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Additional and Supplementary Volumes to the 4th Edition



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# Cyclopropanes: Synthesis

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# METHODS OF ORGANIC CHEMISTRY

## (HOUBEN-WEYL)

## ADDITIONAL AND SUPPLEMENTARY VOLUMES TO THE 4TH EDITION




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VOLUME E 17a

# CARBOCYCLIC THREE- AND FOUR-MEMBERED RING COMPOUNDS


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# Preface

Methods of Organic Chemistry – or synonymously Houben-Weyl – would be severely incomplete in this decade without the coverage of small ring chemistry. The first, and only, Houben-Weyl volume on Carbocyclic Three- and Four-membered Ring Compounds was published 25 years ago. Until that time small ring chemistry was, in the main, considered a domain for mechanistic and physical organic investigations, although many of the basic preparative methods had already been developed and the majority of important transformations thoroughly studied and reasonably well understood. Nevertheless, the notion, which started to evolve slowly in the sixties, of small ring compounds being useful and, frequently, uniquely applicable building blocks for other carbocyclic and also acyclic organic skeletons, has only since fully matured.

Quite a number of cyclopropane and cyclobutane derivatives have gained importance in their own right. For instance, the cyclopropyl group has turned out to be an essential feature in natural and non-natural products with insecticidal, cytostatic, various plant physiological, as well as antiinfective, activities and has, therefore, entered the realm of industrially applied chemistry. A recent survey listed 191 pharmaceutically important compounds containing an aminocyclopropane substructure, the best known example being the widely used broad-spectrum antibiotic Ciprofloxacin.

Yet the discovery of new types of natural small ring compounds continues. For example, a few years ago an antibiotic natural product with an unusual fatty acid side chain containing four adjacent cyclopropyl groups was described, and more recently, a similar compound with five adjacent, and a total of six, cyclopropyl groups has been reported. The vast progress in the development of stereoselective synthetic methodology (see Houben-Weyl Volume E21) has also brought about new methods for stereoselective cyclopropanations, and this has gone hand in hand with efforts towards enantioselective total syntheses of cyclopropyl-group-containing natural and non-natural products. So far these developments have only scratched the surface, as most of these methods are still hampered by severe constraints, and so the race goes on.

In view of this progress, it appeared to be time to publish an up-to-date comprehensive treatment of the methods of preparation and transformation of carbocyclic three- and four-membered-ring compounds. Certainly, the access to cyclopropane derivatives via carbene additions to alkenes, which represents one of the most general methods, has been covered – albeit from a different perspective – in the Houben-Weyl volume on Carbenes (E19b), and cross-references are frequently made to Houben-Weyl E19b in the corresponding sections of this volume. Yet this earlier volume cannot even be considered to be a comprehensive summary of the methods for the synthesis of cyclopropanes, let alone of the preparations and transformations of cyclopropenes, cycloproparenes, cyclopropenones and triafulvenes, all of which are covered here.

Twenty five years ago, all of the material on cyclopropane and cyclobutane chemistry was compiled by two single authors, which at the time must have been a truly Herculean task. Nowadays, this would simply be impossible. Thus, Houben-Weyl E17 has come to life only through the joint efforts of more than 60 authors, some of whom have invested a lot of their time with major contributions. An estimated 20,000

publications were read and evaluated, well over 13,000 references actually being quoted in the three-membered-ring sections alone. An editorial staff of 6 native speakers took care to make the presentation uniform and polish the language, especially of the non-native English writing authors. All the art work was redrawn by a group of 4.

The editor is indebted to all the authors, the editorial staff and the artists for the fruitful collaboration which made this book possible. We all hope that this handbook will serve the chemical community well and will become an indispensable reference tool for those engaged in Synthetic Organic Chemistry.

Göttingen, August 1996 Armin de Meijere

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**Volume E 17a**

# Introduction

K. B. WIBERG

## 1. Theoretical Models of Bonding

Compounds containing cyclopropane and cyclobutane rings have played a special role in the development of an understanding of the nature of carbon–carbon bonds.[1] Whereas simple alkanes, and cycloalkanes such as cyclopentane and cyclohexane, have essentially no interesting C–C bond chemistry other than high temperature pyrolysis or combustion, the increased energy of the small ring compounds, which results from the deformation of their bond angles from the normal values, allows them to participate in a variety of processes.

The first real understanding of the nature of cyclopropanes came with the work of Förster[2] and the more detailed studies of Coulson and Moffitt.[3] Here, they recognized that the hybridization characteristic of most alkanes, i.e. $\sim sp^3$, was not appropriate, and they set out to determine in what way the hybridization would change as a result of bond angle distortion. They concluded that the C–C bonds would be formed using bond orbitals relatively rich in p character in order to minimize the difference between the interorbital angle and the conventional bond angle (Figure 1). This led to the concept of bent C–C bonds, and C–H bond orbitals which are relatively rich in s character. Their conclusions were confirmed twenty years later when it was found that the NMR $^{13}C$–H coupling constant for cyclopropane was 160 Hz, essentially the same as that for ethylene, and much greater than that for ethane (125 Hz).[4] It had been shown that there was a correlation between the % s character and the coupling constant.[5] Futher evidence for this model was obtained via X-ray crystallographic studies of cyclopropane derivatives, in which it was found that the deformation density of the C–C bonds lies outside the triangle formed by the three carbons.[6] A plot of this type, based on the theoretically calculated electron density, is shown in Figure 2.

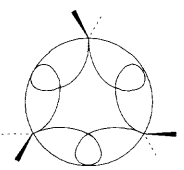


**Figure 1.** Förster–Coulson–Moffitt model for cyclopropane.

A second model for cyclopropane was presented by Walsh.[7] Recognizing the increased s character of the C–H bonds, he suggested a model in which $sp^2$ orbitals were directed toward the hydrogens, and toward the center of the ring. There then remain in-plane p orbitals at each of the carbons, which may overlap to form part of the C–C bonding interaction (Figure 3). Again, the model predicts the formation of bent bonds. However, in contrast to the bond orbitals in Figure 1, it is not possible to convert the Walsh orbitals to the bonding canonical molecular orbitals via a unitary transformation.[8] Therefore, the Walsh description is not equivalent to the Förster–Coulson–Moffitt model, and is not a correct description of the ground state of cyclopropane. The degenerate pair of highest occupied molecular orbitals for cyclo-

*for references see p 24*

propane (Figure 4A) are sometimes referred to as Walsh orbitals, but this is not correct. Cyclobutane has a similar set of highest occupied molecular orbitals (Figure 4B).[9]

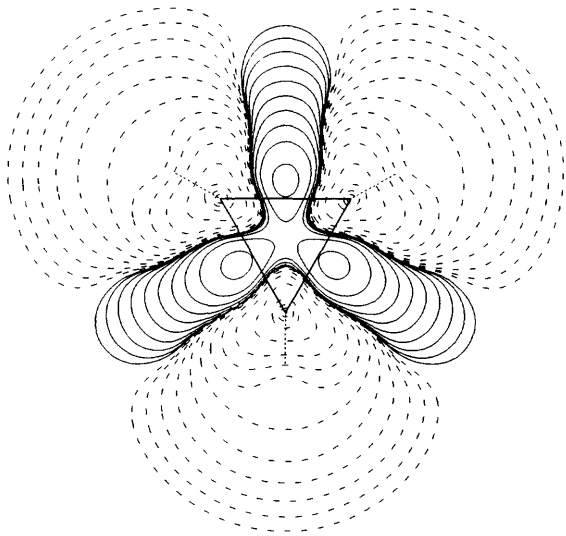


**Figure 2.** Deformation density plot for cyclopropane.

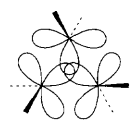


**Figure 3.** Walsh model of cyclopropane.

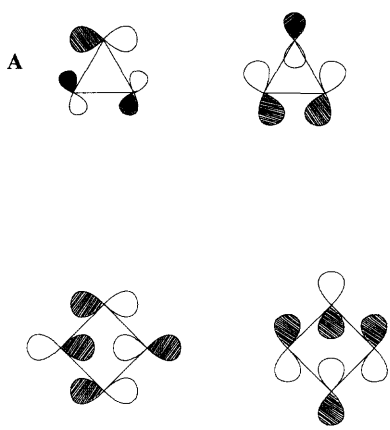



**Figure 4.** HOMOs of: **A** cyclopropane, and **B** cyclobutane.

Among the difficulties in trying to gain a detailed understanding of bonding and intramolecular interactions in small-ring compounds has been the lack of experimental data and the difficulty in determining the nature of intramolecular interactions from experimental data alone. The effect of substituents on structures, energies and rotational barriers has been studied for only a few compounds, and experimental studies often provide only part of the information that is needed. The availability of fast computers and of efficient ab initio molecular orbital codes has made it possible to study these compounds in much greater detail than is possible from experimental data alone.

The first requirement of any theoretical study is the demonstration that it can reproduce the available experimental data for related compounds. Extensive tests have shown that a split valence basis set is needed along with polarization functions at the first-row elements in order to reproduce trends in energies and geometries.[10] A typical basis set of this type is 6-31G*. Here, six Gaussian functions ($\phi = a\exp\text{-}br^2$) are used to represent the 1 s electrons of first-row elements. (Hydrogen atom functions are properly given by $\phi = a\exp\text{-}br$, but this form presents problems with the calculation of electron–electron repulsion. The Gaussian functions allow more rapid calculations, but it is necessary to use a group of them with different widths at half-height in order to reasonably reproduce the hydrogen atom function.) The valence electrons are represented by a group of three Gaussian functions with one "size" and one Gaussian of a larger "size". The size of a carbon depends on its environment and on its hybridization, and the use of this split valence function allows each carbon (or other atom) to adjust its size by taking appropriate proportions of the two sets of Gaussians.

Bent bonds are not well reproduced by simple nuclear-centered s and p functions. One way in which to improve the directionality of the functions is to add d functions to the p functions. The d functions are known as polarization functions and are indicated by *. They are also important in representing the polarization of a p function in the presence of an electric field such as that produced in bonds between atoms having different electronegativities.

The structures obtained in a Hartree–Fock (HF) calculation generally have bond lengths that are somewhat (1–2%) too short.[11] Better structural data may be obtained by correcting for electron correlation. In the HF calculations, the repulsion between electrons is calculated as the repulsion between the average distribution for each of the two electrons. In reality, the motions of electrons are correlated in order to minimize the electron repulsion. Thus, the charge density in a given bond will usually decrease slightly when electron correlation is taken into account,[12] and the bonds become slightly longer. At the same time, the energy decreases and becomes much closer to the true energy. A commonly used theoretical level is MP2/6-31G*, which makes use of a second order correction for electron correlation.[10]

It is very difficult to calculate the last parts of the correlation energy, and it is therefore difficult to obtain accurate total energies. However, the part of the correlation energy that is the most difficult to calculate is associated with the atom type and will, to a very good approximation, cancel if the energy change for a reaction is found. Thus, the use of isodesmic reactions, such as that of cyclobutyne **(1)**,[13] provides a way in which to obtain reasonable estimates of energies. Some examples of the use of such reactions will be given. In this connection, it should be noted that the G2[14] and G2/MP2[15] theoretical models recently developed by Pople et al. now provide energies that are generally in very good agreement with experimental.


**1**

*for references see p 24*

# 2. Structures of Cyclopropanes and Cyclobutanes

A comparison of experimental and MP2/6-31 G* calculated structures for some cyclopropanes and cyclobutanes is given in Table 1.[16a-c] It can be seen that there is generally good agreement between the experimental and observed structures. Cyclopropane rings always have C–C bonds that are shorter than normal, whereas cyclobutane rings usually have bonds that are longer than normal. The short bonds in cyclopropanes are readily explained in terms of the bent bonds. The true length lies along the curved path that is significantly longer than the distance

**Table 1.** Observed and Calculated Structures for Some Cyclopropanes and Cyclobutanes

| Compound | Parameter | Obsd | Calcd MP2/6-31 G* | Ref |
|---|---|---|---|---|
| cyclopropane | $r$(CC) | 1.512 ± 0.003 | 1.502 | 16a |
| | $r$(CH) | 1.082 ± 0.003 | 1.084 | |
| | <HCH | 114.0 ± 0.7 | 114.2 | |
| cyclobutane | $r$(CC) | 1.552 ± 0.001 | 1.543 | 16b |
| | r(CH) | 1.093 ± 0.003 | 1.094 | |
| | <HCH | 106.4 ± 1.3 | 108.8 | |
| | α | 27.9 ± 1.6 | 15.7 | |
| bicyclo[1.1.0]butane | $r$(C1C2) | 1.498 ± 0.005 | 1.492 | 16a |
| | $r$(C1C3) | 1.497 ± 0.005 | 1.496 | |
| | $r$(C1H) | 1.07 ± 0.005 | 1.080 | |
| | $r$(C2$H_e$) | 1.093 ± 0.010 | 1.088 | |
| | $r$(C2$H_a$) | 1.093 ± 0.010 | 1.092 | |
| | <C3C1H | 128.4 ± 0.5 | 128.1 | |
| | <HC2H | 115.5 ± 1.4 | 114.1 | |
| | α | 121.7 ± 1.0 | 123.4 | |
| bicyclo[1.1.1]pentane | $r$(C1C2) | 1.557 ± 0.002 | 1.547 | 16a |
| | $r$(C1C3) | 1.874 ± 0.004 | 1.872 | |
| | $r$(C1H) | 1.109 ± 0.004 | 1.094 | |
| | $r$(C2H) | 1.109 ± 0.004 | 1.095 | |
| | <HCH | 111.7 ± 1.8 | 111.5 | |
| | <C1C2C3 | 74.2 ± 0.2 | 74.4 | |
| [1.1.1]propellane | $r$(C1C2) | 1.522 ± 0.002 | 1.514 | 16c |
| | $r$(C1C3) | 1.594 ± 0.005 | 1.592 | |
| | $r$(C2H) | 1.090 ± 0.005 | 1.088 | |
| | <HC2H | 116.0 ± 1.9 | 114.9 | |
| cyclopropene | $r$(C1C2) | 1.296 ± 0.001 | 1.301 | 16a |
| | $r$(C2C3) | 1.509 ± 0.002 | 1.505 | |
| | $r$(C1H) | 1.072 ± 0.002 | 1.078 | |
| | $r$(C3H) | 1.088 ± 0.004 | 1.091 | |
| | <C2C1H | 149.9 ± 0.2 | 150.1 | |
| | <HC3H | 114.6 ± 0.4 | 113.5 | |
| cyclobutene | $r$(C1C2) | 1.342 ± 0.004 | 1.346 | 16a |
| | $r$(C2C3) | 1.517 ± 0.003 | 1.512 | |
| | $r$(C3C4) | 1.566 ± 0.003 | 1.564 | |
| | $r$(C1H) | 1.083 ± 0.005 | 1.087 | |
| | $r$(C3H) | 1.094 ± 0.005 | 1.095 | |
| | <C1C2C3 | 94.2 ± 0.3 | 94.1 | |
| | <C2C3C4 | 85.8 ± 0.2 | 85.9 | |
| | <C2C1H | 133.5 ± 0.5 | 133.6 | |
| | <HC3H | 109.2 ± 0.5 | 108.6 | |

between carbons. The longer bonds in cyclobutane have been attributed to cross-ring repulsion between methylene groups.[17] The distance between these groups is shorter in cyclobutane than in compounds with larger rings, and so this effect should be largest with cyclobutane. Cyclopropanes, of course, have no such cross-ring interactions since all of the carbons are bonded to each other. The cyclobutane ring is significantly puckered in order to relieve eclipsing interactions between adjacent methylene groups. This leads to a decrease in the C–C–C bond angle, from the 90° for planar cyclobutane, to 88°.

The C–H bonds in cyclopropanes are shorter than those in most alkanes, and this is probably related to their high s character. The bond lengths and angles are similar to those found in alkenes. As a consequence, the C–H bonds in cyclopropane have properties similar to those of ethene. The C–H bond dissociation energy is 109 kcal/mol,[18] much greater than that for the $CH_2$ group of propane (97 kcal/mol) and close to that of ethene (110 kcal/mol).[19] The high s character of the C–H bonds also leads to increased acidity, corresponding to a 5 kcal/mol lower gas phase ionization energy than for propane,[20] and this also carries over to cyclopropane derivatives such as bicyclo[1.1.0]butane.[21]

The C–H bonds in cyclobutanes are relatively normal, but it has been found that the methylene groups are tilted inward,[22] whereas one might have expected cross-ring steric interactions to lead to an outward puckering. Bartell and Andersen have explained this as resulting from the bent bonds in cyclobutane.[23] In order to retain approximate $C_{2v}$ symmetry at the methylene groups, the bent C–C–C bonds lead to the inward tilt (Figure 5).

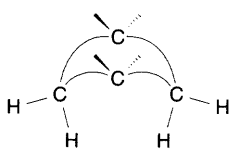



**Figure 5.** Inward tilt for the methylene groups of cyclobutane.

As noted above, one of the problems in dealing with small-ring compounds is that the conventional bonds (i.e. lines drawn between nuclei) do not well represent the true bonding interactions. A more satisfactory quantity is the bond path, which is the path of highest charge density between a pair of bonded nuclei.[24] The path may be defined either from the experimental charge density map obtained in an X-ray crystallographic study, or from the theoretical charge density derived from the molecular orbital wave functions. The bond path angle is the angle between a pair of bond paths at a given atom, and a deviation between the bond path angle and the conventional angle gives information on the extent of bond bending.

This quantity has been examined for a variety of small-ring compounds using theoretically calculated charge densities,[25] and some of the results are shown in Figure 6. It can be seen that the deviation between the two angles is generally of the order of 18° for cyclopropanes, but drops to only ~ 5° with cyclobutanes. It is interesting that some cyclopropanes having unusually high strain energies, such as [1.1.1]propellane, have bond path angles less than the conventional angles, indicating that the nature of bonding has changed from that found in most conventional cyclopropanes. The $\sigma$-bridged $\pi$-type of bonding suggested by Allen and Jackson for [1.1.1]propellane may explain the change in bond paths.[26]

Changes in structural parameters which result from the introduction of a substituent or fusion with another ring often provide useful insights into intramolecular interactions. Some of the available structural data for substituted cyclopropanes are recorded in Figure 7. With cyclopropylamine, the C–C bond attached to the substituent is shortened, whereas the remote C–C bond is lengthened,[27] and the same is seen with cyclopropyl chloride.[28] This trend is reproduced by ab initio calculations. Many explanations have been given for the effect, but the simplest is that electronegative substituents prefer to be bonded to orbitals with high p character (Bent's rule[29]) resulting in a change in hybridization in the cyclopropane ring.[27] The reversed change

*for references see p 24*

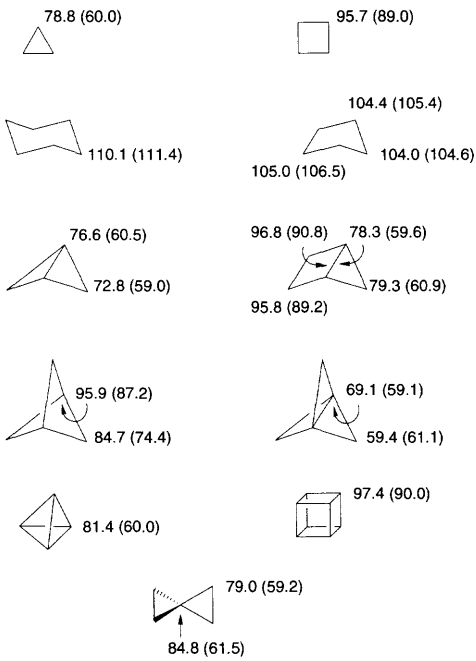
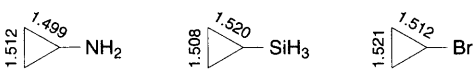



**Figure 6.** C–C–C Bond path angles for some cycloalkanes. The bond path angle is given first, followed by the conventional angle in parentheses.

in bond length with cyclopropylsilane[30] is in accord with this idea, since silicon is electropositive with respect to carbon. The results of the calculations are uniformly in agreement with the hybridization argument. Thus, in the case of cyclopropanethiol, in which carbon and sulfur have essentially the same electronegativity, the C–C bonds are essentially equal in length.

**A.** Experimental Structures




**B.** Calculated Structures, 6-31G*

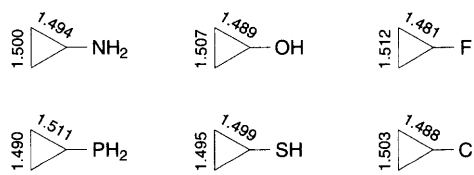
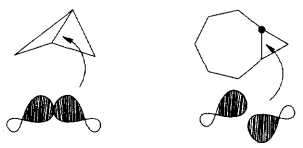



**Figure 7.** Structures of some substituted cyclopropanes.

The structures of bicyclic and polycyclic small-ring compounds have attracted some interest. The relationship between the C–C–H bond angles at the bridgehead of bicyclo[1.1.0]butane **(2)** and the angle between its cyclopropane rings has been studied.[31] Bicyclobutane and most other cyclopropane derivatives have bonds that are formed from orbitals that are bent in the same direction. However, with some *trans*-fused bicyclic compounds containing a cyclopropane

ring, such as *trans*-bicyclo[5.1.0]octane **(3)**, the orbitals are bent in opposite directions forming a twist–bent bond.[32]



**2** **3**

The bonding in [1.1.1]propellane **(4)** has also been of interest because of its inverted tetrahedral geometry with all of the bonds pointing in the same general direction. The central C–C bond length is 1.54 Å, very close to that for a normal C–C bond, and the electron density at the center of this bond is 80% that of the C2–C3 bond of butane.[33] Two different estimates of the bond energies give 60 kcal/mol as compared to 84 kcal/mol for a normal C–C bond.[34, 35] Thus, despite its unusual geometry, the central bond is structurally and energetically close to that of a normal C–C bond.

**4**

Another example of a remarkably distorted cyclopropane derivative is tricyclo[2.1.0.$0^{1,3}$]pentane **(5)**, which has a C–C–C bond angle of 164.5°. Not surprisingly, it is a relatively unstable compound that can only be observed by NMR at − 55 °C.[36]

**5**

# 3. Energies of Cyclopropanes and Cyclobutanes

The increased reactivity of cyclopropanes results from the presence of bent bonds which can interact with electrophiles, and can be more easily cleaved thermally than ordinary C–C bonds. One indication of the consequences of the distortion is found in the strain energies (SE)[37] that are calculated as the difference between the observed heat of formation and that estimated for a strain-free model. One might, for example, consider cyclohexane as strain-free, and then a model for cyclopropane would be half the heat of formation for cyclohexane. The available data for heats of formation of cyclopropane and cyclobutane derivatives are given in Table 2.[38] The heat of formation of cyclohexane is − 29.4 kcal/mol, and the strain energy of cyclopropane is 12.7–0.5(− 29.4) or 27.5 kcal/mol.

Although there has been some discussion of how the energy of the strain-free model should be obtained,[39] it should be recognized that the strain energies are always used in a comparative sense, and so any well-defined procedure will be satisfactory. One of the simplest is the use of Franklin's group equivalents[40] which are − 10.12 for a $CH_3$ group, − 4.93 for $CH_2$, − 1.09 for CH, + 0.8 for C, + 24.57 for C=C, + 20.19 for CH=C, + 18.88 for HC=CH (*cis*), + 16.89 for $CH_2$=C and + 15.00 for CH=$CH_2$. The equivalents are multiplied by the number of groups of a given type and summed to give the model energy. The strain energies obtained by subtracting the model energies from the observed energies are recorded in Table 2.

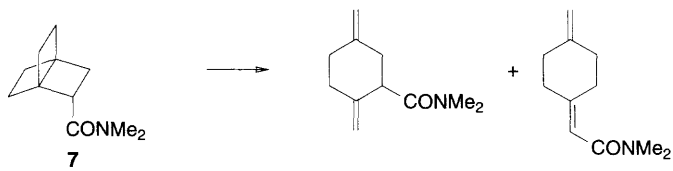
*for references see p 24*

In many cases, the strain energies for bicyclic compounds are approximately the sum of the strain energies of the component rings. This is seen with bicyclo[2.1.0]pentane, bicyclo[3.1.0]hexane, and many other compounds. It applies even to cubane, in which the strain energy is equal to six times the strain energy of a cyclobutane ring.

However, in some cases, large deviations from this rule are found. With spiropentane, the strain energy is 8 kcal/mol greater than that of two cyclopropanes. Here, the central carbon is forced by symmetry to use $sp^3$ hybridization, leading to less efficient bonding to the methylene carbons. The type of ring fusion found with spiropentane has been expanded to a family of "triangulenes" such as **6a** and **6b**, which have unusual properties.[41] Another type of ring fusion is found with bicyclo[1.1.0]butane, and here the strain energy is 9 kcal/mol greater than that of two cyclopropanes. Again, the distortion at the bridgehead carbons leads to changes in hybridization and an increased strain energy.

**6a** **6b**

The small-ring propellanes are among the most highly strained of hydrocarbons. The strain energy of [1.1.1]propellane is available from experimental data and is 97 kcal/mol.[35] The strain energies of [2.1.1]- and [2.2.1]propellane are not known experimentally, but theoretical calculations lead to values of 104 and 102 kcal/mol, respectively.[42] Despite the similarities in strain energies for the three propellanes, the properties are quite different. [1.1.1]Propellane is stable at room temperature and undergoes thermal rearrangement at a relatively high temperature.[43] The other two propellanes can be isolated as argon matrices at 20 K, but when the matrices are warmed to the softening point, 50 K, the infrared spectral absorptions of the propellanes disappear, presumably due to polymerization.[44] The low stability of the latter compounds is probably due to the large difference in strain between the propellane and the corresponding bicycloalkane, whereas with [1.1.1]propellane this difference is relatively small. Another case in which strain effects are evident is [2.2.2]propellane. It has a strain energy of about 96 kcal/mol, most of which may be relieved on going to the bicyclo[2.2.2]octane-1,4-diyl. Correspondingly, a derivative of this propellane **7** undergoes thermal cleavage to a 1,4-dimethylenecyclohexane with a half-life of only one hour at 25 °C.[45,46]




**7**

The tricyclopentane **5** mentioned previously is the most highly strained of the known simple cyclopropane derivatives (140 kcal/mol), and it has one of the highest strain energies per carbon of all known hydrocarbons.

In the case of alkenes, the difference in strain energy between the alkene and the corresponding alkane is of interest because this gives the driving force available for an addition to the double bond. This quantity has been called the olefinic strain (OS)[47] and it is given for the alkenes in Table 2. Among the simple compounds, the largest olefinic strain is found with cyclopropene, and it amounts to 13 kcal/mol per trigonal center. It is much less with cyclobutene, being only about 1 kcal/mol per trigonal center. This has a major effect on the chemistry of these compounds. For example, cyclopropene undergoes a very rapid ene reaction with itself at room temperature,[48] whereas cyclobutene is indefinitely stable at a temperature below that at which it rearranges to butadiene ($\sim$ 150 °C).[49]

**Table 2.** Heats of Formation and Strain Energies[a]

| Compound | $\Delta H_f$(25 °C) | | Strain Energy kcal/mol | Olefinic Strain kcal/mol |
|---|---|---|---|---|
| | kJ/mol | kcal/mol | | |
| (1) cycloalkanes | | | | |
| cyclopropane | 53.3 ± 0.6 | 12.7 ± 0.2 | 27.5 | |
| methylcyclopropane | 1.7 ± 0.6 (l) | 0.4 ± 0.2 (l) | | |
| ethylcyclopropane | − 24.8 ± 0.8 (l) | − 5.9 ± 0.2 (l) | | |
| 1,1-dimethylcyclopropane | − 8.2 ± 1.2 | − 2.0 ± 0.3 | 25.4 | |
| *cis*-1,2-dimethylcyclopropane | − 26.3 ± 0.7 (l) | − 6.3 ± 0.2 (l) | | |
| *trans*-1,2-dimethylcyclopropane | − 30.7 ± 0.8 (l) | − 7.3 ± 0.2 (l) | | |
| *cis*-1,2-diethylcyclopropane | − 79.9 ± 1.4 (l) | − 19.1 ± 0.3 (l) | | |
| *trans*-1,2-diethylcyclopropane | − 83.3 ± 2.1 (l) | − 19.9 ± 0.5 (l) | | |
| 1,1-dimethyl-2-ethylcyclopropane | − 90.2 ± 0.9 (l) | − 21.6 ± 0.2 (l) | | |
| 1,1,2,2-tetramethylcyclopropane | − 119.7 ± 0.9 (l) | − 28.6 ± 0.2 (l) | | |
| cyclopropylcyclohexane | − 314.6 ± 4.2 (l) | − 75.2 ± 1.0 (l) | | |
| cyclobutane | 28.4 ± 0.6 | 6.8 ± 0.2 | 26.5 | |
| methylcyclobutane | − 44.5 ± 1.4 (l) | − 10.6 ± 0.3 (l) | | |
| ethylcyclobutane | − 26.3 ± 1.1 | − 6.3 ± 0.3 | 24.6 | |
| (2) cycloalkenes | | | | |
| cyclopropene | 277.1 ± 2.5 | 66.2 ± 0.6 | 52.3 | 24.8 |
| methylenecyclopropane | 200.5 ± 1.8 | 47.9 ± 0.4 | 40.9 | 13.4 |
| 1-methylcyclopropene | 243.6 ± 1.2 | 58.2 ± 0.3 | 53.1 | |
| vinylcyclopropane | 122.4 ± 4.2 (l) | 29.3 ± 1.0 (l) | | |
| cyclopropylbenzene | 150.5 ± 0.9 | 36.0 ± 0.2 | | |
| cyclobutene | 156.7 ± 1.5 | 37.5 ± 0.4 | 28.5 | 1.6 |
| methylenecyclobutane | 121.5 ± 0.7 | 29.1 ± 0.2 | 27.0 | |
| *cis*-divinylcyclobutane | 166.5 ± 3.5 | 39.8 ± 0.8 | 22 | |
| *trans*-divinylcyclobutane | 143.5 ± 3.4 | 34.3 ± 0.8 | 16 | |
| (3) bicyclo- and polycycloalkanes | | | | |
| spiropentane | 185.2 ± 0.8 | 44.3 ± 0.2 | 63.2 | |
| biscyclopropyl | 129.4 ± 3.6 | 30.9 ± 0.9 | 52.8 | |
| bicyclo[1.1.0]butane | 217.1 ± 0.8 | 51.9 ± 0.2 | 63.9 | |
| bicyclo[2.1.0]pentane[b] | 158.2 ± 1.3 | 37.8 ± 0.3 | 54.7 | |
| bicyclo[3.1.0]hexane | 38.3 ± 0.7 | 9.2 ± 0.2 | 31.1 | |
| bicyclo[2.2.0]hexane | 124.7 ± 1.3 | 29.8 ± 0.3 | 51.8 | |
| 1-methylbicyclo[3.1.0]heptane | 1.5 ± 1.3 | 0.4 ± 0.3 | 30.5 | |
| bicyclo[4.1.0]heptane | 1.5 ± 2.7 | 0.4 ± 0.6 | 27.2 | |
| 1-methylbicyclo[4.1.0]heptane | − 20.8 ± 1.5 | − 5.0 ± 0.4 | | |
| bicyclo[4.2.0]octane | − 26.2 ± 2.7 | − 6.3 ± 0.6 | 25.5 | |
| *cis*-bicyclo[5.1.0]octane | − 16.6 ± 1.8 | − 4.0 ± 0.4 | 27.8 | |
| *cis*-bicyclo[6.1.0]nonane | − 31.1 ± 2.9 | − 7.4 ± 0.7 | 29.3 | |
| *trans*-bicyclo[6.1.0]nonane | − 39.7 ± 3.2 | − 9.5 ± 0.8 | 27.2 | |
| quadricyclane | 339.1 ± 2.4 | 81.0 ± 0.6 | 92.5 | |
| [1.1.1]propellane[c] | 351.5 ± 4.0 | 84.0 ± 1.0 | 97.2 | |
| [3.2.1]propellane | 163 ± 8 | 39 ± 2 | 67 | |
| tricyclo[2.2.1.$0^{2,5}$]heptane | 82.2 ± 2.2 | 19.6 ± 0.5 | 38.8 | |
| tricyclo[4.1.0.$0^{2,4}$]heptane | 149.2 ± 1.5 | 35.7 ± 0.4 | 54.9 | |
| cubane | 622.1 ± 3.7 | 148.7 ± 0.9 | 157.4 | |
| bicyclo[2.1.0]pent-2-ene | 333.5 ± 2.1 | 79.7 ± 0.5 | 67.9 | 13.2 |
| bicyclo[2.2.0]hex-2-ene | 261.5 ± 1.3 | 62.4 ± 0.3 | 55.7 | 3.9 |
| (4) substituted compounds | | | | |
| cyclobutane-1,3-dione | − 186.3 ± 3.0 | − 44.5 ± 0.7 | | |
| methyl cyclobutanecarboxylate | − 355.3 ± 1.4 | − 84.9 ± 0.3 | | |
| methyl bicyclobutanecarboxylate | − 164.6 ± 0.7 | − 39.3 ± 0.2 | | |
| cyclopropylamine | 77.0 ± 0.7 | 18.4 ± 0.2 | | |
| cyclobutylamine | 41.2 ± 0.8 | 9.8 ± 0.2 | | |
| cyclopropanecarbonitrile | 181.8 ± 1.0 | 43.5 ± 0.2 | | |
| cyclobutanecarbonitrile | 143.1 ± 1.3 | 34.2 ± 0.3 | | |

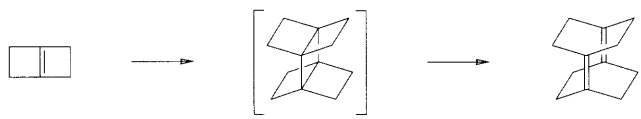
*for references see p 24*

**Table 2.** (cont.)

| Compound | $\Delta H_f$(25 °C) | | Strain Energy kcal/mol | Olefinic Strain kcal/mol |
|---|---|---|---|---|
| | kJ/mol | kcal/mol | | |
| 3-methylenecyclobutanecarbonitrile | 252.5 ± 2.1 | 60.3 ± 0.5 | | |
| bicyclobutane-1-carbonitrile | 304.6 ± 1.3 | 72.8 ± 0.3 | | |
| bicyclo[2.1.0]pentane-1-carbonitrile | 272.1 ± 1.2 | 65.0 ± 0.3 | | |
| bicyclo[3.1.0]hexane-1-carbonitrile | 142.1 ± 1.8 | 34.0 ± 0.4 | | |
| (5) estimated energies derived from theoretical calculations[d] | | | | |
| bicyclo[1.1.1]pentane | | 51 | 68 | |
| bicyclo[2.1.1]hexane | | 15 | 37 | |
| [2.1.1]propellane | | 89 | 107 | |
| [2.2.1]propellane | | 83 | 106 | |
| [2.2.2]propellane | | 68 | 96 | |
| tetrahedrane | | 136 | 140 | |
| bicyclo[1.1.0]butene | | 145 | 130 | 66 |
| bicyclo[2.1.0]pent-1(4)-ene | | 136 | 126 | 71 |
| bicyclo[2.1.0]pent-1(5)-ene | | 129 | 120 | 65 |
| bicyclo[2.1.0]pent-1(2)-ene | | 131 | 122 | 67 |
| bicyclo[2.2.0]hex-1-(4)-ene | | 92 | 87 | 35 |
| bicyclo[2.2.0]hex-1(2)-ene | | 88 | 84 | 32 |
| bicyclo[3.2.0]hex-1(5)-ene | | 91 | 91 | 58 |
| bicyclo[2.1.1]hex-2-ene | | 58 | 51 | 14 |

[a] Unless otherwise stated, the data were taken from ref 38a. The data are given for the gas phase except for the cases where the heat of vaporization is not known (marked "l").
[b] From ref 38b.
[c] From ref 38c.
[d] From refs 50 and 56.

Bicyclo[2.2.0]hex-1(4)-ene **(8)** is one of the most highly strained of the alkenes (SE = 87, OS = 35)[50] that can be observed at room temperature.[51] In dilute solution, it undergoes moderately rapid dimerization at room temperature, presumably giving the pentacyclic propellane **9** as an intermediate in the formation of the diene **10**.



**8** **9** **10**

Highly strained bridged cyclopropenes have received considerable attention.[52] The parent compounds undergo a rapid ene reaction leading to a dimer which reacts with itself to form a tetramer. Although bicyclo[1.1.0]but-1(3)-ene has not been observed directly,[53] it has been possible to obtain information on its energy via a unique reaction of the bridgehead anion of bicyclo[1.1.0]butane with $O_2^{\cdot}$.[54]

It is unfortunately not possible to obtain experimental thermochemical data for all of the compounds of interest. Here, theoretical calculations frequently give useful information. The calculated energies and structures of cyclobutane derivatives,[55] propellanes,[56] and small-ring alkenes[50] have been summarized. The energies of these compounds may be derived from the calculated total energies via the use of isodesmic reactions such as that for cyclobutyne illustrated above. An equivalent approach is to obtain the energy of an unstrained $CH_3$, $CH_2$ and C, and to use these energies in calculating the heat of formation:[57]

$$\Delta H_f = 627.5\,(E_{calc} - n_{CH_3}E_{CH_2} - n_{CH_2}E_{CH_2} - n_{CH}E_{CH} - n_C E_C)$$

Here, $E_{calc}$ is the calculated total energy, 627.5 is the conversion factor from Hartrees (the units used in the calculations) to kcal/mol, n refers to the numbers of groups present in the molecule, and $E$ to the energy associated with the unstrained groups. The $E$ values are obtained by fitting experimental heats of formation using the equation. With 6-31G* energies, it is possible to reproduce the heats of formation of a wide range of hydrocarbons with a root mean square error of only 1 kcal/mol.[44] An equivalent approach using atom equivalents rather than group equivalents is also available.[58] Some of the data for small-ring compounds obtained in this fashion are given in Table 2.

A theoretical examination of the consequences of bond angle deformation has made use of a procedure to separate molecules into atomic domains, and then to calculate the properties of the atoms by numerical integration of the appropriate function of the molecular wave function over each atomic domain.[25] This has allowed the electron populations and energies of each of the atoms to be calculated. In the case of cyclopropane, it was found that the carbon of each methylene group had a higher electron population and a lower energy than a normal methylene carbon, and that the hydrogens had a lower than normal electron population and a higher energy. These changes are in accord with the increased s character of the C–H bonds in cyclopropane. The energy of the hydrogen increased more rapidly than the energy of the carbon decreased, and the total energy of each cyclopropane methylene group was 9 kcal/mol higher than that of a normal methylene group. From this point of view, the origin of the strain energy of cyclopropane is the increased energy of the hydrogens as compared with normal alkene hydrogens. Many other cyclopropane and cyclobutane derivatives have been examined in this fashion.[18]

Little experimental data are available concerning the effect of substituents on the energies of cyclopropanes or cyclobutanes. However, one may use computed energies to gain information on the relative effects on cyclopropane and propane via isodesmic reactions. The data obtained using the 6-31G* basis set are given in Table 3.[59]

**Table 3.** Group Transfer Energies (kcal/mol)


| X | $\Delta E$ | X | $\Delta E$ |
|---|---|---|---|
| Li | −7.3 | | |
| BeH | −7.2 | | |
| $BH_2$ | −8.3 | | |
| $CH_3$ | −1.4 | $SiH_3$ | −4.5 |
| $NH_2$ | −0.9 | $PH_2$ | −3.3 |
| OH | +2.1 | SH | −0.9 |
| F | +5.5 | Cl | +3.3 |

The results provide a clear indication of the importance of the change in hybridization between cyclopropane ($\sim sp^2$ for the external bonds) and propane ($\sim sp^3$). Electropositive groups prefer to be bonded to the more electron-withdrawing cyclopropane ring, whereas electronegative substituents prefer to be bonded to C2 of propane. The one anomaly in Table 3 is found with the $BH_2$ substituent which leads to the most exothermic group transfer reaction. This is presumably a result of the interaction of the cyclopropane ring with the empty p orbital at boron. This type of interaction will be discussed in the next section.

A difference between cyclopropane and propane is also seen in the barrier to rotation about the bonds to the substituents. Isopropyl alcohol and amine have normal threefold rota-

*for references see p 24*

tional barriers, which are little different from those for methyl and ethyl derivatives. However, with the substituted cyclopropanes such as cyclopropanol, the rotational profile is quite different (Figure 8)[59] and the relative energy does not drop to essentially zero at 180°. The reasons for these differences remain to be determined.

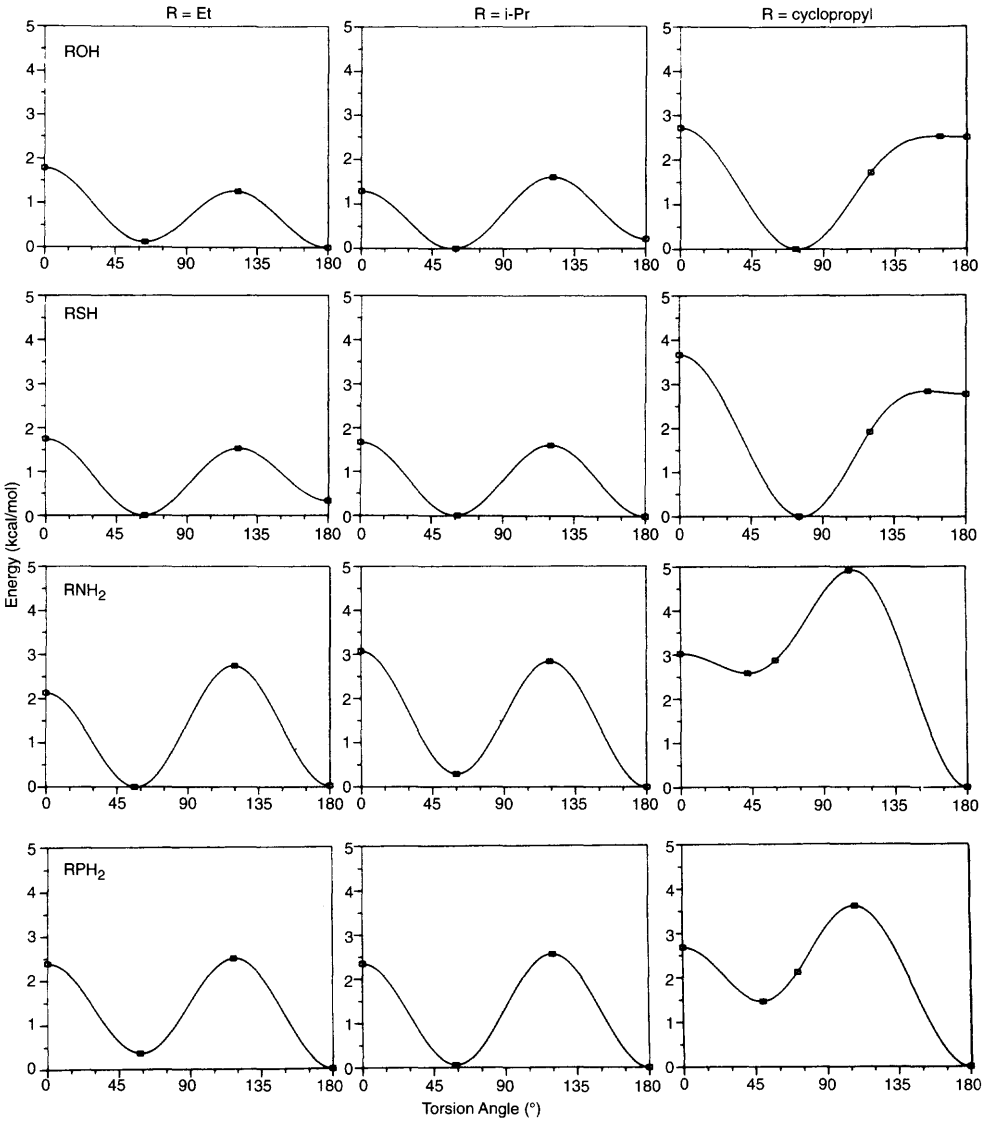



**Figure 8.** Rotational profiles for methyl, isopropyl and cyclopropyl derivatives (reproduced from ref 59 with permission of the American Chemical Society).

# 4. Interaction with Electron-Deficient Centers

In many ways, cyclopropane behaves in the same fashion as an alkene. This is particularly evident in its interactions with electron-deficient centers. Thus, it undergoes a relatively facile reaction with a proton, and it interacts strongly with an attached cationic center.[1]

These interactions may usefully be described as an acid–base type interaction, in which the cyclopropane ring acts as a base (electron donor) and the proton or cationic center acts as the acid (electron acceptor). One of the factors that controls the basicity of a hydrocarbon is the energy of the highest occupied molecular orbital (HOMO).[60] The 6-31 G* HOMO energies of some cycloalkanes and cycloalkenes are given in Table 4.[61]

**Table 4.** 6-31 G* HOMO Energies of Cycloalkanes and Cycloalkenes

| Compound | HOMO energy (eV) |
|---|---|
| cyclopropane | − 11.35 |
| cyclobutane | − 11.73 |
| cyclohexane | − 11.53 |
| bicyclobutane | − 9.71 |
| bicyclo[2.1.0]pentane | − 10.15 |
| spiropentane | − 10.53 |
| ethylene | − 10.19 |
| propene | − 9.73 |
| *cis*-2-butene | − 9.26 |

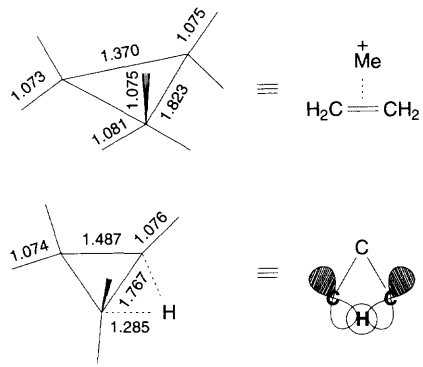
It can be seen that the HOMO energy of cyclopropane is higher than that of cyclobutane or cyclohexane, and that the much more reactive bicyclo[1.1.0]butane has a much higher HOMO energy, which is close to that of propene. Another important factor is the polarizability, which reflects how easily the electron density may be shifted in the presence of an electric field (such as that developed by a proton). Here again, cyclopropanes have significantly higher polarizability than other cycloalkanes.[62]

Protonated cyclopropanes have received extensive study, both experimentally and theoretically.[63] Both edge- and corner-protonated species are possible, and both experiment and theory agree that their energies are very similar. The structures calculated using the 6-31 G* basis set are given in Figure 9 A.[64, 65] The corner-protonated species has a very short C2–C3 bond, similar to that of an alkane, whereas the other C–C bonds are very long. In this way, it resembles a $\pi$-complex of a methyl cation with ethene. The edge-protonated ion has a longer C–C bond at the site of protonation, as might be expected for the formation of a three-center two-electron bond. The bent C–C bonds allow good overlap with the proton's orbital without excessive nuclear repulsion.

Structures of protonated cyclobutanes have been studied in the same fashion (see Figure 9 B). In the corner-protonated cyclobutane, the structure corresponds essentially to a methyl cation interacting with a trimethylene diyl, and is much less favorable than that for cyclopropane. Similarly, for the edge-protonated ion, the proton must come much closer to the carbons to form a bond than for cyclopropane, and as a result, cyclobutane is much less basic.

*for references see p 24*

**A.** Cyclopropanes




**B.** Cyclobutanes

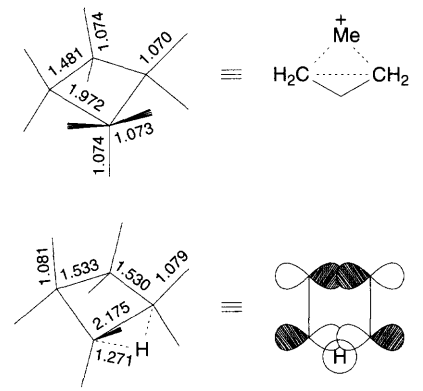
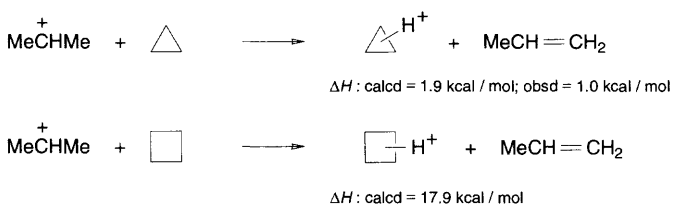



**Figure 9.** Protonated cyclopropane and cyclobutane structures calculated using the 6-31G* basis set.

The energies for transferring a proton from isopropyl cation to cyclopropane and cyclobutane are:




The calculated energies again confirm that cyclopropane is much more easily attacked by electrophiles than is cyclobutane, and this accounts for the common observation that cyclobutanes are much less reactive toward electrophiles than are cyclopropanes, despite the similar strain energy relief for these compounds.[65] The reactions of cyclopropane with other electrophiles, such as mercuric ion,[66] and metal radical cations,[67] have also been studied.