10

Concerted Pericyclic Reactions

Introduction

Concerted reactions occur without an intermediate. The transition structure involves both bond breaking and bond formation, although not necessarily to the same degree. There are numerous examples of both unimolecular and bimolecular concerted reactions. A particularly important group consists of the *concerted pericyclic reactions*,[1] which are characterized by a continuous reorganization of electrons through *cyclic transition structures*. Furthermore, the cyclic TS must correspond to an arrangement of the participating orbitals that can maintain a bonding interaction between the reacting atoms throughout the course of the reaction. We shall see shortly that these requirements make pericyclic reactions predictable in terms of relative reactivity, regioselectivity, and stereoselectivity.

A key to understanding the mechanisms of the concerted pericyclic reactions was the recognition by Woodward and Hoffmann that the pathway of such reactions is determined by the symmetry properties of the orbitals that are directly involved.[2] Specifically, they stated the requirement for *conservation of orbital symmetry*. The idea that the symmetry of each participating orbital must be conserved during the reaction process dramatically transformed the understanding of concerted pericyclic reactions and stimulated much experimental work to test and extend their theory.[3] The Woodward and Hoffmann concept led to other related interpretations of orbital properties that are also successful in predicting and interpreting the course of concerted pericyclic reactions.[4] These various approaches conclude that TSs with certain orbital alignments are energetically favorable (allowed), whereas others lead to high-energy (forbidden) TSs. The stabilized TSs share certain electronic features with aromatic systems, whereas the high-energy TSs are more similar to antiaromatic systems.[4b,c] As we will see shortly, this leads to rules similar to the Hückel and Mobius relationships for aromaticity (see Section 8.1) that allow prediction of the outcome of the reactions on the basis of the properties of the orbitals of the reactants. Because these reactions proceed through highly ordered cyclic transition structures with specific orbital alignments, the concerted pericyclic reactions often have characteristic and predictable stereochemistry. In many cases, the reactions exhibit regioselectivity that can be directly related to the effect of orbital interactions on TS structure. Similarly, substituent effects on reactivity can be interpreted in terms of the effect of the substituents on the interacting orbitals.

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[1] R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, 1970.

[2] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

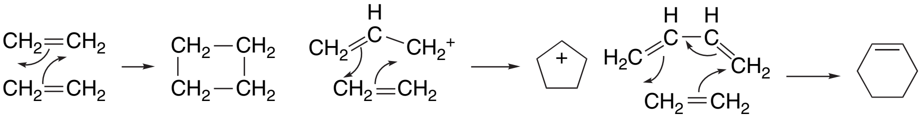
[3] For reviews of several concerted reactions within the general theory of pericyclic reactions, see A. P. Marchand and R. E. Lehr, eds., *Pericyclic Reactions*, Vols. I and II, Academic Press, New York, 1977.

A great deal of effort has been expended to model the transition structures of concerted pericyclic reactions.[5] All of the major theoretical approaches, semiempirical MO, ab initio MO, and DFT have been applied to the problem and some comparisons have been made.[6] The conclusions drawn generally parallel the orbital symmetry rules in their prediction of reactivity and stereochemistry and provide additional insight into substituent effects.

We discuss several categories of concerted pericyclic reactions, including Diels-Alder and other *cycloaddition reactions*, *electrocyclic reactions*, and *sigmatropic rearrangements*. The common feature is a concerted mechanism involving a cyclic TS with continuous electronic reorganization. The fundamental aspects of these reactions can be analyzed in terms of orbital symmetry characteristics associated with the TS. For each major group of reactions, we examine how regio- and stereoselectivity are determined by the cyclic TS.

10.1. Cycloaddition Reactions

Cycloaddition reactions involve the combination of two molecules to form a new ring. Concerted pericyclic cycloadditions involve reorganization of the π-electron systems of the reactants to form two new σ bonds. Examples might include cyclodimerization of alkenes, cycloaddition of allyl cation to an alkene, and the addition reaction between alkenes and dienes (Diels-Alder reaction).



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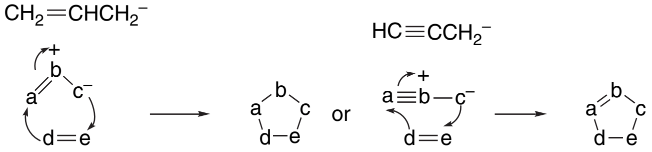
[4] (a) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965); (b) M. J. S. Dewar, *Angew. Chem. Int. Ed. Engl.*, **10**, 761 (1971); M. J. S. Dewar, *The Molecular Orbital Theory of Organic Chemistry*, McGraw-Hill, New York, 1969; (c) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971); (d) K. N. Houk, Y. Li, and J. D. Evanseck, *Angew. Chem. Int. Ed. Engl.*, **31**, 682 (1992).

[5] O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem. A*, **101**, 8378 (1997).

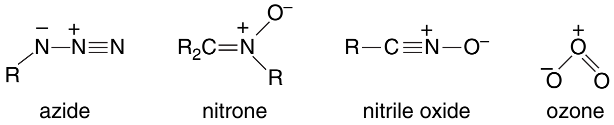
[6] D. Sperling, H. U. Reissig, and J. Fabian, *Liebigs Ann. Chem.*, 2443 (1997); B. S. Jursic, *Theochem*, **358**, 139 (1995); H.-Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997); V. Aviente, H. Y, Yoo, and K. N. Houk, *J. Org. Chem.*, **62**, 6121 (1997); K. N. Houk, B. R. Beno, M. Nendal, K. Black, H. Y. Yoo, S. Wilsey, and J. K. Lee, *Theochem*, **398**, 169 (1997); J. E. Carpenter and C. P. Sosa, *Theochem*, **311**, 325 (1994); B. Jursic, *Theochem*, **423**, 189 (1998); V. Brachadell, *Int. J. Quantum Chem.*, **61**, 381 (1997).

The cycloadditions can be characterized by specifying the number of π electrons involved for each species, and for the above three cases, this would be [2+2], [2+2], and [2+4], respectively. Some such reactions occur readily, whereas others are not observed. We will learn, for example, that of the three reactions above, only the alkene-diene cycloaddition occurs readily. The pattern of reactivity can be understood by application of the principle of conservation of orbital symmetry.

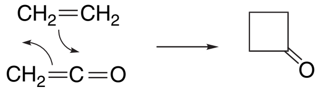
The most important of the concerted cycloaddition reactions is the *Diels-Alder reaction* between a diene and an alkene derivative to form a cyclohexene. The alkene reactant usually has a substituent and is called the *dienophile*. We discuss this reaction in detail in Section 10.2. Another important type of [2+4] cycloaddition is *1,3-dipolar cycloaddition*. These reactions involve heteroatomic systems that have four π electrons and are electronically analogous to the allyl or propargyl anions.



Many combinations of atoms are conceivable, among them azides, nitrones, nitrile oxides, and ozone. As these systems have four π electrons, they are analogous to dienes, and cycloadditions with alkenes and alkynes are allowed [4+2] reactions. These are discussed in Section 10.3.



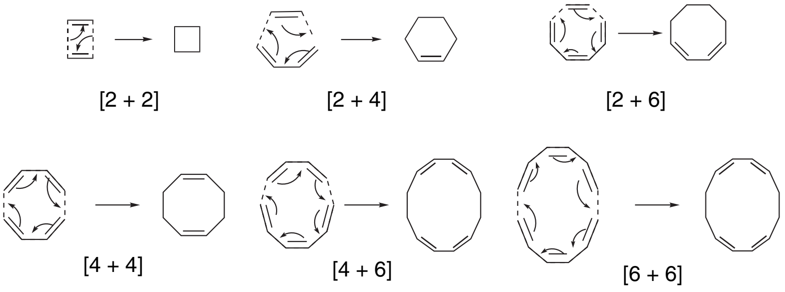
In a few cases [2+2] cycloadditions are feasible, particularly with ketenes, and these reactions are dealt with in Section 10.4.



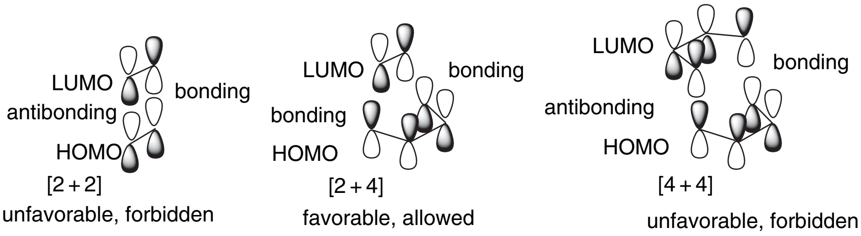
We begin the discussion of concerted cycloaddition reactions by exploring how the orbital symmetry requirements distinguish between reactions that are favorable and those that are unfavorable. Cycloaddition reactions that occur through a pericyclic concerted mechanism can be written as a continuous rearrangement of electrons. If we limit consideration to conjugated systems with from two to six π electrons, the reactions shown in Scheme 10.1 are conceivable.

We recognize immediately that some of these combinations would encounter strain and/or entropic restrictions. However, orbital symmetry considerations provide a fundamental insight into the electronic nature of the cycloaddition reactions and allow us to see that some of the TS structures are electronically favorable, whereas others are not. Woodward and Hoffmann formulated the orbital symmetry principles for cycloaddition reactions in terms of the frontier orbitals. An energetically accessible TS requires overlap of the frontier orbitals to permit smooth formation of the new

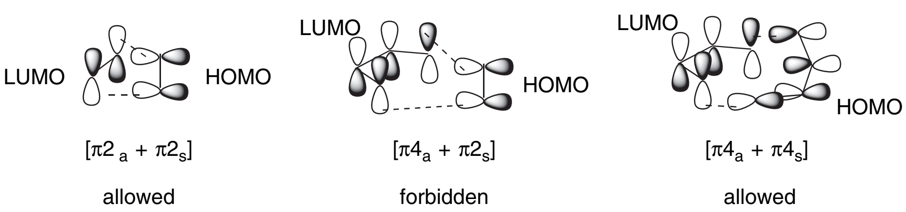
Scheme 10.1. Possible Combinations for Cycloaddition Reactions of Conjugated Polyenes


[2 + 2]
[2 + 4]
[2 + 6]
[4 + 4]
[4 + 6]
[6 + 6]

σ bonds. If it is assumed that the reactants approach one another face-to-face, as would be expected for reactions involving π orbitals, the requirement for bonding interactions between the HOMO and LUMO are met for $[2+4]$ but not for $[2+2]$ or $[4+4]$ cycloadditions. (See Section 1.2 to review the MOs of conjugated systems.) More generally, systems involving $4n+2$ π electrons are favorable (allowed), whereas systems with $4n$ π electrons are not.


LUMO
antibonding
HOMO
bonding
[2+2]
unfavorable, forbidden
LUMO
bonding
bonding
HOMO
[2+4]
favorable, allowed
LUMO
bonding
antibonding
HOMO
[4+4]
unfavorable, forbidden

There is another aspect of cycloaddition TS structure that must be considered. It is conceivable that some systems might react through an arrangement with Mobius rather than Hückel topology (see p. 736). Mobius systems can also be achieved by addition to opposite faces of the π system. This mode of addition is called *antarafacial* and the face-to-face addition is called *suprafacial*. In order to specify the topology of cycloaddition reactions, subscripts *s* and *a* are added to the numerical classification. For systems of Mobius topology, as for aromaticity, $4n$ combinations are favored and $4n+2$ combinations are unfavorable.[4c]

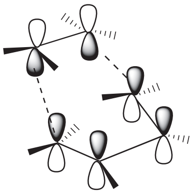

LUMO
HOMO
$[\pi 2_a + \pi 2_s]$
allowed
LUMO
HOMO
$[\pi 4_a + \pi 2_s]$
forbidden
LUMO
HOMO
$[\pi 4_a + \pi 4_s]$
allowed

The generalized Woodward-Hoffmann rules for cycloaddition are summarized below.

Orbital Symmetry Rules for $m+n$ Cycloaddition

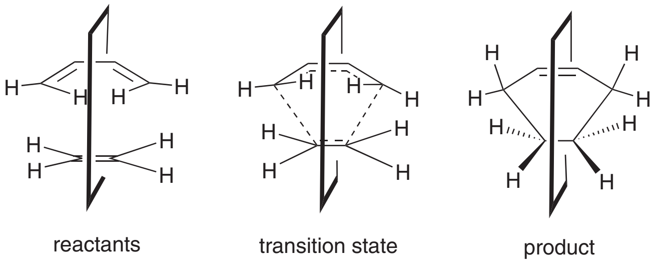
$m+n$	Supra/supra	Supra/antara	Antara/antara
$4n$	Forbidden	Allowed	Forbidden
$4n+2$	Allowed	Forbidden	Allowed

The selection rules for $[\pi 4_s + \pi 2_s]$ and other cycloaddition reactions can also be derived from consideration of the aromaticity of the TS.[4b,c] In this approach, the basis set *p* orbitals are aligned to correspond with the orbital overlaps that occur in the TS. The number of nodes in the array of orbitals is counted. If the number is zero or even, the system is classified as a Hückel system. If the number is odd, it is a Mobius system. Just as was the case for ground state molecules (see p. 736), Hückel systems are stabilized with $4n+2$ electrons, whereas Mobius systems are stabilized with $4n$ electrons. For the $[\pi 4 + \pi 2]$ suprafacial-suprafacial cycloaddition the transition state is aromatic.



Basis set orbitals for *supra,supra* $[\pi 2 + \pi 4]$ cycloaddition. Six electrons, zero nodes: aromatic

The orbital symmetry principles can also be applied by constructing an *orbital correlation diagram*.[4a] Let us construct a correlation diagram for the addition of butadiene and ethene to give cyclohexene. For concerted addition to occur, the diene must adopt the *s-cis* conformation. Because the electrons that are involved are the π electrons in both the diene and dienophile, the reaction occurs via a face-to-face rather than an edge-to-edge orientation. When this orientation of the reacting complex and TS is adopted, it can be seen that a plane of symmetry perpendicular to the planes of the reacting molecules is maintained during the course of the cycloaddition.



An orbital correlation diagram can be constructed by examining the symmetry of the reactant and product orbitals with respect to this plane, as shown in Figure 10.1. An additional feature must be taken into account in the case of cyclohexene. The cyclohexene orbitals σ_1, σ_2, σ_1^*, and σ_2^* are called *symmetry-adapted orbitals*. We might be inclined to think of the σ and σ^* orbitals as being localized between specific pairs of carbon atoms, but this is not the case for the MO treatment because localized

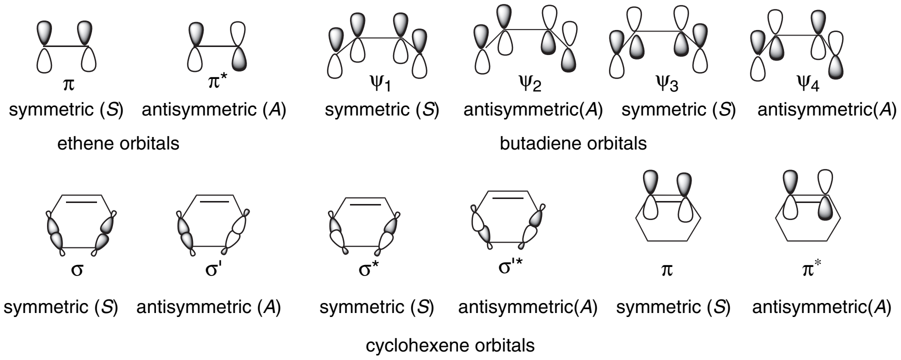

π
π*
ψ1
ψ2
ψ3
ψ4
symmetric (S)
antisymmetric (A)
symmetric (S)
antisymmetric(A)
symmetric (S)
antisymmetric(A)
ethene orbitals
butadiene orbitals
σ
σ'
σ*
σ'*
π
π*
symmetric (S)
antisymmetric (A)
symmetric (S)
antisymmetric(A)
symmetric (S)
antisymmetric(A)
cyclohexene orbitals

Fig. 10.1. Symmetry properties of ethene, butadiene, and cyclohexene orbitals with respect to a plane bisecting the reacting system.

orbitals would fail the test of being either symmetric or antisymmetric with respect to the plane of symmetry (see p. 37). In the construction of orbital correlation diagrams, *all* of the orbitals involved must be either symmetric or antisymmetric with respect to the element of symmetry being considered.

When the orbitals have been classified with respect to symmetry, they are arranged according to energy and the correlation lines are drawn as in Figure 10.2. From the orbital correlation diagram, it can be concluded that the thermal concerted cycloaddition reaction between butadiene and ethylene is allowed. All bonding levels of the reactants correlate with product ground state orbitals. Extension of orbital correlation analysis to cycloaddition reactions with other numbers of π electrons leads to the conclusion that suprafacial-suprafacial addition is allowed for systems with $[4n+2]$ π electrons but forbidden for systems with $4n$ π electrons.

The frontier orbital analysis, basis set orbital aromaticity, and orbital correlation diagrams can be applied to a particular TS geometry to determine if the reaction is symmetry allowed. These three methods of examining TS orbital symmetry are equivalent and interchangeable. The orbital symmetry rules can be generalized from conjugated polyenes to any type of conjugated π system. Conjugated anions and cations such as allylic and pentadienyl systems fall within the scope of the rules. The orbital symmetry considerations can also be extended to isoelectronic systems

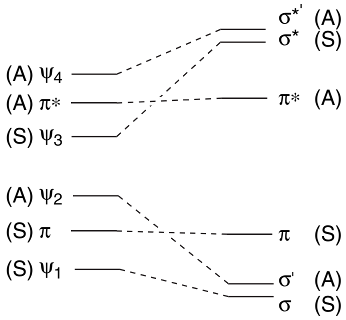

σ*' (A)
σ* (S)
(A) ψ4
(A) π*
π* (A)
(S) ψ3
(A) ψ2
(S) π
π (S)
(S) ψ1
σ' (A)
σ (S)

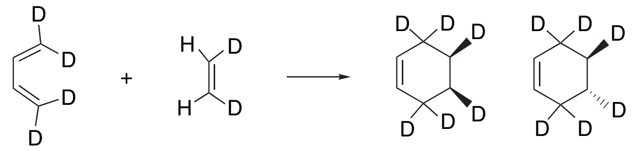
Fig. 10.2. Orbital symmetry correlation diagram for $[\pi 2_s + \pi 4_s]$ cycloaddition of ethene and 1,3-butadiene.

containing heteroatoms. Thus the C=C double bonds can be replaced by C=N, C=O, C=S, N=O, N=N, and other related multiple bonds.

10.2. The Diels-Alder Reaction

10.2.1. Stereochemistry of the Diels-Alder Reaction

The $[\pi 4_s + \pi 2_s]$ cycloaddition of alkenes and dienes is a very useful method for forming substituted cyclohexenes. This reaction is known as the Diels-Alder (abbreviated D-A in this chapter) reaction.[7] The transition structure for a concerted reaction requires that the diene adopt the *s-cis* conformation. The diene and substituted alkene (called the *dienophile*) approach each other in approximately parallel planes. This reaction has been the object of extensive mechanistic and computational study, as well as synthetic application. For most systems, the reactivity pattern, regioselectivity, and stereoselectivity are consistent with a concerted process. In particular, the reaction is a stereospecific *syn* (suprafacial) addition with respect to both the alkene and the diene. This stereospecificity has been demonstrated with many substituted dienes and alkenes and also holds for the simplest possible example of the reaction, ethene with butadiene, as demonstrated by isotopic labeling.[8]



The issue of the concertedness of the D-A reaction has been studied and debated extensively. It has been argued that there might be an intermediate that is diradical in character.[9] D-A reactions are almost always stereospecific, which implies that if an intermediate exists, it cannot have a lifetime sufficient to permit rotation or inversion. The prevailing opinion is that the majority of D-A reactions are concerted reactions and most theoretical analyses agree with this view.[10] It is recognized that in reactions between unsymmetrical alkenes and dienes, bond formation might be more advanced at one pair of termini than at the other. This is described as being an *asynchronous* process. Loss of stereospecificity is expected only if there is an intermediate in which one bond is formed and the other is not, permitting rotation or inversion at the unbound termini.

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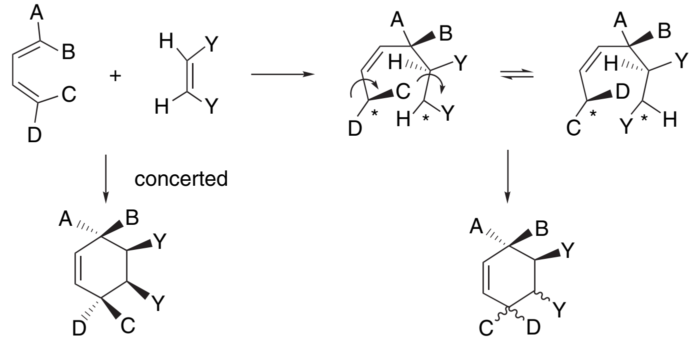
[7] L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949); M. C. Kloetzel, *Org. React.*, **4**, 1 (1948); A. Wasserman, *Diels-Alder Reactions*, Elsevier, New York (1965); R. Huisgen, R. Grashey, and J. Sauer, in *Chemistry of Alkenes*, S. Patai, ed., Interscience, New York, 1964, pp. 878–928; J. G. Martin and R. K. Hill, *Chem. Rev.*, **61,** 537 (1961); J. Hamer, ed., 1,*4-Cycloaddition Reactions: The Diels-Alder Reaction in Heterocyclic Syntheses*, Academic Press, New York, 1967; J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, **19**, 779 (1980); R. Gleiter and M. C. Boehm, *Pure Appl. Chem.*, **55**, 237 (1983); R. Gleiter and M. C. Boehm, in *Stereochemistry and Reactivity of Systems Containing π Electrons*, W. H. Watson, ed., Verlag Chemie, Deerfield Beach, FL, 1983; F. Fringuelli and A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, Wiley, Chichester, 2002.

[8] K. N. Houk, Y.-T. Lin, and F. K. Brown, *J. Am. Chem. Soc.*, **108,** 554 (1986).

[9] M. J. S. Dewar, S. Olivella, and J. P. Stewart, *J. Am. Chem. Soc.*, **108**, 5771 (1986).

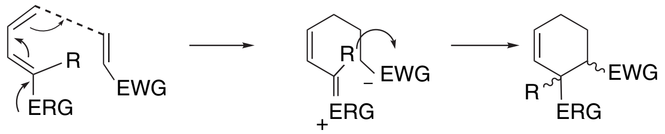
[10] J. J. Gajewski, K. B. Peterson, and J. R. Kagel, *J. Am. Chem. Soc.*, **109**, 5545 (1987); K. N. Houk, Y.-T. Lin, and F. K. Brown, *J. Am. Chem. Soc.*, **108**, 554 (1986); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996); V. Branchadell, *Int. J. Quantum Chem.*, **61**, 381 (1997).



stereospecific product of *supra,supra* cycloaddition

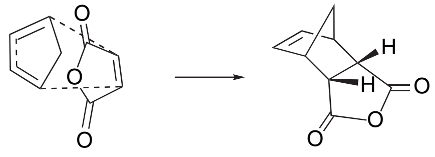
mixture of stereoisomers from non-stereospecific cycloaddition

Loss of stereospecificity is observed when ionic intermediates are involved. This occurs when the reactants are of very different electronic character, with one being strongly electrophilic and the other strongly nucleophilic. Usually more than one substituent of each type is required for the ionic mechanism to occur.



For a substituted dienophile, there are two possible stereochemical orientations with respect to the diene. In the *endo* TS the reference substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* TS the substituent is oriented away from the π system. The two possible orientations are called *endo* and *exo*, as illustrated in Figure 10.3.

For many substituted butadiene derivatives, the two TSs lead to two different stereoisomeric products. The *endo* mode of addition is usually preferred when an EWG substituent such as a carbonyl group is present on the dienophile. This preference is called the *Alder rule*. Frequently a mixture of both stereoisomers is formed and sometimes the *exo* product predominates, but the Alder rule is a useful initial guide to prediction of the stereochemistry of a D-A reaction. The *endo* product is often the more sterically congested. For example, the addition of dienophiles to cyclopentadiene usually favors the *endo*-stereoisomer, even though this is the sterically more congested product.



endo addition

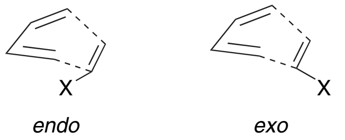
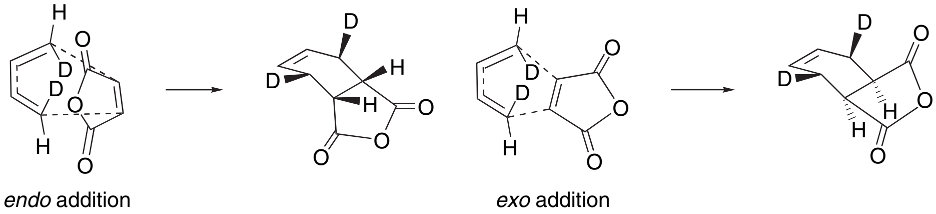
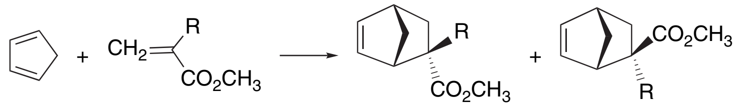


Fig. 10.3. *Exo* and *endo* transition structures for the Diels-Alder reaction.

The preference for the *endo* mode of addition is not restricted to cyclic dienes such as cyclopentadiene. By using deuterium labels it has been shown that in the addition of 1,3-butadiene and maleic anhydride, 85% of the product arises from the *endo* TS.[11]

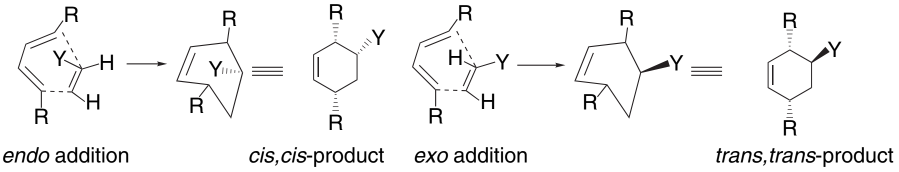

H
O
D
D
O
H
O
D
H
D
H
O
O
O
H
O
D
D
H
O
O
O
D
O
D
H
O
H
O
endo addition
exo addition

The stereoselectivity predicted by the Alder rule is independent of the requirement for suprafacial-suprafacial cycloaddition because both the *endo* and *exo* TSs meet this requirement. There are many exceptions to the Alder rule and in most cases the preference for the *endo* isomer is relatively modest. For example, although cyclopentadiene reacts with methyl acrylate in decalin solution to give mainly the *endo* adduct (75%), the ratio is solvent sensitive and ranges up to 90% *endo* in methanol. When a methyl substituent is added to the dienophile (methyl methacrylate) the *exo* product predominates.[12]


+
CH_2
R
CO_2CH_3
R
CO_2CH_3
+
CO_2CH_3
R

	endo	exo
R = H	75 – 90%	25 – 10%
R = CH_3	22 – 40%	78 – 60%

Stereochemical predictions based on the Alder rule are made by aligning the diene and dienophile in such a way that the unsaturated substituent on the dienophile overlaps the diene π system.


R
Y
H
R
H
R
Y
R
R
Y
R
R
H
Y
R
H
R
Y
R
R
Y
R
endo addition
cis,cis-product
exo addition
trans,trans-product

There are probably several factors that contribute to determining the *endo*:*exo* ratio in any specific case, including steric effects, electrostatic interactions, and London dispersion forces.[13] Molecular orbital interpretations emphasize *secondary orbital interactions* between the π orbitals on the dienophile substituent(s) and the developing π bond between C(2) and C(3) of the diene.

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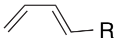
[11] L. M. Stephenson, D. E. Smith, and S. P. Current, *J. Org. Chem.*, **47**, 4170 (1982).

[12] J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).

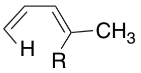
D-A cycloadditions are sensitive to steric effects. Bulky substituents on the dienophile or on the termini of the diene can hinder the approach of the two components to each other and decrease the rate of reaction. This effect can be seen in the relative reactivity of 1-substituted butadienes toward maleic anhydride.[14]



R	k_{rel} (25° C)
H	1
CH_3	4.2
$C(CH_3)_3$	< 0.05

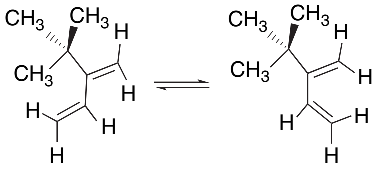
Substitution of hydrogen by methyl results in a slight rate *increase* as a result of the electron-releasing effect of the methyl group. A *t*-butyl substituent produces a large rate *decrease* because the steric effect is dominant.

Another type of steric effect has to do with interactions between diene substituents. Adoption of the *s-cis* conformation of the diene in the TS brings the *cis*-oriented 1- and 4-substituents on diene close together. *trans*-1,3-Pentadiene is 10^3 times more reactive than 4-methyl-1,3-pentadiene toward the very reactive dienophile tetracyanoethene, owing to the unfavorable steric interaction between the additional methyl substituent and the C(1) hydrogen in the *s-cis* conformation.[15]



R	k_{rel}
H	1
CH_3	10^{-3}

Relatively small substituents at C(2) and C(3) of the diene exert little steric influence on the rate of D-A addition. 2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene because of the electron-releasing effect of the methyl groups. 2-*t*-Butyl-1,3-butadiene is 27 times more reactive than butadiene. The *t*-butyl substituent favors the *s-cis* conformation because of the steric repulsions in the *s-trans* conformation.



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[13] Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Funco, *J. Am. Chem. Soc.*, **94**, 3633 (1972); K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).

[14] D. Craig, J. J. Shipman, and R. B. Fowler,*J. Am. Chem. Soc.*, **83**, 2885 (1961).

[15] C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

The presence of a *t*-butyl substituent on *both* C(2) and C(3), however, prevents attainment of the *s-cis* conformation, and D-A reactions of 2,3-di-(*t*-butyl)-1,3-butadiene have not been observed.[16]

10.2.2. Substituent Effects on Reactivity, Regioselectivity and Stereochemistry

There is a strong electronic substituent effect on the D-A cycloaddition. It has long been known that the reaction is particularly efficient and rapid when the dienophile contains one or more EWG and is favored still more if the diene also contains an ERG. Thus, among the most reactive dienophiles are quinones, maleic anhydride, and nitroalkenes. α,ß-Unsaturated esters, ketones, and nitriles are also effective dienophiles. The D-A reaction between unfunctionalized alkenes and dienes is quite slow. For example, the reaction of cyclopentadiene and ethene occurs at around 200°C.[17] These substituent effects are illustrated by the data in Table 10.1. In the case of the diene, reactivity is increased by ERG substituents. Data for some dienes are given in Table 10.2. Note that ERG substituents at C(1) have a larger effect than those at C(2). Scheme 10.2 gives some representative examples of dienophiles activated by EWG substitution.

It is significant that if an electron-poor diene is utilized, the preference is reversed and electron-rich alkenes, such as vinyl ethers and enamines, are the best dienophiles. Such reactions are called *inverse electron demand Diels-Alder reactions*, and the reactivity relationships are readily understood in terms of frontier orbital theory. Electron-rich dienes have high-energy HOMOs that interact strongly with the LUMOs of electron-poor dienophiles. When the substituent pattern is reversed and the diene is electron poor, the strongest interaction is between the dienophile HOMO and the diene LUMO. The FMO approach correctly predicts both the relative reactivity and regioselectivity of the D-A reaction for a wide range of diene-dienophile combinations.

Table 10.1. Relative Reactivity toward Cyclopentadiene in the Diels-Alder Reaction

Dienophile	Relative rate[a]
Tetracyanoethene	43,000,000
1,1-Dicyanoethene	450,000
Maleic anhydride	56,000
p-Benzoquinone	9,000
Z-1,2-Dicyanoethene	91
E-1,2-Dicyanoethene	81
Dimethyl fumarate	74
Dimethyl maleate	0.6
Methyl acrylate	1.2
Cyanoethene	1.0

a. From second-order rate constants in dioxane at 20°C, as reported by J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).

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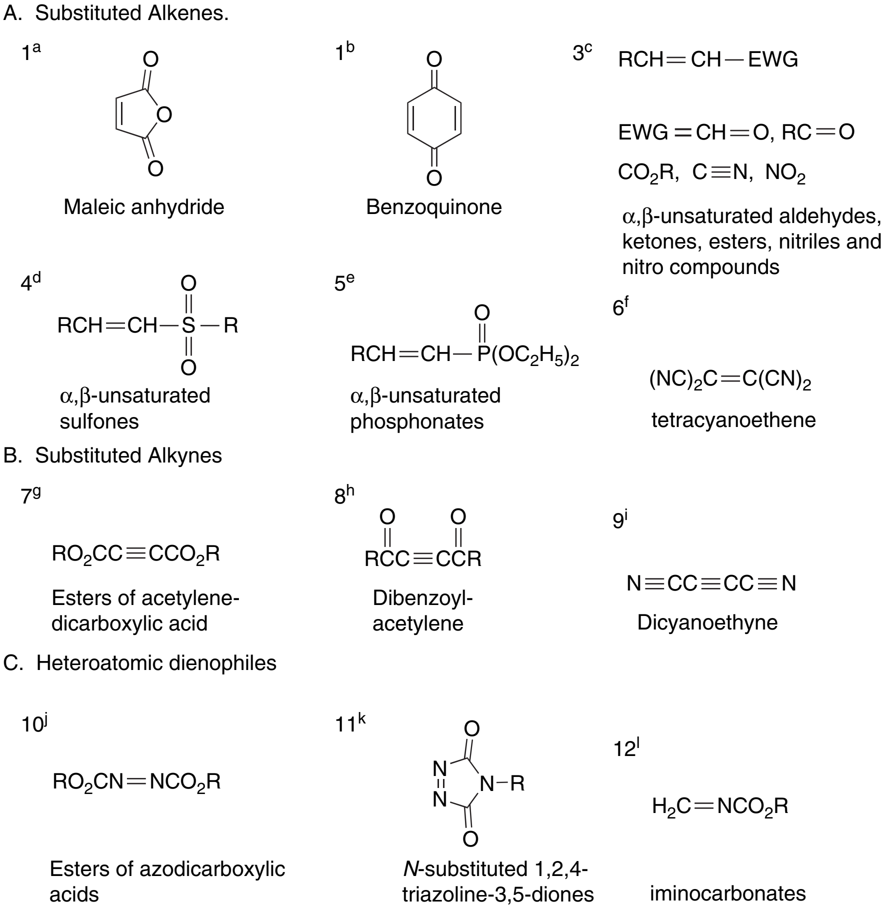
[16] H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **58**, 643 (1939).

[17] J. Meinwald and N. J. Hudak, *Org. Synth.*, **IV**, 738 (1963).

Scheme 10.2. Representative Electrophilic Dienophiles


A. Substituted Alkenes.
1a
Maleic anhydride
1b
Benzoquinone
3c
RCH═CH—EWG
EWG ═ CH═O, RC═O
CO2R, C≡N, NO2
α,β-unsaturated aldehydes, ketones, esters, nitriles and nitro compounds
4d
RCH═CH—S(═O)2—R
α,β-unsaturated sulfones
5e
RCH═CH—P(═O)(OC2H5)2
α,β-unsaturated phosphonates
6f
(NC)2C═C(CN)2
tetracyanoethene
B. Substituted Alkynes
7g
RO2CC≡CCO2R
Esters of acetylene-dicarboxylic acid
8h
RC(═O)C≡CC(═O)R
Dibenzoyl-acetylene
9i
N≡CC≡CC≡N
Dicyanoethyne
C. Heteroatomic dienophiles
10j
RO2CN═NCO2R
Esters of azodicarboxylic acids
11k
N–R
N-substituted 1,2,4-triazoline-3,5-diones
12l
H2C═NCO2R
iminocarbonates

a. M. C. Kloetzel, *Org. React.*, **4**, 1 (1948).
b. L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949).
c. H. L. Holmes, *Org. React.*, **4**, 60 (1948).
d. J. C. Phillips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).
e. W. M. Daniewski and C. E. Griffin, *J. Org. Chem.*, **31**, 3236 (1966).
f. E. Ciganek, W. J. Linn, and O. W. Webster, *The Chemistry of the Cyano Group*, Z. Rappoport, ed., John Wiley & Sons, New York, 1970, pp. 423–638.
g. J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).
h. J. D. White, M. E. Mann, H. D. Kirshenbaum, and A. Mitra, *J. Org. Chem.*, **36**, 1048 (1971).
i. C. D. Weis, *J. Org. Chem.*, **28**, 74 (1963).
j. B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 3177 (1963).
k. B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).
l. M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, and K. Bessho, *J. Org. Chem.*, **30**, 3772 (1965); G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Panella, G. De Vicaris, and M. Grippi, *J. Am. Chem. Soc.*, **95**, 5273 (1973).

The question of regioselectivity arises when both the diene and alkene are unsymmetrically substituted. Generally, there is a preference for the "*ortho*" and "*para*" orientations, respectively, as in the examples shown.[18]

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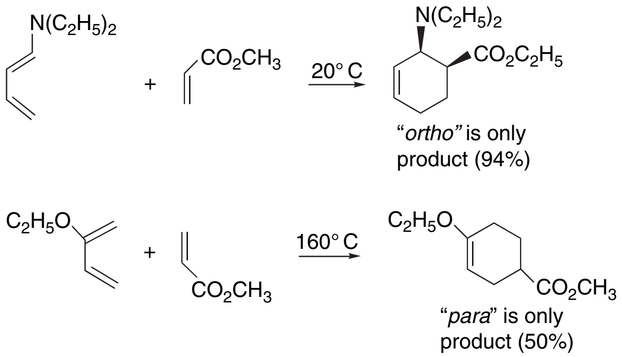
[18] J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).

Table 10.2. Relative Reactivity of Some Substituted Butadienes in the Diels-Alder Reaction[a]

Diene Substituents	Dienophile Tetracyanoethene	Maleic anhydride
None	1	1
1-Methyl	103	3.3
2-Methyl	45	2.3
1,4-Dimethyl	1,660	
1-Phenyl	385	1.65
2-Phenyl	191	8.8
1-Methoxy	50,900	12.4
2-Methoxy	1,750	
1,4-Dimethoxy	49,800	
Cyclopentadiene	2,100,000	1,350

a. C. Rücker, D. Lang, J. Sauer, H. Friege, and R. Sustmann, *Chem. Ber.*, **113**, 1663 (1980).



The regioselectivity of the D-A reaction is determined by the nature of the substituents on the diene and dienophile. FMO theory has been applied by calculating the energy and orbital coefficients of the frontier orbitals.[19] When the dienophile bears an EWG and the diene an ERG, the strongest interaction is between the HOMO of the diene and the LUMO of the dienophile, as indicated in Figure 10.4. The reactants are preferentially oriented with the carbons having the highest coefficients of the two frontier orbitals aligned for bonding. Scheme 10.3 shows the preferred regiochemistry for various substitution patterns. The combination of an electron donor in the diene and an electron acceptor in the dienophile gives rise to cases **A** and **B**. Inverse electron demand D-A reactions give rise to combinations **C** and **D**. In reactions of types **A** and **B**, the frontier orbitals will be the diene HOMO and the dienophile LUMO. The strongest interaction is between ψ_2 and π^* because the donor substituent on the diene raises the diene orbitals in energy, whereas the acceptor substituent lowers the dienophile orbitals. In reaction types **C** and **D**, the pairing of the diene LUMO and dienophile HOMO is the strongest interaction.

The regiochemical relationships summarized in Scheme 10.3 can be understood by considering the atomic coefficients of the frontier orbitals. Figure 10.5 gives the approximate energies and orbital coefficients for the various classes of dienes and dienophiles. 1-ERG substituents (X:) raise the HOMO level and increase the coefficient

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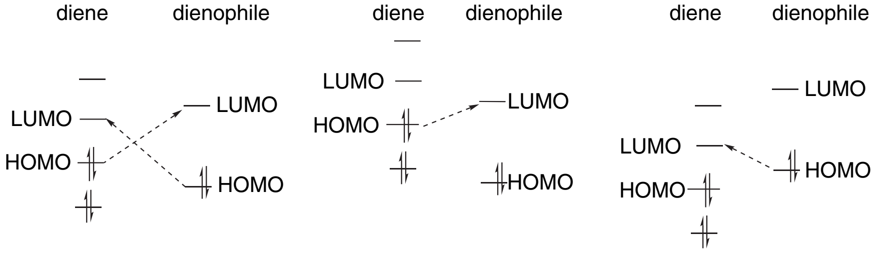
[19] K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4092 (1973).



I. Unperturbed system
Both HOMO – LUMO interactions are comparable, but weak

II. Normal electron demand; diene HOMO and dienophile LUMO interactions are dominant

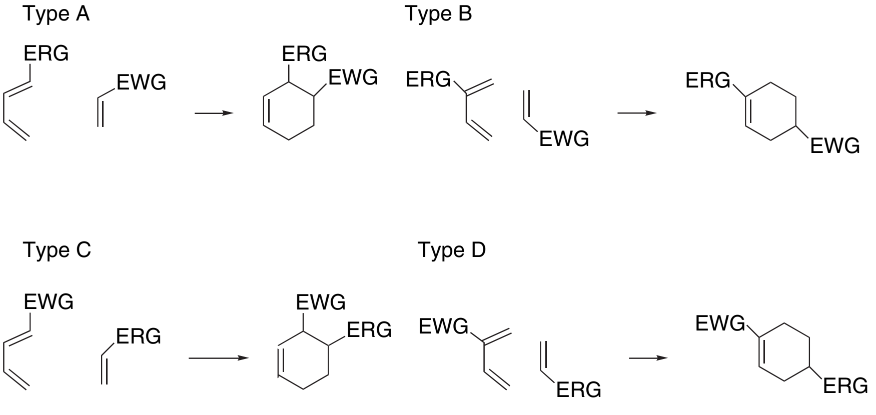
III. Inverse electron demand; diene LUMO and dienophile HOMO are dominant

Fig. 10.4. Frontier orbital interactions in Diels-Alder reactions.

on C(4) of the diene. 2-ERG substituents raise the HOMO and result in the largest HOMO coefficient at C(1). For EWG substituents, the HOMO and LUMO are lowered in energy. For dienophiles, the largest LUMO coefficient is at C(2).

The regiochemistry can be predicted by the generalization that the strongest interaction is between the centers on the frontier orbitals having the largest orbital coefficients. For dienophiles with EWG substituents, π^* has its largest coefficient on the ß-carbon atom. For dienes with ERG substituents at C(1) of the diene, the HOMO has its largest coefficient at C(4). This is the case designated **A** in Scheme 10.3, and is the observed regiochemistry for the type **A** Diels-Alder addition. A similar analysis of each of the other combinations in Scheme 10.3 using the orbitals in Figure 10.5 leads to the prediction of the favored regiochemistry. Note that in the type **A** and **C** reactions this leads to preferential formation of the more sterically congested 1,2-disubstituted cyclohexene. The predictive capacity of these frontier orbital relationships for D-A reactions is excellent.[20]

Scheme 10.3. Regioselectivity of the Diels-Alder Reaction



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[20] For discussion of the development and application of frontier orbital concepts in cycloaddition reactions, see K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); K. N. Houk, *Topics Current Chem.*, **79**, 1 (1979); R. Sustmann and R. Schubert, *Angew. Chem. Int. Ed. Engl.*, **11**, 840 (1972); J. Sauer and R. Sustmann, *Angew. Chem. Int. Ed. Engl.*, **19**, 779 (1980).

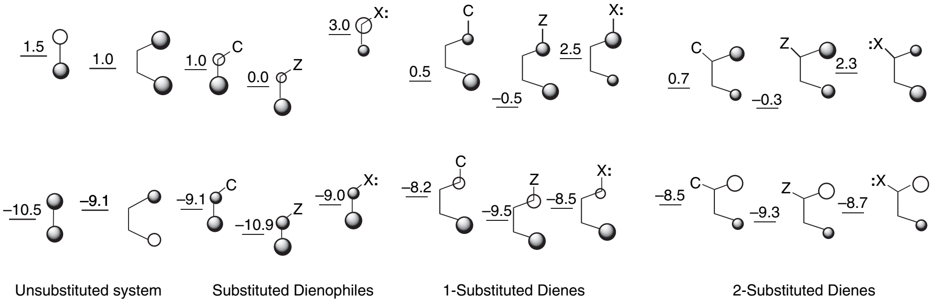

1.5
1.0
1.0
C
0.0
Z
3.0
X:
C
0.5
Z
–0.5
2.5
X:
C
0.7
Z
–0.3
2.3
:X
–10.5
–9.1
–9.1
C
–10.9
Z
–9.0
X:
C
–8.2
Z
–9.5
–8.5
X:
–8.5
C
Z
–9.3
–8.7
:X
Unsubstituted system
Substituted Dienophiles
1-Substituted Dienes
2-Substituted Dienes

Fig. 10.5. Coefficients and relative energies of dienophile and diene frontier MOs. Orbital energies are given in eV. The sizes of the circles give a relative indication of the orbital coefficient. Z stands for a conjugated EWG, e.g., C=O, C≡N. NO_2; C is a conjugated substituent without strong electronic effect, e.g., phenyl, vinyl; X is a conjugated ERG, e.g., OCH_3, NH_2. From *J. Am. Chem. Soc.*, **95**, 4092 (1973).

From these ideas, we see that for substituted dienes and dienophiles there is *charge transfer* in the process of formation of the TS. The more electron-rich reactant acts as an electron donor (*nucleophilic*) and the more electron-poor reactant accepts electron density (*electrophilic*). It also seems from the data in Tables 10.1 and 10.2 that reactions are faster, the *greater the extent of charge transfer*. The reactivity of cyclopentadiene increases with the electron-acceptor capacity of the dienophile. Note also that the very strongly electrophilic dienophile, tetracyanoethene, is more sensitive to substituent effects in the diene than the more moderately electrophilic dienophile, maleic anhydride. These relationships can be understood in terms of FMO theory by noting that the electrophile LUMO and nucleophile HOMO *are closer in energy the stronger the substituent effect*, as illustrated schematically in Figure 10.6.

The FMO considerations are most reliable when one component is clearly more electrophilic and the other more nucleophilic. When a diene with a 2-EWG substituent reacts with an electrophilic dienophile, the major product is the *para* product, even

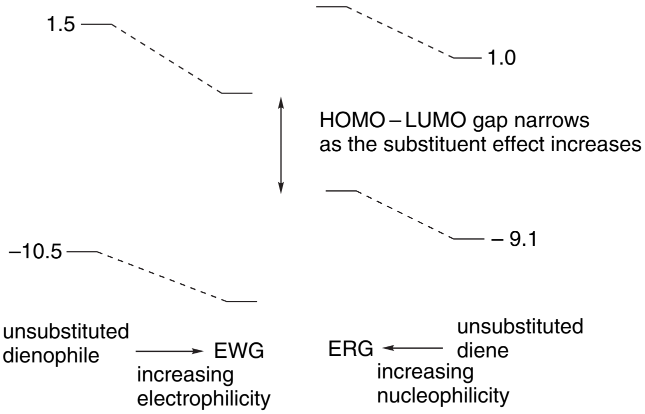
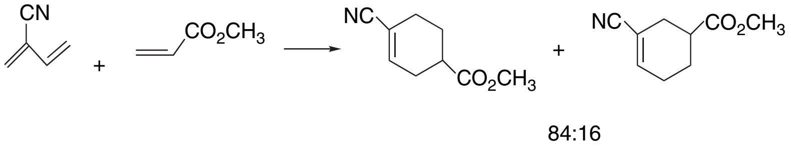
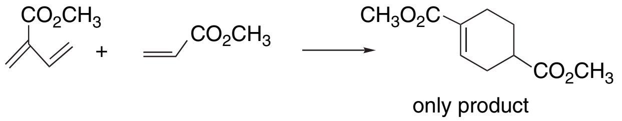

1.5
1.0
HOMO – LUMO gap narrows
as the substituent effect increases
–10.5
– 9.1
unsubstituted dienophile
EWG
increasing electrophilicity
unsubstituted diene
ERG
increasing nucleophilicity

Fig. 10.6. Schematic diagram illustrating substituent effect on reactivity in terms of FMO theory. HOMO-LUMO gap narrows, transition state is stabilized, and reactivity is increased in normal electron-demand Diels-Alder reaction as the nucleophilicity of diene and the electrophilicity of dienophile increase.

though simple resonance consideration would suggest that the *meta* product might be preferred.

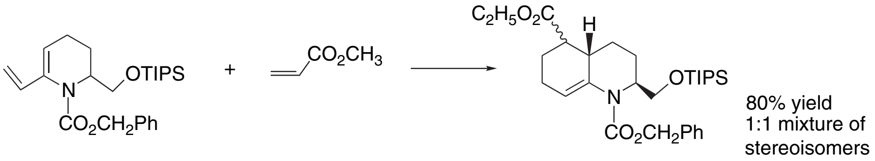

CN
+
CO2CH3
NC
CO2CH3
+
NC
CO2CH3
84:16

Ref. 21


CO2CH3
+
CO2CH3
CH3O2C
CO2CH3
only product

Ref. 22

Another case that goes contrary to simple resonance or FMO predictions are reactions of 2-amido-1,3-dienes. The main product has a *meta* rather than a *para* orientation. These reactions also show little *endo*:*exo* stereoselectivity.

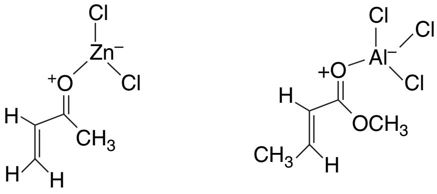

OTIPS
N
CO2CH2Ph
+
CO2CH3
C2H5O2C
H
OTIPS
N
CO2CH2Ph
80% yield
1:1 mixture of
stereoisomers

Ref. 23

Thus, there seems to be reason for caution in application of simple resonance or FMO predictions to 2-substituted dienes. We say more about this Topic 10.1.

10.2.3. Catalysis of Diels-Alder Reactions by Lewis Acids

Diels-Alder reactions are catalyzed by many Lewis acids, including $SnCl_4$, $ZnCl_2$, $AlCl_3$, and derivatives of $AlCl_3$ such as $(CH_3)_2AlCl$ and $(C_2H_5)_2AlCl$.[24] A variety of other Lewis acids are effective catalysts. The types of dienophiles that are subject to catalysis are typically those with carbonyl substituents. Lewis acids form complexes at the carbonyl oxygen and this increases the electron-withdrawing capacity of the carbonyl group. The basic features are well modeled by HF/3-21G level computations on the TS structures.[25]


Cl
Zn⁻
+O
Cl
H
CH3
H
H
Cl
Cl
Al⁻
+O
Cl
H
OCH3
CH3
H

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[21] T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).

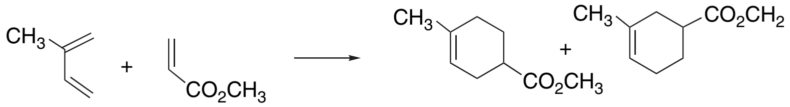
[22] C. Spino, J. Crawford, Y. Cui, and M. Gugelchuk, *J. Chem. Soc., Perkin Trans. 2*, 1499 (1998).

[23] J. D. Ha, C. H. Kang, K. A. Belmore, and J. K. Cha, *J. Org. Chem.*, **63**, 3810 (1998).

[24] P. Laszlo and J. Lucche, *Actual. Chim.*, 42 (1984).

[25] D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990); M. I. Menendez, J. Gonzalez, J. A. Sordo, and T. L. Sordo, *Theochem*, **120**, 241 (1994).

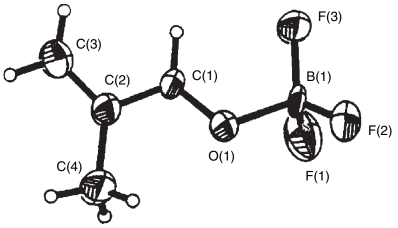
This complexation accentuates both the energy and orbital distortion effects of the substituent and enhances both the reactivity and selectivity of the dienophile relative to the uncomplexed compound.[26] Usually, both regioselectivity and *exo*,*endo* stereoselectivity increase. Part of this may be due to the lower reaction temperature. However, the catalysts also shift the reaction toward a higher degree of charge transfer by making the EWG substituent more electrophilic.



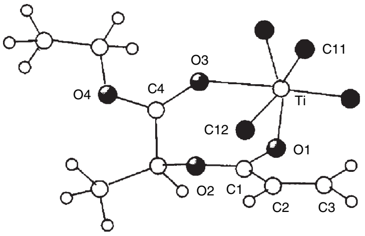
	"*para*"	"*meta*"
Uncatalyzed reaction, 120° C, 6h	70%	30%
$AlCl_3$ -catalyzed 20° C, 3h	95%	5%

Ref. 27

The stereoselectivity of any particular D-A reaction depends on the details of the TS structure. The structures of several enone–Lewis acid complexes have been determined by X-ray crystallography.[28] The site of complexation is the carbonyl oxygen, which maintains a trigonal geometry, but with somewhat expanded angles (130°–140°). The Lewis acid is normally *anti* to the larger carbonyl substituent. Boron trifluoride complexes are tetrahedral, but Sn(IV) and Ti(IV) complexes can be trigonal bipyramidal or octahedral. The structure of the 2-methylpropenal-BF_3 complex is illustrative.[29]



Chelation can favor a particular structure. For example, *O*-acryloyl lactates adopt a chelated structure with $TiCl_4$.[30]



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

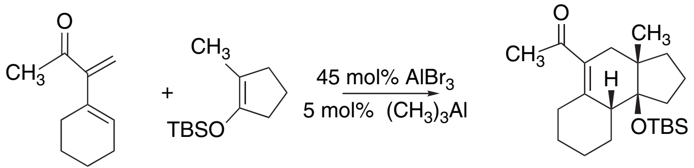
[27] T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

[28] S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **29**, 256 (1990).

[29] E. J. Corey, T.-P. Loh, S. Sarshar, and M. Azimioara, *Tetrahedron Lett.*, **33**, 6945 (1992).

[30] T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985).

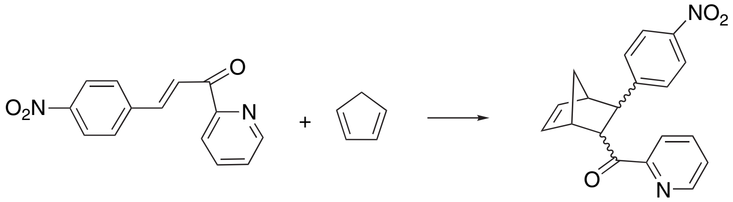
Lewis acid catalysis can also be applied to inverse electron demand D-A reactions, but with the proviso that the strongest interaction must be with the diene in this case.



70% (*exo*) adduct;
also 7% *endo* adduct

Ref. 31

Metal cations can catalyze reactions of certain dienophiles. For example, Cu^{2+} strongly catalyzes addition reactions of 2-pyridyl styryl ketones, presumably through a chelate.[32] DFT (B3LYP/6-31G*) computations indicate that this reaction shifts to a stepwise ionic mechanism in the presence of the Lewis acid.[33]



Solvent	Rate ($M^{-1}s^{-1}$)	Relative Rate
Acetonitrile	1.3×10^{-5}	1
Ethanol	3.8×10^{-5}	2.9
Water	4.0×10^{-3}	310
Water + 0.01 M $Cu(NO_3)_2$	3.25	250,000

The solvent also has an important effect on the rate of D-A reactions. The traditional solvents were nonpolar organic solvents such as aromatic hydrocarbons. However, water and other highly polar solvents, such as ethylene glycol and formamide, accelerate a number of D-A reactions.[34] The accelerating effect of water is attributed to "enforced hydrophobic interactions."[35] That is, the strong hydrogen-bonding network in water tends to exclude nonpolar solutes and forces them together, resulting in higher effective concentrations. There may also be specific stabilization of the developing TS.[36] For example, hydrogen bonding with the TS can contribute to the rate acceleration.[37]

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[31] M. E. Jung and P. Davidov, *Angew. Chem. Int. Ed. Engl.*, **41**, 4125 (2002).

[32] S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).

[33] L. R. Domingo, J. Andres, and C. N. Alves, *Eur. J. Org. Chem.*, 2557 (2002).

[34] D. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980); R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988); T. Dunams, W. Hoekstra, M. Pentaleri, and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).

[35] S. Otto and J. B. F. N. Engberts, *Pure Appl. Chem.*, **72**, 1365 (2000).

[36] R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, **113**, 4340 (1991).

[37] W. Blokzijl, M. J. Blandamer, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991); W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992); S. Otto, W. Blokzijl, and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994); A. Meijer, S. Otto, and J. B. F. N. Engberts, *J. Org. Chem.*, **65,** 8989 (1998); S. Kong and J. D. Evanseck, *J. Am. Chem. Soc.*, **122**, 10418 (2000).

10.2.4. Computational Characterization of Diels-Alder Transition Structures

The idea of complementary electronic interactions between the diene and dienophile provides a reliable qualitative guide to the regio- and stereoselectivity of the D-A reaction. Structural and substituent effects can be explored in more detail by computational analysis of TS structure and energy. Comparison of the relative energy of competing TSs allows prediction and interpretation of the course of the reaction. Ab initio HF calculations often can be relied on to give the correct order of isomeric TS structures. Accurate E_a estimates require a fairly high-level treatment of electron correlation. Reliable results have been achieved with B3LYP/6-31G*, MP3/6-31G*, and CCSD(T)/6-31G* computations.[38] These calculations permit prediction and interpretation of relative reactivity and regio- and stereoselectivity by comparison of competing TSs. There are other aspects of TS character that can be explored, including the degree of asynchronicity in bond formation and the nature of the electronic reorganization within the TS. Kinetic isotope effects can be calculated from the TS and provide a means of validation of TS characteristics by comparison with experimental results.[39]

A range of quantum chemical computations were applied to Diels-Alder reactions as the methods were developed. The consensus that emerged is illustrated by typical recent studies.[25,40] For symmetrical dienes and dienophiles without strong EWG substituents, the reaction is *synchronous*, that is the degree of bond making of the C(1)−C(1′) and C(4)−C(2′) bonds is the same. As we will see shortly, this does not always seem to be the case for strongly electrophilic dienophiles, even when they are symmetric. The TS displays aromaticity, as indicated by the computed NICS value (see Section 8.1.3),[41] which implies that there is enhanced delocalization of the six electrons that participate in bonding changes. Fradera and co-workers have used the AIM localization and delocalization parameters λ and δ to investigate the electron distribution in the TS for ethene/butadiene cycloaddition.[42] At the HF/6-31G* level, the delocalization indices are about 0.4 for all the reacting bonds (plus 1.0 for the residual bonds). There is stronger delocalization between the *para* than the *meta* positions. Both of these parameters are very similar to those found for benzene.[43] These similarities support the idea that the electronic distribution in the TS for the D-A reaction resembles that of the π system of benzene, an idea that goes back to the 1930s.[44]

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[38] T. C. Dinadayalane, R. Vijaya, A. Smitha, and G. N. Sastry, *J. Phys. Chem. A*, **106**, 1627 (2002); B. R. Beno, S. Wilsey, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 4816 (1999).

[39] B. R. Beno, K. N. Houk, and D. A. Singleton, *J. Am. Chem. Soc.*, **118**, 9984 (1996); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996).

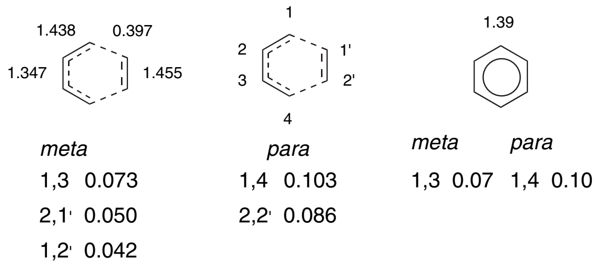
[40] S. Sakai, *J. Phys. Chem. A*, **104**, 922 (2000); R. D. J. Froese, J. M. Coxon, S. C. West, and K. Morokuma, *J. Org. Chem.*, **62**, 6991 (1997).

[41] H. Jiao and P. v. R. Schleyer, *J. Phys. Org. Chem.*, **11**, 655 (1998).

[42] J. Poater, M. Sola, M. Duran, and X. Fradera, *J. Phys. Chem. A*, **105**, 2052 (2001).

[43] X. Fradera, M. A. Austen, and R. F. W. Bader, *J. Phys. Chem. A*, **103**, 304 (1999).

[44] M. G. Evans, *Trans. Faraday Soc.*, **35**, 824 (1939).



The TS of D-A reactions can also be characterized with respect to *synchronicity*. If both new bonds are formed to the same extent the reaction is synchronous, but if they differ it is asynchronous. Synchronicity has been numerically defined in terms of Wiberg bond order indices.[45]

$$S_y^1 = 1 - \frac{\sum_{i=1}^{n} |\delta B_i - \delta B_{\mathrm{av}}| / \delta B_{\mathrm{av}}}{2n-2} \tag{10.1}$$

where n is the number of bonds directly involved in the reaction, δB_i is the relative variation in the B_i at the TS. The terms δB_i and δB_{av} are defined as follows:

$$\delta B_i = \frac{B_i^{TS} - B_i^{R}}{B_i^{P} - B_i^{R}} \tag{10.2}$$

$$\delta B_{av} = n^{-1} \sum_{i=1}^{n} \delta B_i \tag{10.3}$$

Computations have also been applied to the analysis of *exo*:*endo* ratios. The computed differences in energies of the *exo* and *endo* TS are often small and are subject to adjustments when solution models are used.[46] Cyclopentadiene has been a common subject, since there is more experimental data for this compound than for any other. MP3/6-31G*-level computations were used to compare the *exo* and *endo* TS E_a for the reactions with acrylonitrile and but-2-en-3-one (methyl vinyl ketone), and ZPE and thermal corrections were included in the calculations.[47] Good qualitative agreement was achieved with the experimental results, which is little stereoselectivity for acrylonitrile and *endo* stereoselectivity for but-3-en-2-one.

	Acrylonitrile		But-3-en-2-one	
	E_a	$\Delta G^{\ddagger}$	E_a	$G^{\ddagger}$
exo	18.49	31.72	16.16	29.86
endo	18.53	31.69	15.92	29.42
Difference	−0.04	+0.03	+0.24	+0.44

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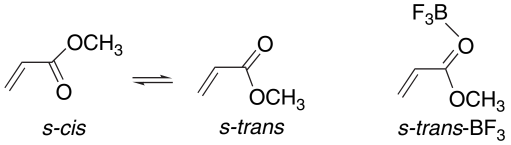
[45] A. Moyano, M. A. Pericas, and E. Valenti, *J. Org. Chem.*, **54**, 573 (1989); B. Lecea, A. Arrieta, G. Roa, F. P. Ugalde, and F. P. Cossio, *J. Am. Chem. Soc.*, **116**, 9613 (1994).

[46] M. F. Ruiz-Lopez, X. Assfeld, J. I. Garcia, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **115**, 8780 (1993).

[47] W. L. Jorgensen, D. Lim, and J. F. Blake, *J. Am. Chem. Soc.*, **115**, 2936 (1993).

Computational studies have revealed some of the distinctive effects of Lewis acid catalysis on TS structure. MO (HF/6-31G*, MP2/6-31G*) and DFT (B3LYP/6-311+G(2*d*,*p*)) calculations have been used to compare the structure and energy of four possible TSs for the D-A reaction of the BF_3 complex of methyl acrylate with 1,3-butadiene. The results are summarized in Figure 10.7. The uncatalyzed reaction favors the *exo-cis* TS by 0.38 kcal/mol over the *endo-cis* TS. For the catalyzed reaction, the *endo* TS with the *s-trans* conformation of the dienophile is preferred to the two *exo* TSs by about 0.8 kcal/mol.[48] Part of the reason for the shift in preferred TS is the difference in the ground state dienophile conformation. The *s-trans* conformation minimizes repulsions with the BF_3 group. There is also a significant difference in the degree of charge transfer between the uncatalyzed and catalyzed reactions, as reflected by the NPA δ values. The catalyzed reaction has a much larger net transfer of electron density to the dienophile. The catalyzed reactions are less synchronous than the uncatalyzed reactions, as can be seen by comparing the differences in the lengths of the forming bonds.



Relative Transition State Energies

Uncatalyzed reaction			BF$_3$-catalyzed reaction		
	Rel *E*	NPAδ		Rel *E*	NPAδ
s-cis Acrylate	0.00	–	*s-cis* Acrylate-BF$_3$	1.71	–
s-trans Acrylate	0.65	–	*s-trans* Acrylate-BF$_3$	0.00	–
endo-cis TS	0.38	0.005	*endo-cis* BF$_3$ TS	2.23	0.276
endo-trans TS	1.65	0.005	*endo-trans* BF$_3$ TS	0.00	0.225
exo-cis TS	0.00	0.006	*exo-cis* BF$_3$ TS	0.82	0.260
exo-trans TS	1.44	0.006	*exo-trans* BF$_3$ TS	0.83	0.216

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

Similar calculations have been done for propenal.[49] For the uncatalyzed reaction, the *endo-cis* TS is slightly favored over the *exo-cis*; the two *trans* TSs are more than 1 kcal/mol higher. The order is the same for the catalyzed reaction, but the differences are accentuated. The TSs for the catalyzed reactions are considerably more asynchronous than those for the uncatalyzed reactions. For example, for the reaction of butadiene and acrolein, the asynchronicity was measured as the difference in bond length of the two forming bonds.

$$\Delta d = [C(1)-C(1'')] - [C(4)-C(2')]$$

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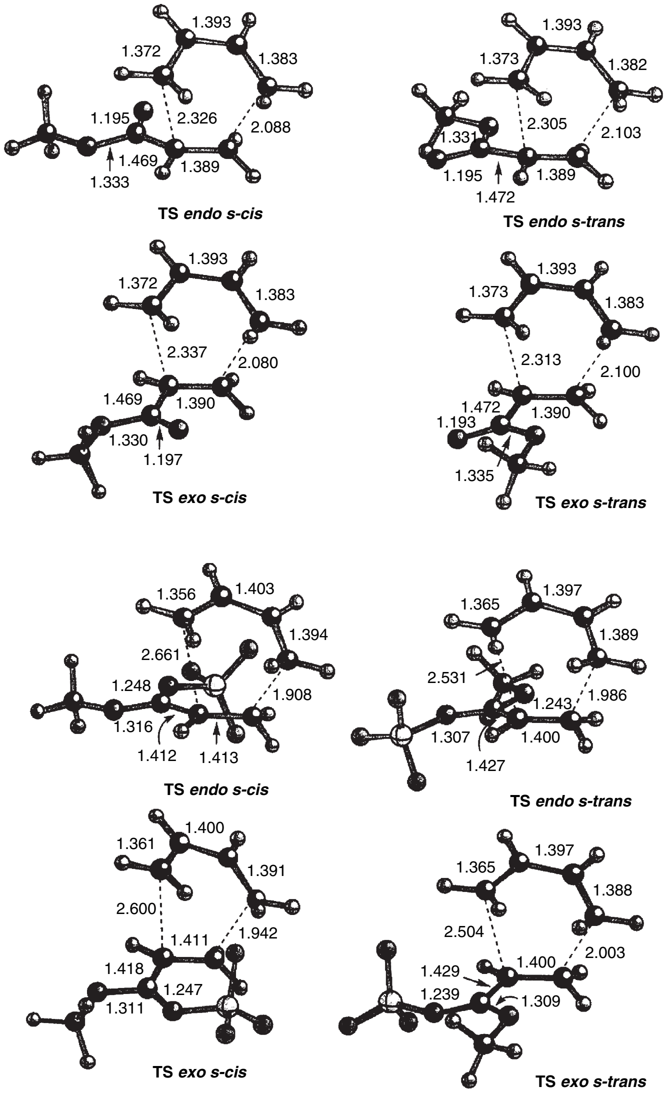
[48] J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Tetrahedron*, **53,** 6057 (1997).

[49] J. I. Garcia, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **118**, 11680 (1996); J. I. Garcia, V. Martinez-Merino, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).


1.393
1.372
1.383
1.195
2.326
2.088
1.469
1.389
1.333
1.393
1.373
1.382
2.305
2.103
1.331
1.195
1.389
1.472
1.393
1.372
1.383
2.337
2.080
1.469
1.390
1.330
1.197
1.393
1.373
1.383
2.313
2.100
1.472
1.193
1.390
1.335
1.356
1.403
1.394
2.661
1.248
1.908
1.316
1.412
1.413
1.365
1.397
1.389
2.531
1.243
1.986
1.307
1.400
1.427
1.361
1.400
1.391
2.600
1.411
1.942
1.418
1.247
1.311
1.365
1.397
1.388
2.504
1.400
2.003
1.429
1.239
1.309

TS ***endo s-cis*** **TS** ***endo s-trans***

TS ***exo s-cis*** **TS** ***exo s-trans***

TS ***endo s-cis*** **TS** ***endo s-trans***

TS ***exo s-cis*** **TS** ***exo s-trans***

Fig. 10.7. Computed transition structures for uncatalyzed and BF_3-catalyzed Diels-Alder reaction of 1,3-butadiene with methyl acrylate. Reproduced from *Tetrahedron*, **53**, 6057 (1997), by permission of Elsevier.

The value of Δd increases from 0.617 to 0.894 going from the uncatalyzed to the BF_3-catalyzed reaction.

Another feature of the catalyzed TS is stronger interaction between the diene and the complexed EWG by a type of secondary orbital interaction. For example, in the butadiene-acrolein/BH_3 catalytic complex,[50] there is a quite close approach of diene C(1) to the complexed carbonyl carbon.[51] This aspect of the TS was examined for the BF_3-catalyzed reaction by comparing the electron density between C(1) and

[50] D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990).

[51] D. A. Singleton, *J. Am. Chem. Soc.*, **114**, 6563 (1992).

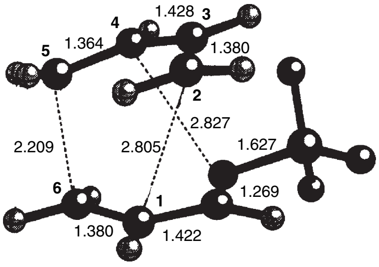
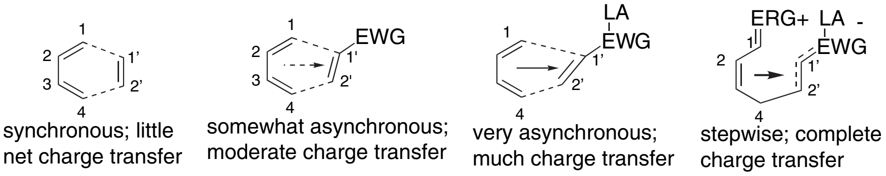

1.428
4
3
5
1.364
1.380
2
2.827
2.209
2.805
1.627
6
1
1.269
1.380
1.422

Fig. 10.8. Secondary orbital interaction between carbonyl oxygen and butadiene in BF_3-catalyzed transition structure. Reproduced from *J. Am. Chem. Soc.*, **120**, 2415 (1998), by permission of the American Chemical Society.

the carbonyl carbon as shown in Figure 10.8. Significant bonding was noted and is represented by the second dashed line in the TS structure.[49]

The extent of this interaction is different in the *endo* and *exo* TSs and contributes to the enhanced *endo* stereoselectivity that is observed in catalyzed reactions. This structural feature is consistent with the catalyzed reaction having more extensive charge transfer, owing to the more electrophilic character of the complexed dienophile. In the limiting case, the reaction can become a stepwise ionic process.


1
2
3
1'
2'
4
synchronous; little net charge transfer
1
2
3
EWG
1'
2'
4
somewhat asynchronous; moderate charge transfer
LA
1
EWG
1'
2'
4
very asynchronous; much charge transfer
ERG+
LA -
1
EWG
2
1'
2'
4
stepwise; complete charge transfer

One might expect that a D-A reaction of butadiene with any *symmetrical* dienophile would have a synchronous TS, since the new bonds that are being formed are *identical.* However, that does not seem to be the case, at least for highly electrophilic dienophiles. For example, highly asynchronous TSs are found for maleic acid[52] and 1,2,4-triazoline, as shown in Figure 10.9.[53]

There is, however, disagreement in the case of the results for another very reactive dienophile, dimethyl acetylenedicarboxylate. Froese and co-workers also found the TS of cyclopentadiene and dimethyl acetylenedicarboxylate to be unsymmetrical by B3LYP/6-31G computation,[54] but another group discovered that a symmetrical TS was favored for 1,3-butadiene.[55] These unsymmetrical TSs seem to reflect the same trend noted in comparing Lewis acid–catalyzed reactions with uncatalyzed reactions.

---

[52] D. A. Singleton, B. E. Schulmeier, C. Hang, A. A. Thomas, S.-W. Leung, and S. R. Merrigan, *Tetrahedron*, **57**, 5149 (2001).

[53] J. S. Chen, K. N. Houk, and C. S. Foote, *J. Am. Chem. Soc.*, **120**, 12303 (1998).

[54] R. D. J. Froese, J. M. Coxon, S. C. West, and K. Morokuma, *J. Org. Chem.*, **62**, 6991 (1997).

[55] L. R. Domingo, M. Arno, R. Contreras, and P. Perez, *J. Phys. Chem. A*, **106**, 952 (2002).

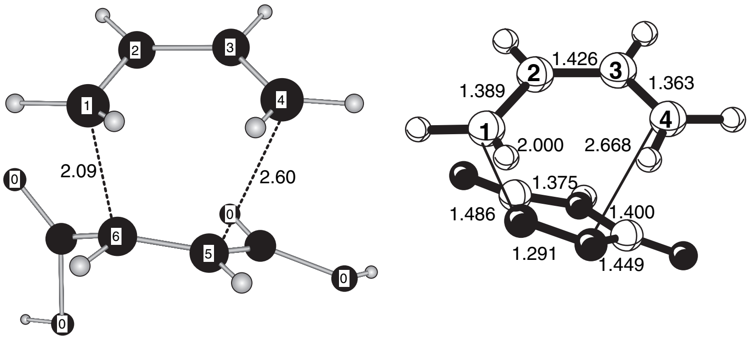
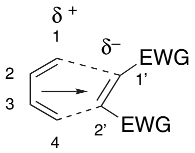
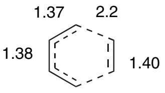


Fig. 10.9. Asynchronous transition structures for Diels-Alder reactions of butadiene with maleic acid and 1,2,4-triazoline using B3LYP/6-31G* calculations. Reproduced from *Tetrahedron*, **57**, 5149 (2001) and *J. Am. Chem. Soc.*, **120**, 12303 (1998), by permission of Elsevier and the American Chemical Society, respectively.

The asynchronous TS results from an increase in the extent of charge transfer, leading to partial ionic character in the TS.



There seems to be another element of asynchronicity associated with bond formation in D-A reactions. The formation of the new double bond and the lengthening of the reacting dienophile bond seem to *run ahead* of the formation of the new σ bonds. For example, in the MP4SDTQ/6-31G* TS for the reaction of butadiene and ethene, the new σ bonds are only 22% formed at the TS. The same picture emerges by following the transformations of the orbitals during the course of the reaction.[56] The transfer of π-electronic characteristics from the dienophile π bond to the product π bond seems to occur ahead of the reorganization of electrons to form the two new σ bonds.



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A wide variety of diene substituents were surveyed using B3LYP/6-31G(d,p) calculations to determine the effect on the E_a for D-A addition with ethene.[57] There was stabilization of the TS by EWG substituents, which was accompanied by a small positive charge (NPA) on ethene. This indicates that the electronic interaction involves the diene as a net electron acceptor; that is, the reactions are diene LUMO-controlled inverse electron demand reactions. The size of the stabilization and the charge transfer correlated reasonably well with a *combination* of the polar and resonance substituent constants. A polarization effect was also noted in several series. In each instance, the stabilization *increased* with substituent size and polarizability ($F < Cl < Br$; $CH_3 < CF_3 < CCl_3 < CBr_3$; $OCH_3 < SCH_3 < SeCH_3$).

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[56] C. Spino, M. Pesant, and Y. Dory, *Angew. Chem. Int. Ed. Engl.*, **37**, 3262 (1998).

[57] R. Robiette, J. Marchand-Brynaert, and D. Peeters, *J. Org. Chem.*, **67**, 6823 (2002).

Computation on TS structure may be useful in predicting and interpreting trends in reactivity, regioselectivity, and stereoselectivity. To the extent observed trends are in agreement with the computations, the validity of the TS structure is supported. One experimental measurement that can be directly connected to TS structure is the kinetic isotope effect (review Section 3.5), which can be measured with good experimental accuracy as well as calculated from the TS structure.[58] Comparisons can be used to examine TS structure at a very fine level of detail. The computed TS for the $(CH_3)_2AlCl$-catalyzed reaction of isoprene with acrolein, ethyl acrylate, and but-3-en-2-one indicated highly asynchronous TSs and gave calculated isotope effects in agreement with experiment.[59] For example, the study of the $(CH_3)_2AlCl$-catalyzed D-A reaction of isoprene with propenal found good agreement between observed and computed isotope effects, except at one position. A later study located an alternative TS that gave better agreement with the isotope effect at this position.[60] This structure incorporates a formyl H bond, as postulated in other Lewis acid–catalyzed reactions of aldehydes.[61] Although this structure was computed to be slightly higher in energy, it was favored when a PCM solvent model was used. The TSs are shown in Figure 10.10.

Several studies have looked at the TS of D-A reactions in which the extent of aromaticity increases or decreases in going from reactants to products. For example, aromaticity is enhanced with *o*-quinodimethanes, where a new benzene ring is formed. The benzo[c] fused heterocycles contain an *o*-quinoid structure. The aromaticity of the heterocyclic ring is lost, but a new benzenoid ring is formed by cycloaddition. When polycyclic aromatic compounds undergo D-A reactions, the aromaticity of the reacting central ring is lost, but the peripheral rings have increased aromaticity per carbon.

Calculated E_a's in several cases are in accord with the experimental trends.[62] Quinodimethanes are more reactive than benzo[c]heterocycles and the reactivity of the linear polycyclic hydrocarbons increases with the number of rings. The changes in the NICS values for the rings is consistent with the changing aromaticity. In the case of polycyclic hydrocarbons, the aromaticity in the peripheral rings increases. The aromaticity of the center ring is transformed to the aromaticity of the TS and then diminishes as the reaction is completed.[63]

[58] B. R. Beno, K. N. Houk, and D. A. Singleton, *J. Am. Chem. Soc.*, **118**, 9984 (1996); E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996).

[59] D. A. Singleton, S. R. Merrigan, B. R. Beno, and K. N. Houk, *Tetrahedron Lett.*, **40**, 5817 (1999).

[60] O. Acevedo and J. D. Evanseck, *Org. Lett.*, **5**, 649 (2003).

[61] E. J. Acevedo Corey, J. J. Rohde, A. Fischer, and M. D. Alimiora, *Tetrahedron Lett.*, **38**, 33 (1997).

[62] C. Di Valentin, M. Freccero, M. Sarzi-Amade, and R. Zanaletti, *Tetrahedron*, **56**, 2547 (2000).

[63] M. Manoharan, F. De Proft, and P. Geerlings, *J. Chem. Soc., Perkin Trans. 2*, 1767 (2000); M.-F. Cheng and W.-K. Li, *Chem. Phys. Lett.*, **368**, 630 (2003).

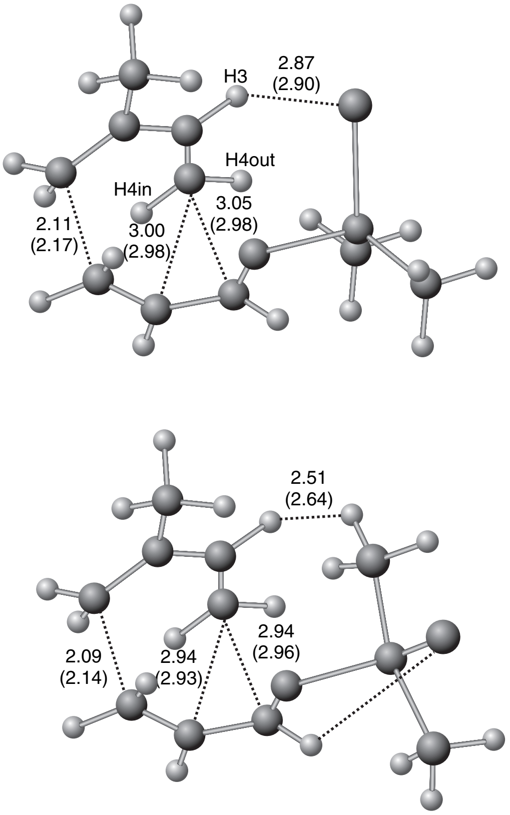
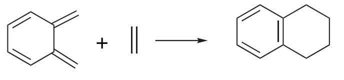
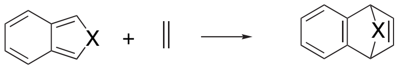


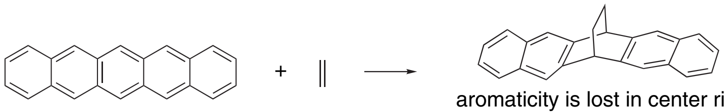
Fig. 10.10. Alternate transition structures for Diels-Alder reaction of isoprene with propenal: (a) structure without formyl hydrogen bond; (b) structure with formyl hydrogen bond. Dimensions are from B3LYP/6-31G(d) computations in the gas phase and in PMC with $\varepsilon = 4.335$ (shown in parentheses). Adapted from *Org. Lett.*, **5**, 649 (2003), by permission of the American Chemical Society.



quinodimethane
aromaticity increases at TS



X = O, NH, S benzo[c]heterocycles
aromaticity is lost in the heterocyclic ring but
enhanced in the benzenoid ring



polycyclic aromatic hydrocarbon

aromaticity is lost in center ring but
enhanced in the peripheral rings

In the case of the benzo[c] heterocycles, the ΔE, E_a, and degree of charge transfer in the TS were calculated. The E_a correlated with the exothermicity of the reaction for the second-row elements. The extent of charge transfer at the TS increased from carbon to oxygen to nitrogen, but was low for the benzo[c]thiophene.[64]

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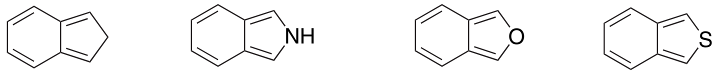
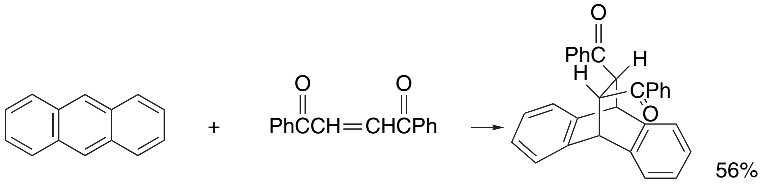
[64] T. C. Dinadayalane and G. N. Sastry, *J. Chem. Soc., Perkin Trans. 2*, 1902 (2002).



E_a	10.8	21.4	15.4	24.7
ΔE	−48.8	−16.2	−29.8	−27.1
c.t.	0.022	0.092	0.043	0.001

These results are consistent with experimental results. Polycyclic aromatic hydrocarbons are moderately reactive as the diene component of Diels-Alder reactions. Although benzene and naphthalene show no reactivity toward maleic anhydride at 90° C, anthracene does give an adduct.[65] A variety of dienophiles react with anthracene, including benzoquinone, dimethyl fumarate, nitroethene, and phenyl vinyl sulfoxide.[66] The addition occurs at the center ring. There is no net loss of resonance stabilization, since the anthracene ring (resonance energy $= 1.60\,\text{eV}$) is replaced by two benzenoid rings (total resonance energy $= 2 \times 0.87 = 1.74\,\text{eV}$).[67]



Ref. 68

A B3LYP/6-31+G(*d*,*p*) computational investigation of the reaction between anthracene and tetracyanoethene indicates that the reaction proceeds through a charge transfer complex.[69] Mulliken population analysis was used to follow the transfer of charge at the various stages of the reaction. At the CT complex, 0.20 electron had been transferred. This increased to 0.46 electron at the TS, but then dropped to 0.32 electron in the product. There is partial pyramidalization of both the dienophile and anthracene in the CT complex. This distortion is believed to make the transformation of the reactants to the TS more facile. The formation of the CT complex also begins the process of decreasing the aromaticity of the center ring, which makes the distortion of the ring toward the TS easier.

In the case of the reaction of anthracene with tetracyanoethene, there is kinetic evidence for an intermediate that is distinct from the rapidly formed charge transfer complex.[70] The intermediate is proposed to be a tight complex with a geometry favorable for formation of the adduct. The formation of the charge transfer complex is fast and reversible and may also lie on the overall reaction path.

$$\text{ANTH} + \text{TCNE} \overset{\substack{\text{very}\\ \text{fast}}}{\rightleftharpoons} \text{CT complex} \underset{k = 14.8\ \text{s}^{-1}}{\overset{k = 5.5\ \text{M}^{-1}\text{s}^{-1}}{\rightleftharpoons}} \text{intermediate} \xrightarrow{k = 12.4\ \text{s}^{-1}} \text{adduct}$$

---

[65] B. Biermann and W. Schmidt, *J. Am. Chem. Soc.*, **102**, 3163 (1980).

[66] J. C. C. Atherton and S. Jones, *Tetrahedron*, **59**, 9039 (2003).

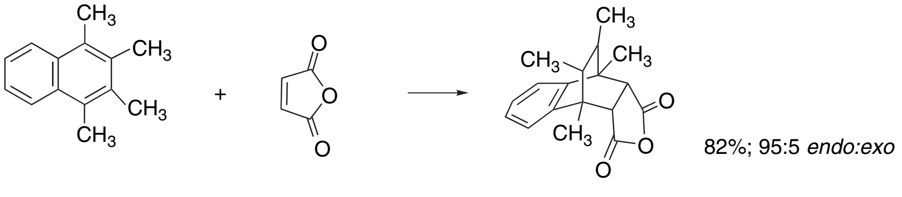
[67] M. J. S. Dewar and C. de Llano, *J. Am. Chem. Soc.*, **91**, 789 (1969).

[68] D. M. McKinnon and J. Y. Wong, *Can. J. Chem.*, **49**, 3178 (1971).

[69] K. E. Wise and R. A. Wheeler, *J. Phys. Chem. A*, **103**, 8279 (1999).

[70] K. L. Handoo, Y. Lu, and V. D. Parker, *J. Am. Chem. Soc.*, **125**, 9381 (2003).

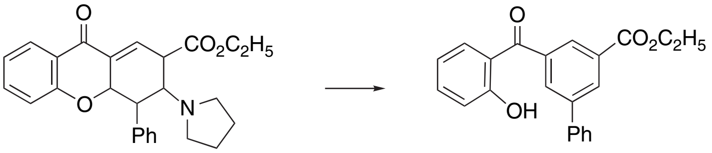
The naphthalene ring is much less reactive. Polymethylnaphthalenes are more reactive than the parent molecule and 1,2,3,4-tetramethylnaphthalene gives an adduct with maleic anhydride in 82% yield. Reaction occurs exclusively in the substituted ring because it is more electron rich.[71] The steric repulsions between the methyl groups, which are relieved in the nonplanar adduct, may also exert an accelerating effect.



10.2.5. Scope and Synthetic Applications of the Diels-Alder Reaction

Examples of some compounds that exhibit a high level of reactivity as dienophiles are shown in Scheme 10.2 (p. 844). Scheme 10.4 presents some typical uncatalyzed D-A reactions. Part A shows normal electron demand reactions. Each of the reactive dienophiles has at least one strongly electron-attracting substituent on the carbon-carbon double or triple bond. Part B shows several inverse electron demand D-A reactions. Ethene, ethyne, and their alkyl derivatives are poor dienophiles and react only under vigorous conditions.

Entries 1 to 3 are classical examples of D-A reactions between simple dienes and electrophilic dienophiles. Note the *endo* stereoselectivity in Entry 2. Entries 4 to 6 are examples with dienes having activating ERG substituents. There is no regiochemical issue with the symmetrical diene in Entry 4, but the all-*cis* stereochemistry results from an *endo* TS. Entry 5 exhibits the expected regiochemistry, with C(1) of the diene bonded to the more electrophilic β-carbon of the dienophile. Entries 7 and 8 are inverse electron demand reactions with ERGs in the dienophiles and an EWG in the diene. The reaction in Entry 8 leads to formation of an aromatic ring by elimination of pyrrolidine and opening of the pyrone ring.



The regiochemistry of this reaction is consistent with expectation. The more nucleophilic β-carbon of the enamine bonds to C(2) of the pyrone ring, which is activated by both the C(4) ring carbonyl and the ester substituent.

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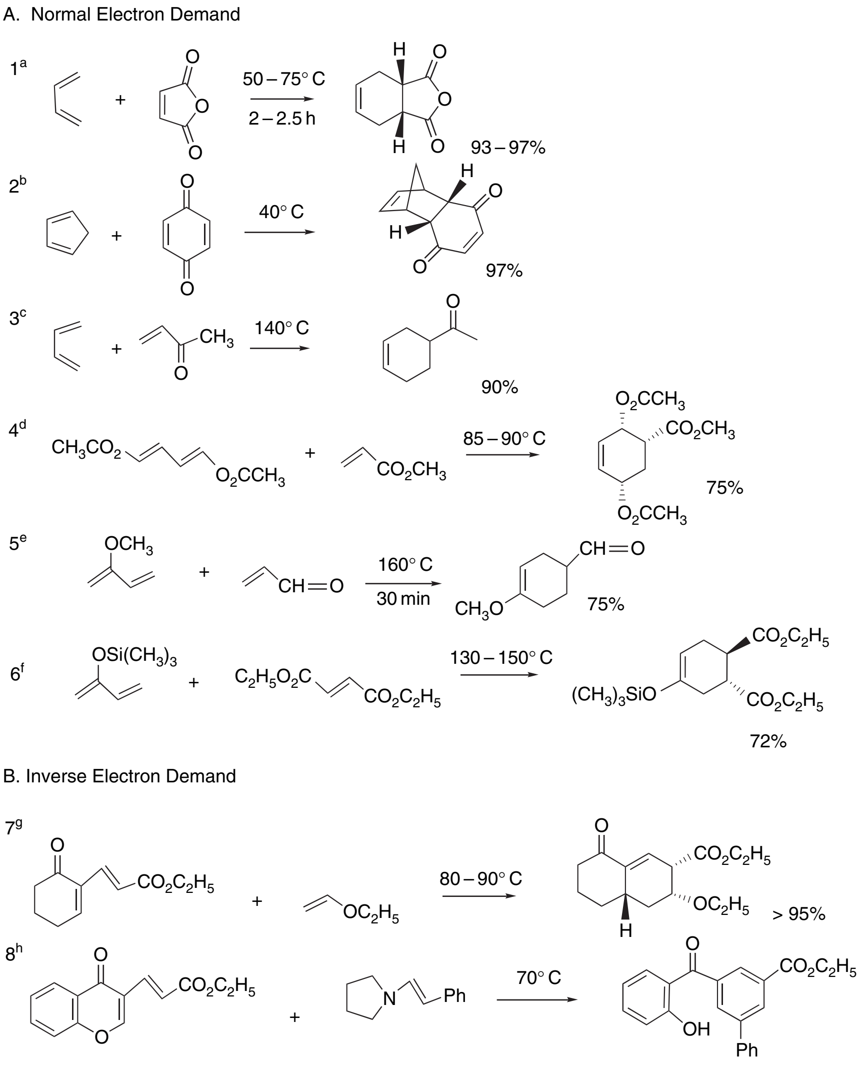
[71] A. Oku, Y. Ohnishi, and F. Mashio, *J. Org. Chem.*, **37**, 4264 (1972).

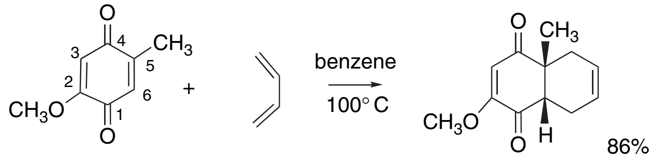
Scheme 10.4. Typical Thermal Diels-Alder Reactions


A. Normal Electron Demand
1a
50–75° C
2–2.5 h
93–97%
2b
40° C
97%
3c
140° C
90%
4d
85–90° C
75%
5e
160° C
30 min
75%
6f
130–150° C
72%
B. Inverse Electron Demand
7g
80–90° C
> 95%
8h
70° C

---

a. A. C. Cope and E. C. Herrichy, *Org. Synth.*, **IV**, 890 (1963).
b. A. Wasserman, *J. Chem. Soc.*, 1511 (1935).
c. W. K. Johnson, *J. Org. Chem.*, **29**, 864 (1959).
d. R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960); R. K. Hill and G. R. Newkome, *Tetrahedron Lett.*, 1851 (1968).
e. J. I. DeGraw, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1156 (1961).
f. M. E. Jung and C. A. McCombs, *Org. Synth.*, **VI**, 445 (1988).
g. G. J. Bodwell and Z. Pi, *Tetrahedron Lett.*, **38**, 309 (1997).
h. G. J. Bodwell, K. M. Hawco, and R. P. da Silva, *Synlett*, 179 (2003).

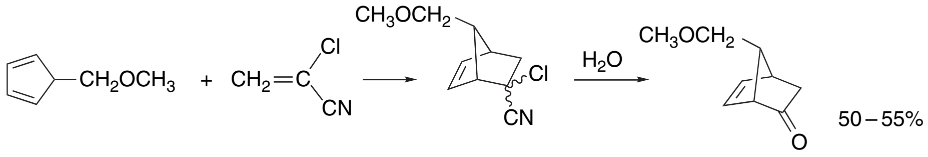
10.2.5.1. Dienophiles There are many examples of synthetic applications of D-A reactions where it is necessary to have additional substituents. The reaction of a substituted benzoquinone and 1,3-butadiene, for example, was the first step in early syntheses of steroids. The angular methyl group was introduced via the quinone and the other functional groups were used for further elaboration.



Ref. 72

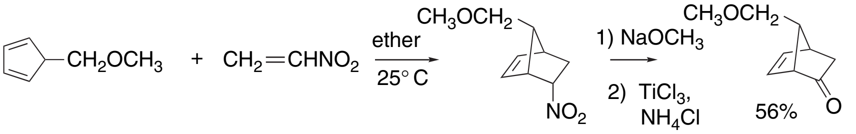
Note that the unsymmetrically substituted quinone exhibits excellent regioselectivity. The stronger donor effect of the methoxy group deactivates the C(4) carbonyl relative to the C(1)carbonyl, making the C(5)−C(6) double bond the more reactive dienophile.

The synthetic utility of the D-A reaction can be expanded by the use of dienophiles that contain *masked functionality* and are the *synthetic equivalent* of unreactive or inaccessible species. For example, α-chloroacrylonitrile shows satisfactory reactivity as a dienophile. The α-chloronitrile functionality in the adduct can be hydrolyzed to a carbonyl group, so α-chloroacrylonitrile can function as the equivalent of ketene, CH_2=C=O.[73] Ketene itself is not a suitable dienophile because it reacts with dienes by [2+2] cycloaddition, rather than in the desired [4+2] fashion.



Ref. 74

Nitroalkenes are good dienophiles and the variety of transformations that are available for nitro groups makes them versatile intermediates.[75] Nitro groups can be converted to carbonyl groups by reductive hydrolysis, so nitroethene can also be used as a ketene equivalent.[76]



Ref. 77

The adducts from both the α-chloroacrylonitrile and nitroethene and 5-methoxymethylcyclopentadiene are intermediates for the synthesis of prostaglandins.

Vinyl sulfones are useful dienophiles. The sulfonyl group can be removed reductively with sodium amalgam. In this two-step reaction sequence, the vinyl sulfone functions as an ethene equivalent. The sulfonyl group also allows for alkylation of the

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[72] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

[73] V. K. Aggarwal, A. Ali, and M. P. Coogan, *Tetrahedron*, **55**, 293 (1999).

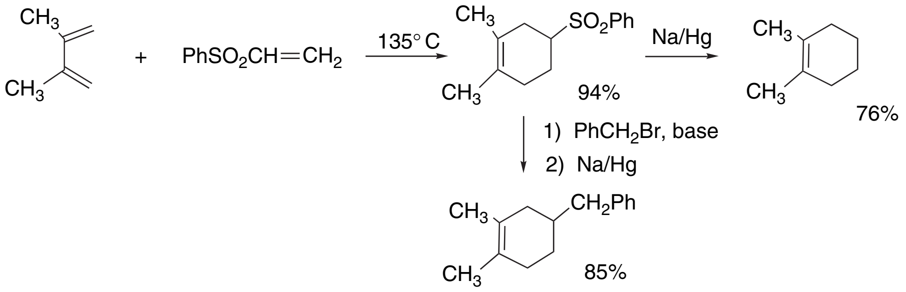
[74] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

[75] D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, *J. Org. Chem.*, **45**, 1185 (1980).

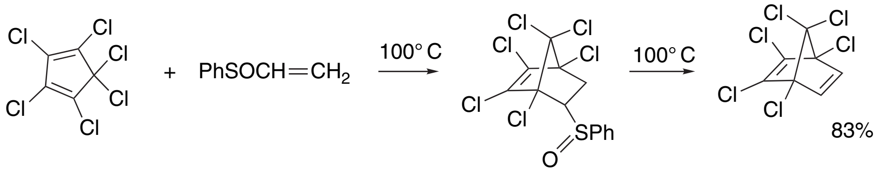
[76] For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).

[77] S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974).

adduct, via the carbanion. This three-step sequence permits the vinyl sulfone to serve as the synthetic equivalent of a terminal alkene.[78]

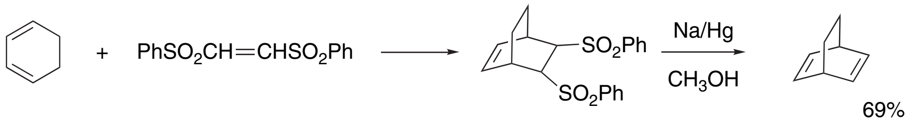

CH3
CH3
+
PhSO2CH=CH2
135° C
CH3
SO2Ph
CH3
94%
Na/Hg
CH3
CH3
76%
1) PhCH2Br, base
2) Na/Hg
CH3
CH2Ph
CH3
85%

Phenyl vinyl sulfoxide can serve as an ethyne equivalent. Its Diels-Alder adducts can undergo thermal elimination of benzenesulfenic acid.


Cl
Cl
Cl
Cl
Cl
Cl
+
PhSOCH=CH2
100° C
Cl
Cl
Cl
Cl
Cl
Cl
SPh
O
100° C
Cl
Cl
Cl
Cl
Cl
Cl
83%

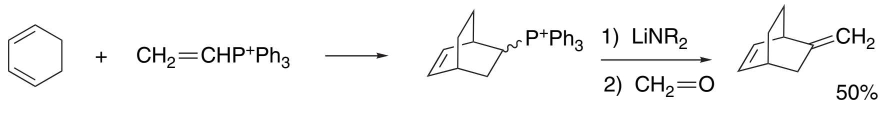
Ref. 79

E- and *Z*-*bis*-(benzenesulfonyl)ethene are also ethyne equivalents. The two sulfonyl groups undergo reductive elimination on reaction with sodium amalgam.


+
PhSO2CH=CHSO2Ph
SO2Ph
SO2Ph
Na/Hg
CH3OH
69%

Ref. 80

Vinylphosphonium salts are reactive as dienophiles as a result of the electron-withdrawing capacity of the phosphonium substituent. The D-A adducts can be deprotonated to give ylides that undergo the Wittig reaction to introduce an exocyclic double bond (see Part B, Section 2.4.1). This sequence of reactions corresponds to a D-A reaction employing allene ($CH_2{=}C{=}CH_2$) as the dienophile.[81]


+
CH2=CHP+Ph3
P+Ph3
1) LiNR2
2) CH2=O
CH2
50%

---

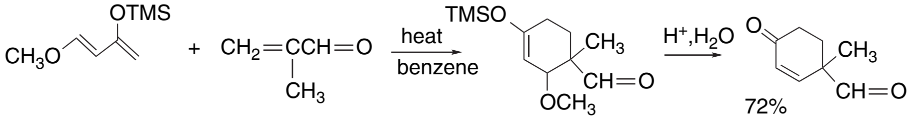
[78] R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, **102**, 853 (1980); R. V. C. Carr, R. V. Williams, and L. A. Paquette, *J. Org. Chem.*, **48**, 4976 (1983); W. A. Kinney, G. O. Crouse, and L. A. Paquette, *J. Org. Chem.*, **48**, 4986 (1983).

[79] L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978).

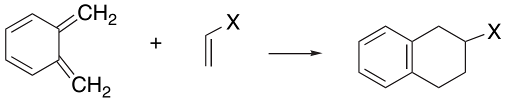
[80] O. DeLucchi, V. Lucchini, L. Pasquato, and G. Modena, *J. Org. Chem.*, **49**, 596 (1984).

[81] R. Bonjouklian and R. A. Buden, *J. Org. Chem.*, **42**, 4095 (1977).

10.2.5.2. Dienes Simple dienes react readily with good dienophiles in D-A reactions. Functionalized dienes are also important in organic synthesis. One example that illustrates the versatility of such reagents is 1-methoxy-3-trimethylsiloxy-1,3-butadiene (*Danishefsky's diene*).[82] Its D-A adducts are trimethylsilyl enol ethers that can be readily hydrolyzed to ketones. The ß-methoxy group is often eliminated during hydrolysis, leading to an enone.

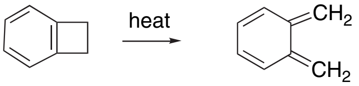


Unstable dienes can be generated in situ in the presence of a dienophile. Among the most useful examples of this type of diene are the quinodimethanes.[83] These compounds are especially reactive as dienes because the cycloaddition reestablishes a benzenoid ring and results in aromatic stabilization (see p. 858).



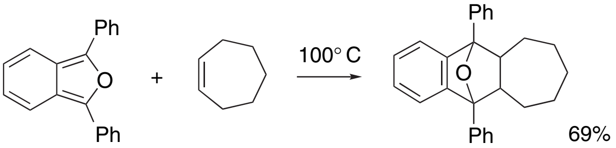
quinodimethane

There are several possible routes to quinodimethanes, including pyrolysis of benzocyclobutenes.[84]



The reaction is accelerated by ERG substituents, particularly trialkylsiloxy groups, on the cyclobutene ring.[85] Quinodimethanes have been especially useful in intramolecular Diels-Alder reactions, as is illustrated in Section 10.2.7.

Another group of dienes with extraordinarily high reactivity is made up of the derivatives of benzo[c]furan (isobenzofuran).[86] Here again, the high reactivity can be traced to the gain of aromatic stabilization in the adduct.



Ref. 87

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[82] S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).

[83] W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975); J. J. McCullogh, *Acc. Chem. Res.*, **13**, 270 (1980); W. Oppolzer, *Synthesis*, 793 (1978); J. L. Charlton and M. M. Alauddin, *Tetrahedron*, **43**, 2873 (1987); H. N. C. Wong, K.-L. Lau, and K. F. Tam, *Top. Curr. Chem.*, **133**, 85 (1986); P. Y. Michellys, H.Pellissier, and M. Santelli, *Org. Prep. Proc. Int.*, **28**, 545 (1996); J. L. Segura and N. Martin, *Chem. Rev.*, **99**, 3199 (1999).

[84] M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, Chap. 6; I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970); R. P. Thummel, *Acc. Chem. Res.*, **13**, 70 (1980); G. Mehta and S. Kotha, *Tetrahedron*, **57**, 625 (2001); A. K. Sadana, R. K. Saini, and W. E. Billups, *Chem. Rev.*, **103**, 1539 (2003).

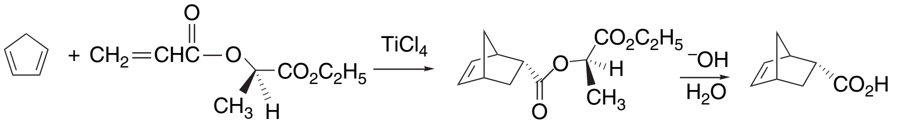
[85] J. G. Allen, M. F. Hentemann, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **122**, 571 (2000).

[86] M. J. Haddadin, *Heterocycles*, **9**, 865 (1978); W. Friedrichsen, *Adv. Heterocycl. Chem.*, **26**, 135 (1980).

[87] G. Wittig and T. F. Burger, *Liebigs Ann. Chem.*, **632**, 85 (1960).

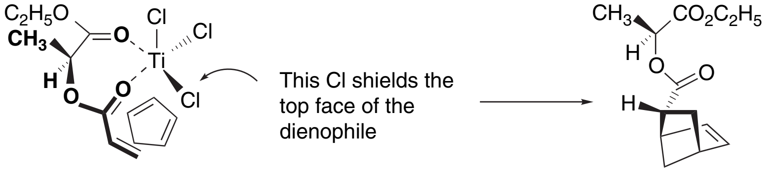
10.2.6. Enantioselective Diels-Alder Reactions

10.2.6.1. Chiral Auxiliaries for Diels-Alder Reactions The highly ordered cyclic TS of the Diels-Alder reaction permits design of reactants and catalysts that lead to a preference between diastereomeric or enantiomeric adducts. (See Section 2.4) to review the principles of diastereoselectivity and enantioselectivity.) One way to achieve diastereoselectivity is to install a chiral auxiliary.[88] The cycloaddition proceeds to give two diastereomeric products that can be separated and purified. Because of the lower temperature and the greater stereoselectivity, the best diastereoselectivity is often observed in Lewis acid–catalyzed reactions. Chiral esters and amides of acrylic acid are particularly useful because the chiral auxiliary can be easily recovered by hydrolysis of the purified adduct to give the enantiomerically pure carboxylic acid.



Ref. 89

Prediction and analysis of diastereoselectivity is based on steric, stereoelectronic, and chelating interactions in the TS.[90] For example, the facial selectivity of the reaction above is governed by a chloride ligand on titanium, which shields one face of the dienophile.



The lactone of 2,4-dihydroxy-3,3-dimethylpentanoic acid (known as pantolactone) has been successfully employed as a chiral auxiliary in several D-A reactions. For example, in conjunction with $TiCl_4$, it provides a 92% de in the reaction of 2,3-dimethylbutadiene with α-cyanocinnamic acid.[91] The diastereoselectivity is consistent with a chelated structure similar to that shown above for acryloyl lactate. In the absence of $TiCl_4$, this same ester gives a 64% de of the opposite configuration. This result suggests that the uncatalyzed reaction goes through a conformation in which the two carbonyl groups are *anti* to one another.

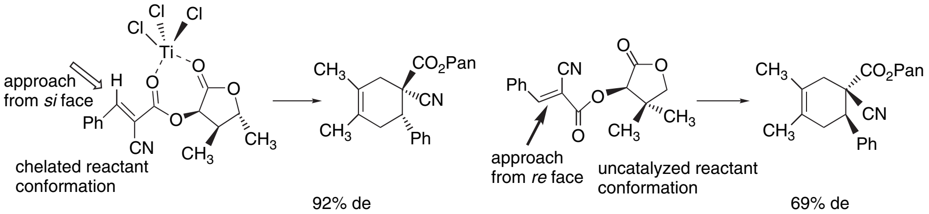
---

[88] W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **23**, 876 (1984); M. J. Tascher, in "*Organic Synthesis, Theory and Applications*," Vol. 1, T. Hudlicky, ed., JAI Press, Greenwich, CT, 1989, pp. 1–101; H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992); K. Narasaka, *Synthesis*, 16 (1991).

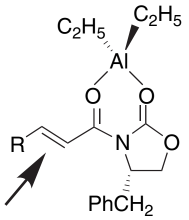
[89] T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).

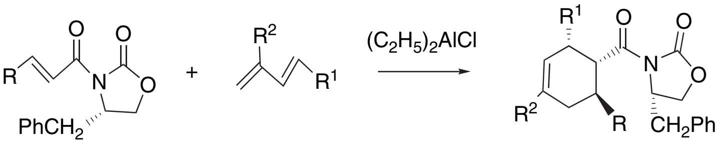
[90] For example, see T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Lett.*, **26**, 3095 (1985).

[91] A. Avenoza, C. Cativiela, J. A. Mayoral, and J. M. Peregrina, *Tetrahedron: Asymmetry*, **3**, 913 (1992); C. Cativiela, J. A. Mayoral, A. Avenoza, J. M. Peregrina, F. J. Lahoz, and S. Gimeno *J. Org. Chem.*, **57**, 4664 (1992).


approach from *si* face
chelated reactant conformation
92% de
approach from *re* face
uncatalyzed reactant conformation
69% de

α, β-Unsaturated derivatives of chiral oxazolidinones have proven to be especially useful for enantioselective D-A additions.[92] Reaction occurs at low temperatures in the presence of such Lewis acids as $SnCl_4$, $TiCl_4$, and $(C_2H_5)_2AlCl$.[93] Both the 4-isopropyl (derived from valine) and the 4-benzyl (derived from phenylalanine) derivative are frequently used. Both carbonyl oxygens are coordinated with the Lewis acid and the oxazolidione substituent provides steric shielding of one face of the dienophile. We discuss a number of other chiral auxiliaries for D-A reactions in Section 6.1.5 of Part B.





R	R^1	R^2	Yield (%)	dr
H	H	CH_3	85	95:5
H	CH_3	H	84	>100:1
CH_3	H	CH_3	83	94:6
CH_3	CH_3	H	77	95:5

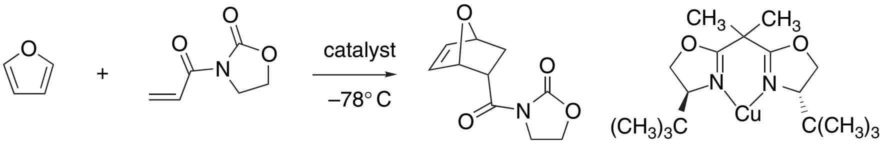
---

[92] D. J. Ager, J. Prakash, and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996); D. J. Ager, J. Prakash, and D. R. Schaad, *Aldrichimica Acta*, **30**, 3 (1997).

[93] D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

10.2.6.2. Enantioselective Catalysts for Diels-Alder Reactions Enantioselectivity can also be achieved with chiral catalysts.[94] Many of the most efficient catalysts involve a chiral ligand in conjunction with a metal ion that acts as a Lewis acid. The metal ion provides the electron-attracting capacity and in conjunction with the ligand establishes a chiral environment at the catalytic site. Several boron compounds are also good catalysts, with the boron playing the role of the Lewis acid. The ligands typically have bulky substituents, often substituted aromatic rings. The ligands are usually derived from readily available chiral substances, such as amino acids. In addition to the Lewis acid complexation and steric effects, π stacking and hydrogen bonding can contribute to the structure of the catalytic complex. The effectiveness of the catalyst is related to the proximity of the chiral features to the reaction center. If the chiral environment is too remote from the catalytic site, it does not control the enantioselectivity effectively. This proposition was tested for a number of catalysts for the D-A reaction and generally found to be true.[95]

One group of chiral catalysts consists of metal ion complexes, usually Cu^{2+},[96] of *bis*-oxazolines (referred to as box catalysts).[97]



Ref. 98

Based on a crystal structure of the catalyst and PM3 modeling of the complex, the reaction is proposed to proceed preferentially from the *re* face as a result of steric shielding by a *t*-butyl group, as shown in Figure 10.11.

Chiral oxazaborolidines have also been found to be useful catalysts in D-A reactions. The tryptophan-derived catalyst shown in TS **A**, for example, can achieve 99% enantioselectivity in the D-A reaction between 5-benzyloxymethyl-1,3-cyclopentadiene and 2-bromopropenal. The adduct is an important intermediate in the synthesis of prostaglandins.[99] The aldehyde is bound to the catalyst by a Lewis interaction. There is also believed to be a hydrogen bond between the formyl C−H and the oxygen bound to boron. This type of hydrogen bonding has been recognized in several Lewis acid complexes of aldehydes.[100] The upper face of the aldehyde is shielded by the indole ring. The benzyloxymethyl substituent provides a steric differentiation of the two faces of the cyclopentadiene ring, as shown in TS **A**.

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[94] Y. Hayashi, in *Cycloaddition Reactions in Organic Synthesis*, S. Kobayashi and K. A. Jorgensen, eds., Wiley-VCH, Weinheim, 2002, pp. 5–55.

[95] K. B. Lipkowitz, C. A. D'Hue, T. Sakamoto, and J. N. Stack, *J. Am. Chem. Soc.*, **124,** 14255 (2002).

[96] D. A. Evans, S. J. Miller, and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993); D. A. Evans, J. P. Murry, P. von Matt, R. D. Norcross, and S. J. Miller, *Angew. Chem. Int. Ed. Engl.*, **34**, 798 (1995); J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, **33**, 325 (2000).

[97] A. K. Ghosh, P. Mathivanan, and J. Cappiello, *Tetrahedron: Asymmetry*, **9**, 1 (1998).

[98] D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, **38**, 57 (1997).

[99] E. J. Corey and T. P. Loh, *J. Am. Chem. Soc.*, **113**, 8966 (1991).

[100] E. J. Corey, J. J Rohde, A. Fischer, and M. D. Azimioara, *Tetrahedron Lett.*, **38**, 33 (1997).

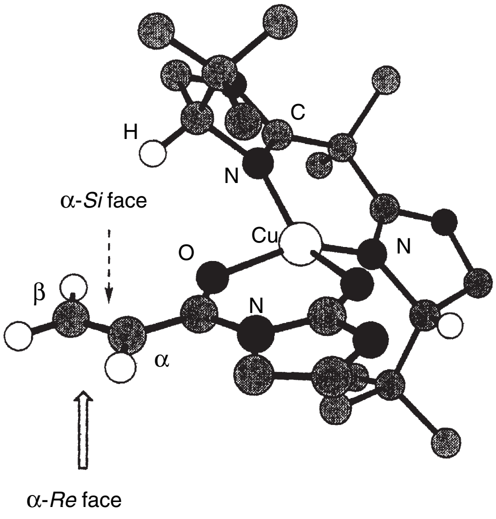
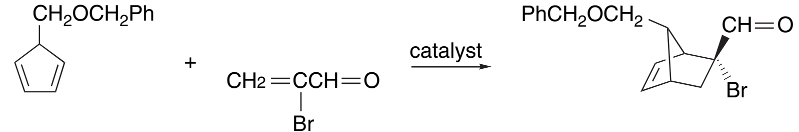
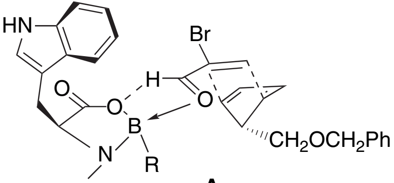

H
C
N
α-*Si* face
Cu
O
N
β
N
α
α-*Re* face

Fig. 10.11. Model of Cu(*S*,*S*-*t*-BuBox catalyst with *N*-acryloyloxazolidinone showing facial stereodifferentiation. Reproduced from *J. Am. Chem. Soc.*, **121**, 7559 (1999), by permission of the American Chemical Society.


CH2OCH2Ph
+
CH2=CCH=O
Br
catalyst
PhCH2OCH2
CH=O
Br


HN
Br
H
O
O
O
B
N
R
Ts
CH2OCH2Ph

A

Other enantioselective catalysts for the D-A reactions have been developed. The chiral ligands used include the TADDOLs (α, α, α, α-tetraaryl-1,3-dioxolane-4,5-dimethanols)[101] and BINOL derivatives.[102] These are discussed in Section 6.4 of Part B.

10.2.7. Intramolecular Diels-Alder Reactions

Intramolecular Diels-Alder (IMDA) reactions are very useful in the synthesis of polycyclic compounds.[103] Two new rings are created by the reaction, and the stereochemistry of the ring junction is determined by TS geometry. In addition to the *exo* and *endo* relationships present in intermolecular D-A reactions, the conformation of the intervening linkage influences the stereochemistry. For example, in the case of an *E*,*E*-undeca-1,7,9-trienes with 1-EWG substituents, four TSs are possible. Two lead to a *trans* ring junction with *cis* orientation of the substituents, whereas the other two lead to a *cis* ring junction and *trans* orientation of the substituents. As for intermolecular D-A reactions, the reaction is stereospecific with respect to the diene and dienophile substituents, so that the *Z*,*E*- , *E*,*Z*- , and *Z*,*Z*-reactants also give specific stereoisomers.

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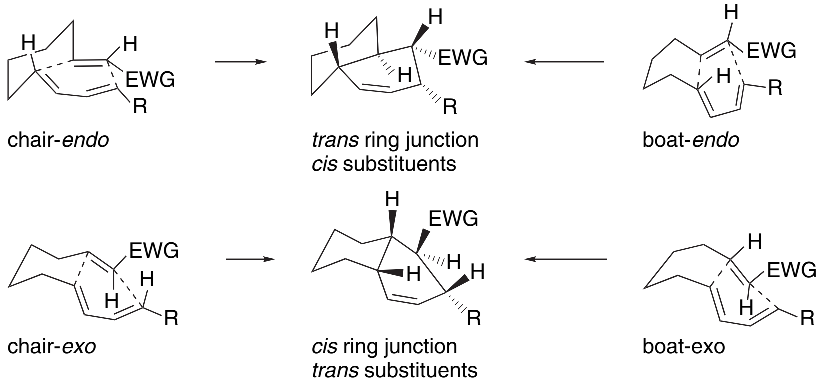
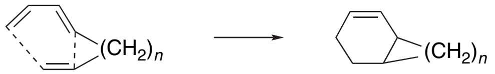
[101] D. Seebach, A. K. Back, and A. Heckel, *Angew. Chem. Intl. Ed. Engl.*, **40**, 93 (2001).

[102] K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 6920 (1995); S. Kobayashi, M. Araki, and I. Hachiya, *J. Org. Chem.*, **59**, 3758 (1994); S. Kobayashi, M. Sugiura, H. Kitagawa, and W.-L. Lam, *Chem. Rev.*, **102**, 2227 (2002).

[103] W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); G. Brieger and J. N. Bennett, *Chem. Rev.*, **80**, 63 (1980); E. Ciganek, *Org. React.*, **32**, 1 (1984); D. F. Taber, *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag, Berlin, 1984.



One of the factors that affect TS structure is the length of the connecting chain. Sastry and co-workers looked systematically at this factor in the unsubstituted triene system with from one to four linking CH_2 groups.[104] Single-point B3LYP/6-31G* energies were calculated at the PM3 structural minima. Because of strain, a *cis* ring juncture is strongly favored for $n = 1$ and $n = 2$ and slightly for $n = 3$. The *trans* ring juncture is favored somewhat for $n = 4$. The effect of strain is reflected in the energy of both the TS and the product and indicates the rudimentary features associated with the linking group. The E_a and reaction energies are given below and are plotted in Figure 10.12. The synchronicity of the reaction was computed. (See p. 852 for the numerical definition of synchronicity.) Synchronicity was quite high for $n = 2$ to $n = 4$, but was lower (0.669) for $n = 1$ (*cis*), where the formation of the peripheral bond is leading. According to these results, formation of a bicyclo[4.3.0]non-2-ene ring system ($n = 3$) is slightly preferred kinetically to a bicyclo[4.4.0]dec-2-ene ring for both *cis* and *trans* ring junctions.



	E_{act}		ΔE_{react}		Synchronicity	
n	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
1	35.7	57.2	−11.0	+25.6	0.6692	0.8987
2	37.0	41.1	−18.2	−4.3	0.9816	0.9730
3	17.9	19.6	−40.9	−38.8	0.9248	0.9473
4	26.1	23.3	−41.8	−47.7	0.9267	0.9054

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[104] R. Vijaya and G. N. Sastry, *Theochem*, **618**, 201 (2002).

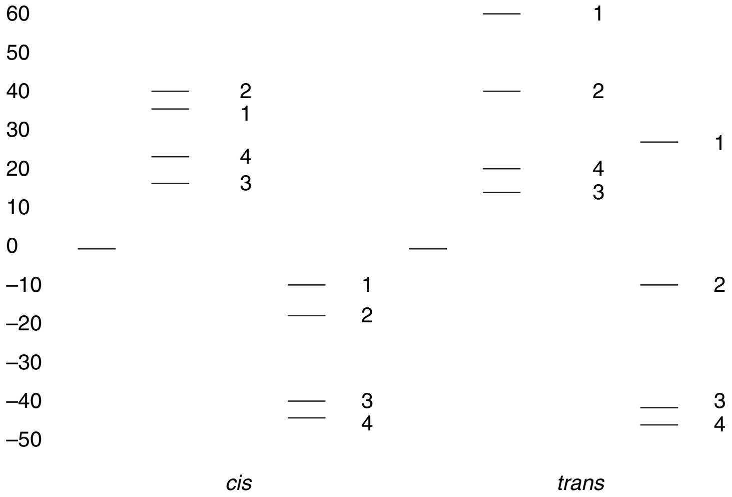
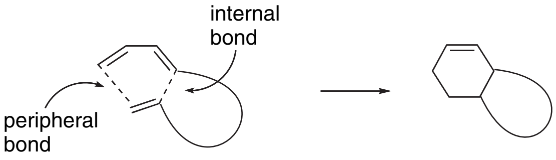


Fig. 10.12. Activation and reaction energies (B3LYP/6-31G*) in kcal/mol for intramolecular Diels-Alder reactions of $CH_2{=}CH(CH_2)_nCH{=}CHCH{=}CH_2$ for $n = 1$ to 4. Adapted from *Theochem*, **618**, 201 (2002).

In several IMDA reactions involving substituted systems, the direction of the asynchronicity appears to be controlled by steric and torsional, rather than electronic, factors. Often the internal bond formation is more advanced than the peripheral bond, regardless of the location and electronic characteristics of the substituents.[105] This is presumably due to the proximity (entropic) factor and is in contrast to intermolecular D-A reactions, where electronic effects are dominant.



Lewis acid catalysis usually substantially improves the stereoselectivity of IMDA reactions, just as it does in intermolecular cases. For example, the thermal cyclization of **1** at 160° C gives a 50:50 mixture of two stereoisomers, but the use of $(C_2H_5)_2AlCl$ as a catalyst permits the reaction to proceed at room temperature, and *endo* addition is favored by 7:1.[106]

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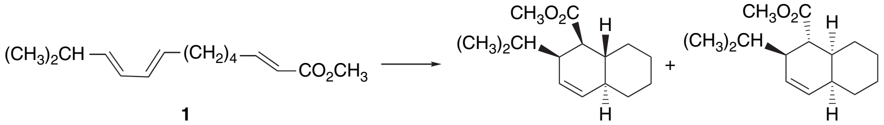
[105] C. I. Turner, R. M. Williamson, M. N. Paddon-Row, and M. S. Sherburn, *J. Org. Chem.*, **66**, 3963 (2001); T. N. Cayzer, L. S. M. Wong, P. Turner, M. N. Paddon-Row, and M. S. Sherburn, *Chem. Eur. J.*, **8**, 739 (2002).

[106] W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **47**, 4825 (1982).

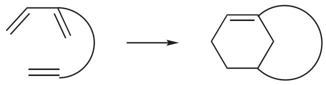


1

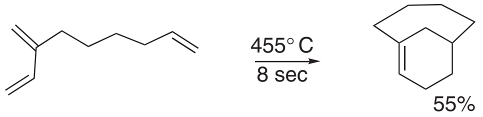
	endo TS	*exo* TS
thermal, 160° C	50%	50%
$(Et)_2AlCl$	88%	12%

The general pattern of IMDA stereoselectivity suggests that although electronic interactions govern the regioselectivity, conformational effects are the main factors in determining stereoselectivity.[107] Because the conformational interactions depend on the substituent pattern in the specific case, no general rules for stereoselectivity can be put forward. Molecular modeling can frequently identify the controlling structural features.[108]

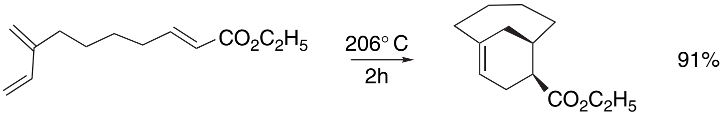
A less common type of IMDA reaction leads to bicyclic rings with bridgehead double bonds.[109]



Both activated and unactivated systems have been observed to react, and the reaction is subject to Lewis acid catalysis.



Ref. 110



Ref. 110

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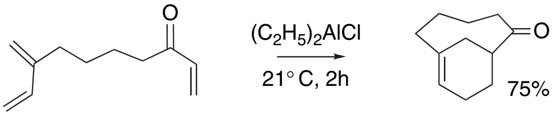
[107] W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980); R. K. Boeckman, Jr., and S. S. Ko, *J. Am. Chem. Soc.*, **102**, 7146 (1980); W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, **103**, 5200 (1981); J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984); T.-C. Wu and K. N. Houk, *Tetrahedron Lett.*, **26**, 2293 (1985); K. A. Parker and T. Iqbal, *J. Org. Chem.*, **52**, 4369 (1987); W. R. Roush, A. P. Eisenfeld, and J. S. Warmus, *Tetrahedron Lett.*, **28**, 2447 (1987).

[108] K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988); L. Raimondi, F. K. Brown, J. Gonzalez, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 4796 (1992); D. P. Dolata and L. M. Harwood, *J. Am. Chem. Soc.*, **114**, 10738 (1992); F. K. Brown, U. C. Singh, P. A. Kollman, L. Raimondi, K. N. Houk, and C. W. Bock, *J. Org. Chem.*, **57**, 4862 (1992); J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).

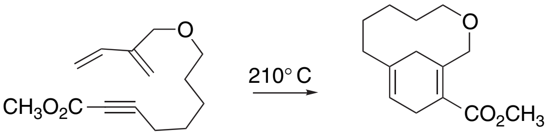
[109] B. R. Bear, S. M. Sparks, and K. J. Shea, *Angew. Chem. Int. Ed. Engl.*, **40**, 821 (2001).

[110] K. J. Shea, S. Wise, L. D. Burke, P. D. Davis, J. W. Gilman, and A. C. Greeley, *J. Am. Chem. Soc.*, **104**, 5708 (1982).



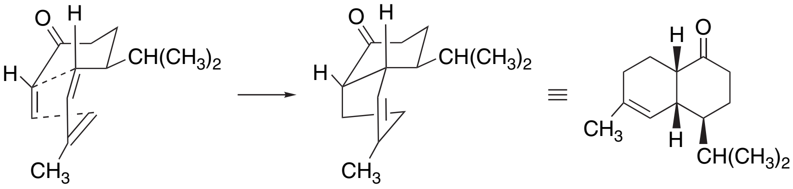
Ref. 111

Alkynes give cyclohexadienes.

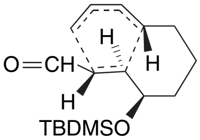


Ref. 112

We can illustrate some of the features of the IMDA reaction by considering some specific examples given in Scheme 10.5. In Entry 1 the dienophilic portion bears a carbonyl substituent and cycloaddition occurs easily. Two stereoisomeric products are formed, but both have *cis* ring fusion, which is the stereochemistry expected for an *endo* TS.



In Entry 2 a similar triene that lacks the activating carbonyl group undergoes reaction, but a much higher temperature is required. In this case the ring junction is *trans*. This corresponds to an *exo*-transition state and may reflect the absence of secondary orbital interaction between the diene and dienophile. Entry 3 is an example of the use of a benzocylobutene to generate a quinodimethane intermediate. The IMDA reaction creates the steroidal skeleton.[113] Entries 4 and 5 illustrate the use of Lewis acid catalysts in IMDA. The *trans* ring junctions arise from *endo* TSs.



transition structure corresponding to Entry 4

Note that all the reactions are stereospecific with respect to the configuration at the diene and dienophile double bonds.

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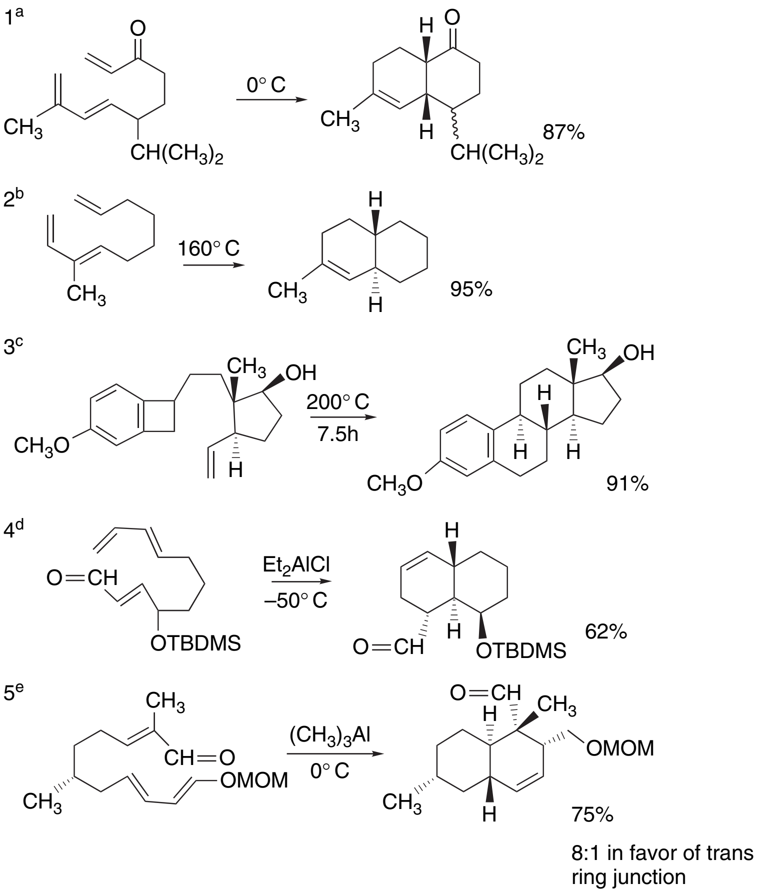
[111] K. J. Shea and J. W. Gilman, *Tetrahedron Lett.*, **24**, 657 (1983).
[112] K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988).
[113] H. Nemoto and K. Fukumoto, *Tetrahedron*, **54**, 5425 (1998).

Scheme 10.5. Intramolecular Diels-Alder Reactions


1a
O
CH3
CH(CH3)2
0° C
H O
CH3
H
CH(CH3)2
87%
2b
CH3
160° C
H
CH3
H
95%
3c
CH3 OH
CH3O
H
200° C
7.5h
CH3 OH
H
H H
CH3O
91%
4d
O=CH
OTBDMS
Et2AlCl
–50° C
H
O=CH
H
OTBDMS
62%
5e
CH3
CH=O
OMOM
CH3
(CH3)3Al
0° C
O=CH
H CH3
OMOM
CH3
H
75%
8:1 in favor of trans ring junction

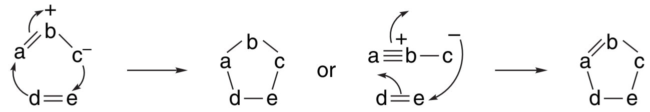
a. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, **101**, 3992 (1979); T. Kitahara, H. Kurata, T. Matsuoka, and K. Mori, *Tetrahedron*, **41**, 5475 (1985).
b. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, **100**, 6289 (1978).
c. P. A. Grieco, T. Takigawa, and W. J. Schilling, *J. Org. Chem.*, **45**, 2247 (1980).
d. J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984).
e. K. Yuki, M. Shindo, and K. Shishido, *Tetrahedron Lett.*, **42**, 2517 (2001).

10.3. 1,3-Dipolar Cycloaddition Reactions

There is a large class of reactions known as *1,3-dipolar cycloaddition reactions* (1,3-DPCA) that are analogous to the Diels-Alder reaction in that they are concerted $[\pi 4_s + \pi 2_s]$ cycloadditions.[114] 1,3-DPCA reactions can be represented as shown in the following diagram. The entity *a-b-c* is called the *1,3-dipole* and *d-e* is the *dipolarophile*.

---

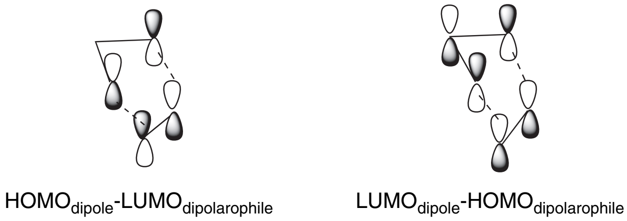
[114] (a) R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **2**, 565 (1963); (b) R. Huisgen, R. Grashey, and J. Sauer, in *The Chemistry of the Alkenes*, S. Patai, ed., Interscience, London, 1965, pp. 806–878; (c) G. Bianchi, C. DeMicheli, and R. Gandolfi, in *The Chemistry of Double Bonded Functional Groups*, Part I, Supplement A, S. Patai, ed., Wiley-Interscience, New York, 1977, pp. 369–532; (e) A. Padwa, ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984; (d) For a review of intramolecular 1,3-dipolar cycloaddition reactions, see A. Padwa, *Angew. Chem. Int. Ed. Engl.*, **15**, 123 (1976).



The 1,3-dipoles have a π-electron system consisting of two filled and one empty orbital and are analogous with the allyl or propargyl anion. Each 1,3-dipole has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship. It is this structural feature that leads to the name 1,3-dipole for this class of reactants. The dipolarophiles are typically substituted alkenes or alkynes but all that is essential is a π bond, and other multiply bonded functional groups such as carbonyl, imine, azo, and nitroso can also act as dipolarophiles. The reactivity of dipolarophiles depends both on the substituents present on the π bond and on the nature of the 1,3-dipole involved in the reaction. Owing to the wide range of structures that can serve either as a 1,3-dipole or as a dipolarophile, the 1,3-DPCA is a very useful reaction for the construction of five-membered heterocyclic rings. Scheme 10.6 gives some examples using both ethenyl and ethynyl dipolarophiles. Some of the structures shown can undergo hydrogen shifts to more stable heterocyclic molecules, if there is one or more R = H.

10.3.1. Relative Reactivity, Regioselectivity, Stereoselectivity, and Transition Structures

The bonding changes for 1,3-DPCA reactions involve four π electrons from the 1,3-dipole and two from the dipolarophile. In most cases, the reaction is a concerted $[\pi 2_s + \pi 4_s]$ cycloaddition.[115] As in the D-A reaction, the reactants approach one another in parallel planes. There is interaction between the complementary HOMO-LUMO combinations, and depending on the combination, either reactant can be the electrophilic or the nucleophilic component. Generally speaking, the reactant 1,3-dipoles are more polar than the TS or the reaction product. The rate of reaction is not strongly sensitive to solvent polarity.


$\text{HOMO}_{\text{dipole}}$-$\text{LUMO}_{\text{dipolarophile}}$
$\text{LUMO}_{\text{dipole}}$-$\text{HOMO}_{\text{dipolarophile}}$

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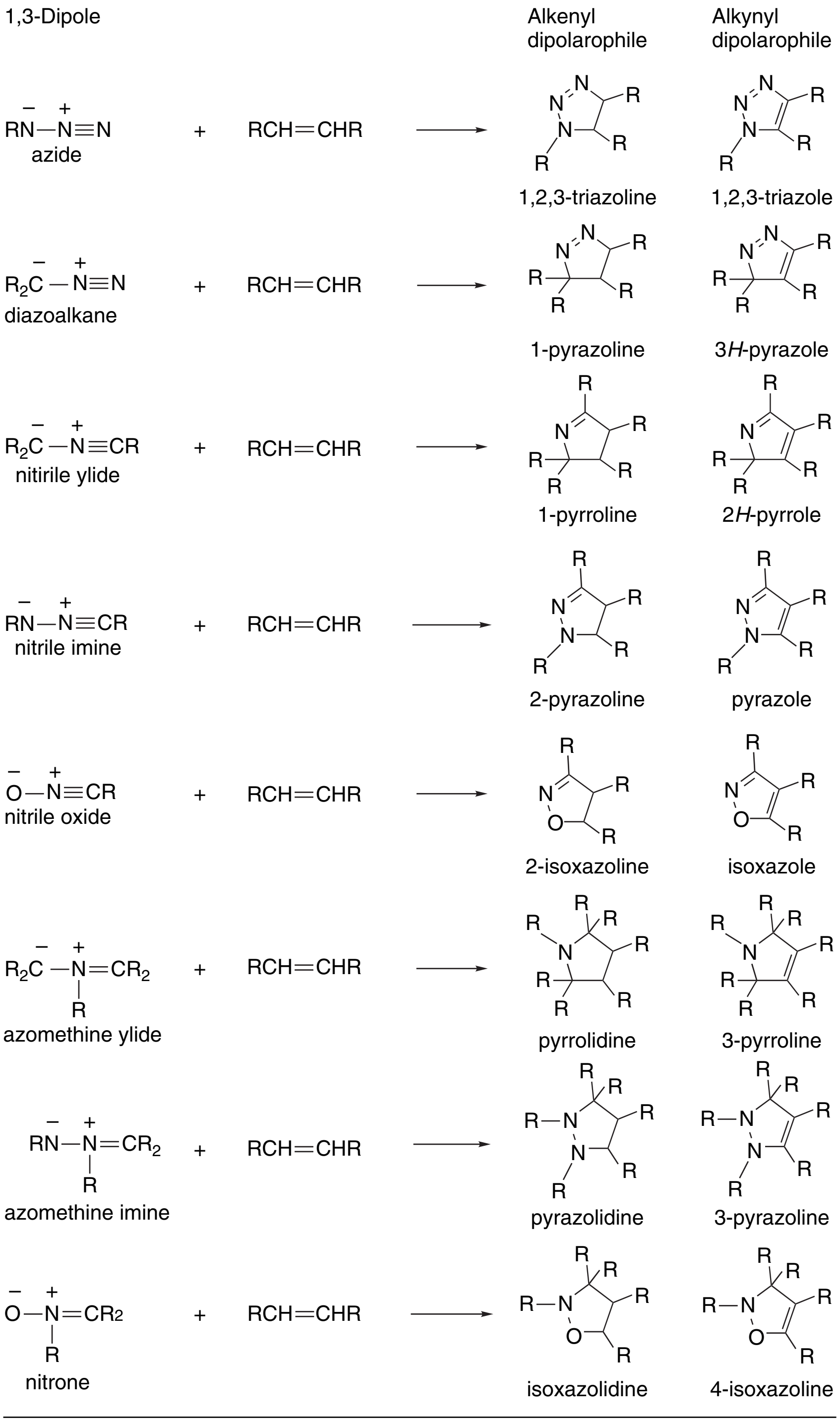
[115] P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969); R. Huisgen, G. Szeimes, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967); P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).

Scheme 10.6. 1,3-Dipolar Cycloadditions


1,3-Dipole
Alkenyl dipolarophile
Alkynyl dipolarophile
RN−N≡N
azide
+
RCH=CHR
1,2,3-triazoline
1,2,3-triazole
R2C−N≡N
diazoalkane
+
RCH=CHR
1-pyrazoline
3H-pyrazole
R2C−N≡CR
nitirile ylide
+
RCH=CHR
1-pyrroline
2H-pyrrole
RN−N≡CR
nitrile imine
+
RCH=CHR
2-pyrazoline
pyrazole
O−N≡CR
nitrile oxide
+
RCH=CHR
2-isoxazoline
isoxazole
R2C−N=CR2
R
azomethine ylide
+
RCH=CHR
pyrrolidine
3-pyrroline
RN−N=CR2
R
azomethine imine
+
RCH=CHR
pyrazolidine
3-pyrazoline
O−N=CR2
R
nitrone
+
RCH=CHR
isoxazolidine
4-isoxazoline

There have been many computational analyses of 1,3-DPCA TSs, and they are generally regarded to be aromatic in character. Typical TSs are characterized by aromatic NICS values.[116] The ring current associated with this aromaticity is primarily due to the six electrons undergoing bonding changes.[117] The orbital interactions in the cyclic TS serve as the focal point for discussion of relative reactivity, regioselectivity, and stereoselectivity of 1,3-DPCA reactions.

The most widely applied interpretation of substituent effects on relative reactivity is based on FMO theory. According to FMO theory, interacting orbitals are most stabilized when they are closest in energy. Substituent effects on dipolar cycloadditions can be interpreted in terms of matching of HOMO and LUMO orbitals of the two reactants.[118] This is the same concept used in applying FMO theory to D-A reactions (see p. 844–848). In the D-A reaction, it is fairly clear which reactant is electrophilic and which is nucleophilic, and the interpretation of substituent effects follows directly. This choice is not always so obvious for 1,3-DPCA reactions. In fact, for several of the 1,3-dipoles both EWGs and ERGs in the dipolarophile enhance reactivity. These 1,3-dipoles are called *ambiphilic*. Let us look carefully to see why they have this property.

Much of the relative reactivity data on 1,3-DPCA reactions has been tabulated and discussed in reviews by R. Huisgen, a pioneer researcher in the field.[114b] Some representative data are presented in Table 10.3. The dipolarophiles are shown in decreasing order of electrophilicity. The data from these monosubstituted dipolarophiles should be relatively free of steric influences on reactivity. Note that for phenyl azide and benzonitrile oxide, reactivity is at a minimum for unfunctionalized alkenes and is increased by both donor and acceptor substituents.

Table 10.3. Representative Relative Rate Data for 1,3-Dipolar Cycloadditions[a]

$CH_2{=}CHX$	Ph_2CN_2[b]	PhN_3[c]	$PhC{\equiv}NO$[d]	$PhCH{=}NCH_3$[e]	$PhC{\equiv}NNPh$[f]	CH_2N_2[g]
Dimethyl fumarate	996	31	94	18.3	283	
Dimethyl maleate	27.8	1.25	1.61	6.25	7.94	
Ethyl acrylate	288	36.5	66	11.1	48.2	175
Ethyl crotonate	1.0	1.0	1.0	1.0	1.0	1.0
Norbornene	1.15	700	97	0.13	3.12	3.3×10^{-2}
1-Alkene		0.8	2.6	0.072	0.146	6.9×10^{-4}
Styrene	0.57	1.5	9.3	0.32	1.60	6.9×10^{-2}
Cyclopentene		6.9	1.04	0.022	0.128	4.2×10^{-4}
Cyclohexene			0.055		0.011	1.6×10^{-5}
Vinyl ether		1.5	15			8.5×10^{-6}
Vinyl amine		$\sim 1 \times 10^5$				

a. Relative to ethyl crotonate as tabulated in Ref. 114b .
b. R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).
c. R. Huisgen, G. Szeimies, and L. Mobius, *Chem. Ber.*, **100**, 2494 (1967).
d. K. Bast, M. Christl, R. Huisgen, and W. Mack, *Chem. Ber.*, **106**, 3312 (1973).
e. R. Huisgen, H. Seidl, and I. Brunig, *Chem. Ber.*, **102**, 1102 (1969).
f. E. Eckell, R. Huisgen, R. Sustmann, D. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192 (1967).
g. J. Geittner, R. Huisgen, and R. Sustmann, *Tetrahedron Lett.*, 881 (1977).

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[116] F. P. Cossio, I. Morao, H. Jiao, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **121**, 6737 (1999).

[117] I. Maroa, B. Lecea, and F. P. Cossio, *J. Org. Chem.*, **62**, 7033 (1997); I. Marao and F. P. Cossio, *J.'Org. Chem.*, **64**, 1868 (1999).

[118] R. Sustmann and H. Trill, *Angew. Chem. Int. Ed. Engl.*, **11**, 838 (1972); R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974).

In addition to the electronic effects of substituents, several other structural features affect the reactivity of dipolarophiles. Strain increases reactivity. Norbornene, for example, is consistently more reactive than cyclopentene in 1,3-dipolar cycloadditions. Cyclopentene is also more reactive than cyclohexene. Conjugating substituents, such as the phenyl group in styrene, usually increase reactivity of dipolarophiles (compare styrene with 1-alkenes in Table 10.3).

An interesting series of compounds for which a fairly broad range of data exists is diazomethane, methyl diazoacetate, and diethyl diazomalonate, in which each additional ester group should make the 1,3-dipole successively more electrophilic. The data are given in Table 10.4. We see that diazomethane is primarily nucleophilic in character, dropping sharply in reactivity from electrophilic to nucleophilic dipolarophiles. The other two reactants clearly show an ambiphilic reactivity. These reagents show increased reactivity with both EWG and ERG dipolarophiles, with the diazomalonate shifted somewhat more toward electrophilic character.

Sustmann and Trill[118] summarized these and related reactivity relationships in terms of FMO theory and pointed out that 1,3-DPCA reactions could be of three types, depending on relative placement of the frontier orbitals: (**A**) $\text{HOMO}_{\text{dipole}}$-$\text{LUMO}_{\text{dipolarophile}}$ dominant; (**B**)$\text{LUMO}_{\text{dipole}}$-$\text{HOMO}_{\text{dipolarophile}}$ dominant; (**C**) both HOMO-LUMO interactions are significant. The first type should be accelerated by ERG in the dipole and EWG in the dipolarophile. The second type should be facilitated by an EWG in the dipole and an ERG in the dipolarophile. These relationships suggest a parabolic substituent effect as the Type **C** reactions shift from $\text{LUMO}_{\text{dipolarophile}}$ to mixed to $\text{HOMO}_{\text{dipolarophile}}$ controlled. Figure 10.13 illustrates this relationship for aryl azides. The Hammett ρ is positive for reaction with nucleophilic enamines but negative for the electrophilic dipolarophile maleic anhydride, showing that the direction of the substituent effect depends on the relative importance of the two HOMO-LUMO interactions. The unfunctionalized alkenes cyclopentene and norbornene are nucleophilic in character, but less so than the enamine. Using a wider range of reactants, Sustmann and Trill demonstrated a parabolic rate relationship and developed a mathematical treatment in terms of FMO theory that provided a semiquantitative explanation of relative reactivity.[118] We pursue the application of FMO theory to the regiochemistry of the 1,3-DPCA reaction in more detail below.

As with the D-A reaction, the concerted pericyclic mechanism can account for many aspects of the stereochemistry and regiochemistry of the 1,3-DPCA reaction. Most 1,3-DPCA reactions are highly *stereospecific* with respect to the dipolarophile. In one case, it was established that a pair of isomeric dipolarophiles both reacted

Table 10.4. Relative Reactivity for Diazo Compounds

$CH_2{=}CHX$	CH_2N_2[a]	RO_2CCHN_2[b]	$(RO_2C)_2CN_2$[c]
Acrylate	250,000	930	35
1-Alkene	1	1	1
Styrene	100	2.5	1.5
Vinyl ether	0.02	0.1	0.15
Vinyl amine	0.07	470	620

a. J. Geittner, R. Huisgen, and R. Sustmann, *Tetrahedron Lett.*, 881 (1977).
b. W. Bihlmaier, R. Huisgen, H.-U. Reissig and S. Voss, *Tetrahedron Lett.*, 2621 (1979).
c. H. U. Reissig, Ph. D. Thesis, University of Munich, 1978, as quoted in Ref. 114b.

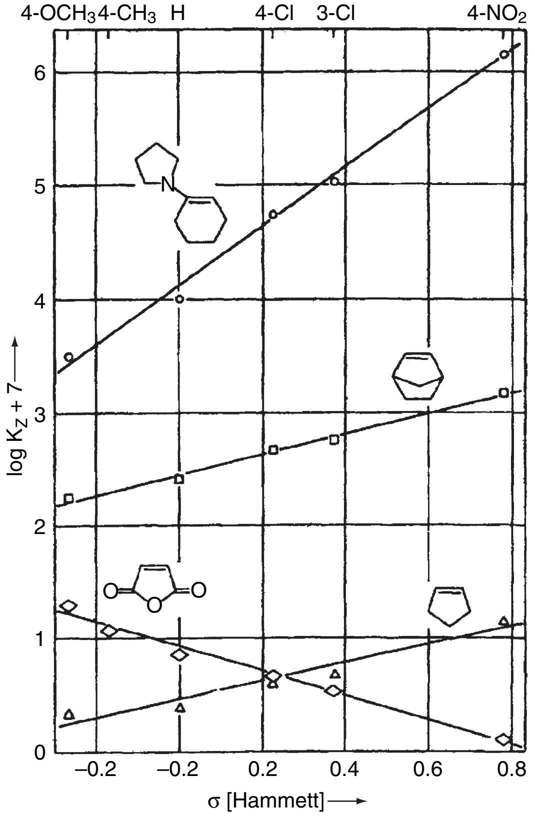
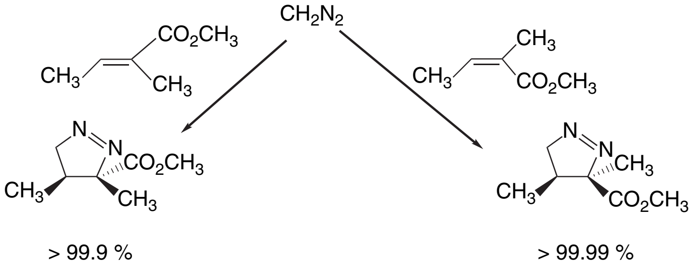


Fig. 10.13. Hammett plots of cycloaddition rates of substituted aryl azides with nucleophilic, electrophilic, and unsubstituted alkenes showing the ambiphilic character of the azide cycloaddition. Reaction with maleic anhydride (electrophilic) is favored by donor substituents. Reaction with pyrrolidinocyclohexene (nucleophilic) is favored by acceptor substituents. Reactions with cyclopentene and norbornene are modestly favored by acceptor substituents. Reproduced from *Chem. Ber.*, **100**, 2494 (1967), by permission of Wiley-VCH.

with more than 99.9% stereospecificity, and there are numerous other examples of stereospecific additions.



Ref. 119

With some 1,3-dipoles, two possible stereoisomers can be formed. These products result from two differing orientations of the reacting molecules and are analogous to

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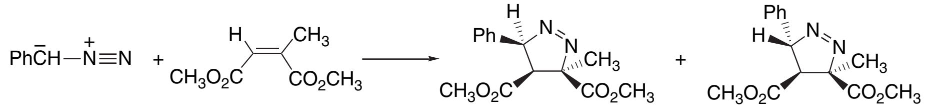
[119] W. Bihlmaier, J. Geittner, R. Huisgen, and H. U. Reissig, *Heterocycles*, **10**, 147 (1978).

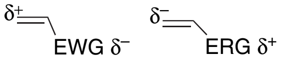
the *endo* and *exo* TSs in D-A reactions. Substituted diazoalkanes, for example, can add to unsymmetrical dipolarophiles to give two diastereomers.



Ref. 120

For unsymmetrical dipolarophiles, two regioisomeric products are also possible. The prediction and interpretation of the stereo- and regioselectivity of 1,3-DPCA reactions have been of ongoing interest. The issues are the same as in the D-A reaction. The reactions are usually under kinetic control, so TS energy is the controlling factor. As the reactants come together, charge transfer and polarization occur, with one reactant donating electron density to the other. As the TS is reached, the degree of bond formation and electron delocalization are important. The TS can be characterized by the extent of orbital interaction, charge transfer, and the degree of bond formation.[121] Reactant conformation may also be a factor in distinguishing between *exo* and *endo* TSs. For any given reaction, computational comparison of TS energies can be informative, but there is also a need for qualitative understanding of the factors that contribute to TS energy and therefore to regio- and stereocontrol.

The polarity of the common dipolarophiles can be recognized from the nature of the substituent.



When both the 1,3-dipole and the dipole are unsymmetrical, there are two possible orientations for addition. Both steric and electronic factors play a role in determining the regioselectivity of the addition. The most generally satisfactory interpretation of the regiochemistry of 1,3-DPCA is based on frontier orbital concepts.[122] As with the D-A reaction, the most favorable orientation is the one that gives the strongest interaction between the frontier orbitals of the 1,3-dipole and the dipolarophile. Most 1,3-DPCA are of the type in which the frontier orbitals are the LUMO of the dipolarophile and the HOMO of the 1,3-dipole. There are a number of systems in which the relationship is reversed, as well as some in which the two possible HOMO-LUMO interactions are of comparable magnitude.

The analysis of the regioselectivity of a 1,3-dipolar cycloaddition by FMO theory requires information about the energy and atomic coefficients of the frontier orbitals of the 1,3-dipole and the dipolarophile. Most of the more common 1,3-dipoles have been examined using CNDO/2 calculations.[122b] Figure 10.14 gives estimates of the energies of the HOMO and LUMO orbitals of some representative 1,3-dipoles. By using these orbital coefficients and calculating or estimating the relative energies

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[120] R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4343 (1971).

[121] P. Merino, J. Revuelta, T. T. Tejero, U. Chiacchio, A. Rescifina, and G. Romeo, *Tetrahedron*, **59**, 3581 (2003).

[122] (a) R. Sustmann and H. Trill, *Angew. Chem. Int. Ed. Engl.*, **11**, 838 (1972); (b) K. N. Houk, J. Sims, B. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); (c) R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974); (d) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1977; (e) K. N. Houk, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, pp. 181–271; (f) K. N. Houk, *Top. Curr. Chem.*, **79**, 1 (1979).

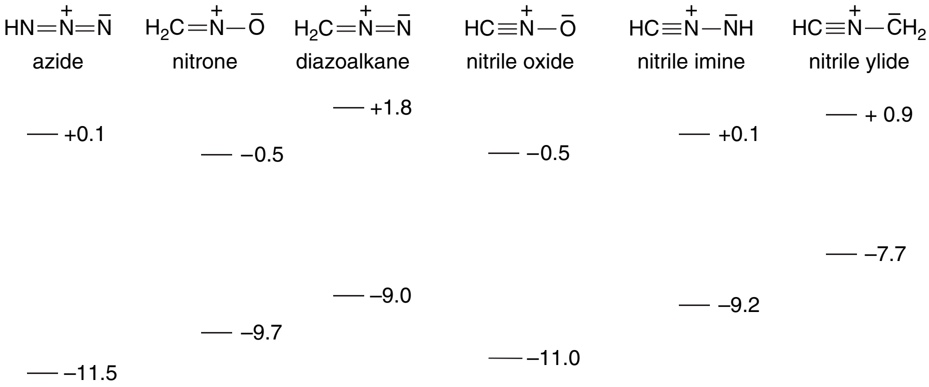
$HN{=}\overset{+}{N}{=}\bar{N}$
azide
$H_2C{=}\overset{+}{N}{-}\bar{O}$
nitrone
$H_2C{=}\overset{+}{N}{=}\bar{N}$
diazoalkane
$HC{\equiv}\overset{+}{N}{-}\bar{O}$
nitrile oxide
$HC{\equiv}\overset{+}{N}{-}\bar{N}H$
nitrile imine
$HC{\equiv}\overset{+}{N}{-}\bar{C}H_2$
nitrile ylide
+0.1
−11.5
−0.5
−9.7
+1.8
−9.0
−0.5
−11.0
+0.1
−9.2
+ 0.9
−7.7

Fig. 10.14. Estimated energies (eV) of frontier π MOs for some 1,3-dipoles. Data from *J. Am. Chem. Soc.*, **95**, 7287 (1973).

of the interacting orbitals, it is possible to make predictions of the regiochemistry of 1,3-DPCA reactions. The most important dipolarophiles are the same types of compounds that are dienophiles in the D-A reaction. The orbital coefficients given in Figure 10.5 can be used in analyses of 1,3-DPCA reactions. In conjunction with the orbital coefficients given in Figure 10.15, this information allows conclusions as to which HOMO-LUMO combination will interact most strongly for a given pair of reactants.

This procedure is illustrated for two specific cases in Figure 10.16. The reaction of a nitrile oxide with an alkene is considered on the left. The smallest energy gap is for the alkene HOMO and the 1,3-dipole LUMO. This is qualitatively reasonable in that the atoms in the 1,3-dipole are more electronegative than those in the dipolarophile. Reference to Figure 10.15 shows that the LUMO coefficient is largest at carbon for the nitrile oxide group. The largest coefficient for a terminal alkene HOMO is at C(1). The matching of the largest coefficients of the 1,3-dipole LUMO and the dipolarophile HOMO leads to the predicted (and observed) product. The same procedure can be applied to the case shown at the right of Figure 10.16. In this case, the 1,3-dipole is the nucleophile and the dipolarophile is the electrophile. The largest coefficient of the nitrone HOMO is at oxygen and the largest coefficient for the acrylate ester LUMO is at the β-carbon.

Although the FMO approach provides a good foundation for understanding the regioselectivity of 1,3-cycloadditions, there are many specific cases in which it fails to provide a complete understanding. Steric factors are not considered by the FMO analysis and in many instances steric factors control regiochemistry. 1,3-DPCA can be broadly classified as *sterically controlled* or *electronically controlled*. There may also be specific interactions in the TSs that are not considered by the FMO analysis.

There have been many studies of individual systems by MO and DFT methods and these provide further insight into the factors that control regio- and stereoselectivity. For example, there are two possible regioisomers from the reaction of diazomethane and methyl vinyl ether, but only the 3-methoxy isomer is formed. Calculations at several levels of theory (AM1, HF/6-31G, and MP2/6-31G*) found lower activation

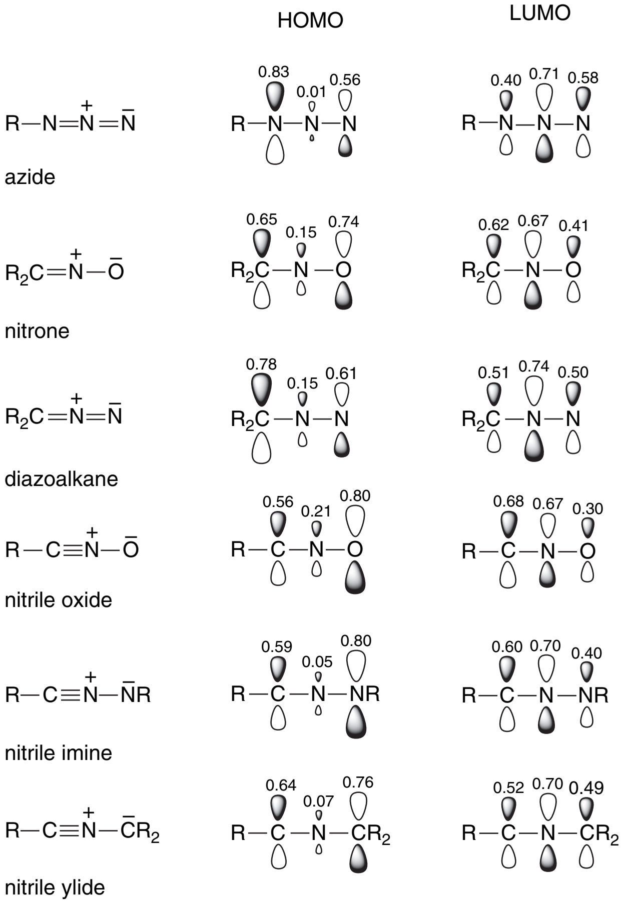
HOMO
LUMO
R—N=N̊=N̄
azide
0.83 0.01 0.56
0.40 0.71 0.58
R₂C=N̊—Ō
nitrone
0.65 0.15 0.74
0.62 0.67 0.41
R₂C=N̊=N̄
diazoalkane
0.78 0.15 0.61
0.51 0.74 0.50
R—C≡N̊—Ō
nitrile oxide
0.56 0.21 0.80
0.68 0.67 0.30
R—C≡N̊—N̄R
nitrile imine
0.59 0.05 0.80
0.60 0.70 0.40
R—C≡N̊—C̄R₂
nitrile ylide
0.64 0.07 0.76
0.52 0.70 0.49

Fig. 10.15. Orbital coefficients for HOMO and LUMO of some common 1,3-dipoles. Data from *J. Am. Chem. Soc.*, **95**, 7287 (1973).

energies for the TS leading to the observed product.[123] The energies (MP2/6-31G*) of the four different TSs are shown in Figure 10.17.

To dissect the factors involved, the TSs were approached in stepwise fashion and the energies associated with each step were assessed. The steps were: (a) deformation of the reactants to their TS geometry; (b) approach of the reactants to the TS geometry; and (c) bond formation. The picture that emerged was that the *earliest* TS had the lowest E_a. Although the total binding energy was less in this looser TS, there was a smaller cost in terms of deformations and repulsions for bringing the reactants together. The favored TS was also characterized by the lowest dipole moment and reflects a favorable alignment of the electrostatic features of the reactants. Finally, bond formation was favored in this TS by a relatively strong donor-acceptor interaction between the HOMO of the electron-rich vinyl ether and the LUMO of the dipolarophile, in agreement with the qualitative FMO analysis.

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[123] Y. L. Pascal, J. Chanet-Ray, R. Vessiere, and A. Zeroual, *Tetrahedron*, **48**, 7197 (1992); A. Rastelli, M. Bagatti, R. Gandolfi, and M. Burdisso, *J. Chem. Soc., Faraday Trans.*, **90**, 1077 (1994).

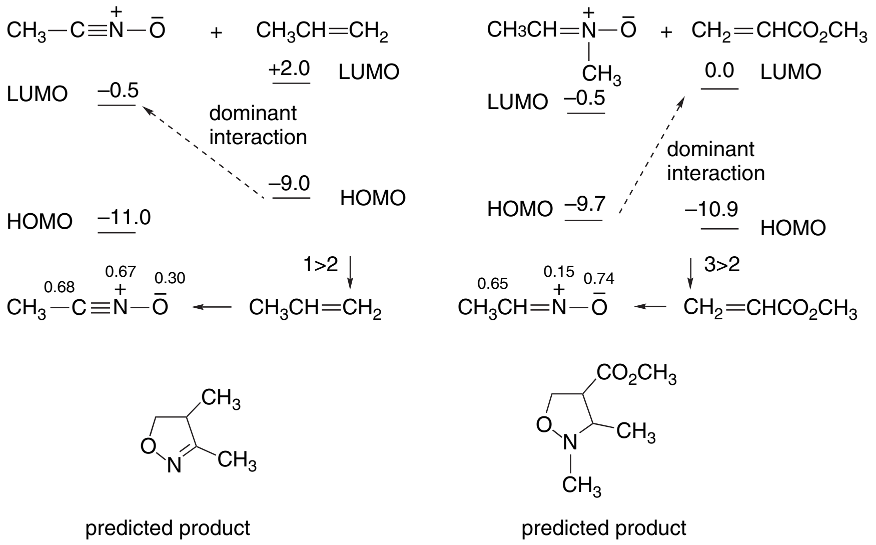
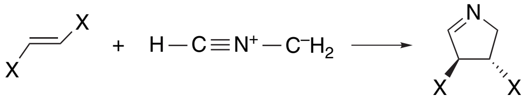

CH3—C≡N—O
+
CH3CH=CH2
LUMO −0.5
+2.0 LUMO
dominant interaction
−9.0 HOMO
HOMO −11.0
1>2
0.68
0.67
0.30
CH3—C≡N—O
CH3CH=CH2
predicted product
CH3CH=N—O
CH3
CH2=CHCO2CH3
0.0 LUMO
LUMO −0.5
dominant interaction
HOMO −9.7
−10.9 HOMO
3>2
0.65
0.15
0.74
CH3CH=N—O
CH2=CHCO2CH3
CO2CH3
CH3
predicted product

Fig. 10.16. Prediction of the regioselectivity of 1,3-dipolar cycloaddition reactions on the basis of FMO interactions. The orbital energies of the reactants (in eV) are indicated.

In another study, the role of dipolarophile substituents on reactivity was assessed using disubstituted ethenes with the nitrile ylide 1,3-dipole. A DFT (B3LYP/6-31G*) study examined E_a and the degree of synchronicity as a function of substituent electronic character. The reaction had successively smaller E_a and less synchronicity as the substituent became more electron attracting in the order $CH_3 < Cl < OH < C{\equiv}N < N{=}O$.[124]


X
X
H—C≡N+—C−H2
N
X
X

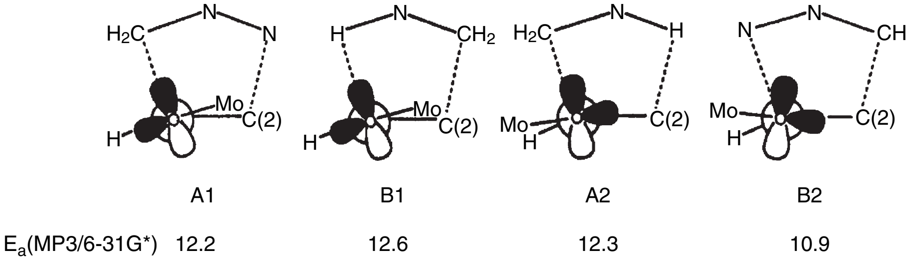

H2C
N
N
Mo
C(2)
H
A1
H
N
CH2
Mo
C(2)
H
B1
H2C
N
H
Mo
C(2)
H
A2
N
N
CH2
Mo
C(2)
H
B2
Ea(MP3/6-31G*) 12.2
12.6
12.3
10.9

Fig. 10.17. Transition structures for 1,3-dipolar addition of methoxyethene and diazomethane. Structures **A1** and **B1** correspond to the *syn* conformation of methoxyethene, whereas **A2** and **B2** correspond to the *anti* conformation. The TS with the lowest energy corresponds to the observed product. From *J. Chem. Soc., Faraday Trans.*, **90**, 1077 (1994).

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[124] H. Liao, M. D. Su, W.-S. Chung, and S.-Y. Chu, *Int. J. Quantum Chem.*, **83**, 318 (2001).

X	E_a	Degree of Asynchronicity
N = O	−1.4	0.309
C≡N	+1.4	0.198
Cl	+10.1	0.107
OH	+13.2	0.154
CH_3	+14.3	0.025

Note that there is no barrier for the (hypothetical) reaction with dinitrosoethene. For X = N=O and C≡N, shallow energy minima for prereaction complexes were identified. The conclusion that can be drawn from this study is that stronger EWGs in the dipolarophile lead to greater electrophile/nucleophile character and higher reactivity. This is the same qualitative trend noted for D-A reactions (see p. 847). The nitrile ylide is clearly an electron donor in these reactions, which is consistent with the relatively high energy of the HOMO, as indicated in Figure 10.14.

Computations were also applied to representative 1,3-dipoles in reaction with ethene.[125] The E_a and ΔE for the reactions were calculated using CCSD(T)/6-311G** energies at B3LYP/6-31G* structural minima.

1,3-Dipole	E_a	ΔE	Leading bond (Å)
$H{-}C{\equiv}N^+{-}CH_2^-$	+6.9	−72.1	2.443
$H{-}C{\equiv}N^+{-}NH^-$	+6.9	−62.6	2.326
$H{-}C{\equiv}N^+{-}O^-$	+11.4	−45.9	2.235
$N{\equiv}N^+{-}CH_2^-$	+14.3	−37.0	2.225
$N{\equiv}N^+{-}NH^-$	+17.2	−26.2	2.143
$N{\equiv}N^+ - O^-$	+23.5	−10.7	2.036

A number of factors appear to be involved here. There is an Bell-Evans-Polyani type correlation with the most stable products (most negative ΔE) having the lowest E_a. There is also a trend toward a later TS with the slower reactions, as indicated by the length of the leading bond in the TS. This is consistent with the Hammond postulate, with the smaller E_a correlating with an early TS. Within the 1,3-dipoles, there is a negative correlation with electronegativity. The most electrophilic 1,3-dipoles are the least reactive in this case. This trend suggests a dominant $\text{HOMO}_{\text{dipole}}$-$\text{LUMO}_{\text{dipolarophile}}$ interaction, but it also may reflect the strength of the bonds being formed, which decreases in the same direction.

In broad terms, there is similarity in the reactivity and regiochemistry relationships for 1,3-DPCA and those of the D-A reaction. The most favorable reactions are those with the most complementary electronic character, that is, high nucleophilicity in one reactant with high electrophilicity in the other. Such reactions have high charge transfer character, early TS, and lower TS energy. Bond formation is more advanced in the TS between the most complementary pair of reaction centers and asynchronicity is high. The best match between HOMO and LUMO predicts the preferred regiochemistry. Relative reactivity trends should also be governed by these criteria, but as yet no broad quantitative analyses of relative reactivity have been developed.

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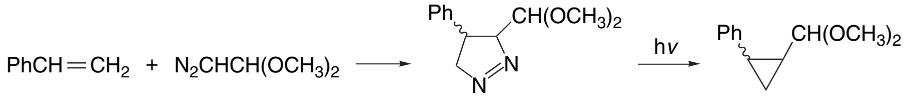
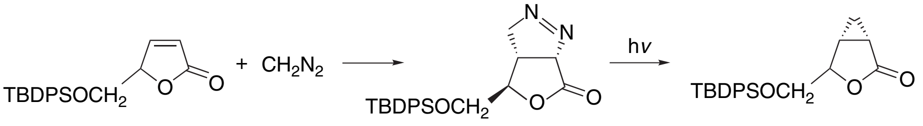
[125] M.-D. Su, H.-L. Liao, W.-S. Chung, and S.-Y. Chu, *J. Org. Chem.*, **64,** 6710 (1999).

10.3.2. Scope and Applications of 1,3-Dipolar Cycloadditions

As can be judged from Scheme 10.6, a wide variety of five-membered heterocyclic compounds can be made by the 1,3-DPCA reaction. Sometimes, these products are not the final target but rather intermediates for preparation of other compounds. Pyrazolines, which are formed from alkenes and diazo compounds, for example, can be pyrolyzed or photolyzed to give cyclopropanes.

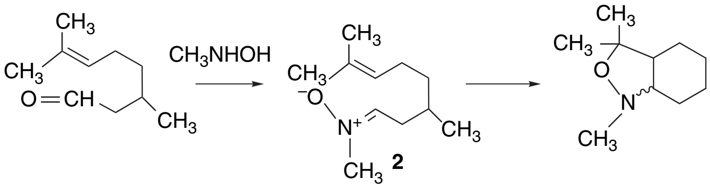


Ref. 126



Ref. 127

The addition of nitrones to alkenes serves both to form a carbon-carbon bond and to introduce oxygen and nitrogen functionality.[128] The products are isoxazolines and the oxygen-nitrogen bond can be cleaved by reduction, leaving both an amino and a hydroxy function in place. A number of imaginative syntheses have employed this strategy. Intramolecular 1,3-dipolar cycloaddition has proven to be especially useful in synthesis. The nitrone **2** is generated by condensation of the aldehyde group with *N*-methylhydroxylamine and then goes on to product by intramolecular cycloaddition.



Ref. 129

Scheme 10.7 gives some other examples of 1,3-DPCA reactions. Entries 1 to 3 are typical intermolecular 1,3-DPCA. The 1,3-dipoles in each instance are isolatable compounds. Entries 4 and 5 are intramolecular nitrone cycloadditions. The product from Entry 5 was used in the synthesis of the alkaloid pseudotropine. The proper stereochemical orientation of the hydroxyl group is ensured by the structure of the isoxazoline from which it is formed.

An interesting variation of the 1,3-DPCA involves generation of 1,3-dipoles from three-membered rings. As an example, aziridines **3** and **4** give adducts derived from apparent formation of 1,3-dipoles **5** and **6**, respectively.[130]

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[126] P. Carrie, *Heterocycles*, **14**, 1529 (1980).

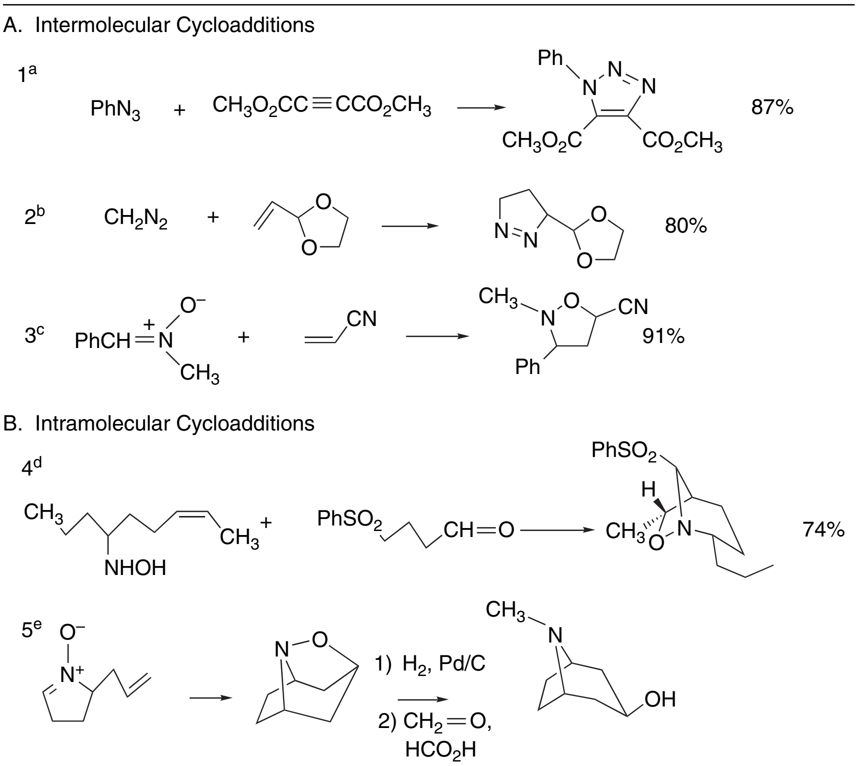
[127] M. Martin-Vila, N. Hanafi, J. M. Jimenez, A. Alvarez-Larena, J. F. Piniella, V. Branchadell, A. Oliva, and R. M. Ortuno, *J. Org. Chem.*, **63**, 3581 (1998).

[128] For reviews of nitrone cycloadditions, see D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); J. J. Tufariello, *Acc. Chem. Res.*, **12**, 396 (1979); P. N. Confalone and E. M. Huie, *Org. React.*, **36**, 1 (1988).

[129] N. LeBel and D. Hwang, *Org. Synth.*, **58**, 106 (1978).

[130] R. Huisgen and H. Maeder, *J. Am. Chem. Soc.*, **93**, 1777 (1971).

Scheme 10.7. Examples of 1,3-Dipolar Cycloaddition Reactions


A. Intermolecular Cycloadditions
1a
PhN3 + CH3O2CC≡CCO2CH3
87%
2b
CH2N2 +
80%
3c
PhCH=N(O−)CH3 +
CN
91%
B. Intramolecular Cycloadditions
4d
NHOH
PhSO2 CH=O
74%
5e
1) H2, Pd/C
2) CH2=O, HCO2H
OH

---

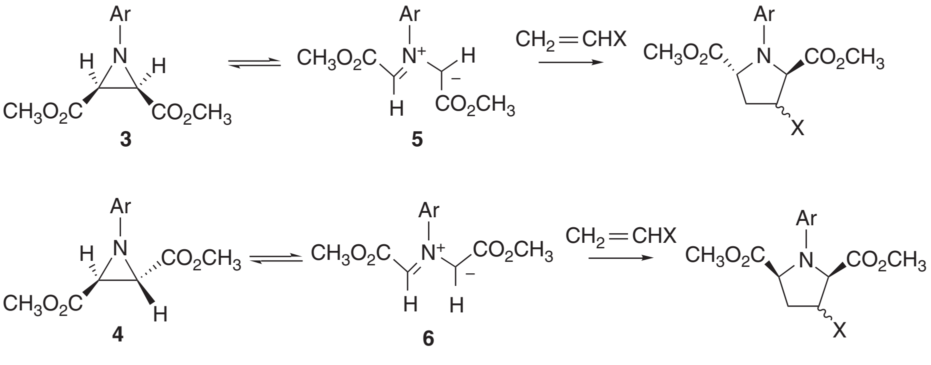
a. R. Huisgen, R. Knorr, L. Mobius, and G. Szeimies, *Chem. Ber.*, **98**, 4014 (1965).

b. J. M. Stewart, C. Carlisle, K. Kem, and G. Lee, *J. Org. Chem.*, **35**, 2040 (1970).

c. R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).

d. N. A. LeBel and N. Balasubramanian, *J. Am. Chem. Soc.*, **111**, 3363 (1989).

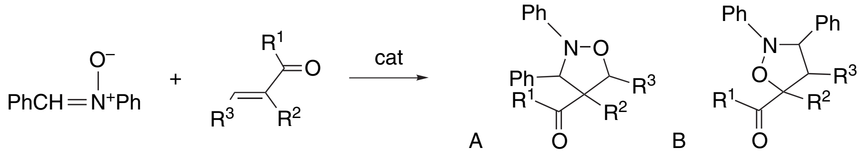
e. J. J. Tufariello, G. B. Mullen, J. J. Tegler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, **101**, 2435 (1979).


3
5
CH2=CHX
4
6
CH2=CHX

Ring opening is most facile for aziridines that have an EWG to stabilize the carbanion center in the dipole. The evidence for the involvement of 1,3-dipoles as discrete intermediates includes the observation that the reaction rates are independent of dipolarophile concentration. This fact indicates that the ring opening is the rate-determining step in the reaction. Note that the ring opening is a stereospecific electrocyclic process. (The stereochemistry of electrocyclic ring opening is discussed in Section 10.5).

10.3.3. Catalysis of 1,3-Dipolar Cycloaddition Reactions

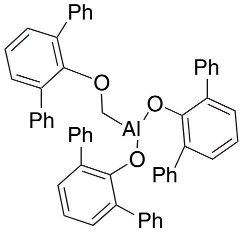
The role of catalysts in 1,3-DPCA reactions is similar to that in D-A reactions. Most catalysts are Lewis acids. Effective catalysts include $Yb(O_3SCF_3)_3$ with BINOL,[131] Mg^{2+}-*bis*-oxazolines,[132] and oxazaborolidines.[133] Intramolecular nitrone cycloadditions can be facilitated by Lewis acids such as $ZnCl_2$.[134] The catalysts function by enhancing the reactivity of *the more electrophilic component of the reaction*. Although the diene is often nonpolar and inert to Lewis acids in D-A reactions, that is not the case for 1,3-DPCA. Consideration of catalysts must include the potential interaction with both the dipole and dipolarophile. Catalyst interaction with the 1,3-dipole is likely to be detrimental if the dipole is the more nucleophilic component of the reaction. For example, with nitrones and enones, formation of a Lewis acid adduct with the nitrone in competition with the enone is detrimental. One approach to this problem is to use highly substituted catalysts that are selective for the less substituted reactant. Bulky aryloxyaluminum compounds are excellent catalysts for nitrone cycloaddition and also enhance regioselectivity.[135] The reaction of diphenylnitrone with enones is usually subject to steric regiochemical control. With the catalyst **B** high *electronic regiochemical control* is achieved and reactivity is greatly enhanced, but the catalyst does not strongly influence the *exo*:*endo* selectivity, which is 23:77 for propenal.



R^1	R^2	R^3	catalyst	Yield(%)	A:B ratio
H	H	H	no	5	20:80
			yes	100	>99:1
CH_3	H	H	no	7	8:92
			yes	82	100:0
H	CH_3	H	no	5	0:100
			yes	100	91:9
H	H	CH_3	no	2	100:0
			yes	100	100:0

electronically-controlled product

sterically-controlled product



catalyst **B**

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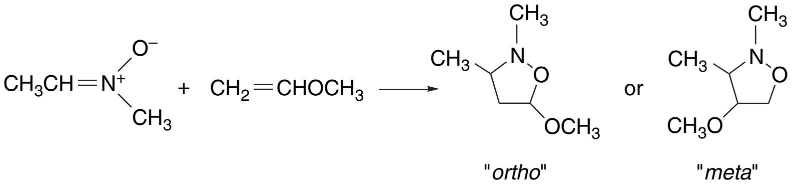
[131] M. Kawamura and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3213 (1999).

[132] G. Desimoni, G. Faita, A. Mortoni, and P. Righetti, *Tetrahedron Lett.*, **40**, 2001 (1999); K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **63**, 5483 (1998).

[133] J. P. G. Seerden, M. M. M. Boeren, and H. W. Scheeren, *Tetrahedron*, **53**, 11843 (1997).

[134] J. Marcus, J. Brussee, and A. van der Gen, *Eur. J. Org. Chem.*, 2513 (1998).

[135] S. Kanemasa, N. Ueno, and M. Shirahase, *Tetrahedron Lett.*, **43**, 657 (2002).



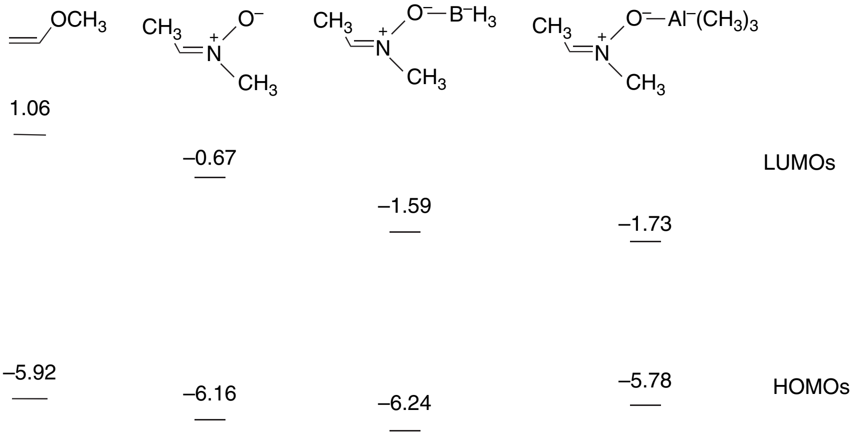


Fig. 10.18. Shift in FMO energy levels (in eV) (B3LYP/6-31G*) on complexation with BH_3 or $(CH_3)_3Al$ with nitrone reactant. Data from *Eur. J. Org. Chem.*, 2265 (2000).

Domingo examined computationally the effect of Lewis acid catalysis in the reaction of a nitrone with a vinyl ether, a combination in which the nitrone is the electrophilic reagent.[136] The results are summarized in Figure 10.18. The Lewis acid, modeled by BH_3 or $Al(CH_3)_3$, is attached at the nitrone oxygen. The Lewis acid decreases the E_a for "*ortho*" addition, while increasing it for "*meta*" addition. The catalyst also increases the selectivity for the *exo* TS. These results are consistent with the energy changes of the FMO of the reactants. The catalyst lowers the energy of the nitrone LUMO, enhancing its interaction with the vinyl ether HOMO. The reaction takes on enhanced charge transfer character in the presence of the catalyst. These overall effects are similar to those found in D-A reactions catalyzed by Lewis acids.

As with D-A reactions, it is possible to achieve enantioselective cycloaddition in the presence of chiral catalysts.[137] Many of the catalysts are similar to those used in enantioselective D-A reactions. The catalysis usually results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating a metal ion and associated ligands, then enforces a preferred orientation of the reagents. For example, the bulky aryl groups in the catalyst **C** favor one direction of approach of the nitrone reactant.[138]

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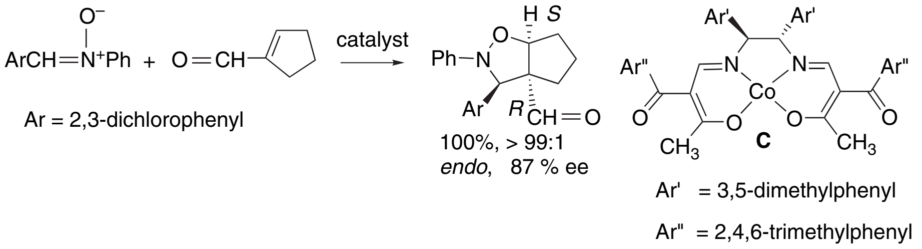
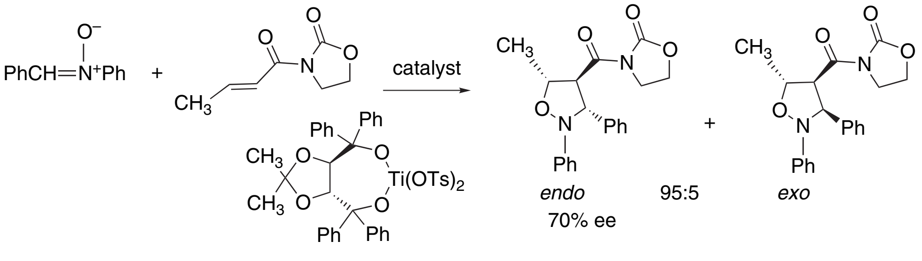
[136] L. R. Domingo, *Eur. J. Org. Chem.*, 2265 (2000).

[137] K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998); M. Frederickson, *Tetrahedron*, **53**, 403 (1997).

[138] T. Mita, N. Ohtsuki, T. Ikeno, and T. Yamada, *Org. Lett.*, **4**, 2457 (2002).



The Ti(IV) TADDOL catalyst **D** leads to moderate to high enantioselectivity in nitrone cycloaddition with *N*-acyloxazolidinones.[139]



catalyst **D**

10.4. [2 + 2] Cycloaddition Reactions

As indicated in the Introduction, [2 + 2] cycloadditions are forbidden for the $[\pi 2_s + \pi 2_s]$ topology but allowed for the $[\pi 2_a + \pi 2_s]$ topology.[140] One example of $[2\pi_s + 2\pi_a]$ cycloaddition involves ketenes.[141] An alternative description of the orbital array for this reaction is a $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ addition.[142] The basis set orbital arrays for both arrangements are shown in Figure 10.19. The $[\pi 2_a + \pi 2_s]$ system has Mobius topology, whereas the $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ system has Hückel topology with six π electrons involved and is an allowed process.

The TS found for addition is very asynchronous with a strong initial interaction of the ketene *sp* carbon with both carbons of the alkene and considerable polar character.[143] Analysis of the electronic interactions at the TS by NPA shows substantial charge transfer from ethene to ketene, as would be expected on the basis

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[139] K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, **50**, 652 (1996); K. B. Jensen, K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **62**, 2471 (1997); K. B. Jensen, K. V. Gothelf, and K. A. Jorgensen, *Helv. Chim. Acta*, **80**, 2039 (1997).

[140] R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

[141] W. T. Brady and R. Roe, *J. Am. Chem. Soc.*, **93**, 1662 (1971); W. T. Brady, in *The Chemistry of Ketenes, Allenes and Related Compounds*, S. Patai, ed., John Wiley, Chichester, 1980, Chap. 8.

[142] E. Valenti, M. A. Pericas, and A. Moyano, *J. Org. Chem.*, **55**, 3582 (1990).

[143] L. A. Burke, *J. Org. Chem.*, **50**, 3149 (1985); X. Wang and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 1754 (1990); S. Yamabe, T. Minato, and Y. Osamura, *J. Chem. Soc., Chem. Commun.*, 53 (1993); S. Yamabe, K. Kuwata, and T. Minato, *Theo. Chem. Acc.*, **102**, 139 (1999).

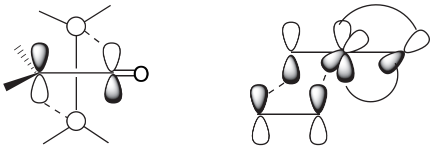
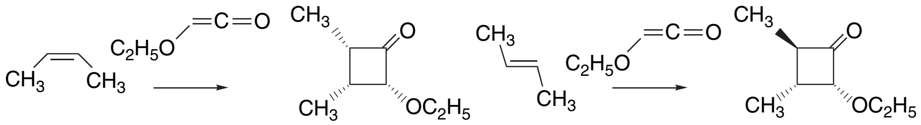


Fig. 10.19. $[\pi 2_a + \pi 2_s]$ and $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ orbital arrays for alkene-ketene [2 + 2] cycloaddition.

of relative electrophilicity.[144] Figure 10.20 gives the bond distances and NPA charges as determined by DFT (BP86/III) computations.

Predictions of stereoselectivity and reactivity based on the $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ TS are in better accord with experimental results than predictions derived from the $[\pi 2_s + \pi 2_a]$ TS.[145] Minimization of interaction between the substituents leads to a cyclobutanone in which the substituents at C(2) and C(3) are *cis*, which is the stereochemistry usually observed in these reactions. For example, *E*- and *Z*-2-butene give stereoisomeric products with ethoxyketene.[146]


CH3
CH3
C2H5O
=C=O
CH3
O
CH3
OC2H5
CH3
CH3
C2H5O
=C=O
CH3
O
CH3
OC2H5

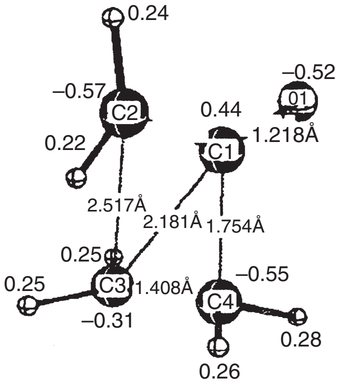

0.24
–0.57
C2
0.22
–0.52
O1
0.44
C1
1.218Å
2.517Å
2.181Å
1.754Å
0.25
0.25
C3
1.408Å
–0.31
C4
–0.55
0.28
0.26

Fig. 10.20. Bond distances and NPA charges for the DFT (BP86/III) transition structure for addition between ketene and ethene. Reproduced from *J. Phys. Chem. A*, **106**, 431 (2002), by permission of the American Chemical Society.

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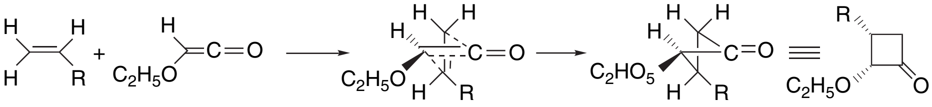
[144] D. V. Deubel, *J. Phys. Chem., A*, **106**, 431 (2002).

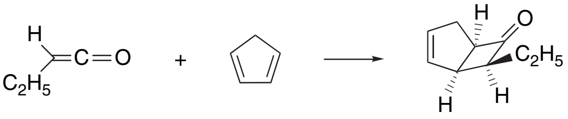
[145] D. J. Pasto, *J. Am. Chem. Soc.*, **101**, 37 (1979).

[146] T. DoMinh and O. P. Strausz, *J. Am. Chem. Soc.*, **92**, 1766 (1970).

For monosubstituted alkenes, the substituent is vicinal and *cis* to the ethoxy group in the cyclobutanone product, a structure that maximizes the separation of the alkyl and ethoxy substituents in the TS.



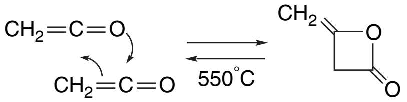
Similarly, ethyl ketene reacts with cyclopentadiene to give the ethyl group in the *endo* position.



Ref. 147

Note also the preference for [2 + 2] rather than [2 + 4] cycloaddition with cyclopentadiene. A computational comparison of the [2 + 2] and [2 + 4] modes of reaction between cyclopentadiene and ketene found the former to have a lower E_a (by about 10 kcal/mol).[148]

The best yields are obtained when the ketene has an electronegative substituent, such as halogen. Simple ketenes are not very stable and are usually generated in situ. The most common method for generating ketenes for synthesis is by dehydrohalogenation of acyl chlorides, which is usually done with an amine such as triethylamine.[149] Ketene itself and certain alkyl derivatives can be generated by pyrolysis of carboxylic anhydrides.[150] Ketene can also be generated by pyrolysis of acetone.[151] Ketene forms a dimer, from which it can be regenerated at 550°C.[152]



Intramolecular ketene cycloadditions are possible if the ketene and alkene functionalities can achieve an appropriate orientation.[153]

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[147] M. Rey, S. M. Roberts, A. S. Dreiding, A. Roussel, H. Vanlierde, S. Toppet, and L. Ghosez, *Helv. Chim. Acta*, **65**, 703 (1982).

[148] U. Salzner and S. M. Bachrach, *J. Org. Chem.*, **61**, 237 (1996).

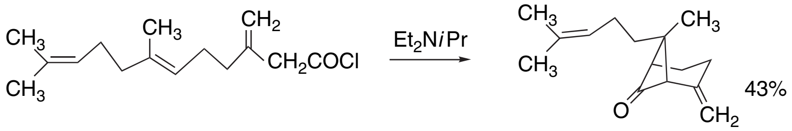
[149] K. Shishido, T. Azuma, and M. Shibuya, *Tetrahedron Lett.*, **31**, 219 (1990).

[150] G. J. Fisher, A. F. MacLean, and A. W. Schnizer, *J. Org. Chem.*, **18**, 1055 (1953).

[151] C. D. Hurd, *Org. Synth.*, **I**, 330 (1941).

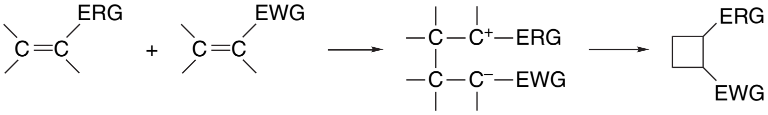
[152] S. Andreades and H. D. Carlson, *Org. Synth.*, **V**, 679 (1973).

[153] B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985); B. B. Snider and R. A. H. F. Hui, *J. Org. Chem.*, **50**, 5167 (1985); W. T. Brady and Y. F. Giang, *J. Org. Chem.*, **50**, 5177 (1985).

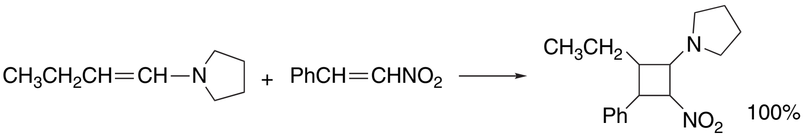


Ref. 154

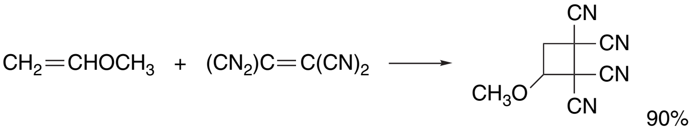
Cyclobutanes can also be formed by nonconcerted processes involving zwitterionic intermediates. The combination of an electron-rich alkene (enamine, vinyl ether) and an electrophilic one (nitro- or polycyanoalkene) is required for such processes.



Below are two examples of this reaction type.



Ref. 155



Ref. 156

The stereochemistry of these reactions depends on the lifetime of the dipolar intermediate, which, in turn, is influenced by the polarity of the solvent. In the reactions of enol ethers with tetracyanoethylene, the stereochemistry of the vinyl ether portion is retained in nonpolar solvents. In polar solvents, cycloaddition is nonstereospecific as a result of a longer lifetime for the zwitterionic intermediate.[157]

The [2 + 2] cycloaddition of ketenes and imines is an important route to the β-lactam ring (azetidinone),[158] which is a crucial structural feature of the penicillin class of antibiotics. A number of theoretical treatments of this reaction indicate that in solution phase this is a two-step reaction, with the second step being rate determining.[159] The stepwise nature of the reaction is accommodated by the relative stability of both charged moieties, an iminium cation and an enolate anion.

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[154] E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).

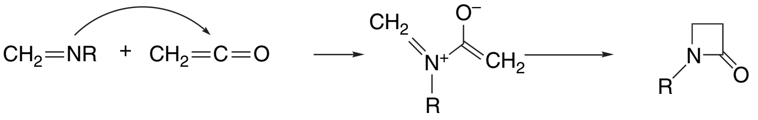
[155] M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).

[156] J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).

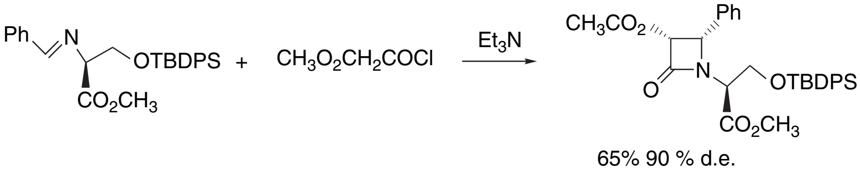
[157] R. Huisgen, *Acc. Chem. Res.*, **10**, 117, 199 (1977).

[158] C. Palomo, J. M. Aizpurua, I. Ganboa, and M. Oiarbide, *Eur. J. Org. Chem.*, 3223 (1999); I. Ojima and F. Dalaloge, *Chem. Soc. Rev.*, **26**, 377 (1997).

[159] X. Assfeld, J. A. Sordo, J. Gonzalez, M. F. Ruiz-Lopez, and T. L. Sordo, *Theochem*, **106**, 193 (1993); X. Assfeld, M. F. Ruiz-Lopez, J. Gonzalez, R. Lopez, J. A. Sordo, and T. L. Sordo, *J. Comput. Chem.*, **15**, 479 (1994); T. N. Truong, *J. Phys. Chem. B*, **102**, 7877 (1998).



In addition to its application in the synthesis of β-lactams, this reaction has been used for stereoselective synthesis of the side chain of the taxol class of antitumor agents.

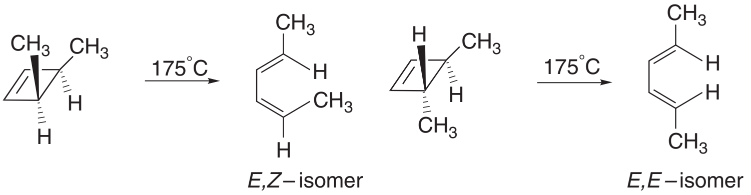


Ref. 160

10.5. Electrocyclic Reactions

10.5.1. Overview of Electrocyclic Reactions

An electrocyclic reaction is defined as the formation of a single bond between the terminal atoms of a linear conjugated system of π electrons and the reverse process. One example is the thermal ring opening of cyclobutenes to butadienes.



Ref. 161

It is not surprising that thermolysis of cyclobutenes leads to ring opening because the strain in the four-membered ring is relieved. The ring opening of cyclobutene to 1,3-butadiene is exothermic by 11 kcal/mol. The E_a for simple alkyl-substituted cyclobutene is in the range of 30–35 kcal/mol.[162] *What is particularly significant about these reactions is that they are stereospecific.* *cis*-3,4-Dimethylcyclobutene is converted to *E*,*Z*-2,4-hexadiene, whereas *trans*-3,4-dimethylcyclobutene yields the *E*,*E*-isomer. The level of stereospecificity is very high. In the ring opening of *cis*-3,4-dimethylcyclobutene, for example, only 0.005% of the minor product *E*,*E*-2,4-hexadiene is formed, even though it is more stable than the *E*,*Z*-isomer.[163]

The reason for the stereospecificity is that the groups bonded to the breaking bond rotate in the same sense during the ring-opening process. Such motion, in which all

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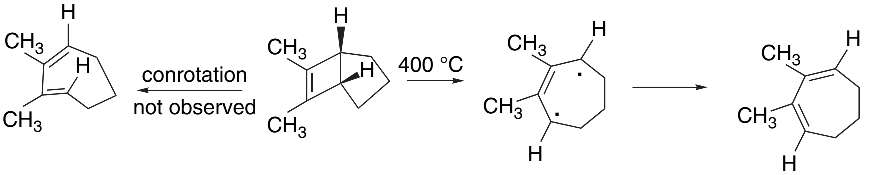
[160] V. Farina, S. I. Hauck, and D. G. Walker, *Synlett*, 761 (1992).

[161] R. F. K. Winter, *Tetrahedron Lett.*, 1207 (1965).

[162] W. Kirmse, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.*, **106**, 7989 (1984).

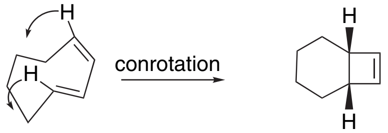
[163] J. I. Brauman and W. C. Archie, Jr., *J. Am. Chem. Soc.*, **94**, 4262 (1972).

the substituents rotate either clockwise or counterclockwise, is called the *conrotatory* mode. When the conrotatory motion is precluded by some structural feature, ring opening requires a much higher temperature. In the bicyclo[3.2.0]hept-6-ene example shown below, the five-membered ring prevents a conrotatory ring opening because it would lead to the very strained *Z*,*E*-cycloheptadiene. The reaction takes place only at very high temperature, 400°C, and probably involves the diradical shown as an intermediate.



Ref. 164

The *principle of microscopic reversibility* (see p. 275) requires that the reverse process, ring closure of a butadiene to a cyclobutene, also be conrotatory. Usually this is thermodynamically unfavorable, but a case in which the ring closure is energetically favorable is conversion of *E*,*Z*-1,3-cyclooctadiene to *cis*-bicyclo[4.2.0]oct-7-ene. The ring closure is favorable in this case because of the strain associated with the *E*-double bond. The ring closure occurs by a conrotatory process.



Ref. 165

Electrocyclic reactions of 1,3,5-trienes lead to 1,3-cyclohexadienes. Note that only the 3-*Z*-isomer can attain a conformation suitable for cyclization. The ring closure is normally the favored direction of reaction for conjugated trienes because of the greater thermodynamic stability of the cyclic compound, which has six σ bonds and two π bonds, whereas the triene has five σ and three π bonds. The closure of *Z*-1,3,5-hexatriene to cyclohexa-1,3-diene is exothermic by 16.4 kcal/mol.[166] The E_a is about 30 kcal/mol.[167] These ring closure reactions also exhibit a high degree of stereospecificity, illustrated with octatrienes **7** and **8.** *E*,*Z*,*E*-2,4,6-Octatriene (**7**) cyclizes only to *cis*-5,6-dimethyl-1,3-cyclohexadiene, whereas the *E*,*Z*,*Z*-2,4,6-octatriene (**8**) leads exclusively to the *trans* cyclohexadiene isomer.[168] A point of particular importance regarding the stereochemistry of this reaction is that the groups at the termini of the triene system rotate in the opposite sense during the cyclization process, a mode of electrocyclic reaction known as *disrotatory*.

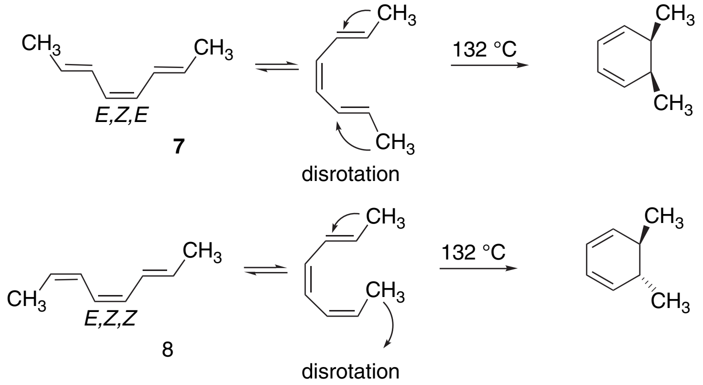
[164] R. Criegee and H. Furr, *Chem. Ber.*, **97**, 2949 (1964).

[165] K. M. Schumate, P. N. Neuman, and G. J. Fonken, *J. Am. Chem. Soc.*, **87**, 3996 (1965); R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).

[166] R. B. Turner, B. J. Mallon, M. Tichy, W. von E. Doering, W. R. Roth, and G. Schroeder, *J. Am. Chem. Soc.*, **95**, 8605 (1973); W. R. Roth, O. Adamczak, R. Breuckmann, H.-W. Lennartz, and R. Boese, *Chem. Ber.*, **124**, 2499 (1991).

[167] K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 3080 (1964).

[168] E. N. Marvell, G. Caple, and B. Schatz, *Tetrahedron Lett.*, 385 (1965); E. Vogel, W. Grimme, and E. Dinne, *Tetrahedron Lett.*, 391 (1965); J. E. Baldwin and V. P. Reddy, *J. Org. Chem.*, **53**, 1129 (1988).



10.5.2. Orbital Symmetry Basis for the Stereospecificity of Electrocyclic Reactions

A mechanistic description of electrocyclic reactions must explain not only the high degree of stereospecificity, but also why four π-electron systems undergo conrotatory reactions, whereas six π-electron systems undergo disrotatory reactions. Woodward and Hoffman proposed that the stereochemistry of the reactions is controlled by the symmetry properties of the highest occupied molecular orbital (HOMO) of the reacting system.[169] The idea that the HOMO should control the course of the reaction is another example of *frontier molecular orbital theory* (FMO), which holds that it is the electrons of highest energy, i.e., those in the HOMO, that are of prime importance in determining the course of the reaction (see p. 43).[170]

Why do the symmetry properties of the HOMO determine the stereochemistry of the electrocyclic reaction? For convenience, let us examine the microscopic reverse of the ring opening. The stereochemical features of the reaction are the same in both the forward or reverse directions. For conjugated dienes, the HOMO is ψ_2. For bonding to occur between C(1) and C(4), the positive lobe on C(1) must overlap with the positive lobe on C(4) (or negative with negative, since the signs are interchangeable). This overlap of lobes of the same sign can be accomplished only by a conrotatory motion. Disrotatory motion causes overlap of orbitals of opposite sign, leading to an antibonding overlap that would preclude bond formation. Other conjugated dienes have identical orbital symmetries, so the conrotatory mode is preferred for all thermal electrocyclic processes of 1,3-dienes. The conrotatory process is illustrated in Figure 10.21.

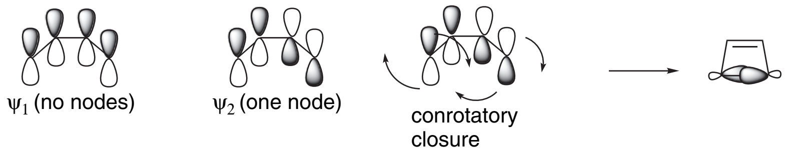


Fig. 10.21. Symmetry properties of the occupied π orbitals of a conjugated diene.

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[169] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965).

[170] K. Fukui and H. Fujimoto, in *Mechanisms of Molecular Migrations*, Vol. 2, B. S. Thyagarajan, ed., Interscience, New York, 1968, p. 117; K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971); K. Fukui, *Angew. Chem. Int. Ed. Engl.*, **21**, 801 (1982).

The analysis for the 1,3,5-triene system according to FMO theory proceeds in the same way as for a diene, but leads to the conclusion that a bonding interaction between C(1) and C(6) of the triene will require a disrotatory motion. This is because the HOMO, ψ_3, has positive lobes on the same face of the π system and these must overlap to permit bond formation. The symmetry properties of other six π-electron conjugated triene systems are the same, so disrotatory ring closure (or opening) is general for conjugated trienes. The π orbitals for the hexatriene system are shown in Figure 10.22.

When we recall the symmetry patterns for linear polyenes that were discussed in Chapter 1 (see p. 29), we can further generalize the predictions based on the symmetry of the polyene HOMO. The HOMOs of the $4n$ systems are like those of 1,3-dienes in having opposite phases at the terminal atoms. The HOMOs of other $4n+2$ systems are like trienes and have the same phase at the terminal atoms. Systems with $4n$ π electrons will undergo electrocyclic reactions by conrotatory motion, whereas systems with $4n+2$ π electrons will react by the disrotatory mode.

The analysis of electrocyclic reactions can also be done using *orbital correlation diagrams*.[171] This approach focuses attention on the orbital symmetries of both reactants and products and considers the symmetry properties of all the orbitals. In any concerted process, the orbitals of the starting material must be smoothly transformed into orbitals of product having the same symmetry. If this process of orbital conversion leads to the ground state electronic configuration of the product, the process will have a relatively low activation energy and be an *allowed* process. If, on the other hand, the orbitals of the reactant are transformed into a set of orbitals that does not correspond to the ground state of the product, a high-energy TS occurs and the reaction is *forbidden*, since it would lead to an excited state of the product.

The cyclobutene-butadiene interconversion can serve as an example of the construction of an orbital correlation diagram. For this reaction to occur, the four π orbitals of butadiene must be converted smoothly into the two π and two σ orbitals of the ground state of cyclobutene. The π orbitals of butadiene are ψ_1, ψ_2, ψ_3, and ψ_4. For cyclobutene, the four orbitals are σ, π, σ^*, and π^*, with each of them classified with respect to the symmetry elements that are maintained in the course of the transformation. The relevant symmetry features depend on the structure of the reacting system. The most common elements of symmetry to be considered are planes of symmetry and rotation axes. An orbital is classified as symmetric, *S*, if it is unchanged by reflection in a plane of symmetry or by rotation about an axis of symmetry. If the orbital changes sign (phase) at each lobe as a result of the symmetry operation, it is called antisymmetric, *A*. Proper molecular orbitals must be either symmetric or antisymmetric. If an orbital is neither *S* nor *A*, it must be adapted by combination with other orbitals to meet this requirement.

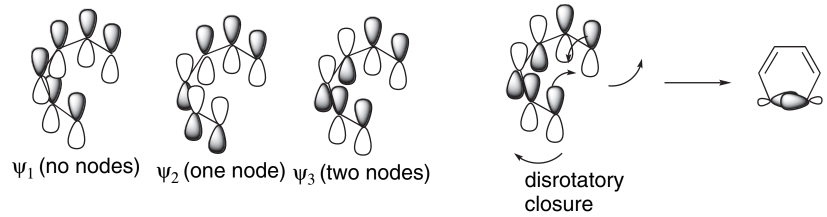

Fig. 10.22. Symmetry properties of the occupied π orbitals of a conjugated triene.

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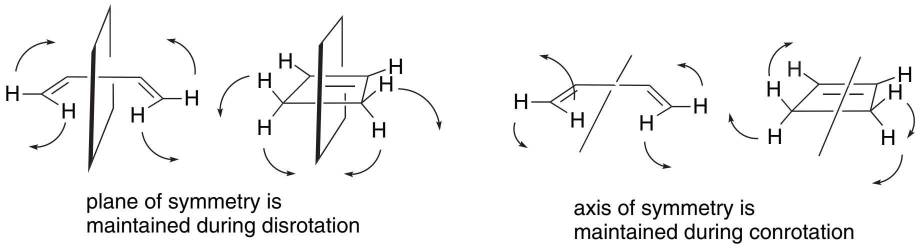
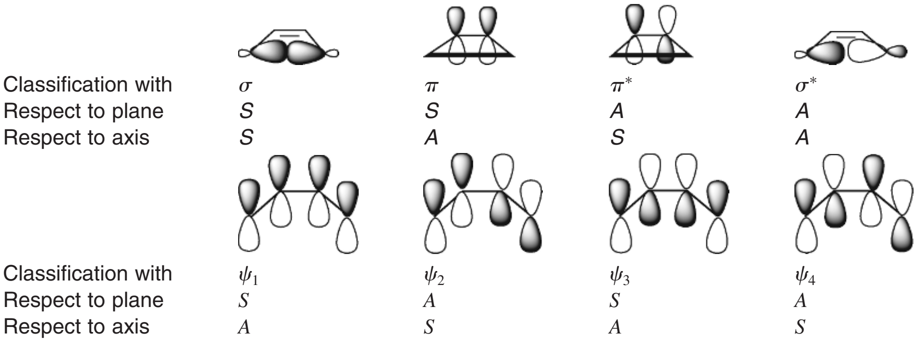
[171] H. C. Longuet-Higgins and E. W. Abrahamson, *J. Am. Chem. Soc.*, **87**, 2045 (1965).

Figure 10.23 illustrates the classification of the MOs of butadiene and cyclobutene. There are two elements of symmetry that are common to both *s-cis*-butadiene and cyclobutene: a plane of symmetry and a twofold axis of rotation. The plane of symmetry is maintained during a disrotatory transformation of butadiene to cyclobutene. In the conrotatory transformation, the axis of rotation is maintained throughout the process. Therefore to analyze the disrotatory process, the orbitals must be classified with respect to the plane of symmetry, and to analyze the conrotatory process, they must be classified with respect to the axis of rotation.


plane of symmetry is maintained during disrotation
axis of symmetry is maintained during conrotation

Both the disrotatory and the conrotatory process can be analyzed by comparing the symmetry classification of reactant and product orbitals given in Figure 10.23. The orbitals are arranged according to energy in Figure 10.24, and the states of like symmetry for the disrotatory process are connected. It is seen that in the disrotatory process, not all of the ground state orbitals of cyclobutene correlate with ground state orbitals of butadiene. The bonding π orbital of cyclobutene is transformed into an antibonding orbital (ψ_3) of butadiene. In the reverse process, ψ_2 of butadiene is transformed into the antibonding π^* orbital of cyclobutene. Because of the failure of the orbitals of the ground state molecules to correlate, the transformation would lead to a high-energy TS, and the disrotatory reaction is said to be *symmetry forbidden*.

Analysis of the conrotatory process is carried out in exactly the same way. In this case the element of symmetry that is maintained throughout the reaction process is the twofold rotation axis. The resulting correlation diagram is shown in Figure 10.24. The conrotatory reaction is *symmetry allowed*, since the bonding orbitals of butadiene correlate with the bonding orbitals of cyclobutene and vice versa. Figure 10.25 is a pictorial representation of the orbital in the reactant, transition structure, and product.



Classification with	σ	π	π^*	σ^*
Respect to plane	S	S	A	A
Respect to axis	S	A	S	A

Classification with	ψ_1	ψ_2	ψ_3	ψ_4
Respect to plane	S	A	S	A
Respect to axis	A	S	A	S

Fig. 10.23. Elements of symmetry for and classification of orbitals for disrotatory and conrotatory interconversion of 1,3-butadiene and cyclobutene.

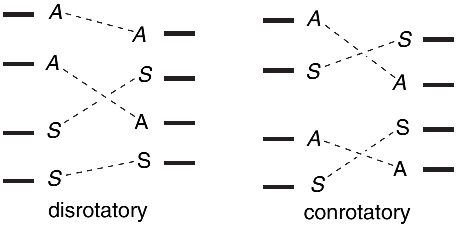

A
A
A
S
S
A
S
S
disrotatory
A
S
S
A
A
S
S
A
conrotatory

Fig. 10.24. Correlation diagrams for interconversion of cyclobutene and 1,3-butadiene: (left) symmetry forbidden disrotatory reaction; (right) symmetry allowed conrotatory reaction.

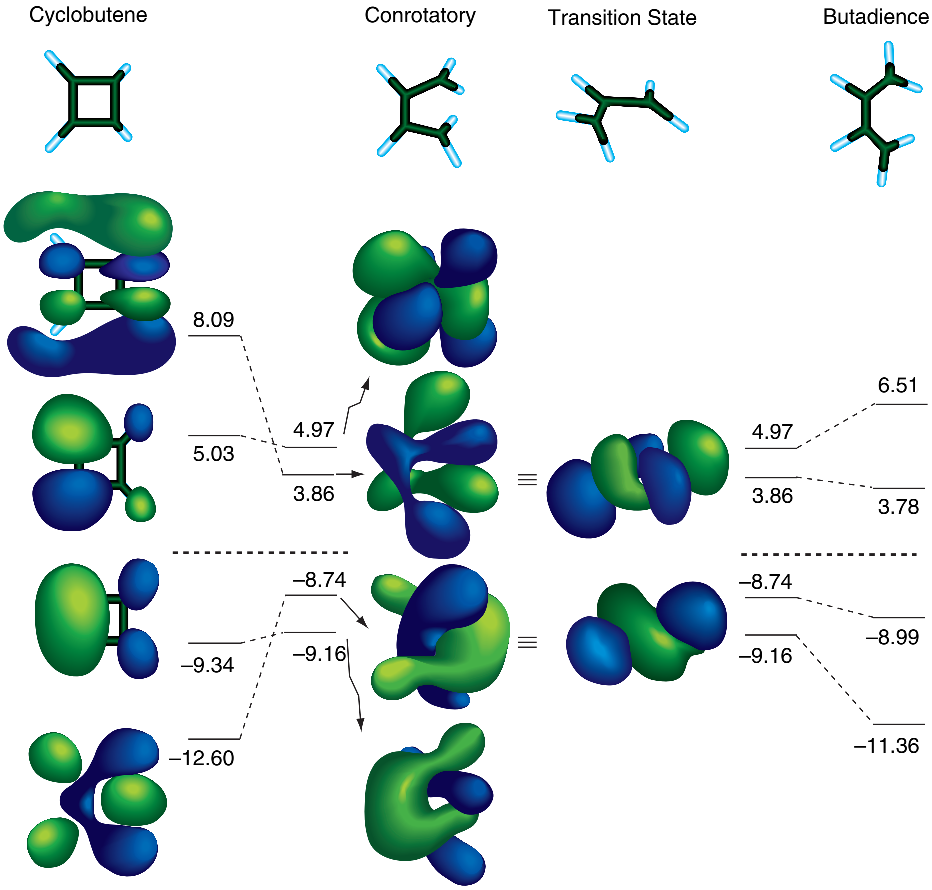
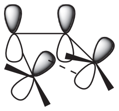

Cyclobutene
Conrotatory
Transition State
Butadience
8.09
5.03
4.97
3.86
≡
4.97
3.86
6.51
3.78
–8.74
–9.34
–9.16
–12.60
≡
–8.74
–9.16
–8.99
–11.36

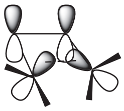
Fig. 10.25. Correlation of orbitals of cyclobutene with the conrotatory transition state and the product, 1,3-butadiene. Energies (in eV) are from HF/6-31G(d) computations. Reproduced from *J. Am. Chem. Soc.*, **125**, 5072 (2003), by permission of the American Chemical Society.

Correlation diagrams can be constructed in an analogous manner for the disrotatory and conrotatory modes for interconversion of 1,3,5-hexatriene and cyclohexadiene. They lead to the prediction that the disrotatory mode is an allowed process, whereas the conrotatory reaction is forbidden, which is in agreement with the experimental results on this reaction. Other electrocyclizations can be analyzed by the same method. Substituted derivatives of polyenes obey the orbital symmetry rules, even in cases where the substitution pattern does not correspond in symmetry to that of the orbital system. It is the symmetry of the participating orbitals, not of the molecule as a whole, that is crucial to the analysis.

Electrocyclic reactions can also be analyzed on the basis of the idea that transition states can be classified as aromatic or antiaromatic, just as is the case for ground state molecules.[172] A stabilized aromatic TS results in a low activation energy, i.e., an allowed reaction. An antiaromatic TS has a high energy barrier and corresponds to a forbidden process. The analysis of electrocyclizations by this process consists of examining the array of basis set orbitals that is present in the transition structure and classifying the system as aromatic or antiaromatic. For the butadiene-cyclobutene interconversion, the TSs for conrotatory and disrotatory interconversion are shown below. The array of orbitals represents the *basis set orbitals*, that is, the complete set of $2p$ orbitals involved in the reaction process, not the individual molecular orbitals. The tilt at C(1) and C(4) as the butadiene system rotates toward the TS is different for the disrotatory and conrotatory modes. The dashed line represents the σ bond that is being broken (or formed).



basis set orbitals
for conrotation; 4
electrons, one node
aromatic



basis set orbitals
for disrotation; 4
electron, zero nodes
antiaromatic

For the cyclobutene-butadiene TS, the conrotatory closure results in a Mobius system, whereas a disrotatory TS gives a Hückel system. The same rules of aromaticity apply as for ground state molecules. A Hückel system is aromatic when it has $4n+2$ electrons. A Mobius system is aromatic when it has $4n$ electrons. In the case of the cyclobutene-butadiene interconversion, which involves four electrons, it is the conrotatory Mobius TS that is the favored aromatic transition state.

Basis set orbital analysis of the hexatriene-cyclohexadiene system leads to the conclusion that the disrotatory process will be favored. The basis set orbitals for the conrotatory and disrotatory transition states are shown below. Here, with six electrons involved, it is the disrotatory mode (Hückel system) that gives a stabilized TS.

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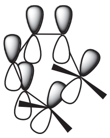
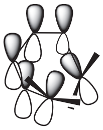
[172] H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971); M. J. S. Dewar, *Angew. Chem. Int. Ed. Engl.*, **10**, 761 (1971).



conrotation: one node Mobius system forbidden

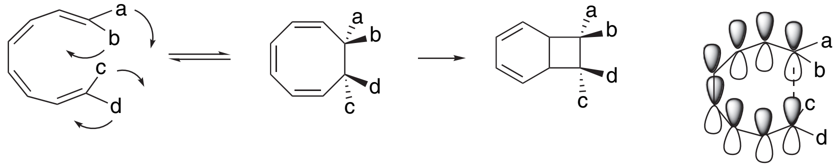


disrotation: no nodes Huckel system allowed

There have been a number of computational studies of the 1,3-butadiene-cyclobutene electrocyclization.[173] The approaches usually involve location of the minimum energy TS (as described in Section 3.2.2.3) and evaluation of its characteristics. These computational approaches confirm the preference for the conrotatory process, and DFT and CI-MO calculations can provide good estimates of E_a.[174] The aromaticity of the TS structures can also be evaluated computationally. The criteria are the same as for ground state molecules, namely energy, bond lengths, and magnetic properties.[175]

A number of theoretical analyses of the 1,3,5-hexatriene electrocyclization support the preference for the disrotatory mode. For example, MP2/CAS/6-311+G(d,p) calculations found the TSs for both modes of cyclization, as shown in Figure 10.26. The disrotatory mode is 11 kcal/mol lower in energy.[176]

For conjugated tetraenes, $n = 8$, conrotation should be preferred. The expectation that cyclization of eight π-electron systems will be conrotatory has been confirmed by study of isomeric 2,4,6,8-decatetraenes. Electrocyclic reaction occurs near room temperature. The unsubstituted system, has an E_a of 17.0 kcal/mol and ΔH of -11.2 kcal/mol.[177] At slightly higher temperatures, the cyclooctatriene system that is formed undergoes a subsequent disrotatory cyclization, establishing equilibrium with the corresponding bicyclo[4.2.0]octa-2,4-diene.[178]



MO calculations (MP2/6-31G*) on the TS confirmed that it is helical and conforms to the expected conrotatory mode.[179] This is a Mobius type TS. The NICS and magnetic properties attributed to the TS by MO calculation also indicate that it has aromatic character.[180]

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[173] N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, **107**, 2099 (1985); J. Breulet and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **106**, 1221 (1984); O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem. A*, **101**, 8378 (1997).

[174] L. O. Deng and T. Ziegler, *J. Phys. Chem.*, **99**, 612 (1995); S. Sakai, *Theochem*, **461**, 283 (1999).

[175] H. Jiao and P. v. R. Schleyer, *J. Phys. Org. Chem.*, **11**, 655 (1998).

[176] S. Sakai and S. Takane, *J. Phys. Chem. A*, **103**, 2878 (1999).

[177] G. Desimoni, G. Faita, S. Guidetti, and P. P. Righetti, *Eur. J. Org. Chem.*, 1921 (1999).

[178] R. Huisgen, A. Dahmen, and H. Huber, *Tetrahedron Lett.*, 1461 (1969); R. Huisgen, A. Dahmen, and H. Huber, *J. Am. Chem. Soc.*, **89**, 7130 (1967); A. Dahmen and R. Huisgen, *Tetrahedron Lett.*, 1465 (1969).

[179] B. E. Thomas, IV, J. D. Evanseck, and K. N. Houk, *J. Am. Chem. Soc.*, **115**, 4165 (1993); B. E. Thomas, J. D. Evanseck, and K. N. Houk, *Isr. J. Chem.*, **33**, 287 (1993).

[180] H. Jiao and P. v. R. Schleyer, *J. Chem. Soc., Perkin Trans. 2*, 407 (1994).

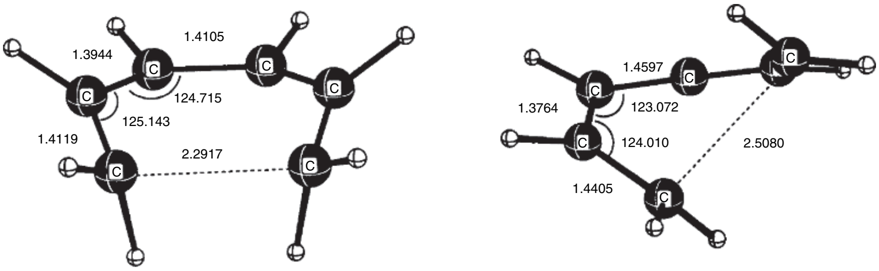


Fig. 10.26. Disrotatory (left) and conrotatory (right) transition structures for 1,3,5-hexatriene electrocyclization from MP2/CAS/6-311+G(d,p) calculations. Reproduced from *J. Phys. Chem. A*, **103**, 2878 (1999), by permission of the American Chemical Society.

We have considered three viewpoints from which thermal electrocyclic processes can be analyzed: symmetry characteristics of the frontier orbital, orbital correlation diagrams, and transition state aromaticity. All arrive at the same conclusions about the stereochemistry of electrocyclic reactions. *Reactions involving 4n + 2 electrons are disrotatory and involve a Hückel-type transition structure, whereas those involving 4n electrons are conrotatory and the orbital array are of the Mobius type*. These general principles serve to explain and correlate many specific experimental observations. The chart that follows summarizes the relationship between transition structure topology, the number of electrons, and the feasibility of the reaction.

Orbital Symmetry Rules for Electrocyclic Reactions

Electrons	Hückel (disrotatory)	Mobius (conrotatory)
2	Aromatic	Antiaromatic
4	Antiaromatic	Aromatic
6	Aromatic	Antiaromatic
8	Antiaromatic	Aromatic

Figure 10.27 summarizes the energy relationships for the four-, six-, and eight-electron systems relative to the polyenes. We see that for cyclobutene-1,3-butadiene, ring opening is favored and the E_a is 32 kcal/mol. The E_a is similar for the 1,3,5-triene cyclization (30 kcal/mol), but ring closure is favored. The E_a drops to 17.0 kcal/mol for the Z,Z-1,3,5,7-octatriene to 1,3,5-cyclooctatriene cyclization, whereas the E_a for the reverse reaction is 28.2 kcal/mol.

For cyclobutenes, there is another interesting aspect to the stereochemistry of the electrocyclic reactions. There are two stereochemically distinct possibilities for the conrotatory process. A substituent group at C(3) might move away from or toward the breaking bond.

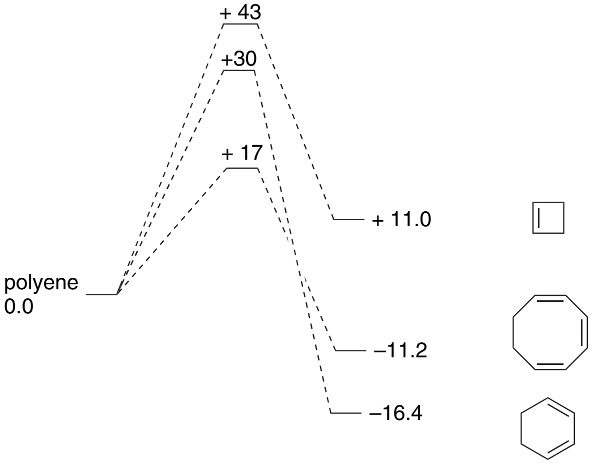
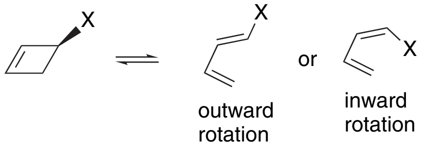
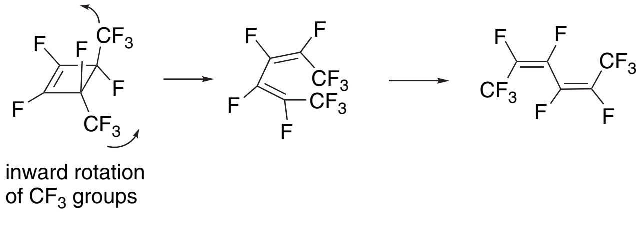


Fig. 10.27. Summary of relative E_a and ΔH relationships in kcal/mol for electrocyclic reactions of conjugated dienes, trienes, and tetraenes.



Steric factors should cause a preference for the larger group to move outward. It was observed, however, that in the case of 1,2,3,4-tetrafluoro-*trans*-3,4-*bis*-(trifluoromethyl)cyclobutene, ring opening occurred with an inward rotation of the trifluoromethyl groups, leading to the *Z*,*Z*-product.[181]



MO calculations (HF/6-21G) for the case of Y = CH=O found that the formyl group preferred to rotate inward and this was confirmed experimentally.[182] A general theoretical analysis indicates that the preference is for donor substituents to rotate outward, whereas acceptor substituents prefer to rotate inward.[183] A qualitative understanding of this stereoselectivity is based on analysis of the interaction of the substituents with the C(3)−C(4) σ bond that is breaking. The σ and σ* orbitals of the reacting bond become much closer in energy in the TS, making them better donors and acceptors, respectively, in interactions with substituents. The orbital orientations are such that donors interact with the LUMO best by outward rotation (**A**) while leading to a repulsive interaction with the HOMO by inward rotation (**B**). In contrast, acceptor substituents stabilize the HOMO in the TS best by inward rotation because a π*-substituent orbital can provide a stabilizing interaction with the C(3)−C(4) HOMO (**C**). The largest outward preferences are for strong donor groups such as O^- and NH_2, whereas CH=O and $CH{=}NH_2^+$ favor inward rotation.

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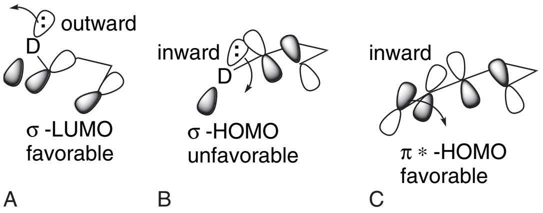
[181] W. R. Dolbier, Jr., H. Koroniak, D. J. Burton, and P. Heinze, *Tetrahedron Lett.*, **27**, 4387 (1986).

[182] K. Rudolf, D. C. Spellmeyer, and K. N. Houk, *J. Org. Chem.*, **52**, 3708 (1987).

[183] D. C. Spellmeyer and K. N. Houk, *J. Am. Chem. Soc.*, **110**, 3412 (1988); W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, and C. Sheu, *Acc. Chem. Res.*, **29**, 471 (1996).



The rotational preferences for a number of groups have been analyzed by HF/6-31G* computation of TS energies. The trends agree with the rotational preference that is observed experimentally.[184] Some of the substituents have also been examined by DFT [B3LYP/6-31G(*d*)] computations.[185] Some of the data are given in Table 10.5.

The acetyl group is calculated to have a slight preference for outward rotation. Lewis acids increase the tendency toward inward rotation by making the substituent more electrophilic.[186] In accordance with this expectation, a Lewis acid (ZnI_2) changes the ratio from 2:1 favoring outward rotation to 5:1 favoring inward rotation.

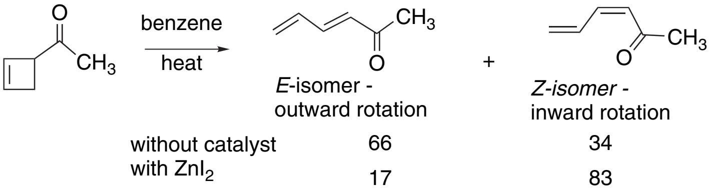


Table 10.5. Directive Effect of Substituents on Inward/Outward Conrotation in Cyclobutene Ring Opening

Donor substituent Δ^a_{in-out}			Acceptor substituent Δ^a_{in-out}		
	HF/6-31G*[a]	B3LYP/6-311G*		HF/6-31G*[b]	B3LYP/6-31G*[c]
O^-	24.4		CH=O	−4.6	−3.9
NH_2	17.5	14.7	$CH{=}NH_2^+$	−10.1	
OH	17.2		NO_2	7.3	
F	16.9		N=O	−2.6	
Cl	13.6		CF_3	2.6	2.3
CH_3	6.8	6.5	CN	4.3	

a. Δ_{in-out} is energy difference in kcal/mol between transition states for inward and outward rotation.
b. S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. M. Sheu and K. N. Houk, *J. Org. Chem.*, **61**, 2813 (1996).
c. P. S. Zhang, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 5072 (2003).

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[184] E. A. Kallel, Y. Wang, D. C. Spellmeyer, and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 6759 (1990); S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. Sheu, and K. N. Houk, *J. Org. Chem.*, **61**, 2813 (1996); W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, and C. Sheu, *Acc. Chem. Res.*, **29**, 471 (1996).

[185] P. S. Lee, X. Zhang, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 5072 (2003).

[186] S. Niwayama and K. N. Houk, *Tetrahedron Lett.*, **34**, 1251 (1993); S. Niwayama, *J. Org. Chem.*, **61**, 640 (1996).

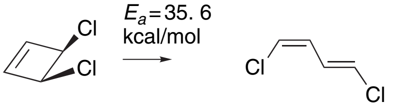
Table 10.6. Effect of Substituents on E_a for Outward or Inward Rotation.

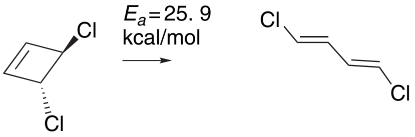
Strong outward		Moderate outward		Inward		Deactivating (both)	
O^-Li^+	−17.2	NO_2	−3.3	BH_2	−24.5	CF_3	+3.5 (out)
NH_2	−14.6	Cl	−3.0	$CH{=}N^+H_2$	−19.5	CF_3	+5.4(in)
OH	−9.3	$CH_3C{=}O$	−2.6	$C^+(OH)_2$	−18.3	NH_3^+	+0.5 (out)
F	−6.1	CN	−2.3	N=O	−7.1	NH_3^+	+8.2(in)
				CH=O	−6.9		

These substituents also have an effect on the reaction rate, which is indicated by the E_a, relative to the unsubstituted compound, as shown in Table 10.6. The strongly outwardly directing donor substituents decrease the E_a more for outward rotation, whereas the inward-directing groups preferentially stabilize the TS for inward rotation. A few substituents, e.g., CF_3 and NH_3^+, are destabilizing toward both types of TS.

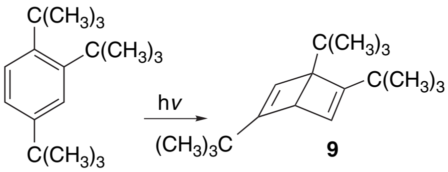
10.5.3. Examples of Electrocyclic Reactions

In addition to the 3,4-dimethylcyclobutene case discussed in Section 10.5.1, there are many other examples of electrocyclic ring opening of cyclobutanes, and *cis*- and *trans*-3,4-dichlorocyclobutene have been examined carefully. The products are those expected for conrotation.[187] In the case of the *trans*-isomer, the product results from outward rotation of both chlorine atoms, in agreement with the calculated substituent effect. The *cis*-isomer, in which one of the chlorines must rotate inward, has a substantially higher E_a.





A particularly interesting case involves the bicyclo[2.2.0]hexa-2,5-diene system. This ring system is a valence isomer of the benzene ring and is often referred to as *Dewar benzene*. Attempts prior to 1960 to prepare Dewar benzene derivatives failed, and the pessimistic opinion was that such efforts would be fruitless because Dewar benzene would be so unstable as to immediately revert to benzene. Then in 1962, van Tamelen and Pappas isolated a stable Dewar benzene derivative **9** by photolysis of 1,2,4-tri-(*t*-butyl)benzene.[188] The compound was reasonably stable, reverting to the aromatic starting material only on heating. Part of the stability of this particular derivative can be attributed to steric factors. The *t*-butyl groups are farther apart in the Dewar benzene structure than in the aromatic structure.



9

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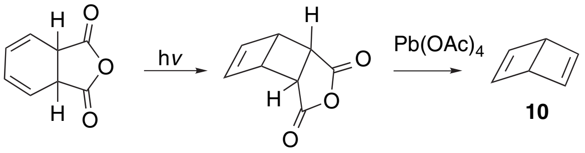
[187] R. Criegee, D. Seebach, R. E. Winter, B. Boerretzen, and H. Brune, *Chem. Ber.*, **98**, 2339 (1963); G. Maier and A. Bothur, *Eur. J. Org. Chem.*, 2063 (1998).

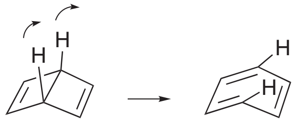
[188] E. E. van Tamelen. S. P. Pappas, and K. L. Kirk, *J. Am. Chem. Soc.*, **93**, 6092 (1971); this paper contains references to the initial work and describes subsequent studies.

The unsubstituted Dewar benzene **10** was successfully prepared in 1963.



10

This compound is less stable than **9** and reverts to benzene with a half-life of about 2 days at 25°C, with $\Delta H^{\ddagger} = 23$ kcal/mol.[189] Nevertheless, the relative kinetic stability of Dewar benzene is surprisingly high when one considers that its conversion to benzene is exothermic by 71 kcal/mol. Furthermore, the central bond is not only strained but also *bis*-allylic. The kinetic stability of Dewar benzene is related to the orbital symmetry requirements for concerted electrocyclic transformations. The concerted thermal pathway would be conrotatory, since the reaction is the ring opening of a cyclobutene and therefore leads not to benzene, but to a highly strained *Z*,*Z*,*E*-cyclohexatriene. A disrotatory process, which would lead directly to benzene, is forbidden.



There have been several computational studies of the process.[190] CAS-SCF/6-311G++ calculations found a TS that leads from Dewar benzene to benzene without the intermediacy of the *Z*,*Z*,*E*-isomer. Both a conrotatory and a disrotatory TS were found, as shown in Figure 10.28. The conrotatory TS is calculated to be about 22.9 kcal/mol above Dewar benzene and 99.3 kcal/mol less stable than benzene.[191] Thus, although a route for ring opening exists, the energy barrier is sufficient to permit the isolation of Dewar benzene.

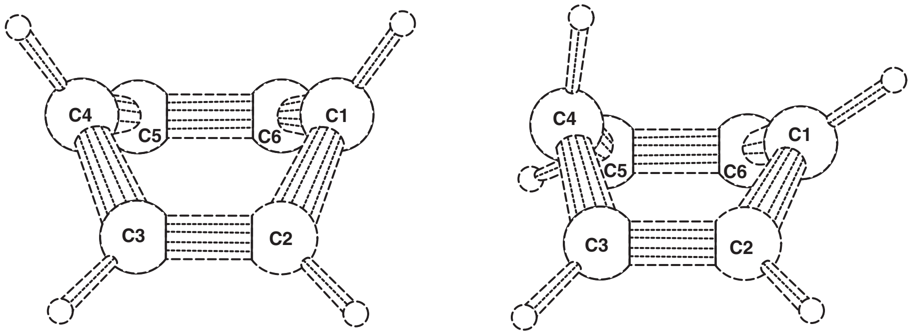


Fig. 10.28. Disrotatory (left) and conrotatory (right) transition structures for conversion of *cis*-bicyclo[2.2.0]hexa-2,5-diene (Dewar benzene) to benzene. The conrotatory TS is 6.6 kcal/mol lower in energy than the disrotatory TS. Reproduced from *Theochem*, **492**, 217 (1999), by permission of Elsevier.

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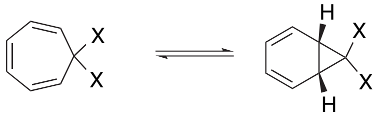
[189] M. J. Goldstein and R. S. Leight, *J. Am. Chem. Soc.*, **99**, 8112 (1977).

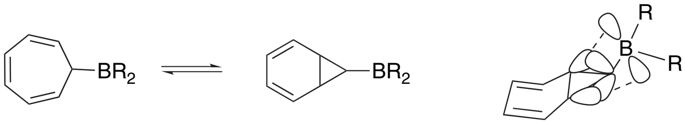
[190] R. P. Johnson and K. J. Daoust, *J. Am. Chem. Soc.*, **118**, 7381 (1996).

[191] R. W. A. Havenith, L. W. Jenneskens, and J. H. van Lenthe, *Theochem*, **492**, 217 (1999).

There are numerous examples of interconversion of 1,3,5-trienes and 1,3-cyclohexadiene systems by the electrocyclic mechanism.[192] An especially interesting case of hexatriene-cyclohexadiene interconversion is the equilibrium between cycloheptatrienes and bicyclo[4.1.0]hepta-2,4-dienes.[193]



The energy requirement for this electrocyclic transformation is so low that the process occurs at room temperature, as determined by NMR measurements. Low-temperature NMR measurements give a E_a value of about 7 kcal/mol when R = CO_2CH_3.[194] This transformation is an example of *valence tautomerism*, a rapid process involving only reorganization of bonding electrons. The reason the reaction is much more rapid than electrocyclization of acyclic trienes is that the ring holds the reacting termini together, reducing the negative entropy of activation. In contrast to the ring opening of Dewar benzene, disrotatory opening of bicyclo[4.1.0]hepta-2,4-diene involves six electrons, is allowed by orbital symmetry rules, and is easily accommodated by the ring geometry. For unsubstituted bicyclo[4.1.0]hepta-2,4-diene the equilibrium constant for ring closure is small, about 3×10^{-3} at 100°C. Alkyl groups do not have much of an effect on the position of equilibrium but EWGs such as cyano and trifluoromethyl shift the equilibrium more in favor of the bicyclic ring.[195] A boron derivative has been studied both experimentally and computationally.[196] The experimental $\Delta G^{\ddagger}$ is 8.2 kcal/mol. The *exo*-bicyclic structure is stabilized by interaction of the cyclopropyl σ orbitals with the empty boron *p* orbital. This interaction is analogous to the one that stabilizes the cyclopropylcarbinyl cation (see p. 427)



Synthetic applications of electrocyclic reactions are normally designed to take advantage of their stereospecificity, especially for the construction of *Z*-double bonds. Scheme 10.8. shows some examples. Entries 1 and 2 illustrate the inward rotation of formyl groups in cyclobutenes to generate *Z*-enals. The product in Entry 3 results from outward rotation of the substituents. Although they are EWGs, their reduced electrophilicity and enhanced steric demands favor outward rotation. Entries 4 to 6 illustrate the formation of cyclohexadienes by triene electrocyclization. Note that in Entry 6, there has also been a hydrogen migration, presumably by a 1,5-hydrogen shift (see Section 10.6).

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[192] V. A. Bakulev, *Russ. Chem. Rev.*, **64**, 99 (1995).

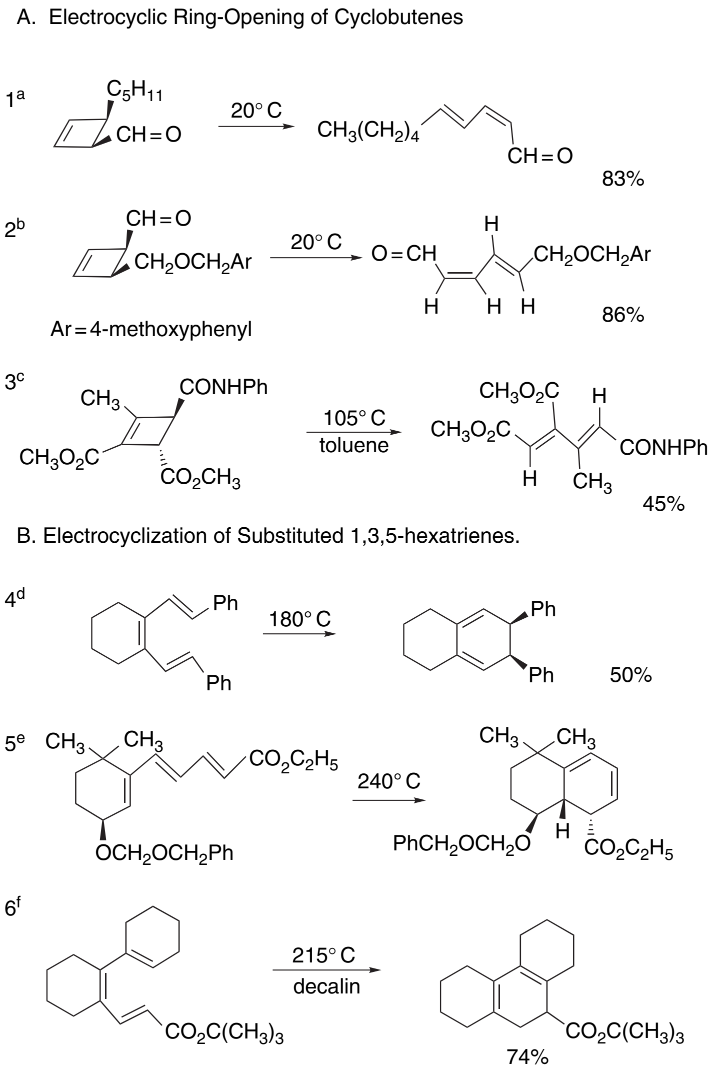
[193] G. Maier, *Angew. Chem. Int. Ed. Engl.*, **6**, 402 (1967).

[194] M. Gorlitz and H. Gunther, *Tetrahedron*, **25**, 4467 (1969).

[195] P. Warner and S.-L. Lu, *J. Am. Chem. Soc.*, **95**, 5099 (1973); P. M. Warner and S.-L. Lu, *J. Am. Chem. Soc.*, **102**, 331 (1980); K. Takeuchi, H. Fujimoto, and K. Okamoto, *Tetrahedron Lett.*, **22**, 4981 (1981); T.-H. Tang, C. S. Q. Lew, Y.-P.Cui, B. Capon, and I. G. Csizmadia, *Theochem*, **305**, 49 (1994); Y. Guzel, E. Saripinar, and L. Yildirim, *Monatsh. Chem.*, **123**, 513 (1996).

[196] I. D. Gridnev, O. L. Tok, N. A. Gridneva, Y. N. Bubnov, and P. R. Schreiner, *J. Am. Chem. Soc.*, **120**, 1034 (1998).

Scheme 10.8. Electrocyclic Reactions


A. Electrocyclic Ring-Opening of Cyclobutenes
1a
C5H11
CH=O
20° C
CH3(CH2)4
CH=O
83%
2b
CH=O
CH2OCH2Ar
20° C
O=CH
H
CH2OCH2Ar
H
H H
86%
Ar = 4-methoxyphenyl
3c
CH3
CONHPh
CH3O2C
CO2CH3
105° C
toluene
CH3O2C
H
CH3O2C
CONHPh
H
CH3
45%
B. Electrocyclization of Substituted 1,3,5-hexatrienes.
4d
Ph
Ph
180° C
Ph
Ph
50%
5e
CH3
CH3
CO2C2H5
OCH2OCH2Ph
240° C
CH3
CH3
PhCH2OCH2O
H
CO2C2H5
6f
CO2C(CH3)3
215° C
decalin
CO2C(CH3)3
74%

---

a. K. J. Hodgetts, S. T. Saengchantara, C. J. Wallis, and T. W. Wallace, *Tetrahedron Lett.*, **34**, 6321 (1993).

b. F. Binns, R. Hayes, S. Ingham, S. T. Saengchantara, R. W. Turner, and T. W. Wallace, *Tetrahedron*, **48**, 515 (1992).

c. I. Yavari and S. Asghari, *Tetrahedron*, **55**, 11853 (1999).

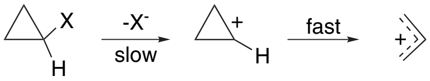
d. K. Voigt, P. von Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser, and A. de Meijere, *Eur. J. Org. Chem.*, 1521 (2001).

e. H. Venkataraman and J. K. Cha, *J. Org. Chem.*, **54**, 2505 (1989).

f. P. von Zezschwitz, F. Petry, and A. de Meijere, *Chem. Eur. J.*, **7**, 4035 (2001).

10.5.4. Electrocyclic Reactions of Charged Species

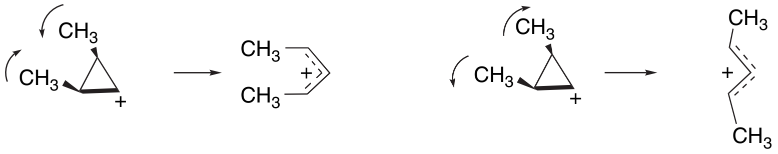
The Woodward-Hoffmann orbital symmetry rules are not limited in application to the neutral polyene systems that have been discussed up to this point. They also apply to charged systems, just as the Hückel aromaticity rule can be applied to charged ring systems. The conversion of a cyclopropyl cation to an allyl cation is the simplest possible case of an electrocyclic process because it involves only two π electrons.[197] Owing to the strain imposed by the cyclopropyl ring, cyclopropyl cations do not form easily, and cyclopropyl halides and sulfonates are quite unreactive under ordinary solvolytic conditions. For example, solvolysis of cyclopropyl tosylate in acetic acid requires a temperature of 180°C. The product is allyl acetate rather than cyclopropyl acetate.[198] This transformation might occur by formation of the cyclopropyl cation, followed by ring opening to the allyl cation or (see below) the reaction might occur in a single step.



Formation of allylic products is characteristic of solvolytic reaction of other cyclopropyl halides and sulfonates. Similarly, diazotization of cyclopropylamine in aqueous solution gives allyl alcohol.[199]

The ring opening of a cyclopropyl cation is an electrocyclic process of the $4n+2$ type, where n equals zero, and should therefore be a disrotatory process. CCSD(T)/6-311G(2*d*) and B3LYP/6-31G(2*d*) computations on the reaction indicate that the cyclopropyl cation is not a stable intermediate and that there is no barrier to electrocyclic ring opening.[200] This result implies that the ring opening occurs as a concerted process in conjunction with rupture of the bond to the leaving group.

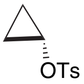
As with cyclobutenes, there are two possible directions for the allowed disrotation in substituted cyclopropyl cations. For a *cis*-2,3-dimethylcyclopropyl cation, for example, two different disrotatory modes are possible, leading to structurally distinct allyl cations.



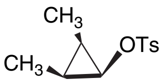
inward rotation U-shaped cation

outward rotation W-shaped cation

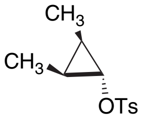
The W-shaped allylic cation should be formed in preference to the sterically less favorable U-shaped cation. This issue was investigated by comparing the rates of solvolysis of the cyclopropyl tosylates **11** to **13**.



11



12



13

	11	12	13
Relative Rate	1	4	41,000

---

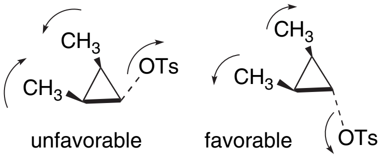
[197] P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schollkopf, J. Paust, and K. Fellenberger, *J. Am. Chem. Soc.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer,*J. Am. Chem. Soc.*, **94**, 133 (1972).

[198] J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

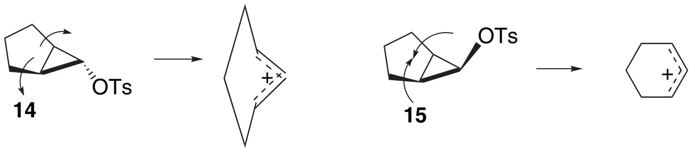
[199] P. Lipp, J. Buchkremer, and H. Seeles, *Justus Liebigs Ann. Chem.*, **499**, 1 (1932); E. J. Corey and R. F. Atkinson,*J. Org. Chem.*, **29**, 3703 (1964).

[200] P. A. Arnold and B. K. Carpenter, *Chem. Phys. Lett.*, **328**, 90 (2000).

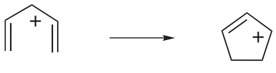
Some very significant conclusions can be drawn from the data. If formation of the cyclopropyl cation were the rate-determining step, **12** would be more reactive than **13** because the steric interaction between the tosylate leaving group and the methyl substituents in **12** is relieved as ionization occurs. Since **12** is 10,000 times less reactive than **13**, some other factor must be determining the relative rates of reaction and it is doubtful that rate-limiting ionization to a cyclopropyl cation is occurring. The results can be explained, as proposed by DePuy,[201] if the ionization and ring opening are part of a single, concerted process. In such a process, the ionization is assisted by the electrons in the breaking C(2)−C(3) bond, which provide maximum assistance when positioned toward the back side of the leaving group. This, in turn, requires that the substituents *anti* to the leaving group rotate outward as the ionization proceeds. This concerted process explains why **12** reacts more slowly than **13**. In **12** such a rotation moves the methyl groups together, resulting in increased steric interaction and the formation of the U-shaped allylic anion. In **13**, the methyl groups move away from one another and form the W-shaped allylic ion.



This interpretation is supported by results on the acetolysis of the bicyclic tosylates **14** and **15**. With **14**, after 3 months in acetic acid at 150°C, 90% of the starting material is recovered. This means that both ionization to a cyclopropyl cation and a concerted ring opening are extremely slow. The preferred disrotatory ring-opening process would lead to an impossibly strained structure, the *trans*-cyclohexenyl cation. In contrast, the stereoisomer **15** reacts at least 2 × 10^6 more rapidly, since it can proceed to a stable *cis*-cyclohexenyl cation.[197]



Pentadienyl cations can undergo electrocyclization to cyclopentenyl cations. As this is a four π-electron system, it should occur by conrotation. Based on gas phase ion stability data, the reaction is exothermic by 18 kcal/mol.[202]



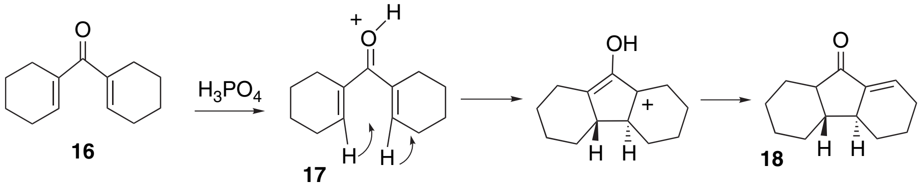
This cyclization has been employed synthetically and is known as the *Nazarov reaction*.[203] An example of preferred conrotatory cyclization of four π-electron cation systems can be found in the acid-catalyzed cyclization of the dienone **16**, which proceeds through the 3-hydroxypentadienyl cation **17.** The final product **18** arises from ketonization and deprotonation, and the stereochemistry is that expected for a conrotatory process.[204]

---

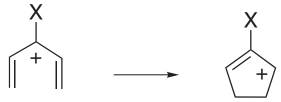
[201] C. H. DePuy, *Acc. Chem. Res.*, **1**, 33 (1968).

[202] F. P. Lossing and J. L. Holmes, *J. Am. Chem. Soc.*, **106**, 6917 (1984).

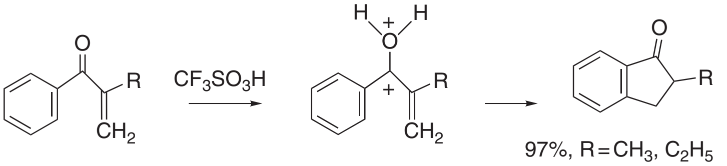
[203] K. L. Habermas, S. E. Denmark, and T. K. Jones, *Org. React.*, **45**, 1 (1994).



Although most synthetic examples of this cyclization have involved protonation of divinyl ketones to give 3-hydroxy-1,4-pentadienyl cations, computational studies suggest that the cyclization would occur even more readily with alternative substituents at C(3).[205] For example, the parent ($X = H$) and the boron derivative ($X = BH_2$) are calculated to be more reactive.

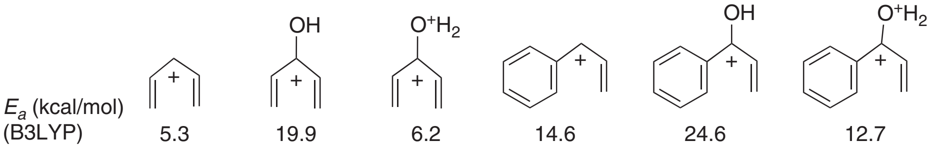


Experimental support for this idea comes from the study of cyclization of 1-arylprop-2-en-1-ones to 1-indanones by strong acid.



97%, $R = CH_3, C_2H_5$ Ref. 206

The acidity dependence of this reaction suggests that it passes through the *diprotonated intermediate* shown. B3LYP/6-31G* and MP2/6-31G* calculations find the E_a to be considerably smaller for the dication than for the corresponding monocation.



There are also examples of electrocyclic processes involving anionic species. Since the pentadienyl anion is a six π-electron system, thermal cyclization to a cyclopentenyl anion should be disrotatory. Examples of this electrocyclic reaction are rare. NMR studies of pentadienyl anions indicate that they are stable and do not tend to cyclize.[207] Cyclooctadienyllithium provides an example where cyclization does occur, with the first-order rate constant being 8.7×10^{-3} min^{-1}. The stereochemistry of the ring closure is consistent with the expected disrotatory nature of the reaction.

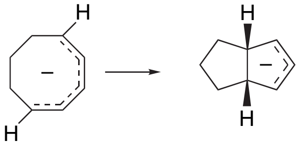
---

[204] R. B. Woodward, in *Aromaticity*, Chemical Society Special Publication No. 21, 217 (1969).

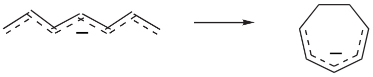
[205] D. A. Smith and C. W. Ulmen, *J. Org. Chem.*, **62**, 5110 (1997).

[206] T. Suzuki, T. Ohwada, and K. Shudo, *J. Am. Chem. Soc.*, **119**, 6774 (1997).

[207] R. B. Bates, D. W. Gosselink, and J. A Kaczynski, *Tetrahedron Lett.*, 199, 205 (1967); R. B. Bates and D. A. McCombs,*Tetrahedron Lett.*, 977 (1969); R. B. Bates, S. Brenner, C. M. Cole, E. W. Davidson, G. D. Forsythe, D. A. McCombs, and A. S. Roth, *J. Am. Chem. Soc.*, **95**, 926 (1973).

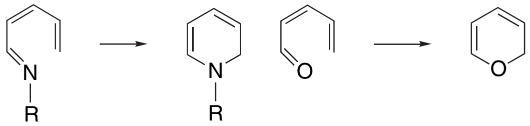


In contrast to pentadienyl anions, heptatrienyl anions cyclize readily to cycloheptadienyl anions.[208] The transformation of heptatrienyl anion to cycloheptadienyl anion proceeds with a half-life of 13 min at −13°C. The Woodward-Hoffmann rules predict that this would be a conrotatory closure.[209]



10.5.5. Electrocyclization of Heteroatomic Trienes

Electrocyclization can also occur when heteroatoms are incorporated into diene, triene, or polyene systems. Most attention has focused on 1-azatriene and 1-oxatrienes, which lead to dihydropyridines and pyrans, respectively.



Comparison of the energy requirements of these reactions with the all-carbon system indicates reduced barriers for the aza and oxa systems, but because of the loss of the C=O bond, the 1-oxahexatriene electrocyclization is slightly endothermic.[210] Marvell and co-workers estimated the acceleration as being a factor of 10^5 to 10^6.[211] This result suggests a change in mechanism for the heteroatom cases.

A computational study has examined these effects.[212] The reaction energy comparisons are given in Figure 10.29 and the transition structure for 1-aza-1,3,5-hexatriene is shown in Figure 10.30. NPA analysis indicates that an unshared pair of the heteroatom participates in the reaction, which leads to a strong preference for outward rotation of the N−H or N−R group in the azatrienes. There is also a change of the TS geometry, relative to 1,3,5-hexatriene. Whereas the C(2)X(1)C(6)C(5) dihedral angle is nearly 0° for X=C, it increases to 30°–40° for X=O or N. It is the involvement of unshared electrons on oxygen and nitrogen that lowers the energy barrier.

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[208] E. A. Zuech, D. L. Crain, and R. F. Kleinschmidt, *J. Org. Chem.*, **33**, 771 (1968); R. B. Bates, W. H. Deines, D. A. McCombs, and D. E. Potter, *J. Am. Chem. Soc.*, **91**, 4608 (1969).

[209] S. W. Staley, in *Pericyclic Reactions*, Vol. 1, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, Chap. 4.

[210] J. Rodriguez-Otero, *J. Org. Chem.*, **64**, 6842 (1999).

[211] E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *J. Am. Chem. Soc.*, **88**, 619 (1966).

[212] M. J. Walker, B. N. Hietbrink, B. E. Thomas, IV, K. Nakamura, E. A. Kallel, and K. N. Houk, *J. Org. Chem.*, **66**, 6669 (2001).

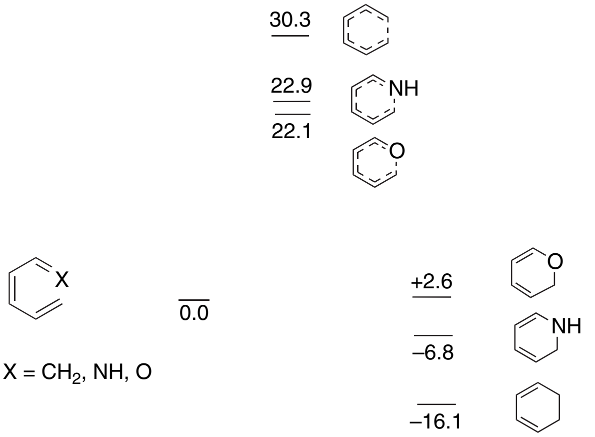

Fig. 10.29. Energy comparisons for electrocyclization of 1-aza- and 1-oxa-1,3,5-hexatriene to 1,3,5-hexatriene in kcal/mol.

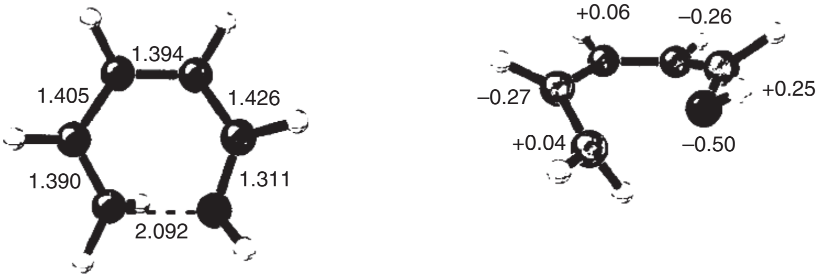

Fig. 10.30. Bond lengths and CHELPG charges of transition structure for electrocyclization of 1-aza-1,3,5-hexatriene. Reproduced from *J. Org. Chem.*, **66**, 6669 (2001) by permission of the American Chemical Society.

10.6. Sigmatropic Rearrangements

10.6.1. Overview of Sigmatropic Rearrangements

Sigmatropic rearrangements constitute another important class of concerted pericyclic reactions governed by orbital symmetry.[213] They involve a reorganization of electrons during which a group attached by a σ bond migrates to the other terminus of a conjugated π-electron system, with a simultaneous shift of the π electrons. Sigmatropic rearrangements are described by stating the relationship between the reacting centers in the migrating fragment and the π system. The order $[i, j]$ specifies the number of atoms in the migrating fragment and in the π system, respectively. As with other concerted reactions, the topology of the interacting orbitals determines the facility and the stereochemistry of each sigmatropic rearrangement. There are two topologically distinct processes by which a sigmatropic migration can occur. If the migrating group remains associated with the same face of the conjugated π system throughout the reaction, the migration is termed *suprafacial*. In the alternative mode, called *antarafacial*, the migrating group moves to the opposite face of the π system during the course of the migration. There is another important element of stereochemistry for the migration of alkyl groups. The migrating group can retain its original configuration (retention) or undergo inversion. The stereochemical features and the number of electrons involved determine whether a reaction is allowed or forbidden.

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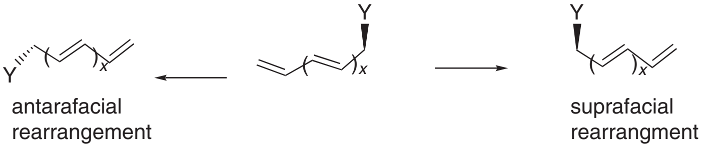
[213] R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 2511 (1965).



The generalized orbital symmetry selection rules[213] are given below. The bases of these rules are discussed for each of the major classes of sigmatropic rearrangements.

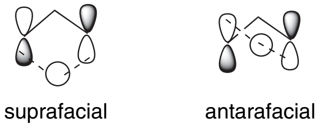
Generalized Orbital Symmetry Rules for Sigmatropic Processes

	Supra/ Retention	Supra/ Inversion	Antara/ Retention	Antara/ Inversion
Order [1, *j*] 1 + *j*				
4*n*	Forbidden	Allowed	Allowed	Forbidden
4*n* + 2	Allowed	Forbidden	Forbidden	Allowed
	Supra/Supra	Supra/Antara	Antara/Antara	
Order [*i*, *j*] *i* + *j*				
4*n*	Forbidden	Allowed	Forbidden	
4*n* + 2	Allowed	Forbidden	Allowed	

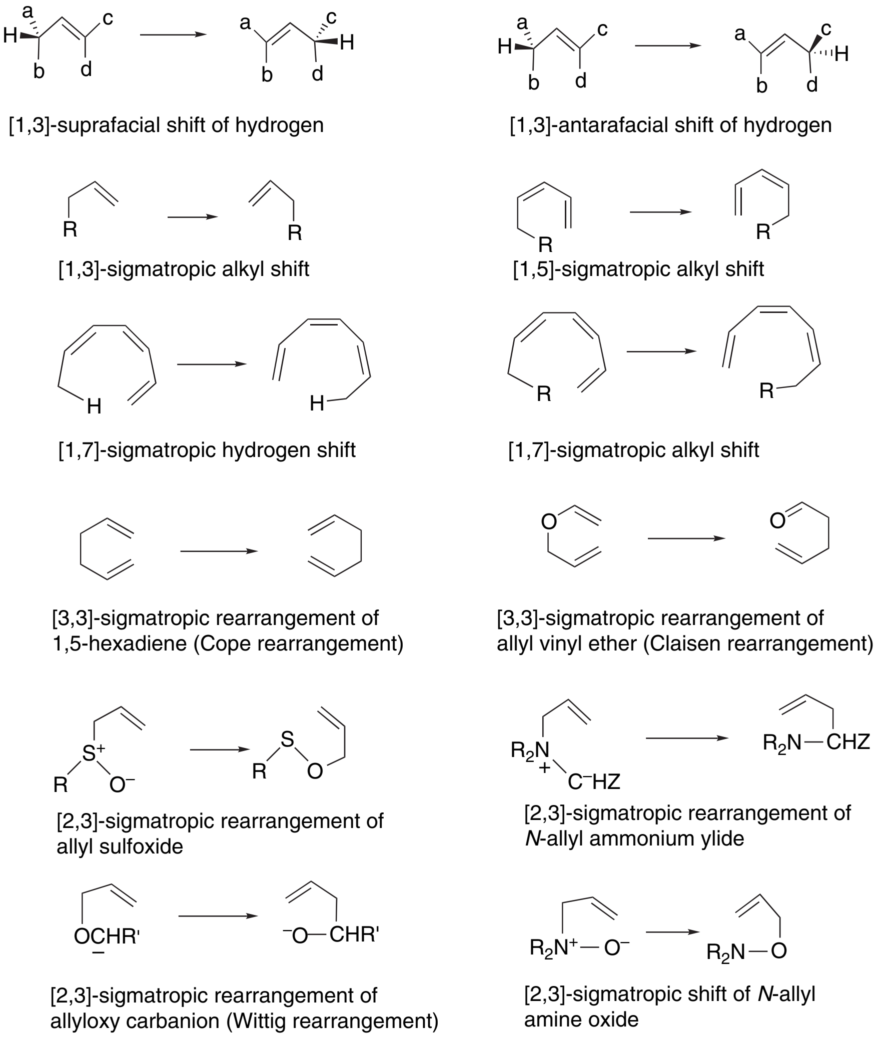
Several important types of sigmatropic reactions are listed in Scheme 10.9. We first discuss shifts of hydrogen and alkyl groups, concentrating on [1,3]-, [1,5]-, and [1,7]-shifts. There is also a large and synthetically important group of [3,3]-sigmatropic shifts, which include the Cope and Claisen rearrangements that are dealt with in Section 10.6.3. Finally, [2,3]-sigmatropic shifts are considered in Section 10.6.4.

10.6.2. [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts of Hydrogen and Alkyl Groups

The orbital symmetry requirements of sigmatropic reactions can be analyzed by considering the interactions between the frontier orbitals of the π system and those of the migrating fragment. The simplest case, 1,3-sigmatropic shift of a hydrogen is illustrated in the first entry in Scheme 10.9. An FMO analysis of this process treats the system as a hydrogen atom interacting with an allyl radical. The frontier orbitals are the hydrogen 1*s* and the allyl ψ_2 orbitals. These interactions are depicted below for both the suprafacial and antarafacial modes.



Scheme 10.9. Examples of Sigmatropic Rearrangements



[1,3]-suprafacial shift of hydrogen

[1,3]-antarafacial shift of hydrogen

[1,3]-sigmatropic alkyl shift

[1,5]-sigmatropic alkyl shift

[1,7]-sigmatropic hydrogen shift

[1,7]-sigmatropic alkyl shift

[3,3]-sigmatropic rearrangement of 1,5-hexadiene (Cope rearrangement)

[3,3]-sigmatropic rearrangement of allyl vinyl ether (Claisen rearrangement)

[2,3]-sigmatropic rearrangement of allyl sulfoxide

[2,3]-sigmatropic rearrangement of *N*-allyl ammonium ylide

[2,3]-sigmatropic rearrangement of allyloxy carbanion (Wittig rearrangement)

[2,3]-sigmatropic shift of *N*-allyl amine oxide

A bonding interaction can be maintained only in the antarafacial mode. The 1,3-suprafacial shift of hydrogen is therefore forbidden by orbital symmetry considerations. The antarafacial process is symmetry allowed, but it involves such a contorted geometry that this shift, too, would be expected to be energetically difficult. As a result, orbital symmetry considerations indicate that concerted [1,3]-shifts of hydrogen are unlikely processes. Computational studies also find that the 1,3-shift of hydrogen should be antarafacial, but in agreement with expectations based on molecular geometry, the TS that is found is so energetic that it is close to a stepwise bond dissociation process.[214,215]

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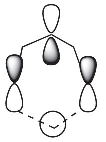
[214] B. A. Hess, Jr., L. J. Schaad, and J. Pancir, *J. Am. Chem. Soc.*, **107**, 149 (1985).

[215] F. Bernardi, M. A. Robb, H. B. Schlegel, and G. Tonachini, *J. Am. Chem. Soc.*, **106**, 1198 (1984).

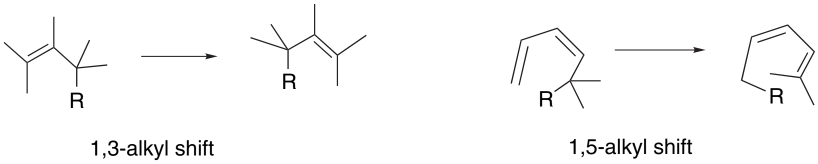
Orbital symmetry analysis of the 1,5-sigmatropic shift of hydrogen leads to the opposite conclusion. The relevant frontier orbitals in this case are the hydrogen 1*s* and ψ_3 of the pentadienyl radical. The suprafacial mode is allowed, whereas the antarafacial mode is forbidden. The suprafacial shift corresponds to a geometrically favorable six-membered ring.



allowed [1,5]-suprafacial
hydrogen shift in 1,3-pentadiene

An alternative analysis of sigmatropic reactions involves drawing the basis set atomic orbitals and classifying the resulting system as Hückel or Mobius in character. When this classification has been done, the electrons involved in the process are counted to determine if the TS is aromatic or antiaromatic. The conclusions reached are the same as for the frontier orbital approach. The suprafacial 1,3-shift of hydrogen is forbidden but the suprafacial 1,5-shift is allowed. Analysis of a 1,7-shift of hydrogen shows that the antarafacial shift is allowed. This analysis is illustrated in Figure 10.31. These conclusions based on orbital symmetry considerations are supported by HF/6-31G* calculations, which conclude that 1,5-shifts should be suprafacial, whereas 1,7-shifts should be antarafacial.[214]

Sigmatropic migration involving alkyl group shifts can also occur.


R
R
R
R
1,3-alkyl shift
1,5-alkyl shift

When an alkyl group migrates, there is an additional stereochemical feature to consider. The shift can occur with retention or inversion at the migrating center. The analysis of sigmatropic shifts of alkyl groups is illustrated in Figure 10.32. The allowed processes include the suprafacial 1,3-shift with inversion and the suprafacial 1,5-shift with retention.

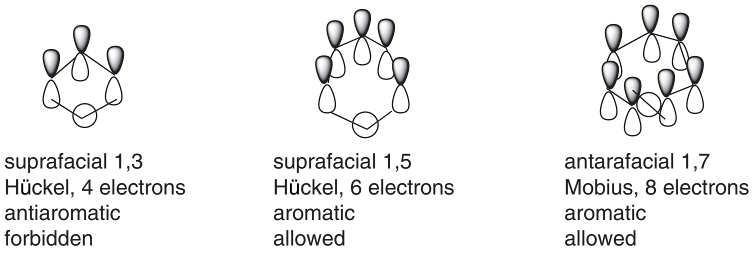
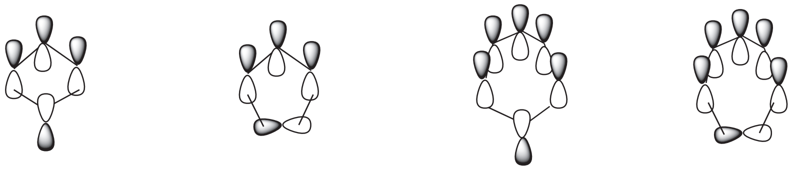

suprafacial 1,3
Hückel, 4 electrons
antiaromatic
forbidden
suprafacial 1,5
Hückel, 6 electrons
aromatic
allowed
antarafacial 1,7
Mobius, 8 electrons
aromatic
allowed

Fig. 10.31. Classification of sigmatropic hydrogen shifts with respect to basis set orbitals.



1,3-suprafacial
retention
Hückel, 4 electrons
antiaromatic
forbidden

1,3-suprafacial
inversion
Mobius, 4 electrons
aromatic
allowed

1,5-suprafacial
retention
Hückel, 6 electrons
aromatic
allowed

1,5-suprafacial
inversion
Mobius, 6 electrons
antiaromatic
forbidden

Fig. 10.32. Classification of sigmatropic shifts of alkyl groups with respect to basis set orbitals.

10.6.2.1. Computational Characterization of Transition Structures for [1,3]-, [1,5]-, and [1,7]-Sigmatropic Shifts There have been a number of computational studies aimed at providing information about the TSs of the sigmatropic rearrangements. Chamorro and co-workers characterized the TS for prototypical [1,3]-sigmatropic shifts of hydrogen and methyl.[216] The 1,3-hydrogen shift is an antarafacial process, whereas the methyl migration is a suprafacial process that occurs with inversion at the alkyl group. The corresponding nuclear positions are depicted in Figure 10.33.

Computational studies on [1,5]-sigmatropic hydrogen shifts are also in agreement with the qualitative predictions based on orbital symmetry relationships. The TS shows aromatic character. Activation energies are calculated[217] to be in the range 35–37 kcal/mol, in good agreement with the experimental value of 36.3.[218]

Lee and co-workers compared the activation barrier and TS structure for suprafacial migration of BH_2, CH_3, and NH_2 at several levels of theory.[219]

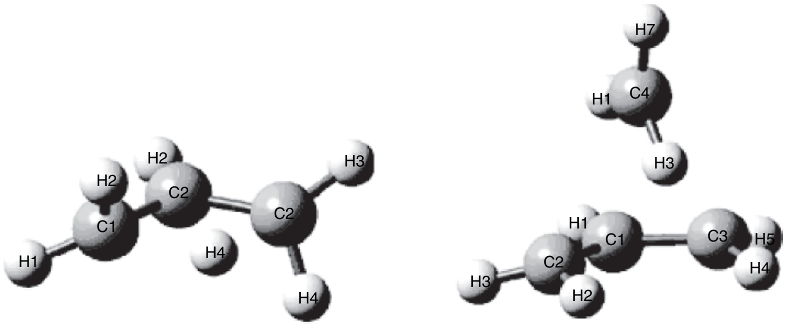


Fig. 10.33. Nuclear positions and for antarafacial [1,3]-sigmatropic migration of hydrogen and for suprafacial [1,3]-sigmatropic migration of methyl with inversion (B3LYP/6-311++G(*d*,*p*)), Reproduced from *J. Phys. Chem. A*, **106**, 11533 (2002), by permission of the American Chemical Society.

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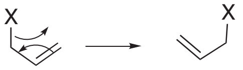
[216] E. Chamorro, J. C. Santos, B. Gomez, R. Contreras, and P. Fuentealba, *J. Phys. Chem. A*, **106**, 11533 (2002).

[217] I. Alkorta and J. Elguero, *J. Chem. Soc., Perkin Trans.*, **2**, 2497 (1998); B. S. Jursic, *Theochem*, **423**, 189 (1998); N. J. Saettel and O. Wiest, *J. Org. Chem.*, **65**, 2331 (2000).

[218] W. R. Roth and J. Konig, *Liebigs Ann. Chem.*, **699**, 24 (1966).

[219] J. Y. Choi, C. K. Kim, C. K. Kim, and I. Lee, *J. Phys. Chem. A*, **106**, 5709 (2002).



X	BH_2	CH_3	NH_2
B3LYP/6-311++G**	3.72	81.12	69.20
G3	1.52	73.93	67.80
CBS-APNO	0.46	75.82	68.90

The barrier for boron migration is very low, but for $X = CH_3$ and NH_2, the barriers are close to the bond dissociation energies, indicating that the reaction would be stepwise. No antarafacial pathways were found. The suprafacial migration is facile for BH_2 because the empty *p* orbital is available. Figure 10.34 shows the lowest-energy (QCISD/6-311G**) TS and the NPA bond orders associated with them. We see that the vacant *p* orbital allows for continuous bonding during the migration of BH_2, whereas the absence of such an orbital for CH_3 and NH_2 results in electronic repulsion and a much higher-energy TS. Note the much greater bond lengths of the allyl fragment. In the case of $X = CH_3$ and NH_2, these bonds are close to single-bond lengths, indicating substantial loss of the π bond. It is also worth noting that the allylborane system is isoelectronic with the nonclassical $C_4H_7^+$ carbocation (see p. 453). The computed TS for BH_2 migration corresponds in structure to the bicyclobutenyl carbocation.

10.6.2.2. Examples of Sigmatropic Shifts of Hydrogen and Alkyl Groups With the generalized selection rules as a unifying theoretical framework (see p. 912), we can consider specific examples of sigmatropic rearrangements. In accordance with the orbital symmetry concepts, there are many examples of sigmatropic [1,5]-hydrogen migrations in molecules that incorporate a pentadienyl fragment. The activation energies for such reactions are usually in the vicinity of 35 kcal/mol, so the reactions require moderately elevated temperatures.[220] Two examples are given below. The first rearrangement is detected by migration of the isotopic label. The second results in transformation to a more stable diene.

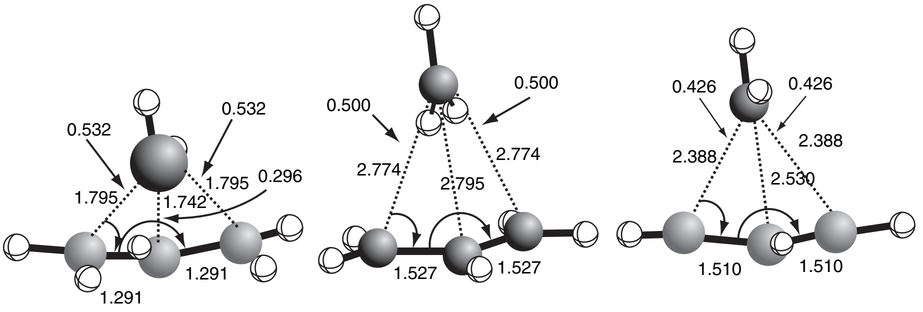


Fig. 10.34. Transition structures for suprafacial 1,3-migrations of BH_2 (left), CH_3 (center), and NH_2 (right) at the QCISD/6-311+G** level. Bond distances and NPA bond orders are shown. Adapted from *J. Phys. Chem. A*, **106**, 5709 (2002), by permission of the American Chemical Society.

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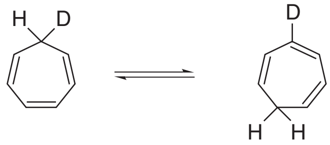
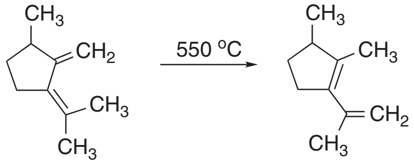
[220] W. R. Roth and J. Koenig, *Liebigs Ann. Chem.*, **699**, 24 (1966).

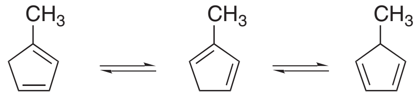


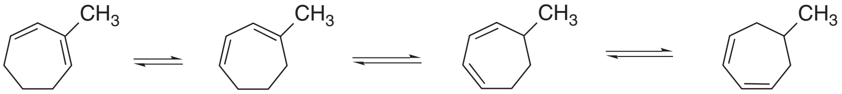
Ref. 221



Ref. 222

Sigmatropic shifts of hydrogens have been systematically examined in cyclic systems. Early studies demonstrated equilibration among the methylcyclopentadienes[223] and methylcycloheptadienes by 1,5-hydrogen shift.[224]





Computational studies (B3LYP/6-31G*) have been carried out on cyclopentadiene ($E_a = 27$ kcal/mol),[225] 1,3-cyclohexadiene ($E_a = 41.9$ kcal/mol),[226] 1,3-cycloheptatriene ($E_a = 32.7$–35.3 kcal/mol),[227] and 1,3-cyclooctadiene ($E_a = 32.2$ kcal/mol).[226] In each case, there is reasonable agreement with experimental data. The energy requirement depends on the structure of the TS, which is influenced by the ring geometry. For example, in methyl-substituted 1,3-cycloheptadienes, there are seven minima and seven TS for [1,5]-sigmatropic shifts. The E_a range from 29.6 (**4**→**TS34**) to 35.3 (**2**→**TS34**) kcal/mol. These energy relationships are depicted in Figure 10.35.

Like the thermal 1,3-hydrogen shift, a 1,7-hydrogen shift is allowed when antarafacial but forbidden when suprafacial. Because a π system involving seven carbon atoms is more flexible than one involving only three carbon atoms, the geometrical restrictions on the antarafacial TS are not as severe as in the 1,3-case. For the conversion of *Z*,*Z*-1,3,5-octatriene to *Z*,*Z*,*E*-2,4,6-octatriene, the E_a is 20.2 kcal/mol.

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[221] A. P. ter Borg, H Kloosterziel, and N. Van Meurs, *Proc. Chem. Soc.*, 359 (1962).

[222] J. Wolinsky, B. Chollar, and M. D. Baird, *J. Am. Chem. Soc.*, **884**, 2775 (1962).

[223] V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963).

[224] V. A. Mironov, O. S. Chizhov, I. M. Kimelfeld, and A. A. Akhrem, *Tetrahedron Lett.*, 499 (1969).

[225] I. Alkorta and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 2497 (1998).

[226] B. A. Hess, Jr., and J. E. Baldwin, *J. Org. Chem.*, **67**, 6025 (2002).

[227] B. A. Hess, Jr., *Int. J. Quantum Chem.*, **90**, 1064 (2002).

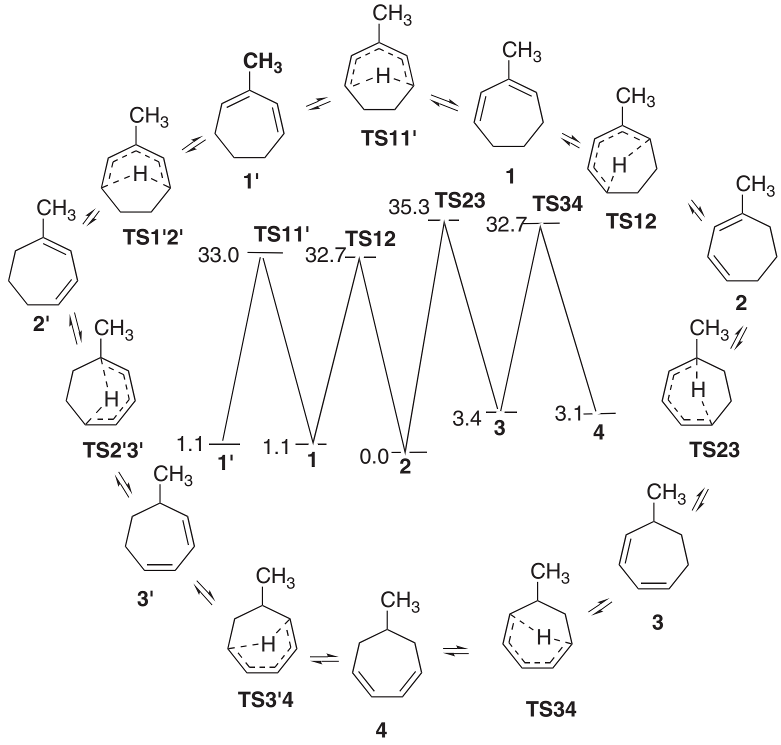
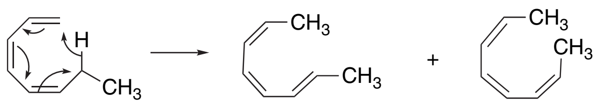


Fig. 10.35. Structures and relative energies of isomeric methyl-1,3-cycloheptatrienes and TS for [1,5]-sigmatropic hydrogen shift between them. Data from *Int. J. Quantum Chem.*, **90**, 1064 (2002).

The *Z*,*Z*,*Z*-isomer is also formed, but with a slightly higher activation energy. The kinetic isotope for the transferred hydrogen is around 7, consistent with C−H bond-breaking being involved in the rate-determining step.[228] A similar E_a has been measured for the unsubstituted *Z*,*Z*-1,3,5-heptatriene.[229]



More complex structures such as **19** exhibit similar activation energies. This compound was used to demonstrate that the stereochemistry is *antarafacial*, as predicted by the general selection rules.[230]

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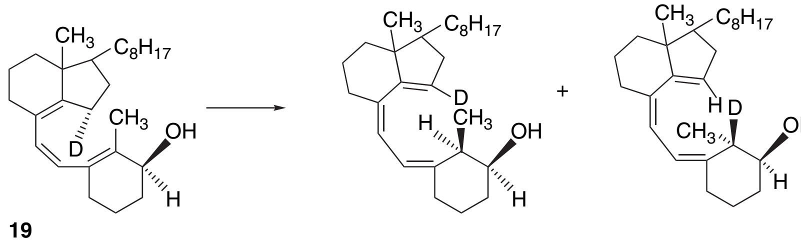
[228] J. E. Baldwin and V. P. Reddy, *J. Am. Chem. Soc.*, **109**, 8051 (1987).

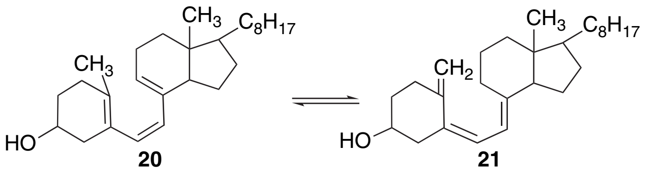
[229] M. Gurski, I. D. Gridnev, Y. V. Il'ichev, A. V. Ignatenko, and Y. N. Bubnov, *Angew. Chem. Int. Ed. Engl.*, **31**, 781 (1992).

[230] C. A. Hoeger, A. D. Johnston, and W. H. Okamura, *J. Am. Chem. Soc.*, **109**, 4690 (1987); W. H. Okamura, C. A. Hoeger, K. J. Miller, and W. Reischl, *J. Am. Chem. Soc.*, **110**, 973 (1988).



19

An especially important case of 1,7-hydrogen shift is the thermal equilibrium between precalciferol (previtamin D_3, **20**) and calciferol (vitamin D_3, **21**).[231,232] This reaction has an E_a of 19.2 kcal/mol.

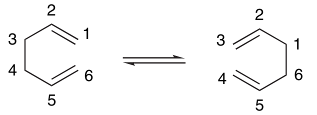


20 **21**

Figure 10.36 summarizes the comparative E_a for [1,3]- , [1,5]- , and [1,7]-hydrogen shifts.

10.6.3. Overview of [3,3]-Sigmatropic Rearrangements

[3,3]-Sigmatropic rearrangements are very important and useful reactions. The most important [3,3]-sigmatropic rearrangement from the synthetic point of view are those that form new carbon-carbon bonds. The [3,3]-sigmatropic rearrangement of 1,5-hexadienes is called the *Cope rearrangement*.



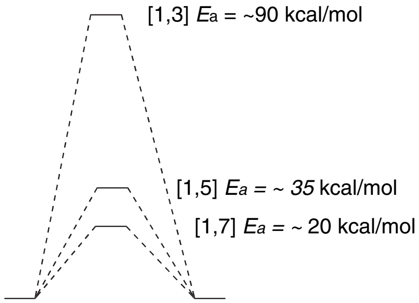


Fig. 10.36. Schematic comparison of E_a for 1,3-, 1,5-, and 1,7-sigmatropic hydrogen shifts.

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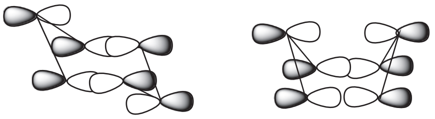
[231] J. L. M. A. Schlatmann, J. Pot, and E. Havinga, *Rec. Trav. Chim.*, **83**, 1173 (1964).

[232] For a historical review of this reaction, see L. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, Chap. 4.

The TS for [3,3]-sigmatropic rearrangements can be considered to be two interacting allyl fragments. When the process is suprafacial in both groups, an aromatic orbital array results and the process is thermally allowed. Usually a chairlike TS is involved but a boatlike conformation is also possible.[233]

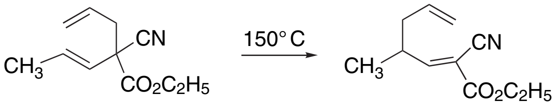


chair transition structure   boat transition structure

Basis set orbitals for chair and boat transition structures for [3,3]-sigmatropic shifts. 6 π electrons, Hückel, aromatic

Heteroatoms can be present in the conjugated system or as substituents. From a synthetic point of view, the most important cases have oxygen or nitrogen at position 3. The oxygen case is known as the *Claisen rearrangement*. Oxygen and nitrogen substituents at C(2) or C(3) also provide important variations of [3,3]-sigmatropic rearrangements. Scheme 10.10 gives the structural pattern and names of some of the most important [3,3]-sigmatropic rearrangements. We discuss these variations in the sections that follow.

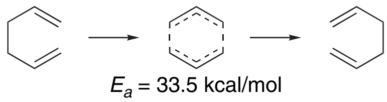
10.6.3.1. Cope Rearrangements The thermal [3,3]-sigmatropic rearrangement of 1,5-dienes is called the *Cope rearrangement*. Cope rearrangements are reversible reactions and as there is no change in the number or in the types of bonds, to a first approximation the total bond energy is unchanged. The reaction is under thermodynamic control and establishes equilibrium between the two 1,5-dienes. The position of the final equilibrium is governed by the relative stability of the starting material and product. The conversion of **22** to **23** is an example. The equilibrium in this case is controlled by the conjugation with the carbonyl and cyano groups in the product.



22 **23**

Ref. 234

The rearrangement of the simplest possible case, 1,5-hexadiene, has been studied using deuterium labeling. The E_a is 33.5 kcal/mol and the entropy of activation is −13.8 eu.[235] The substantially negative entropy reflects the formation of the cyclic TS.



The Cope rearrangement usually proceeds through a chairlike TS. The stereochemistry of the reaction can be predicted and analyzed on the basis of a chair TS that minimizes steric interactions between the substituents. The reaction is both

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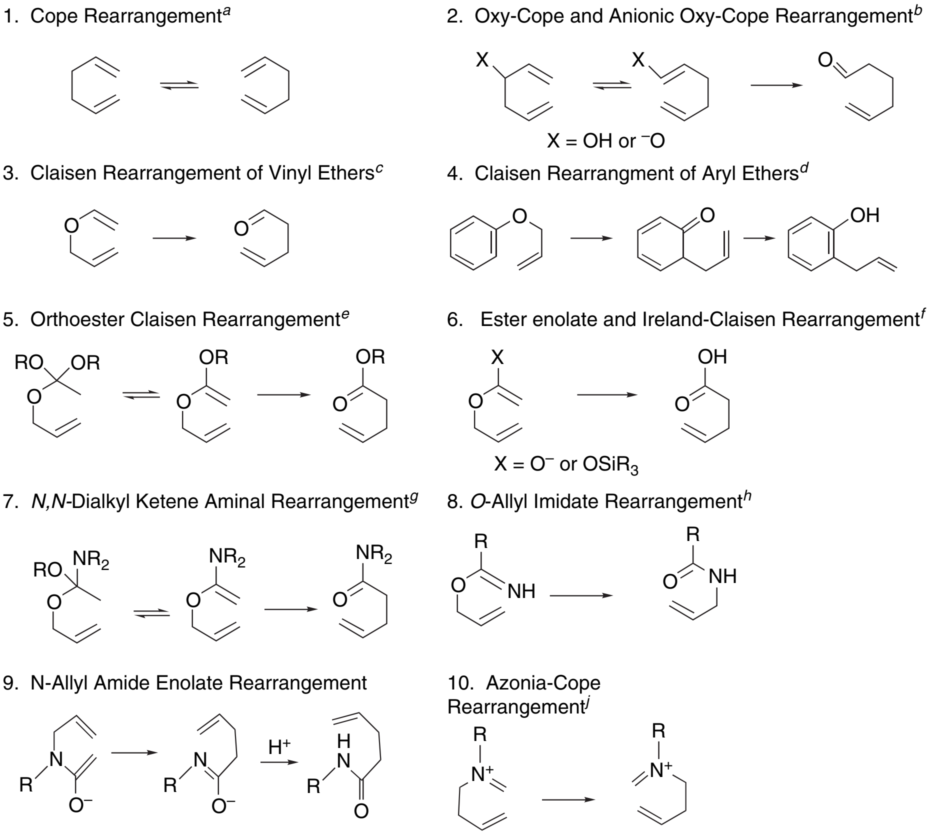
[233] K. J. Shea, G. J. Stoddard, W. P. England, and C. D. Haffner, *J. Am. Chem. Soc.*, **114**, 2635 (1992).

[234] A. C. Cope and E. M. Hardy, *J. Am. Chem. Soc.*, **62**, 441 (1940).

[235] W. v. E. Doering, V. G. Tascano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971); K. A. Black, S. Wilsey, and K. N. Houk, *J. Am. Chem. Soc.*, **120**, 5622 (1998).

Scheme 10.10. Examples of [3,3]-Sigmatropic Rearrangements



1. Cope Rearrangement[a]
2. Oxy-Cope and Anionic Oxy-Cope Rearrangement[b]
3. Claisen Rearrangement of Vinyl Ethers[c]
4. Claisen Rearrangment of Aryl Ethers[d]
5. Orthoester Claisen Rearrangement[e]
6. Ester enolate and Ireland-Claisen Rearrangement[f]
7. *N,N*-Dialkyl Ketene Aminal Rearrangement[g]
8. *O*-Allyl Imidate Rearrangement[h]
9. N-Allyl Amide Enolate Rearrangement
10. Azonia-Cope Rearrangement[j]

a. S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
b. J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5019 (1964); D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
c. A. M. M. Castro, *Chem. Rev.*, **104**, 2939 (2004).
d. D. S. Tarbel, *Org. React.*, **2**, 1 (1944).
e. W. S. Johnson, L. Wethermann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
f. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5898 (1972); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
g. D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).
h. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).
i. U. Nubbemeyer, *Synthesis*, 961 (2003).
j. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

stereospecific and stereoselective. It is stereospecific in that a *Z*- or *E*-configurational relationship at either double bond is maintained in the TS and governs the stereochemical relationship at the newly formed single bond in the product.[236] However, the relationship depends upon the conformation of the TS. When a chair TS is favored the *E*,*E*- and *Z*,*Z*-dienes lead to *anti*-3,4-diastereomers, whereas the *E*,*Z*- and *Z*,*E*-isomers give the 3,4-*syn* product. The reaction is stereoselective with respect to the configuration of the newly formed double bond. If both *E*- and *Z*- stereoisomers are possible for the product, the product ratio reflects product (and TS) stability. Thus an *E*-arrangement is normally favored for the newly formed double bonds. The stereochemical aspects of the Cope rearrangements for relatively simple reactants are consistent with a chairlike TS in which the larger substituent at C(3) or C(4) adopts an equatorial-like conformation.

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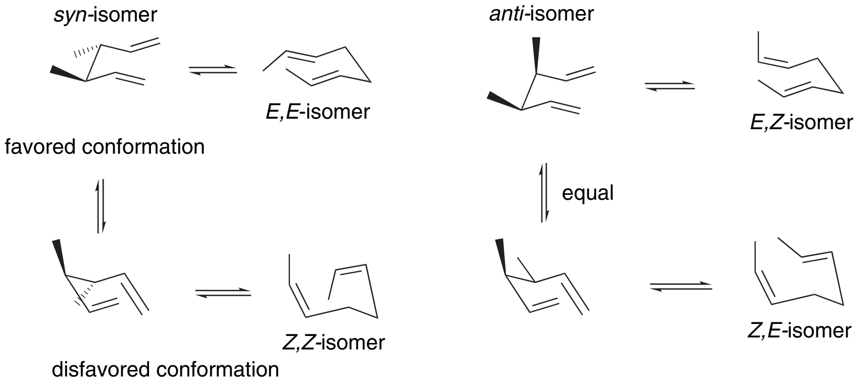
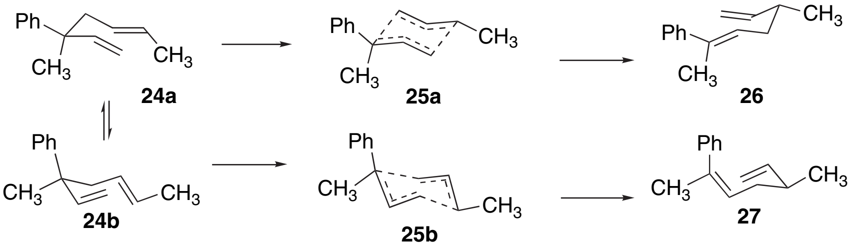
[236] W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).



Because of the concerted mechanism, chirality at C(3) or C(4) leads to enantiospecific formation of the new stereocenters at C(1) or C(6).[237] These relationships are illustrated in the example below. Both the configuration of the new stereocenter and the new double bond are those expected on the basis of a chairlike TS. Since there are two stereogenic centers, the double bond and the asymmetric carbon, there are four possible stereomers of the product. Only two are formed. The *E*-isomer has the *S*-configuration at C(4), whereas the *Z*-isomer has the *R* configuration. The stereochemistry of the new double bond is determined by the relative stability of the two chair TSs. TS **25b** is less favorable than **25a** because of the axial placement of the larger phenyl substituent. Thus compound **24** reacts primarily through TS **25a** to give **26** as the major product. Minor product **27** is formed through the less sterically favorable TS **25b**.



When enantiomerically pure **24** is used, the product has an e.e. >95% and the configuration shown above. This result establishes that chirality is maintained throughout the course of the reaction. This stereospecificity is a general feature of [3,3]-sigmatropic shifts and has made them valuable reactions in enantiospecific syntheses.[238]

There is a second possible TS for the Cope rearrangement having a boatlike geometry. The products corresponding to a boatlike TS are usually not observed for acyclic dienes. However, this TS is allowed by orbital symmetry rules and if steric factors make a boat TS preferable to a chair, reaction proceeds through a boat.

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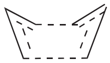
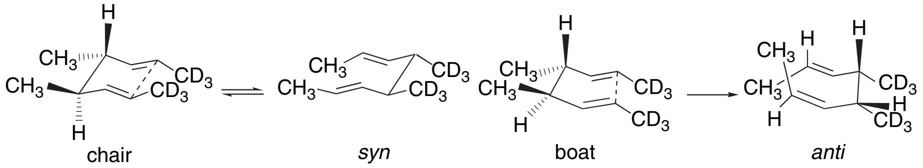
[237] R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).

[238] R. K. Hill, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., 1984, Chap. 8; D. Enders, M. Knopp and R. Schiffers, *Tetrahedron: Asymmetry*, **7**, 1847 (1996).

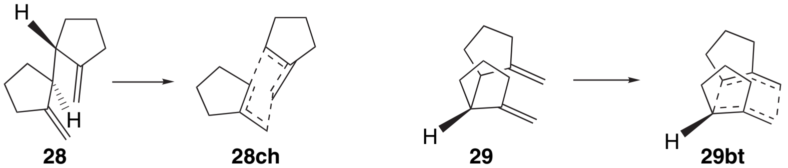


It is generally agreed that the boat TS is higher in energy than the chair TS. There have been several studies aimed at determining the energy difference between the two. One study involved 1,1,1,8,8,8-*deuterio*-4,5-dimethyloctadienes. The chair and boat TSs predict different stereoisomeric products.



Although the process is further complicated by *cis-trans* isomerizations not considered in the above structures, by analysis of the product ratio it was possible to determine that the boat TS is about 6 kcal/mol less stable than the chair.[239] Related experiments on deuterated 1,5-hexadiene itself indicated a difference of 5.8 kcal in $\Delta G^{\ddagger}$ for the chair and boat TSs.[240]

Another approach to determining the energy difference between the chair and boat TSs is based on measurement of the activation parameters for the isomeric alkenes **28** and **29**.[241] These two compounds are diastereomeric. Whereas **28** can attain a chairlike TS **28ch**, **29** can achieve bonding between the 1,6-carbons only in a boatlike TS, **29bt**.



28 **28ch** **29** **29bt**

chair-like TS boat-like TS

Comparison of the rate of rearrangement of **28** and **29** showed **28** to react faster by a factor of 18,000. This corresponds to a difference of about 14 kcal/mol in the measured $\Delta H^{\ddagger}$, but is partially compensated for by a more favorable $\Delta S^{\ddagger}$ for **29**. In the corresponding methylenecyclohexane analogs, the $\Delta H^{\ddagger}$ favors the chairlike TS by 16 kcal/mol.

The TS involves six partially delocalized electrons being transformed from one 1,5-diene system to another. Theoretical calculations on reactions with delocalized TSs, such as [3,3]-sigmatropic rearrangements, require special care. Correlation effects are especially important and either CI or DFT calculations are required.[242] The most advanced MO and DFT calculations support the idea of an aromatic TS.[243] The TS can range in character from a 1,4-cyclohexadiyl diradical to two nearly independent allyl radicals, depending on whether bond making or bond breaking is more advanced.[244] The *electrons remain paired* in either case, however, and the two representations are best considered to be resonance structures. The energy surface in the transition region seems to be quite flat; that is, there does not seem to be a strong difference in the energy over the range from 1.64 to 2.19 Å.[245]

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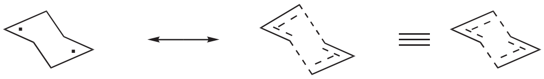
[239] J. J. Gajewski, C. W. Benner, and C. M. Hawkins, *J. Org. Chem.*, **52**, 5198 (1987).

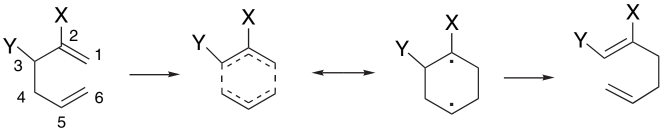
[240] M. J. Goldstein and M. S. Benzon, *J. Am. Chem. Soc.*, **94**, 7147 (1972).

[241] K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.*, **102**, 3156 (1980).

[242] O. Wiest, D. C. Montiel, and K. N. Houk, *J. Phys. Chem.*, **101,** 8378 (1997).

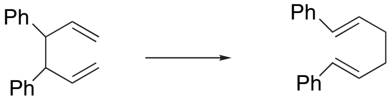


Substituent effects provide other insights into the nature of the TS for the Cope rearrangement. Conjugated substituents at C(2), C(3), C(4), or C(5) accelerate the reaction.[246] Donor substituents at C(2) and C(3) have an accelerating effect.[247] The net effect on the reaction rate of any substituent is determined by the relative stabilization of the TS and ground state.[248] The effect of substituents on the stabilization of the TS can be analyzed by considering their effect on two interacting allyl systems. We consider the case of phenyl substituents in detail.



As shown in Table 10.7, phenyl substituents at positions 2 and 3 reduce the $\Delta H^{\ddagger}$. On the other hand, a 1-substituent, which is conjugated in the reactant but not the product, increases the $\Delta H^{\ddagger}$.

The first step in interpreting these substituent effects is to recognize how they affect the reactant and product energy. Substituents that are conjugated, such as cyano and phenyl, are more stabilizing on a double bond than at a saturated carbon. For example, the rearrangement of 3,4-diphenyl-1,5-hexadiene to 1,6-diphenyl-1,5-hexadiene is exothermic by 10.2 kcal/mol, indicating about 5 kcal/mol of stabilization at each conjugated double bond.



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[243] D. A. Hrovat, W. T. Borden, R. L. Vance, N. G. Rondan, K. N. Houk, and K. Morokuma, *J. Am. Chem. Soc.*, **112**, 2018 (1990); D. A. Hrovat, K Morokuma, and W. T. Borden, *J. Am. Chem. Soc.*, **116**, 1072 (1994); O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 10336 (1994); M. D. Davidson, I. H. Hillier, and M. A.Vincent, *Chem. Phys. Lett.*, **246**, 536 (1995); S. Yamada, S. Okumoto, and T. Hayashi, *J. Org. Chem.*, **61**, 6218 (1996); W. T. Borden and E. R. Davidson, *Acc. Chem. Res.*, **29**, 57 (1995); P. M. Kozlowski, M. Dupuis, and E. R. Davidson, *J. Am. Chem. Soc.*, **117**, 774 (1995); K. N. Houk, B. R. Beno, M. Nendel, K. Block, H.-Y. Yoo, S. Wilsey, and J. K. Lee, *Theochem*, **398**, 169 (1997); E. R. Davidson, *Chem. Phys. Lett.*, **284**, 301 (1998).

[244] J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **100**, 6268, 6269 (1978); J. J. Gajewski and K. E. Gilbert, *J. Org. Chem.*, **49**, 11 (1984).

[245] P. M. Kozlowski, M. Dupuis, and E. R. Davidson, *J. Am. Chem. Soc.*, **117**, 774 (1995); E. R. Davidson, *J. Phys. Chem.*, **100**, 6161 (1996).

[246] M. J. S. Dewar and L. E. Wade, *J. Am. Chem. Soc.*, **95**, 290 (1972); *J. Am. Chem. Soc.*, **99**, 4417 (1977); R. Wehrli, H. Schmid, D. E. Bellus, and H. J. Hansen, *Helv. Chim. Acta*, **60**, 1325 (1977).

[247] M. Dollinger, W. Henning, and W. Kirmse, *Chem. Ber.*, **115**, 2309 (1982).

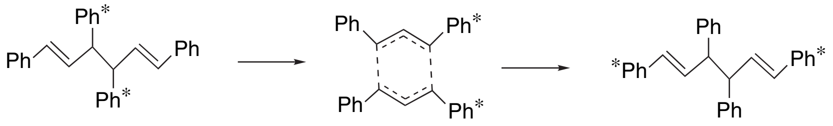
[248] For analysis of substituent effects in molecular orbital terminology, see B. K. Carpenter, *Tetrahedron*, **34**, 1877 (1978); F. Delbecq and N. T. Anh, *Nouv. J. Chim.*, **7**, 505 (1983).

Table 10.7. Effect of Phenyl Substituents on Activation Enthalpy of Cope Rearrangements

R^1	R^2	R^3	R^4	R^5	R^6	$\Delta H^{\ddagger}$(calc.)[a]	$\Delta H^{\ddagger}$(exp)
H	H	H	H	H	H	33.2	33.5[b]
Ph	H	H	H	H	H	36.2	–
H	Ph	H	H	H	H	29.4	29.3[c]
H	H	Ph	H	H	H	28.4	28.1[c]
Ph	H	Ph	H	H	H	30.2	30.5[d]
Ph	H	H	Ph	H	H	29.2	29.9[c]
H	Ph	H	Ph	H	H	24.6	26.7[c]
H	Ph	H	H	Ph	H	21.3	21.3[f]
H	H	Ph	Ph	H	H	–	24.0[g]
Ph	H	Ph	H	Ph	H	29.2	27.8[d]
Ph	H	Ph	Ph	H	Ph	19.1	21.3[g]

a. Calculated from D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122,** 7456 (2000)
b. W. v. E. Doering, V. G. Toscano, and G. H. Beasley, *Tetrahedron*, **27**, 5299 (1971).
c. M. J. S. Dewar and L. E. Wade, Jr., *J. Am. Chem. Soc.*, **99**, 4417 (1977).
c. E. G. Foster, A. C. Cope, and F. Daniels, *J. Am. Chem. Soc.*, **69**, 1893 (1947).
d. W. von E. Doering and Y. Wang, *J. Am. Chem. Soc.*, **121**, 10112 (1999).
e. W. von E. Doering, L. Birlandeanu, K. Sarma, J. H. Teles, F.-G. Klaerner, and J.-S. Gehrke, *J. Am. Chem. Soc.*, **110**, 4289 (1994).
f. W. R. Roth, H.-W. Lennartz, W. v. E. Doering, L. Birladeanu, C. A. Guyton, and T. Kitagawa, *J. Am. Chem. Soc.*, **112**, 1722 (1990).
g. W. von E. Doering, L. Birlandeanu, K. Sarma, G. Blaschke, U. Scheidemantel, R. Boese, J. Benet-Bucholz, F.-G. Klarner, J. S. Zinny, R. Sustmann, and H.-G. Korth, *J. Am. Chem. Soc.*, **122**, 193 (2000).

On the other hand, the degenerate rearrangement of *syn*-1,3,4,6-tetraphenyl-1,6-hexadiene is equi-energetic.



The next step is to understand how the *position* of the substitution influences the direction and magnitude of the rate effect and TS structure. If the TS is best represented by two loosely interacting allyl radicals, substituents at the 1, 3, 4, and 6 positions should have the strongest influence. This is because the 2 and 5 positions are at nodes of the frontier orbitals in allyl radicals and should not strongly influence radical stability. On the other hand, a cyclohexadiyl diradical intermediate should be affected most strongly by 2- and 5-substituents. The 1, 3, 4, and 6 positions have been called "active" and the 3 and 5 positions "nodal" to distinguish their relationship to the allyl HOMO orbitals.[249] It was suggested that substituents at the "active" positions would move the TS toward the diallyl radical structure (by preferentially stabilizing that structure), whereas substituents at the "nodal" positions would favor the 1,4-cyclohexadiyl structure.

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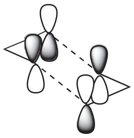
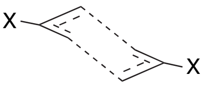
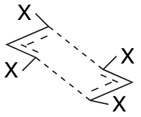
[249] (a) W. v. E. Doering and Y. Wang, *J. Am. Chem. Soc.*, **121**, 10112 (1999); (b) W. von E. Doering, L. Birladeanu, K. Sarma, G. Blaschke, U. Scheidelmantel, R. Boese, J. Benet-Bucholz, F.-G. Klaerner, J. S. Gehrke, B. U. Zimny, R. Sustmann, and H.-G. Korth, *J. Am. Chem. Soc.*, **122**, 193 (2000).



frontier orbitals for two interacting allyl radical



"nodal" positions



"active" positions

Borden, Houk, and co-workers evaluated the various phenyl-substituted cases using B3LYP/6-31G* calculations.[250] They found that the TS structure did indeed respond to the placement of phenyl substituents. Phenyl groups at the 2 and 5 positions resulted in a tighter, more 1,4-cyclohexadiyl TS, whereas 1- and 4-phenyl substituents resulted in a looser, more diallylic TS. When several substituents of the same type (matched) were present, the effects were reinforced. On the other hand, 1,5-diphenyl-1,3,5-hexatriene, where the substituents are of different types (unmatched) led to little change from the unsubstituted system. The bond lengths for some of the relevant systems are shown in Figure 10.37. The C−C bond length in the TS for 1,3,4,6-tetraphenyl-1,3,5-hexatriene corresponds to a bond order of only 0.06.

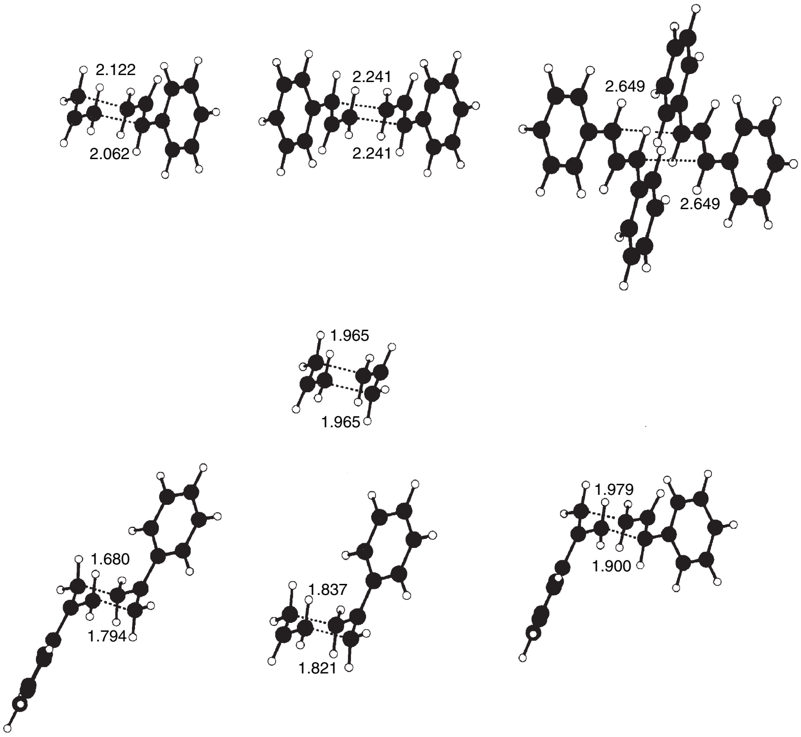


Fig. 10.37. Changes in bond length at the TS for [3,3]-sigmatropic rearrangement of phenyl-substituted 1,3,5-hexatrienes. (a) Top: cumulative loosening of the TS with one, two, and four phenyl groups in "active" positions. (b) Center: unsubstituted system. (c) Lower Left: cumulative tightening of TS by 2- and 2,5-phenyl substitution. (d) Lower Right. "unmatched" 2- and 4-substituents are competitive, leading to little structural change. Reproduced from *J. Am. Chem. Soc.*, **122**, 7456 (2000), by permission of the American Chemical Society.

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[250] D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122**, 7456 (2000).

In the case of the 2,5-diphenyl derivative, the bond distance corresponds to a bond order of 0.94. Thus these TS structures span a range from nearly "diallylic" to nearly "cyclohexadiyl" character. The substituent effects are also reflected in TS energies. An additional "matched" phenyl substituent lowers TS energy more than an addition "unmatched" substituent.

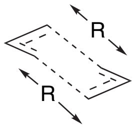
Effect of Phenyl Substitution on E_a (kcal/mol) for Rearrangement of 1,3,5-Hexatrienes

Unsubstituted	1-Phenyl	1,4-Diphenyl	1,3,4,6-Tetraphenyl
33.2	36.2	29.2	19.1 (matched)
	2-Phenyl	2,5-Diphenyl	
	29.4	21.3 (matched)	
	2-Phenyl	2,4-Diphenyl	
	29.4	27.1 (unmatched)	

The role of cyano substituents has also been explored in detail. The symmetrical "matched" 2,5- and 1,3,4,6-systems and the unmatched (but still symmetrical) 1,3,5-cyano system were investigated.[251] The effect of the substituents on TS energy was examined, as were the 1–6 and 3–4 bond distances. The energies of the TSs were evaluated relative to two allyl radicals by an isodesmic reaction.

$$2\ CH_2{=}CHCH_2^* + n\ CH_3CN \rightarrow [C_6H_{10-n}(CN)_n]^* + n\ CH_4$$

Several levels of calculations were performed with the 6-31* basis set using a type of CAS-SCF computation. Cyano substituents at both positions were stabilizing, but more so at 2,5 than at 1,3,4,6. The energetic and geometric effects are similar to those in the phenyl-substituted compounds. The TS is tightened (cyclohexadiyl-like) by 2,5-substituents, but loosened (diallyl-like) by 1,3,4,6-substitution. The 2,5-cyano substituents provide the highest TS stabilization. The distribution of unpaired electron density was used to assess radical character. In contrast to the significant energy and geometry differences, there was little change in the radical character of the TS with substitution.



Effect of Cyano Substituents on Transition State Energy and Structure

Substitution	$R(1,6) = (3,4)$ Å	ΔE(isodesmic) kcal/mol
None	1.9661	−22.7
2,5-	1.7524	−41.0
1,3,5-	2.1062	−32.1
1,3,4,6-	2.4670	−29.4

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[251] V. N. Staroverov and E. R. Davidson, *J. Am. Chem. Soc.*, **122**, 7377 (2000).

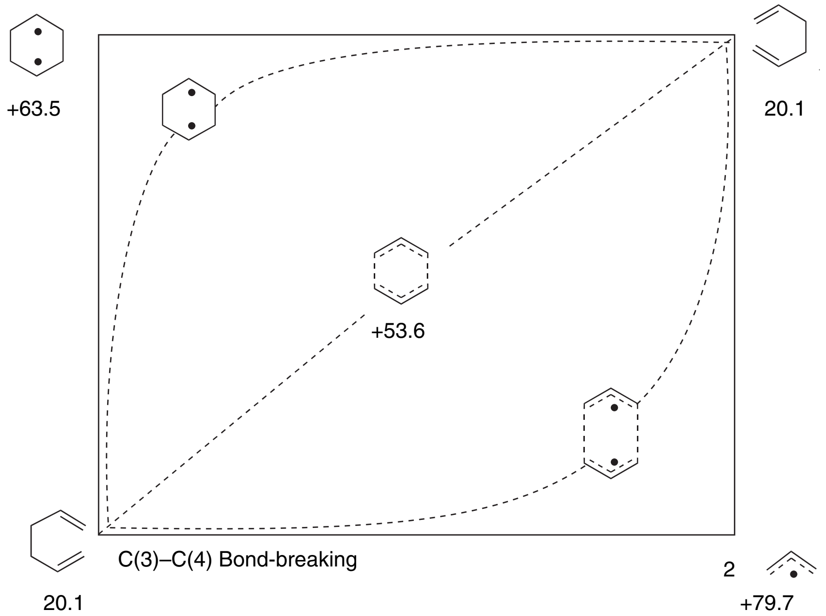
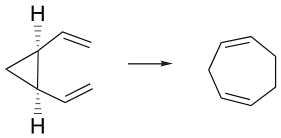


Fig. 10.38. More-O'Ferrall-Jencks diagram representing the variable transition structure for the Cope rearrangement. Energies (in kcal/mol) are from thermodynamic data, as quoted by D. A. Hrovat, J. Chen, K. N. Houk, and W. T. Borden, *J. Am. Chem. Soc.*, **122**, 7456 (2000).

The idea that the nature of the Cope rearrangement TS is variable can be expressed in terms of a More-O'Ferrall-Jencks energy diagram, as in Figure 10.38.[252] The 1,4-cyclohexadiyl diradical is believed to have a ΔH_f of 63.5 kcal/mol, which is 43.4 kcal/mol above 1,5-hexadiene. Two separate allyl radicals are at 79.7 kcal/mol, which is 59.6 kcal/mol above the reactant.[249a] The unsubstituted TS is at 53.6 kcal/mol, which is well below either the 1,4-diyl radicals or two allyl radicals, and the reaction proceeds by a concerted process. For the unsubstituted compound, there is a nearly equal amount of bond making and bond breaking at the TS, with a C(1)−C(6) and C(3)−C(4) bond order of 0.49.[250] The substituent effects can be interpreted by analyzing how they affect reactant and product energies and how they change TS character.

When strain is relieved, Cope rearrangements can occur at much lower temperatures and with complete conversion to ring-opened products. Some particularly striking examples of Cope rearrangement can be found in the rearrangement of *cis*-divinylcyclopropanes. An example is the conversion of *cis*-divinylcyclopropane to 1,4-cycloheptadiene, a reaction that occurs readily at temperatures below −40° C.[253]



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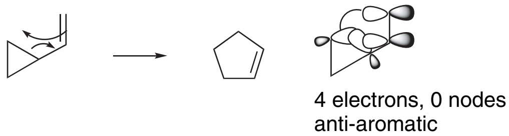
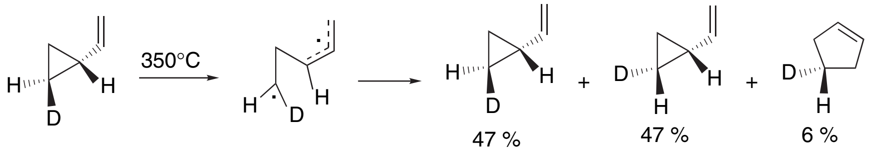
[252] J. J. Gajewski, *Acc. Chem. Res.*, **13**, 142 (1980); K. N. Houk, S. M. Gustafson, and K. A. Black, *J. Am. Chem. Soc.*, **114**, 8565 (1992); J. J. Gajewski, *Acc. Chem. Res.*, **30**, 219 (1997).

[253] W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

Before we go into these reactions in detail, let us examine vinylcyclopropane itself, which rearranges at high temperature to cyclopentene.[254]



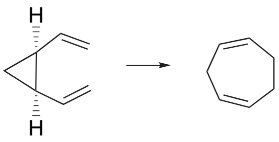
The most geometrically accessible TS corresponds to a forbidden 1,3-suprafacial alkyl shift with retention of configuration. The rearrangement requires a temperature of at least 200°–300° C.[255] The measured E_a is about 50 kcal/mol, which is consistent with a stepwise reaction beginning with rupture of a cyclopropane bond and formation of an allylic fragment.[256] Support for a nonconcerted mechanism comes from the observation that *cis-trans* isomerization occurs faster than the rearrangement. This isomerization presumably occurs by reversible cleavage of the C(1)−C(2) cyclopropane bond.



Ref. 257

When this prior stereoisomerization is accounted for, the rearrangement is found to have resulted from a mixture of all possible suprafacial, antarafacial, inversion, and retention combinations in roughly equal amounts, indicating lack of stereoselectivity.[258] Thus, the rearrangement of vinylcyclopropane occurs with nearly complete bond rupture. Computational modeling of the reaction finds no intermediate, and the TS is diradical in character.[259]

A dramatic difference in reactivity is evident when *cis*-divinylcyclopropane is compared with vinylcyclopropane.[260] *cis*-Divinylcyclopropane can only be isolated at low temperature because it very rapidly undergoes Cope rearrangement to 1,4-cycloheptatriene.[261] At 0°C $\Delta H^{\ddagger}$ is 18.8 kcal/mol and $\Delta S^{\ddagger}$ is −9.4 eu.



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[254] C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.*, **82**, 1007 (1960).

[255] T. Hudlicky, T. M. Kutchan, and S. M. Naqui, *Org. React.*, **33**, 247 (1984); T. Hudlicky and J. D. Price, *Chem. Rev.*, **89**, 1467 (1989); J. E.Baldwin, in *Chemistry of the Cyclopropyl Group*, Vol. 2, Z. Rapoport, ed., Wiley, 1995, pp. 469–494.

[256] D. K. Lewis, D. J. Charney, B. L. Kalra, A. M. Plate, M. H. Woodard, S. J. Cianciosi, and J. E. Baldwin, *J. Phys. Chem.*, **101,** 4097 (1997).

[257] M. R. Willcott and V. H. Cargle, *J. Am. Chem. Soc.*, **89**, 723 (1967).

[258] J. J. Baldwin, K. A. Villarica, D. I. Freedberg, and F. A. L. Anet, *J. Am. Chem. Soc.*, **116**, 10845 (1994).

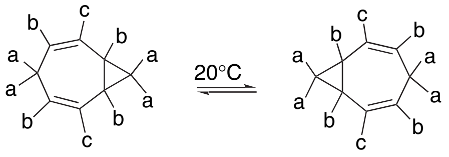
[259] E. R. Davidson and J. J. Gajewski, *J. Am. Chem. Soc.*, **119**, 10543 (1997); K. N. Houk, M. Nendal, O. Wiest, and J. W. Storer, *J. Am. Chem. Soc.*, **119**, 10545 (1997); J. E. Baldwin, *J. Comput. Chem.*, **19**, 222 (1998).

[260] T. Hudlicky, R. Fan, J. W. Reed, and K. G. Gadamasetti, *Org. React.*, **41**, 1 (1992).

[261] J. M. Brown, B. T. Bolding, and J. F. Stofko, Jr., *Chem. Commun.*, 319 (1973); M. Schneider, *Angew. Chem. Int. Ed. Engl.*, **14**, 707 (1975); M. P. Schneider and A. Rau, *J. Am. Chem. Soc.*, **101**, 4426 (1979).

Owing to unfavorable molecular geometry, the corresponding rearrangement of *trans*-divinylcyclopropane to cycloheptatriene cannot be concerted and requires temperatures on the order of 190° C. The very low energy requirement for the Cope rearrangement of *cis*-divinylcyclopropane reflects several favorable circumstances. The *cis*-orientation facilitates interaction of the diene termini, so the loss in entropy in going to the TS is smaller than for an acyclic diene. The breaking bond is strained and this reduces the E_a. The importance of the latter factor can be appreciated by comparison with *cis*-divinylcyclobutane and *cis*-divinylcyclopentane. The former compound has $\Delta H^{\ddagger} = 23$ kcal/mol for rearrangement to cyclooctadiene.[262] *cis*-Divinylcyclopentane does not rearrange to cyclononadiene, even at 250°C.[263] In the latter case, the rearrangement is presumably thermodynamically unfavorable, since there is no strain release from ring opening.

Divinylcyclopropane rearrangements can proceed with even greater ease if the $\Delta S^{\ddagger}$ is made less negative by incorporating both vinyl groups into a ring. An example of this is found in the degenerate homotropilidene rearrangement. A *degenerate rearrangement* is a reaction process in which no overall change in structure occurs, and the product of rearrangement is structurally identical to the starting material. Depending on the rate at which the reaction occurs, the existence of a degenerate rearrangement can be detected by use of isotopic labels or by interpretation of the temperature dependence of NMR spectra. In the case of homotropilidene, **30**, the occurrence of a dynamic equilibrium is evident from the NMR spectrum. At low temperature the rate of interconversion is slow and the spectrum indicates the presence of four vinyl protons, two allylic protons, and two pairs of cyclopropyl protons. As the temperature is raised and the rate of the rearrangement increases, it is observed that two of the vinyl protons remain essentially unchanged with respect to their chemical shift, whereas the other two coalesce with one of the pairs of cyclopropyl protons. Coalescence is also observed between the allylic protons and the other two cyclopropyl protons.[264] The sets of protons that coalesce undergo sufficiently rapid interchange with one another to result in an averaged signal (see p. 155).



30

Many other examples of this type of rearrangement are known. Another interesting case is bullvalene, which is converted into itself with a first-order rate constant of $3.4 \times 10^3\ \mathrm{s}^{-1}$ at 25° C.[265] At 10° C, the ^{1}H-NMR spectrum of bullvalene exhibits a single peak at 4.22 ppm, which indicates the "fluxional" nature of the molecule. Owing to the threefold axis of symmetry present in bullvalene, the degenerate rearrangement results in all of the carbons having an identical averaged environment. This is illustrated in the diagram below by the interchanging environments of the labeled carbons. The E_a for the rearrangement has been determined to be 13.9 kcal/mol.[266] Substituted bullvalenes have also been studied.[267]

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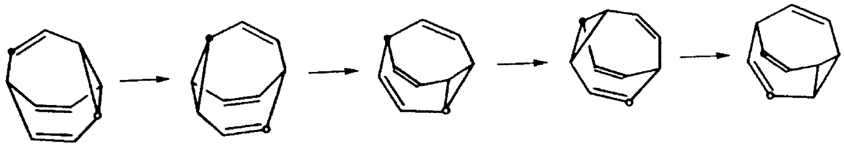
[262] E. Vogel, *Justus Liebigs Ann. Chem.*, **615**, 1 (1958); G. S. Hammond and C. D. DeBoer, *J. Am. Chem. Soc.*, **86**, 899 (1964).

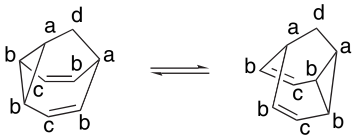
[263] E. Vogel, W. Grimme, and E. Dinne, *Angew. Chem.*, **75**, 1103 (1963).

[264] G. Schroeder, J. F. M. Oth, and R. Merenyi, *Angew. Chem. Int. Ed. Engl.*, **4**, 752 (1965); H. Gunther, J. B. Pawliczek, J. Ulmen, and W. Grimme, *Angew. Chem. Int. Ed. Engl.*, **11**, 517 (1972); W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

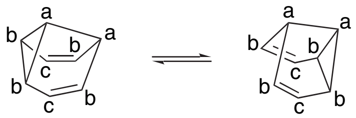
[265] G. Schroeder and J. F. M. Oth, *Angew. Chem. Int. Ed. Engl.*, **6**, 414 (1967).



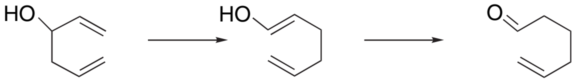
Other degenerate rearrangements have been discovered that are even faster than that of bullvalene. Barbaralane rearranges to itself with a rate constant of $1.7 \times 10^7\ \mathrm{s}^{-1}$ at 25° C.[268] The E_a of this rearrangement is only 7.7 kcal/mol. The lowered energy requirement is attributed to an increase in ground state energy owing to strain. Barbaralane is less symmetrical than bullvalene. There are four different kinds of carbons and protons in the averaged structure. Only the methylene group labeled "d" is unaffected by the degenerate rearrangement.



A further reduction in the barrier and increase in rate is seen with semibullvalene in which strain is increased still more. The $\Delta G^\ddagger$ for this rearrangement is 5.5 kcal/mol at −143° C.[269]



When there is a hydroxy substituent at C(3) of the diene system, the Cope rearrangement product is an enol that is subsequently converted to the corresponding carbonyl compound. This is called the *oxy-Cope* rearrangement.[270] The formation of the carbonyl compound provides a net driving force for the reaction.[271]



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[266] R. Poupko, H. Zimmerman, and Z. Luz, *J. Am. Chem. Soc.*, **106**, 5391 (1984).

[267] R. Poupko, H. Zimmermann, K. Muller, and Z. Luz, *J. Am. Chem. Soc.*, **118**, 7995 (1996).

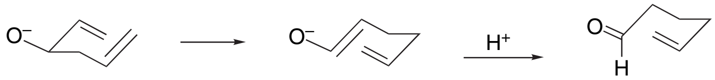
[268] W. v. E. Doering, B. M. Ferrier, E. T. Fossel, J. H. Hartenstein, M. Jones, Jr., G. Klumpp, R. M. Rubin, and M. Saunders, *Tetrahedron*, **23**, 3943 (1967); H. Gunther, J. Runsink, H. Schmickler, and P. Schmitt, *J. Org. Chem.*, **50**, 289 (1985).

[269] A. K. Cheng, F. A. L. Anet, J. Mioduski, and J. Meinwald, *J. Am. Chem. Soc.*, **96**, 2887 (1974); D. Moskau, R. Aydin, W. Leber, H. Gunther, H. Quast, H.-D. Martin, K. Hassenruck, L. S. Miller, and K. Grohmann, *Chem. Ber.*, **122**, 925 (1989).

[270] S. R. Wilson, *Org. React.*, **43**, 93 (1993); L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990); L. A. Paquette, *Tetrahedron*, **53**, 13971 (1997).

[271] A. Viola, E. J. Iorio, K. K. N. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).

There is a very powerful substituent effect for dienes having anionic oxygen substituents at C(3), a reaction known as the *anionic oxy-Cope reaction*.[272] When the C(3) hydroxy group is converted to its alkoxide, the reaction is accelerated by factors of 10^{10}–10^{17}.[273]



The rates of anionic oxy-Cope rearrangements depend on the degree of cation coordination at the oxy anion. The reactivity trend is $K^+ > Na^+ > Li^+$. Crown ethers catalyze reaction by promoting ion pair dissociation.[274] Catalytic amounts of *tetra-n*-butylammonium salts lead to accelerated rates in some cases. This presumably results from the dissociation of less reactive ion pair species promoted by the *tetra-n*-butylammonium ion.[275] As with other [3,3]-sigmatropic rearrangements, the stereochemistry of the anionic oxy-Cope rearrangement depends on TS conformation. There is no strong stereochemical preference associated with the $C-O^-$ bond, and in the absence of other controlling steric factors, products arising from both equatorial and axial orientations are formed.[276]

The origin of the rate acceleration has been explored by computation. The B3LYP/6-31+G* computational results give a $\Delta G^\ddagger$ of 6.3 kcal/mol, some 30 kcal/mol less than the unsubstituted system.[277] Another study found the barrier to be only 8.3 kcal/mol in the gas phase. This is raised substantially (to 31.8 kcal/mol) by coordination of an Li^+ cation at the oxygen.[278] As shown in Figure 10.39, the TS for the anionic oxy-Cope reaction is much more asynchronous than for the parent system. The TS is much looser and closer to two dissociated fragments. Note that the C(3)−C(4) bond has lengthened substantially in the TS, whereas the C(1)−C(6) bond distance is still quite long. Several factors probably contribute to the large rate acceleration. The anionic oxy substituent substantially weakens the C(3)−C(4) bond.[279] The delocalization of the negative charge in the enolate is also likely a factor, in view of the dissociative nature of the TS.

3-Amino groups also accelerate the Cope rearrangement.[280] The products are enamines and subsequent reactions of the enamine are feasible, such as α-alkylation.

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[272] L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990).

[273] D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975); D. A. Evans, D. J. Baillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, **100**, 2242 (1978).

[274] J. J. Gajewski and K. R. Gee, *J. Am. Chem. Soc.*, **113**, 967 (1991).

[275] M. George, T.-F. Tam, and B. Fraser-Reid, *J. Org. Chem.*, **50**, 5747 (1985).

[276] L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, **114**, 5018 (1992); E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim, and J. S. Yun, *J. Org. Chem.*, **59**, 1444 (1994).

[277] H. Bauman and P. Chen, *Helv. Chim. Acta*, **84**, 124 (2001).

[278] F. Haeffner, K. N. Houk, S. M. Schulze, and J. K. Lee, *J. Org. Chem.*, **68**, 2310 (2003).

[279] (a) M. L. Steigerwald, W. A. Goddard, III, and D. A. Evans, *J. Am. Chem. Soc.*, **101**, 1994 (1979); (b) H. Y. Yoo, K. N. Houk, J. K. Lee, M.A. Scialdone, and A. I. Meyers, *J. Am. Chem. Soc.*, **120**, 205 (1998).

[280] R. W. Jemison, W. D. Ollis, I. O. S. Sutherland, and J. Tannock, *J. Chem. Soc., Perkin Trans. 1*, 1462 (1980); J. P. Hagen, K. D. Lewis, S. W. Lovell, P. Rossi, and A. Z. Tescan, *J. Org. Chem.*, **60**, 7471 (1995).

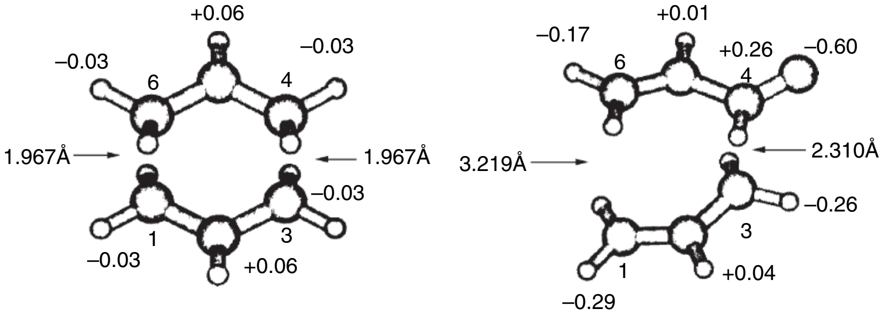
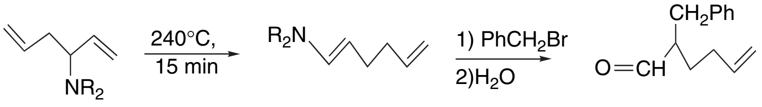
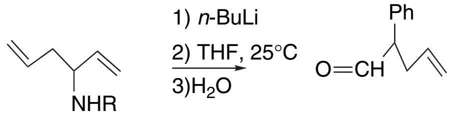

+0.06
−0.03
−0.03
6
4
1.967Å
1.967Å
−0.03
1
3
−0.03
+0.06
+0.01
−0.17
+0.26
−0.60
6
4
3.219Å
2.310Å
−0.26
3
1
+0.04
−0.29

Fig. 10.39. Comparison of transition structure geometry for anionic oxy-Cope (right) rearrangement with Cope rearrangement (left) showing atom separation distances and Mulliken charges (B3LYP/6-311G*). Reproduced from *Helv. Chim. Acta*, **84**, 124 (2001), by permission of Wiley-VCH.


NR$_2$
240°C, 15 min
R$_2$N
1) PhCH$_2$Br
2)H$_2$O
CH$_2$Ph
O=CH

Ref. 281

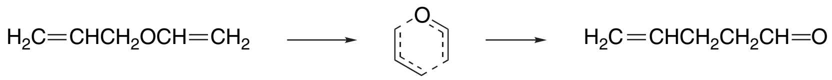
When secondary amines are used, an anionic version of the reaction occurs when the amine is deprotonated by *n*-BuLi.


NHR
1) *n*-BuLi
2) THF, 25°C
3)H$_2$O
Ph
O=CH

Ref. 282

However, as implied by computations on the anionic amino-Cope reaction,[279b] a dissociative pathway is competitive and can complicate the outcome of the reaction.[283]

10.6.3.2. [3,3]-Sigmatropic Rearrangement in Triene Systems Containing Oxygens The [3,3]-sigmatropic reaction pattern is quite general for other systems that incorporate one or more heteroatoms in place of carbon in the 1,5-hexadiene unit. The most synthetically useful and widely studied of these reactions is the Claisen rearrangement, in which an oxygen atom is present at position 3.[284] The simplest example of a Claisen rearrangement is the thermal conversion of allyl vinyl ether to 4-pentenal.


H$_2$C=CHCH$_2$OCH=CH$_2$
O
H$_2$C=CHCH$_2$CH$_2$CH=O

This reaction occurs with an E_a of 30.6 kcal/mol and an $\Delta S^\ddagger$ of −7.7 eu at 180°C.[285] Both computational modeling of the TS and analysis of kinetic isotope effects are in accord with a concerted mechanism in which C−O bond cleavage is more advanced

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[281] S. M. Allin, M. A. C. Button, and S. J. Shuttleworth, *Synlett*, 725 (1997).

[282] S. M. Allin, M. A. C. Button, and R. D. Baird, *Synlett*, 1117 (1998).

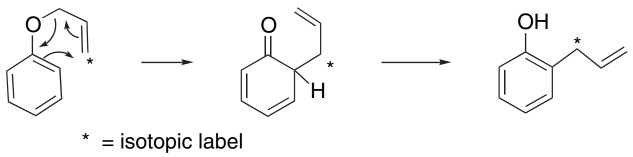
[283] S. M. Allin and M. A. C. Button, *Tetrahedron Lett.*, **40**, 3801 (1999).

[284] G. B. Bennett, *Synthesis*, 589 (1977); S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).

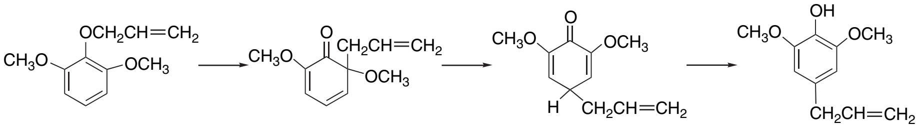
[285] F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.*, **72**, 3155 (1950).

than C−C bond formation.[286] Claisen rearrangements show a considerable sensitivity to solvent polarity, with reaction rates increasing with solvent polarity.[287] Water is an especially favorable solvent.[288] The solvent effect is believed to be due to differential solvation of the reactants and TS. Hydrogen bonding contributes to stabilization of the TS.[289]

Allyl ethers of phenols undergo [3,3]-sigmatropic rearrangements and some aspects of the mechanism were developed by studying these compounds.[290] For example, an important clue as to the mechanism of the Claisen rearrangement was obtained by use of ^{14}C-labeled allyl phenyl ether. It was found that the rearrangement was specific as to which carbon atom of the allyl group became bonded to the ring, which is consistent with a cyclic mechanism.[291]



If both *ortho*-positions are substituted, the allyl group undergoes a second migration, giving the *para*-substituted phenol.



Ref. 292

The intramolecular nature of the rearrangement was established by a crossover experiment in which **31** and **32** were heated simultaneously and found to yield the same products as when they were heated separately. There was no evidence for the formation of the crossover products **35** and **36,**[293] which indicates that the rearrangement must be intramolecular.

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[286] J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, **101**, 6693 (1979); R. L. Vance, N. G. Rondan, K. N. Houk, H. F. Jensen, W. T. Borden, A. Komornicki, and E. Winner, *J. Am. Chem. Soc.*, **110**, 2314 (1988); L. Kupczyk-Subotkowska, W. H. Saunders, Jr., H. J. Shine, and W. Subotkowski, *J. Am. Chem. Soc.*, **115**, 5957 (1993); M. P. Meyer, A. J. Del Monte, and D. A. Singleton, *J. Am. Chem. Soc.*, **121**, 10865 (1999).

[287] B. Ganem, *Angew. Chem. Int. Ed. Engl.*, **35**, 937 (1996).

[288] P. A. Grieco, E. B. Brandes, S. McCann, and J. D. Clark, *J. Org. Chem.*, **54**, 5849 (1989); A. Lubineau, J. Auge, N. Bellanger, and S. Caillebourdin, *J. Chem. Soc., Perkin Trans. 2*, 1631 (1992).

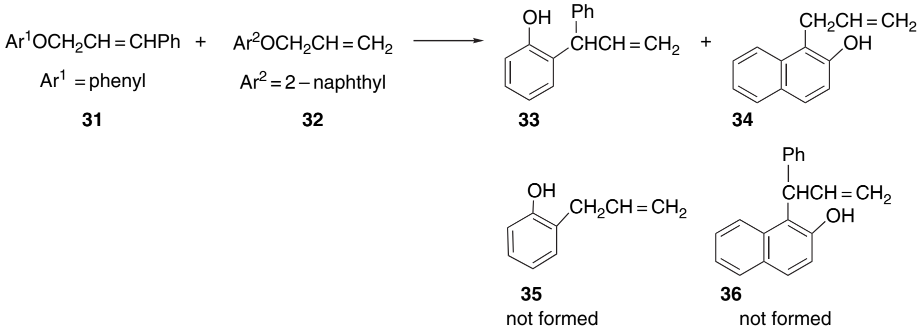
[289] D. L. Severance and W. L. Jorgensen, *J. Am. Chem. Soc.*, **114**, 10966 (1992); M. M. Davidson and I. H. Hillier, *J. Phys. Chem.*, **99**, 6748 (1995); J. J. Gajewski, *Acc. Chem. Res.*, **30**, 219 (1997).

[290] D. S. Tarbell, *Org. React.*, **2**, 1 (1944); S. J. Rhoads, in *Molecular Rearrangements*, Vol. 1, P. de Mayo, ed., Interscience, New York, 1963, pp. 655–684.

[291] J. P. Ryan and P. R. O’Connor, *J. Am. Chem. Soc.*, **74**, 5866 (1952).

[292] I. A. Pearl, *J. Am. Chem. Soc.*, **70**, 1746 (1948).

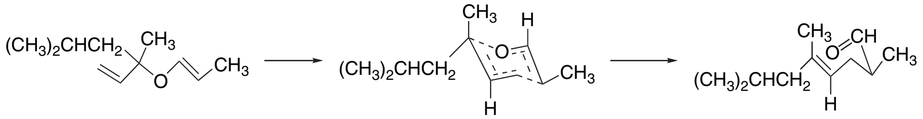
[293] C. D. Hurd and L. Schmerling, *J. Am. Chem. Soc.*, **59**, 107 (1937).


Ar¹OCH₂CH=CHPh
Ar¹ = phenyl
Ar²OCH₂CH=CH₂
Ar² = 2-naphthyl
OH
Ph
CHCH=CH₂
CH₂CH=CH₂
OH
OH
CH₂CH=CH₂
Ph
CHCH=CH₂
OH

31 **32** **33** **34**

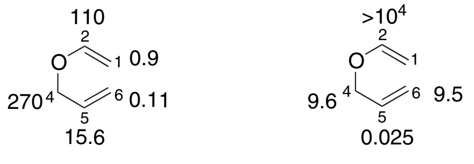
35 not formed **36** not formed

The stereochemical features of the Claisen rearrangement are very similar to those described for the Cope rearrangement, and stereochemical predictions can be made on the basis of the preference for a chairlike TS. The major product has the *E*-configuration at the newly formed double bond because of the preference for placing the larger substituent in the pseudoequatorial position in the TS.[294]


(CH₃)₂CHCH₂
CH₃
O
CH₃
CH₃
H
(CH₃)₂CHCH₂
O
CH₃
H
CH₃
CH
O
CH₃
(CH₃)₂CHCH₂
H

Studies of chiral substrates have also demonstrated that chirality is maintained in the reaction.[295] Examples of the synthetic application of the Claisen rearrangement are discussed in Section 6.4.2.1 of Part B.

Like the Cope rearrangement, the Claisen rearrangement is sensitive to substituents on the reacting system. Cyano groups promote the rearrangement by a factor of 10^2 at positions 2 and 4 and have smaller effects at the other positions, as shown in the diagram below.[296] Experimental data are also available for methoxy groups at positions 2, 4, 5, and 6.[297] The methoxy substituent is very activating at C(2). These substituents set the pattern for π-conjugated EWG and σ-donor substituents, respectively.


110
2
O
1
0.9
270
4
6
0.11
5
15.6
>10⁴
2
O
1
9.6
4
6
9.5
5
0.025

cyano methoxy

Relative rate effect of cyano and methoxy substituents

As in the case of the Cope rearrangement, the interpretation of these substituent effects is best approached by considering the effect on TS stability. The effect on the TS for the Claisen rearrangement by hydroxy substituents has been probed using both HF/6-31G* and B3LYP/6-31G* calculations.[298] The effect of cyano, amino, and trifluoromethyl groups has also been calculated.[299] The effect of methoxy groups has been examined using a combination AM1-MM method. The predicted changes in E_a, as summarized in Table 10.8, are in qualitative agreement with experimental results.

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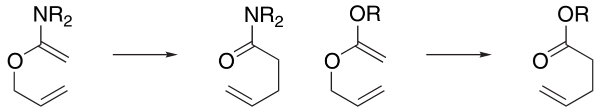
[294] R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 2095 (1967); A. W. Burgstahler, *J. Am. Chem. Soc.*, **82**, 4681 (1960); C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969).

[295] H. L. Goering and W. I. Kimoto, *J. Am. Chem. Soc.*, **87**, 1748 (1965).

[296] C. J. Burrows and B. K. Carpenter, *J. Am. Chem. Soc.*, **103**, 6983 (1981).

[297] R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck, and D. P. Curran, *J. Am. Chem. Soc.*, **109**, 1160 (1987).

These substituent effects can be analyzed by considering the effect on reactants, products, and the TS. For example, the large accelerating effect of 2-alkoxy and 2-amino substituents is due in substantial part to the amide and ester resonance stabilization that develops in the products.



The analysis can be done in terms of the Marcus theory by considering the effect on overall reaction energy ΔE_{rxn} and $\Delta E_0^{\ddagger}$, the *intrinsic barrier*, using a version of the Marcus equation.[300] (See Section 3.3.2.3 to review the Marcus equation.)

$$\Delta E^{\ddagger} = \Delta E_0^{\ddagger} + \tfrac{1}{2}\Delta E_{\text{rxn}} + (\Delta E_{\text{rxn}})^2/16(\Delta E_0^{\ddagger})$$

For the HF/6-31G* calculations, the barriers were separated into effects owing to changes in reaction energy and changes in TS energy.[299b] Changes in TS energy can be analyzed in terms of radical stabilization effects, as was done for the Cope rearrangement. (see p. 924ff). In addition, there may be variation in the extent of the polar character at the TS. The TS for the Claisen rearrangement has some ionic character, resembling an enolate for C(1), C(2), and O(3) and allyl cation for C(4), C(5), C(6). For the parent reaction, charge transfer is calculated to be 0.21*e*. The stabilizing effect of the 4- and 6-oxy substituents may be due to stabilization of the cationic fragment, as indicated by the charge distribution below.

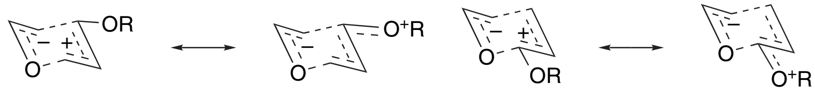


Table 10.8. Calculated Substituent Effects on E_a in kcal/mol for Claisen Rearrangement

Position	OH[a]	CN[b]	NH_2[b]	CF_3[b]	OCH_3[c]
1	−2.7	+0.1	−5.5	+1.1	
2	−9.1	−3.8	−6.7	−3.8	−9.1
4	−1.0	−4.8	−8.6	−1.2	−4.7
5	+5.0	−2.4	+4.5	−1.8	+4.0
6	−0.6	+2.6	−2.3	+1.6	−1.2

a. HF/6-31G*: H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997);
b. B3LYP/6-31G*: V. Aviyente and K. N. Houk, *J. Phys. Chem. A*, **105**, 383 (2001).
c. AM1-MM: A. Sehgal, L. Shao, and J. Gao, *J. Am. Chem. Soc.*, **117**, 11337 (1995).

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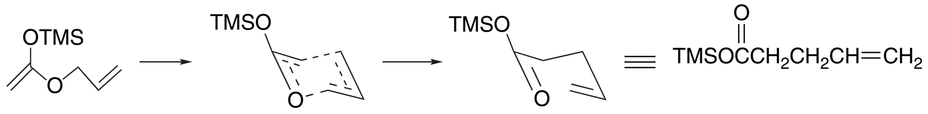
[298] H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, **119**, 2877 (1997).

[299] (a) V. Aviyente, H. Y. Yoo, and K. N. Houk, *J. Org. Chem.*, **62**, 6121 (1997); (b) V. Aviyente and K. N. Houk, *J. Phys. Chem. A*, **105**, 383 (2001).

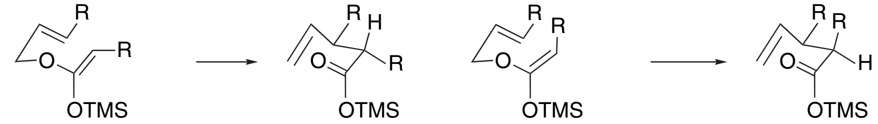
[300] M. Y. Chen and J. R. Murdoch, *J. Am. Chem. Soc.*, **106**, 4735 (1984).

The decelerating effect of the 5-substituent is primarily on TS energy and is reflected in the intrinsic barrier. Structurally, this may be due to a repulsive interaction between the 5-oxy substituent and the ring oxygen.

Other donor substituents, e.g., trimethylsilyloxy, at C(2) are strongly accelerating.[301] This effect is the basis of the synthetic importance of ester enolate Claisen rearrangements, in which enolates or silyl ketene acetals of allylic esters are rearranged into 4-pentenoate esters.[302] This reaction is known as the *Ireland-Claisen rearrangement.*

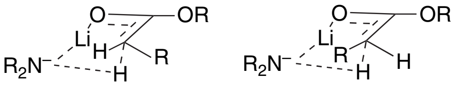


The stereoselectivity of the Ireland-Claisen rearrangement is controlled by the configuration of the double bonds in both the allylic alcohol and the silyl ketene acetal. The chair TS model predicts that the configuration at the newly formed C−C bond will be determined by the *E*- or *Z*-configuration of the silyl ketene acetal.



Z-silyl ketene acetal *syn*-isomer *E*-silyl ketene acetal *anti*-isomer

The stereochemistry of the silyl ketene acetal can be controlled by the conditions of preparation. The base that is usually used for enolate formation is lithium diisopropylamide (LDA). If the enolate is prepared in pure THF, the *E*-enolate is generated and this stereochemistry is maintained in the silyl derivative. The preferential formation of the *E*-enolate can be explained in terms of a cyclic TS in which the proton is abstracted from the stereoelectronically preferred orientation, more or less perpendicular to the carbonyl plane. Steric interaction between the base and the α-substituent disfavors the TS for the *Z*-enolate.



TS for *E*-enolate favored

TS for *Z*-enolate disfavored

If HMPA is included in the solvent, the *Z*-enolate predominates.[303] DMPU also favors the *Z*-enolate. The switch to the *Z*-enolate with HMPA or DMPU is attributed to a looser, perhaps acyclic, TS being favored as the result of strong solvation of the lithium ion by the cosolvent. The steric factors favoring the *E*-TS are therefore diminished.[304]

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[301] J. J. Gajewski and J. Emrani, *J. Am. Chem. Soc.*, **106**, 5733 (1984); S. E. Denmark and M. A. Harmata, *J. Am. Chem. Soc.*, **104**, 4972 (1982).

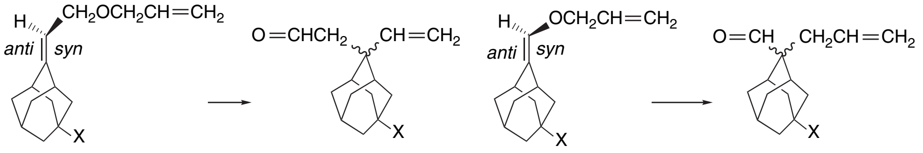
[302] S. Pereira and M. Srebnik, *Aldrichimica Acta*, **26**, 17 (1993).

[303] R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1972); R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

[304] C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

These general principles of solvent control of enolate stereochemistry are applicable to other systems.[305]

The sensitivity of the Claisen rearrangement to remote substituent effects has been examined using 2-adamantyl vinyl ethers and allyl 2-adamantylidene ethers.[306] σ-EWG substituents favor formation of the *syn*-isomer.

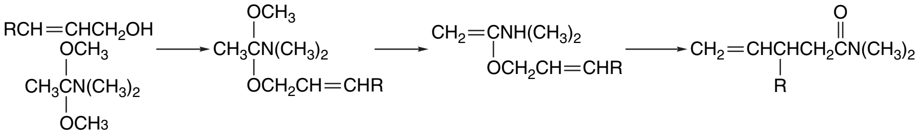


X = Ph: *syn:anti* = 57:43

X = F: *syn:anti* = 61:39

The conclusion drawn is that the TS is relatively electron deficient and is preferentially stabilized by the more electron rich (unsubstituted) of the two adamantyl bonds. A significant feature of this interpretation is that it applies to *both* the cationic and enolate fragments. Although the ionic character of both fragments is relatively small, it appears that the ability to interact with electrons from alkyl groups stabilizes both fragments. This result is consistent with the radical character of the two fragments. A similar facial selectivity was observed in the anionic oxy-Cope rearrangements.[307] In this case, the TS bears a *negative charge*, but is still stabilized by the better donor bond.

10.6.3.3. [3,3]-Sigmatropic Rearrangement of Trienes Containing Nitrogen A reaction that is closely related to the orthoester Claisen rearrangement utilizes an amide acetal, such as dimethylacetamide dimethyl acetal, in the exchange reaction with allylic alcohols and gives amides of γ, δ-unsaturated carboxylic acids.[308] The stereochemistry of the reaction is analogous to the other variants of the [3,3]-sigmatropic rearrangement.[309]



O-allyl imidate esters undergo [3,3]-sigmatropic rearrangements to *N*-allyl amides. This is sometimes referred to as an *aza-Claisen rearrangement* and the resonance stabilization of the amide bond that is formed provides a thermodynamic driving force. Trichloromethyl imidates can be easily made from allylic alcohols by reaction with trichloroacetonitrile. The rearrangement then provides trichloroacetamides of *N*-allylamines.[310] Yields in the reaction are sometimes improved by inclusion of K_2CO_3 in the reaction mixture.[311]

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[305] J. Corset, F. Froment, M.-F. Lautie, N. Ratovelomanana, J. Seyden-Penne, T. Strzalko, and M. C. Roux-Schmitt, *J. Am. Chem. Soc.*, **115**, 1684 (1993).

[306] A. Mukherjee, Q. Wu, and W. J. le Noble, *J. Org. Chem.*, **59**, 3270 (1994).

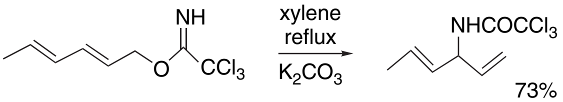
[307] M.-H. Lin, W. H. Watson, R. P. Kashyap, and W. J. le Noble, *J. Org. Chem.*, **55**, 3597 (1990).

[308] A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).

[309] W. Sucrow, M. Slopianka, and P. P. Calderia, *Chem. Ber.*, **108**, 1101 (1975).

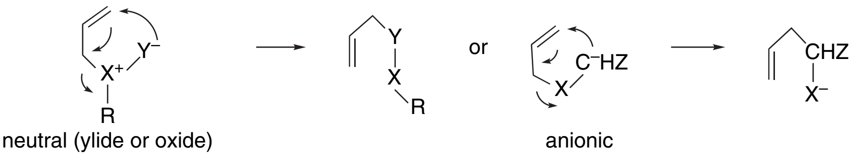
[310] L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976); L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

[311] T. Nishkawa, M. Asai, N. Ohyabu, and M. Isobe, *J. Org. Chem.*, **63**, 188 (1998).



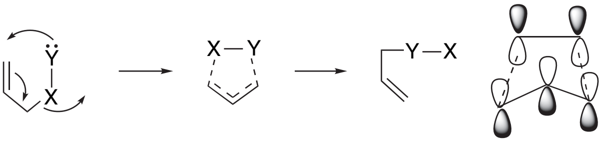
10.6.4. [2,3]-Sigmatropic Rearrangements

10.6.4.1. Mechanism of [2,3]-Sigmatropic Rearrangements There are also concerted rearrangements that exhibit a [2,3]-sigmatropic reactivity pattern. The [2,3]-sigmatropic class of rearrangements is represented by two generic charge types, one involving ylides or oxides and the other those of anions.



One requirement for a facile [2,3]-sigmatropic process is that the atom X at the allylic position be able to act as a leaving group as the adjacent atom Y begins bonding to the allyl system, so X is normally an electronegative element. The reaction is most facile in systems where the atoms X and Y bear formal charges, as in the case of ylides and oxides. The most well developed of these reactions are rearrangements of allyl sulfoxides[312] and selenoxides[313] and of ammonium[314] and sulfonium[315] ylides. In the anionic variation, the group Z must be able to facilitate formation of the carbanion. The most useful examples of the anionic type are rearrangements of carbanions of allyl ethers. Scheme 10.11 outlines these kinds of [2,3]-sigmatropic rearrangements.

The TS for 2,3-sigmatropic shifts is viewed as involving an allylic system and the migrating fragment. There are six participating electrons in a Hückel-type array, so the TS is aromatic.



There have been several computational studies of [2,3]-sigmatropic rearrangements. MP3/3-21G*-level calculations of the allyl sulfoxide rearrangement reproduce the stereoselectivity and activation energies.[316] This and several related rearrangements exhibit TS aromaticity in terms of magnetic criteria (NICS and magnetic susceptibility).[317] The mechanism of the anionic [2,3]-sigmatropic Wittig rearrangement has

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[312] D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

[313] K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973); D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978); Y. Nishibayashi and S. Uemura, *Top. Curr. Chem.*, **208**, 201 (2000).

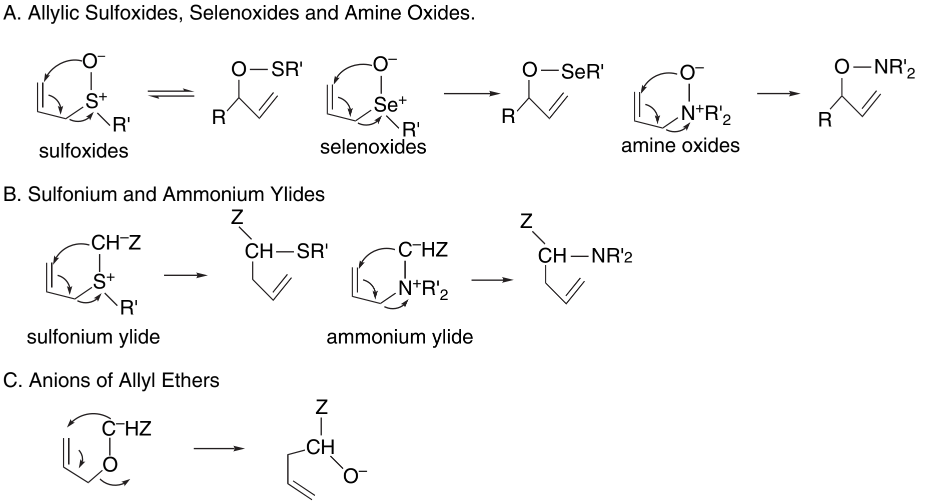
[314] E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.*, **43**, 1185 (1978).

[315] B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York, 1975.

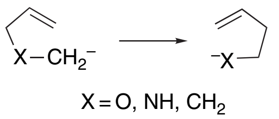
[316] D. K. Jones-Hertzog and W. L. Jorgensen, *J. Am. Chem. Soc.*, **117**, 9077 (1995); D. K. Jones-Hertzog and W. L. Jorgensen, *J. Org. Chem.*, **60**, 6682 (1995); B. S. Jursic, *Theochem*, **338**, 131 (1995).

[317] F. P. Cossio, I. Morao, H. Jiao, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **121**, 6737 (1999); A. A. Fonkin, A. O. Kushko, A. V. Kirij, A. G. Yurchenko, and P. v. R. Schleyer, *J. Org. Chem.*, **65**, 2984 (2000).

Scheme 10.11. Examples of [2,3]-Sigmatropic Rearrangements

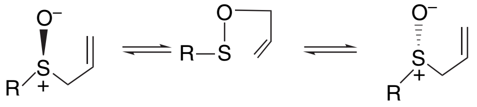

A. Allylic Sulfoxides, Selenoxides and Amine Oxides.
O⁻
S⁺
R'
sulfoxides
O—SR'
R
O⁻
Se⁺
R'
selenoxides
O—SeR'
R
O⁻
N⁺R'2
amine oxides
O—NR'2
R
B. Sulfonium and Ammonium Ylides
CH⁻Z
S⁺
R'
sulfonium ylide
Z
CH—SR'
C⁻HZ
N⁺R'2
ammonium ylide
Z
CH—NR'2
C. Anions of Allyl Ethers
C⁻HZ
O
Z
CH
O⁻

been probed by B3LYP/6-31+G* computations and comparisons made for carbon, nitrogen, and oxygen prototypes.[318]


X−CH2⁻
⁻X
X = O, NH, CH2

Computation in the gas phase did not locate a concerted TS, but indicated instead that the reactions proceed by dissociation-reassociation. The reassociation process has no barrier, whereas the dissociation has a very small one (2.4–2.6 kcal/mol). For the oxy anion, inclusion of a Li^+ counterion resulted in a concerted process with a barrier of about 12 kcal/mol. Since this more closely approximates solution conditions, it suggests that a concerted mechanism is feasible in solution. The dissociation mechanism is favored for both nitrogen and carbon.

10.6.4.2. [2,3]-Sigmatropic Rearrangements of Oxides and Ylides The rearrangement of allylic sulfoxides to allylic sulfenates first received attention in connection with the mechanism of racemization of allyl aryl sulfoxides.[319] Although the allyl sulfoxide structure is strongly favored at equilibrium, rearrangement through the achiral allyl sulfenate provides a low-energy pathway for racemization.



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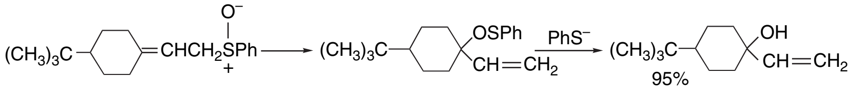
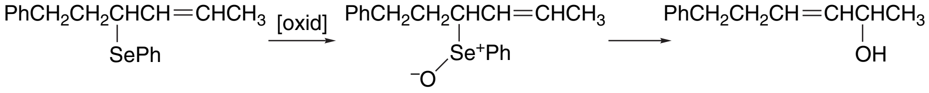
[318] F. Haeffner, K. N. Houk, S. M. Schulze, and J. K. Lee, *J. Org. Chem.*, **68**, 2310 (2003).
[319] R. Tang and K. Mislow, *J. Am. Chem. Soc.*, **92**, 2100 (1970).

The allyl sulfoxide–allyl sulfenate rearrangement can be used to prepare allylic alcohols. The reaction is carried out in the presence of a reagent, such as phenylthiolate or trimethyl phosphite, that traps the sulfenate by cleaving the S−O bond.

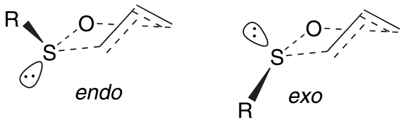

(CH3)3C
=CHCH2SPh
O−
+
(CH3)3C
OSPh
CH=CH2
PhS−
(CH3)3C
OH
CH=CH2
95%

Ref. 320

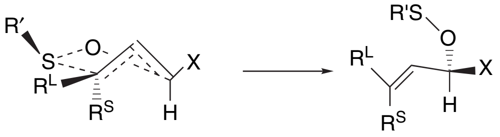
An analogous transposition occurs with allylic selenoxides, which can be generated in situ by oxidation of allylic seleno ethers.[321]


PhCH2CH2CHCH=CHCH3
SePh
[oxid]
PhCH2CH2CHCH=CHCH3
Se+Ph
−O
PhCH2CH2CH=CHCHCH3
OH

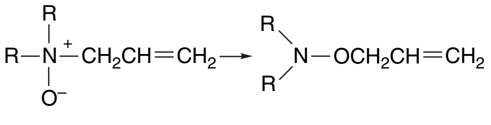
There are two possible TS structures for the rearrangement of allylic sulfoxides, known as *exo* and *endo*. For acyclic systems, the *endo* TS, that is, with the sulfur substituent pointed toward the allylic fragment, is preferred.[322]


R
O
S
endo
O
S
R
exo

The stereochemistry of the new double bond depends on the conformational preference of the α-substituents. The preference is not high for primary groups, but branched groups prefer a pseudoequatorial position and lead to the E-isomer.[323]


R′
S
O
X
RL
RS
H
R'S
O
RL
X
H
RS

N-Allylamine oxides represent the pattern for [2,3]-sigmatropic rearrangement where X = N and Y = O^-. The rearrangement provides O-allyl hydroxylamine derivatives.


R
R−N−CH2CH=CH2
+
O−
R
N−OCH2CH=CH2
R

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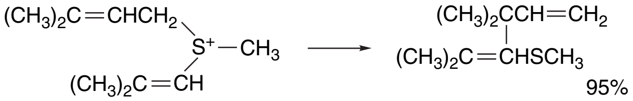
[320] D. A. Evans, G. C. Andrews, and C. L. Sims,*J. Am. Chem. Soc.*, **93**, 4956 (1971).

[321] H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); D. L. J. Clive, G. Chittatu, N. J. Curtis, and S. M. Menchen, *Chem. Commun.*, 770 (1978).

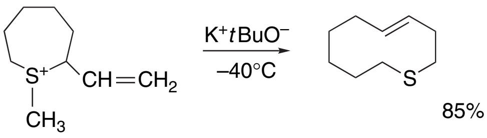
[322] R. W. Hoffmann and N. Maak, *Tetrahedron Lett.*, 2237 (1976); H. J. Reich, K. E. Yelm, and S. Wollowitz, *J. Am. Chem. Soc.*, **105**, 2503 (1983).

[323] T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.*, **54**, 2779 (1989).

Allylic sulfonium ylides readily undergo [2,3]-sigmatropic rearrangement.[324]

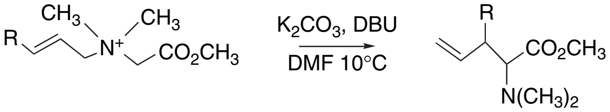

$(CH_3)_2C{=}CHCH_2$
$S^+{-}CH_3$
$(CH_3)_2C{=}CH$
$(CH_3)_2CCH{=}CH_2$
$(CH_3)_2C{=}CHSCH_3$
95%

This reaction results in formation of a new carbon-carbon bond. The reaction proceeds best when the ylide has a carbanion-stabilizing substituent. It has found synthetic application in ring-expansion sequences for generation of medium-sized rings.

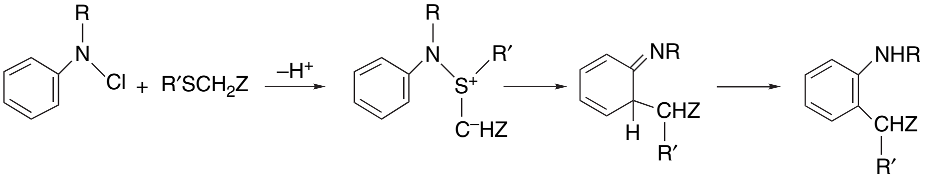

S^+
$CH{=}CH_2$
CH_3
K^+tBuO^-
–40°C
S
85%

Ref. 325

The corresponding ammonium ylides can also be generated when one of the nitrogen substituents has an anion-stabilizing group on the α-carbon. For example, quaternary salts of *N*-allyl α-aminoesters readily rearrange to α-allyl products.[326]


R
CH_3
CH_3
N^+
CO_2CH_3
K_2CO_3, DBU
DMF 10°C
R
CO_2CH_3
$N(CH_3)_2$

A useful method for *ortho*-alkylation of aromatic amines is based on [2,3]-sigmatropic rearrangement of *S*-anilinosulfonium ylides. These ylides are generated from anilinosulfonium ions, which can be prepared from *N*-chloroanilines and sulfides.[327]


R
N
Cl
+ $R'SCH_2Z$
$-H^+$
R
N
R′
S^+
C^-HZ
NR
CHZ
H
R′
NHR
CHZ
R′

This method is the basis for synthesis of nitrogen-containing heterocyclic compounds when Z is a carbonyl-containing group that can undergo cyclization with the amino group.[328]

10.6.4.3. [2,3]-Sigmatropic Rearrangements of Anions The [2,3]-sigmatropic rearrangement pattern is also observed with anionic species. The most important case for synthetic purposes is the *Wittig rearrangement*, in which a strong base converts allylic ethers to α-allyl alkoxides.[329]

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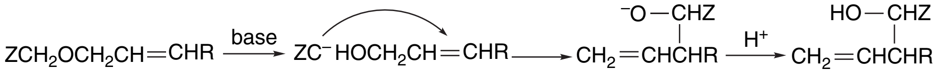
[324] J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537 (1968).

[325] V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978).

[326] I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2951 (1997); I. Coldham, M. L. Midleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1998).

[327] P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **100**, 7600 (1978).

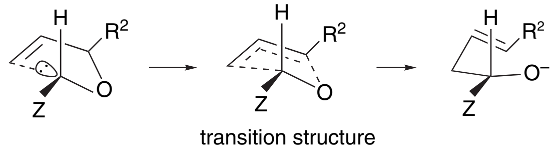
[328] P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).



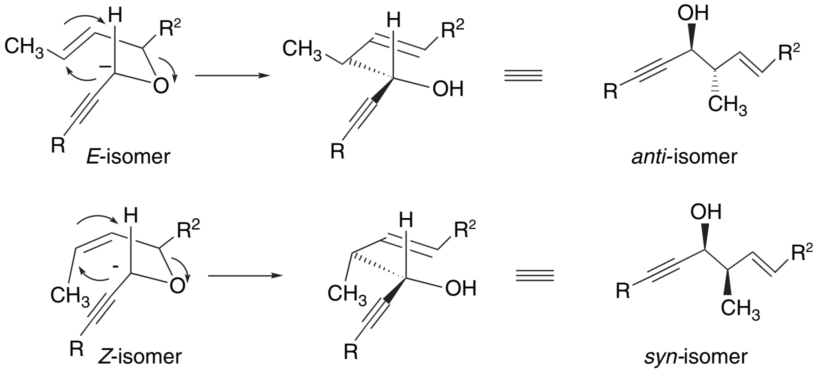
$$\mathrm{ZCH_2OCH_2CH{=}CHR} \xrightarrow{\text{base}} \mathrm{ZC^{-}HOCH_2CH{=}CHR} \longrightarrow \begin{array}{c} ^{-}\mathrm{O{-}CHZ} \\ | \\ \mathrm{CH_2{=}CHCHR} \end{array} \xrightarrow{H^+} \begin{array}{c} \mathrm{HO{-}CHZ} \\ | \\ \mathrm{CH_2{=}CHCHR} \end{array}$$

As the deprotonation at the α'-carbon must compete with deprotonation of the α-carbon in the allyl group, most examples involve a conjugated or electron-withdrawing substituent Z that can facilitate deprotonation.[330] In addition to direct deprotonation, there are other means of generating the anions of allyl ethers.[331,332]

The stereochemistry of the Wittig rearrangement can be predicted in terms of a cyclic TS in which the α-substituent R^2 prefers an equatorial orientation.[333]



A consistent feature of the stereochemistry is a preference for *E*-stereochemistry at the newly formed double bond, but the reaction can also show stereoselectivity at the newly formed single bond. This stereoselectivity has been carefully studied for the case where the substituent Z is an acetylenic group.



The preferred stereochemistry arises from the TS that minimizes interaction between the alkynyl and R^2 substituents. This stereoselectivity is exhibited in the rearrangement of **37** to **38**.

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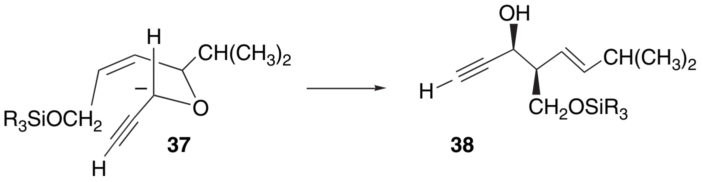
[329] J. Kallmarten, in *Stereoselective Synthesis, Houben Weyl Methods in Organic Chemistry*, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., G. Thieme Verlag, Stuttgart, 1996, pp. 3810; T. Nakai and K. Mikami, *Org. Reactions*, **46**, 105 (1994).

[330] For reviews of [2,3]-sigmatropic rearrangement of allyl ethers, see T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).

[331] W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, **100**, 1927 (1978).

[332] K. Hioki, K. Kono, S. Tani, and M. Kunishima, *Tetrahedron Lett.*, **39**, 5229 (1998).

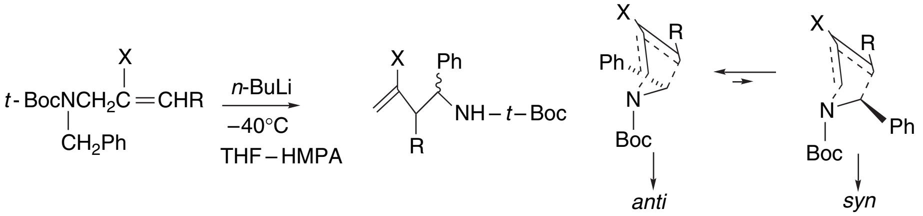
[333] R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **18**, 563 (1979); K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983); K. Mikami, K. Azuma, and T. Nakai, *Tetrahedron*, **40**, 2303 (1984); Y.-D. Wu, K. N. Houk, and J. A. Marshall, *J. Org. Chem.*, **55**, 1421 (1990).



Ref. 334

The effect of substituents on the TS has been explored using MP3/6-31+G* computations.[335] An alkynyl group at C(5) results in a much later TS than in the unsubstituted case and the TS has greater cyclic character. This tighter TS would be expected to be more sensitive to the steric effects that lead to stereoselectivity. These computations also indicated a preference for carbonyl substituents to adopt an *s-trans-endo* conformation that leads to the observed *syn* stereoselectivity. Inclusion of a Li^+ cation leads to a chelated TS, again in accord with observed stereochemistry. These TSs are depicted in Figure 10.40. α-Carboxy substituents also lead to reaction through chelated TSs.[336]

[2,3]-Sigmatropic rearrangements of anions of *N*-allyl amines have also been observed and are known as aza-Wittig rearrangements.[337] The reaction requires anion-stabilizing substituents and is favored by *N*-benzyl and by silyl or sulfenyl substituents on the allyl group.[338] The reaction is further facilitated by *N*-acyl groups and by EWGs on the amide nitrogen.[339] These groups all facilitate the initial deprotonation and the charge redistribution that accompanies rearrangement. The steric interactions between the benzyl group and allyl substituent govern the stereoselectivity, which markedly improved in the trimethylsilyl derivatives.[340]



R	X	*syn:anti*
CH_3	H	3:2
C_2H_5	H	1:1
$(CH_3)_2CH$	H	4:3
CH_3	$Si(CH_3)_3$	<1:20
C_2H_5	$Si(CH_3)_3$	1:18
$(CH_3)_2CH$	$Si(CH_3)_3$	1:11

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[334] M. M. Midland and J. Gabriel, *J. Org. Chem.*, **50**, 1143 (1985).

[335] K. Mikami, T. Uchida, T. Hirano, Y.-D. Wu, and K. N. Houk, *Tetrahedron*, **50**, 5917 (1994).

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[338] J. C. Anderson, S. C. Smith, and M. E. Swarbrick, *J. Chem. Soc., Perkin Trans. 1*, 1517 (1997).

[339] J. C. Anderson, A. Flaherty, and M. E. Swarbrick, *J. Org. Chem.*, **65**, 9152 (2000).

[340] J. C. Anderson, D. C. Siddons, S. C. Smith, and M. E. Swarbrick, *J. Org. Chem.*, **61**, 4820 (1996).

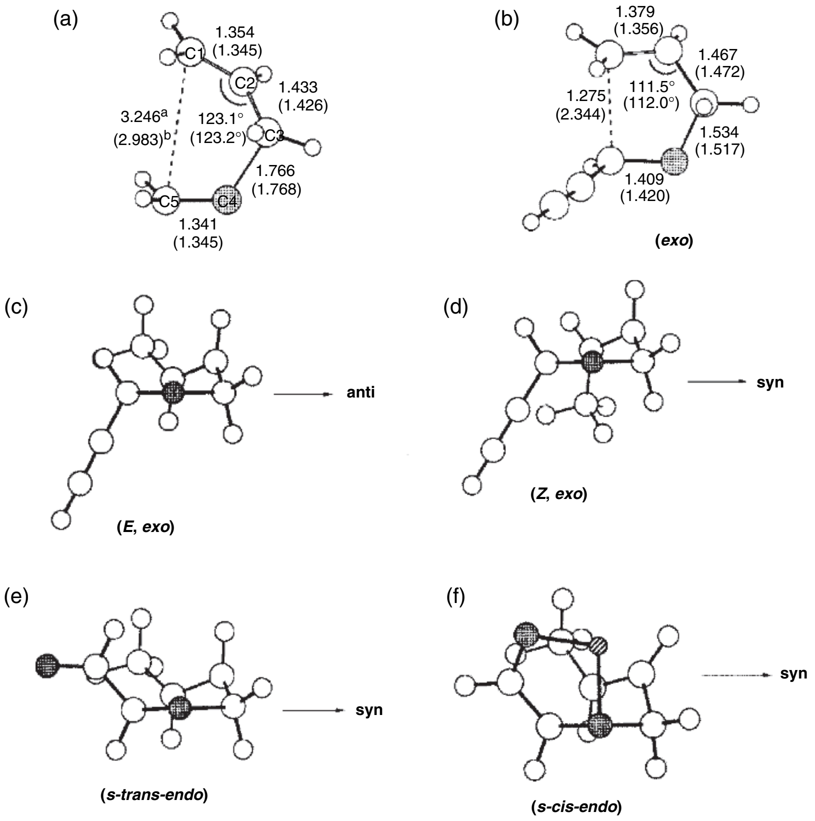
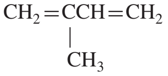
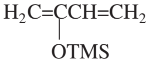

(a)
1.354
(1.345)
C1
C2
1.433
(1.426)
3.246a
(2.983)b
123.1°
(123.2°)
C3
1.766
(1.768)
C5
C4
1.341
(1.345)
(b)
1.379
(1.356)
1.467
(1.472)
1.275
(2.344)
111.5°
(112.0°)
1.534
(1.517)
1.409
(1.420)
(exo)
(c)
anti
(E, exo)
(d)
syn
(Z, exo)
(e)
syn
(s-trans-endo)
(f)
syn
(s-cis-endo)

Fig. 10.40. Relationship between TS structure and stereoselectivity in [2,3]-sigmatropic rearrangement of alloxy carbanions: (a) early TS for unsubstituted allyloxymethyl anion; (b) tighter cyclic TS for stabilized allyloxypropargyl anion; (c,d) preferred conformation of *E*- and *Z*-crotyloxypropargyl anions leading to the *E* → *anti* and *Z* → *syn* stereoselectivity; (e,f) unchelated and chelated TSs for α-crotyloxy ethanal enolate leading to the *E* → *syn* stereoselectivity. Reproduced from *Tetrahedron*, **50**, 5917 (1994), by permission of Elsevier.

Topic 10.1. Application of DFT Concepts to Reactivity and Regiochemistry of Cycloaddition Reactions

Recently, attempts have been made to understand both the relative reactivity and regioselectivity of the Diels-Alder reaction in terms of the DFT concepts of hardness and softness. Several DFT parameters have been examined as potential indicators of D-A reactivity. (See Topic 1.5 to review the DFT concepts of hardness, softness, Fukui functions, and global electrophilicity.) The D-A reaction can be thought of as having two components in the overall electronic reorganization, corresponding to initial charge transfer between the diene and dienophile, followed by electronic reconfiguration to generate the new bonds. These ideas parallel FMO theory, but DFT considers the total electron density rather than the distribution of the frontier orbitals.

Table 10.9. DFT Global Electrophilicity of Representative Dienes and Dienophiles[a]

Primarily Electrophilic		Balanced		Primarily Nucleophilic	
$(NC)_2C=C(CN)_2$	5.96	$CH_3CO_2CH=CHCH=CH_2$	1.10	$CH_3OCH=CHCH=CH_2$	0.77
Maleic anhydride	3.24	$CH_2=CHCH=CH_2$	1.05	$CH_2=CH_2$	0.73
$CH_2=CHCH=O^+B^-H_3$	3.20	 $CH_2=\underset{\substack{\vert\\ CH_3}}{C}CH=CH_2$	0.94	$TMSOCH=CHCH=CH_2$	0.73
$CH_2=C(CN)_2$	2.82			Furan	0.59
$CH_2=CHNO_2$	2.61	$CH_3CH=CHCH=CH_2$	0.93	$(CH_3)_2NCH=CHCH=CH_2$	0.57
$CH_3O_2CC\equiv CCO_2CH_3$	2.27	 $H_2C=\underset{\substack{\vert\\ OTMS}}{C}CH=CH_2$	0.88	$HC\equiv CH$	0.54
$CH_2=C(CO_2CH_3)_2$	1.93			2-Methylfuran	0.52
$CH_2=CHCH=O$	1.84	$(CH_3)_2C=CHCH=CH_2$	0.86		
$CH_2=CHCN$	1.74	Cyclopentadiene	0.83	$CH_3OCH=CH$	0.42
$CH_2=CHCOCH_3$	1.65			Pyrrole	0.31
$HC\equiv CCO_2CH_3$	1.52			$(CH_3)_2NCH=CH_2$	0.27
$CH_2=CHCO_2CH_3$	1.50				

a. From L. R. Domingo, M. Aurell, P. Perez, and R. Contreras, *Tetrahedron*, **58**, 4417 (2002).

Domingo investigated the *global electrophilic parameter*, ω, as an indicator of relative reactivity.[341] Table 10.9 gives the value of this parameter calculated for a number of dienes and dienophiles.

This parameter gives an ordering that is in good qualitative agreement with the reactivity trends that would be expected on the basis of polar and resonance substituent interactions, although the parent molecules, ethene and ethyne, are somewhat more toward the nucleophilic side of the scale than might have been anticipated. The electrophilic group includes the traditional dienophiles such as acrolein and acrylonitrile. Dienes with donor substituents, such as 1-methoxy-1,3-butadiene, exhibit the anticipated nucleophilic characteristics. Note that a 1-ERG seems to have a stronger effect than a 2-ERG (compare the isomeric trimethylsiloxy-1,3-butadienes). This is consistent with the greater reactivity of 1-methoxy-1,3-butadiene than the 2-isomer (see Table 10.2). Methoxyethene and dimethylaminoethene are among the most nucleophilic dienophiles in the list. It should be noted that ω is a *global* parameter; that is, it pertains to the molecule as a whole. Thus, it gives no indication of the regioselectivity of the reaction, but is an indicator of the direction and extent of electron transfer between the reactants. The idea that increased charge transfer increases reactivity suggests that mutual reactivity will be highest for compounds that have the largest difference in ω. This is equivalent to the FMO concept that the strongest donors and strongest acceptors will have the highest mutual reactivity.

The issue of regiochemistry can be addressed by identifying sites of *local electrophilicity* and *local nucleophilicity*. This was done by calculation of a *local electrophilicity index*.[342] The index of nucleophilicity can be taken as f^-, the local Fukui function for electrophilic attack. The regiochemistry is then predicted by matching the highest local electrophilicity in the electrophilic component with the largest f^- for the nucleophilic component. Table 10.10 gives some values of representative dienes and dienophiles.

We see that a terminal ERG on the diene leads to $f^-_{(1)} > f^-_{(4)}$, that is, the carbon at the *end* of the conjugated system is the most nucleophilic. For example, compare the f^- values for the substituted (4) and unsubstituted (1) atoms for 1,3-pentadiene, and

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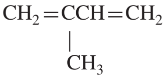
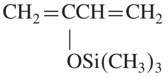
[341] L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *Tetrahedron*, **58**, 4417 (2002).

[342] L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Phys. Chem. A*, **106**, 6871 (2002).

Table 10.10. Local Electrophilicity and Fukui Functions for Some Dienes and Dienophiles[a]

Dienes	C(1)		C(4)	
1 4	ω	f^-	ω	f^-
$CH_2=CHCH=CH_2$	0.355	0.338	0.355	0.338
$CH_2=CHCH=CHCH_3$	0.300	0.309	0.282	0.2296
 $CH_2{=}\underset{\underset{CH_3}{\vert}}{C}CH{=}CH_2$	0.316	0.380	0.354	0.289
$CH_2=CHC=C(CH_3)_2$	0.277	0.273	0.234	0.277
$CH_2=CHCH=CHOCH_3$	0.251	0.290	0.240	0.217
$CH_2=CHCH=CHOSi(CH_3)_3$	0.232	0.264	0.217	0.218
 $CH_2{=}\underset{\underset{OSi(CH_3)_3}{\vert}}{C}CH{=}CH_2$	0.240	0.465	0.315	0.212
$CH_2=CHCH=CHN(CH_3)_2$	0.173	0.304	0.230	0.117
Dienophiles	C(1)		C(2)	
1 2	ω	f^+	ω	f^+
$CH_2{=}CH{=}O^+{-}B^-H_3$	1.144	0.357	0.253	0.079
$CH_2=C(CN)_2$	1.407	0.499	0.589	0.209
$CH_2=CHNO_2$	0.726	0.279	0.200	0.077
$CH_2=CHCH=O$	0.685	0.372	0.253	0.137
$CH_2=CHCN$	0.816	0.469	0.461	0.265
$CH_2=CHCOCH_3$	0.579	0.351	0.250	0.152
$CH_2=CHCO_2CH_3$	0.617	0.409	0.300	0.199
$CH_2=CH_2$	0.365	0.500	0.365	0.500
$CH\equiv CH$	0.268	0.500	0.268	0.500
$CH_2=CHOCH_3$	0.183	0.435	0.194	0.463
$CH_2=CHN(CH_3)_2$	0.108	0.399	0.119	0.442

[a] From L. R. Domigo, M. J. Aurell, P. Perez, and R. Contreras, *J. Phys. Chem. A*, **106**, 6871 (2002).

for the cases substituted by methoxy, trimethylsilyloxy, and dimethylamino groups. This implies that the *unsubstituted* terminal carbon will be the most nucleophilic site of the diene, which is the same prediction that is made by resonance or FMO treatment of terminally substituted butadienes. For dienophiles having EWG substituents, the $\omega_{(local)}$ or f^+ parameters can indicate relative electrophilicity. For such dienophiles, the β-(unsubstituted)carbon is more electrophilic than the α-(substituted)carbon, again consistent with resonance and FMO conclusions. The local electrophilicity of ethene (0.365) is less than for EWG-substituted derivatives, in agreement with its lower reactivity as a dienophile.

In all the cases studied by this approach so far, the diene is the nucleophile and the dienophile is the electrophile. For this combination, the dienophile $\omega_{(global)}$ shows a correlation with reactivity, whereas comparison of the f^+ between C(1) and C(2) gives an indication of the regioselectivity. Dienophiles with EWG substituents have higher f^+ at the unsubstituted carbon, in agreement with observed regioselectivity. For ERG cases (methoxyethene and dimethylaminoethene) the ω value is small and the highest f^+ value shifts to the substituted carbon. For the dienes, the position with the largest f^- is predicted to be the most nucleophilic. The challenging case of dienes with 2-EWG groups (see p. 844) has not yet been addressed by DFT analysis.

Another DFT-based approach to regioselectivity focused on softness. It has been suggested, based on the DFT definitions, that maximum reactivity should occur when the local softness of reacting positions is matched.[343] This proposal has been explored in a quantitative way.[344] Local softness values were calculated for a number of substituted dienes and dienophiles. Then the alternative regioisomers were evaluated by comparing the alternative pairs:

$$\textit{Ortho}\ \text{regioisomer} = (s^{-}{}_{1} - \mathrm{s}^{+}{}_{1'})^2 + (s^{-}{}_{4} - s^{+}{}_{2'})^2 \qquad (10.4)$$

$$\textit{Meta}\ \text{regioisomer} = (s^{-}{}_{1} - s^{+}{}_{2'})^2 + (s^{-}{}_{4} - s^{+}{}_{1'})^2 \qquad (10.5)$$

where s^{-} and s^{+} are the local softness values for nucleophilic and electrophilic reactivity, as appropriate for the reaction of a nucleophilic diene with and electrophilic dienophile.

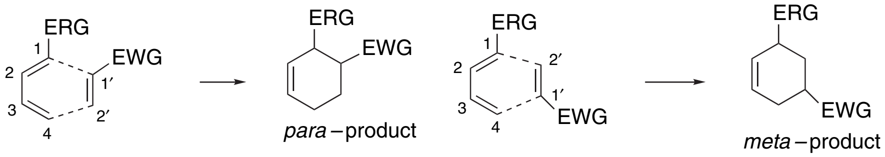


Table 10.11 gives the value of the local softness for some representative diene and dienophiles.

Qualitatively comparing these numbers to the traditional polar and resonance substituent effects, we see that for a donor substituent $s^{-}{}_{4} > s^{-}{}_{1}$. EWG substituents make $s^{+}{}_{2} > s^{+}{}_{1}$. However, the trend that dominates the sum of the differences in

Table 10.11. Local Softness Parameters for Dienes and Dienophiles[a]

Dienes 1-Substituent	$s^{+}{}_{1}$	$s^{-}{}_{1}$	$s^{+}{}_{4}$	$s^{-}{}_{4}$
CH_3	0.266	0.277	0.309	0.282
CH_3O	0.363	0.193	0.293	0.201
C_2H_5O	0.369	0.177	0.294	0.198
$(CH_3)_2N$	0.413	−0.137	0.321	0.193
$(C_2H_5)_2N$	0.396	−0.298	0.281	0.103
CO_2H	0.271	0.118	0.224	0.131
CN	0.416	0.354	0.264	0.319
Dienophiles 1-Substituent	$s^{+}{}_{1'}$	$s^{-}{}_{1'}$	$s^{+}{}_{2'}$	$s^{-}{}_{2'}$
CO_2H	0.167	0.073	0.306	0.150
CO_2CH_3	0.166	0.077	0.300	0.139
$CH=O$	0.030	0.024	0.309	0.276
CH_3CO	0.038	0.101	0.327	0.188
CN	0.296	−0.014	0.278	0.140
NO_2	−0.53	−0.073	0.291	0.258

a. From J. Damoun, G. Van de Woude, F. Mendez, and P. Geerlings, *J. Phys. Chem. A*, **101**, 886 (1997).

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[343] J. L. Gazquez and F. Mendez, *J. Phys. Chem.*, **98**, 4591 (1994).

[344] J. Damoun, G. Van de Woude, F. Mendez, and P. Geerlings, *J. Phys. Chem. A*, **101**, 886 (1997).

Equations (10.4) and (10.5) is the fact that the more remote positions (4 and 2′) *change less than the substituted positions.* Local softness parameters have also been calculated by a bond electronegativity equalization approach.[345] All the computations reported to date refer to diene (HOMO)-dienophile (LUMO) combination pairs, so it is not possible to see if this approach successfully predicts the case in which both the diene and the dienophile carry EWG substituents.

By comparing the FMO and DFT analyses, we see that most combinations of diene and dienophiles lead to the same prediction. The underlying physical basis of the predictions is also quite similar. In FMO theory it is the closeness in energy of the FMOs that is considered to be the origin of relative reactivity. Regioselectivity is attributed to maximum orbital overlap, as judged by the FMO coefficients. In the DFT approach, the extent of charge transfer (as measured by the global electrophilicity and nucleophilicity parameters) is considered to be the indicator of reactivity and local softness is considered to govern regioselectivity. The physical picture of the D-A reaction that emerges is one of *complementary electronic interactions* between the diene and dienophile that reduce the electron-electron repulsions that are otherwise dominant in the early stages of the reaction. Although both approaches can provide predictive relationships for a range of diene-dienophile combinations, neither has yet developed quantitative predictions of relative rates over a wide range of reactant combinations. This, of course, would be inherently difficult for combinations in which steric effects are significant, since neither FMO coefficients nor the DFT parameters take account of steric effects directly. It would be interesting to know, however, perhaps with cyanoethenes and cyanoethynes, if some combination of the local electrophilicity and softness parameters could account for relative reactivity.

Domingo and co-workers applied the DFT concepts of electrophilicity and softness in a study of all the possible cyanoethenes in reaction with cyclopentadiene, calculating the TS geometries, energies, and charge transfer at the B3LYP/6-31G* level.[346] Both gas phase and benzene solution E_a values were calculated. The geometries indicated that the TS is slightly earlier in benzene. For symmetrically substituted ethenes, the reactions are nearly synchronous, whereas for unsymmetrical dienophiles they are asynchronous. The global and local ω parameters were determined and the local electrophilicity parameter ω_2 was found to correlate with the number of cyano substituents, as would be expected.

Substitution	ω	ω_1	$f^+{}_1$	ω_2	$f^+{}_2$
1-CN	1.74	0.46	0.266	0.82	0.469
1,1-diCN	2.82	0.59	0.209	1.41	0.499
E-1,2-diCN	3.08	0.92	0.300	0.92	0.300
Z-1,2-diCN	3.01	0.92	0.306	0.92	0.306
1,1,2-triCN	4.38	1.03	0.236	1.46	0.333
1,1,2,2-tetraCN	5.96	1.53	0.257	1.53	0.257

The calculated E_a decreased with the value of ω, whereas the extent of charge transfer at the TS increased.

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[345] Y. Cong, Z. Z. Yang, C. S. Wang, X. C. Liu, and Y. H. Bao, *Chem. Phys. Lett.*, **357**, 59 (2002).

[346] L. R. Domingo, M. J. Aurell, P. Perez, and R. Contreras, *J. Org. Chem.*, **68**, 3884 (2003).

Substitution	E_a(gas)	E_a(benzene)	Charge transfer
1-CN	17.5	16.7	0.15
1,1-diCN	10.5	8.7	0.28
E-1,2-diCN	15.2	14.3	0.25
Z-1,2-diCN	16.3	14.5	0.24
1,1,2-triCN	11.3	9.0	0.36
1,1,2,2-tetraCN	11.5	8.7	0.43

The extent of charge transfer is more closely related to the total number of CN substituents rather than their position, i.e., 1,1- ~ *E*-1,2- ~ *Z*-1,2, but CN < diCN < triCN < tetraCN. On the other hand, the E_a is more sensitive to the placement of the substituents with those reactants with 1,1-diCN substitution having $E_a$near 9 kcal/mol, whereas those with 1-CN substitution are near 15 kcal/mol. Note that the decrease of E_a is also somewhat greater in benzene for the 1,1-diCN cases. These trends suggest that ability to accept negative charge at a 1,1-disubstituted carbon facilitates the reaction. It is also worth noting that according to these calculations, tetracyanoethene *does not* have an asynchronous TS, in contrast to several other very electrophilic dienophiles such as dimethyl acetylene dicarboxylate and maleic acid (see p. 855)

The application of DFT concepts to interpretation of relative reactivity and regioselectivity of 1,3-DPCA is being explored.[347] DFT recognizes both charge transfer interactions between the reactants and electron redistribution in the TS as key parts of the reaction process.[348] As discussed earlier for D-A reactions, DFT theory can also be

Table 10.12. Global Electrophilicity and $\Delta N_{\max}$ Parameters for 1,3-Dipoles[a]

Strongly Electrophilic			Moderately Electrophilic			Marginally Electrophilic		
	ω	$\Delta N_{\max}$		ω	$\Delta N_{\max}$		ω	$\Delta N_{\max}$
$O{=}\overset{+}{O}{-}\overset{-}{O}$	6.10	1.73	$H_2C{=}\overset{+}{N}{=}\overset{-}{N}$	1.40	0.77	$HC{\equiv}\overset{+}{N}{-}\overset{-}{O}$	0.73	0.43
$HN{=}\overset{+}{O}{-}\overset{-}{O}$	4.18	1.39	$N{\equiv}\overset{+}{N}{-}\overset{-}{O}$	1.37	0.56	$H_2C{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{NH}$	0.72	0.54
$HN{=}\overset{+}{O}\ \overset{-}{NH}$	2.88	1.17						
$H_2C{=}\overset{+}{O}{-}\overset{-}{O}$	2.43	1.08	$HN{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{NH}$	1.22	0.66	$HN{=}\overset{+}{N}{=}\overset{-}{N}$	0.66	0.40
$O{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{O}$	2.38	0.86	$H_2C{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{O}$	1.06	0.62	$HC{\equiv}N{-}\overset{-}{CH_2}$	0.65	0.55
$HN{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{O}$	1.70	0.74	$CH_2{=}\overset{+}{O}{-}\overset{-}{CH_2}$	0.93	0.70	$H_2C{=}\underset{\substack{\vert\\ H}}{\overset{+}{N}}{-}\overset{-}{CH_2}$	0.37	0.41
$H_2C{=}\overset{+}{O}{-}\overset{-}{NH}$	1.65	0.91				$HC{\equiv}\overset{+}{N}{-}\overset{-}{NH}$	0.28	0.28

a. From P. Perez, L. R. Domingo, M. J. Aurell, and R. Contreras, *Tetrahedron*, **59**, 3117 (2003).

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[347] P. Geerlings and F. De Proft, *Int. J. Quantum Chem.*, **80**, 227 (2000).

[348] F. Mendez, J. Tamariz, and P. Geerlings, *J. Phys. Chem. A*, **102**, 6292 (1998).

applied to interpretation of the regiochemistry of 1,3-dipolar cycloaddition reactions.[349] The DFT concept of local softness (see Topic 1.5) has been applied to regioselectivity. Chandra and co-workers have emphasized in particular that softness matching may be a determining factor in regiochemistry.[350] As discussed in connection with the D-A reaction, the global electrophilicity parameter ω, as defined in DFT,[341] can provide some insight into relative reactivity of 1,3-dipoles. Domingo and co-workers have calculated ω and $\Delta N_{\max}$ for representative 1,3-dipoles are given in Table 10.12.

There are some anomalies in Table 10.12; for example, the nitro group is listed as strongly electrophilic, but in fact is not reactive at all in normal 1,3-dipolar cycloadditions. The ω scale is also applicable only to the reactions in which the dipolarophile is acting as the electrophilic component; that is, in FMO terminology, the $\text{LUMO}_{\text{dipole}}$-$\text{HOMO}_{\text{dipolarophile}}$ interaction is dominant.

Problems

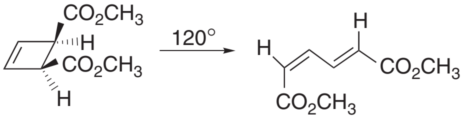
(*References for these problems will be found on page 1165.*)

10.1. Show, by construction of both a TS orbital array and an orbital symmetry correlation diagram, which of the following electrocyclizations are allowed.

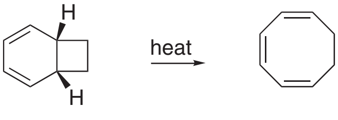
a. disrotatory cyclization of the pentadienyl cation to the cyclopent-2-enyl cation.
b. disrotatory cyclization of the pentadienyl anion to the 3-cyclopentenyl anion.
c. disrotatory cyclization of the heptatrienyl anion to the cyclohepta-3,5-dienyl anion.

10.2. Which of the following reactions are allowed according to orbital symmetry conservation rules? Explain. Discuss any special structural features that might influence the facility of the reaction.

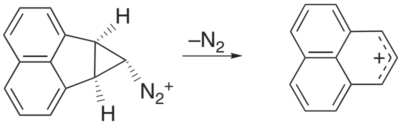
a.



b.



c.



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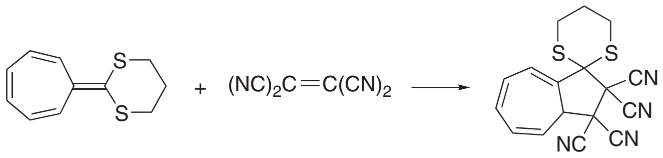
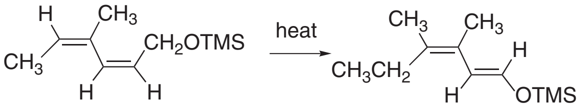
[349] F. Mendez, J. Tamariz, and P. Geerlings, *J. Phys. Chem. A*, **102**, 6292 (1998); A. K. Chandra and M. T. Nguyen, *J. Comput. Chem.*, **19**, 195 (1998).

[350] J. Korchowiec, A. K. Chandra, and T. Uchimaru, *Theochem.*, **572,**193 (2001).

d.


S
S
+ (NC)₂C=C(CN)₂
S
S
CN
CN
NC
CN

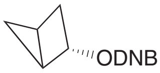
e.

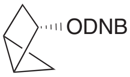

H
CH₃
CH₂OTMS
CH₃
H
H
heat
CH₃
CH₃
H
CH₃CH₂
H
OTMS

10.3. *Z*,*Z*,*Z*,*Z*-1,3,5,7-cyclononatetraene undergoes a spontaneous electrocyclic ring closure at 25°C. Predict the most likely structure for this cyclization product. Describe an alternative, symmetry-allowed electrocyclic reaction that would lead to an isomeric product. Explain why this alternate reaction pathway is not followed.

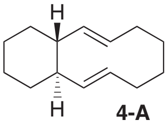
10.4. Offer a mechanistic explanation for each of the following reactions:

a. The 3,5-dinitrobenzoate esters of the stereoisomeric bicyclo[2.1.0]pentan-2-ols shown below both yield cyclopent-3-enol on hydrolysis in dioxane-water. The relative rates, however, differ by a factor of 10 million! Which is more reactive and why?



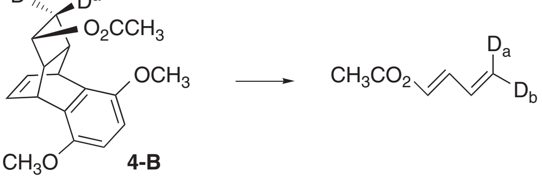


b. Optically active **4-A** racemizes on heating at 50°C with a half-life of 24 h.



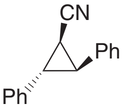
4-A

c. On being heated to 320°–340°C, compound **4-B** produces 1,4-dimethoxynaphthalene and 1-acetoxybutadiene. Furthermore, deuterium labeling has shown that the reaction is stereospecific as indicated.

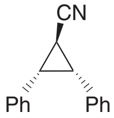

Dᵇ
Dᵃ
O₂CCH₃
OCH₃
CH₃O
CH₃CO₂
Dₐ
D_b

4-B

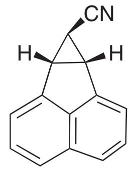
d. It has been found that compounds **4-C** and **4-D** are opened at −25°C to allylic anions in the presence of strong bases such as lithium *t*-butylamide. In contrast, **4-E**, opens only slowly at 25°C.



4-C

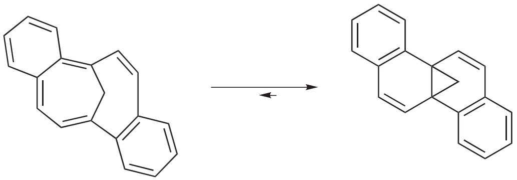


4-D



4-E

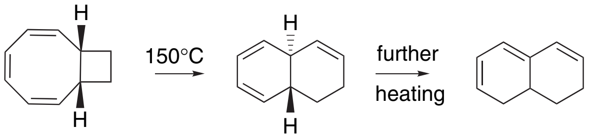
e. When the 1,6-methano-1,3,5,7,9-pentaene structure is modified by fusion of two benzene rings as shown in **4-Fa**, a valence isomer **4-Fb** is the dominant structure.



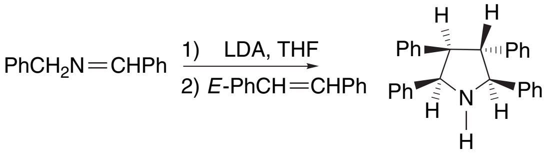
4-Fa **4-Fb**

10.5. Suggest a mechanism by which each transformation could occur. More than one step may be involved.

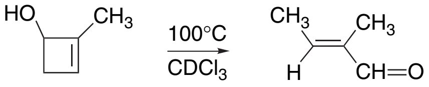
a.


H
H
150°C
H
H
further
heating

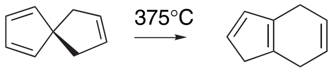
b.


PhCH$_2$N=CHPh
1) LDA, THF
2) *E*-PhCH=CHPh
H
H
Ph
Ph
Ph
Ph
H
N
H
H

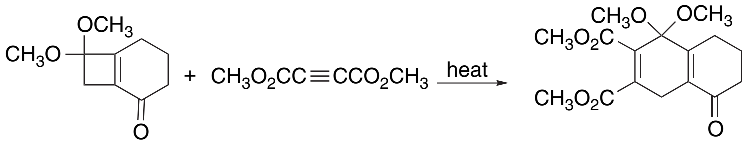
c.


HO
CH$_3$
100°C
CDCl$_3$
CH$_3$
CH$_3$
H
CH=O

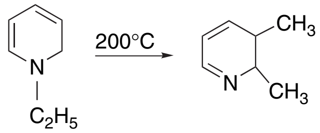
d.



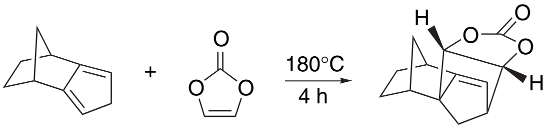
e.


OCH3
CH3O
O
+ CH3O2CC≡CCO2CH3
heat
CH3O
OCH3
CH3O2C
CH3O2C
O

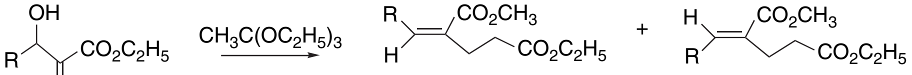
f.


N
C2H5
200°C
CH3
N
CH3

g.


+
O
O
O
180°C
4 h
H
O
O
O
H

10.6. It has been found that 3-substituted methyl 3-hydroxy-2-methylene alkanoates give rise to a preference for the *Z*-isomer if R is alkyl, but for the *E*-isomer if R is aryl under the conditions of the thermal orthoester Claisen rearrangement.


OH
R
CO2C2H5
CH3C(OC2H5)3
R
CO2CH3
H
CO2C2H5
+
H
CO2CH3
R
CO2C2H5

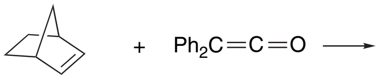
preferred by 3:1 to 4:1
for R = alkyl

preferred by 3:1 to 4:1
for R = aryl

Analyze the transition structure for the reaction in terms of steric interactions and suggest a reason for the difference in stereoselectivity.

10.7. Give the structure, including stereochemistry, of the product expected for the following reactions:

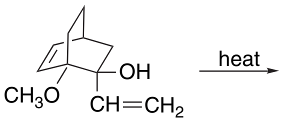
a.



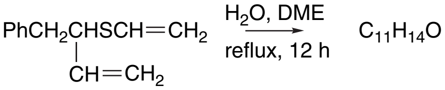
b.

$$(CH_3)_2C{=}C{=}O \; + \; C_2H_5OC{\equiv}CH \xrightarrow{0°C}$$

c.

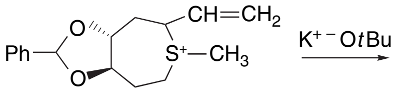

OH
CH3O
CH=CH2
heat

d.

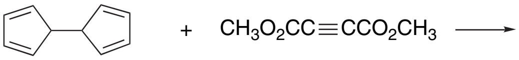


$$\underset{\displaystyle CH{=}CH_2}{PhCH_2CHSCH{=}CH_2} \xrightarrow[\text{reflux, 12 h}]{H_2O,\ DME} C_{11}H_{14}O$$

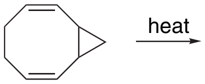
e.


Ph
O
O
CH=CH2
S+—CH3
K+ −OtBu

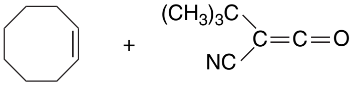
f.


+
CH3O2CC≡CCO2CH3

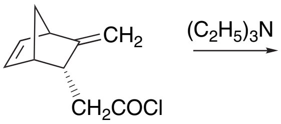
g.



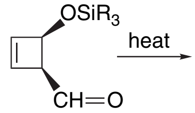
h.


+
(CH3)3C
C=C=O
NC

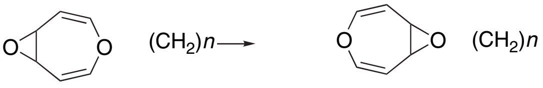
i.


CH2
CH2COCl
(C2H5)3N

j.


OSiR3
heat
CH=O

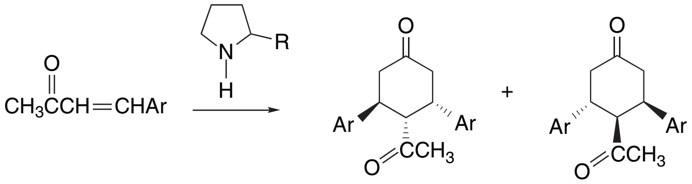
10.8. In the series of bicyclic oxepins **10-A** ($n = 3, 4, 5$), only the compound with $n = 5$ undergoes rearrangement (at 60°C) to the isomeric oxepin **10-B**. The other two compounds ($n = 3$ or 4) are stable, even at much higher temperature. When **10-B** ($n = 3$) was synthesized by another route, it showed no tendency to revert to **10-A** ($n = 3$). Offer an explanation for these observations.


O
O
(CH2)n
O
O
(CH2)n

10-A **10-B**

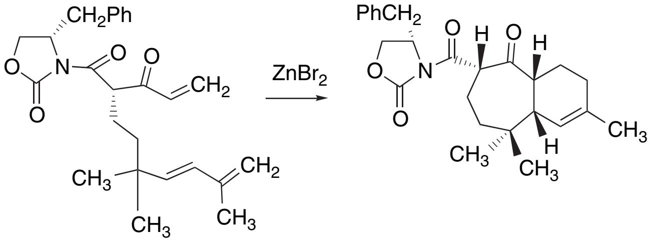
10.9. Bromocyclooctatetraene rearranges to *E*-β-bromostyrene. The rate of the rearrangement is solvent dependent, with the first-order rate constant increasing from about $10^{-7}\,s^{-1}$ in cyclohexane to about $10^{-3}\,s^{-1}$ in acetonitrile at 80°C. In the presence of lithium iodide, the product is *E*-β-iodostyrene, although *E*-β-bromostyrene is unaffected by lithium iodide under the reaction conditions. Suggest a mechanism for the rearrangement.

10.10. Pyrrolidine derivatives catalyze the formation of 3,5-diaryl-4-acetylcyclohexanones from 4-arylbut-3-en-2-ones. A Diels-Alder reaction is believed to be involved. Suggest a mechanism.

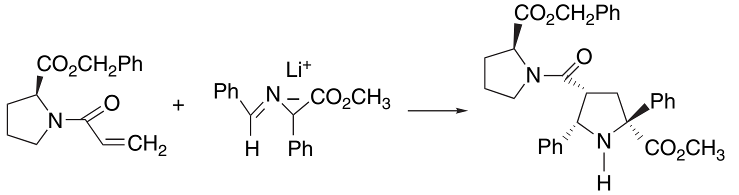

O
CH3CCH=CHAr
N
R
H
O
Ar
Ar
CCH3
O
+
O
Ar
Ar
CCH3
O

10.11. Propose a transition structure that would account for the stereochemistry observed in each of the following reactions:

a.

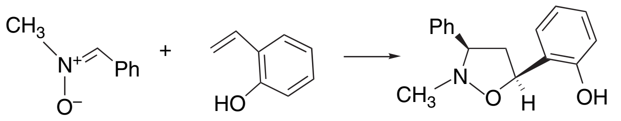

CH2Ph
O
N
O
O
O
CH2
CH3
CH3
CH2
CH3
ZnBr2
PhCH2
O
N
O
O
H
O
H
CH3
CH3
H
CH3

b.


CO2CH2Ph
N
O
CH2
+
Li+
Ph
N
CO2CH3
H
Ph
CO2CH2Ph
N
O
Ph
Ph
N
H
CO2CH3

> 99:1 ee

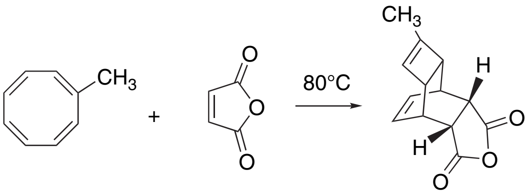
c.


CH3
N+
Ph
O−
+
HO
Ph
N
CH3
O
H
OH

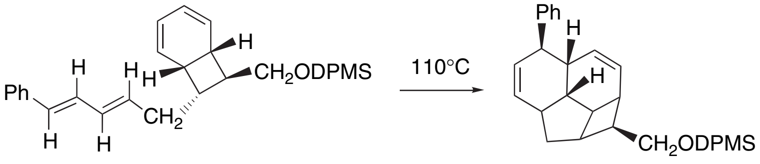
the *cis* selectivity is 100%. In the absence of the *o*-hydroxy,*cis* selectivity is 2:1.

10.12. Classify the following reactions as electrocyclizations, sigmatropic rearrangement, cycloaddition, etc., and give the correct symbolism for the electrons involved in each process. Some of the reactions proceed in two steps.

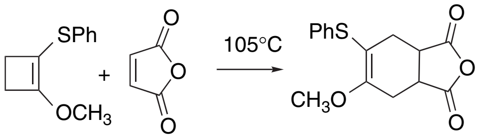
a.


CH3
80°C
H
O
CH3
O
H
O
O
O
O
+

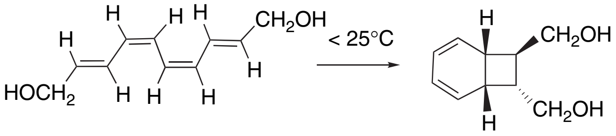
b.


Ph
H
H
H
H
H
H
CH2ODPMS
CH2
110°C
Ph
H
H
CH2ODPMS

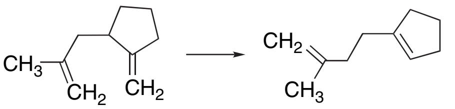
c.


SPh
OCH3
+
O
O
O
105°C
PhS
CH3O
O
O
O

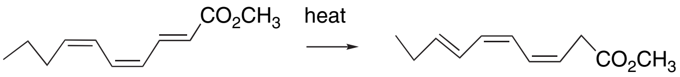
d.


H
H
H
H
CH2OH
HOCH2
H
H
H
H
< 25°C
H
CH2OH
CH2OH
H

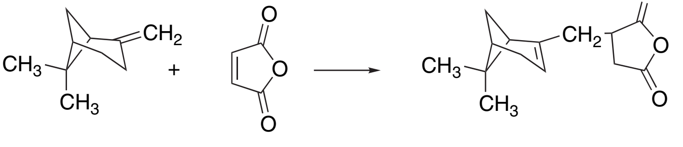
e.


CH3
CH2
CH2
CH2
CH3

f.


CO2CH3
heat
CO2CH3

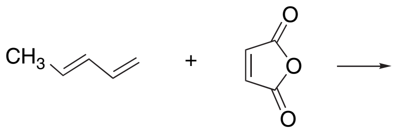
10.13. The "ene" reaction is a concerted reaction in which addition of an alkene and an electrophilic olefin occurs with transfer of a hydrogen to the electrophile and with a double-bond shift. For example:


CH2
CH3
CH3
+
O
O
O
CH3
CH3
CH2
O
O
O

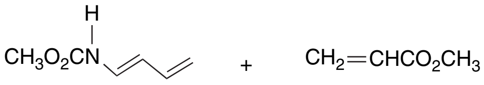
Depict the orbital array through which this reaction can occur as a concerted process.

10.14. Predict the regiochemistry and stereochemistry of the following cycloaddition reactions and indicate the basis for your prediction.

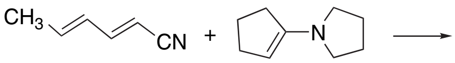
a.



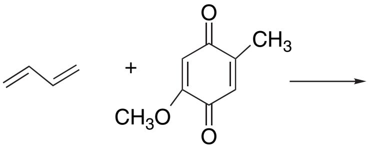
b


H
CH3O2CN
+
CH2=CHCO2CH3

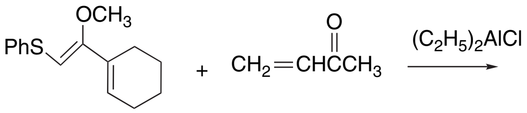
c.



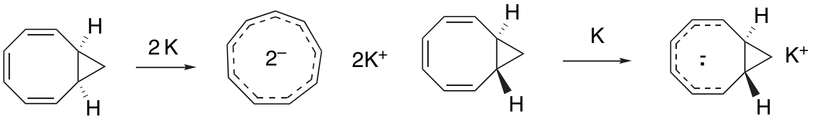
d.



e.

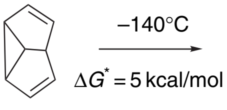

OCH3
PhS
+
O
CH2=CHCCH3
(C2H5)2AlCl

10.15. On treatment with potassium metal, *cis*-bicyclo[6.1.0]nona-2,4,6-triene gives a monocyclic aromatic dianion. The *trans* isomer under similar conditions give a bicyclic radical anion that does not undergo further reduction. Explain how the stereochemistry of the ring junction can control the course of these reductions.

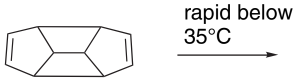

H
H
2 K
2–
2K+
H
H
K
H
H
K+

10.16. The following compounds are capable of degenerate rearrangement at the temperature given. Identify reaction processes that are consistent with the temperature and would lead to a degenerate rearrangement. Indicate by an appropriate labeling scheme the carbons and hydrogens that become equivalent as a result of the rearrangement process you have suggested.

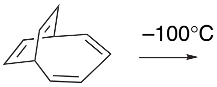
a.


–140°C
ΔG* = 5 kcal/mol

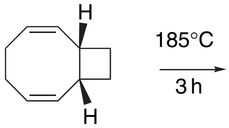
b.



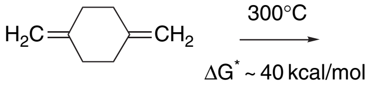
c.



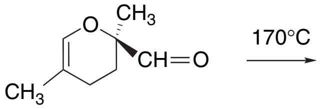
d.



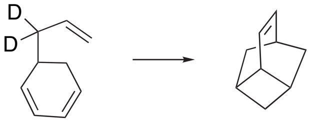
e.



f.

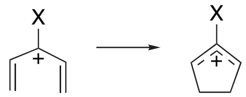


10.17. On heating at 225°C, 5-allylcyclohexa-1,3-diene, **17-A**, undergoes intramolecular cycloaddition to give the tricyclononene **17-B**. The same product is predicted for both [2 + 2] and [2 + 4] cycloaddition. The mechanism of the reaction has been probed by using the deuterium-labeled derivative, as shown. Indicate the position of the deuterium labeling in the product if the reaction proceeds by (a) a [2 + 2] cycloaddition or (b) a [2 + 4] cycloaddition.



17-A **17-B**

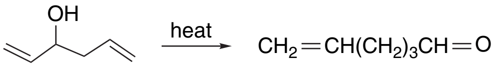
10.18. Computations on the cyclization of pentadienyl cations to cyclopentenyl cations has indicated increasing reactivity in the order X= $NH_2 < OH < H < O^+H_2$.



Based on these results, indicate which of the following types of groups would be favorable relative to the unsubstituted system: (a) alkyl; (b) π-conjugated EWGs, e.g., CN, CH=O; (c) σ-EWGs, e.g., CF_3, CF_3SO_2.

10.19. Suggest mechanisms for the following reactions. Classify the orbital symmetry character of the process as completely as you can.

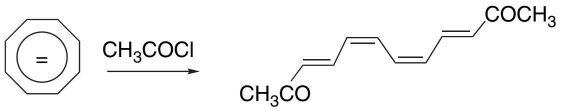
a.


OH
heat
CH2=CH(CH2)3CH=O

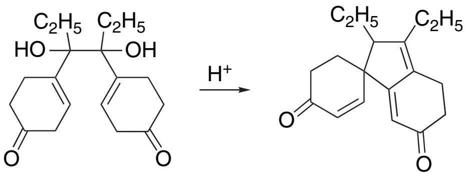
b.

$$(CH_2{=}CH)_2CHOH + CH_2{=}CHOC_2H_5 \xrightarrow{Hg^{2+}} CH_2{=}CHCH{=}CHCH_2CH_2CH{=}O$$

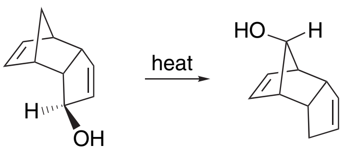
c.


=
CH3COCl
COCH3
CH3CO

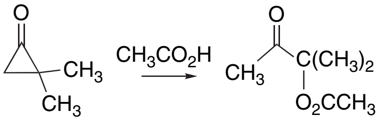
d.


C2H5
C2H5
HO
OH
O
O
H+
C2H5
C2H5
O
O

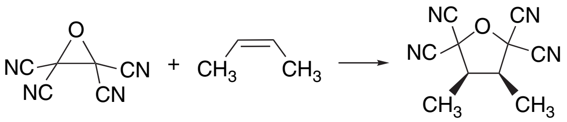
e.


H
OH
heat
HO
H

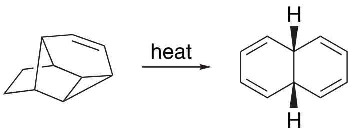
f.


O
CH3
CH3
CH3CO2H
O
CH3
C(CH3)2
O2CCH3

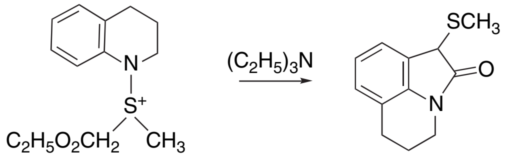
g.


O
NC
NC
CN
CN
+
CH3
CH3
NC
CN
O
NC
CN
CH3
CH3

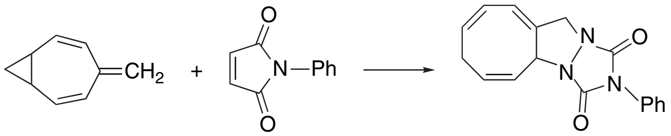
h.



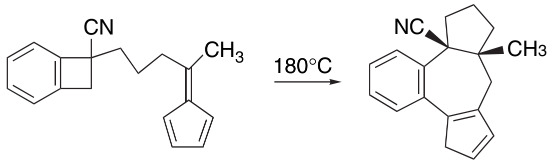
i.



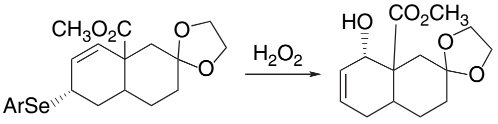
j.



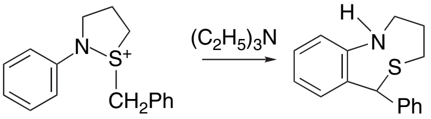
k.



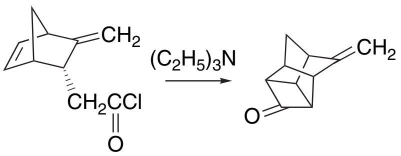
l.



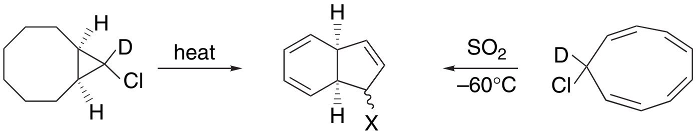
m.



n.



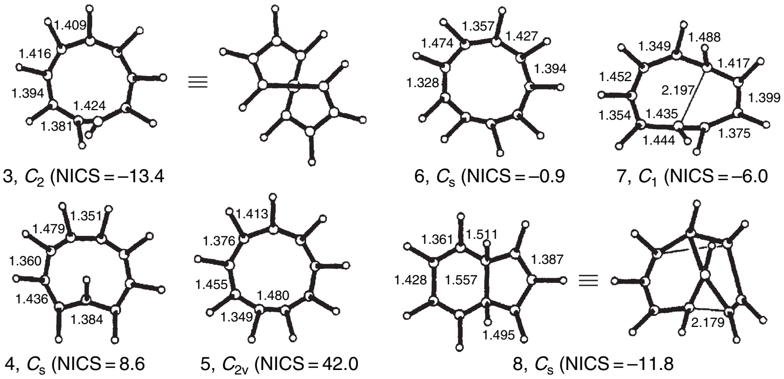
10.20. Both compounds **20-A** and **20-B** undergo solvolysis in polar solvents at low temperature. The isolated product is **20-C**. When **20-B** is labeled with deuterium it is found that there is complete scrambling of label *equally among all positions* in the product.


heat
SO_2
–60°C

20-A **20-C** **20-B**

X = Cl, OH

It has been suggested that the cyclononatetraenyl cation might be an intermediate, and several $[C_9H_9]^+$ structures have been compared computationally to determine their relative energy. Structure **3** has the lowest energy among the monocations. It has an *E*-configuration at one double bond. Structure **4** is also an energy minimum, but it is 21.6 kcal/mol higher in energy than **3**. The calculated relative energy and nucleus independent chemical shift (NICS) values are given for several structures, including structure **6**, which gives rise to the observed product. Formulate a mechanism that is in accord with the experimental observation of label scrambling. Discuss the role of structure **3** in the mechanism.


1.409
1.416
1.394
1.424
1.381
≡
1.357
1.474
1.427
1.394
1.328
1.488
1.349
1.417
1.452
2.197
1.399
1.354
1.435
1.375
1.444
1.351
1.479
1.360
1.436
1.384
1.413
1.376
1.455
1.480
1.349
1.361
1.511
1.387
1.428
1.557
1.495
≡
2.179

3, C_2 (NICS = −13.4

6, C_s (NICS = −0.9

7, C_1 (NICS = −6.0

4, C_s (NICS = 8.6

5, C_{2v} (NICS = 42.0

8, C_s (NICS = −11.8

10.21. Reaction of ketene with cyclopentadiene proceeds in a [2 + 2] rather than a [2 + 4] manner. A number of potential TSs have been characterized computationally. The diagrams below show product and TS energy, TS bond orders, and TS NPA

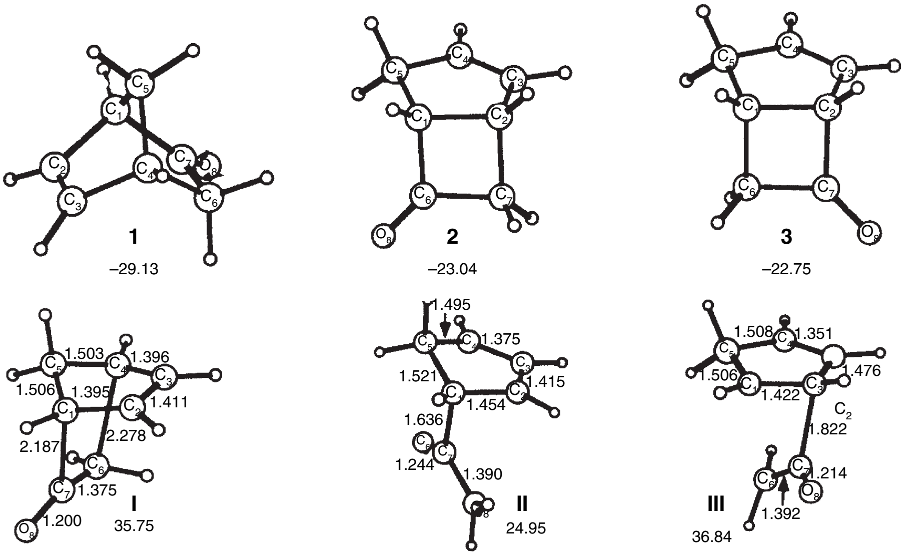

C_1
C_2
C_3
C_4
C_5
C_6
C_7
O_8
1
−29.13
2
−23.04
3
−22.75
1.503
1.396
1.506
1.395
1.411
2.187
2.278
1.375
1.200
I
35.75
1.495
1.375
1.521
1.415
1.454
1.636
1.244
1.390
II
24.95
1.508
1.351
1.506
1.476
1.422
C_2
1.822
1.214
1.392
III
36.84

Fig. 10.P21a. Δ*E* and and E_a (MP4SDQ/6-31G* + ZPE) for products **1** to **3** and the corresponding lowest-energy transition structures **I, II,** and **III**. Reproduced by Permission of the American Chemical Society.

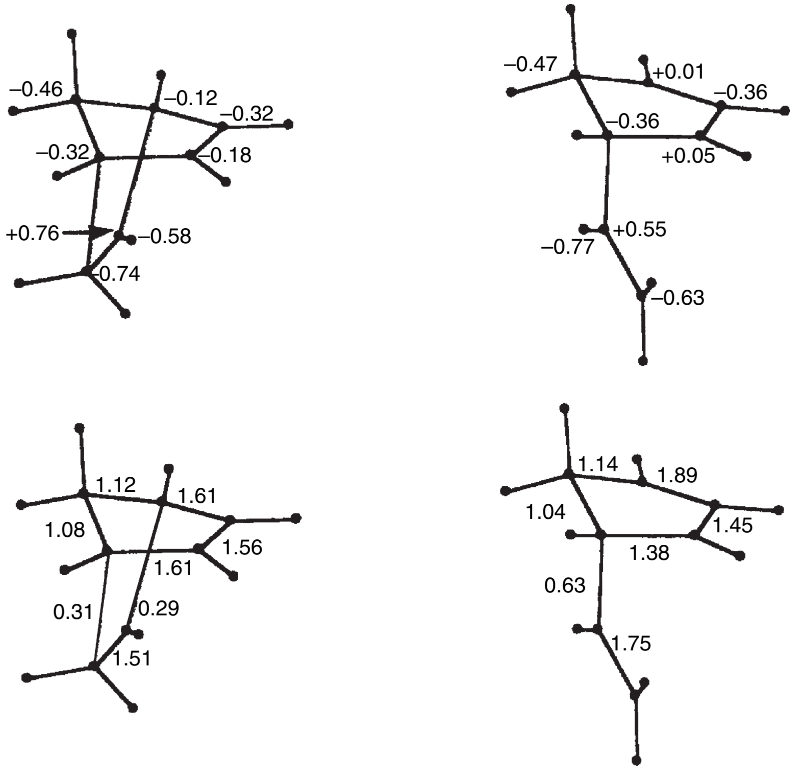

−0.46
−0.12
−0.32
−0.32
−0.18
+0.76
−0.58
−0.74
−0.47
+0.01
−0.36
−0.36
+0.05
+0.55
−0.77
−0.63
1.12
1.61
1.08
1.56
1.61
0.31
0.29
1.51
1.14
1.89
1.04
1.45
1.38
0.63
1.75

Fig. 10.P21b. NPA charges and bond orders for TS **I** and **II**. Reproduced by Permission of the American Chemical Society.

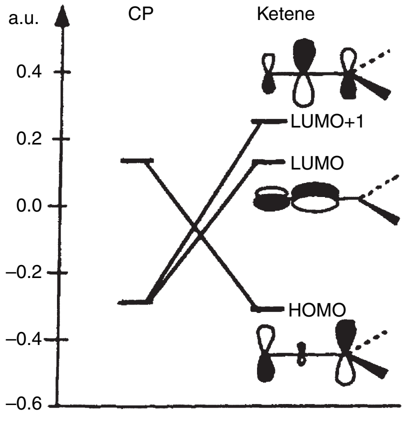
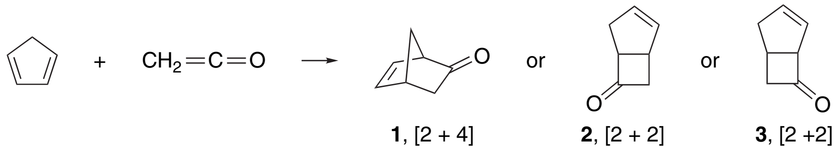

a.u.
CP
Ketene
0.4
0.2
0.0
−0.2
−0.4
−0.6
LUMO+1
LUMO
HOMO

Fig. 21Pc. Relative energy (in au) of cyclopentadiene HOMO and LUMO and ketene π, $\pi^*_{C=O}$, and π^* orbitals. Reproduced by permission of the American Chemical Society.

charges from MP4SDQ/6-31G*+ ZPE computations. Analyze the computational output in order to answer the following questions:



a. In very broad terms, why is the [2 + 2] product **2** favored over the other possible products? Draw a reaction potential energy diagram to illustrate your conclusion.

b. More specifically, why is product **2** preferred to product **3**? What structural features account for this preference?

c. What structural features of TS **1** make it less favorable than TS **2**?