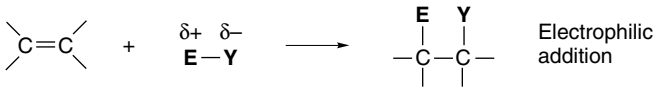
5

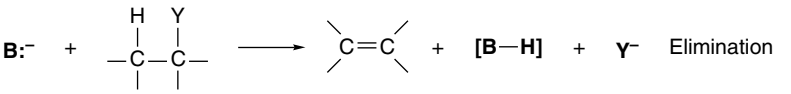
Polar Addition and Elimination Reactions

Introduction

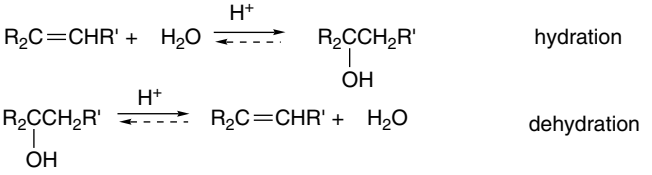
In this chapter, we discuss reactions that either add adjacent (*vicinal*) groups to a carbon-carbon double bond (*addition*) or remove two adjacent groups to form a new double bond (*elimination*). The discussion focuses on addition reactions that proceed by electrophilic polar (*heterolytic*) mechanisms. 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.



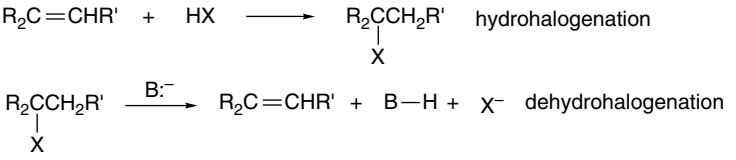
The discussion of elimination reactions considers the classical E2, E1, and E1cb eliminations that involve removal of a hydrogen and a leaving group. We focus on the kinetic and stereochemical characteristics of elimination reactions as key indicators of the reaction mechanism and examine how substituents 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.



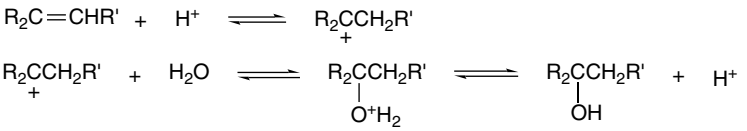
Addition and elimination processes are the formal reverse of one another, and in some cases the reaction can occur in either direction. For example, acid-catalyzed hydration of alkenes and dehydration of alcohols are both familiar reactions that constitute an addition-elimination pair.



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

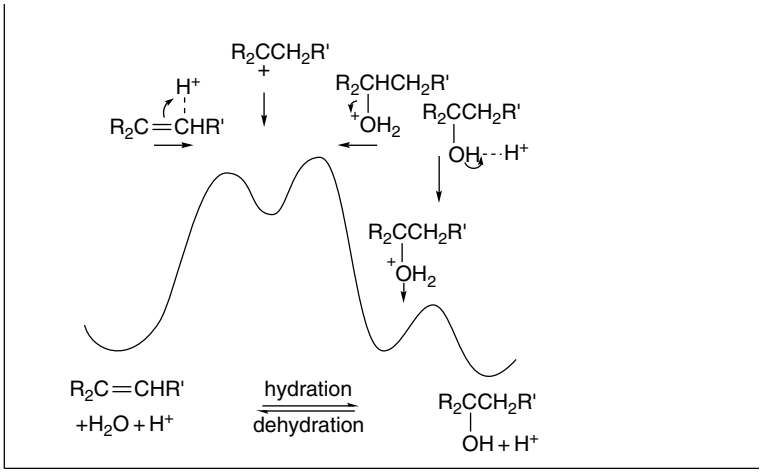
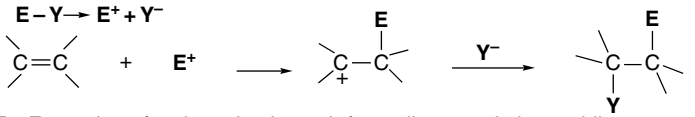


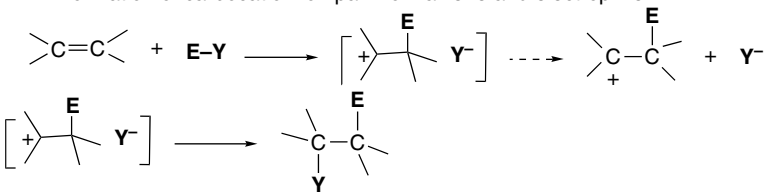
Fig. 5.1. Conceptual representation of the reversible reaction path for the hydration-dehydration reaction pair.

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.

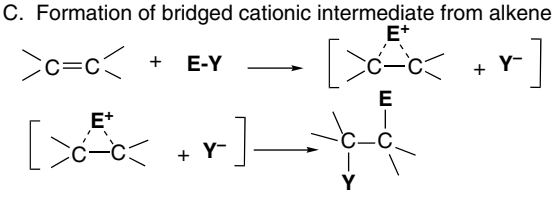
A. Prior dissociation of electrophile and formation of carbocation intermediate



B. Formation of carbocation ion pair from alkene and electrophile



C. Formation of bridged cationic intermediate from alkene and electrophile



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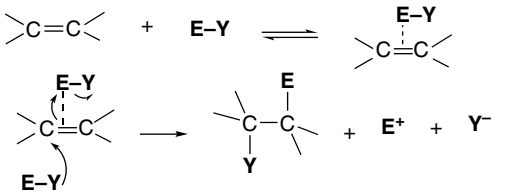
D. Concerted addition of electrophile and nucleophile in a termolecular reaction



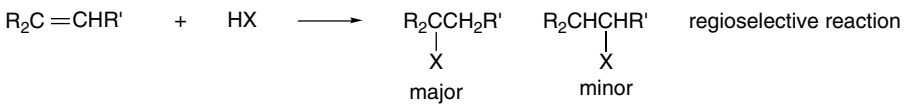
All of these mechanisms are related in that they involve electrophilic attack on the π bond of the alkene. Based on the electron distribution and electrostatic potential maps of alkenes (Section 1.4.5), the initial attack is expected to be perpendicular to the plane of the double bond and near the midpoint 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 dealt with 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.

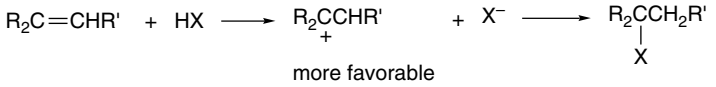
5.1. Addition of Hydrogen Halides to Alkenes

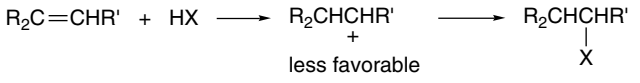
The addition of hydrogen halides to alkenes has been studied from a mechanistic perspective for many years. One of the first aspects of the mechanism to be established was its regioselectivity, that is, the direction of addition. A reaction is described as *regioselective* if an unsymmetrical alkene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

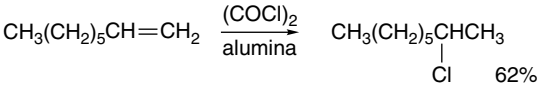




As is indicated when the mechanism is discussed in more detail, discrete carbocations are not always formed. Unsymmetrical alkenes nevertheless follow the Markovnikov rule, because the partial positive charge that develops is located predominantly at the carbon that is better able to accommodate an electron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

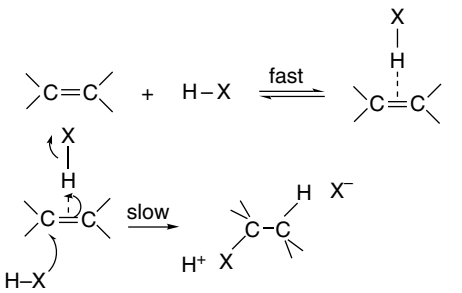


2. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.*, **96**, 1858 (1974).
3. P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. C. Craig, M. M. Baillargeon, and G. W. Breton, *J. Am. Chem. Soc.*, **115**, 3071 (1993).

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.

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

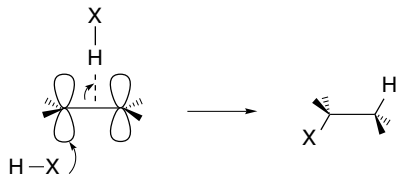
Among the cases in which this type of kinetics has been observed are the addition of HCl to 2-methyl-1-butene, 2-methyl-2-butene, 1-methylcyclopentene,[4] and cyclohexene.[5] The addition of HBr to cyclopentene also follows a third-order rate expression.[2] The TS associated with the third-order rate 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.



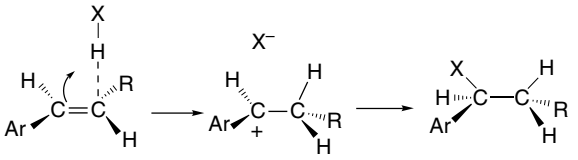
The stereochemistry of addition of hydrogen halides to unconjugated alkenes is usually *anti*. This is true for addition of HBr to 1,2-dimethylcyclohexene,[6] cyclohexene,[7] 1,2-dimethylcyclopentene,[8] cyclopentene,[2] *Z*- and *E*-2-butene,[2] and 3-hexene,[2] among others. *Anti* stereochemistry 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).

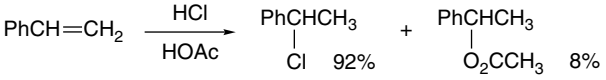


A change in the stereoselectivity is observed when the double bond is conjugated with a group that can stabilize a carbocation intermediate. Most of the specific cases involve an aryl substituent. Examples of alkenes that give primarily *syn* addition are *Z*- and *E*-1-phenylpropene,[11] *cis*- and *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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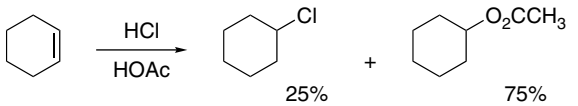
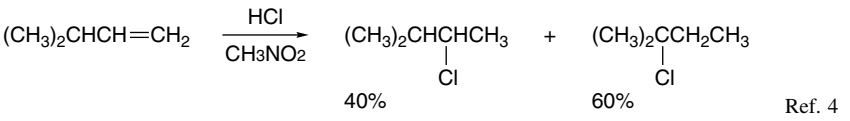


Ref. 5

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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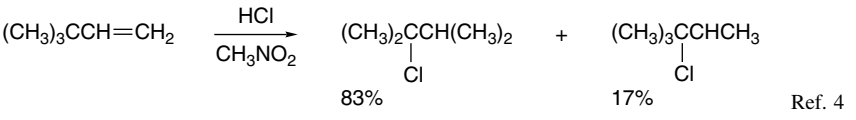
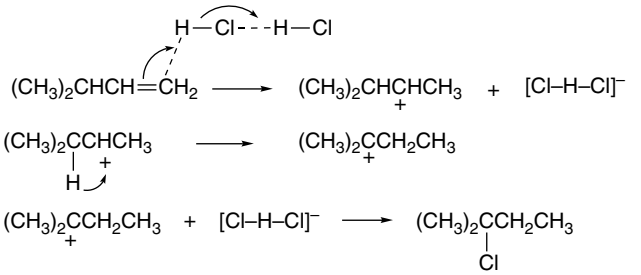
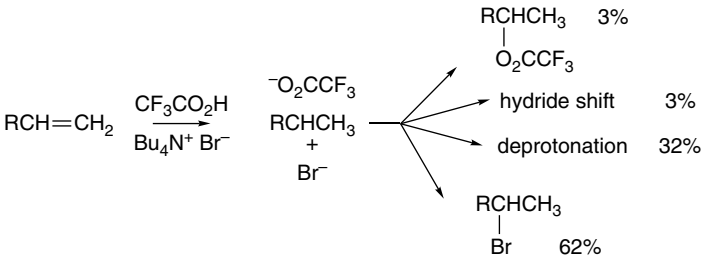


Ref. 4

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.

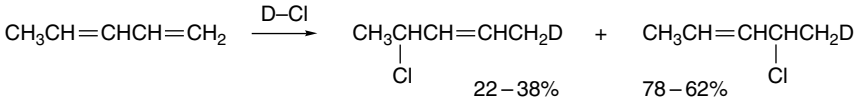


This behavior of the cationic intermediates generated by alkene protonation is consistent with the reactivity associated with carbocations generated by leaving-group

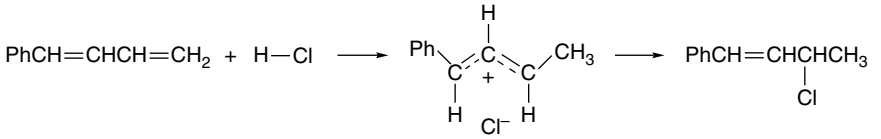
16. H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1517 (1998).

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]

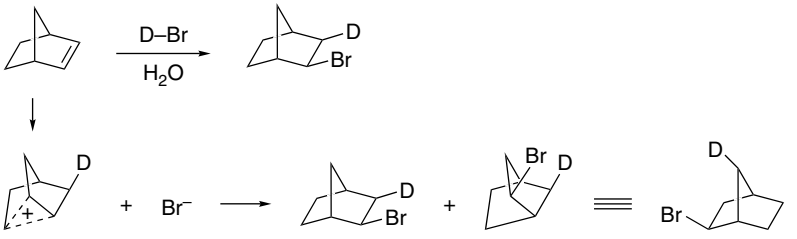


With 1-phenyl-1,3-butadiene, the addition of HCl is exclusively at the 3,4-double bond. This reflects the greater stability of this product, which retains styrene-type conjugation. Initial protonation at C(4) is favored by the fact that the resulting carbocation benefits from both allylic and benzylic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

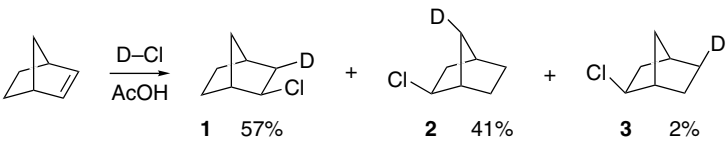
The additions of HCl or HBr to norbornene are interesting cases because such factors as the stability and facile rearrangement of the norbornyl cation come into consideration. (See Section 4.4.5 to review the properties of the 2-norbornyl cation.) Addition of deuterium bromide to norbornene gives *exo*-norbornyl 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]



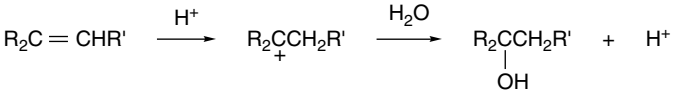
1 57% **2** 41% **3** 2%

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.

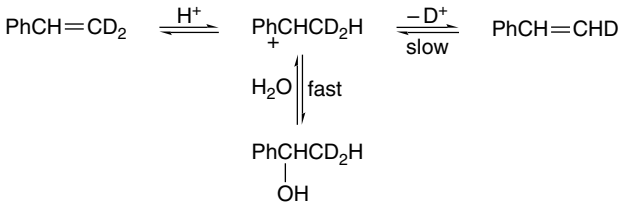


This mechanism explains the formation of the more highly substituted alcohol from unsymmetrical alkenes (Markovnikov's rule). A number of other points must be considered in order to provide a more complete picture of the mechanism. Is the protonation step reversible? Is there a discrete carbocation intermediate, 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?

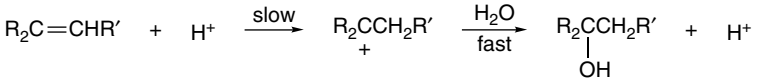
Much of the early mechanistic work on hydration reactions was done with conjugated alkenes, particularly styrenes. Owing to the stabilization provided by the phenyl group, this reaction involves a relatively stable carbocation. With styrenes, the rate of hydration is increased by ERG substituents and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

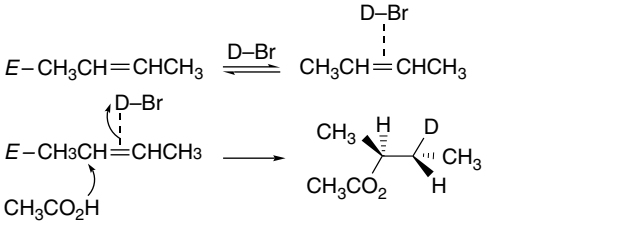
[27] Y. Chiang and A. J. Kresge, *J. Am. Chem. Soc.*, **107**, 6363 (1985).

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

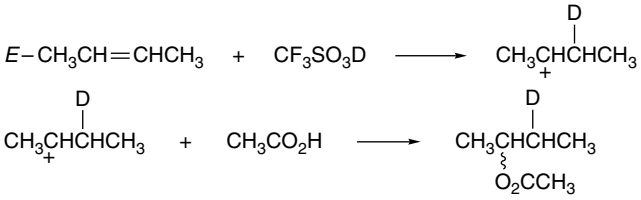
Alkene	$k_2(M^{-1}s^{-1})$	k_{rel}
$CH_2{=}CH_2$	1.56×10^{-15}	1
$CH_3CH{=}CH_2$	2.38×10^{-8}	1.6×10^7
$CH_3(CH_2)_3CH{=}CH_2$	4.32×10^{-8}	3.0×10^7
$(CH_3)_2C{=}CHCH_3$	2.14×10^{-3}	1.5×10^{12}
$(CH_3)_2C{=}CH_2$	3.71×10^{-3}	2.5×10^{12}
$PhCH{=}CH_2$	2.4×10^{-6}	1.6×10^9

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

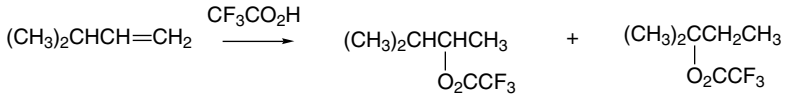


nucleophilic participation not required: nonstereospecific addition

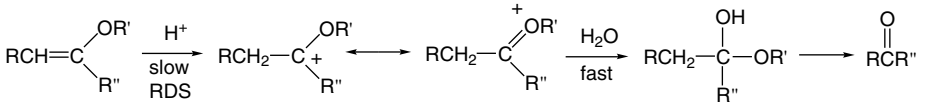
Trifluoroacetic acid adds to alkenes without the necessity of a stronger acid catalyst.[30] The mechanistic features of this reaction are similar to addition of water catalyzed by strong acids. For example, there is a substantial isotope effect when CF_3CO_2D is used ($k_H/k_D = 4.33$)[31] and the reaction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



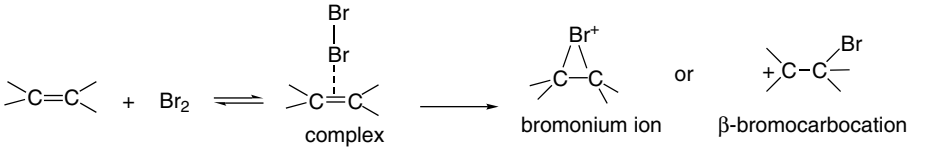
5.3. Addition of Halogens

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).

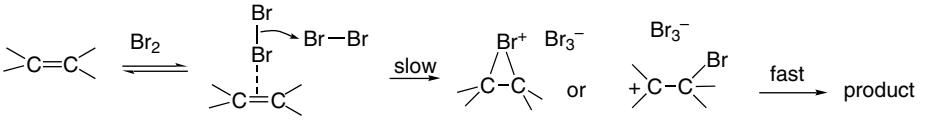
The formation of the complex can be observed spectroscopically, and they subsequently disappear at a rate corresponding to the formation of bromination product.[36,37] The second step in bromination involves formation of an ionic intermediate, which can be either a bridged bromonium ion or a β-bromocarbocation. 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).

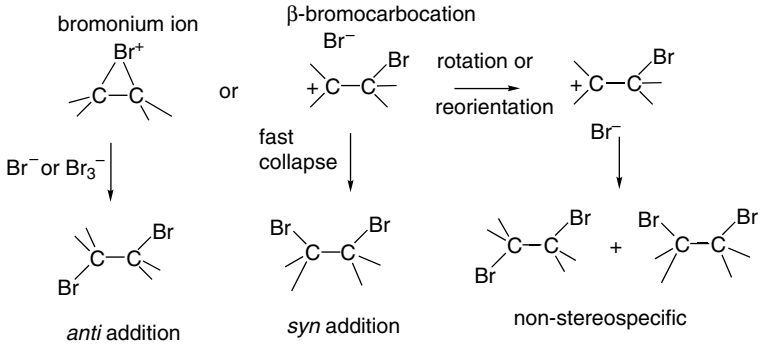
Table 5.3. Stereochemistry of Alkene Halogenation

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).

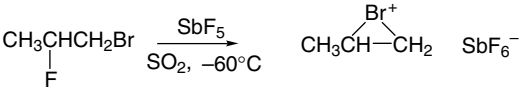


Substituent effects on stilbenes provide examples of the role of bridged ions versus nonbridged carbocation intermediates. In aprotic solvents, stilbene gives clean *anti* addition, but 4, 4′-dimethoxystilbene gives a mixture of the *syn* and *anti* addition products indicating a carbocation intermediate.[51]

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]

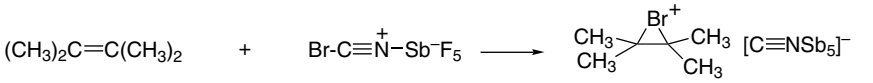
There is direct evidence for the existence of bromonium ions. The bromonium ion related to propene can be observed by NMR when 1-bromo-2-fluoropropane is subjected to superacid conditions.



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.

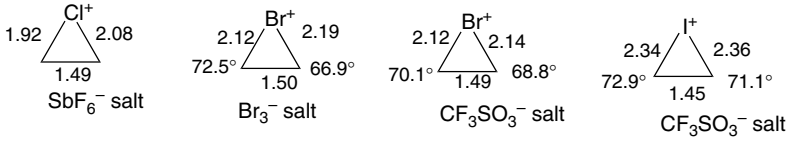
51. G. Bellucci, C. Chiappe, and G. Lo Moro, *J. Org. Chem.*, **62**, 3176 (1997).
52. M.-F. Ruasse, G. Lo Moro, B. Galland, R. Bianchini, C. Chiappe, and G. Bellucci, *J. Am. Chem. Soc.*, **119**, 12492 (1997).
53. R. W. Nagorski and R. S. Brown, *J. Am. Chem. Soc.*, **114**, 7773 (1992).
54. K. Yates 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.



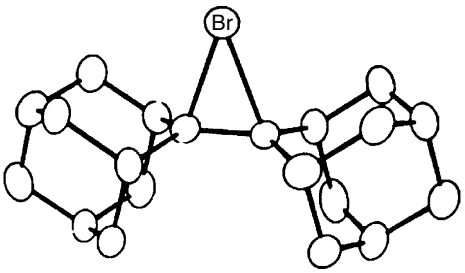
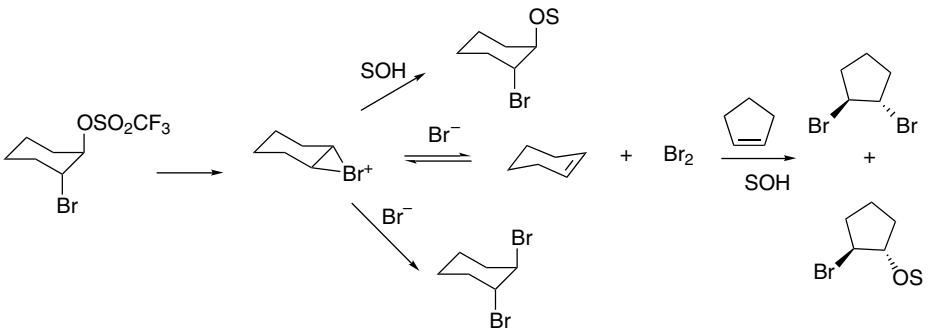


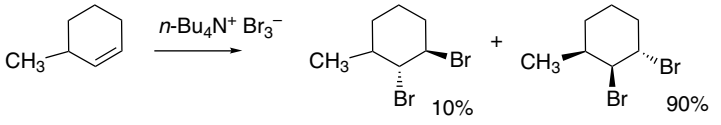
Fig. 5.2. X-ray crystal structure of the bromonium ion from adamantylideneadamantane. Reproduced from *J. Am. Chem. Soc*., **107**, 4504 (1985), by permission of the American Chemical Society.

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]

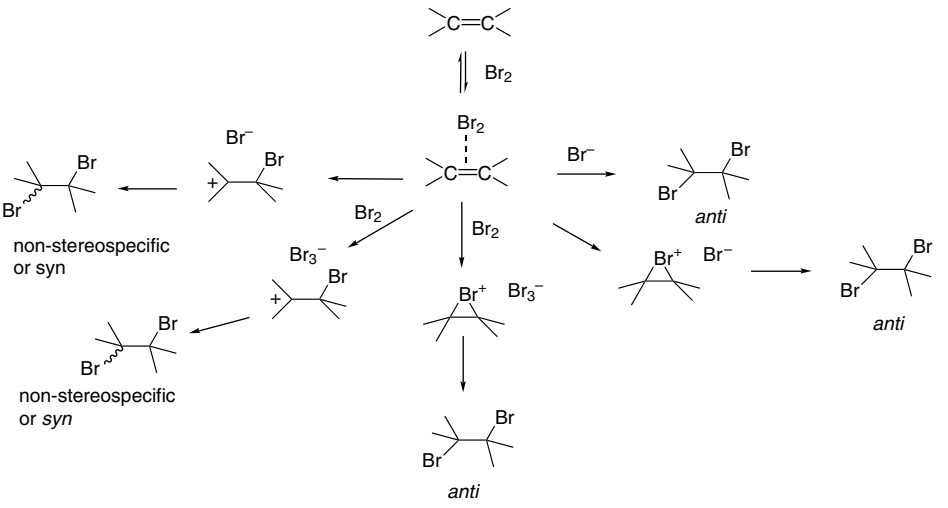


Bromination also can be carried out with reagents that supply bromine in the form of the Br_3^- anion. One such reagent is pyridinium bromide tribromide. Another is tetrabutylammonium tribromide.[65] These reagents are believed to react via the Br_2-alkene complex and have a strong preference for *anti*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

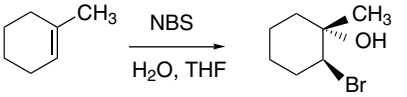


In summary, it appears that bromination usually involves a complex that collapses to an ion pair intermediate. The ionization generates charge separation and is assisted by solvent, acids, or a second molecule of bromine. The cation can be a β-carbocation, as in the case of styrenes, or a bromonium ion. 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).

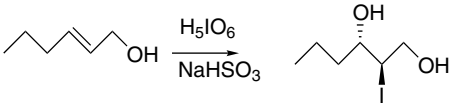


The cationic intermediates also can be captured by solvent. Halogenation with solvent capture is a synthetically important reaction, especially for the preparation of chlorohydrins and bromohydrins.[66] Chlorohydrins can be prepared using various sources of electrophilic chlorine. Chloroamine T is a 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.



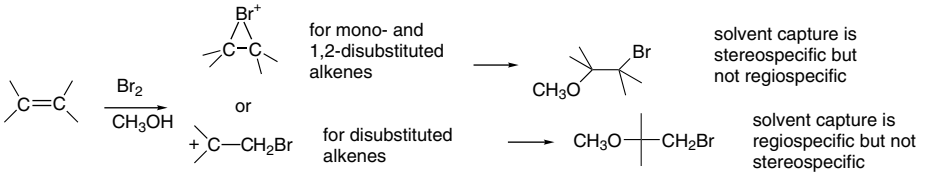
Ref. 69

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.

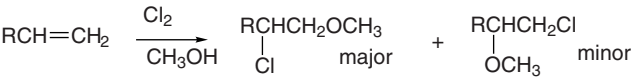


66. J. Rodriguez and J. P. Dulcere, *Synthesis*, 1177 (1993).
67. B. Damin, J. Garapon, and B. Sillion, *Synthesis*, 362 (1981).
68. J. N. Kim, M. R. Kim, and E. K. Ryu, *Synth. Commun.*, **22**, 2521 (1992); V. L. Heasley, R. A. Skidgel, G. E. Heasley, and D. Strickland, *J. Org. Chem.*, **39**, 3953 (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.

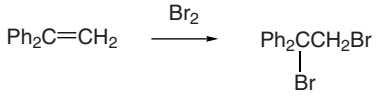


Similar results were obtained for chlorination of several of alkenes in methanol.[73] Whereas styrene gave only the Markovnikov product, propene, hexene, and similar alkenes gave more of the *anti* Markovnikov product. This result is indicative of strong bridging in the chloronium ion.



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.

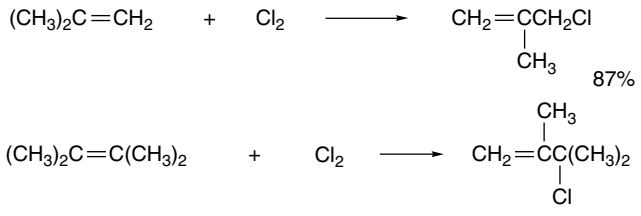
Some alkenes react with halogens to give substitution rather than addition. For example, with 1,1-diphenylethene, substitution is the main reaction at low bromine concentration. Substitution occurs when loss of a proton is faster than capture by bromide.



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

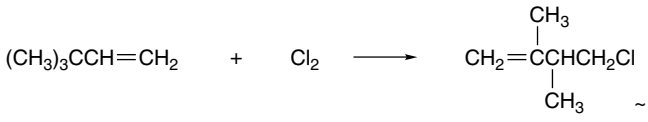
Similarly, in chlorination, loss of a proton can be a competitive reaction of the cationic intermediate. 2-Methylpropene and 2,3-dimethyl-2-butene give products of this type.

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).

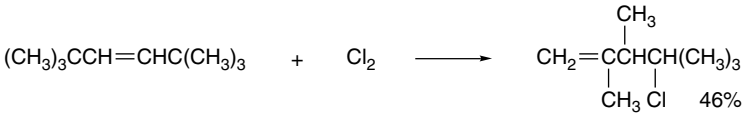


Ref. 74

Alkyl migrations can also occur.



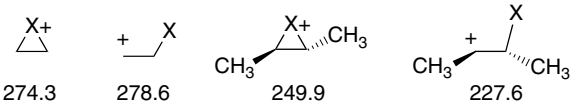
Ref. 74



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.

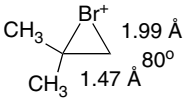


X				
F	274.3	278.6	249.9	227.6
Cl	253.4	277.8	233.8	230.6
Br	239.9	270.8	221.6	225.0

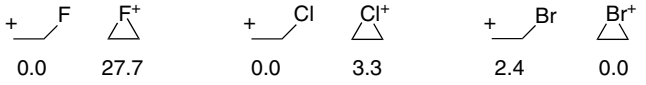
Hydride affinity in kcal/mol

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.

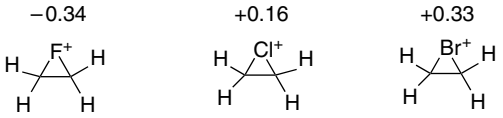


Another study gives some basis for comparison of the halogens.[79] QCISD(T)/6-311(d, p) calculations found the open carbocation to be the most stable for $[C_2H_4F]^+$ and $[C_2H_4Cl]^+$ but the bridged ion was more stable for $[C_2H_4Br]^+$. The differences were small for Cl and Br.

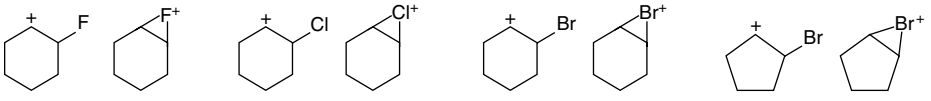


Relative energy in kcal/mol of open and bridged $[C_2H_4X]^+$ ions

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.



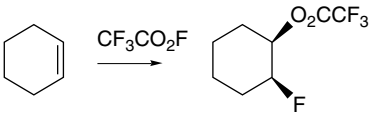
Relative stability of open and bridged cations in kcal/mol

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.

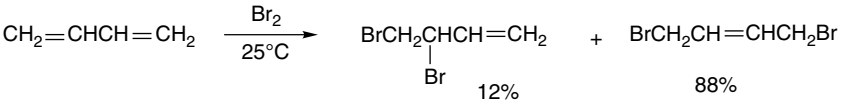
78. M. Klobukowski and R. S. Brown, *J. Org. Chem.*, **59**, 7156 (1994).
79. R. Damrauer, M. D. Leavell, and C. M. Hadad, *J. Org. Chem.*, **63**, 9476 (1998).
80. G. K. S. Prakash, R. Aniszefeld, T. Hashimoto, J. W. Bausch, and G. A. Olah, *J. Am. Chem. Soc.*, **111**, 8726 (1989).

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]

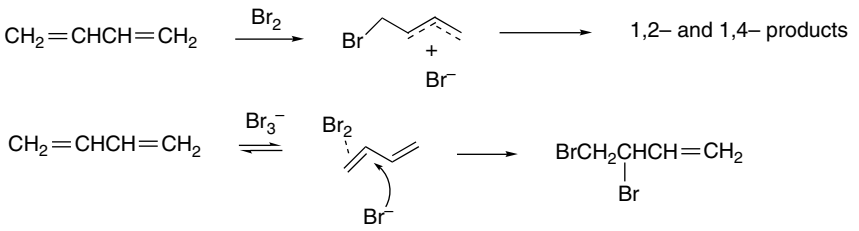
As with other electrophiles, halogenation can give 1,2- or 1,4-addition products from conjugated dienes. When molecular bromine is used as the brominating agent in chlorinated solvent, the 1,4-addition product dominates by ~ 7:1 in the case of butadiene.[89]



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.

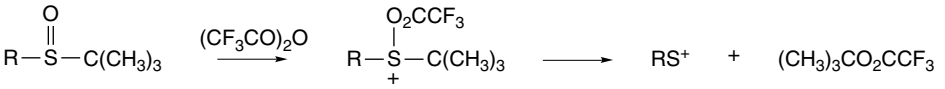


The stereochemistry of both chlorination and bromination of several cyclic and acyclic dienes has been determined. The results show that bromination is often stereospecifically *anti* for the 1,2-addition process, whereas *syn* addition is preferred for 1,4-addition. Comparable results for chlorination 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.

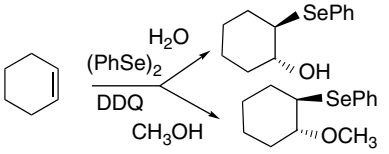
5.4. Sulfenylation and Selenenylation

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.



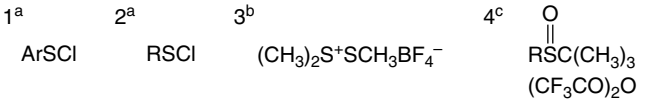
Ref. 91

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

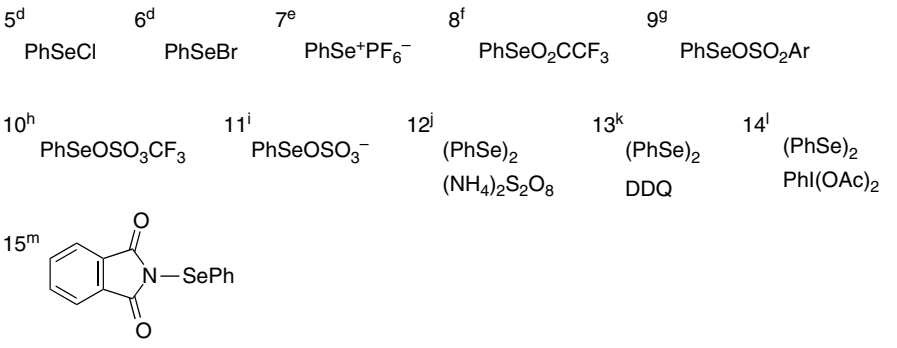
90. G. E. Heasley, D. C. Hayes, G. R. McClung, D. K. Strickland, V. L. Heasley, P. D. Davis, D. M. Ingle, K. D. Rold, and T. L. Ungermann, *J. Org. Chem.*, **41**, 334 (1976).
91. M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, and C. Santi, *Synlett*, 1767 (2001).

Scheme 5.1. Electrophilic Sulfur and Selenium Reagents

A. Sulfenylation Reagents



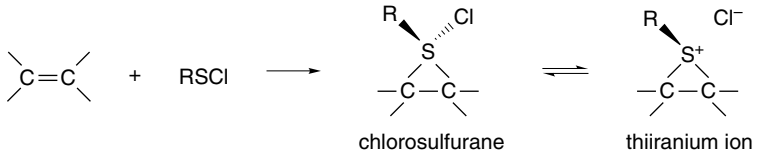
B. Selenenylation Reagents



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).

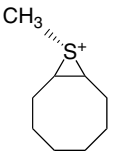
5.4.1. Sulfenylation

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]

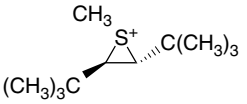


The sulfur atom is a stereogenic center in *both* the sulfurane and the thiiranium ion, and this may influence the stereochemistry of the reactions of stereoisomeric alkenes. Thiiranium ions can be prepared in various ways, and several have been characterized, such as the examples below.

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

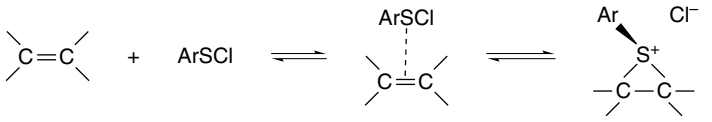


Ref. 93



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]

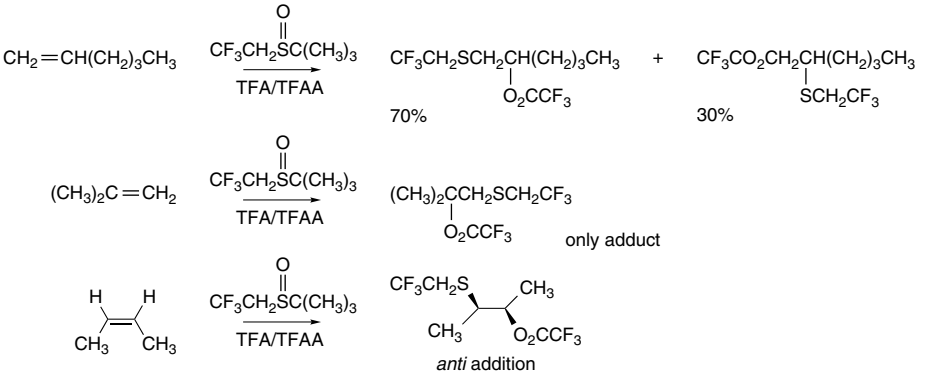
Similar results have been observed for other sulfenylating reagents. The somewhat more electrophilic trifluoroethylsulfenyl group shows a shift toward Markovnikov regioselectivity but retains *anti* stereospecificity, indicating a bridged intermediate.[97]

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).

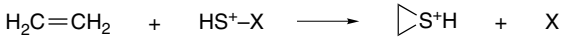
Table 5.4. Regiochemistry of Some Sulfenylation Reactions with Sulfenyl Chlorides

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

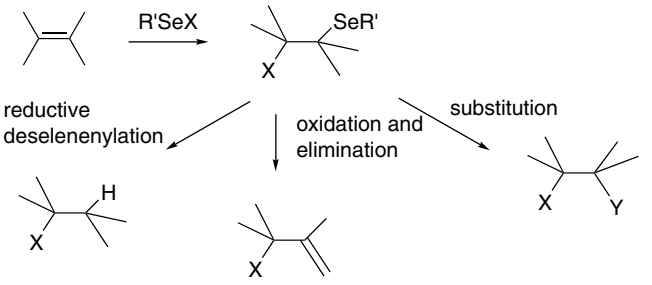
5.4.2. Selenenylation

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

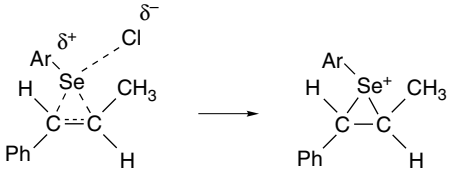
98. T. I. Solling and L. Radom, *Chem. Eur. J.*, 1516 (2001).

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.

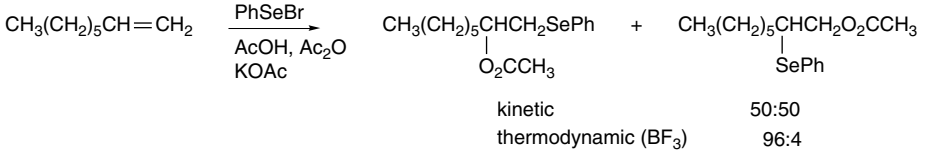


The various selenenylation reagents shown in Part B of Scheme 5.1 are characterized by an areneselenenyl group substituted by a leaving group. Some of the fundamental mechanistic aspects of selenenylation were established by studies of the reaction of *E*- and *Z*-1-phenylpropene with areneselenenyl chlorides.[100] The reaction is accelerated by an ERG in the arylselenenides. These data were interpreted in terms of a concerted addition with 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).

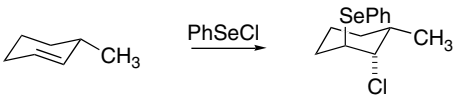
Table 5.5. Relative Reactivity of Some Alkenes toward 4-Chlorophenylsulfenyl Chloride and Phenylselenenyl Chloride[a]

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.

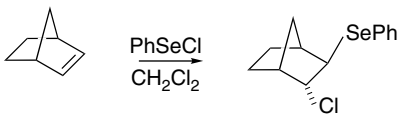
Styrene, on the other hand, is regioselective for the Markovnikov product, with the nucleophilic component bonding to the aryl-substituted carbon as the is the result of weakening of the bridging by the phenyl group.

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



Ref. 106

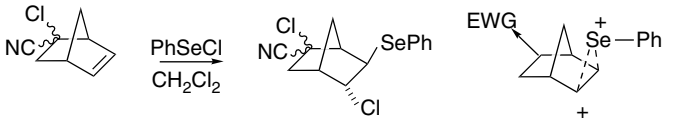
Norbornene gives highly stereoselective *exo-anti* addition, pointing to an *exo* bridged intermediate.



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

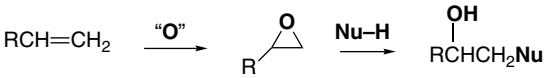
This regioselectivity is consistent with an unsymmetrically bridged seleniranium intermediate in which the more positive charge is remote from the EWG substituent. The directive effect is contrary to regiochemistry being dominated by the chloride ion approach, since chloride addition should be facilitated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