Mechanistic and Theoretical Studies on Stereoselectivity in Diels-Alder reactions

(*Formerly:* **Theoretical Studies on the Diels-Alder Reaction**)

Evans Group Seminar
Jeff Johnson
6/98

Leading References:

"Mechanistic Aspects of Diels-Alder Reactions: A Critical Survey." Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Eng.* **1980**, *19*, 779.

"Regio- and Stereoselectivity in Diels-Alder Reactions. Theoretical Considerations." Gleiter, R.; Böhm M. C. *Pure Appl. Chem.* **1983**, *55*, 237.

"Transition Structures of Hydrocarbon Pericyclic Reactions." Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 682.

"Pericyclic Reaction Transtion States: Passions and Punctilios, 1935-1995." Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81.

"Modeling of Solvent Effects on the Diels-Alder Reaction." Cativiela, C.; García, J. I.; Mayoral J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209

"Theoretical Computational Methods." Allison, B. D. Evans Group Seminar, 2/2/96.

# The Beginning: Cis Addition and Alder's Rule
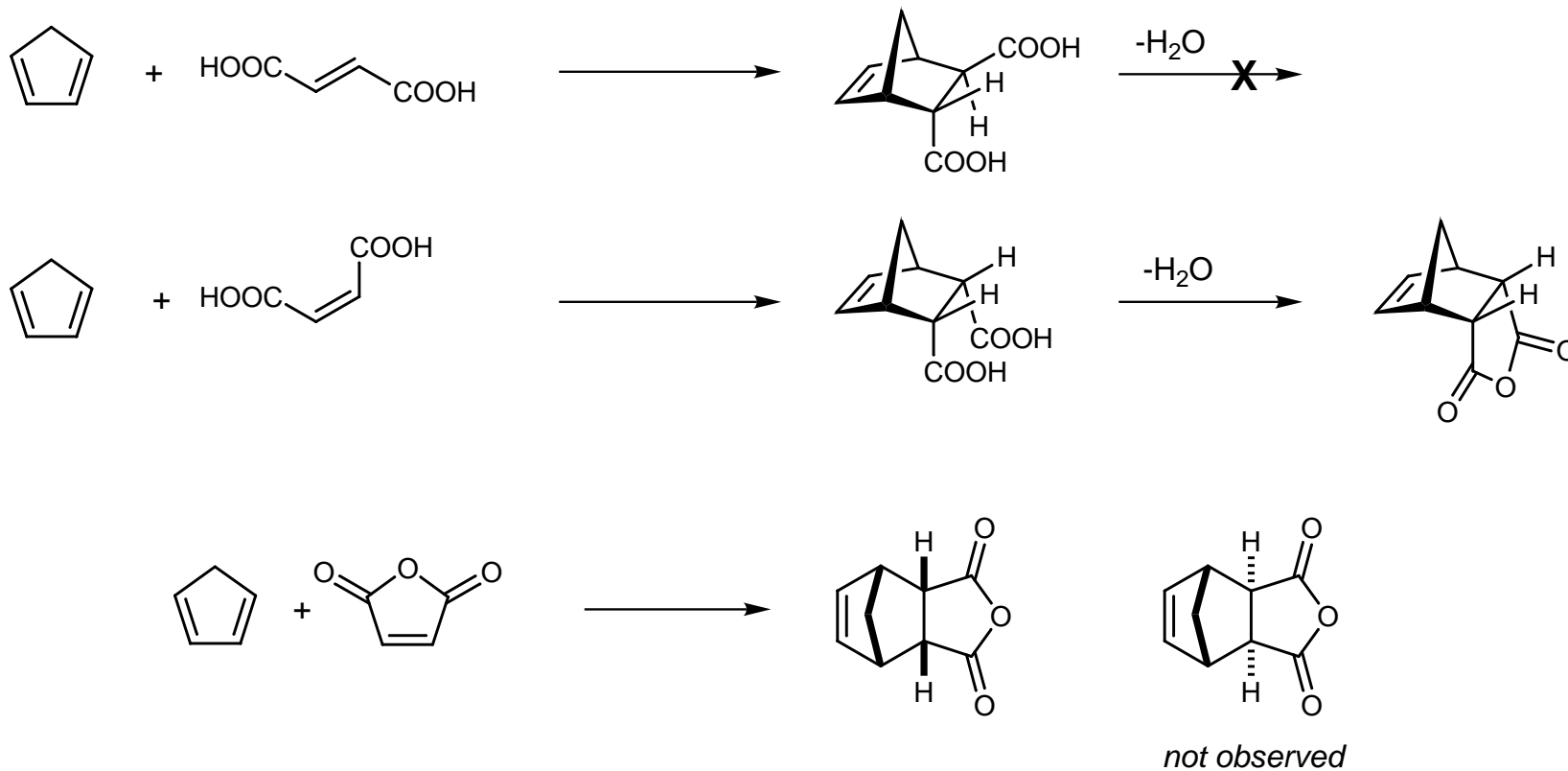
not observed

Explanation: *Endo* and *exo* complexes form at the beginning of the reaction; the complex having the maximum accumulation of double bonds is favored as a result of mutual attraction; such a complex affords the observed product

exo adduct ← ... → *endo* adduct
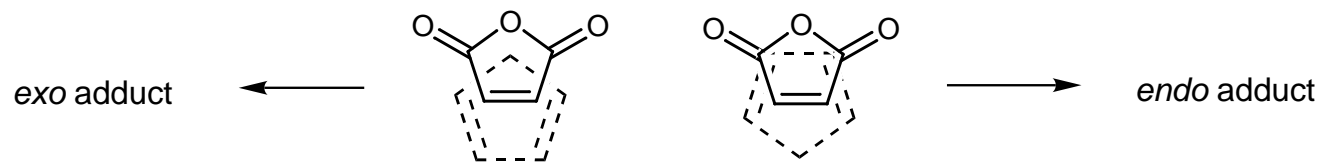
Alder, *Angew. Chem.* **1937**, *50*, 510

The Orbital Symmetry Explanation of Endo Stereoselection

[4+2]:
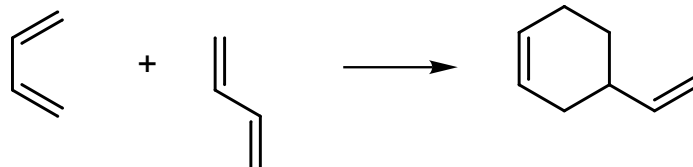
Symmetry-allowed mixing of occupied with unoccupied levels

HOMO(diene)

LUMO(dienophile)

LUMO(diene)
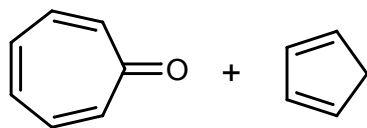
HOMO(dienophile)

[6+4]:
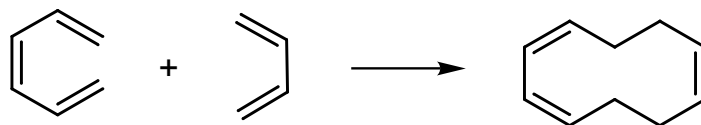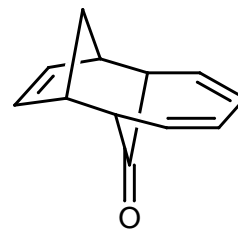

2° antibonding interactions
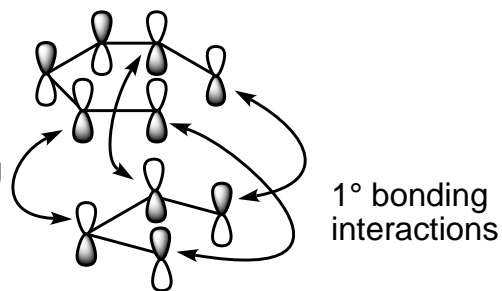
1° bonding interactions

∴ Symmetry-allowed [6+4] should be *exo* selective

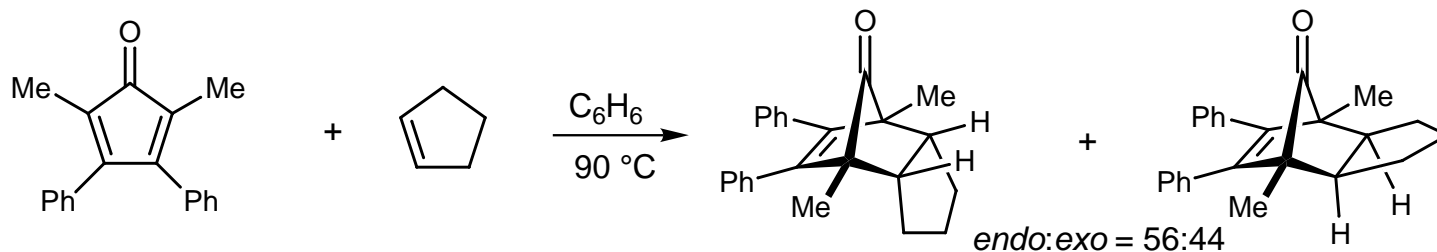Hoffmann, Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 4388

25 °C

Cookson, *Chem. Commun* **1966**, 15

Secondary Orbital Interaction Squabbles, Part 1

Work of Houk:

1

>97:3

endo:*exo* = 56:44
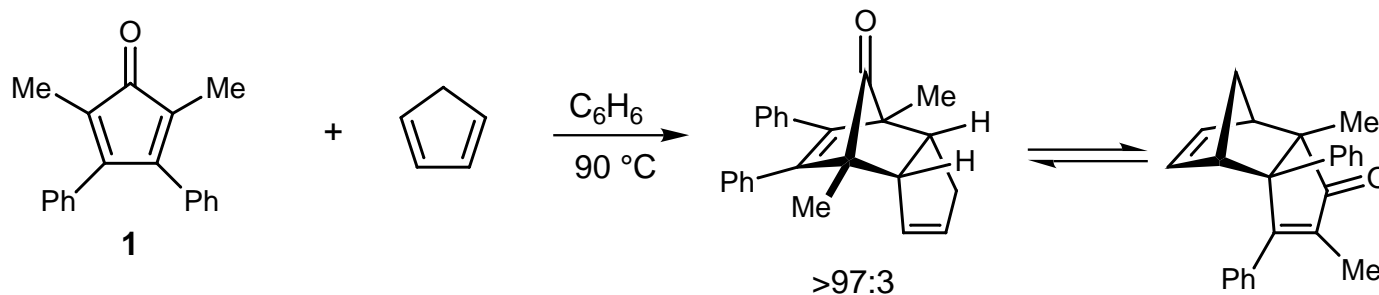
❏ Taken as evidence for 2° orbital overlap

Houk, *Tetrahedron Lett.* **1970**, *2621*

❏ Stereoselectivities vary with the diene:

endo/*exo*	$\diagup\diagup\diagdown CO_2Me$	CO_2Me (with Me)	$Me\diagup\diagdown CO_2Me$
With **1**	18:1	16:1	12:1
With CP	3:1	0.4:1	1:1
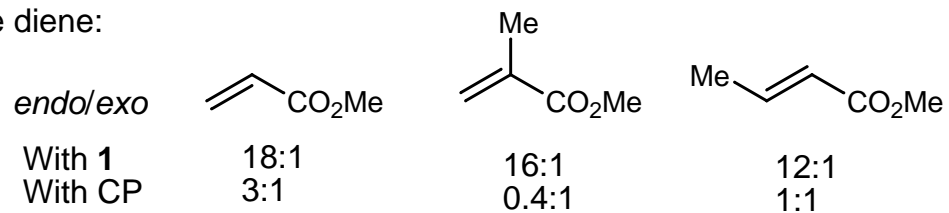
Houk, *J. Am. Chem. Soc.* **1971**, *93*, 4606

❏ Furukawa discounts this on the basis of polarization of the diene (not a straightforward correlation between **1** and cyclopentadiene)

Secondary Orbital Interaction Squabbles, Part 2

The contention: Attractive van der Waals forces between the methyl group of the dienophile and the unsaturation of the diene stabilizes the *exo* transition state

Work of Furukawa:

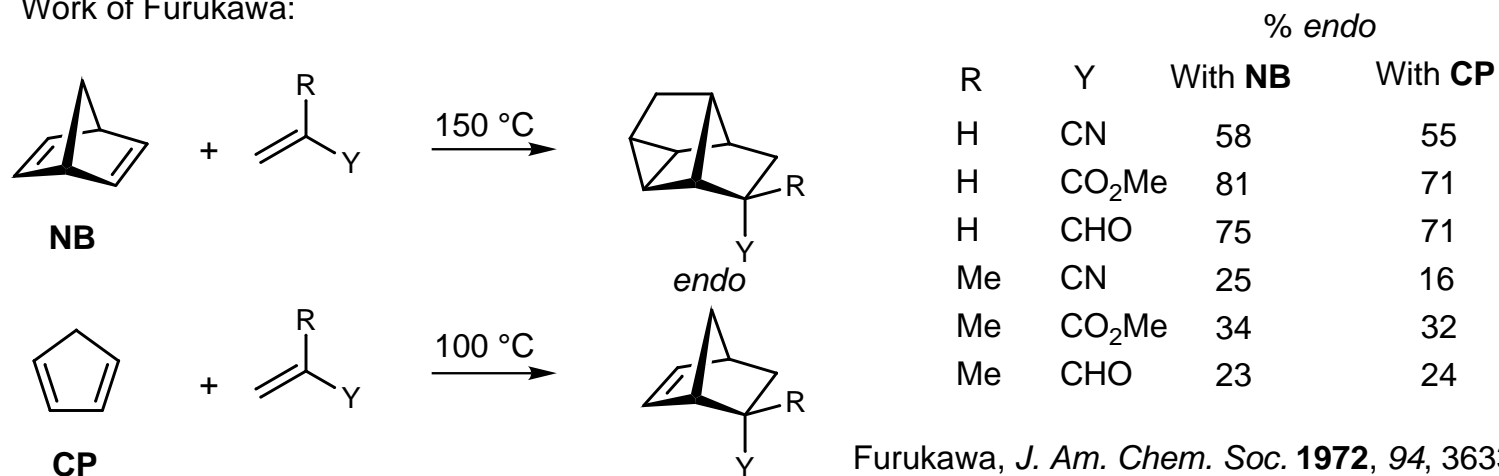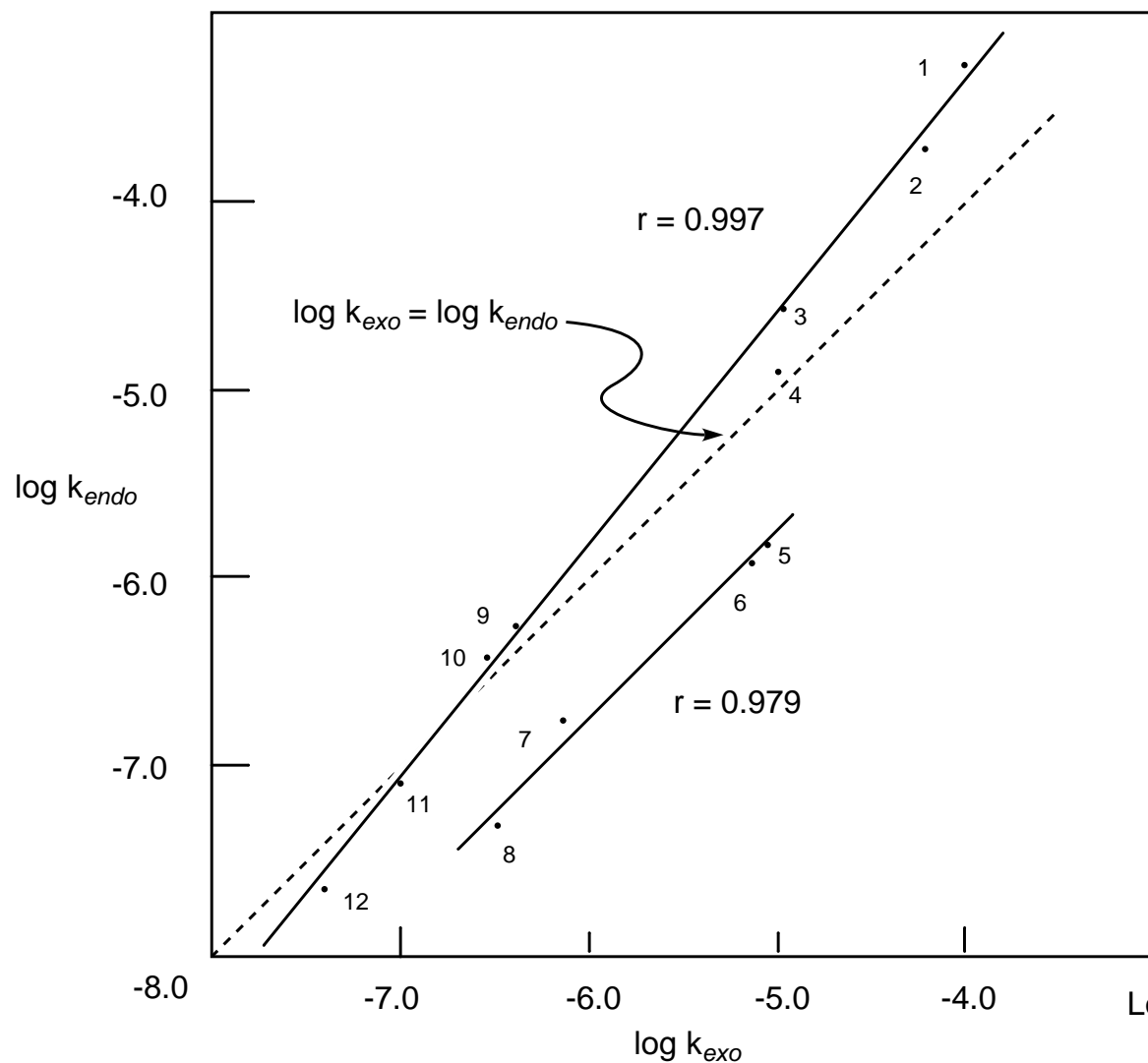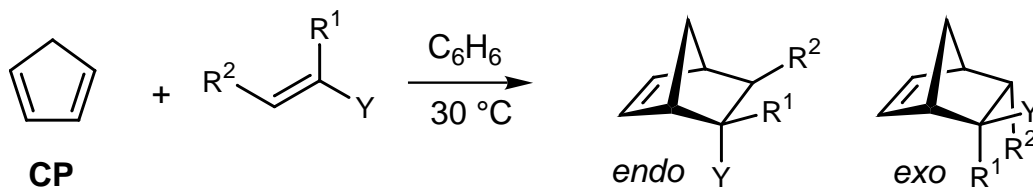|		% *endo*	
R	Y	With **NB**	With **CP**
H	CN	58	55
H	CO$_2$Me	81	71
H	CHO	75	71
Me	CN	25	16
Me	CO$_2$Me	34	32
Me	CHO	23	24

Furukawa, *J. Am. Chem. Soc.* **1972**, *94*, 3633

See also: *J. Am. Chem. Soc.* **1970**, *92*, 6548

❏ Houk's criticism: The same van der Waals effects that are purported to control the diastereoselectivity should manifest themselves for his dienone also

❏ Highlights the problems with attempting to extend designed systems to the analysis of simpler reactions

Why Are Methacrylate Derivatives Exo Selective?

CP + dienophile (R^2, R^1, Y) $\xrightarrow[\text{30 °C}]{C_6H_6}$ *endo* / *exo*

entry	dienophile
1	$H_2C=CHCO_2H$
2	$H_2C=CHCHO$
3	$H_2C=CHCO_2Me$
4	$H_2C=CHCN$
5	$H_2C=C(Me)CO_2H$
6	$H_2C=C(Me)CHO$
7	$H_2C=C(Me)CO_2Me$
8	$H_2C=C(Me)CN$
9	$MeHC=CHCO_2H$
10	$MeHC=CHCHO$
11	$MeHC=CHCO_2Me$
12	$MeHC=CHCN$

Plot of $\log k_{endo}$ vs $\log k_{exo}$

r = 0.997

$\log k_{exo} = \log k_{endo}$

r = 0.979

❏ Selectivities are accounted for by different factors in the methacrylate series of dienophiles (versus the acrylate and crotonate series)

Why Are Methacrylate Derivatives Exo Selective?
Separating Steric and Electronic Components
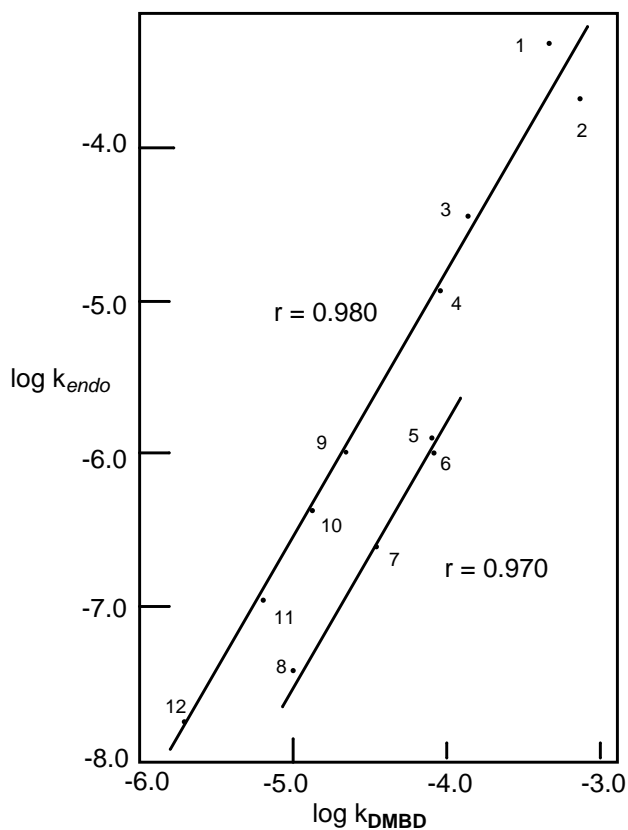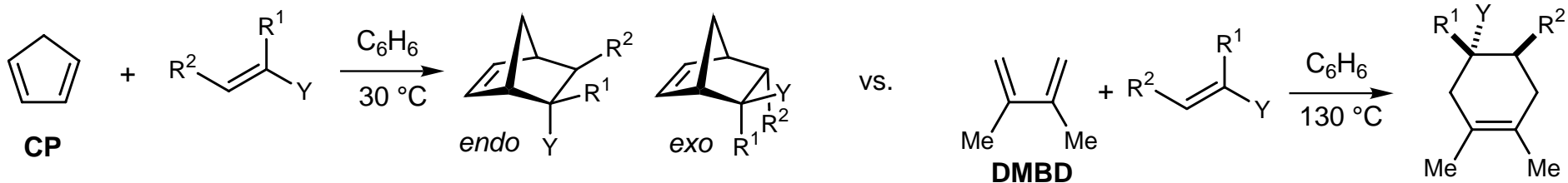
CP + R^2—Y (R^1) $\xrightarrow[\text{30 °C}]{C_6H_6}$ *endo* Y *exo* R^1 R^2 vs.   **DMBD** + R^2—Y (R^1) $\xrightarrow[\text{130 °C}]{C_6H_6}$

entry	dienophile
1	$H_2C=CHCO_2H$
2	$H_2C=CHCHO$
3	$H_2C=CHCO_2Me$
4	$H_2C=CHCN$
5	$H_2C=C(Me)CO_2H$
6	$H_2C=C(Me)CHO$
7	$H_2C=C(Me)CO_2Me$
8	$H_2C=C(Me)CN$
9	$MeHC=CHCO_2H$
10	$MeHC=CHCHO$
11	$MeHC=CHCO_2Me$
12	$MeHC=CHCN$

Left plot: $\log k_{endo}$ vs $\log k_{DMBD}$; $r = 0.980$, $r = 0.970$

Right plot: $\log k_{exo}$ vs $\log k_{DMBD}$; $r = 0.971$
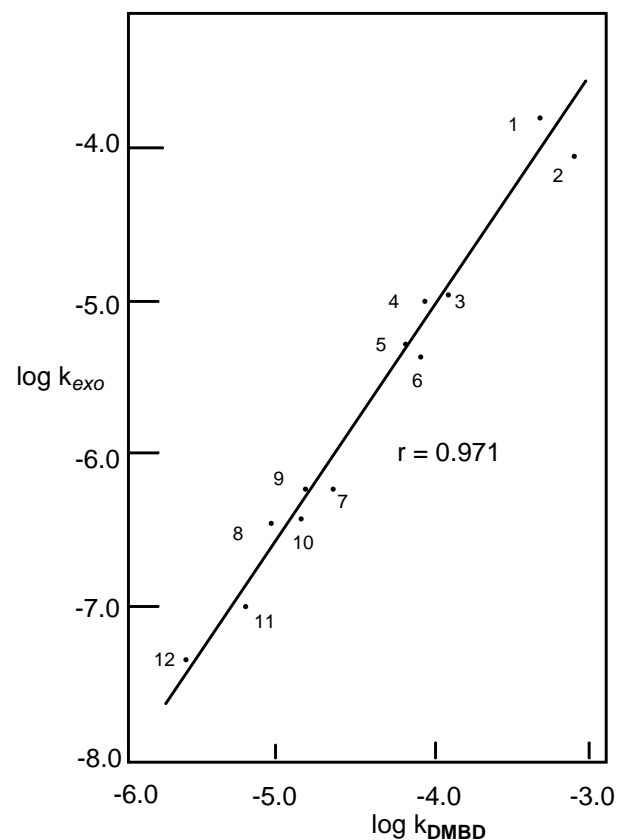
❑ Steric effect of the bridging CH_2 group is absent for **DMBD**; retardation of the *endo* cycloaddition is consistent with an unfavorable CH_3-CH_2 interaction

❑ For a counterpoint to this study, based on perturbational Hückel MO theory, see: Kobuke, *Tetrahedron Lett.* **1976**, 1587.

Secondary Orbital Overlap for Cyclopropene?

0 °C
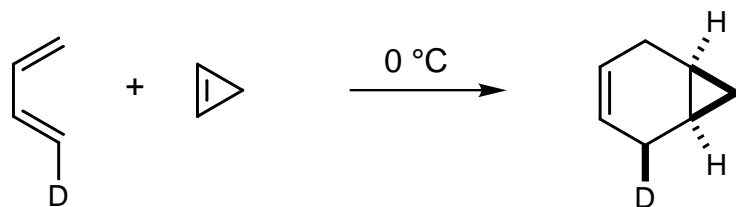
exclusively *endo* by ^{2}H NMR;
stereochemistry indicated by epoxidation

Baldwin, *J Org. Chem.* **1989**, *54*, 5264

A hypothesis: If 2° orbital interactions are operative,
it should be possible to observe a correlation
between the *endo/exo* ratio and the energy
gap between the interacting frontier orbitals for
various dienes with cyclopropene

diene **LUMO**

dienophile **HOMO**

orbital
coefficients

$$\Delta E(FMO) = (c_1 c_2 \beta)^2 / \Delta \varepsilon \longleftarrow \text{energy gap between reacting orbitals}$$

stabilization
due to 2°
orbital
overlap

resonance
integral
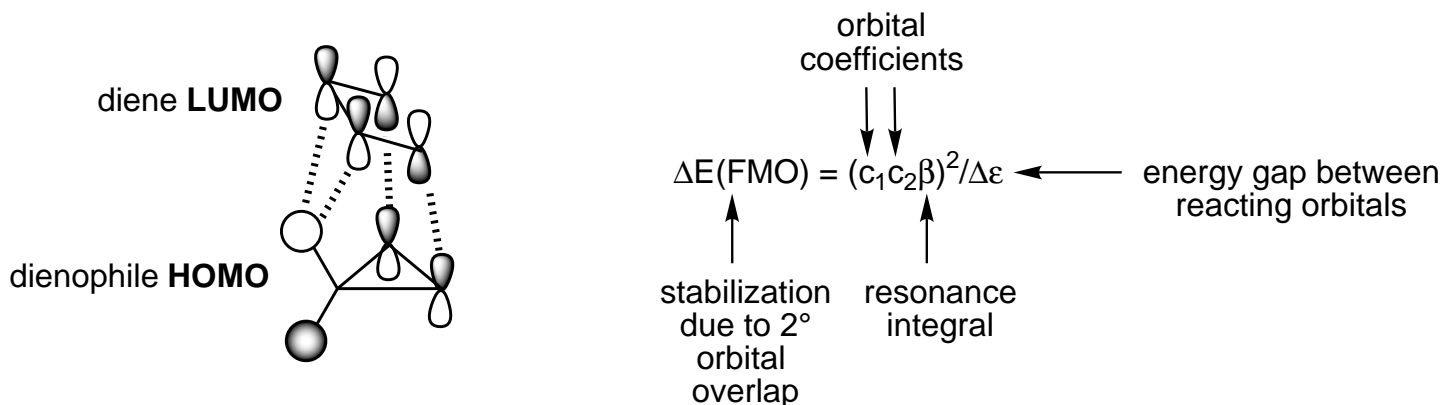
Secondary Orbital Overlap for Cyclopropene?

The experiment:

X
|
C=C—Y
|
(diene)
Z

or

(pyrrole/furan ring with X at 2-position, M in ring)

+

△ (cyclopropene)
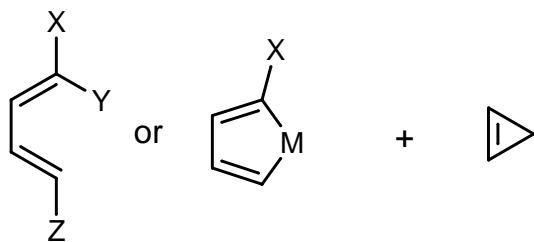
Calculate at RHF//3-21G level ΔE_a and Mulliken overlap populations (MOPs), a term which is proportional to $(\Delta E(FMO))^{1/2}$

$\Delta\varepsilon$ = LUMO(diene) - HOMO (dienophile)

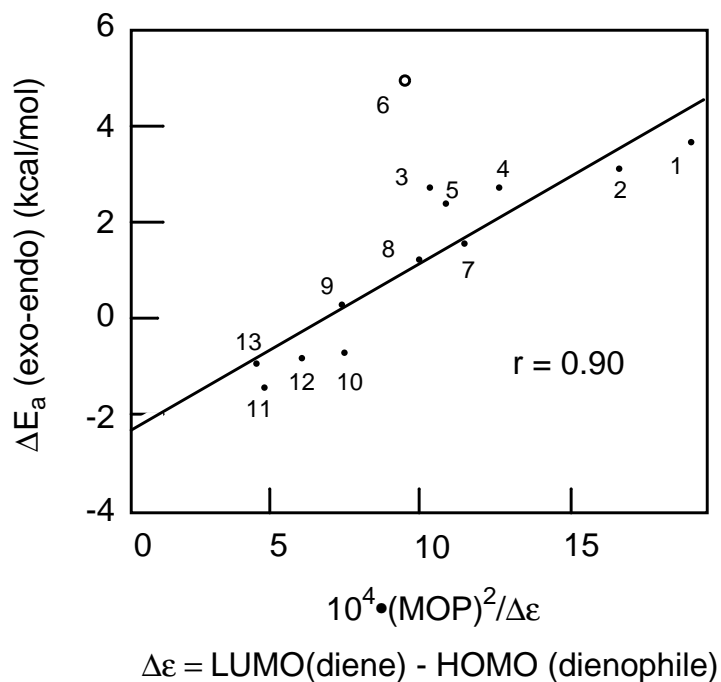| entry	X	Y	Z	M
1	BH_2	H	H	
2	CN	H	H	
3	H			S
4	F	H	H	
5 *	H	H	H	
6 *	H			CH_2
7	H	OH	H	
8 *	OH	H	H	
9	OH	H	OH	
10 *	H			O
11	OH			O
12	H			NH
13	OH			NH

* Reasonable correlation with experimental *endo*/*exo* ratios

Apeloig, *J. Am. Chem. Soc.* **1995**, *117*, 5375
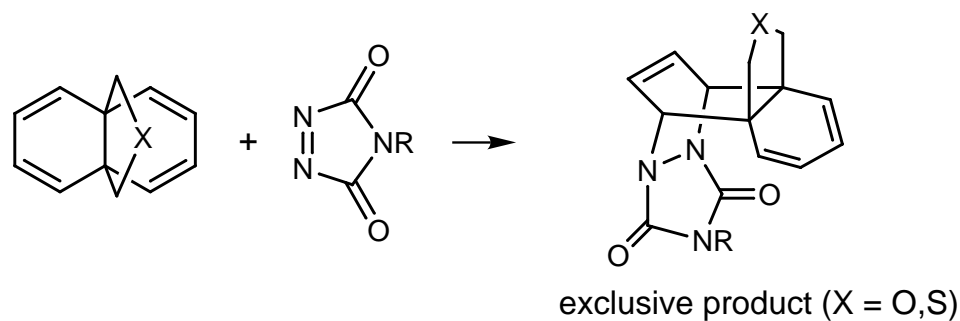
Counterpoint: Complete perturbation treatment (interactions between all pairs of orbitals, not only FMOs) suggests the existence of a kind of C-H → π hydrogen bond and thus a complex, or minimum on the reaction energy surface

Dannenberg, *J. Am. Chem. Soc.* **1997**, *119*, 4232

Nonconventional Orbital Overlap and Polar effects

exclusive product (X = O)
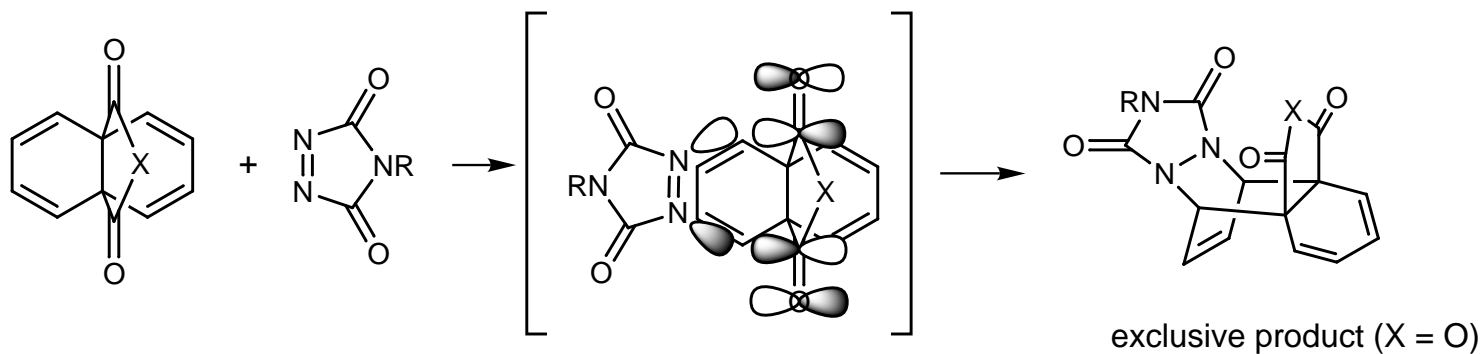
Occupied n orbital stabilized by interaction with an empty π^* orbital

exclusive product (X = O,S)

Absence of carbonyl groups leads to the dominance of steric effects

$syn/anti$ = 95:5 (X = SO_2)

Polar effect overcomes steric effect?

Gleiter, Ginsburg, *Pure Appl. Chem.* **1979**, *51*, 1301
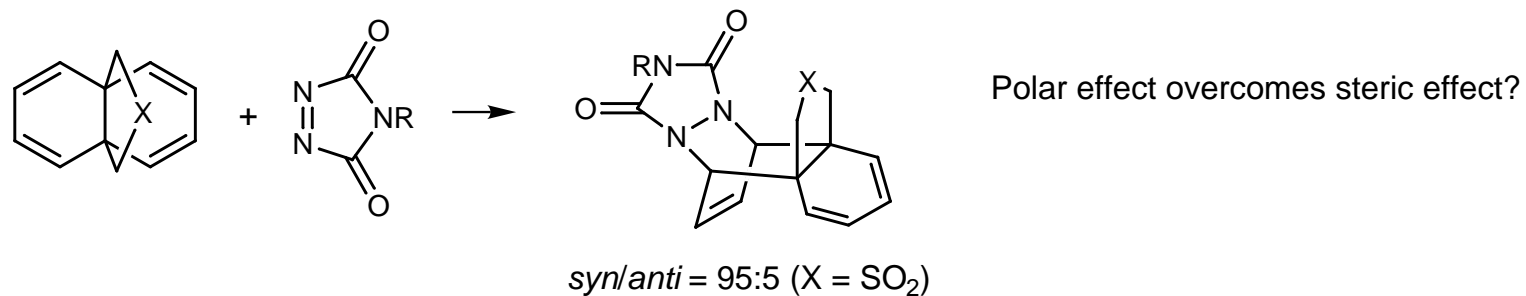
Arguments Against Secondary Orbital Overlap

$$CP + AN \longrightarrow$$

CP   **AN**

endo   *exo*
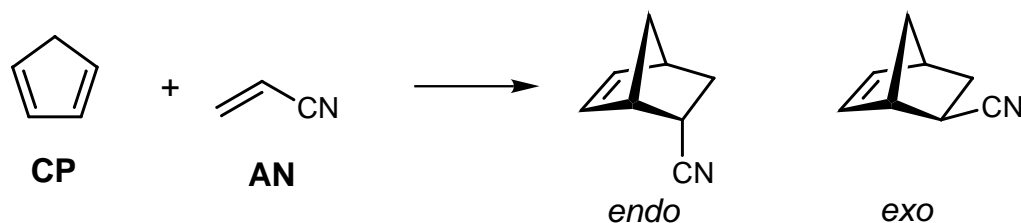
<u>Method</u>: Apply dielectric continuum model of solvation to quantum-chemical calculations. Essentially, the model entails placing the substrate in a cavity surrounded by a dielectric continuum; the medium effect is accounted for iteratively

Ab initio bond lengths in the transition state (MNDO PM3):

$C_2 \to CN$ = 2.94Å

2.13 Å   2.29Å
(2.09)   (2.21)

2.13 Å   2.29Å
(2.09)   (2.21)

E_a = 26.0 kcal/mol (RHF/3-21G)* ⟷ E_a = 25.7 kcal/mol (RHF/3-21G)*

exo favored

= 32.95 kcal/mol (PM3) ⟶ = 32.70 kcal/mol (PM3)

= 32.08 kcal.mol (PM3 in CH_2Cl_2) ⟵ = 32.54 kcal.mol (PM3 in CH_2Cl_2)

endo favored
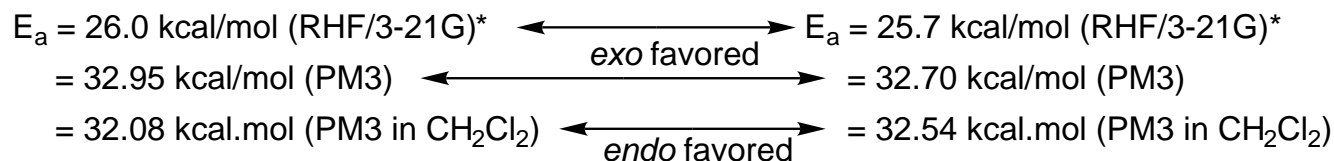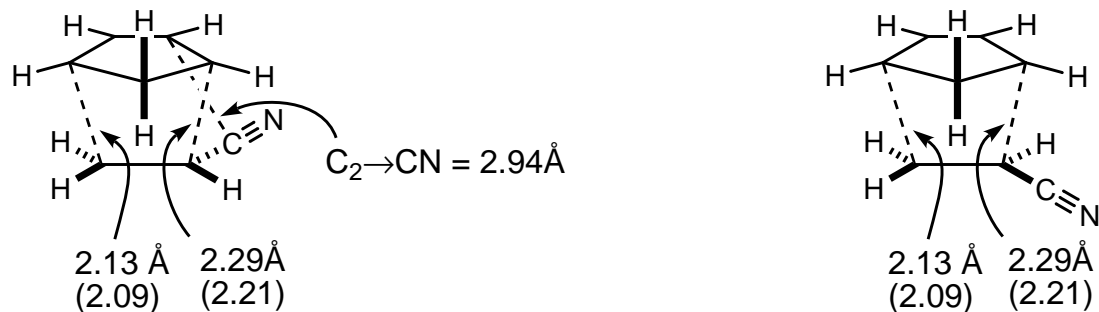
Experimentally, **AN** plus **CP** favors the *endo* adduct by 0.2 kcal/mol (dioxane, ε = 2.21). Calculations were redone (!) in hexane (ε = 1.98, $\Delta E_{endo\text{-}exo}$ = 0.03), benzene (ε = 2.27, $\Delta E_{endo\text{-}exo}$ = -0.18), and acetonitrile (ε = 35.94, $\Delta E_{endo\text{-}exo}$ = -0.34)

<u>Conclusion</u>: 2° orbital overlap should manifest itself in the gas phase calculations; however, they apparently do not override other factors in this case. The authors conclude that the trend toward heightened *endo* selectivity can be attributed to medium effects. This trend is further reflected in reactions of 1,3-butadiene with acrylo- and maleonitrile.

Sustmann, *Tetrahedron Lett.* **1992**, *33*, 8027
* Houk, Jorgensen, *J. Am. Chem. Soc.* **1989**, *111*, 9172

Solvent Effects: Berson's Linear Free Energy Relationship

CP   endo CO_2Me exo
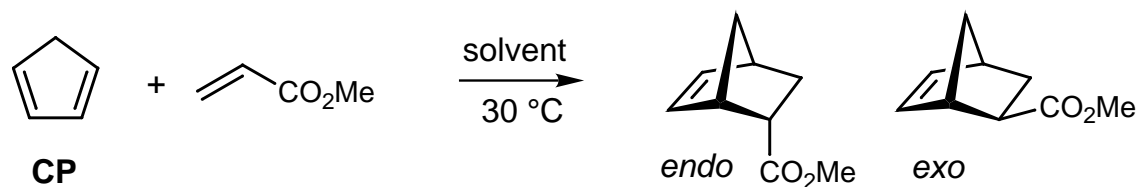
Study diastereoselectivity as a function of 12 solvents ranging in polarity from decalin to MeOH

Define Ω_t as log (*endo/exo*) for the **CP**/methyl acrylate (**A**) reaction at a specified temperature

When Ω_t is plotted against log (*endo/exo*) for **CP**/methyl crotonate (**B**) or **CP**/methylmethacrylate(**C**) reactions, a linear relationship is observed. Linear relationship also observed with the following empirical solvent parameters:

1) Kosower's **Z** (derived from the effect of solvent on charge-transfer electronic absorption band of pyridinium iodides); energy range sampled = 24 kcal/mol
2) log k_{ion} (ionization of *p*-methoxyneophyl *p*-toluenesulfonate); energy range sampled = 7 kcal/mol
3) log k_{rearr} (Curtius rearrangement of benzoyl azide)

Ω_t samples only a 0.5 kcal/mol energy range, leading Berson to conclude: "In this respect, a set of solvents behaves like an elephant, which can lift a log or a peanut with equal dexterity."

Generalized results:

log (*endo/exo*)
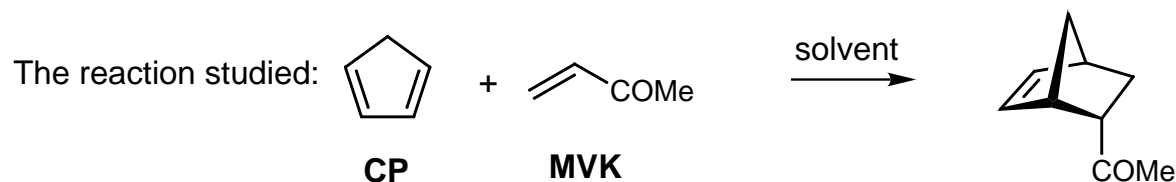
nonpolar   polar
Solvent polarity
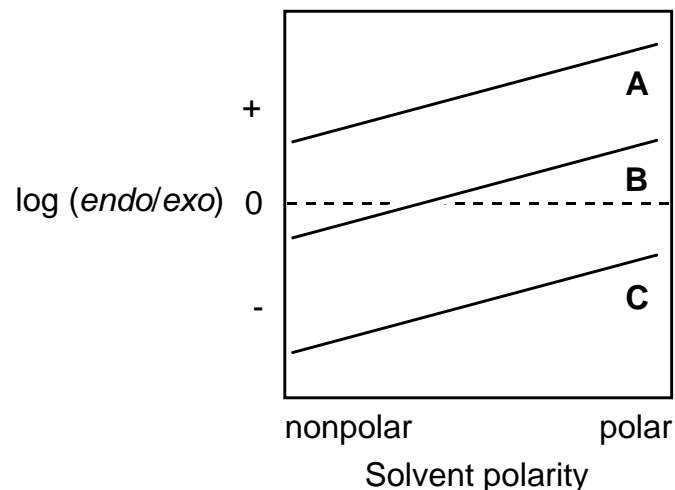
The rationale:
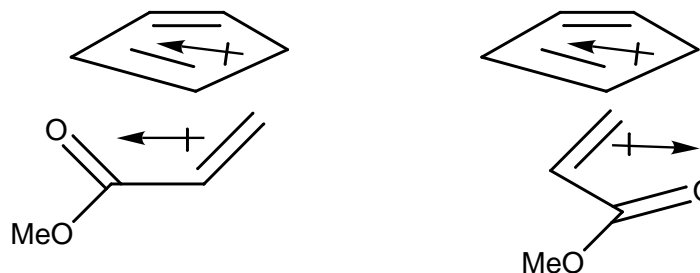
The electric dipole moment of the *endo* transition state is greater than that of the *exo* [Note: *s-cis* reactive conformer assumed]

Berson, *J. Am. Chem. Soc.* **1962**, *84*, 297

# Solvent Effects: Jorgensen's Ab Initio Calculations

The reaction studied:

CP + **MVK** (COMe) $\xrightarrow{\text{solvent}}$ product (COMe)

Steps in the experiment:

1) Determine the minimum energy reaction path (MERP) in the gas phase with ab initio MO techniques

2) From the four transition states obtained, find the lowest at the 6-31G-(d)//3-21G level

3) The *endo/s-cis* transition state serves as a starting point for tracing the path from t.s.‡ to reactants and products

} *Gas Phase*

4) Choose an intermolecular potential function for the fluid simulations (based on Coulombic and Lennard-Jones interactions)

5) Obtain Mulliken charges from 6-31G-(d)//3-21G calculations on all 65 reacting frames (small charge shifts observed)

6) Obtain dipole moments: MVK 3.06D, TS‡ 3.44, Product 2.89 D

7) Execute the Monte Carlo simulations (cubic cell contains >250 solvent molecules)

What was found:

Diels-Alder Free Energy Profiles
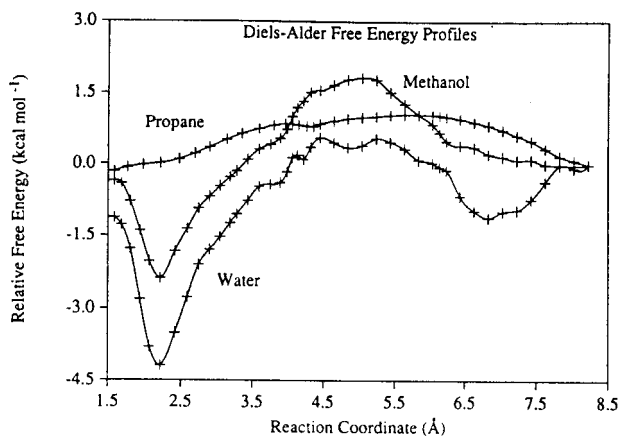
Miscellaneous:

❏ For water, the number of H-bonds to the carbonyl remains constant (2-2.5), but the strength is 1-2 kcal/mol greater at t.s.‡

❏ By setting all partial charges equal to 0, the contribution of hydrophobic effects was estimated to be *ca.* -1.5 kcal/mol

Jorgensen, *J. Am. Chem. Soc.* **1991**, *113*, 7430

For dramatic rate accelerations in water, see:
Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816
Breslow, *Acc. Chem. Res.* **1991**, *24*, 159

Non-Hydrogen Bonding Effects of Water

The reaction studied:

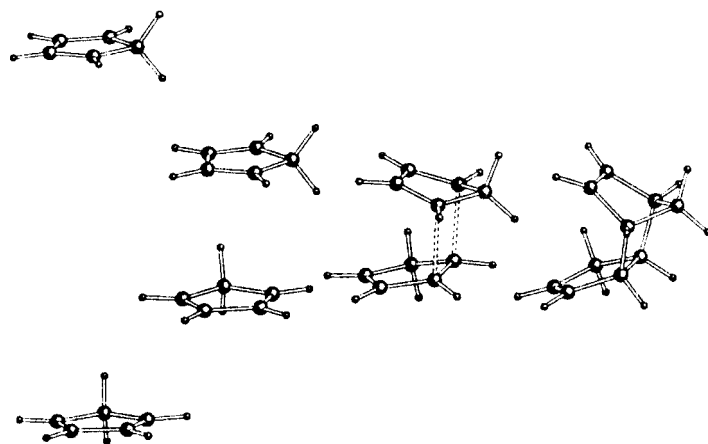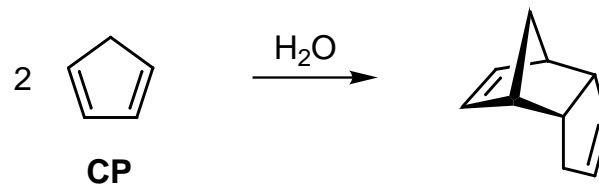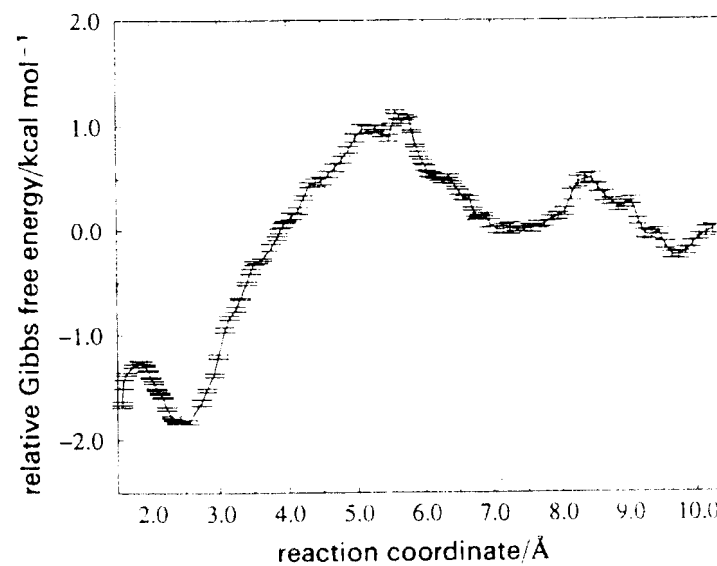$$2 \quad \text{CP} \quad \xrightarrow{\text{H}_2\text{O}}$$

CP

Fig. 3 Structures along the MERP for cyclopentadiene dimerization at r_c = 10.3, 4.0, 2.2 (transition state) and 1.6 Å


❐ Reaction measures the contribution of the hydrophobic effect to rate enhancement
❐ Transition state may be slightly earlier in water than in the gas phase

Jorgensen, *J. Chem. Soc. Faraday Trans.* **1994**, *90*, 1727

Synchronicity of the Diels-Alder Reaction: Isotope Effects

<u>Key Definitions:</u>[*][''] "A *concerted* reaction is one which takes place in a single kinetic step. A *two*-step reaction is one which takes place in two distinct steps via a stable intermediate. A *synchronous* reaction is a concerted reaction in which all the bond-breaking and bond-forming processes take place in parallel, all having proceeded to comparable extents in the TS. A *two-stage* reaction is concerted but not synchronous, some of the changes in bonding taking place mainly in the first half of the reaction, between the reactants and the TS, while the rest takes place in the second half, between the TS and the products."

<u>Method</u>: Take advantage of the change in hybridization in the t.s.[‡] by studying 2° kinetic isotope effects and determine the extent of bond breaking or formation at either carbon of the diene terminus
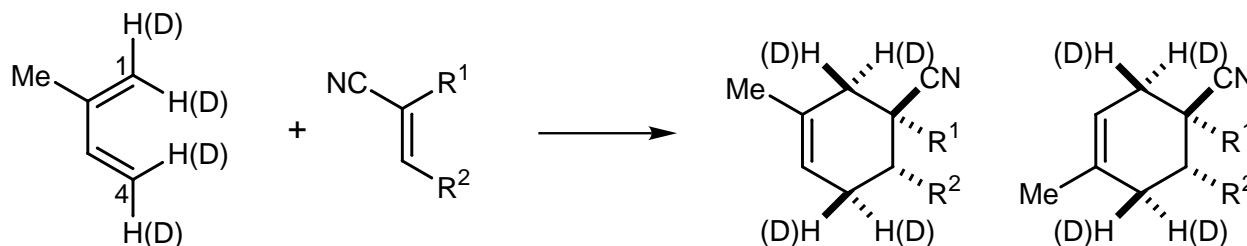

Relative rates:

	R^1	R^2	*"meta"*	*"para"*	maximum
$d_0/4,4$-d_2	H	H	1/1.11	1/0.99	1/1.22
$d_0/1,1$-d_2	H	H	1/1.02	1/1.13	1/1.22
$d_0/4,4$-d_2	H	CN	1/1.05		1/1.22
$d_0/1,1$-d_2	H	CN	1/1.05		1/1.22
$d_0/4,4$-d_2	CN	H	1/1.26	1/0.98	1/1.35
$d_0/1,1$-d_2	CN	H	1/1.02	1/1.28	1/1.35
$d_0/4,4$-d_2	H	CO_2Me	1/1.13	1/1.14	1/1.35
$d_0/1,1$-d_2	H	CO_2Me	1/1.11	1/1.09	1/1.35

❏ A two-stage reaction should exhibit the maximum inverse KIE since bond formation would be complete at one site and nonexistent at the second site of the dienophile → **NOT OBSERVED**

Gajewski, *J. Am. Chem. Soc.* **1987**, *109*, 5545; **1989**, *111*, 9078

For Dewar's objections to the synchronous mechanism, see:[*]*J. Am. Chem. Soc.* **1986**, *108*, 5771; **1984**, *106*, 209

Merged Theoretical and Experimental Probes of Kinetic Isotope Effects
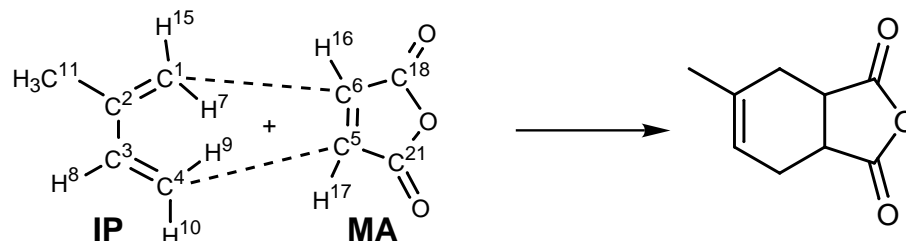
<u>Method</u>: Compare experimental and theoretical (RHF and hybrid HF/DFT) secondary kinetic isotope effects (KIEs) for reaction of isoprene (**IP**) with maleic anhydride (**MA**) to determine extent of bond breaking/forming in the t.s.‡
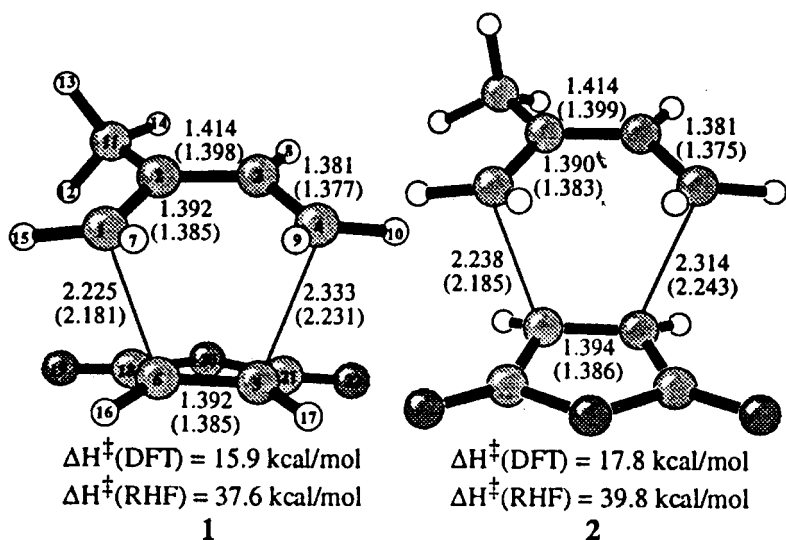

$\Delta H^{\ddagger}(DFT) = 15.9$ kcal/mol
$\Delta H^{\ddagger}(RHF) = 37.6$ kcal/mol
1

$\Delta H^{\ddagger}(DFT) = 17.8$ kcal/mol
$\Delta H^{\ddagger}(RHF) = 39.8$ kcal/mol
2

Figure 1. Becke3LYP/6-31G* endo (**1**) and exo (**2**) transition structures for the Diels—Alder reaction of isoprene and maleic anhydride. Becke3LYP and RHF/6-31G* bond lengths are in plain text and parentheses, respectively. All bond lengths are in angstroms (Å).
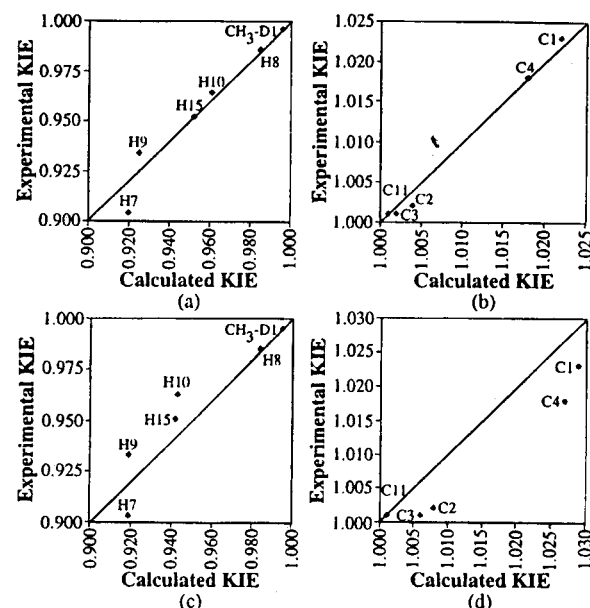
Figure 2. Comparison of experimental and calculated kinetic isotope effects: (a) Becke3LYP ²H secondary KIEs; (b) Becke3LYP ¹³C KIEs; (c) RHF ²H secondary KIEs; (d) RHF ¹³C KIEs. The numbering system is shown in Figure 1.

❒ Experimental activation parameters (C_6H_6, 298 K) are $\Delta H^{\ddagger} = 11.8$ kcal/mol; $\Delta S^{\ddagger} = -37.1$ eu. When solvation ($\varepsilon = 2.27D$) is included in the DFT calculations, the activation enthalpy is within 2 kcal/mol. Little mention is made of the huge discrepancy with the RHF calculations.

❒ **IP** induces a slightly asynchronous transition state; this is probably the most sophisticated combination of experimental and theoretical work to provide a "snapshot" of the t.s.‡
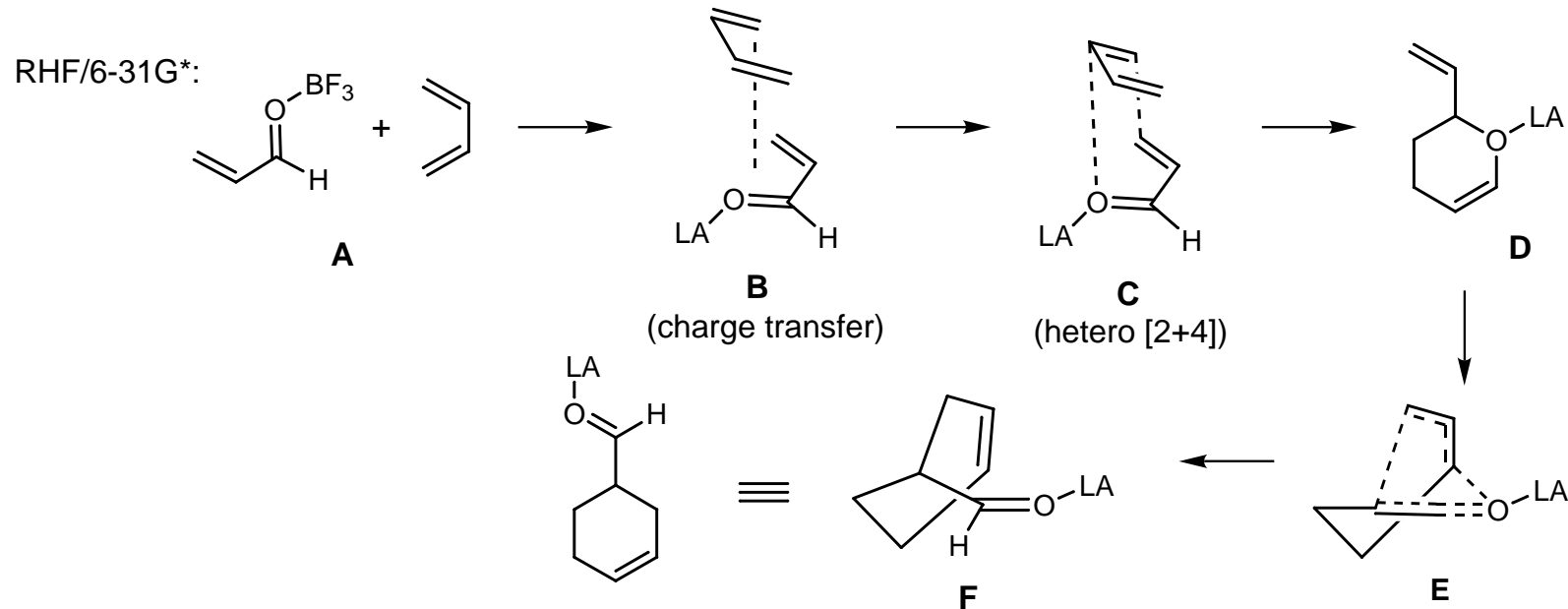
Ab Initio *Structures of Lewis Acid-Catalyzed Cycloadditions*

<u>Method</u>: Locate the transition structures of the Diels-Alder reaction of acrolein with butadiene promoted by borane at the RHF/3-21G and 6-31G* levels


NC E_{rel} = 0.0 kcal/mol

NT E_{rel} = 4.7

XC E_{rel} = 2.2

XT E_{rel} = 7.3
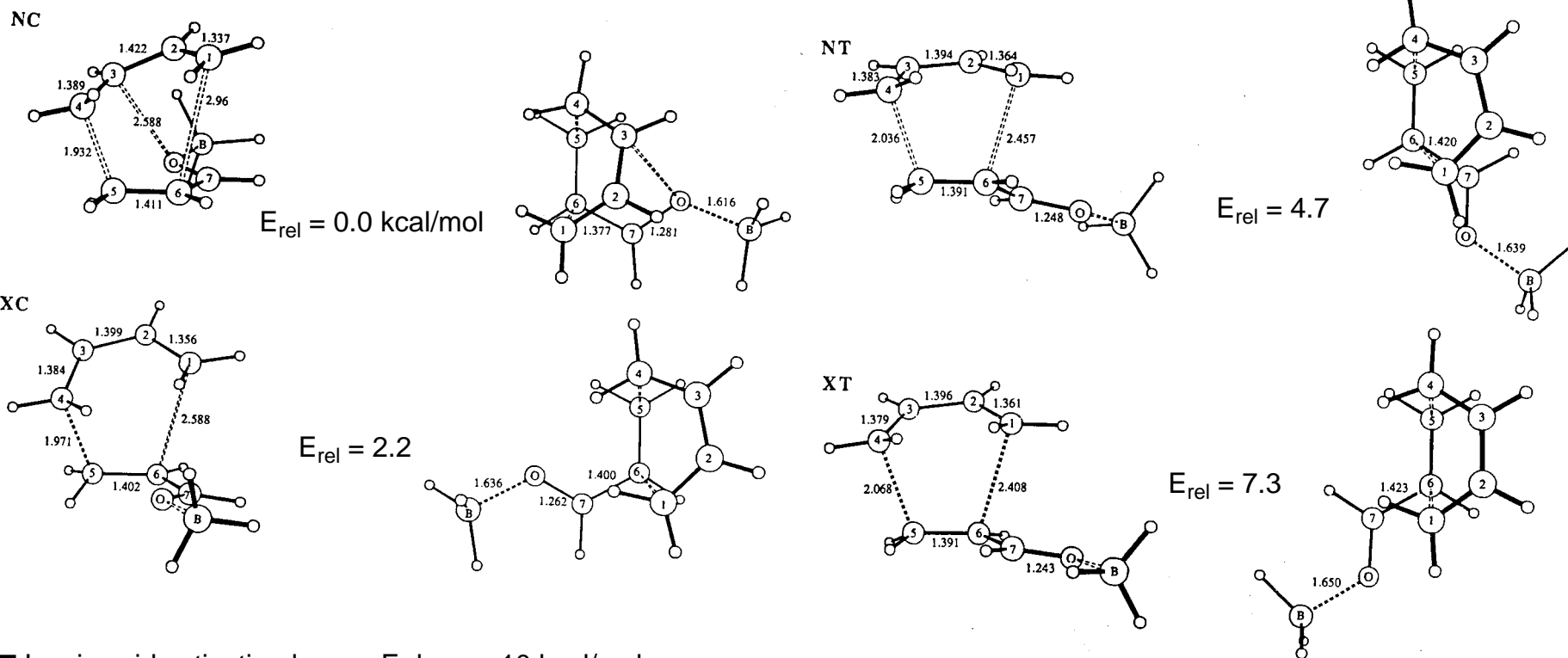
❏ Lewis acid activation lowers E_a by *ca.* 10 kcal/mol

❏ No energy minimum corresponding to an intermediate was located; *i.e.* reaction is still concerted

❏ Normal mode displacements (indicating transition state vectors) show C1 and C6 moving toward each other (smallest for**NC**)

❏ Pyramidalization of the termini give further evidence for reaction asynchronicity

❏ Stereochemical rationale: Differences in t.s.[‡] energy stem HOMO(diene)→LUMO(dienophile) charge transfer; geometry of the *endo s-cis* t.s.[‡] minimizes the physical separation of the induced charges and is thus favored

Houk, *J. Am. Chem. Soc.* **1990**, *112*, 4127

A Proposed Intermediate in BF$_3$-Mediated Reactions

RHF/6-31G*:

A

B
(charge transfer)

C
(hetero [2+4])

D

F

E
[3,3]

a = -6.5 kcal/mol
b = -7.0
c = +16.8
d = +6.1
e = +2.6
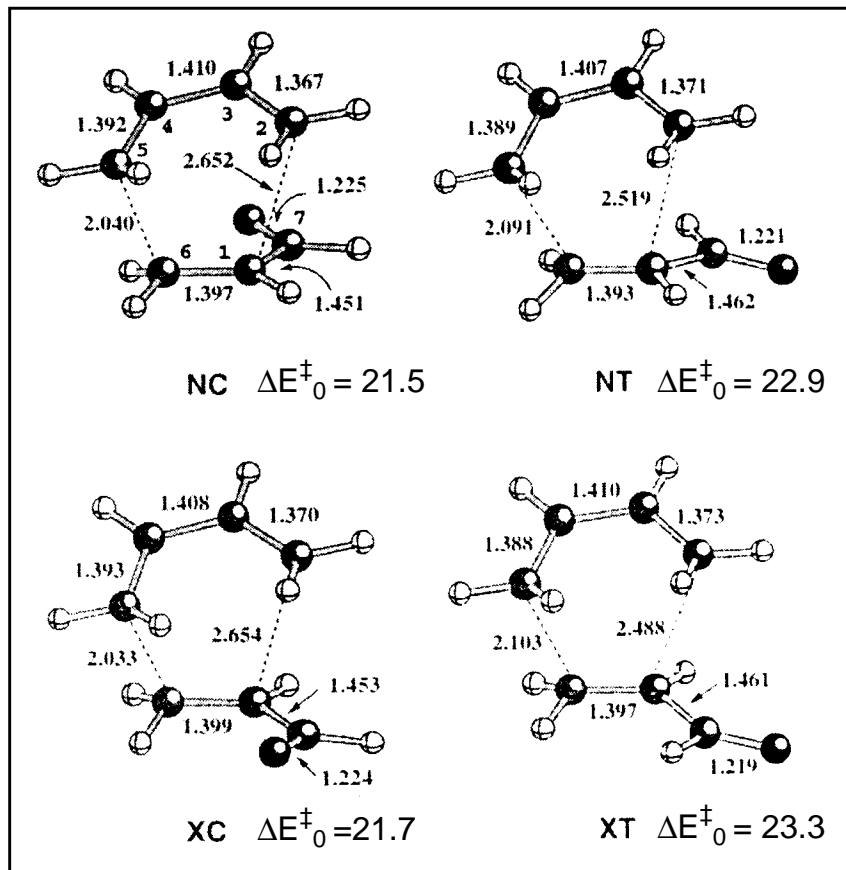f = -30.8
g = -2.7
h = -47.5
i = -50.0
j = -53.5
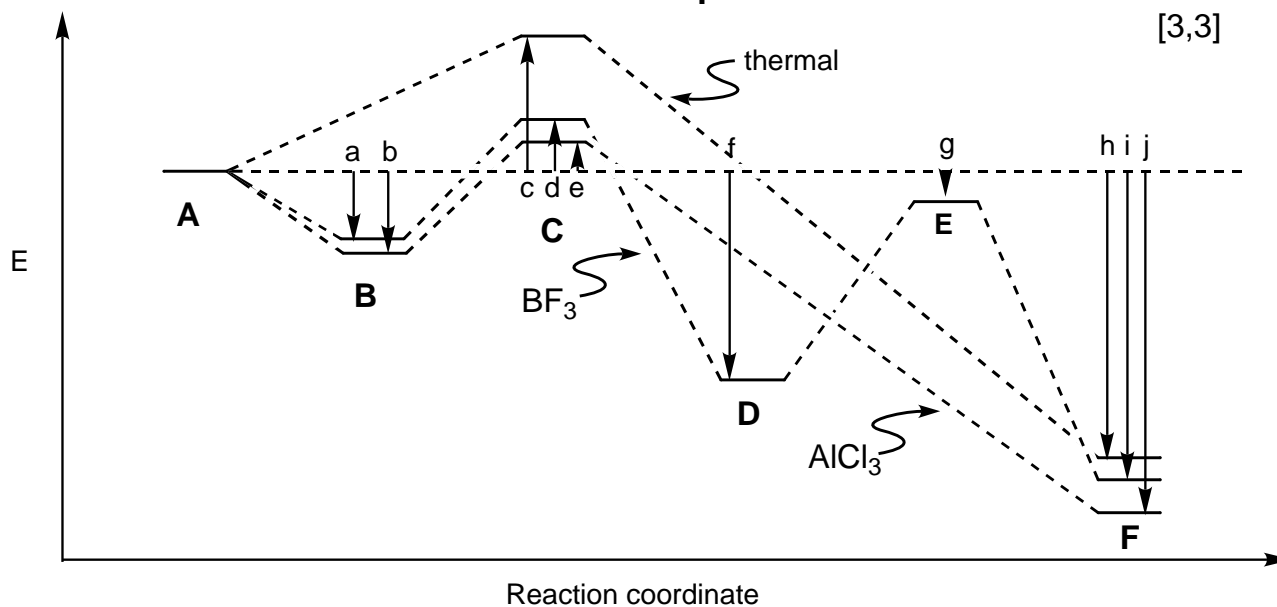
Yamabe, *J. Am. Chem. Soc.* **1995**, *117*, 10994
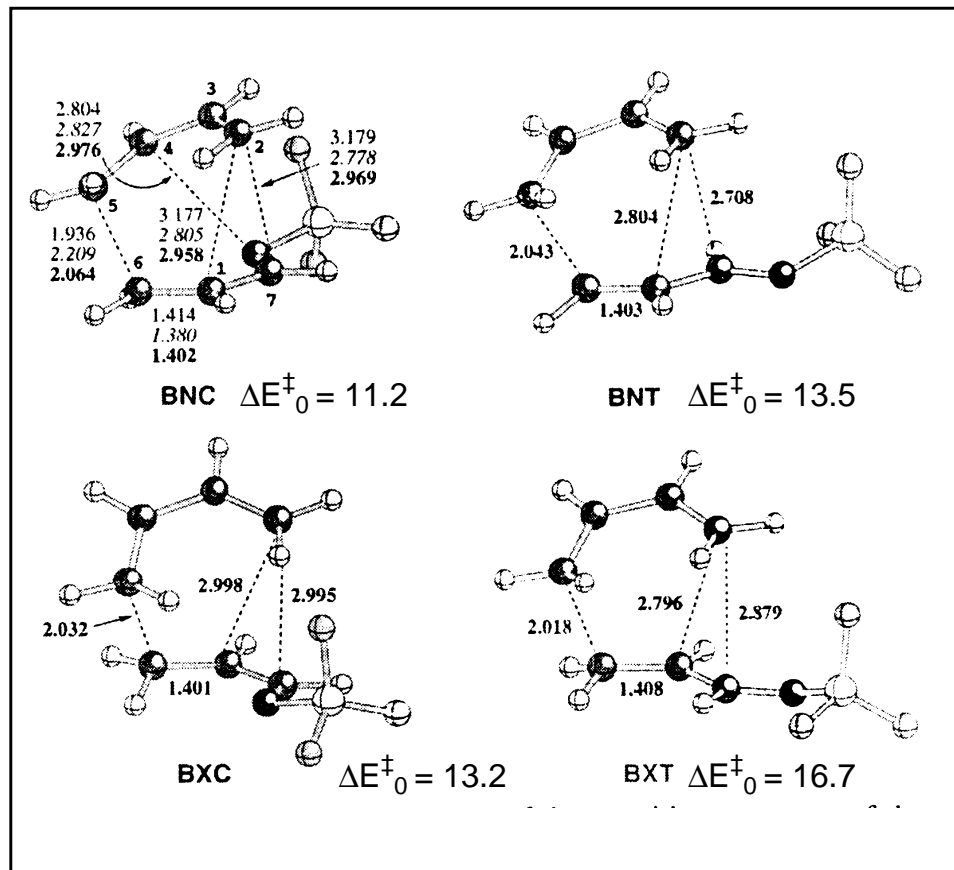Counterpoint: *J. Am. Chem. Soc.* **1998**, *120*, 2415

Ab Initio *Structures of Lewis Acid-Catalyzed Cycloadditions, II*

<u>Method</u>: Locate the transition structures of the Diels-Alder reaction of acrolein with butadiene promoted by BF_3 using Density Functional Theory (DFT) calculations

Uncatalyzed: **Catalyzed:**

NC $\Delta E^{\ddagger}_0 = 21.5$ NT $\Delta E^{\ddagger}_0 = 22.9$

BNC $\Delta E^{\ddagger}_0 = 11.2$ BNT $\Delta E^{\ddagger}_0 = 13.5$

XC $\Delta E^{\ddagger}_0 = 21.7$ XT $\Delta E^{\ddagger}_0 = 23.3$

BXC $\Delta E^{\ddagger}_0 = 13.2$ BXT $\Delta E^{\ddagger}_0 = 16.7$
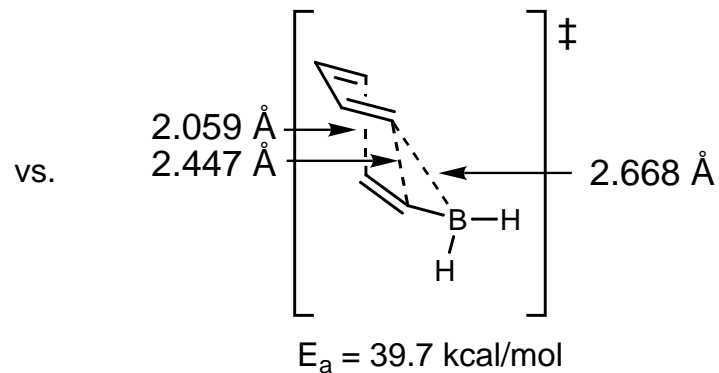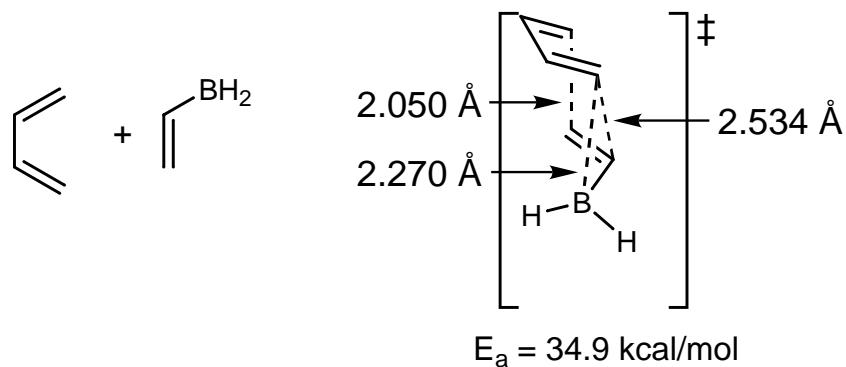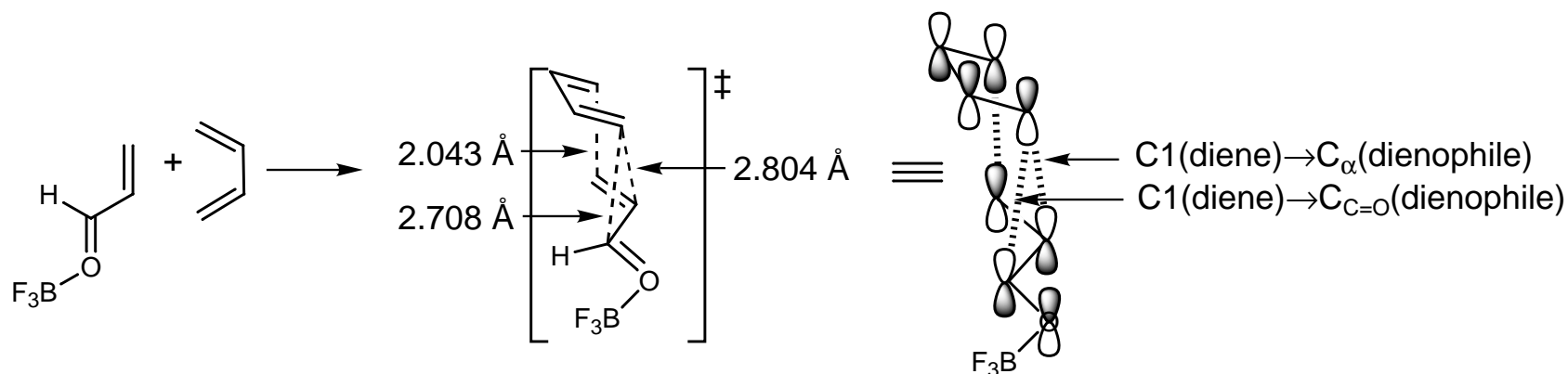
❑ DFT constitutes an excellent compromise between computational cost and accurate energetic results
❑ [4+3] interaction observed for all four transition structures
❑ Relative energies are explained by number and strength of secondary interactions

A [4+3] Transition State for the [4+2] Cycloaddition

6-31*/6-31G*:

2.050 Å → ← 2.534 Å

2.270 Å →

vs.

2.059 Å →
2.447 Å →

← 2.668 Å

E_a = 34.9 kcal/mol

E_a = 39.7 kcal/mol

Singleton, *J. Am. Chem Soc.* **1992**, *114*, 6563

2.043 Å → ← 2.804 Å

2.708 Å →

≡

← C1(diene)→C_α(dienophile)
← C1(diene)→$C_{C=O}$(dienophile)

❑ Classical secondary orbital interactions do not play a significant role in the cycloaddition

García, Mayoral, *J. Am. Chem Soc.* **1998**, *120*, 2415

Pre-reactive van der Waals Complexes as Stereochemical Determinants

MP2/6-31G*:

Reaction of: +

TS1
14.1

TS2
16.2

Relative energy (kcal/mol)

vdw1→3
-2.1

vdw2→3
-3.1

-3.2
vdW3

-3.8
vdW1

-4.3
vdW2

-29.0
endo adduct

-29.6
exo adduct

Reaction coordinate
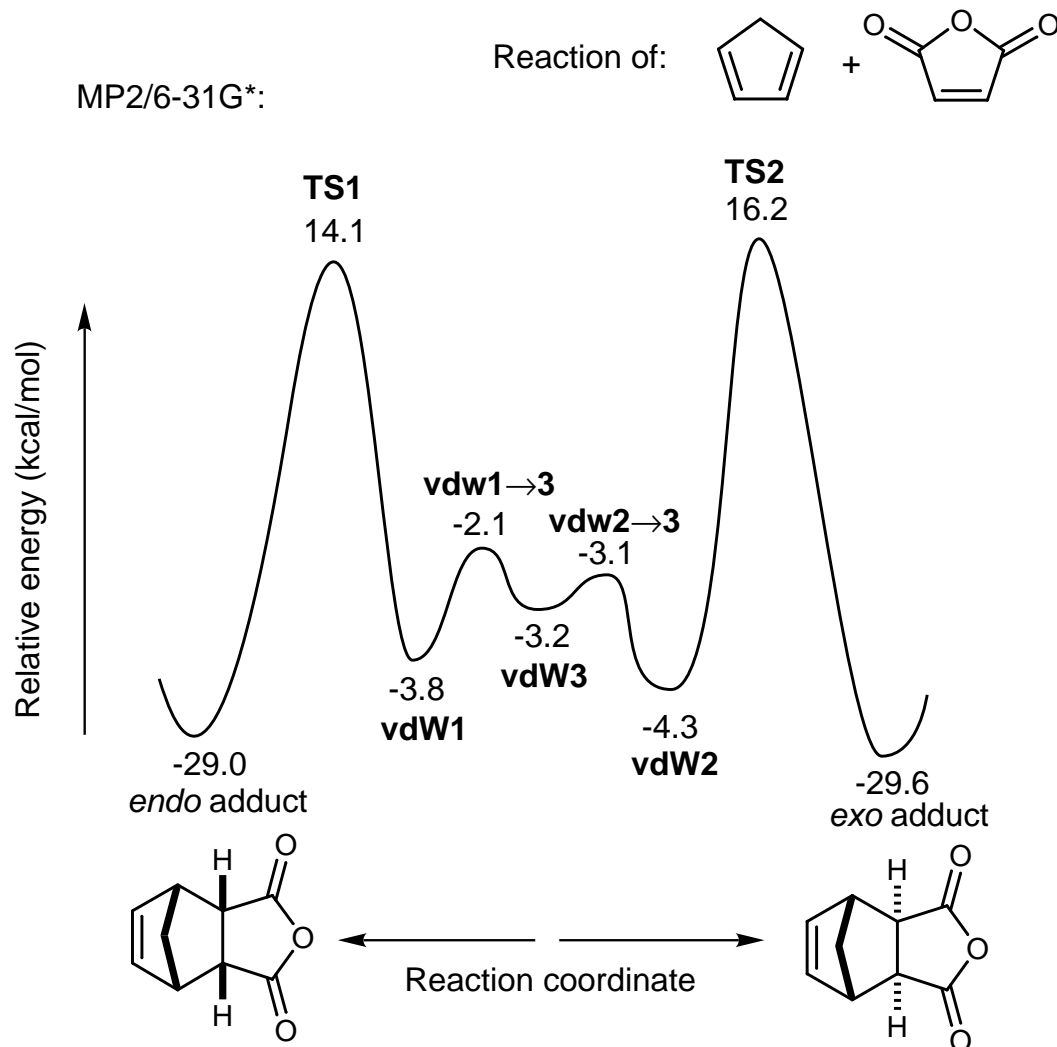
❒ **vdW3** is a (nonproductive) T-shaped structure intermediate between **vdW1** and **vdW2**

❒ Without consideration of the van der Waals complexes, $\Delta\Delta E^{\ddagger}$ = **TS2-TS1** = 2.1 kcal/mol (97.1% *endo* at 298 K); considering prereactive complexes, $\Delta\Delta E^{\ddagger}$ = [(**TS2-vdW2**)]-[(**TS1-vdW1**)] = 2.6 kcal/mol (98.8% *endo* at 298 K). Experimentally found: 98.5% *endo* at 298K

❒ Configurational analysis on the corresponding wavefunctions shows that the most significant interactions found in the **TS** structures are already present in the **vdW** structures

Sordo, *Chem. Commun.*, **1998**, 385

For spectroscopic evidence for these types of complexes in cycloaddition reactions, see: *J. Am Chem Soc.* **1991**, *113*, 2412

Caveats for Semi-Empirical Computations

<u>Method</u>: AM1 and PM3 studies of the Diels-Alder reaction of isoprene or cyclopentadiene with acrylonitrile, acrolein, methyl vinyl ketone, or methyl acrylate. Hydrogen bond donor (HBD) effects of the solvent were studied (PM3, continuum models) considering a single water molecule coordinated to the carbonyl (AM1 known to give unrealistic geometries and solvation energies)
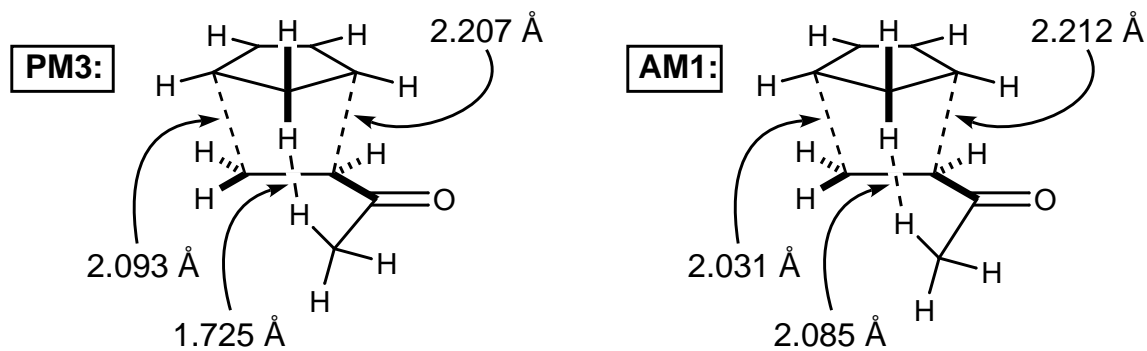
Whoops! PM3 predicts and attractive interaction between methylene and methyl hydrogens! For both AM1 and PM3, *exo s-trans* t.s.[‡] is found to be energetically favored, **contrary** to *ab initio* calculations

Buyer beware:
❒ Inherent weakness of PM3 to describe nonbonded interactions in the range of 1.7 to 1.8 Å due to the form of the core repulsion functions (CRF)
❒ AM1 can produce anomolously short O-H interatomic distances due to overestimated stabilization
❒ Semiempirical methods have trouble accurately describing conformational equilibria of dienophiles
❒ Best for identifying trends, rather than providing quantitative results

Mayoral, *J. Mol. Structure (Theochem)* **1995**, *331*, 37

Conclusions

❐ Alder's rule is important historically and as a mnemonic for predicting stereochemical outcomes of Diels-Alder reactions.

❐ Exceptions exist. Adherence with the rule depends to varying degrees on a complex combination of steric and electronic factors.

❐ Physical organic chemistry and modern computational methods have provided intimate details concerning the transition structures for a number of Diels-Alder reactions.