

σ/π Interaction as a Controlling Factor in the Stereoselectivity of Addition Reactions

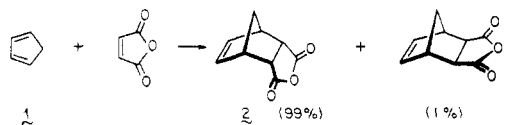
ROLF GLEITER* and LEO A. PAQUETTE*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and Organisch-Chemisches Institut der Universität, D-6900 Heidelberg 1, West Germany

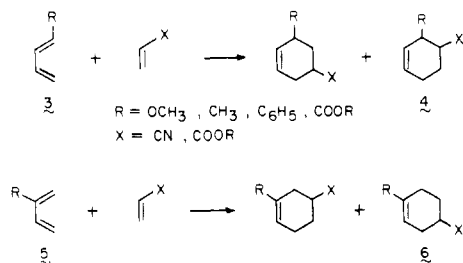
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Woodward and Hoffman's unifying theory of pericyclic reactions¹ gained rapid acceptance because it interconnected a large body of chemical fact previously considered to be unrelated. In their view, Diels-Alder reactions, the general process in which alkenes cycloadd to 1,3-dienes, are controlled by the in-phase relationships of both frontier-orbital pairs [HOMO (diene)-LUMO (dienophile) and HOMO (dienophile)-LUMO (diene)]. These in-phase relationships, known as *first-order* orbital interactions, are strongly favorable and constitute the prime source of reaction stereospecificity.

Several phenomena, especially stereoselectivity and regioselectivity, are controlled by *second-order* orbital interactions. Thus, the frequently observed adherence of [4 + 2] cycloadditions to the Alder rule of endo addition (cf. 1 \rightarrow 2) is believed to arise from symmetry-



allowed mixing of the nonprimary reaction centers when endo oriented.¹ In other settings, two different orientations are possible when unsymmetrical dienes add to unsymmetrical dienophiles. For electron-rich substrates such as 3 and 5, the formation of ortho (4) and para (6), respectively, is strongly preferred. This



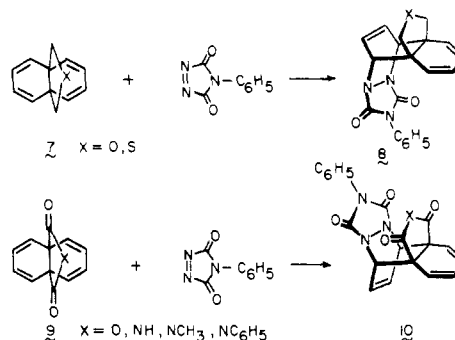
control arises because the coefficients of the orbitals are strongly perturbed by substitution (donor substituent

Rolf Gleiter received his Dr. rer. nat. in the field of synthetic organic chemistry from the University of Stuttgart in 1965. After postdoctoral work at Princeton University (P. v. R. Schleyer) and Cornell University (R. Hoffmann) he went to the University of Basel where he did his habilitation work in the laboratory of E. Heilbronner. In 1973 he joined the Faculty of the Technische Hochschule in Darmstadt as professor of organic chemistry; in 1979 he moved to the University of Heidelberg. His research activities are centered in spectroscopy and applied quantum chemistry.

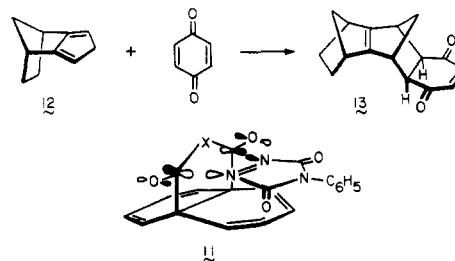
Leo Paquette is Kimberly Professor of Chemistry at The Ohio State University. He was raised in Massachusetts and attended Holy Cross College for his B.S. degree (1956) and M.I.T. for his Ph.D. (1959). After 4 years as a Research Associate at the Upjohn Co., he joined the Ohio State faculty and became Professor in 1969. His current research interests include the synthesis of naturally occurring and unnatural molecules of unusual structure, the interplay between theory and experiment, especially with regard to stereoelectronic control, new methodology based upon silicon and sulfur reagents, and photorearrangements.

enlarging the remote coefficient in HOMO and acceptor group exerting an identical effect in LUMO), and stabilization energy is maximized when the larger coefficients overlap.²

More recently, it has been proposed that more subtle effects can exert a major impact on the course of cycloaddition reactions. For example, the importance of *polar-group influences* has been nicely demonstrated by Ginsburg.³ While reaction between heterocyclic propellanes such as 7 with *N*-phenyltriazolinedione affords the anti adducts 8, replacement of the α -CH₂ groups by carbonyls (9) serves to deliver only syn products (10). While the stereochemical course of the



first reaction can be rationalized in terms of the relative steric contributions of the flanking bridges, this argumentation is not applicable to 9. A convincing explanation for this crossover has been advanced by Gleiter.⁴ When the carbonyl groups are present, the transition state for syn attack is stabilized by interactions between the *n* combination of the NN lone pairs and the antisymmetric π^* orbital of the CO-X-CO bridge of 9 as shown in 11. One can clearly distinguish between two



prevailing electronic situations, namely, the *primary orbital interaction* between the HOMO of the cyclohexadiene moiety and π^* of 9, and a *secondary orbital interaction* between the π system of the anhydride or

(1) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970.



(2) K. N. Houk, *Surv. Prog. Chem.*, 6, 113 (1973); *Acc. Chem. Res.*, 8, 361 (1975); *Chem. Rev.*, 76, 1 (1976).

(3) J. Kalo, E. Vogel, and D. Ginsburg, *Tetrahedron*, 33, 1177 (1977), and related papers from this group.

(4) R. Gleiter and D. Ginsburg, *Pure Appl. Chem.*, 51, 1301 (1979).

imide bridge and the n orbitals of the azo group. The first-mentioned effect is present irrespective of whether the triazolinedione enters into bonding from the syn or anti surface. The second effect operates only during syn approach and contributes added stabilization to this transition state.

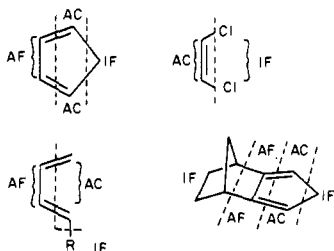
Significant attention has also been directed toward elucidation of the π -facial stereoselectivity associated with the [4 + 2] cycloaddition reactions of isodicyclopentadiene (12).⁵⁻⁸ Many experiments reveal that ex-

		
	12	14
ΔE_{ij}^{exo} [kcal/mol]	9.91	7.02
ΔE_{ij}^{endo} [kcal/mol]	5.45	3.98
$\Delta \Delta E_{ij}$ [kcal/mol]	4.46	3.04

clusive below-plane bonding occurs with all dienophiles except maleic anhydride and singlet oxygen. The cause of this striking behavior cannot be steric in origin since the reacting centers actually experience bond formation on the diene surface that is syn to the larger ethano bridge. Because 12 and similar hydrocarbons have low dipole moments, polar interactions can also be excluded. Rather, comprehensible analysis of the observed stereoselectivity can be made in terms of σ/π interaction. In this Account, we hope to transmit to the reader the essence of this phenomenon, to demonstrate its power in the context of newer laboratory findings, and to develop an appreciation of its possible utilitarian role in chemical terrain that has yet to be explored.

A Reformulation of Perturbation Theory

Cycloaddition stereo- and regiochemistry can be explained more conveniently if some concepts of frontier orbital theory^{2,9} are first reformulated. Thus, we divide the two reacting molecules into easily differentiable regions: (a) the *active centers* (AC), or atomic sites between which the new bonds are formed, (b) the *active frame* (AF), consisting of those atoms that are involved in the π/σ reorganization during reaction but which are not active centers, and (c) the *inactive frame* (IF), which comprises the remaining molecular fragments not involved per se in the cycloaddition. Examples follow.



(5) K. Alder, F. H. Flock, and P. Janssen, *Chem. Ber.*, **89**, 2689 (1956).

(6) T. Sugimoto, Y. Kobuke, and J. Furukawa, *J. Org. Chem.*, **41**, 1457 (1976).

(7) (a) L. A. Paquette, R. V. C. Carr, M. C. Böhm, and R. Gleiter, *J. Am. Chem. Soc.*, **102**, 1186 (1980); (b) M. C. Böhm, R. V. C. Carr, R. Gleiter, and L. A. Paquette, *Ibid.*, **102**, 7218 (1980); (c) L. A. Paquette, R. V. C. Carr, E. Arnold, and J. Clardy, *J. Org. Chem.*, **45**, 4907 (1980); (d) L. A. Paquette, F. Bellamy, M. C. Böhm, and R. Gleiter, *Ibid.*, **45**, 4913 (1980); (e) L. A. Paquette, R. V. C. Carr, P. Charumilind, and J. F. Blount, *Ibid.*, **45**, 4922 (1980); (f) L. A. Paquette and R. V. C. Carr, *J. Am. Chem. Soc.*, **102**, 7553 (1980).

(8) W. H. Watson, J. Galloy, P. D. Bartlett, and A. A. M. Roof, *J. Am. Chem. Soc.*, **103**, 2022 (1981).

(9) (a) K. Fukui, *Fortschr. Chem. Forsch.*, **15**, 1 (1970); (b) W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972); (c) R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1974); (d) G. Klopman, *J. Am. Chem. Soc.*, **90**, 543, 553 (1968).

Whereas most frontier orbital treatments focus only on π orbitals, the present analysis deals with the influence of σ orbitals at the active centers. This may at times lead to σ/π interaction in the frontier orbital pairs, either as the result of transition-state interactions (time dependent) or because of the topology of the inactive frame (time independent). As we shall see, the inactive frame may also exert a polarization effect on the proximal π systems. In the present article, only static time-independent phenomena are analyzed in detail.

With use of second-order perturbation theory, the total energy lost or gained (ΔE_{tot}) when orbitals of one fragment interact with those of another can be expressed as

$$\Delta E_{tot} = \Delta E_1 + \Delta E_2 + \Delta E_P + \Delta E_{\sigma/\pi} \quad (1)$$

In this summation, ΔE_1 comprises an electrostatic term, an expression of the frontier orbital interactions between occupied and unoccupied MO's, and a destabilizing component due to interaction between occupied orbitals (eq 2).¹⁰ The last term is very often neglected

$$E_1 = \sum_{A,B \in \{AC\}} \sum_B \frac{q_A q_B}{r_{AB}} + 2 \left(\sum_{\substack{i \\ \mu, \nu \in \{\pi\} \\ A, B \in \{AC\}}}^{occ} \sum_j^{unocc} + \sum_{i'}^{occ} \sum_{j'}^{unocc} \right) \frac{(c_{\mu i} c_{\nu j} S_{\mu\nu})^2}{\epsilon_j - \epsilon_i} + 4 \sum_{\substack{i \\ \mu, \nu \in \{\pi\} \\ A, B \in \{AC\}}}^{occ} \sum_j^{occ} \frac{[(\epsilon_{ij} - H_{ij}) c_{\mu i} c_{\nu j} S_{\mu\nu}]^2}{1 - S_{\mu\nu}^2} \quad (2)$$

in perturbational treatments. Where nonpolar cycloaddition reactions (e.g., most Diels-Alder processes) are concerned, the first term can be ignored as well. Thus, we end up with the first-order interaction between the AC's of the two reactants as the dominating influence.

A similar expression can be written for those centers that do not belong to the AC. For a simple case involving the two AO's μ and ν , eq 3 results. In this

$$\Delta E_2^{\mu\nu} = \sum_{A,B} \sum_B \frac{q_A q_B}{r_{AB}} + 2 \left(\sum_i^{occ} \sum_j^{unocc} + \sum_{i'}^{occ} \sum_{j'}^{unocc} \right) \frac{(c_{\mu i} c_{\nu j} S_{\mu\nu})^2}{\epsilon_j - \epsilon_i} + 4 \sum_{i,j}^{occ} \frac{[(\epsilon_{ij} - H_{ij}) c_{\mu i} c_{\nu j} S_{\mu\nu}]^2}{1 - S_{\mu\nu}^2} \quad (3)$$

$$A, B \in \{AC\} \quad \mu, \nu \in \{\pi\}, A, B \in \{AC\}$$

$$A \in \{AC\}, B \notin \{AC\} \quad \mu \in \{\pi\}, \nu \notin \{\pi\}$$

$$A \in \{AC\}, B \notin \{AC\} \quad \mu, \nu \notin \{\pi\}, A, B \in \{AC\}$$

$$\Delta E_2 = \sum_{\mu, \nu} \Delta E_2^{\mu, \nu} \quad (4)$$

instance, the first term relates to electrostatic interactions between the active centers from one reactant and the nonactive centers from the other, as well as electrostatic interactions between nonactive centers. While the second term sums up the contributions of AO interactions at the active frame between occupied and unoccupied MO's, the third contains the same inter-

(10) The following abbreviations apply: q_A, q_B = net charges at centers A and B; r_{AB} = intervening distance; C_μ = AO coefficient at center μ ; $S_{\mu\nu}$ = overlap integral; ϵ_i = orbital energy; $\epsilon_{ij} = (\epsilon_i + \epsilon_j)/2$; $H_{ij} = kS_{ij}$; $k = -39.7$ eV; and S_{ij} = group overlap integral.

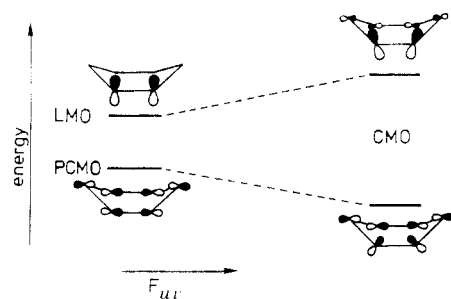


Figure 1. Mixing between the localized π and precanonical σ orbitals in tub cyclohexene with increasing interaction between both.

action between occupied MO's only.

The expression for polarization effects of electron-donating and -withdrawing groups, ΔE_P , is similar to eq 3, except that

$$\Delta C_{\mu i} = C_{\mu i}' - C_{\mu i} \quad (5)$$

must be used instead of the unperturbed LCAO coefficients. Rules to calculate these coefficients have been given by Libit and Hoffmann.¹¹ ΔE_P is a twofold summation where one unperturbed LCAO coefficient ($C_{\mu i}$, $C_{\nu j}$) always must be replaced by the $C_{\mu i}'$ 'th ($\Delta C_{\mu i} C_{\nu j}$, $C_{\mu i} \Delta C_{\nu j}$; $\Delta C_{\mu i} \Delta C_{\nu j}$ elements are neglected).

The term $\Delta E_{\sigma/\pi}$ is given by a perturbational summation wherein the σ orbitals of the AC's are also taken into account. The form of $\Delta E_{\sigma/\pi}$ is completely equivalent to the orbital summation of eq 3.

The σ/π Interaction Model

For the purpose of demonstrating σ/π interaction, let us consider those effects that prevail within the tub conformation of cyclohexene as summarized in Figure 1. The analysis, which involves the transformation of relevant canonical MO's into localized and precanonical MO's,¹² shows that the π orbital interacts predominantly with one ribbon type σ orbital. The changes resulting within the π wave function depend mainly on the relative position of the basis orbital energies of the interacting wave functions and the size of the matrix element $F_{\mu\nu}$ (the interaction element with the μ th localized π orbital and the ν th ribbon orbital). In Figure 1, the basis energy of the localized π orbital (LMO) is situated above that of the precanonical σ orbital (PCMO). With increasing $F_{\mu\nu}$, the level of interaction between both wave functions is increased and the π lobes experience progressively greater disrotatory tilting.

Strong σ/π interaction is also found in norbornadiene.^{7b} In Figure 2, we show the PCMO's that strongly interact with the symmetric $a_1(\pi_+)$ and anti-symmetric $b_2(\pi_-)$ linear combination of the pure localized π orbitals. As a consequence of this σ/π mixing, the π orbitals in the canonical MO's are rotated. The $a_1(\pi_+)$ linear combination is disrotatorily tilted with respect to the xz plane in such a way that the amplitude of the orbital wave function on the side of the methylene bridge is decreased. In the case of $b_2(\pi_-)$, the disrotatory motion increases the shape of the CMO syn to the methylene bridge. Superimposed on this phenomenon is a second type of π deformation that also takes place in the xz plane. Importantly, the $a_1(\pi_+)$

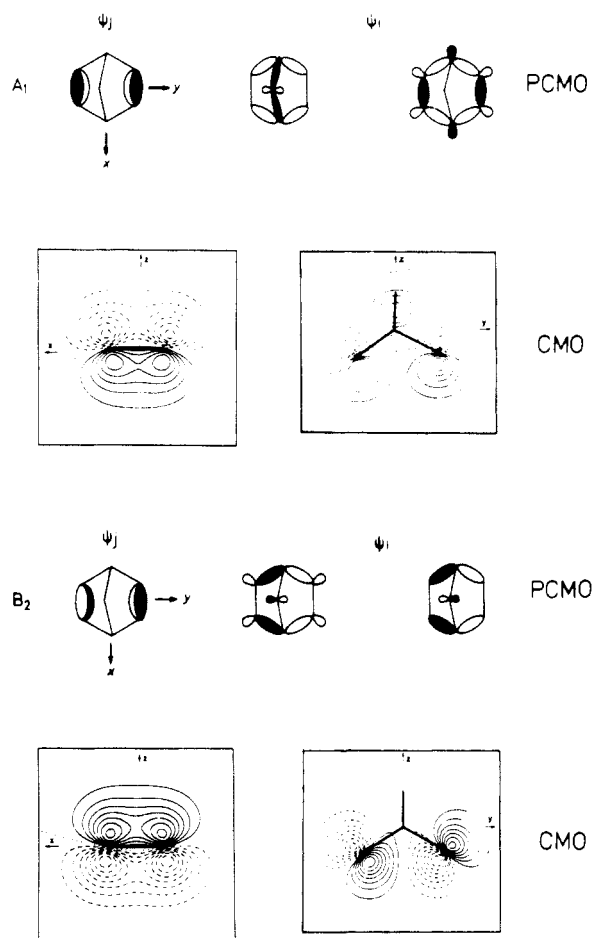


Figure 2. Contour diagrams of the canonical π -MO's (CMO's) a_1 and b_2 of norbornadiene. The CMO's are the result of interaction between the localized π -orbitals ψ_j and the precanonical σ -orbitals ψ_i . Full and dashed lines distinguish between amplitudes of different signs. Nodes are indicated by short dashes. The contours are shown in a plane through atoms 2 and 3 (left) and in the yz plane (right).

linear combination is also found to be bent toward the methano group, while $b_2(\pi_-)$ is tilted in the opposite direction.

The different rotations just described are due to admixture of the semilocalized p_π orbitals and the entire σ frame. This effect must be carefully separated from a nonequivalence due to hybridization,¹³ i.e., a mixing between s and p orbitals. A detailed analysis of the corresponding CMO's of norbornadiene shows that s/p mixing is unimportant; rather, p/p interaction dominates within the molecular fragments.

The Case for Isodicyclopentadiene and Its Dehydro Derivative

Our efforts to rationalize the Diels–Alder stereoselectivities of 12 and 14 began with extensive calculations on 15 and 16 as simpler model systems. When both



semiempirical (SPINDO, EHT, modified INDO) and ab initio (STO-3G) methods were employed, strong

(11) L. Libit and R. Hoffmann, *J. Am. Chem. Soc.*, **96**, 1370 (1974).

(12) E. Heilbronner and A. Schmelzer, *Helv. Chim. Acta*, **58**, 936 (1975).

(13) S. Inagaki, H. Fujimoto, and K. Fukui, *J. Am. Chem. Soc.*, **98**, 4054 (1976); S. Inagaki and K. Fukui, *Chem. Lett.*, 509 (1974).

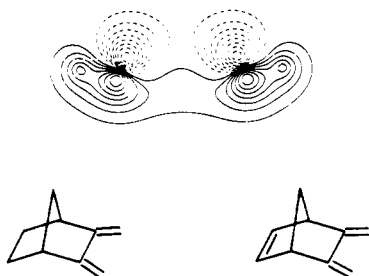


Figure 3. Contour diagram for 15 showing the deformation of the two terminal π lobes.

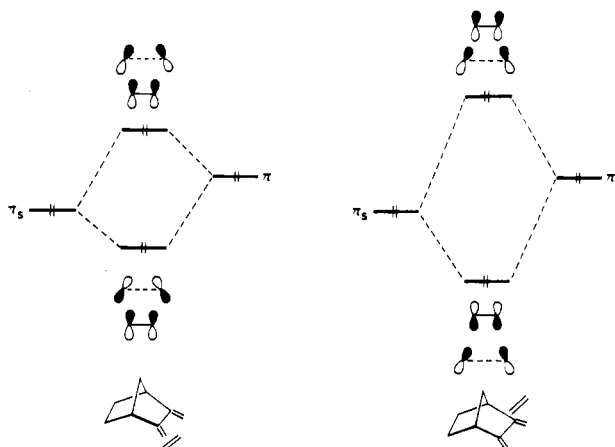


Figure 4. Qualitative diagram of the interaction between π_s of the butadiene unit in 15 and 16 with a π bond. On the left, below-plane approach. On the right, above-plane bonding.

mixing between the lowest occupied π orbital (π_s) and high-lying σ orbitals of proper symmetry was uniformly predicted. The rotation of the terminal p_π lobes for π_s in 15 is shown in the contour diagram of Figure 3. This tilting gives rise to significant differences in the frontier electron distribution on the exo and endo diene surfaces. In actuality, the various theoretical models predict σ concentration levels of 20–40% at the carbon centers of the diene moiety. The remarkable rotation of the π lobes within the CMO π_s results from strong interaction between the semilocalized π_s orbital and the precanonical σ orbitals of comparable energies.

To judge the reliability of these model calculations, the photoelectron spectra (PE) of 15 and 16 were recorded.^{7b} On the assumption that Koopman's theorem applies, these experiments revealed the π orbitals to be situated above the σ orbitals. Comparison of the PE data and computational results indicated the INDO and SPINDO methods to provide MO models most suitable for predicting π orbital distortion resulting from σ/π interaction. Because of its more disparate energy level, π_A (HOMO) is negligibly affected by the σ ribbon.

Like the simpler models, 12 and 14 experience an enhancement of the amplitudes syn to the methano group in π_s . To understand the preferred addition of a dienophile anti to the methano bridge, let us consider Figure 4. If reaction occurs from below, antibonding interaction between π_s of the butadiene moiety and the HOMO of the dienophile is smaller than in the case of syn attack. This is due to the different overlap between the dienophile and the rotated $2p_\pi$ orbitals at the terminal carbon atoms of the diene fragment. To estimate the energy difference for exo and endo attack in 12 and 14, we have calculated the four-electron destabilization

Table I
Four-Electron Destabilization Energies for 12 and 14

	12	14
$\Delta E_{ij}^{\text{exo}}$, kcal/mol	9.91	7.02
$\Delta E_{ij}^{\text{endo}}$, kcal/mol	5.45	3.98
$\Delta \Delta E_{ij}$, kcal/mol	4.46	3.04

energies¹⁴ $\Delta E_{ij}^{\text{exo}}$ and $\Delta E_{ij}^{\text{endo}}$ between the canonical MO's π_s of these dienes and π of ethylene. Assuming

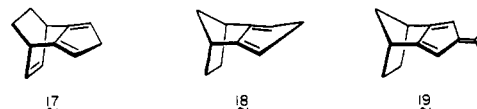
$$\Delta E_{ij} = \frac{4(\epsilon_{ij}S_{ij} - H_{ij}S_{ij})}{1 - S_{ij}^2} \quad (6)^{10}$$

a mean distance of 2.18 Å for the respective transition states, energy differences ($\Delta \Delta E_{ij}$) on the order of 12–18 kJ/mol are obtained, favoring endo attack (Table I). These relatively large energy differences explain why below-plane attack is kinetically favored.

In the case of 17, $\Delta \Delta E_{ij}$ is seen to be significantly reduced and only a slight preference for endo attack is predicted. This small value conforms to the observations that mixtures of isomers result except with *N*-methyltriazolidinone (100% endo).⁷

Answering the Counterarguments

As an extension of his π orbital distortion arguments for norbornene, Houk considered 2-methylidenenorbornane and observed by calculation that the exocyclic double bond was pyramidalized so as to bend the terminal hydrogens in the exo direction.¹⁵ The analogous pyramidalization of 12 and 14 (see 18) was cited as a



possible reason for preferential approach of the dienophile from below plane. To test this theory, we examined the π -facial stereoselectivity of Diels–Alder additions to norbornyl-fused dimethylfulvene systems such as 19.¹⁶ We expect these fulvenes to be planar on the basis of X-ray crystallographic and electron diffraction data for 6,6-dimethylfulvene and related molecules. Detailed MO calculations disclosed strong σ – π interaction of subjacent orbitals of 19, resulting in π lobe tilting reminiscent of that present in 12. These structural and electronic factors clearly remain conducive to fully stereocontrolled endo dienophile capture in every example studied.¹⁶

Vogel has argued that cycloaddition stereoselectivity in these systems may be governed by the relative stabilities of the isomeric adducts.¹⁷ It is widely recog-

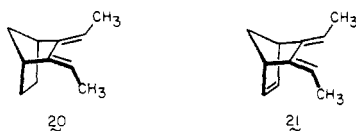
(14) (a) K. Müller, *Helv. Chim. Acta*, **53**, 1112 (1970); (b) N. C. Baird and R. M. West, *J. Am. Chem. Soc.*, **93**, 4427 (1971); (c) N. D. Epiotis and R. L. Yates, *Ibid.*, **98**, 461 (1976).

(15) (a) P. H. Mazzocchi, B. Stahly, J. Dodd, N. G. Rondan, L. N. Domelsmith, M. D. Rozeboom, P. Caramella, and K. N. Houk, *J. Am. Chem. Soc.*, **102**, 6482 (1980); (b) N. G. Rondan, M. N. Paddon-Row, P. Caramella, and K. N. Houk, *Ibid.*, **103**, 2436 (1981); (c) P. Caramella, N. G. Rondan, M. G. Paddon-Row, and K. N. Houk, *Ibid.*, **103**, 2438 (1981).

(16) L. A. Paquette, T. M. Kravetz, M. C. Böhm, and R. Gleiter, *J. Org. Chem.*, **48**, 1250 (1983).

(17) J. P. Hagenbuch, P. Vogel, A. A. Pinkerton, and D. Schwarzenbach, *Helv. Chim. Acta*, **64**, 1818 (1981).

nized that this phenomenon is not generally encountered in Diels–Alder chemistry (adherence to the Alder rule, etc). Notwithstanding, the point had to be dismissed by experiment. Where **20** and **21** are concerned,

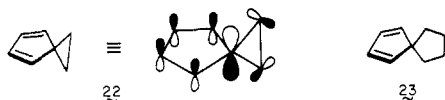


the methylene carbon that would generate a cyclopentadiene ring is lacking, and consequently sesquionbornene-type products are not produced. For this reason, there should exist little thermodynamic difference between syn and anti dienophile capture in these cases. Reagents such as *N*-phenylmaleimide, *p*-benzoquinone, and phenyl vinyl sulfone give products resulting exclusively from below-plane bonding.¹⁸ Consequently, we dismiss the notion of thermodynamic control as a major contributory factor.

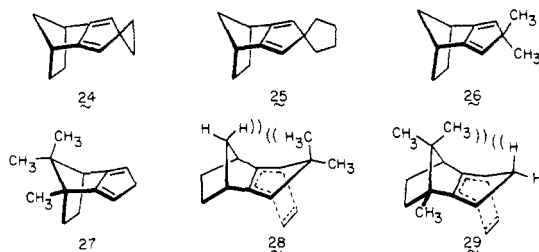
Decreased stereoselectivity was noted during the cycloaddition of dimethyl acetylenedicarboxylate (DMAD) and *N*-methyltriazolinedione (MTAD) to **20** and **21**. Apparently, the situation becomes more complex if either the inactive frame carries an additional norbornene double bond or the dienophile possesses a second occupied MO with a π system perpendicular to the bonding network. As noted earlier, the polarization induced by 2_π reagents of this type in the respective transition states must be given due consideration on a time-dependent basis.

Effects of Peripheral Alkyl Substitution

As the direct result of Heilbronner's investigation of the photoelectron spectra of **22** and **23** over a decade



ago,¹⁹ it is now obvious that substituents placed at C_5 of a cyclopentadiene ring exert a strong influence on the orbital energies of the π electrons. For example, the second PE band of **22** that is assigned to ionization from the π_g level is appreciably destabilized due to conjugative interaction with the symmetric Walsh orbital of the three-membered ring. Of course, **23** lacks this particular type of σ/π interaction. These differences were expected to persist in the ground-state structures of **24**–**26**.



When the long-range interactions of the norbornyl fragments are superimposed upon the symmetrically substituted cyclopentadiene networks in this manner, the two faces of each of the diene rings again become nonequivalent and differentiable. We had to give

(18) L. A. Paquette, A. G. Schaefer, and J. F. Blount, *J. Am. Chem. Soc.*, **105**, 3642 (1983).

(19) R. Gleiter, E. Heilbronner, and A. de Meijere, *Helv. Chim. Acta*, **54**, 1029 (1971).

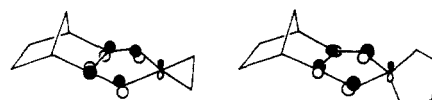


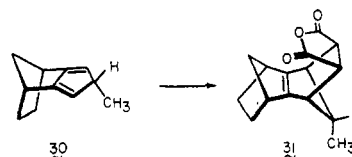
Figure 5. Schematic representation of the bonding linear combinations ($\pi_g + \text{Walsh}$) of **24** and the π_g MO of **25**.

particular attention to the possibility that nonbonded steric hindrance to product formation might now modulate π -facial stereoselectivity. For this reason, diene **27**²⁰ was included in order to examine the complementary state of affairs depicted in transition states **28** and **29**.

The spirocyclopropane system **24** was found once again to exhibit strong predilection for below-plane attack by a wide range of dienophiles to give adducts having *syn*-sesquionbornene geometry.²¹ In striking contrast, [4 + 2] cycloadditions of spirocyclopentane **25** yielded only *anti*-sesquionbornene derivatives, except with DMAD.¹⁸ The *gem*-dimethyl system **26** behaved analogously.²² The interesting questions pertaining to **27** were quickly answered when X-ray crystallography established its adducts to be *syn*-sesquionbornenes.²²

Clearly, the π -facial stereoselectivity shown by isodicyclopentadienes can be strongly modified by substitution of the tetrahedral carbon of the cyclopentadiene ring. The observed crossover from *anti* to *syn* is not kinetically linked if the relative rates of DMAD cycloaddition from the below-plane direction are any measure: **27** ($k_{\text{rel}} = 1$), **12** (0.95), **20** (0.44), **30** (0.30), **24** (0.20), **14** (0.19), **25** (0.15), **19** (0.018), and **26** (0.001).²² The steric influences delineated in **28** and **29** are also not of primary importance as revealed by X-ray data on several adducts that show the inside apical methyl group to be well beyond the van der Waals range of the opposed apical hydrogen. Data compiled from the PE spectra of **24**–**27** and INDO computations revealed that the terminal π lobes of **25**, **26**, and **30** in their individual π_g MO's are disrotatorily rotated away from the methano bridge, quite unlike the situation prevailing in **12**, **14**, **19**, **24**, and **27** (Figure 5). The fate suffered by alkyl-substituted isodicyclopentadienes of the first type is avoided by spirocyclopropane **24** only because of spiroconjugation.

It was briefly mentioned above that **30** shares an orbital construct in common with **25** and **26**. If this is so, then **30** should prefer to undergo *exo* bonding under Diels–Alder conditions. In fact, adducts such as **31** are produced in isomerically pure condition within our limits of detection.²²



Spectroscopic Evidence Supportive of π Orbital Tilting

If isodicyclopentadienes do indeed have this penchant for π orbital tilting in their ground state, the phenom-

(20) A. W. Burgstahler, D. L. Boger, and N. C. Naik, *Tetrahedron*, **32**, 309 (1976).

(21) L. A. Paquette, P. Charumilind, M. C. Böhm, R. Gleiter, L. S. Bass, and J. Clardy, *J. Am. Chem. Soc.*, **105**, 3136 (1983).

(22) L. A. Paquette, P. C. Hayes, P. Charumilind, M. C. Böhm, R. Gleiter, and J. F. Blount, *J. Am. Chem. Soc.*, **105**, 3148 (1983).

enon might well be detected by spectroscopic means. Reliance must be placed to some extent on long-range orbital interactions since the probes have been substantially removed from the immediate vicinity of the norbornyl framework and arranged symmetrically about the fused nodal plane. However, large orbital interactions through four or more bonds are well-known.²³

Expectedly, the carbon atoms within the three-membered ring of **24** exhibit different ¹³C chemical shifts. The upfield position of the above-plane carbon (see **32**) was ascertained by two complementary series of experiments.²⁴ The four methylene carbons within the spirocyclic five-membered ring of **25** also emerge with distinctively different chemical shifts. Suitable deuterium-labeling studies revealed that the carbon-shielding effects operating in **25** are reversed relative to those in **24** (see **33**)! Although a technique for dis-

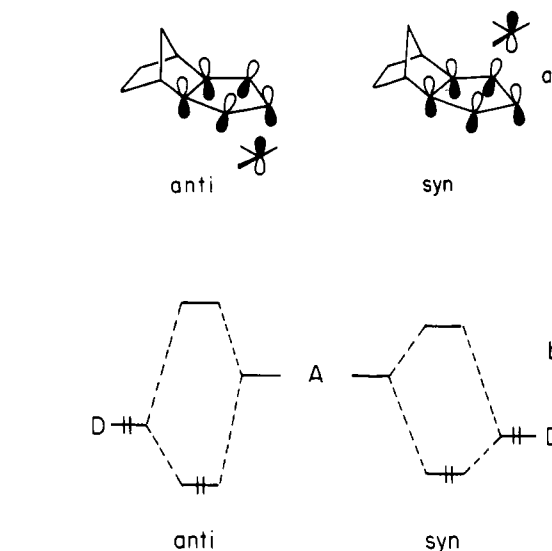
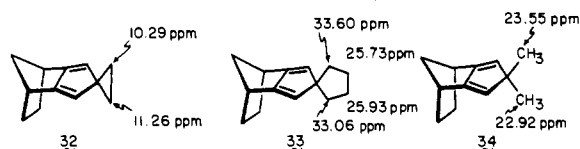


Figure 6. (a) Schematic representation of a transition state for S_N1 reaction between an electrophile and anion **35**; (b) MO interaction diagram between the π orbital of a donor system and the empty orbital of a carbenium ion.

tiguishing directly between the two methyl groups in **26** has not been found, ¹³C data on **30** and its epimer suggest the situation to be as in **34**.

This contrasting behavior appears to be entirely general. Although no direct correlation need exist, the more shielded surface is seen to parallel the directionality of orbital tilting and π -facial stereoselectivity.

The Isodicyclopentadienide Anion

Any complications that might be introduced by adduct formation are seen not to be present during the capture by anion **35** of suitable electrophilic reagents. For steric reasons, bonding was expected to be directed to the center most remote from the bicyclic units to deliver C_s -symmetric products. In this situation, the causative factors underlying the extent of endo/exo stereoselection must clearly be electronic in origin, since the reaction site is still further removed from the methano and ethano bridges that distinguish the π planes. Consequently, **35** and related carbanions offer the potential for providing additional independent experimental evidence for the fact that norbornyl ring systems can indeed exert long-range perturbational effects.

As matters turned out, condensation of **35** with methyl iodide afforded **30** as the only monomethylated product. Similarly, geminal dialkylation of **12** with $\text{Cl}(\text{CH}_2)_3\text{CD}_2\text{I}$ and NaNH_2 led cleanly to **36** and 1,4-dibromo-2-isopropylidenebutane gave only **37**. Deu-

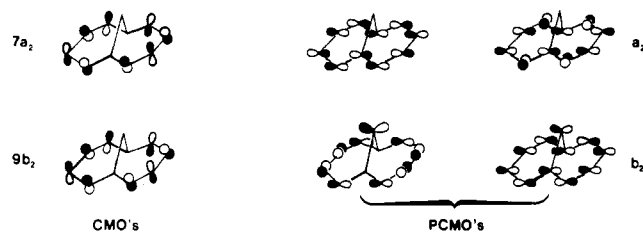
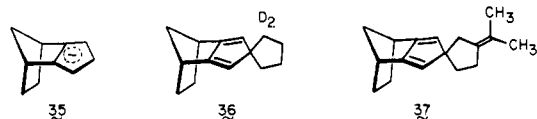
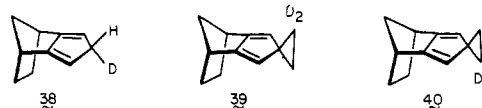


Figure 7. Highest occupied canonical π MO's of **41** (left). Schematic representation of the most important precanonical σ orbitals for orbital mixing in **41** (right).

$\text{BrCH}_2\text{CD}_2\text{Cl}$ and $\text{ClCH}_2\text{CD}_2\text{X}$ ($\text{X} = \text{I}, \text{OTs}$), a preference for endo C-C bond formation continued to prevail.²⁵

INDO calculations have proven uniformly consistent in predicting the observed stereoselectivity, with π orbital tilting within the anion occurring as shown in Figure 6. As a result, bonding interaction between the π donor (D) of **35** and the acceptor (A) of the attacking dienophile is more efficient if alkylation occurs from the endo surface. The loss of stereocontrol experienced during the formation of **39** and **40** is attributed to the



probable productlike nature of the transition states that reflect the rather unusual ground-state electronic properties of the spirocyclopropane products. The more esoteric question of whether ion-pairing effects have any impact remains to be resolved.

Generalizations

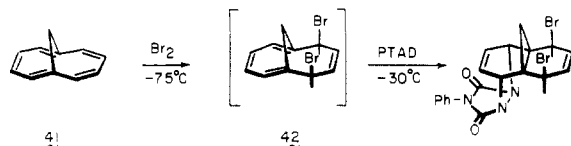
There are many other examples for which σ/π interaction causes a strong rotation of the p_x lobes at the active centers and thus controls stereoselectivity. For instance, 1,6-methano[10]annulene (**41**) undergoes bromine addition syn to the methano bridge.²⁶ 1,6-

teration of **35** at -78°C resulted in highly regioselective formation of **38**. Although a falloff in stereoselection was noted in spirocyclopropanation reactions involving

(23) (a) H.-D. Martin and R. Schwesinger, *Chem. Ber.*, **107**, 3143 (1974); (b) P. Pasman, J. W. Verhoeven, and Th. J. de Boer, *Tetrahedron Lett.*, 207 (1977); (c) R. Bartetzko, R. Gleiter, J. L. Muthard, and L. A. Paquette, *J. Am. Chem. Soc.*, **100**, 5589 (1978); (d) M. N. Paddon-Row, H. K. Patney, R. S. Brown, and K. N. Houk, *Ibid.*, **103**, 5575 (1981).
(24) L. A. Paquette and P. Charumilind, *J. Am. Chem. Soc.*, **104**, 3749 (1982).

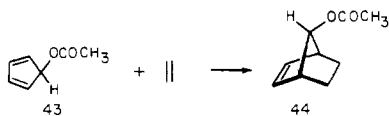
(25) L. A. Paquette, P. Charumilind, T. M. Kravetz, M. C. Böhm, and R. Gleiter, *J. Am. Chem. Soc.*, **105**, 3126 (1983).

(26) E. Vogel, W. A. Böll, and M. Biskup, *Tetrahedron Lett.*, 1569 (1966).



Oxido[10]annulene and 2,7-methanoaza[10]annulene behave comparably.²⁷ The intermediate 42 from 41 was recently trapped at low temperature and adduct stereochemistry established by X-ray analysis.²⁷ INDO calculations of 41 indicate the presence of strong interaction between two high-lying pure π orbitals of the perimeter and four precanonical σ orbitals (PCMO's) as shown at right in Figure 7.²⁸ The result is a rotation of the p_π AO's at C₂/C₅ and C₇/C₁₀ away from the methano bridge. Assuming a symmetrical transition state for Br₂ addition, we find the antibonding interaction between the occupied π levels of the halogen and 9b₂ and 7a₂ of 41 to be smaller if addition occurs syn to the methano bridge.

Similarly, our preliminary calculations on 5-acetoxycyclopentadiene (43) suggests that the remarkable regioselectivity observed in its Diels-Alder reaction with ethylene to give 44²⁹ is due to σ/π interaction and rotation of the p_π at its active centers.³⁰



(27) T. Scholl, J. Lex, and E. Vogel, *Angew. Chem.*, **94**, 924 (1982).

(28) R. Gleiter, M. C. Böhm, and E. Vogel, *Angew. Chem.*, **94**, 925 (1982).

(29) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, **77**, 4183 (1955).

Conclusion

The preceding discussion has shown that σ/π interaction must be carefully evaluated in any rationalization of Diels-Alder stereoselectivity. The entire σ framework must be considered, disrotatory tilting being a sensitive function of the relative positioning of the π and σ orbitals. We emphasize that the energy differences with which we are dealing can often be small (5–20 kJ/mol), the implication being that other influences such as van der Waals forces, induced dipole-dipole interactions, and steric effects must also be given proper consideration.

A point that we stress again is that our arguments are based upon ground-state electronic structures. Extrapolation to any given transition state would profit by being checked with accurate calculations. Also, a time-independent static picture has been employed. This profile can, of course, be modified by an approaching dienophile. In such examples, an extended time-dependent (dynamical) approach with coupling between all components (σ, π diene; σ, π dienophile) as a function of internuclear distance should prove helpful.

The amalgamation of theory and experiment described herein has been brought to fruition by the enthusiasm, dedication, and persistence of a relatively small number of students. These efforts have been made possible by the financial support of the National Cancer Institute (Grant CA12115), the Fonds der Chemischen Industrie, and BASF Aktiengesellschaft, Ludwigshafen.

(30) An alternative explanation has been advanced for this phenomenon: N. T. Anh, *Tetrahedron*, **29**, 3227 (1973).