not available); 173.5 °C (lit. 175 °C)[38a] for 4-NMe_2; 124-125 °C (lit. 126 °C)[38a] for 4-OMe; 84 °C (lit. 85 °C)[38a] for H; 147 °C (lit. 149 °C)[38b] for 3-Cl; 146-148 °C (lit., not available) for 4-CN; 216 °C (lit. 217 °C)[38a] for 4-NO_2. The crude crystals were purified by recrystallization from a mixture of benzene and petroleum ether (bp 35 °C). Morpholine, piperidine, and *N*-methylmorpholine were purified and stored as in a previous work.[39] Cacodylic acid (Sigma, AR grade), boric acid (Mallinckrodt, AR grade), glacial acetic acid (Mallinckrodt), chloroacetic acid (Mallinckrodt), and methoxyacetic acid (Aldrich) were used without further purification. DABCO (Aldrich) was purified by recrystallization from benzene and petroleum ether and was vacuum-dried [mp 159-161 °C (lit. mp 158-160 °C)]. Reagent grade dimethyl sulfoxide (Fisher Scientific) was stored over 4A molecular sieves prior to use. All other chemicals were of AR quality and used without further purification.

Solutions. Solutions were prepared in a similar way as described earlier.[40] All pH measurements were performed on an Orion Research 611 digital pH meter (H_2O, 50% and 90% Me_2SO) and on a Metrohm/Brinkman 104 pH meter (70% Me_2SO). The pH meters were equipped with a Corning No. 476022 glass electrode and a Beckman No. 39400 calomel reference electrode. The pH meters were calibrated for Me_2SO-water mixtures with buffers described by Hallé et al.[17] (for reactions at 20 °C) and by standard buffers in water (at 25 °C).

The pK_a values of the buffers were determined by standard potentiometric procedures, while the $pK_a^{\pm}$ values of morpholine and piperidine adducts of 4-OMe, H, and 3-Cl benzylidene Meldrum's acids (in H_2O) were determined by standard spectrophotometric procedures.[10a]

Kinetic Measurements. A Durrum-Gibson stopped-flow spectrophotometer with computerized data acquisition and analysis[41] was used to monitor all the reactions. The procedures were as described in ref 10a.

Acknowledgment. This research was supported by Grant CHE-8315374 from the National Science Foundation.

Registry No. BMA, 1214-54-6; 4-Et_2N-BMA, 108560-95-8; 4-Me_2N-BMA, 108560-96-9; 4-MeO-BMA, 108560-97-0; 3-Cl-BMA, 108560-98-1; 4-CN-BMA, 108560-99-2; 4-NO_2-BMA, 104143-49-9; piperidine, 110-89-4; morpholine, 110-91-8.

Supplementary Material Available: Kinetic data, Tables S1-S13 (17 pages). Ordering information is given on any current masthead page.

(38) (a) Schuster, P.; Polansky, O. E.; Wessely, F. *Monatsh. Chem.* **1964**, *95*, 53. (b) Schuster, P.; Polansky, O. E.; Stephen, A.; Wessely, F. *Monatsh. Chem.* **1968**, *99*, 1246.
(39) Bernasconi, C. F.; Carré, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 2698.
(40) Bernasconi, C. F.; Fox, J. P.; Kanavarioti, A.; Panda, M. *J. Am. Chem. Soc.* **1986**, *108*, 2372.
(41) Developed by Dr. F. A. Brand.

Modeling of Steric Control of Facial Stereoselectivity. Diels-Alder Cycloadditions of Unsymmetrically Substituted Cyclopentadienes

Frank K. Brown† and K. N. Houk*‡

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

D. Jean Burnell and Z. Valenta*

Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick, Canada, E3B 6E2

Received February 18, 1987

A MM2 model for prediction of stereochemistries of the Diels-Alder reactions of unsymmetrically substituted cyclopentadienes has been devised. The model gives reasonable agreement with experimental results for the reactions of cyclopentadienes which are spiro fused at the 5-position to norbornane or bicyclo[2.2.2]octane and for the reactions of pentamethylcyclopentadiene. The higher stereoselectivity of the Lewis acid catalyzed reactions is postulated to arise from an "earlier" rather than "tighter" transition state, which has flatter addends and closer approach of the out-of-plane substituents.

Introduction

The facial (syn-anti) stereoselectivity of Diels-Alder reactions of several unsymmetrical cyclopentadienes has been observed experimentally[1] and studied theoretically.[2] Secondary orbital interactions and unsymmetrical electron distributions have been proposed to explain observed selectivities. The π-facial stereoselectivity in Diels-Alder reactions of isodicyclopentadiene has been attributed to orbital tilting of the lowest diene π orbital, resulting from mixing of the norbornane framework and the π orbitals of the cyclopentadiene moiety.[3] Alternatively, Brown and Houk proposed that stereoselectivity in isodicyclopentadiene cycloadditions arises from conventional torsional effects in the parent system, which can be augmented or overridden by steric effects in substituted cases.[4]

†Current address: Smith Kline and French Lab, Philadelphia, PA 19101.
‡Address correspondence to this author at: Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA 90024.

(1) (a) Mironov, V. A.; Fadeeva, T. M.; Akren, A. A. *Dokl. Akad. Nauk SSSR* **1967**, *174*, 852. (b) McLean, S.; Haynes, P. *Tetrahedron* **1965**, *21*, 2313. (c) Mironov, V. A.; Fadeeva, T. M.; Pashegorova, V. S.; Stepanyants, A. U.; Akhren, A. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968** 423. Mironov, V. A.; Pashegorova, V. S.; Fadeeva, T. M.; Kimel'Fel'd, Y. M.; Akhren, A. A. *Ibid.* **1968**, 609. (d) Ibbott, D. G.; Payne, N. C.; Shaver, A. *Inorg. Chem.* **1981**, *20*, 2193. (e) Breslow, R.; Hoffman, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 2110. Breslow, R.; Hoffman, J. M.; Perchonock, C. *Tetrahedron Lett.* **1973**, 3723. (f) Shestakova, T. G.; Zaichikova, L. S.; Zyk, N. V.; Zefirov, N. S. *Zh. Org. Khim.* **1982**, *18*, 554. (g) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183. Mironov, V. A.; Dolgaya, M. E.; Luk'yanov, V. T.; Yankovskii, S. A. *Zh. Org. Khim.* **1976**, *12*, 1436. (h) Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1980**, 739. (i) Williamson, K. L.; Hsu, Y.-F. L.; Lacko, R.; Youn, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 6129. (j) Corey, E. J.; Weinshender, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.
(2) (a) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (b) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227. (c) Williamson, K. L.; Hsu, Y.-F. L., *J. Am. Chem. Soc.* **1970**, *92*, 1385.
(3) Gleiter, R.; Paquette, L. A., *Acc. Chem. Res.* **1983**, *16*, 328.

0022-3263/87/1952-3050$01.50/0

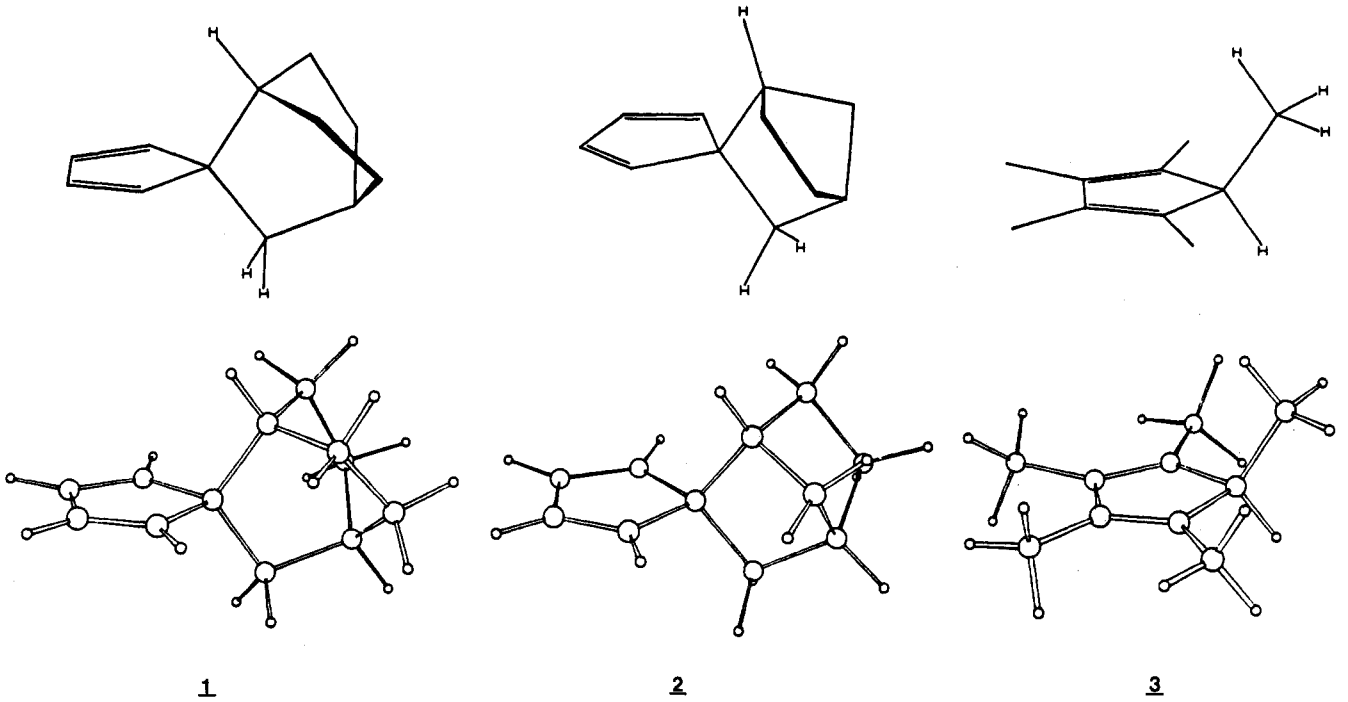


Figure 1. Substituted cyclopentadienes studied in this work.[5,6]

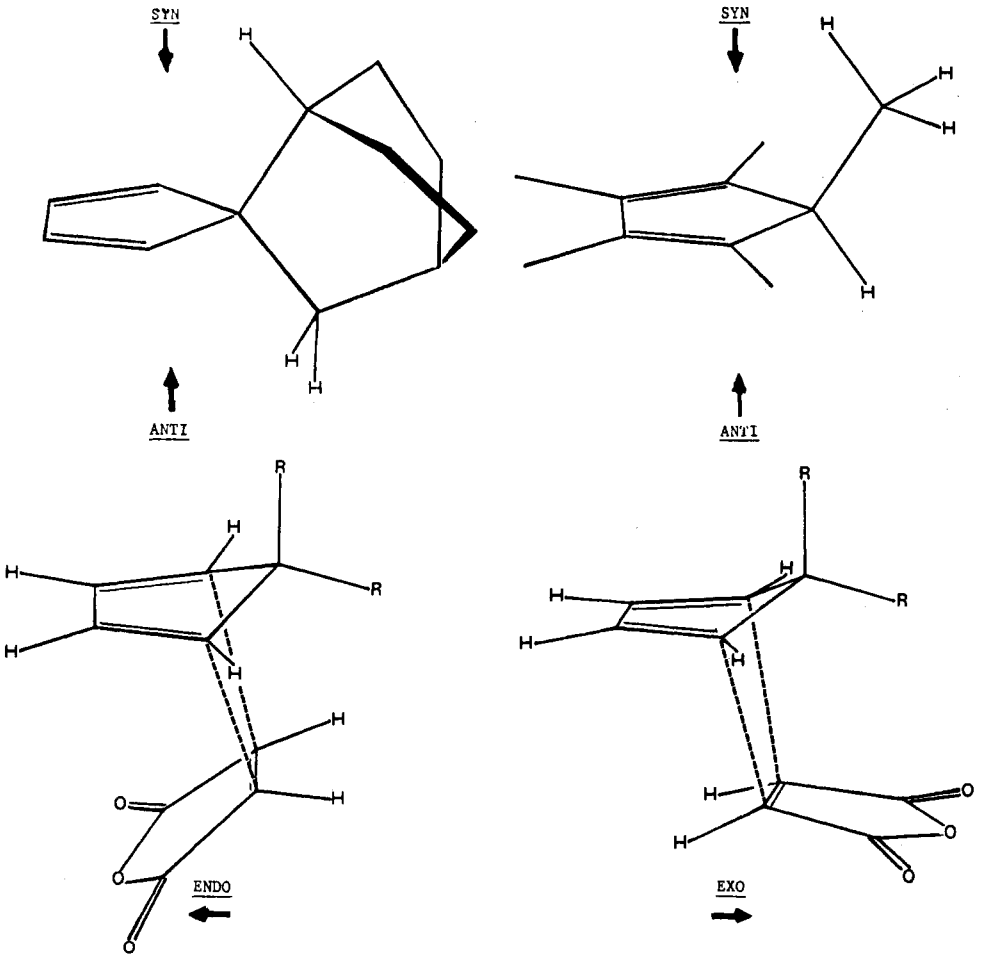


Figure 2. The various modes of attack are illustrated. Syn and anti modes refer to π-facial stereoselectivity, while the exo and endo modes refer to the location of the dienophile substituents relative to the norbornene moiety in the product.

Valenta, Burnell, and co-workers recently synthesized two novel unsymmetrically substituted cyclopentadienes, 1 and 2, and reported Diels–Alder reactions of these and of pentamethylcyclopentadiene with a variety of dienophiles.[5,6] The three dienes are shown in Figure 1 in both

(4) Brown, F. K.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 1971.

(5) Burnell, D. J. Ph.D. Thesis, The University of New Brunswick, Fredericton, NB, Canada, 1983. Burnell, D. J.; Valenta, Z. *J. Chem. Soc., Chem. Commun.* **1985**, 1242.

Table I. Experimental Anti/Syn Product Ratios in Diels–Alder Reactions of Dienes 1–3[a] at 40 °C

	dienophile						
diene	maleic anhydride	*N*-phenyl-maleimide	*p*-benzo-quinone	dimethyl maleate	methyl acrylate[b]	DMAD[c]	TCNE[d]
1	86:14 (90:10)[e]	86:14 (93:7)	86:14 (89:11)	89:11	88:12	92:8	
2	72:28	69:31 (73:27)	69:31				
3[f]	79:21:0	83:17:0	83:17:0	89:11:26	82:18:19	64:36	100:0

[a] For 3 the ratio given is anti (endo)/syn (endo)/anti (exo), while 1 and 2 give exclusively endo products. [b] The reaction of 1 with acrolein and 3-buten-2-one gave anti/syn ratios of 86:14 and 89:11, respectively. [c] DMAD = dimethyl acetylenedicarboxylate. [d] TCNE = tetracyanoethylene. [e] The anti/syn ratios given in parentheses are for the catalyzed reactions. The catalyzed reactions were run at −78 °C. [f] The reactions of 3 were run at room temperature.

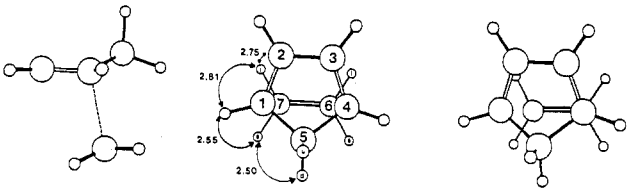
conventional drawings and as computer plots of optimized MM2 structures.[7] The experimental stereoselectivity results are summarized in Table I. Attack from the methylene face of 1 and 2, called anti attack, is preferred over attack from the methine face, which is called syn attack. These attack modes are defined in Figure 2. One criterion in the design of dienes 1 and 2 was that they would exhibit, for obvious steric reasons, exclusive endo selectivity.[5] Steric effects were also proposed as the origin of anti selectivity observed for 1–3.[6]

We have applied the MM2 model described earlier[4] to these reactions and describe here how steric effects can account for both the endo and π-facial stereoselectivities observed for these reactions. The model we have developed is empirical but provides a quantitative test of the hypothesis that the stereoselectivities of these reactions are controlled by steric effects. It also can be used to predict stereoselectivities in related cases.

Results and Discussion

MNDO Transition-Structure and MM2 Models. Dewar's semiempirical MNDO[8] gives transition structures for the Diels–Alder cycloaddition very similar to those obtained by ab initio calculations with the STO-3G basis set,[9] if tne MNDO transition structures are constrained to have a plane of symmetry.[4] When unconstrained, MNDO, with either UHF or RHF techniques, predicts that Diels–Alder reactions occur by two-step mechanisms with biradical intermediates.[10] In order to obtain a reasonable approximation to the transition structures of Diels–Alder reactions of cyclopentadienes, we located the C_s-constrained-synchronous MNDO cyclopentadiene–ethylene transition structure. The geometrical parameters are shown in Table II. During the course of this work, Burke reported an STO-3G transition structure for this reaction.[11] The reaction progress in Burke's cyclopentadiene–ethylene ab initio STO-3G transition structure is similar to that found for the butadiene–ethylene ab initio STO-3G transition structure.[9] The partially formed CC bond lengths are 2.215 Å for cyclopentadiene–ethylene and 2.217 Å for butadiene–ethylene. Subsequent ab initio studies of the butadiene–ethylene transition structure at the 3-21G[9b] and MCSCF[9c] levels are very similar to the STO-3G structure; the forming C–C bonds are 2.210 and 2.244 Å, respectively. The forming CC bond lengths for the MNDO cyclopentadiene–ethylene and butadiene–ethylene transition structures are 2.163 Å. The MNDO transition structures differ from ab initio structures in that the MNDO cyclopentadiene–ethylene transition structure is less pyramidalized at the reacting centers than its ab initio counterpart, while the butadiene–ethylene transition structure is more pyramidalized. The ab initio cyclopentadiene–ethylene transition structure is 8° more pyramidal at C1 and C4, α, and the angle of attack, β, on the ethylene moiety is 1° more obtuse than in the MNDO transition

Table II. C_s Constrained-Synchronous MNDO Cyclopentadiene–Ethylene Transition Structure



Bond Lengths			
C1–C2	1.411	C5–Hu	1.117
C1–C7	2.163	C5–Hd	1.106
C1–H	1.083	C7–C6	1.392
C2–C3	1.426	C7–Hi	1.093
C2–H	1.083	C7–Ho	1.093
C1–C5	1.532		

Bond Angles			
C1–C2–H	126.0	H–C1–C7	101.4
C1–C2–C3	108.5	C5–C1–C7	91.4
C1–C5–C4	98.4	C5–C1–C2	107.0
C1–C5–Hu	110.6	C2–C3–C4	108.5
C1–C5–Hd	115.8	C2–C3–H	125.3
C1–C7–C6	102.4	C2–C1–C7	98.7
C1–C7–Hi	95.7	Hi–C7–C6	121.0
C1–C7–Ho	93.5	Ho–C7–C6	121.1
H–C1–C2	125.5	Hi–C7–Ho	113.1
H–C1–C5	122.4		

Dihedral Angles			
C1–C2–C3–C4	0.0	Hi–C7–C6–Ho	153.6
C1–C2–C3–H	−174.6	Hi–C7–C6–Hi	0.0
C1–C5–C4–C3	−30.4	C2–C1–C5–Hu	−25.5
C1–C7–C6–C4	0.0	C2–C1–C5–Hd	154.5
H–C1–C2–H	10.0	H–C1–C5–Hu	70.6
H–C1–C2–C3	−175.5	H–C1–C5–Hd	−49.4
C5–C1–C2–C3(α)	−20.4	H–C1–C7–Hi	−74.4
C5–C1–C7–C6	38.7	H–C1–C7–Ho	39.2
H–C1–C7–C6	162.1	H–C2–C1–C5	165.1
C2–C1–C7–Hi	54.7	C1–C7–C6–Hi	104.5
C2–C1–C7–Ho	168.3	C1–C7–C6–Ho	−101.9
C2–C1–C7–C6	−68.8	C3–C4–C1–C7(β)	−103.7

(6) Burnell, D. J.; Goodbrand, H. B.; Kaiser, S. M.; Valenta, Z. *Can. J. Chem.* **1984**, *62*, 2398.
(7) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127; Quantum Chemistry Program Exchange, No. 395. For an excellent general description of MM2 and force-field calculations, see: Burkert, U.; Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982.
(8) Dewar, M. J. S. Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907.
(9) (a) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609. (b) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1985**, *108*, 554. (c) Bernardi, F.; Bottini, A.; Robb, M. A.; Field, M. J.; Hillier, I. H.; Guest, M. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1051.
(10) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209.
(11) Burke, L. A., submitted for publication. We thank Professor Burke for his private communication of this information.

Table III. Calculated and Experimental Anti/Syn Ratios at 40 °C

	dienophile type							
	cyclic[a]				acyclic[b]			
diene	expt	$\Delta\Delta G^{\ddagger}$	calcd	ΔE	expt[c]	$\Delta\Delta G^{\ddagger}$	calcd[c]	ΔE
1	86:14	1.1	76:24	0.7	86:14:0:0	0:1.1:>2:>2	73:24:2:1	0:0.7:2.0:2.5
					86:12:0:0	0:1.2:>2:>2		
	(90:10)[d]	0.9	86:14	0.7				
	(93:7)	1.00						
	(89:11)							
2	69:31	0.5	70:30	0.5			65:27:4:4	0:0.5:1.7:1.8
	72:28	0.6						
	(73:27)	0.4	78:22	0.5				
3[e]	79:21	0.8	100:0	4.0	69:15:16:0	0:0.9:0.9:>2	76:0:24:0	0:3.9:0.7:6.6
	83:17	0.9			71:9:20:0[f]	0:1.2:0.8:>2		

[a] Ethylene is the model dienophile representing the cyclic dienophiles. [b] Calculations and experimental data are for methyl acrylate, except where noted. [c] The ratio given is anti (endo)/syn (endo)/anti (exo)/syn (exo). [d] The catalyzed reactions are given in parentheses and correspond to those found in Table I. The $\Delta\Delta G^{\ddagger}$ were determined at −78 °C. [e] The $\Delta\Delta G^{\ddagger}$ for **3** were determined at 25 °C. [f] For reactions of dimethyl maleate.

structure, as shown in Table II.

In order to study larger systems, we constructed an MM2 model like that used earlier to study isodicyclopentadiene Diels–Alder reactions.[4] The general assumption here is that hydrocarbon substituents will not substantially alter the transition structures and that stereoselectivity will arise because there are different steric interactions between the unsymmetrical hydrocarbon cyclopentadiene substituent and the dienophile in diastereomeric transition structures. These steric interactions were evaluated by using Allinger's MM2 force field for substituents[7] and new parameters for new types of atoms present in the transition state. In detail, the MM2 models for these cycloadditions were derived in the following manner: (1) the positions of the seven carbons of cyclopentadiene and ethylene and the hydrogens attached to these carbons were restricted at the C_s MNDO transition-structure geometry; (2) the geometries of the substituents at C5 of cyclopentadiene are optimized in a normal fashion with MM2 parameters; (3) all torsional parameters involving forming or changing bonds are set equal to zero. For reactions involving compounds **1** and **2**, ethylene was used to model all of the cyclic dienophiles. Experimentally, all of these dienophiles give only endo adducts, regardless of which face they attacked. The only difference in steric interactions is between the olefinic hydrogens of the dienophile and the substituent of the cyclopentadiene. However, with compound **3**, both exo and endo products are observed for acyclic dienophiles; therefore, appropriate substituents had to be included on the dienophile. Substituents on the dienophile were optimized by using equilibrium angles for the corresponding hydrogen found in the MNDO transition structure. For instance, if a methyl group replaces one of the hydrogens on the ethylene moiety, to model the cycloaddition of cyclopentadiene with propene, the methyl group is attached to ethylene with the equilibrium angle corresponding to the hydrogen it replaced. Force constants for the substituted carbons in the dienophile were assumed to be the same as those of normal sp^3 carbon.

With this modeling, MM2 steric energies were calculated for each possible transition state. Product ratios were calculated by assuming that the differences in steric energies calculated for isomeric transition states are equal to the difference in activation energies and that A factors are identical for the diastereomeric reactions.

Syn–Anti Stereoselectivity in Reactions of 1–3. Table I summarizes the experimental results for the cycloadditions of **1–3** with a variety of dienophiles. These are compared to the computational results in Table III. The experimental anti/syn ratios for the cycloadditions of all of the dienophiles tested are close to 86:14 and 70:30 with **1** and **2**, respectively. Catalyzed reactions of **1** and **2** with *N*-phenylmaleimide at −78 °C gave ratios of 93:7 and 73:27, respectively. This corresponds to $\Delta\Delta G^{\ddagger}$ values for the thermal additions of 1.1 and 0.5 kcal/mol for **1** and **2**, respectively, while the $\Delta\Delta G^{\ddagger}$ values are 1.0 and 0.4 kcal/mol for **1** and **2**, respectively, for catalyzed additions. The calculated energy differences for the cycloaddition of **1** and **2** with ethylene are 0.7 and 0.5 kcal/mol, respectively, favoring anti attack.

The calculations give quite reasonable agreement with experiment, suggesting that stereoselectivities can be understood on the basis of steric effects. The approach from the methylene (anti) side is favored because the only significant interactions of the methylene hydrogens are with the exo hydrogens on the dienophile, while the methine hydrogen has significant repulsive interactions with both exo hydrogens and carbons of the ethylene moiety, as shown in Figures 3 (for **1**) and 4 (for **2**). However, this difference in van der Waals repulsion accounts only partially for the energy difference calculated for these isomeric transition structures. The remaining portion of the energy difference can be accounted for primarily by differences in bending energies. The syn approach has a higher bending energy for reactions of **1** and **2** by 0.5 and 0.3 kcal/mol, respectively. This increase in bending energy results from the greater van der Waals repulsion on the methine hydrogen than on the methylene. To alleviate some of the van der Waals repulsions, the alkyl substituent will deform, reducing the van der Waals steric energy but increasing the bending energy. Thus, the energy difference between systems can be attributed to steric interactions, although when the energy is decomposed the difference appears in the van der Waals and bending terms.

Experimentally[5] the cycloadditions of **3** with reactive dienophiles such as maleic anhydride give detectable quantities of the two endo products, in a ratio (anti/syn) of 81:19, corresponding to a $\Delta\Delta G^{\ddagger}$ of 0.9 kcal/mol in favor of the anti addition. However, with acyclic, less reactive dienophiles such as methyl acrylate, the situation is complicated by a third product, the anti (exo) adduct. Nevertheless, with methyl acrylate, **3** gave adducts in an anti (endo)/syn (endo)/anti (exo) ratio of 69:15:16, also translating into a $\Delta\Delta G^{\ddagger}$ of 0.9 kcal/mol favoring the anti (endo) over the syn (endo) addition. The experimental anti (endo)/anti (exo) ratio, which corresponds to a $\Delta\Delta G^{\ddagger}$ of 0.9 kcal/mol in favor of anti (endo) over anti (exo) addition, is similar to that observed for the reaction of methyl acrylate with cyclopentadiene.[12]

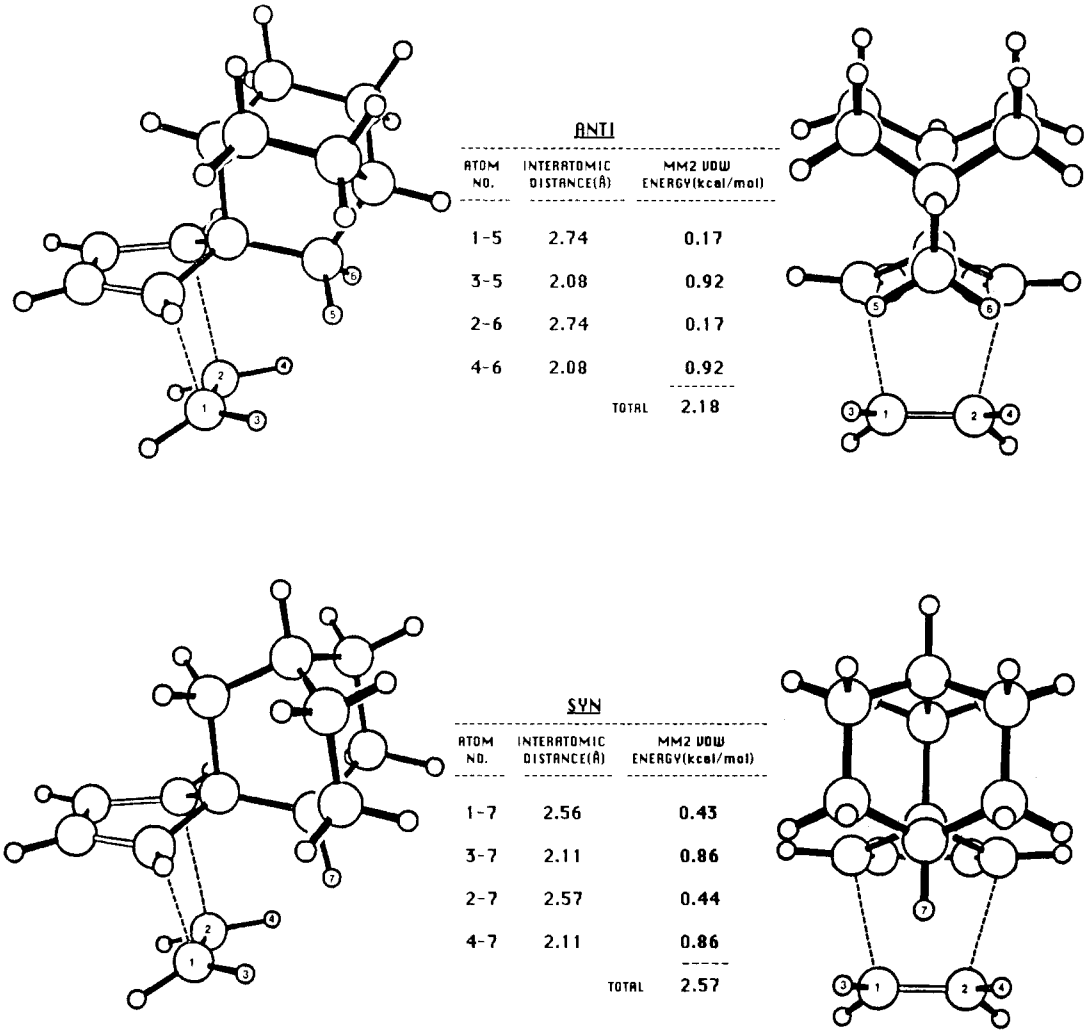


Figure 3. Side and front views of the MM2 anti and syn transition structures for the reactions of 1 with ethylene. The major van der Waals interactions from MM2 calculations are listed and are only a subset of the total interactions.

Obviously, approach anti to the methyl is favored (Figure 5), but the calculations for the cyclic dienophiles predict exclusive anti (endo) approach, with an energy difference of 4.0 kcal/mol. This large overestimation of the energy difference between syn and anti attack arises from the rigid constraints on the model involving the cyclopentadiene and ethylene moieties, which has been noticed in other similar cases.[4] When a dienophile approaches syn, near the C5 methyl group, the transition structure would be expected to adjust to relieve dienophile–methyl repulsions. However, our model holds the dienophile carbon and the C5 of cyclopentadiene fixed so that relief of this repulsion cannot occur readily. With **1** and **2**, this is not a problem, since there is an alkyl substituent on both sides of C5, and any lack of flexibility should influence both transition structures to a similar extent.

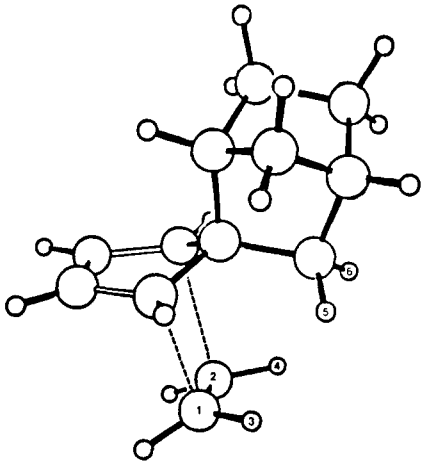
Two different methods of introducing additional flexibility into the model were tested. First, the position of C5 of the cyclopentadiene was no longer fixed, and the preferred location of C5 was controlled by equilibrium angles found in the MNDO transition structure. The result of this slight increase in flexibility in the model was a calculated energy difference of 2.9 kcal/mol, favoring anti attack. This decreased the energy difference by 1.1 kcal/mol from the "rigid" model. Greater flexibility was introduced into the model by allowing freer C5 motion, controlled only by the equilibrium C–C bond lengths to C5 and by use of an sp^3 force constant to control the C1C5C4 bond angle near the MNDO value. Force constants for other angles, C5C*x*C*y* (C*x* and C*y* are any other carbons), were set equal to zero. This allowed for maximum flexibility without giving an unrealistic conformation. The energy difference between syn and anti attack becomes 0.9 kcal/mol with this model. The energy difference of 0.9 kcal/mol predicts an 80:20 anti/syn ratio, close to the experimental ratios.

Table IV. The Calculated Energy Differences (kcal/mol) between Endo and Exo Approaches for the Reactions of Methyl Acrylate with 1–3

	approach	
diene	anti [*E*(exo) – *E*(endo)]	syn [*E*(exo) – *E*(endo)]
1	2.0	1.8
2	1.7	1.3
3	0.7	2.7

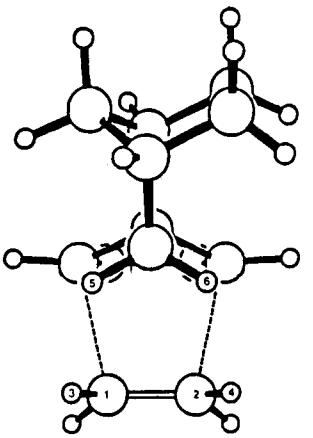
Exo–Endo Stereoselectivity in Reactions of 3. Whereas the cyclic dienophiles maleic anhydride, *N*-phenylmaleimide, and benzoquinone give only endo adducts with all three dienes, the acyclic dienophiles dimethyl maleate and methyl acrylate give both exo and endo adducts in the anti addition to **3**. The results suggest that

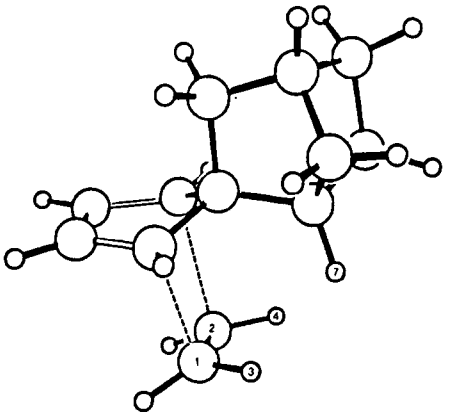
(12) The cycloaddition of cyclopentadiene with methyl acrylate at 50° gives an endo/exo ratio of 73:27, which corresponds to a $\Delta\Delta G^{\ddagger}$ of 0.64 kcal/mol. Kobuke, Y.; Fueno, T.; Furukawa, J. *J. Am. Chem. Soc.* **1970**, *92*, 6548.



ANTI

ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-5	2.80	0.12
3-5	2.13	0.70
2-6	2.85	0.07
4-6	2.20	0.51
	TOTAL	1.40





SYN

ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-7	2.63	0.31
3-7	2.06	1.03
2-7	2.81	0.10
4-7	2.44	0.12
	TOTAL	1.56

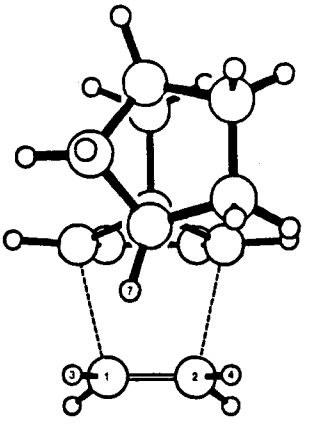


Figure 4. Side and front views of the MM2 anti and syn transition structures for the reaction of **2** with ethylene. The major van der Waals interactions from MM2 calculations are listed and are only a subset of the total interactions.

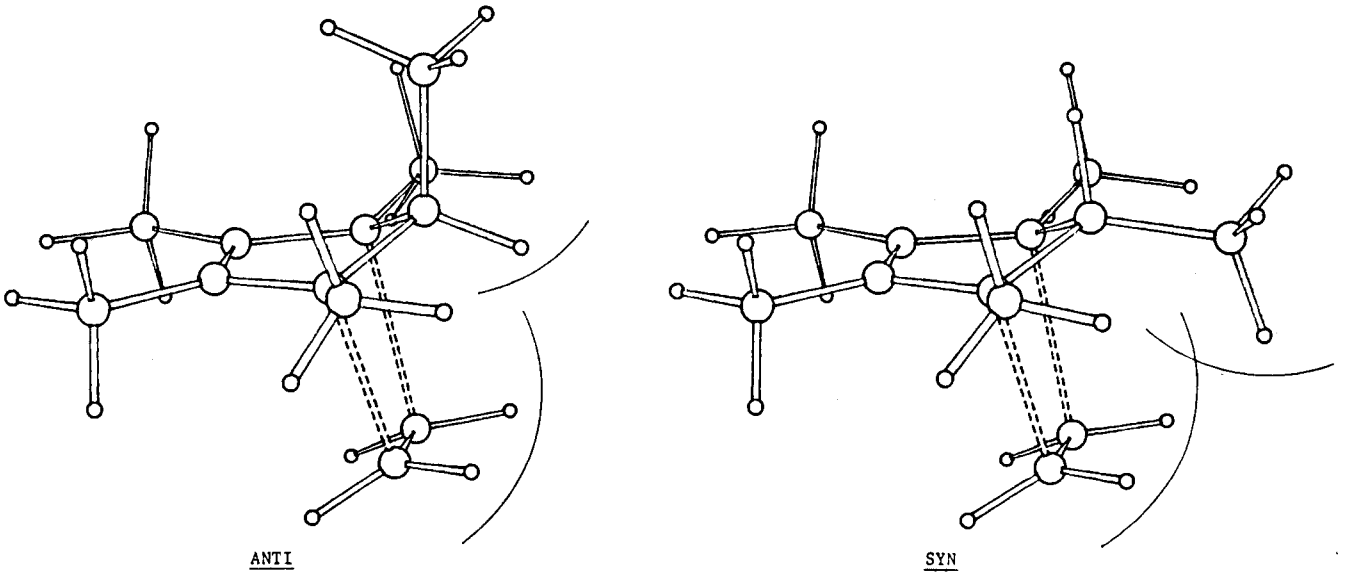


Figure 5. The MM2 syn and anti transition structures for the reaction of **3** with ethylene.

steric effects influence the exo–endo ratios. In all cases where cycloaddition occurs on the same side of the diene as a 5-alkyl substituent, only endo adducts are formed. Only when cycloaddition occurs syn to a 5-H are exo adducts observed.

Calculations on reactions of **1–3** with methyl acrylate are summarized in Tables III and IV. For **1** and **2**, the endo transition structures are highly favored. Only for anti cycloaddition to **3** is the exo addition energetically competitive with endo cycloaddition. The original rigid model calculation predicts exclusive anti products from the reaction of **3**, with an anti (endo)/anti (exo) ratio of 76:24.[10] The experimental ratio is 69:15:16, anti (endo)/syn (endo)/anti (exo). The calculated anti (endo)/anti (exo) ratio is satisfactory, while the energy of the syn transition structure is again too high in this inflexible model. Because

of the tilting of the dienophile with respect to the diene plane, an endo substituent on the dienophile is sterically less crowded than an exo. The difference in steric effects is small when there is a syn hydrogen at C5 of cyclopentadiene, but a syn alkyl at C5 effectively blocks exo cycloaddition.

Compounds **1** and **2** were prepared in part to test whether facial selectivity would increase in the presence of Lewis acid catalysts. Such a selectivity increase appeared probable based on the "tighter" transition structures for the catalyzed cases as suggested by Houk and Strozier to rationalize increases in endo stereoselectivity upon catalysis.[13] The tighter the transition structure, the shorter the distance between the addends. This was suggested to result from the stronger secondary orbital interactions of the coordinated dienophile with the diene, which results in greater endo stereoselectivity.[13] As mentioned previously, the selectivity of the reaction of **1** and **2** with *N*-phenylmaleimide changes from 86:14 and 70:30, respectively, for the uncatalyzed cases to 93:7 and 73:27, respectively, for the catalyzed cases. However, this apparent very small "increase" occurs only because of the lower reaction temperatures possible in the catalyzed cases. Actually, the $\Delta\Delta G^{\ddagger}$ values for the catalyzed reactions are smaller than those for the uncatalyzed reactions, as mentioned previously.

Why does catalysis generally increase exo–endo selectivity but have little effect on syn–anti selectivity? The reaction of cyclopentadiene with methyl acrylate gives an endo/exo ratio of 82:18 (0°) and 99:1 (−70°) for the uncatalyzed and catalyzed reactions, respectively,[14] corresponding to $\Delta\Delta G^{\ddagger}$ of 0.82 and 1.8 kcal/mol, respectively. Thus, the endo preference is enhanced by 1 kcal/mol by catalysis. The $\Delta\Delta G^{\ddagger}$ (syn–anti) for **1** with the three cyclic dienophiles is 1.1 and 0.8 to 1.0 kcal/mol in the thermal and catalyzed cases, respectively, so that there is in fact a small decrease in anti selectivity on catalysis.

Can these results be rationalized by a "tighter" transition structure? The term "tighter" is derived from the idea that when the transition structure involves strong secondary orbital interactions, these interactions pull the dienophile substituents closer to the diene. However, the concept of a tighter transition structure seems contradictory to the idea that the greater the reactivity, the "earlier" the transition state. According to the Hammond postulate,[15] the earlier the transition state the more reactant-like the transition state will be. The lengths of the forming bonds should be longer in the earlier transition state. At the same time, the catalyzed, earlier transition structure will be less pyramidalized than the thermal transition structure. This decrease in pyramidalization may compensate for the increase in forming bond distance resulting in the overall distance between the atoms of the addends to be similar for both the catalyzed and uncatalyzed reactions. The uncatalyzed and catalyzed reaction of 2,3-dimethylbutadiene with butyl acrylate have similar volumes of activation, with the uncatalyzed reaction having a slightly more negative $\Delta V^{\ddagger}$ than the catalyzed reaction.[16] Just the opposite would be expected if the catalyzed reaction had a smaller, tighter transition structure.

MM2 and MNDO calculations were carried out to test how a change in the position of the transition structure influenced the interaction between diene and dienophile.

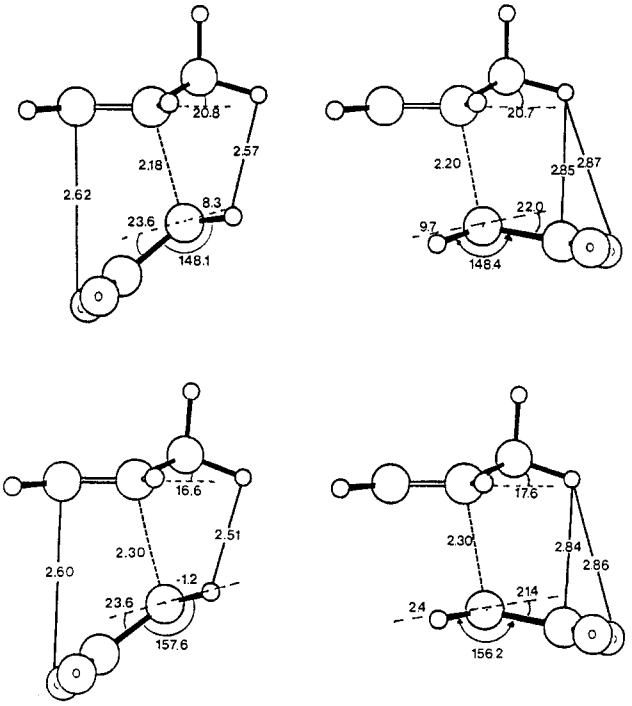
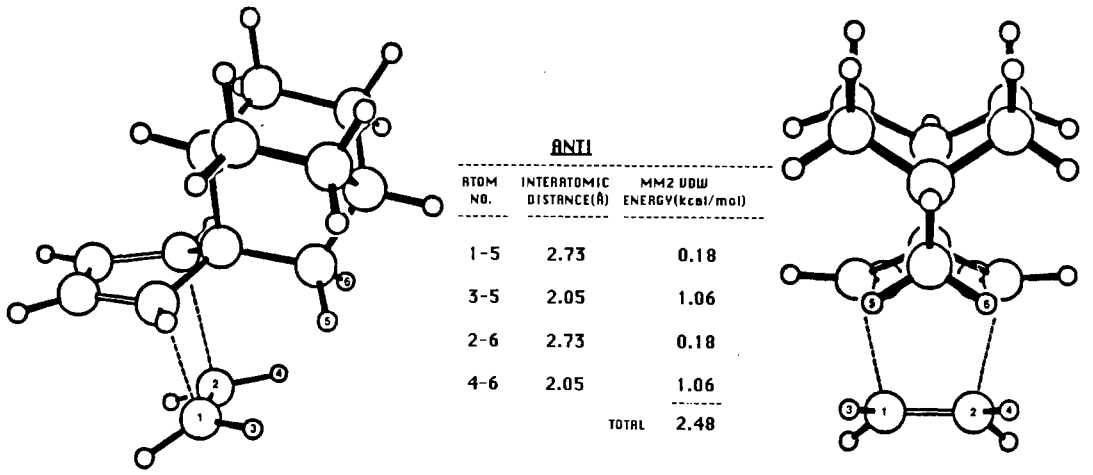


Figure 6. Side views, for which one-half of the atoms are hidden, of the endo and exo transition structure models for the reaction of cyclopentadiene with maleic anhydride. Those at the top are MNDO constrained synchronous transition structures, while those at the bottom are the "earlier" MNDO transition structure models with the forming CC bond distance constrained to 2.30 Å. The dihedral angles shown indicate the degree of pyramidalization of the diene and dienophile. The solid lines pertain to distances in Å between atoms, and the dotted line is the forming bond between the termini of the two addends.

The cyclopentadiene–ethylene transition structure previously reported in this paper has a forming C–C bond length of 2.163 Å. An "earlier" transition structure should have longer forming C–C bonds. The forming C–C bond lengths were set at 2.30 Å, and the C_s transition structure was reoptimized by using MNDO. The "earlier" transition structure was found to be less pyramidalized. To test if the "earlier" transition structure would lead to more selectivity than the parent transition structure, MM2 calculations were carried out. The cyclopentadiene–ethylene transition structure was modified to model the cyclopentadiene–maleic anhydride reaction. The modification was accomplished by replacing the cis hydrogens on the ethylene moiety with CO–O–CO. The modified transition structure model was then optimized by MM2 in the fashion described earlier. Parameters for the anhydride moiety were those reported by Ivanov and Pojarlieff.[17] The result of calculations was a 1.0 kcal/mol preference for the endo isomer for the "parent" model and a 1.9 kcal/mol preference for endo isomer for the "earlier" model.

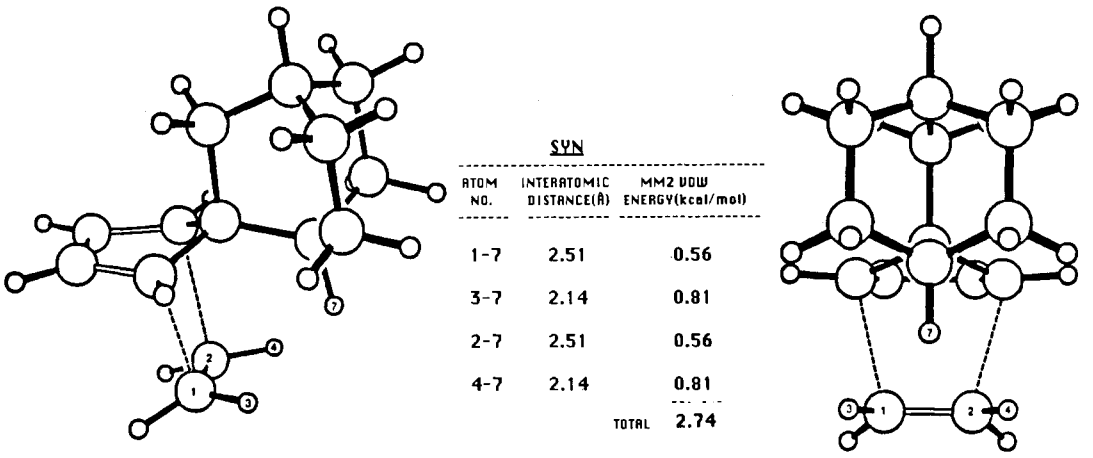
The MM2 calculations were reinforced by MNDO calculations. The constrained-synchronous transition structures for cyclopentadiene with maleic anhydride for both the exo and endo attacks were determined. The "parent" transition structures have forming C–C bond lengths of 2.18 and 2.20 Å for the endo and exo attacks, respectively. The energy difference between endo and exo attack was found to be 1.2 kcal/mol, favoring the endo attack. Earlier transition structures were modeled by lengthening the forming C–C bonds to 2.30 Å for both endo and exo attack

(13) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.
(14) (a) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 731. (b) Inukai, T.; Kojima, T. *J. Org. Chem.* **1966**, 2032.
(15) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.
(16) (a) McCabe, J. R.; Eckert, C. A. *Acc. Chem. Res.* **1974**, *7*, 251. (b) Seguchi, K.; Sera, A.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2242.
(17) Ivanov, P. M.; Pojarlieff, I. G. *J. Chem. Soc., Perkin Trans. 2* **1984**, *2*, 245.



ANTI

ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-5	2.73	0.18
3-5	2.05	1.06
2-6	2.73	0.18
4-6	2.05	1.06
	TOTAL	2.48



SYN

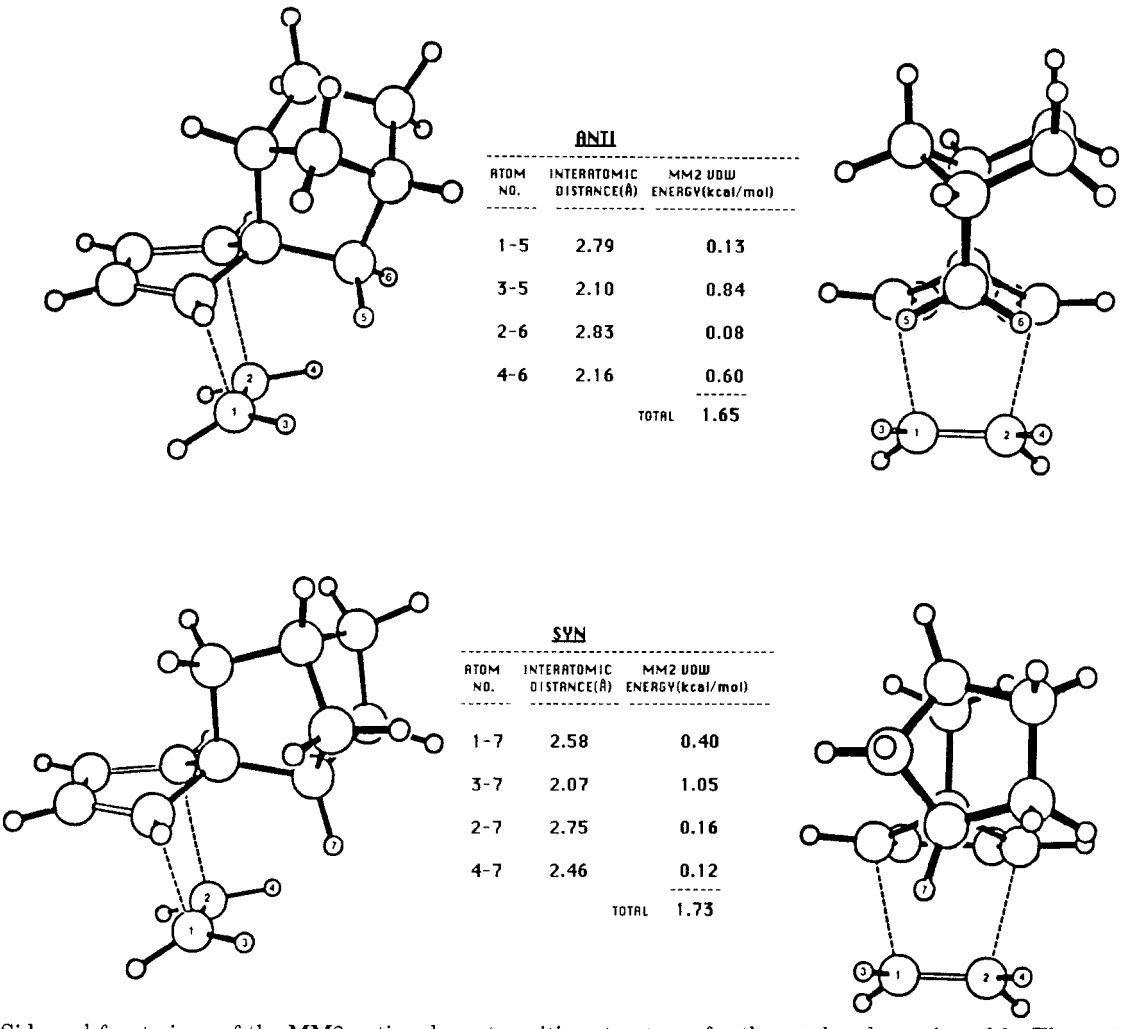
ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-7	2.51	0.56
3-7	2.14	0.81
2-7	2.51	0.56
4-7	2.14	0.81
	TOTAL	2.74

Figure 7. Side and front views of the MM2 anti and syn transition structures for the catalyzed reaction of 1. The major van der Waals interactions from MM2 calculations are listed and are only a subset of the total interactions.

and reoptimizing the remaining atom positions. These calculations show that the carbons involved in bond-making in the "earlier" transition structures are less pyramidalized, as shown in Figure 6. The selectivity also increases for the "earlier" model, with a 1.8 kcal/mol preference for the endo attack.

Both MM2 and MNDO calculations show an increase in endo selectivity for the "earlier" transition structures. Since MM2 has no parameters for secondary orbital interactions, the increase in selectivity must be due to other factors. The angle that the plane of maleic anhydride assumes relative to the diene group upon endo attack would also suggest that secondary orbital interactions would be very small, if they exist at all. The major factor influencing the stereoselectivity for Diels–Alder reactions involving cyclopentadiene and its analogues is probably steric effects. In the "parent" transition structures for the reaction of cyclopentadiene, a methylene hydrogen on the cyclopentadiene moiety obstructs the anhydride moiety upon exo attack. Steric repulsion accounts for most of the 1.2 kcal/mol preference for endo attack. The 0.6 kcal/mol increase in $\Delta\Delta G^{\ddagger}$ favoring the endo attack in the "earlier" model can be attributed to an increase in steric effects. The cyclopentadiene is flatter in the earlier transition state so that there is greater repulsion between a methylene hydrogen and the anhydride in the exo transition state, while steric repulsions upon endo attack are small in either early or late transition states. Thus, the "earlier" transition structure in the catalyzed reaction also explains the increased preference for the endo product in reactions such as that of cyclopentadiene with methyl acrylate. Catalyzed reactions of cyclopentadiene will be more endo selective due to the relative increase in steric repulsions for exo attack as cyclopentadiene becomes less pyramidal.

The decrease in $\Delta\Delta G^{\ddagger}$ for the syn–anti isomers of 1 and 2 can also be explained by the "earlier" model. The controlling factors in uncatalyzed reactions of 1 and 2 are steric interactions between the methylene hydrogens or methine hydrogen of the bicyclic system and the dienophile hydrogens. As the transition state becomes earlier, the steric interactions between the methylene hydrogens and the dienophile hydrogens will increase more than the steric interactions between the methine hydrogen and the dienophile hydrogens. This is due to the relative positions of the methylene hydrogens as compared to the methine hydrogen. The methylene hydrogens are nearly directly above the dienophile hydrogens, whereas the methine hydrogen lies between the dienophile hydrogens. Thus, as the transition structure becomes earlier and there is less pyramidalization, the diene and dienophile become more planar, displacing the atoms involved with the center undergoing rehybridization. This displacement is nearly equivalent to the shortening of the distance between the methylene and dienophile hydrogens. On the other hand, the distance between the methine hydrogen and the dienophile hydrogens decreases only a small fraction compared to the displacement resulting from the loss of pyramidalization.



ANTI

ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-5	2.79	0.13
3-5	2.10	0.84
2-6	2.83	0.08
4-6	2.16	0.60
	TOTAL	1.65

SYN

ATOM NO.	INTERATOMIC DISTANCE(Å)	MM2 VDW ENERGY(kcal/mol)
1-7	2.58	0.40
3-7	2.07	1.05
2-7	2.75	0.16
4-7	2.46	0.12
	TOTAL	1.73

Figure 8. Side and front views of the MM2 anti and syn transition structures for the catalyzed reaction of **2**. The major van der Waals interactions from MM2 calculations are listed and are only a subset of the total interactions.

MM2 models were constructed to test this hypothesis. The "earlier" MNDO transition structure for cyclopentadiene was used for the geometry, of the MM2 model, and the other parameters were treated as described earlier. The Lewis acid was not explicitly included in the model because it would be much too far from the diene to have a van der Waals interaction with the diene and would only add unnecessary complexity to the model. The resulting transition structures of compounds **1** and **2**, with the major van der Waals interactions illustrated, are given in Figures 7 and 8, respectively. Anti attack for compound **1** is now calculated to be favored by 0.5 kcal/mol, a 0.2 kcal/mol decrease in the energy difference as compared to the uncatalyzed case (see Table III). Anti attack for compound **2** is now calculated to be favored by 0.5 kcal/mol, which is the same as the energy difference for the uncatalyzed case. Thus, we would state that the catalyzed reactions of **1** would show a slight decrease in the $\Delta\Delta G^{\ddagger}$ favoring the anti isomer as compared to the uncatalyzed, while case **2** should show no or very little decrease in the $\Delta\Delta G^{\ddagger}$ favoring the anti isomer. Experimentally, **1** shows a 0.1–0.3 kcal/mol decrease in the $\Delta\Delta G^{\ddagger}$ favoring the anti isomer, whereas, **2** shows a 0.1 kcal/mol decrease (see Table III). The calculated ratios are in good agreement with experimental evidence.

The decrease in the energy difference between the anti and syn attack of compound **1** can be rationalized as follows. In Figure 7, the major steric van der Waals interactions are given for the anti and syn transition structures of **1**. The difference in the interactions for the anti and syn attacks is 0.26 kcal/mol, which is 0.13 kcal/mol less than the van der Waals interaction difference for the uncatalyzed case given in Figure 3.

In Figure 8, the major steric interactions are given for the anti and syn transition structures of **2**. The difference in the van der Waals interactions for the anti and syn attacks is 0.08 kcal/mol, which is 0.08 kcal/mol less than the van der Waals interaction difference for the uncatalyzed case given in Figure 4. Thus, the change in the steric interactions from the uncatalyzed to the catalyzed reactions is larger for compound **1** than compound **2**. Once again these steric interactions only comprise a *small* portion of the total energy difference, but they do express the idea that the earlier transition structure effects **1** more than **2**.

Conclusion. The predictions made by the MM2 models are nearly quantitative for the reactions of **1** and **2** but are only qualitative for the reactions of **3**. These calculations indicate that the stereoselectivities found in these reactions can be attributed to steric effects. This supports our hypothesis about the origin of π-facial selectivity in reactions of isodicyclopentadiene and its analogues.[4] Our MM2 model is also a useful tool for the evaluation of the origin of the endo and exo selectivity found in Diels–Alder reactions. The purpose of modeling of these reactions using empirical techniques is twofold. First, it provides a method for evaluation of hypotheses. In the cases under consideration, these models show that a steric explanation of stereoselectivity is plausible. Second, although the force fields developed are empirical in that adjustments can be

made in order to provide reasonable agreement with experiment, once such agreement is achieved, it is possible to make quantitative predictions of the stereochemistries of reactions with similar substituents.

Acknowledgment. We are grateful to the National Institutes of Health and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research, and to an anonymous referee for many helpful suggestions.

Registry No. 1, 93630-46-7; 2, 108563-03-7; 3, 96-38-8; DMAD, 762-42-5; TCNE, 670-54-2; maleic anhydride, 108-31-6; *N*-phenylmaleimide, 941-69-5; *p*-benzoquinone, 106-51-4; dimethyl maleate, 624-48-6; methyl acrylate, 96-33-3.

Functionalized 1,2-Dioxetanes as Potential Phototherapeutic Agents: The Synthesis of Carboxylate, Carbonate, Carbamate, and Ether Derivatives of 3-(Hydroxymethyl)-3,4,4-trimethyl-1,2-dioxetane

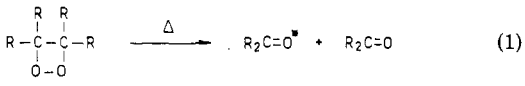
Waldemar Adam,* Vydia Bhushan,† Rainer Fuchs,‡ and Uwe Kirchgässner§

Institute of Organic Chemistry, University of Würzburg, Am Hubland, D-8700 Würzburg, West Germany

Received November 20, 1986

With gentle and efficient synthetic methods, 3-(hydroxymethyl)-3,4,4-trimethyl-1,2-dioxetane (1) can be transformed with appropriate electrophiles in moderate to good yields into functionalized derivatives of dioxetane 1. As electrophiles served carboxylic acids, chlorocarbonates, isocyanates, trialkyloxonium salts, and trialkylsilyl chlorides. With 1 these afford respectively dioxetanes with carboxylate, carbonate, carbamate, ether, and silyl ether functionalities. Nucleophilic activation of the hydroxymethyl substituent in the dioxetane 1 can be achieved under mild conditions by pyridine, 4-(dimethylamino)pyridine, potassium hydride, or butyllithium. Such functionalized dioxetanes serve as chemical sources of triplet excited carbonyl compounds which should find interesting utilization in photobiology and photomedicine, e.g., as potential phototherapeutic agents.

1,2-Dioxetanes have the unique property of generating electronically excited carbonyl products on thermal activation (eq 1), usually triplet states.[1] Thus, these unusual



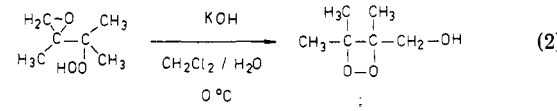
(1)

compounds represent latent excited states, which when appropriately functionalized, would permit releasing on command excited carbonyl fragments for biological, chemical, and physical explorations. Although some functionalized dioxetanes exist,[2] only few attempts have been realized in which dioxetanes with chemical handles have been functionally transformed.[3,4] This synthetic methodology should prove more effective and convenient in derivatizing biomolecules such as sugars, steroids, fatty acids, nucleic acids, amino acids, peptides, etc. by attaching 1,2-dioxetanes through their chemical handles than converting such substrates themselves into 1,2-dioxetanes. Certainly this synthetic modus should provide scope and diversity.

Our specific goal was to expand the still limited[3,4] functional group chemistry of 1,2-dioxetanes so as to permit preparing appropriate biodioxetanes for assessing the photochemical genotoxic potential of such carriers of triplet excited states. Despite their labile nature toward heat, light, bases and nucleophiles, acids and electrophiles, and paramagnetic species such as free radicals and transition-metal ions, etc.,[3a] we demonstrate in the present report that moderately stable 1,2-dioxetanes are sufficiently persistent for functional group manipulation, provided that gentle and efficient synthetic transformations are employed. In fact, the scope and diversity of the synthetic conversions that can be performed on these labile materials is impressive (Scheme I).

Results and Discussion

The moderately stable dioxetane that served as vehicle for the functional group chemistry performed herein is the 3-(hydroxymethyl)-3,4,4-trimethyl-1,2-dioxetane (1), readily available via base-catalyzed cyclization of the 2,3-dimethyl-1,2-epoxy-3-hydroperoxybutane (eq 2).[5] Instead



(2)

of using the recommended tetramethylammonium hydroxide as the phase-transfer base, we found that merely KOH in CH_2Cl_2/H_2O afforded higher yields and purer products.

Previously we showed[3b] that the 1,2-dioxetane 1 could readily be esterified with carboxylic or sulfonic acids. For this purpose the Brewster–Ciotti[6] (benzenesulfonyl chloride in pyridine) and the Mitsunobu[7] (diethyl azocarboxylate and triphenylphosphine) procedures proved especially helpful as mild reagents in converting dioxetane 1 with the appropriate carboxylic or sulfonic acid to the

† A. v. Humboldt Postdoctoral Fellow (1985).
‡ Prospective Dissertation (1986).
§ Undergraduate Research Participant (Spring 1986).

(1) Adam, W.; Yany, F. In *Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1985; Vol. 42, Part 3, Chapter 4, pp 351–429 and references therein.
(2) Meijer, E. W. Dissertation, University of Groningen, 1982.
(3) (a) Adam, W.; Bhushan, V.; Dirnberger, T.; Fuchs, R. *Synthesis* **1986**, 330. (b) Adam, W.; Babatsikos, C.; Cilento, G. *Z. Naturforsch.*, **1984**, *39B*, 679.
(4) Hummelen, J. C. Dissertation, University of Groningen, 1985.
(5) Leclerq, D.; Bats, J. P.; Picard, P.; Moulins, P. *Synthesis* **1982**, 778.
(6) Brewster, J. H.; Ciotti, C. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6214.
(7) Mitsunobu, O. *Synthesis* **1981**, 1.

0022-3263/87/1952-3059$01.50/0