45**, 1319 (1980).

[286] M. Pankova, M. Svoboda, and J. Zavada, *Tetrahedron Lett.*, 2465 (1972). The analysis of the data also requires that account be taken of (a) isotope effects and (b) formation of 4-decene. The method of analysis is described in detail by J. Sicher, J. Zavada, and M. Pankova, *Coll. Czech. Chem. Commun.,* **36**, 3140 (1971).

Table 5.14. Extent of *syn* Elimination as a Function of the Leaving Group in the 5-Decyl System[a]

	Percent *syn* elimination			
	E–product		Z–product	
Leaving group	DMSO	Benzene	DMSO	Benzene
Cl	6	62	7	39
OTs	4	27	4	16
$(CH_3)_3N^+$	93	92	76	84

a. M. Pankova, M. Svoboda, and J. Zavada, *Tetrahedron Lett.*, 2465 (1972); the base used was potassium *t*-butoxide.

conformations in which both the departing proton and the leaving group occupy axial positions. This orientation permits alignment of the orbitals so that concerted *anti* elimination can occur. For example, *cis*-4-*t*-butylcyclohexyl bromide undergoes E2 elimination at a rate about 500 times greater than the *trans* isomer because only the *cis* isomer permits *anti* elimination from the favored chair conformation.[287]

4.1×10^{-3} 8.0×10^{-6}

second order rate constants for E2 reaction with $K^{+-}OC(CH_3)_3$

Other cyclic systems are not so selective. In the decomposition of *N*,*N*,*N*-trimethyl-cyclobutylammonium hydroxide, elimination is 90% *syn*.[288] The cyclobutyl ring resists the conformation required for *anti* elimination. The more flexible five-membered ring analog undergoes about 50% *syn* elimination. Elimination from the

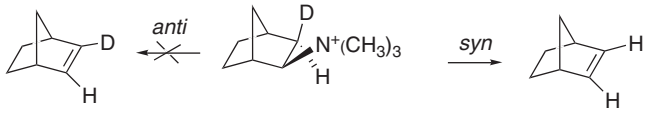
Table 5.15. Stereochemistry of E2 Elimination for Some Acyclic Systems

Reactant	Base/solvent	*% anti*	*% syn*
2-Bromobutane[a]	$K^{+-}OC(CH_3)_3$/*t*-BuOH	100	0
2-Butyl tosylate[b]	$K^{+-}OC(CH_3)_3$/*t*-BuOH	>98	<2
N, *N*, *N*-trimethyl-2-butylammonium[c]	$K^{+-}OC(CH_3)_3$/DMSO	100	0
3-Fluorohexane[d]	$K^{+-}OC(CH_3)_3$/*t*-BuOH	32	68
N, *N*, *N*-trimethyl-4-octylammonium[e]	$K^{+-}OC(CH_3)_3$/DMSO	24	76
5-Decyl tosylate[f]	$K^{+-}OC(CH_3)_3$/ *t*-BuOH	93	7
5-Decyl chloride[g]	$K^{+-}OC(CH_3)_3$/benzene	62	38
5-Decyl fluoride[g]	$K^{+-}OC(CH_3)_3$/benzene	<20	>80
5-Decyl chloride[g]	$K^{+-}OC(CH_3)_3$/DMSO	93	7
5-Decyl fluoride[g]	$K^{+-}OC(CH_3)_3$, DMSO	80	20

a. R. A. Bartsch, *J. Am. Chem. Soc.*, **93**, 3683 (1971).
b. D. H. Froemsdorf, W. Dowd, W. A. Gifford, and S. Meyerson, *J. Chem. Soc., Chem. Commun.,* 449 (1968).
c. D. H. Froemsdorf, H. R. Pinnick, Jr., and S. Meyerson, *J. Chem. Soc., Chem. Commumn.*, 1600 (1968).
d. J. K. Borchardt, J. C. Swanson, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **96**, 3918 (1974).
e. J. Sicher, J. Zavada, and M. Pankova, *Collect. Czech. Chem. Commun.*,**36**, 3140 (1971).
f. J. Zavada, M. Pankova, and J. Sicher, *J. Chem. Soc., Chem. Commun.*, 1145 (1968).
g. M. Pankova, M. Svoboda, and J. Zavada, *Tetrahedron Lett.*, 2465 (1972).

287. J. Zavada, J. Krupicka, and J. Sicher, *Coll. Czech. Chem. Commun.*, **33**, 1393 (1968).
288. M. P. Cooke, Jr., and J. L. Coke, *J. Am. Chem. Soc.,* **90**, 5556 (1968).

N,*N*,*N*-trimethylnorbornylammonium ion is exclusively *syn*.[289] This is another case where the rigid ring prohibits attainment of an *anti*-elimination process. There is also a steric effect operating against removal of an *endo* proton, which is required for *anti* elimination. *Syn* elimination is especially prevalent in the medium-sized ring compounds.[290]



The energy difference between the *anti* and *syn* transition structures has been examined computationally using fluoride as the base and alkyl chlorides as the reactants. Simple primary and secondary chlorides show no barriers for *anti* elimination at the MP4SDQ/6-31+G** level. The *syn* TSs show positive barriers and the total difference between the *syn* and *anti* TSs is on the order of 13 kcal/mol.[291]

$$C_2H_5Cl + F^- : \quad \Delta E(anti) = -5.7\,\text{kcal/mole};\ \Delta\Delta E(syn - anti) = 12.7\,\text{kcal/mol}$$

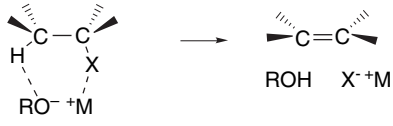
$$n\text{-}C_3H_7Cl + F^- : \quad \Delta E(anti) = -9.9\,\text{kcal/mole};\ \Delta\Delta E(syn - anti) = 12.8\,\text{kcal/mol}$$

$$(CH_3)_2CHCl + F^- : \quad \Delta E(anti) = -10.2\,\text{kcal/mole};\ \Delta\Delta E(syn - anti) = 12.8\,\text{kcal/mol}$$

The preferred TS for *syn* elimination is not periplanar, but rather has a torsion angle of about 30°. The *syn* TS has more E1cb character than the *anti.*

MP2/6-31+G** computations have been used to compare cyclopentyl and cyclohexyl systems.[292] As noted above, cyclohexyl systems have a much stronger preference for the *anti* stereochemistry.[293] The optimum TSs are shown in Figure 5.15. Both the *anti* and *syn* TSs have negative barriers in the cyclopentyl system (-10.2 and -0.9 kcal/mol), whereas the *syn* system shows a positive barrier in the cyclohexyl system (-10.9 and $+5.4$ kcal/mol).

The factors that determine whether *syn* or *anti* elimination predominates are complex.[294] One factor that is believed to be important is whether the base is free or present as an ion pair.[295] The evidence suggests that an ion pair promotes *syn* elimination of anionic leaving groups. This effect can be explained by a TS in which the anion functions as a base and the cation assists in the departure of the leaving group.



This interpretation is in agreement with the solvent effect that is evident for the 5-decyl system data in Table 5.15. The extent of *syn* elimination is much higher in the nondissociating solvent benzene than in DMSO. The ion pair interpretation is also supported by the fact that addition of specific metal ion–complexing agents (crown

289. J. P. Coke and M. P. Cooke, *J. Am. Chem. Soc.*, **89**, 6701 (1967).
290. J. Sicher, *Angew. Chem. Int. Ed. Engl.*, **11**, 200 (1972).
291. S. Gronert, *J. Am. Chem. Soc.*, **113**, 6041 (1991); *J. Am. Chem. Soc.*, **115**, 652 (1993).
292. S. Gronert, *J. Org. Chem.*, **59**, 7046 (1994).
293. C. H. DePuy, G. F. Morris, J. S. Smith, and R. J. Smat, *J. Am. Chem. Soc.*, **87**, 2421 (1965).
294. R. A. Bartsch and J. Zavada, *Chem. Rev.*, **80**, 453 (1980).
295. R. A. Bartsch, G. M. Pruss, R. L. Buswell, and B. A. Bushaw, *Tetrahedron Lett.*, 2621 (1972); J. K. Borchardt, J. C. Swanson, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **96**, 3918 (1974).

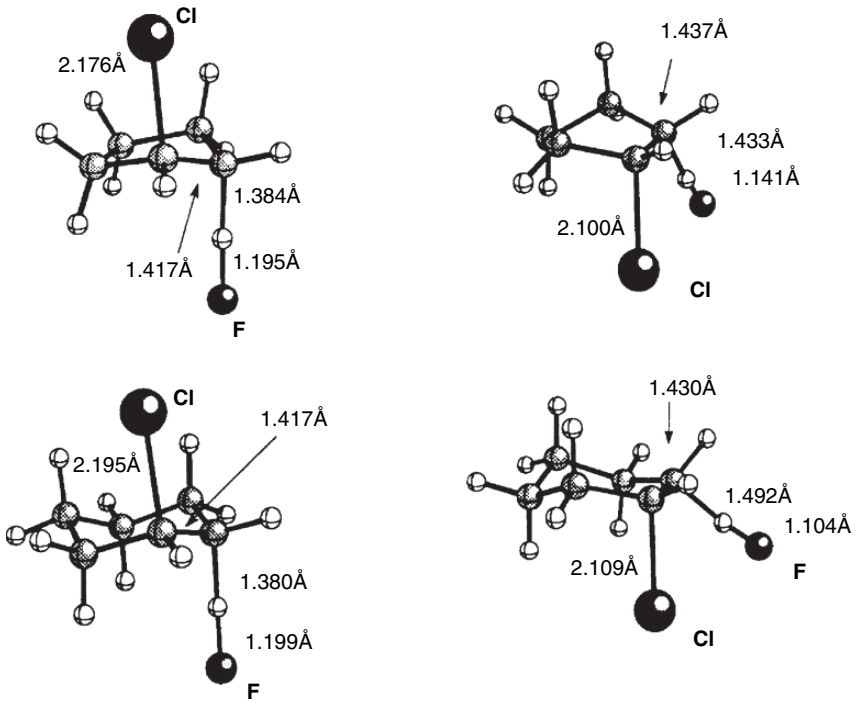
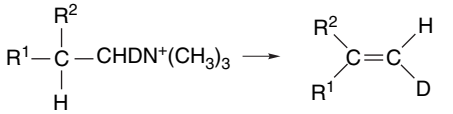


Fig. 5.15. *Anti* and *syn* transition states for fluoride-induced E2 elimination in (a) cyclopentyl and (b) cyclohexyl systems. Reproduced from *J. Org. Chem.*, **59**, 7046 (1994), by permission of the American Chemical Society.

ethers) that promote dissociation of the ion pair leads to diminished amounts of *syn* elimination.[296] Another factor that affects the *syn*:*anti* ratio is the strength of the base. Strong bases exhibit a higher proportion of *syn* elimination.[297]

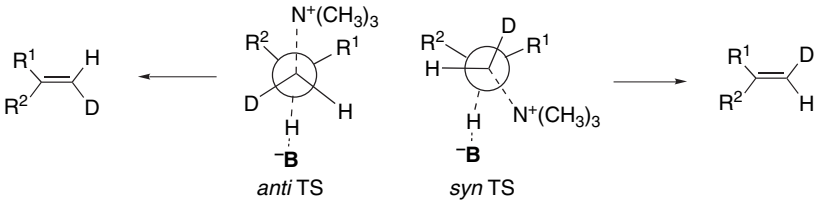
Steric and conformational effects also play a significant role in determining the *syn*:*anti* ratio. With *N*-(ß,ß-disubstituted-ethyl)-*N*,*N*,*N*-trimethylammonium ions, *syn* elimination is more prevalent when the ß-substituents are aryl or branched. As the ß-groups become less bulky, the amount of *syn* elimination decreases. This effect is illustrated by the data below.[298]



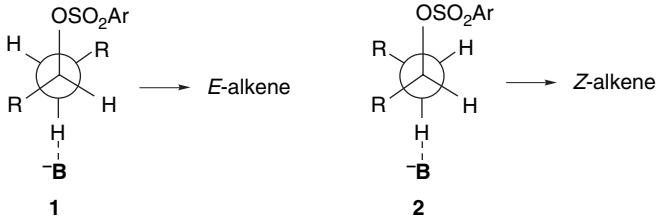
R^1	R^2	% *syn*	% *anti*
Ph	4-MeOPh	62	38
Ph	*i*-Pr	68	32
Ph	Me	26	74
n-Bu	H	<5	>95

296. R.A. Bartsch, E. A. Mintz, and R. M. Parlman, *J. Am. Chem. Soc.*, **96**, 3918 (1974).
297. K. C. Brown and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **92**, 4292 (1970); D. S. Bailey and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **92**, 6904 (1970).
298. Y.-T. Tao and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **105**, 3183 (1983).

The steric dependence is imposed by the bulky trimethylamine leaving group. In the TS for *anti* elimination, steric repulsion is increased as R^1 and R^2 increase in size. When the repulsion is sufficiently large, the TS for *syn* elimination is preferred.



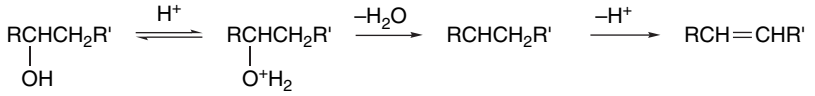
Another aspect of the stereochemistry of elimination reactions is the ratio of *E*-and *Z*-products. The proportion of *Z*-and *E*-isomers of disubstituted internal alkenes formed during elimination reactions depends on the identity of the leaving group. Halides usually give mainly the *E*-alkenes.[299] Bulkier groups, particularly arenesulfonates, give higher proportions of the *Z*-alkene. Sometimes, more *Z*-isomer is formed than *E*-isomer. The preference for *E*-alkene probably reflects the unfavorable steric repulsions present in the E2 transition state leading to *Z*-alkene. High *Z*:*E* ratios are attributed to a second steric effect that becomes important only when the leaving group is large. The conformations leading to *E*-and *Z*-alkene by *anti* elimination are depicted below.



When the leaving group and base are both large, conformation **2** is favored because it permits the leaving group to occupy a position removed from the β-alkyl substituents, while also maintaining an *anti* relationship to the α-hydrogen. *Anti* elimination through a TS arising from conformation **2** gives *Z*-alkene.

5.10.4. Dehydration of Alcohols

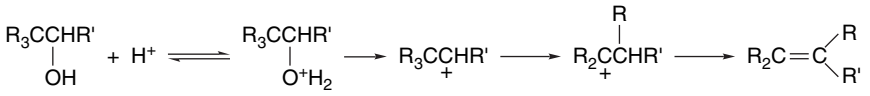
The dehydration of alcohols is an elimination reaction that takes place under acidic rather than basic conditions and involves an E1 mechanism.[300] The function of the acidic reagent is to convert the hydroxy group to a better leaving group by protonation.



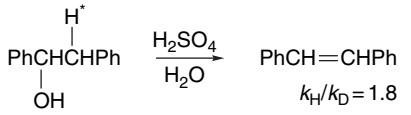
[299] H. C. Brown and R. L. Kliminsch, *J. Am. Chem. Soc.*, **87**, 5517 (1965); I. N. Feit and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **92**, 1630 (1970).

[300] D. V. Banthorpe, *Elimination Reactions*, Elsevier, New York, 1963, pp. 145–156.

This elimination reaction is the reverse of acid-catalyzed hydration, which was discussed in Section 5.2. Since a carbocation or closely related species is the intermediate, the elimination step is expected to favor the more-substituted alkene. The E1 mechanism also explains the trends in relative reactivity. Tertiary alcohols are the most reactive, and reactivity decreases going to secondary and primary alcohols. Also in accord with the E1 mechanism is the fact that rearranged products are found in cases where a carbocation intermediate would be expected to rearrange.



For some alcohols, exchange of the hydroxyl group with solvent competes with dehydration.[301] This exchange indicates that the carbocation can undergo S_N1 capture in competition with elimination. Under conditions where proton removal is rate determining, it would be expected that a significant isotope effect would be seen, which is, in fact, observed.

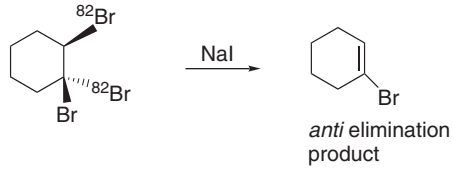


Ref. 302

5.10.5. Eliminations Reactions Not Involving C−H Bonds

The discussion of elimination processes thus far has focused on reactions that involve removal of a proton bound to a ß-carbon, but it is the electrons in the C−H σ bond that are essential to the elimination process. Compounds bearing other substituents that can release electrons undergo β-eliminations. Many such reactions are known, and they are frequently stereospecific.

Vicinal dibromides can be debrominated by certain reducing agents, including iodide ion. The stereochemical course in the case of 1,1,2-tribromocyclohexane was determined using a ^{82}Br-labeled sample prepared by *anti* addition of $^{82}Br_2$ to bromocyclohexene. Exclusive *anti* elimination gave unlabeled bromocyclohexene, whereas ^{82}Br-labeled product resulted from *syn* elimination. Debromination with sodium iodide was found to be cleanly an *anti* elimination.[303]

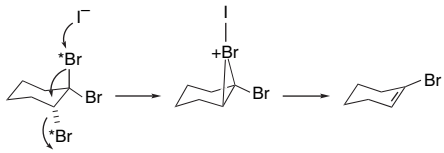


[301] C. A. Bunton and D. R. Llewellyn, *J. Chem. Soc.*, 3402 (1957); J. Manassen and F. S. Klein, *J. Chem. Soc.*, 4203 (1960).

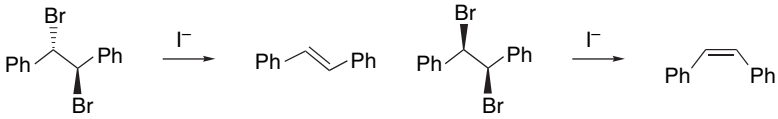
[302] D. S. Noyce, D. R. Hartter, and R. M. Pollack, *J. Am. Chem. Soc.*, **90**, 3791 (1968).

[303] C. L. Stevens and J. A. Valicenti, *J. Am. Chem. Soc.*, **87**, 838 (1965).

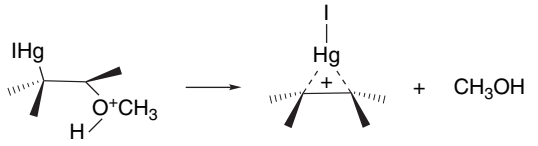
The iodide-induced reduction is essentially the reverse of a halogenation. Application of the principle of microscopic reversibility suggests that the reaction proceeds through a bridged intermediate.[304]



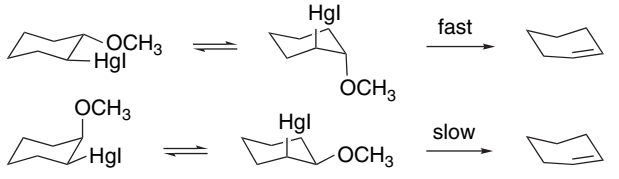
The rate-determining expulsion of bromide ion through a bridged intermediate requires an *anti* orientation of the two bromides. The nucleophilic attack of iodide at one bromide enhances its nucleophilicity and permits formation of the bridged ion. The stereochemical preference in noncyclic systems is also *anti*, as indicated by the fact that *meso*-stilbene dibromide yields *trans*-stilbene, whereas *d*,*l*-stilbene dibromide gives mainly *cis*-stilbene under these conditions.[94]



Structures of type M−C−C−X in which M is a metal and X is a leaving group are very prone to elimination with formation of a double bond. One example is acid-catalyzed deoxymercuration.[305] The ß-oxyorganomercurials are more stable than similar reagents derived from more electropositive metals, but are much more reactive than simple alcohols. For example, $CH_3CH(OH)CH_2HgI$ is converted to propene under acid-catalyzed conditions at a rate that is 10^{11} times greater than dehydration of 2-propanol under the same conditions. These reactions are believed to proceed through a bridged mercurinium ion by a mechanism that is the reverse of oxymercuration (see Section 5.6).

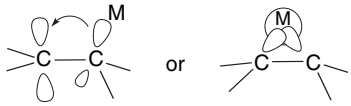


One of the pieces of evidence supporting this mechanism is the fact that the $\Delta H^{\ddagger}$ for deoxymercuration of *trans*-2-methoxycyclohexylmercuric iodide is about 8 kcal/mol less than for the *cis* isomer. Only the *trans* isomer can undergo elimination by an *anti* process through a chair conformation.

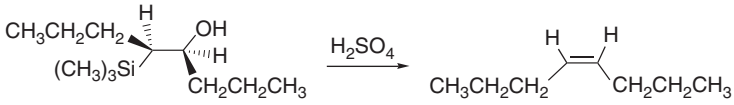


304. C. S. T. Lee, I. M. Mathai, and S. I. Miller, *J. Am. Chem. Soc.*, **92**, 4602 (1970).
305. M. M. Kreevoy and F. R. Kowitt, *J. Am. Chem. Soc.*, **82**, 739 (1960).

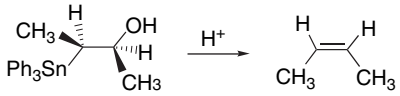
Comparing the rates of acid-catalyzed ß-elimination of compounds of the type MCH_2CH_2OH yields the reactivity order for ß-substituents $IHg \sim Ph_3Pb \sim Ph_3Sn > Ph_3Si > H$. The relative rates are within a factor of ten for the first three, but these are 10^6 greater than for Ph_3Si and 10^{11} greater than for a proton. There are two factors involved in these very large rate accelerations. One is bond energies. The relevant values are $Hg{-}C = 27 < Pb{-}C = 31 < Sn{-}C = 54 < Si{-}C = 60 < H{-}C = 96$ kcal/mol.[306] The metal substituents also have a very strong stabilizing effect for carbocation character at the ß-carbon. This stabilization can be pictured either as a orbital-orbital interaction in which the carbon-metal bond donates electron density to the adjacent *p* orbital, or as formation of a bridged species.



There are a number of synthetically valuable ß-elimination processes involving organosilicon[307] and organotin[308] compounds. Treatment of ß-hydroxyalkylsilanes or ß-hydroxyalkylstannanes with acid results in stereospecific *anti* eliminations that are much more rapid than for compounds lacking the group IV substituent.

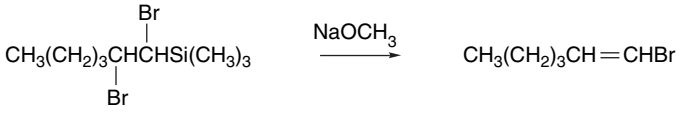


Ref. 309



Ref. 310

ß-Halosilanes also undergo facile elimination when treated with methoxide ion.



Ref. 311

306. D. D. Davis and H. M. Jacocks, III, *J. Organomet. Chem.*, **206**, 33 (1981).

307. A. W. P. Jarvie, *Organomet. Chem. Rev. Sect. A*, **6**, 153 (1970); W. P. Weber, *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983; E. W. Colvin, *Silicon in Organic Synthesis*, Butterworths, London, 1981.

308. M. Pereyre, J. -P. Quintard, and A. Rahm, *Tin in Organic Synthesis*, Butterworths, London, 1987.

309. P. F. Hudrlick and D. Peterson, *J. Am. Chem. Soc*., **97**, 1464 (1975).

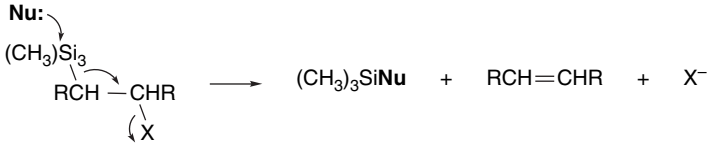
310. D. D. Davis and C. E. Gray, *J. Org. Chem.*, **35**, 1303 (1970).

311. A. W. P. Jarvie, A. Holt, and J. Thompson, *J. Chem. Soc. B,* 852 (1969); B. Miller and G. J. McGarvey, *J. Org. Chem.,* **43**, 4424 (1978).

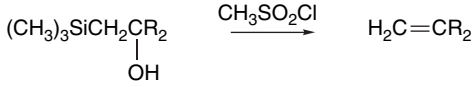
Fluoride-induced ß-elimination of silanes having leaving groups in the ß-position are important processes in synthetic chemistry, as, for example, in the removal of ß-trimethylsilylethoxy groups.

Ref. 312

These reactions proceed by alkoxide or fluoride attack at silicon that results in C−Si bond cleavage and elimination of the leaving group from the ß-carbon. These reactions are stereospecific *anti* eliminations.

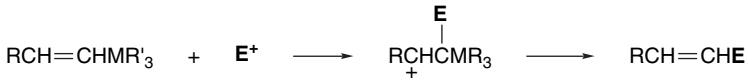


ß-Elimination reactions of this type can also be effected by converting a ß-hydroxy group to a better leaving group. For example, conversion of ß-hydroxyalkylsilanes to the corresponding methanesulfonates leads to rapid elimination.[313]



β-Trimethylsilylalkyl trifluoroacetates also undergo facile *anti* elimination.[314]

The ability to promote ß-elimination and the electron-donor capacity of the ß-metalloid substituents can be exploited in a very useful way in synthetic chemistry.[315] Vinylstannanes and vinylsilanes react readily with electrophiles. The resulting intermediates then undergo elimination of the stannyl or silyl substituent, so that the net effect is replacement of the stannyl or silyl group by the electrophile. The silyl and stannyl substituents are crucial to these reactions in two ways. In the electrophilic addition step, they act as electron-releasing groups that promote addition and control the regiochemistry. A silyl or stannyl substituent strongly stabilizes carbocation character at the ß-carbon atom and thus directs the electrophile to the α-carbon.

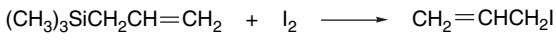


Computational investigations indicate that there is a ground state interaction between the alkene π orbital and the carbon-silicon bond that raises the energy of the π

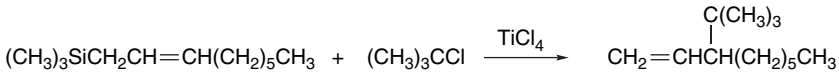
312. P. Sieber, *Helv. Chim. Acta*, **60**, 2711 (1977).
313. F. A. Carey and J. R. Toler, *J. Org. Chem.*, **41**, 1966 (1976).
314. M. F. Connil, B. Jousseaune, N. Noiret, and A. Saux, *J. Org. Chem.*, **59**, 1925 (1994).
315. T. H. Chan and I. Fleming, *Synthesis*, 761 (1979); I. Fleming, *Chem. Soc. Rev.*, **10**, 83 (1981).

HOMO and enhances reactivity.[316] MP3/6-31G* calculations indicate a stabilization of 38 kcal/mol, which is about the same as the value calculated for an α-methyl group.[317] Furthermore, this stereoelectronic interaction favors attack of the electrophile *anti* to the silyl substituent. The reaction is then completed by the elimination step in which the carbon-silicon or carbon-tin bond is broken.

Allyl silanes and allyl stannanes are also reactive toward electrophiles and usually undergo a concerted elimination of the silyl substituent.



Ref. 318



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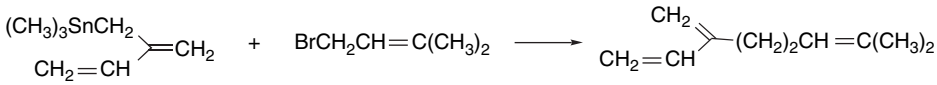

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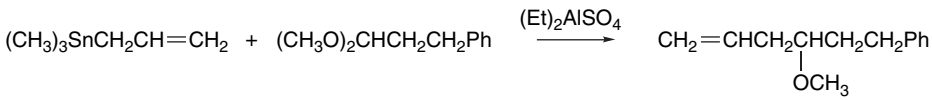
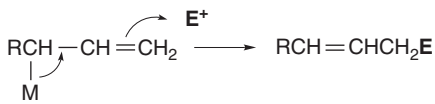


Ref. 321

The common mechanistic pattern in these reactions involves electron release toward the developing electron deficiency on the C(2) of the double bond. Completion of the reaction involves loss of the electron-donating group and formation of the double bond. Further examples of these synthetically useful reactions can be found in Section 9.3 in Part B.



316. S. D. Kahn, C. F. Pau, A. R. Chamberlin, and W. J. Hehre, *J. Am. Chem. Soc.*, **109**, 650 (1987).
317. S. E. Wierschke, J. Chandrasekhar, and W. L. Jorgensen, *J. Am. Chem. Soc.*, **107**, 1496 (1985).
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P. B. de la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, 2nd Edition, Elsevier, New York, 1982.
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G. H. Schmid, in *The Chemistry of Double-Bonded Functional Groups*, Supplement A, Vol. 2, S. Patai, ed., John Wiley & Sons, New York, 1989, Chap. 11.
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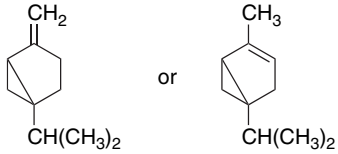
Problems

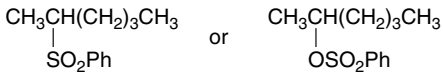
(*References for these problems will be found on page 1160.*)

5.1 Which compound of each pair will react faster with the specified reagent? Explain your answer.

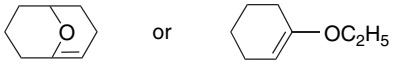
a. 1-hexene or *E*-3-hexene with bromine in acetic acid.
b. *cis*- or *trans*-4-(*t*-butyl)cyclohexylmethyl bromide with $KOC(CH_3)_3$ in *t*-butyl alcohol.
c. 2-phenylpropene or 4-(1-methylethenyl)benzoic acid with sulfuric acid in water.
d.



toward acid-catalyzed hydration.
e.



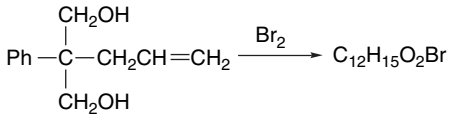
with $KOC(CH_3)_3$ in *t*-butyl alcohol.
f. 4-bromophenylacetylene or 4-methylphenylacetylene with Cl_2 in acetic acid.
g.



toward acid-catalyzed hydration.

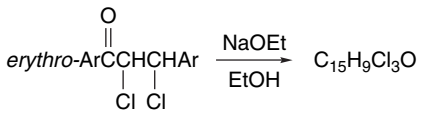
5.2. Predict the structure, including stereochemistry, of the product(s) expected for the following reactions. If more than one product is shown, indicate which is major and which is minor.

a.

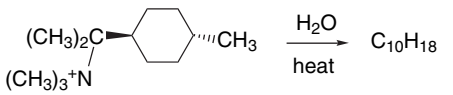


b.

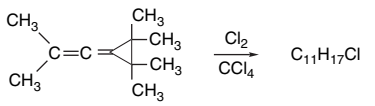
c.



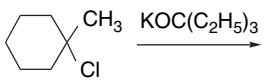
d.



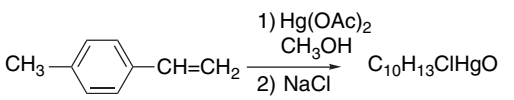
e.



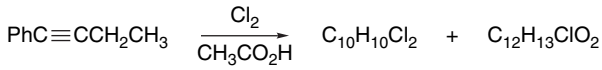
f.



g.



h.



5.3. The reaction of the *cis* and *trans* isomers of *N*,*N*,*N*-trimethyl-(4-*t*-butylcyclohexyl)ammonium chloride with $K^{+-}O$-*t*-Bu in *t*-butyl alcohol have been compared. The *cis* isomer gives 90% 4-*t*-butylcyclohexene and 10% *N*,*N*-dimethyl-(4-*t*-butylcyclohexyl)amine, whereas the *trans* isomer gives only the latter product in quantitative yield. Explain the different behavior of the two isomers.

5.4. For E2 eliminations in 2-phenylethyl systems with several different leaving groups, both the primary kinetic isotope effect and Hammett ρ have been determined. Deduce information about the nature and location (early, late) of the TS in the variable E2 spectrum. How does the identity of the leaving group affect the nature and location of the TS?

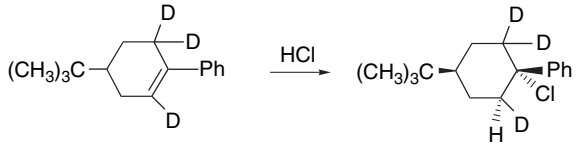
X	k_H/k_D	ρ
Br	7.11	2.1
OTs	5.66	2.3
$^+S(CH_3)_2$	5.07	2.7
$^+N(CH_3)_3$	2.98	3.7

5.5. Predict the effect on the 1-butene, *Z*-2-butene, and *E*-2-butene product ratio when the E2 elimination (KOEt, EtOH) of *erythro*-3-deuterio-2-bromobutane is compared with 2-bromobutane. Which alkene(s) will increase in relative amount and which will decrease in relative amount? Explain the basis of your answer.

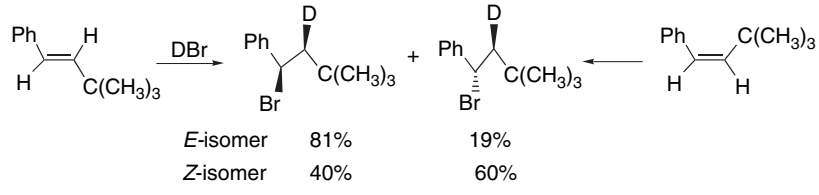
5.6. Arrange the following compounds in order of increasing rate of acid-catalyzed hydration: ethene, propene, 2-cyclopropylpropene, 2-methylpropene, 1-cyclopropyl-1-methoxyethene. Explain the basis of your answer.

5.7. Discuss the factors that are responsible for the regiochemistry and stereochemistry observed for the following reactions.

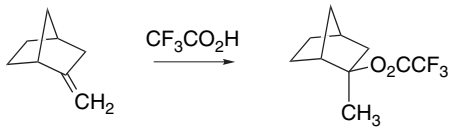
a.



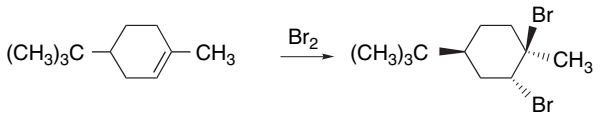
b.



c.

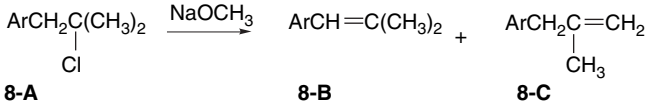


d.



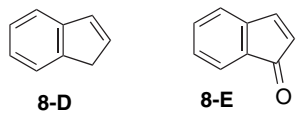
5.8. Explain the mechanistic basis of the following observations and discuss how the observation provides information about the reaction mechanism.

a. When 1-aryl-2-methyl-2-propyl chlorides (**8-A**) react with $NaOCH_3$, roughly 1:1 mixtures of internal (**8-B**) and terminal alkene (**8-C**) are formed. By using the product ratios, the overall reaction rate can be dissected into the rates for formation of **8-B** and **8-C**. The rates are found to be substituent dependent for **8-B** ($\rho = +1.4$) but not for **8-C** ($\rho = -0.1 \pm 0.1$). All the reactions are second order, first order in reactant and first order in base.



b. When 1,3-pentadiene reacts with DCl, more *E*-4-chloro-5-deuterio-2-pentene (60–75%) is formed than *E*-4-chloro-1-deuterio-2-pentene (40–25%).

c. When indene (**8-D**) is brominated in CCl_4, it gives some 15% *syn* addition, but indenone (**8-E**) gives only *anti* addition under these conditions. When the halogenation of indenone is carried out using Br—Cl, the product is *trans*-2-bromo-3-chloroindenone.



d. The acid-catalyzed hydration of allene gives acetone, not allyl alcohol or propanal.

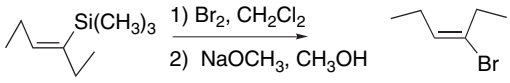
e. In the addition of HCl to cyclohexene in acetic acid, the ratio of cyclohexyl acetate to cyclohexyl chloride drops significantly when tetramethylammonium chloride is added in increasing concentrations. The rate of the reaction is also accelerated. These effects are not observed with styrene.

f. The ρ value for elimination of HF using $K^{+-}O$-*t*-Bu from a series of 1-aryl-2-fluoroethanes increases from the mono- to di- and trifluoro derivatives, as indicated below.

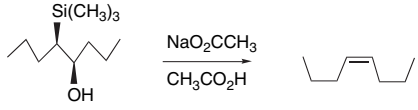
$ArCH_2CF_3$	$ArCH_2CHF_2$	$ArCH_2CH_2F$
$\rho = +4.04$	$\rho = +3.56$	$\rho = +3.24$

5.9. Suggest mechanisms that account for the outcome of the following reactions:

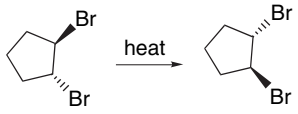
a.



b.

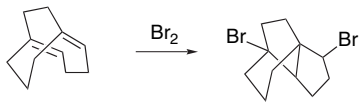


c.



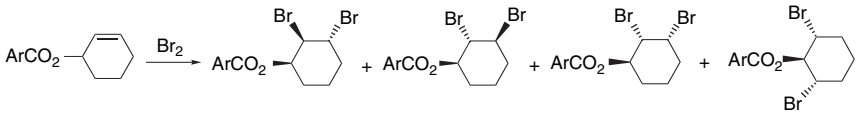
optically active racemic

d.

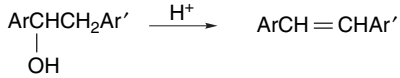


5.10. The rates of bromination of internal alkynes are roughly 100 times greater that the corresponding terminal alkynes. For hydration, however, the rates are less than 10 times greater for the disubstituted compounds. Account for this difference by comparison of the mechanisms for bromination and hydration.

5.11. The bromination of 3-aroyloxycyclohexenes gives rise to a mixture of stereoisomeric and regioisomeric products. The product composition for Ar = phenyl is shown. Account for the formation of each of these products.



5.12. The Hammett correlation of the acid-catalyzed dehydration of 1,2-diaryl ethanols has been studied. The correlation resulting from substitution on both the 1- and 2-aryl rings is: $\log\ k = -3.78(\sigma^{+}_{Ar} + 0.23\sigma_{Ar'}) - 3.18$. Rationalize the form of this correlation equation. What information does it give about the involvement of the Ar′ ring in the rate-determining step of the reaction?



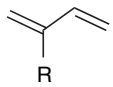
5.13. The addition of HCl to alkenes such as 2-methyl-1-butene and 2-methyl-2-butene in nitromethane follow a third-order rate expression:

$$\text{Rate} = k[\text{HCl}]^2[\text{alkene}]$$

It has also been established that there is no incorporation of deuterium into the reactant at 50% completion when DCl is used. Added tetraalkylammonium chloride retards the reaction, but the corresponding perchlorate salt does not. Propose a reaction mechanism that is consistent with these observations.

5.14. In the bromination of substituted styrenes, a $\rho\sigma^+$ plot is noticeably curved. If the extremes of the curve are taken to represent straight lines, the curve can be resolved into two Hammett relationships with $\rho = -2.8$ for EWG substituents and $\rho = -4.4$ for ERG substituents. The corresponding β-methylstyrenes give a similarly curved plot. The stereoselectivity of the reaction of the β-methylstyrenes is also dependent on the substituents. The reaction is stereospecifically *anti* for strong EWGs, but is only weakly stereoselective, e.g., 63% *anti*:37% *syn*, for methoxy. Discuss a possible mechanistic basis for the curved Hammett plots and the relationship to the observed stereochemistry.

5.15. The second-order rate constants and solvent kinetic isotope effects for acid-catalyzed hydration are given below for several 2-substituted 1,3-butadienes. The products are a mixture of 1,2- and 1,4-addition. What information do these data provide about the mechanism of the reaction?



R	$k_2(M^{-1}s^{-1})$	$k_H{}^+/k_{D^+}$
c-C_3H_5	1.22×10^{-2}	1.2
CH_3	3.19×10^{-5}	1.8
Cl	2.01×10^{-8}	1.4
H	3.96×10^{-8}	1.8
C_2H_5O	60	-

5.16. The reaction of both *E*- and *Z*-2-butene with acetic acid to give 2-butyl acetate is catalyzed by various strong acids. With DBr, DCl, and CH_3SO_3H in CH_3CO_2D, the reaction proceeds with largely $(84 \pm 2\%)$ *anti* addition. If the reaction is stopped short of completion, there is no incorporation of deuterium into unreacted alkene, nor any interconversion of the *E*- and *Z*-isomers. When the catalyst is changed to CF_3SO_3H, the recovered butene shows small amounts of 1-butene and interconversion of the 2-butene stereoisomers. The stereoselectivity of the reaction drops to 60–70% *anti* addition. How can you account for the changes that occur when CF_3SO_3H is used as the catalyst, as compared with the other acids?

5.17. A comparison of rate and product composition of the products from reaction of *t*-butyl chloride with $NaOCH_3$ in methanol and methanol-DMSO mixtures has been reported. Some of the data are shown below. Interpret the changes in rates and product composition as the amount of DMSO in the solvent mixture is increased.

	100% MeOH			36.8% DMSO			64.2% DMSO		
		Product comp.(%)			Product comp.(%)			Product comp.(%)	
[NaOMe] M	Rate $k \times 10^4 s^{-1}$	Ether	Alkene	Rate $k \times 10^4 s^{-1}$	Ether	Alkene	Rate $k \times 10^4 s^{-1}$	Ether	Alkene
0.00	2.15	73.8	26.2	0.81	50	50	0.24	24	76
0.20	2.40			1.52			5.3		
0.25	2.30	62.9	32.1						
0.30	2.26			1.90	10.5	89.5	10.3	0	100
0.40	2.36			2.65			17.5	0	100
0.50	2.56	58.6	41.4				24.2	0	100
0.70				4.11	1.1	98.9			
0.75	2.58	51.7	48.3						
0.80				4.59					
0.90	2.64			6.16	4.1	95.9			
1.00	2.74	52.2	47.8	6.81	3.8	96.2			

5.18 a. The gas phase basicity of substituted α-methyl styrenes follows the Yukawa-Tsuno equation with $r^+ = 1.0$. The corresponding r^+ for 1-phenylpropyne is 1.12 and for phenylacetylene it is 1.21. How are these values related to the relative stability of the carbocations formed by protonation?

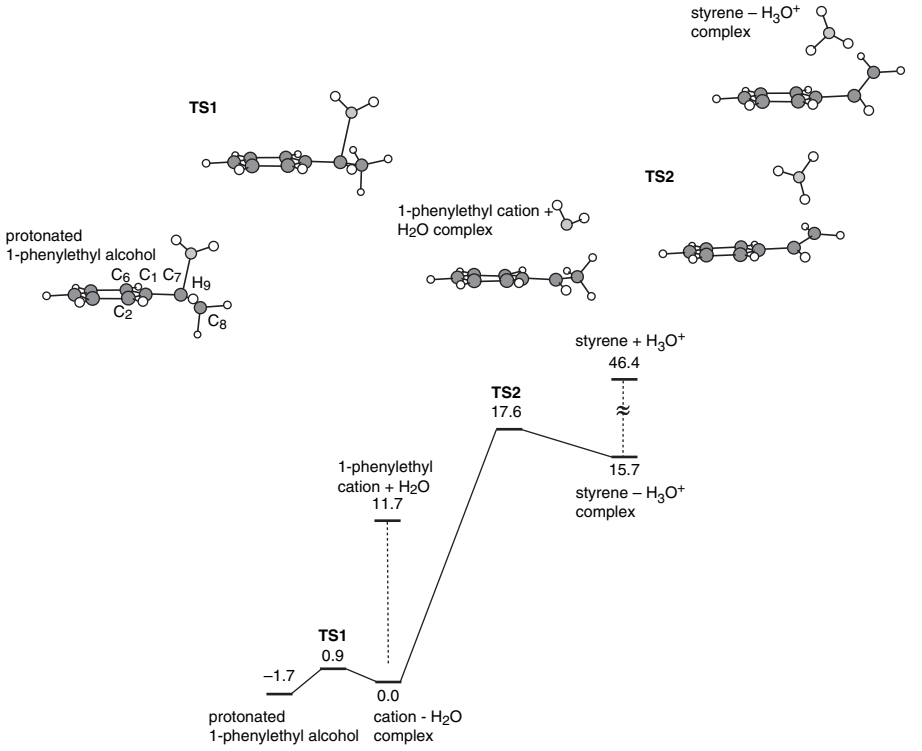


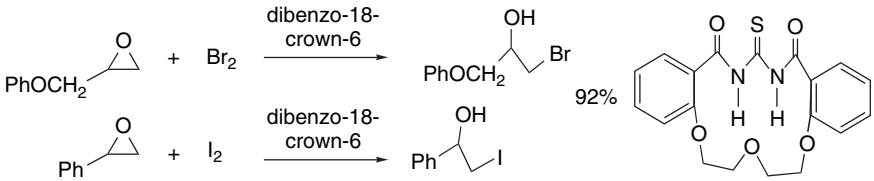
Fig. 5.P18b. Reaction profile for ionization and protonation routes to 1-phenylethylium cation. Relative energies are in kcal/mol. Reproduced from the *Bulletin of the Chemical Society of Japan.,* **71**, 2427 (1998).

Table 5.P18b. Selected Structural Parameters, Charge Densities, and Energies of Reactants and Transition States for Formation of a 1-Phenylethylium Ion

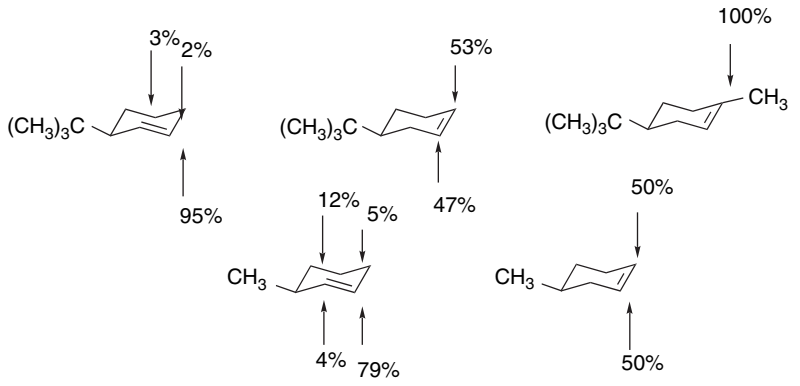
Bond length	Protonated Alcohol	TS1	Phenylethylium Cation-H_2O Complex	TS2	Styrene-H_3O^+ Complex	Styrene
C(1)−C(7)	1.474	1.420	1.395	1.457	1.478	1.472
C(7)−C(8)	1.500	1.481	1.469	1.367	1.353	1.343
C(7)−O	1.641	2.077	2.639			
C(8)−C(10)	1.093	1.091	1.098	1.608	2.118	
Charge on Ph	0.225	0.369	0.468	0.196	0.111	−0.002
Relative energy	−1.7	0.9	0.0	17.6	15.7	46.4

b. The acid-catalyzed hydration of styrene and the dissociation of protonated 1-phenylethanol provide alternative routes to the 1-phenylethylium cation. The resonance component (r^+) of the Yukawa-Tsuno equations are 0.70 and 1.15, respectively. The reactions have been modeled using MP2/6-31G* calculations and Figure 5.P18b gives the key results. Table 5.P18b lists some of the structural features of the reactants, TSs, and products. Interpret and discuss these results.

5.19. Crown ethers have been found to catalyze the ring opening of epoxides by I_2 and Br_2. The catalysts also improve the regioselectivity, favoring addition of the halide at the less-substituted position. A related structure (shown on the right) is an even better catalyst. Indicate a mechanism by which these catalytic effects can occur.

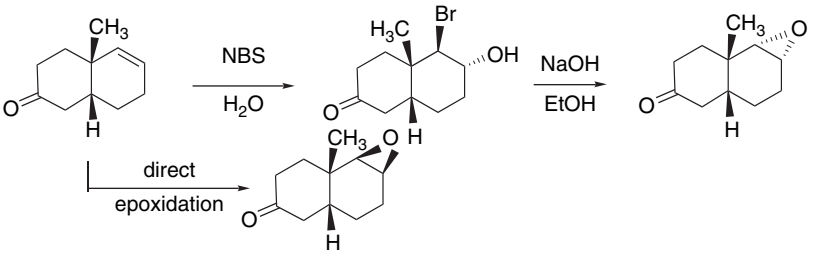


5.20. The chart below shows the regio- and stereoselectivity observed for oxymercuration reduction of some 3- and 4-alkylcyclohexenes. Provide an explanation for the product ratios in terms of the general mechanism for oxymercuration discussed in Section 5.6.1.

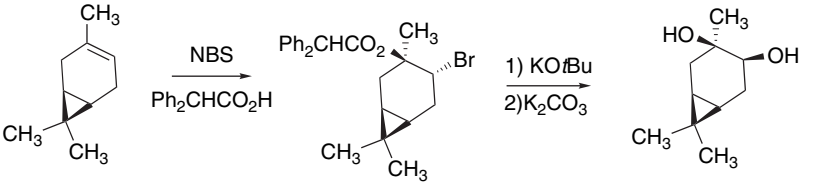


5.21. Solvohalogenation can be used to achieve both regio- and stereochemical control for synthetic purposes in alkene addition reactions. Some examples are shown below. Discuss the factors that lead to the observed regio- or stereochemical outcome.

a. Control of the stereochemistry of an epoxide:



b. Formation of *cis*-diols:



c. Chemoselective functionalization of polyalkenes: