Found: H, 7.07; C, 75.55; N, 5.18.

Acetamide of 2e: mp 140–141 °C (from methanol); ^{1}H NMR δ 1.97 (3 H, s), 3.03 (1 H, dd, J = 13.6 and 7.1 Hz), 3.09 (1 H, dd, J = 13.6 and 6.4 Hz), 3.70 (3 H, s), 3.83 (3 H, s), 5.24 (1 H, q, J = 7.1 Hz), 5.89 (1 H, br d), 6.42 (1 H, s), 6.59 (1 H, d, J = 8.1 Hz), 6.75 (1 H, d, J = 8.1 Hz), 7.17–7.30 (3 H, m); ^{13}C NMR δ 23.38, 42.11, 54.52, 55.72, 55.86, 111.07, 112.62, 121.42, 126.75, 127.42, 128.58, 129.58, 141.39, 147.81, 148.71, 169.34; MS m/e 299 (M^+), 241 (M − NHAc). Anal. Calcd for $C_{18}H_{21}NO_3$: H, 7.07; C, 72.21; N, 4.68. Found: H, 7.02; C, 71.98; N, 4.63.

Acetamide of 2f: ^{1}H NMR δ 1.96 (3 H, s), 3.02 (2 H, d, J = 7.08 Hz), 5.20 (1 H, q, J = 7.6 Hz), 5.88 (1 H, br d), 5.90 (2 H, s), 6.00 (d, J = 7.7 Hz), 6.53 (1 H, s), 6.67 (1 H, d, J = 7.7 Hz), 7.16–7.37 (5 H, m); ^{13}C NMR δ 23.42, 42.21, 54.64, 100.85, 108.07, 109.61, 122.31, 126.64, 127.46, 128.60, 130.99, 141.35, 146.21, 147.54, 169.29; MS m/e 282 (M − 1), 223.

Acetamide of 2g: ^{13}C NMR δ 23.04, 42.82, 54.47, 55.12, 98.73, 107.33, 126.73, 127.19, 128.41, 140.00, 142.00, 160.60, 169.71.

Acetamide of 3g: ^{13}C NMR δ 22.98, 42.60, 54.81, 55.18, 99.02, 104.97, 126.41, 128.23, 129.24, 137.78, 144.54, 160.82, 169.71.

Acetamide of 2i: ^{13}C NMR δ 21.03, 23.37, 42.06, 54.38, 126.63, 127.34, 128.52, 129.04, 129.16, 134.05, 136.07, 141.58, 169.35.

Acetamide of 3i: ^{13}C NMR δ 21.07, 23.37, 42.41, 54.18, 126.50, 126.57, 128.30, 129.24, 129.31, 137.06, 137.42, 138.40, 169.29.

Acetamide of 2j: ^{13}C NMR δ 23.38, 41.76, 54.53, 126.69, 127.65, 128.68, 130.63, 132.38, 135.80, 140.90, 169.38.

Acetamide of 3j: ^{13}C NMR δ 23.31, 42.38, 53.85, 126.78, 128.01, 128.43, 128.48, 129.24, 133.09, 136.79, 140.09, 169.38.

Acetamide of 2k: mp 154–155 °C; ^{1}H NMR δ 1.93 (3 H, s), 2.99 (1 H, dd, J = 13.7 and 7.3 Hz), 3.06 (1 H, dd, J = 13.7 and 6.9 Hz), 3.77 (3 H, s), 3.79 (3 H, s), 5.17 (1 H, q, J = 7.3 Hz), 5.99–6.02 (1 H, br d, J = 7.8 Hz), 6.75–6.85 (4 H, m), 6.96 (2 H, d, J = 8.6 Hz), 7.13 (2 H, d, J = 6.4 Hz); ^{13}C NMR δ 23.32, 41.59, 54.14, 55.17, 55.25, 113.71, 113.90, 127.85, 129.48, 130.29, 133.70, 158.22, 158.79, 169.25; MS m/e 296, 241.

Acetamide of 2l: ^{1}H NMR δ 1.92 (3 H, s), 2.99 (2 H, d, J = 7.0 Hz), 3.73 (6 H, s), 3.76 (3 H, s), 5.15 (1 H, t, J = 7.0 Hz), 5.87 (1 H, br d), 6.26 (1 H, s), 6.34 (2 H, s), 6.76 (2 H, d, J = 8.6 Hz), 6.79 (2 H, d, J = 8.6 Hz); ^{13}C NMR δ 23.35, 41.54, 54.62, 55.32, 98.99, 104.89, 113.76, 130.27, 160.04, 129.24, 144.12, 169.36; MS m/e 329 (M^+), 270 (M − NH_2Ac).

Registry No. *trans*-**1a**, 103-30-0; *trans*-**1b**, 52805-92-2; *trans*-**1c**, 14064-41-6; *trans*-**1d**, 1694-19-5; *trans*-**1e**, 3892-92-0; *trans*-**1f**, 51003-16-8; *trans*-**1g**, 21956-56-9; *trans*-**1h**, 74809-43-1; *trans*-**1i**, 1860-17-9; *trans*-**1j**, 1657-50-7; *trans*-**1k**, 15638-14-9; *trans*-**1l**, 22255-22-7; **2a** acetamide derivative, 2155-90-0; **2b** acetamide derivative, 138435-22-0; **2c** acetamide derivative, 138435-23-1; **2d** acetamide derivative, 93172-54-4; **2e** acetamide derivative, 76306-60-0; **2f** acetamide derivative, 76306-61-1; **2g** acetamide derivative, 138435-24-2; **2i** acetamide derivative, 138435-25-3; **2j** acetamide derivative, 138435-26-4; **2k** acetamide derivative, 93172-56-6; **2l** acetamide derivative, 138435-27-5; **3b** acetamide derivative, 138435-28-6; **3c** acetamide derivative, 138435-29-7; **3g** acetamide derivative, 138435-30-0; **3i** acetamide derivative, 138435-31-1; **3j** acetamide derivative, 138458-90-9.

Supplementary Material Available: ^{1}H NMR spectra for the acetamides of **2a–g,i–l** and **3b,c,e,g,i,j** (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Force Field Modeling of Transition Structures of Intramolecular Ene Reactions and ab Initio Transition Structures for an Activated Enophile

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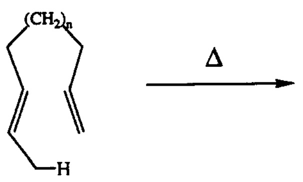
A modification of Allinger's MM2 force field has been developed to rationalize and predict the stereochemistries of intramolecular ene reactions. This force field reproduces the stereochemical trends observed for intramolecular ene reactions with unactivated enophiles, but gives poor results with activated enophiles. Ab initio molecular orbital calculations on the ene reaction of acrylonitrile with propene were performed to investigate the change in the transition structure caused by activating substituents.

Introduction

The intramolecular ene reaction[1,2] has been used frequently in organic synthesis for the formation of five- and six-membered rings, with control of the stereochemistry in the products. With activating substituents and catalysis by Lewis acids, reaction temperatures are usually lower and there is greater control of stereochemistry than in simple hydrocarbon cases.[3,4] The stereochemistry about the forming CC bond is usually cis for five-membered rings and trans for six-membered rings. The relationship between the stereochemistries of substituents on the tether and the stereochemistry of CC bond formation is not as easily predicted. In this paper, we present a simple modification of Allinger's MM2 force field[5] which models the transition structures of intramolecular ene reactions



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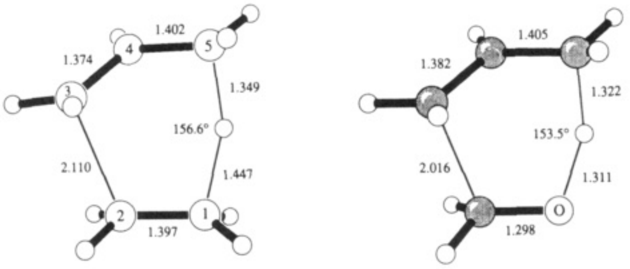

Figure 1. RHF/3-21G transition structures for the ene reactions of ethylene with propene and formaldehyde with propene.

and qualitatively predicts the ratios of the products formed in reactions of substituted compounds.

The Force Field

Recently, we reported the transition structures for the ene reactions of ethylene with propene and formaldehyde with propene.[6] Examination of the transition structures, shown in Figure 1, led to a qualitative rationalization for the preference of the substituents about the new CC bond to be cis upon five-membered ring formation and to be trans in six-membered ring formation in intramolecular ene reactions with unactivated enophiles. It was shown that the dihedral angles H–C–C–H (where the hydrogens would be replaced by the tether and the carbons are those of the forming CC bond) corresponding to the cis products are 38° and 39°, while the dihedral angles corresponding to the trans product are 77° and 154° (see Figure 2).[6] Using molecular mechanics, it was shown that a stretched cyclopentane prefers to have a C–C–C–C dihedral angle of 0° about the stretched bond, while a stretched cyclohexane prefers to have a C–C–C–C dihedral angle of 56° about the stretched bond.[6] In forming the cyclopentane, the cis transition structures require less adjustment of the parent transition structure upon substitution of the tether than does the trans transition structures. Thus, the cis product should be the preferred product. The large adjustment required for the *trans*-cyclopentane to be formed indicates that the preference for the cis product should be large. This is in agreement with experimental results.[7-11] In forming the cyclohexane, the cis and trans transition structures require about the same adjustment of the parent transition structure upon addition of the tether, but steric interactions between substituents at R1, R2, and/or R3 and the tether cause the *trans*-cyclohexane to be preferred (see Figure 2).

While this provides a qualitative explanation of the resulting stereochemistry about the forming CC bond, it does not provide any insight into the relationship between the substituents on the tether and those about the forming CC bond nor does it permit quantitative predictions. We undertook a study to determine whether a model could be constructed using molecular mechanics to mimic the transition structures of intramolecular ene reactions. A frozen transition structure model has previously been used in applying molecular mechanics to the study of the Diels–Alder reaction[12] and hydroborations.[13] We were interested in determining whether a rigid model would be useful for hydrocarbon ene reactions. We also wished to try a simple modeling procedure that could be used readily once a transition structure was known (or guessed), without laborious parameter development.

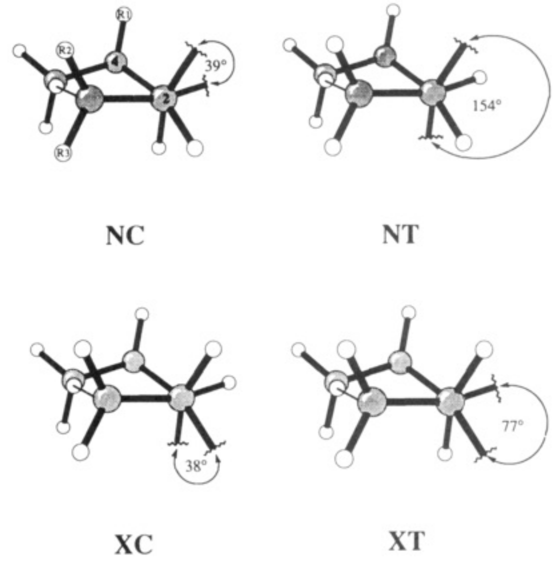

Figure 2. Newman projections looking along the forming bond of the four transition structures of an intramolecular ene reaction with an achiral tether. The broken bonds indicate the site of attachment of the tether. The dihedral angle of the tether about the forming CC bond is shown. Each transition structure is identified by a two letter acronym, with the first letter representing whether the tether is exo or endo at C2 with respect to C4. The second letter indicates the resulting cis or trans stereochemistry about the new CC bond. NC and XT involve a trans alkene, while XC and NT involve a cis alkene. All four transition structures are possible with a single substrate only when the alkene is 1,1-disubstituted by alkyl substituents.

In this approach, the transition-state atoms are kept frozen at the geometry of the ab initio 3-21G transition structure,[6] and each transition state carbon and the transferring hydrogen is assigned a new atom type. All other atoms are standard MM2 atoms. Only the positions of tether and substituent atoms are optimized. In order to simplify the model further, the transition-state carbons were equivalenced to standard MM2 carbons with the same hybridization as that atom has in the reactants. The parameters for dihedral angles described by three or four frozen atoms are set to zero. The bending constants for angles described by three frozen atoms and the stretching constants for bonds described by two frozen atoms are also set to zero. All other parameters are set to the standard MM2 parameters,[14] except the torsional parameters involving the C_{tether}–C_{ts}–C_{ts}–C_{tether} dihedral angle. A substantial amount of staggering is present about the forming CC bond in the transition structure. In order to mimic this correctly, the transition state carbons are taken to be sp^3 hybridized for rotation about this bond. A list of the parameters used is given at the end of the paper.

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(14) In cases where a bond angle is defined by a tether carbon and two frozen transition structure carbons, the optimum bond angle was defined as the average of the corresponding bond angle in the calculated parent transition where a hydrogen replaces the tether carbon.

Table I. Intramolecular Ene Reactions of 1,6-Dienes with Unactivated Enophiles

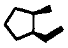
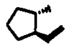
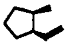
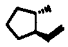
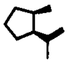
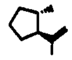
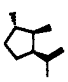
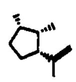
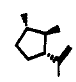
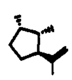
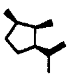
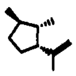
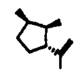
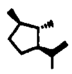
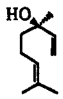
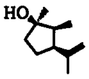
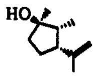
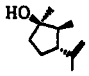
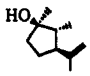
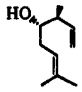
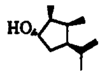
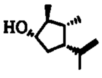
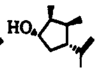
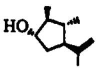
	reactant		products 1	2	3	4
(1)		457°C				
		Exp.[7]	Only Cis Product			
		MM2	99%	1%		
(2)		457°C				
		Exp.[7]	Only Cis Product			
		MM2	Only Cis Product			
(3)		457°C				
		Exp.[7]	Only Cis Product			
		MM2	99%	1%		
(4)		450°C				
		Exp.[8]	75%	25%	----	----
		MM2	79%	20%	1%	----
(5)		480°C				
		Exp.[9]	27%	73%	----	----
		MM2	21%	88%	----	1%
(6)		650°C				
		Exp.[10]	49%	26%	16%	9%
		MM2	64%	33%	2%	1%
(7)		290°C				
		Exp.[11]	29%	68%	----	3%
		MM2	13%	87%	----	----

Table II. Steric and Relative Energies (kcal/mol) of Transition Structures for the Intramolecular Ene Reactions of 1,6-Dienes with an Unactivated Enophile

compd	transn struct	steric energy	rel energy	product
(1) *trans*-1,6-octadiene	NC	7.9	0.0	1
	XT	14.5	6.6	2
(2) *cis*-1,6-octadiene	NT	106.3	97.7	2
	XC	8.6	0.0	1
(3) 7-methyl-1,6-octadiene	NC	9.2	0.6	1
	NT	106.2	97.6	2
	XC	8.6	0.0	1
	XT	14.2	5.6	2
(4) (3*S*)-3.7-dimethyl-1,6-octadiene	NC	9.0	0.0	1
	NCB	10.9	1.9	2
	NT	105.1	96.1	3
	NTB	109.5	100.5	4
	XC	11.3	2.3	2
	XCB	9.2	0.2	1
	XT	16.3	7.3	4
	XTB	14.1	5.1	3
(5) (3*R*)-3.7-dimethyl-1,6-octadiene	NC	10.9	1.9	1
	NCB	9.0	0.0	2
	NT	109.5	100.5	3
	NTB	105.1	96.1	4
	XC	9.2	0.2	2
	XCB	11.3	2.3	1
	XT	14.1	5.1	4
	XTB	16.3	7.3	3
(6) (*R*)-3-hydroxy-3,7-dimethyl-1,6-octadiene	NC	12.1	0.0	1
	NCB	13.4	1.3	2
	NT	108.3	96.2	3
	NTB	110.5	98.4	4
	XC	13.6	1.5	2
	XCB	12.4	0.3	1
	XT	18.4	6.3	4
	XTB	17.1	5.0	3
(7) (3*R*,4*S*)-4-hydroxy-3,7-dimethyl-1,6-octadiene	NC	12.0	2.0	1
	NCB	10.0	0.0	2
	NT	110.0	100.0	3
	NTB	106.7	96.7	4
	XC	10.3	0.3	2
	XCB	12.7	2.7	1
	XT	15.1	5.1	4
	XTB	17.1	7.1	3

Results and Discussion

There are four ways of adding an achiral tether to each of the two enantiomeric propene–ethylene transition structures. Two transition structures lead to the cis product and two transition structures lead to the trans product, as shown in Figure 2. As noted in the caption, not all of these are possible from individual *cis*- or *trans*-alkenes. There are also four additional transition structures which are enantiomers of those in Figure 2. With a chiral center on the tether, there are eight diastereomeric transition structures which lead to four diastereomeric products.

We first studied the ene reactions of 1,6-octadiene and 7-methyl-1,6-octadiene. The results are given in Tables I and II. Our calculations predict a 99:1 or greater preference for the cis product for both *cis*- and *trans*-1,6-octadiene.[15] Experimentally only the cis product is isolated in both cases.[7] As noted in our previous paper, the transition structures leading to the cis products are more stable than those leading to the trans products.[6] For *cis*-1,6-octadiene, only the XC and NT transition structures are possible. XC is much more stable, as expected (Figure 2). For *trans*-1,6-octadiene, the NC and XT transition structures lead to the two possible products. The cis transition structure is more stable by 6.6 kcal/mol. In the case of 7-methyl-1,6-octadiene, all four transition structures are possible. The two cis transition structures, NC and XC, are separated by 0.6 kcal/mol; XC is more stable. XT is the only low-energy trans transition structure, but it is still 5.6 kcal/mol higher in energy than XC. Our calculations predict a 99:1 preference, while only the cis product is isolated experimentally.[7]

Four possible products can be formed from each of the 1,6-octadienes with substituents on the tether (entries 4–7 in Table I). The force field correctly predicts the major product as well as the order of preference of the minor products. Examination of the eight possible transition structures for the ene reaction of (3*S*)-3,7-dimethyl-1,6-octadiene (entry 4 in Table I) leads to a simple explanation of why one product is favored over another. Transition structures NC and NCB represent attack of the alkene on different faces of the enophile (see Figure 3). In this case, NC leads to the major cis product and NCB leads to the minor cis product. The major difference between these transition structures is that in NC the methyl group on the tether is pseudoequatorial while in NCB the methyl group is pseudoaxial. NC is the lower energy transition structure. The situation is the same for the other pairs

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[15] The calculated ratios were determined from a Boltzmann distribution based on the relative energies of all possible transition structures and the temperature at which the reaction takes place.

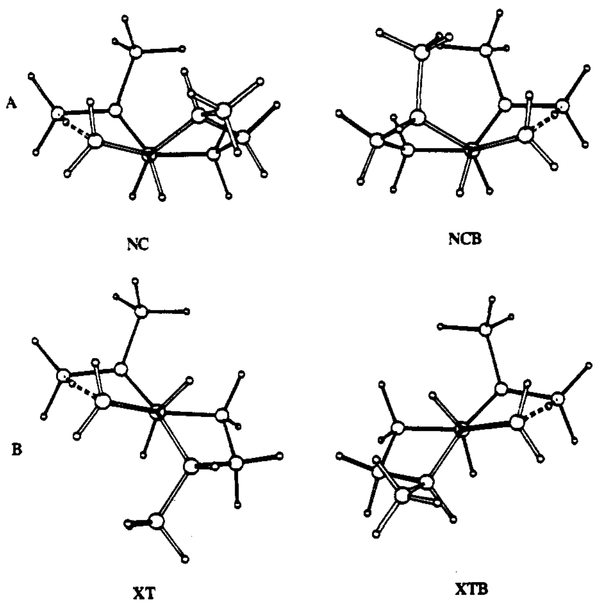


Figure 3. Transition structures of the intramolecular ene reaction of (3*R*)-3,7-dimethyl-1,6-octadiene looking down the forming carbon–carbon bond: (A) leading to the two cyclopentanes with the substituents cis about the new carbon–carbon bond; (B) leading to the two cyclopentanes with the substituents trans about the new carbon–carbon bond.

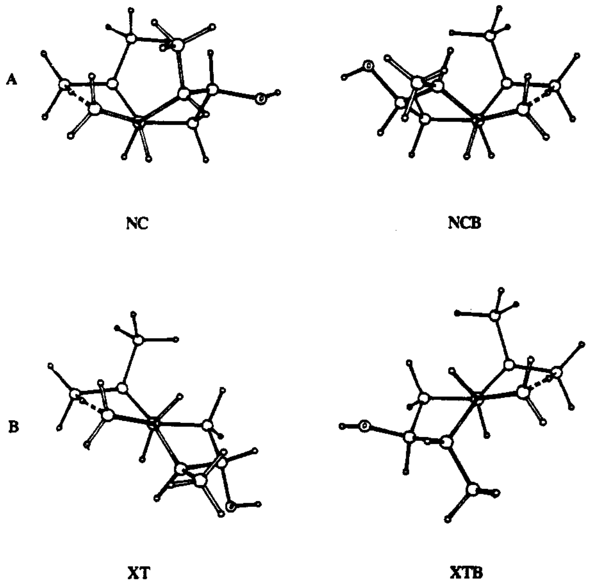
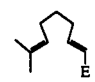
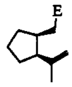
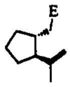
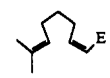
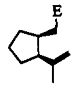
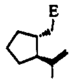
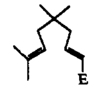
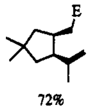
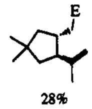
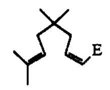
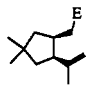
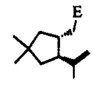


Figure 4. Transition structures of the intramolecular ene reaction of (3*R*,4*S*)-4-hydroxy-3,7-dimethyl-1,6-octadiene looking down the forming carbon–carbon bond: (A) leading to the two cyclopentanes with the substituents cis about the new carbon–carbon bond; (B) leading to the two cyclopentanes with the substituents trans about the new carbon–carbon bond.

of transition structures.[16] As shown in Figure 3, the best transition structure leading to a trans product, XTB, has a pseudoequatorial methyl group, while the methyl group is pseudoaxial in XT. The energy differences are exaggerated, most likely due to the rigid model used.

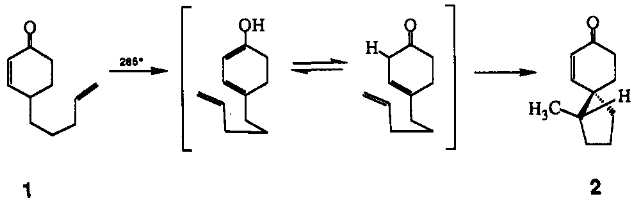
Table III. Intramolecular Ene Reactions of 1,6-Dienes with Activated Enophiles[a]

	reactant		products 1	products 2
(1)		253°C →		
		Exp.[20]	76%	24%
		MM2	100%	0%
(2)		253°C →		
		Exp.[20]	43%	57%
		MM2	99%	1%
(3)		222°C →		
		Exp.[20]	72%	28%
		MM2	100%	0%
(4)		222°C →		
		Exp.[20]	40%	60%
		MM2	98%	2%

[a] E = CO_2CH_3.

Another interesting example is that of (3*R*,4*S*)-4-hydroxy-3,7-dimethyl-1,6-octadiene (entry 7 in Table I). In this case NCB leads to the major product, while NC leads to a minor product (see Figure 4). In NCB the methyl group on the tether is pseudoequatorial, while the hydroxyl group is pseudoaxial. In NC these situations are reversed. The *A* value for a methyl group is 1.8,[17a] while that for a hydroxyl group is 0.5 in nonaqueous solutions.[17b] Thus, a larger group, methyl, prefers the equatorial position more than the smaller hydroxyl group.[18] This is also true for XC and XCB and for XT and XTB. The results of the studies, summarized in Tables I and II, are that the rigid transition structure model can give good qualitative indications of the major products and relative energies of the transition structures of intramolecular ene reactions of unactivated cases.

This model also works well for more complicated systems. In 1989, Kende and Newbold reported on a series of compounds that undergo the vinylogous Conia rearrangement, which is a masked ene reaction.[19] We tested our model on the example shown below. When 1 is heated



1 2

at 285 °C for 5 h, 2 is obtained as the only product in 58% yield.[19] Since the ene is part of the six-membered ring, only two of the transition structures are available to 1. NC leads to 2 and XT leads to the product with inverted stereochemistry at the chiral center. NC is favored by 11.1

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[16] The transition structures NC and NCB are very strained due to the C_{tether}–C_{ts}–C_{ts}–C_{tether} dihedral angle, which is ~154°. This causes a forming five-membered ring to be very strained; thus, these transition structures are very high in energy for 1,6-dienes. In fact, for 1,6-dienes these transition structures do not fully optimize. The reported energies are for partial optimization. For 1,7-dienes, these transition structures are still strained, but are fully optimized. In both cases, the torsional strain is so large that the effects of substituent are negligible.

[17] (a) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1966**, *31*, 804. (b) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

[18] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A*; Plenum Press: New York, 1984.

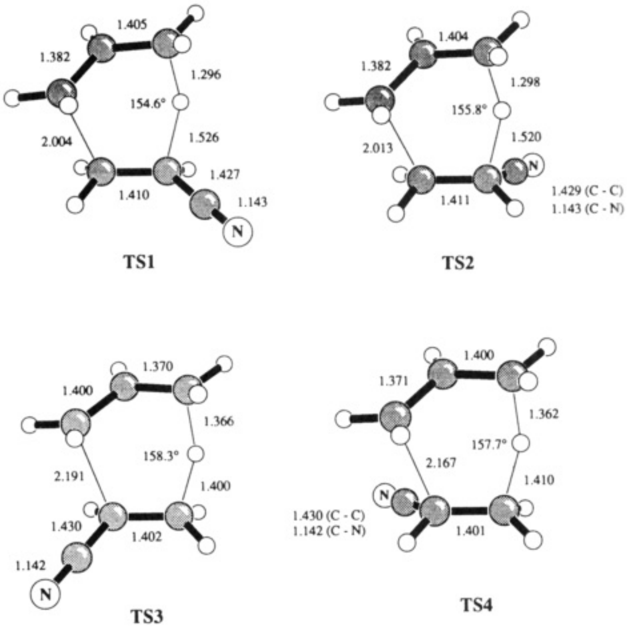
[19] Kende, A. S.; Newbold, R. C. *Tetrahedron Lett.* **1989**, *30*, 4329.

Table IV. Steric and Relative Energies (kcal/mol) of Transition Structures for the Intramolecular Ene Reactions of 1,6-Dienes with an Activated Enophile

compd	transn struct	steric energy	rel energy	product
(1) (*E*)-8-methyl-2,7-octadienoic acid 1-methyl ester	NC	44.3	0.0	1
	NT	144.6	100.3	2
	XC	48.5	4.2	1
	XT	52.6	8.3	2
(2) (*Z*)-8-methyl-2,7-octadienoic acid 1-methyl ester	NC	47.5	0.0	1
	NT	143.5	96.0	2
	XC	48.3	0.8	1
	XT	51.6	4.1	2
(3) (*E*)-5,5,8-trimethyl-2,7-octadienoic acid 1-methyl ester	NC	45.7	0.0	1
	NT	147.2	101.5	2
	XC	51.1	5.4	1
	XT	53.6	7.9	2
(4) (*Z*)-5,5,8-trimethyl-2,7-octadienoic acid 1-methyl ester	NC	49.3	0.0	1
	NT	146.3	97.0	2
	XC	50.6	1.3	1
	XT	52.7	3.4	2

kcal/mol. Our force-field correctly predicts that **2** is the only product.

Reactions of several 1,6-dienes that contain activated enophiles were also tested. The results are shown in Tables III and IV. The force field predicts that the products with cis disubstitution about the new CC bond should be the major product in all examples studied, whereas experimental results of Ghosh and Sarkar show that this is not always the case.[20] When one ester group is trans to the tether, cis disubstitution about the forming CC bond is largely favored. When the ester group is cis to the tether, there is a small preference for trans product. When two ester groups are attached to the enophile, there is a large preference for trans product.[20] Tietze et al. have also found a large preference for the trans product when two activating groups are attached to the enophile.[21] These results imply that the geometries of the transition structures for the ene reaction of alkenes with activated enophiles are different from the transition structure of the propene–ethylene reaction. This is not unexpected, but nevertheless interesting, since the geometry of the calculated transition structure for the ene reaction of propene and formaldehyde is not substantially different from that of the propene–ethylene reaction.[6]



TS1 TS2

TS3 TS4

Figure 5. RHF/3-21G transition structures for the ene reaction of acrylonitrile with propene. TS1 and TS2 lead to 5-cyano-1-hexene (linear isomer), while TS3 and TS4 lead to 4-cyano-1-hexene (branched isomer).

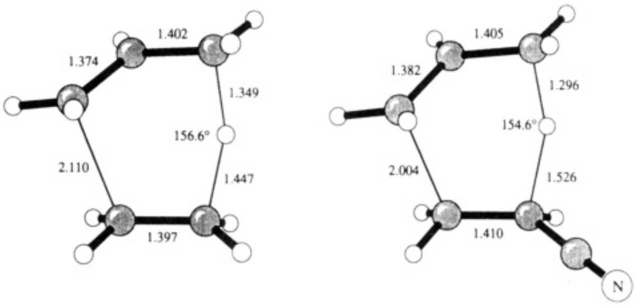


Figure 6. RHF/3-21G transition structures for the ene reactions of ethylene with propene and acrylonitrile with propene.

In order to understand how the geometry of the transition structure changes going from a unactivated enophile to an activated enophile, we undertook calculations of the transition structures for the ene reaction of propene with acrylonitrile with the STO-3G[22] and the 3-21G[23] basis sets using GAUSSIAN 86.[24] Each transition structure was confirmed by a harmonic frequency calculation to have one imaginary frequency. The four possible transition structures are shown in Figure 5. The total energies and activation energies of the transition structures are reported in Table VII. The RHF/3-21G activation energies for all four transitions structures are calculated to be lower than the RHF/3-21G activation energy for the parent reaction (51.7 kcal/mol).[6] This is in accord with the reported RHF/3-21G activation energies reported for the ene reaction of propene and methyl acrylate.[25] The geometries of the propene-acrylonitrile transition structures are very similar to those of the propene-methyl acrylate transition structures reported by Tadafumi et al.[25]

TS1 is calculated to have a lower activation energy than TS4 by 2.7 kcal/mol. TS1 is preferred because the cyano group causes an increase in the electrophilicity of the β-carbon. The length of the forming CC bond is shorter in TS1 as compared to TS4 or the parent reaction. In the reactions of various alkenes with acrylic esters, the linear isomer is preferred by a 3 to 1 margin in most cases.[26]

The transition structure with acrylonitrile as the enophile has changed to some extent from the parent transition structure. A comparison of these transition structures is shown in Figure 6. This type of change in the transition structure upon addition of an activating group to the dienophile has been observed previously in calculations on the Diels–Alder reaction.[27] Originally, we

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[20] Ghosh, S. K.; Sarkar, T. K. *Tetrahedron Lett.* **1986**, *27*, 525.

[21] Tietze, L. F.; Beifuss, U.; Ruther, M.; Ruhlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1186.

[22] Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.

[23] Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

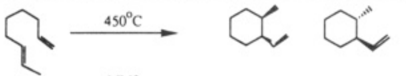
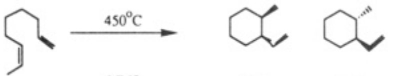
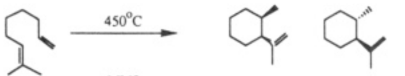
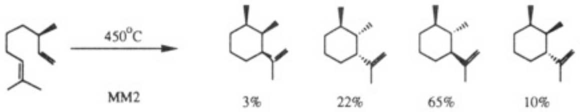
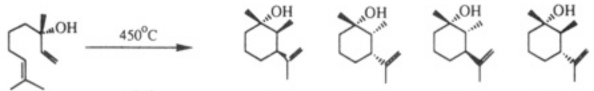
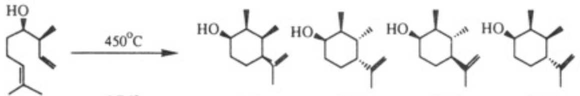
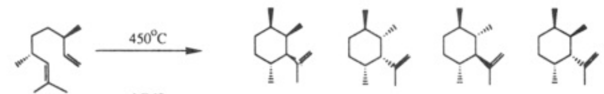
[24] Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R. L.; Stewart, J. J. P.; Bobrowicz, F. W.; Rohlfing, C. M.; Kahn, L. R.; Defrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. GAUSSIAN 86; Carnegie-Mellon Quantum Chemical Publishing Unit, Pittsburgh, PA, 1984.

[25] Tadafumi, U.; Tsuzuki, S.; Tanabe, K.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1861.

[26] Alder, K.; von Brachel, H. *Liebigs. Ann. Chem.* **1962**, *651*, 141.

[27] Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129.

Table V. Predictions of Stereochemistries of Intramolecular Ene Reactions of 1,7-Dienes with Unactivated Enophiles

	reactant	products 1	2	3	4
(1)	 450°C, MM2	100%	0%		
(2)	 450°C, MM2	36%	64%		
(3)	 450°C, MM2	30%	70%		
(4)	 450°C, MM2	3%	22%	65%	10%
(5)	 450°C, MM2	4%	20%	61%	15%
(6)	 450°C, MM2	5%	18%	62%	15%
(7)	 450°C, MM2	4%	7%	88%	1%

thought that rotation about the forming CC bond would be easier in the activated transition structure than in the parent transition structure, explaining the increase in the extent of the formation of trans-disubstituted products in some intramolecular ene reactions with activated enophiles. In order to test this hypothesis, we performed rigid rotations about the forming CC bond followed by optimization for both transition structures. The potential energy curves for rotation about the forming CC bond are shown in Figure 7. The smallest dihedral angle, β, for a trans tether in the parent transition structure is 76.8°, which is 6.1° larger than in the activated transition structure. Rotation of the forming CC bond away from the optimum is approximately harmonic and has about the same force constant in both cases. The distortion is relatively easy in both transition structures for ±15° changes, after which the energy increases rapidly. As stated earlier, the preference of cis-disubstituted five-membered ring formation with cis disubstitution in hydrocarbon intramolecular ene reactions is explained by the smaller distortion required to achieve a cis transition structure with α or γ near 0°.

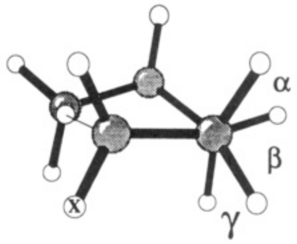


Table VI. Steric and Relative Energies (kcal/mol) of Transition Structures for the Intramolecular Ene Reactions of 1,7-Dienes with Unactivated Enophiles

compd	transn struct	steric energy	rel energy	product
(1) *trans*-1,7-nonadiene	NC	10.4	0.6	1
	XT	9.6	0.0	2
(2) *cis*-1,7-nonadiene	NT	56.9	47.4	2
	XC	12.2	3.7	1
(3) 8-methyl-1,7-nonadiene	NC	11.4	1.4	1
	NT	57.8	50.9	2
	XC	12.6	3.1	1
	XT	9.7	0.0	2
(4) (3*R*)-3,8-dimethyl-1,7-nonadiene	NC	14.8	4.1	1
	NCB	12.3	1.9	2
	NT	60.7	44.5	3
	NTB	57.2	48.8	4
	XC	13.3	3.5	2
	XCB	16.8	6.6	1
	XT	10.2	0.0	4
	XTB	12.9	2.6	3
(5) (*S*)-3-hydroxy-3,8-dimethyl-1,6-nonadiene	NC	17.1	3.6	1
	NCB	14.9	1.6	2
	NT	62.2	48.4	3
	NTB	60.1	44.6	4
	XC	16.9	4.3	2
	XCB	19.5	6.5	1
	XT	13.0	0.0	4
	XTB	15.0	1.9	3
(6) (3*S*,4*R*)-4-hydroxy-3,8-dimethyl-1,7-nonadiene	NC	16.4	3.6	1
	NCB	14.9	2.0	2
	NT	62.2	47.5	3
	NTB	60.1	50.1	4
	XC	16.9	4.2	2
	XCB	19.5	6.2	1
	XT	13.0	0.0	4
	XTB	15.0	2.1	3
(7) (3*R*,6*R*)-3,6,8-trimethyl-1,7-nonadiene	NC	16.9	4.9	1
	NCB	15.2	2.7	2
	NT	63.6	44.8	3
	NTB	57.2	47.2	4
	XC	22.4	11.2	2
	XCB	17.1	5.7	1
	XT	11.6	0.0	4
	XTB	18.3	6.7	3

Table VII. Ab Initio Total Energies and the Activation Energies of the Reactants and the Transition Structures for the Ene Reaction of Acrylonitrile and Propene. The Activation Energies Are in Parentheses. The Transition Structures (1–4) Correspond to Those Shown in Figure 5. Total Energies Are Reported in Hartrees and the Activation Energies Are Reported in kcal/mol

structure	RHF/STO-3G	RHF/3-21G
propene	−115.66030	−116.42401
acrylonitrile	−167.62727	−168.82040
TS1	−283.21073 (48.2)	−285.16805 (47.9)
TS2	−283.20961 (48.9)	−285.16691 (48.6)
TS3	−293.20050 (54.6)	−285.16252 (51.4)
TS4	−283.20226 (53.5)	−285.16368 (50.7)

To achieve the trans-fusion, β must distort from 76.8° to near 0°. In the activated transition structure, it is easier to reduce β to near 0° because it is smaller (70.7°) than in the hydrocarbon case. Activated intramolecular ene reactions give more trans-disubstituted five-membered rings than hydrocarbon intramolecular ene reactions. Our rigid model is incapable of reproducing these changes, even when the propene–acrylonitrile transition structure (TS1) was used in place of the propene–ethylene transition structure. A successful force field model of the activated

Table VIII. New MM2 Parameters for Unactivated Ene Transition State

torsional parameters

dihedral angle				$V1$	$V2$	$V3$	dihedral angle				$V1$	$V2$	$V3$
50	49	48	47	0.000	0.000	0.000	50	49	48	5	0.000	0.000	0.000
50	49	48	1	0.000	0.000	0.000	50	49	1	5	0.000	0.000	0.540
50	49	1	1	0.400	0.030	0.500	50	45	46	47	0.000	0.000	0.000
50	45	46	5	0.000	0.000	0.000	50	45	46	3	0.000	0.000	0.000
50	45	46	1	0.000	0.000	0.000	50	3	1	5	0.000	0.000	0.130
50	3	1	1	0.550	−0.180	0.400	49	50	45	46	0.000	0.000	0.000
49	50	3	7	0.000	0.000	−0.350	49	50	3	1	0.000	0.000	0.000
49	48	47	46	0.000	0.000	0.000	49	48	47	5	0.000	0.000	0.000
49	48	47	1	0.000	0.000	0.000	49	48	1	5	0.000	0.000	−0.240
49	48	1	1	−0.440	0.240	0.060	49	1	1	5	0.000	0.000	0.500
49	1	1	1	0.170	0.270	0.093	48	49	50	45	0.000	0.000	0.000
48	49	50	5	0.000	0.000	0.000	48	49	50	3	0.000	0.000	0.000
48	49	50	1	0.000	0.000	0.000	48	49	1	5	0.000	0.000	−0.240
48	49	1	1	−0.440	0.240	0.060	48	47	46	45	0.000	0.000	0.000
48	47	46	5	0.000	0.000	0.000	48	47	46	3	0.000	0.000	0.000
48	47	46	1	0.000	0.000	0.000	48	47	1	6	0.000	0.000	0.000
48	47	1	5	0.000	0.000	−0.240	48	47	1	1	−0.440	0.240	0.060
48	1	1	6	0.000	0.000	0.180	48	1	1	5	0.000	0.000	0.500
48	1	1	3	0.000	0.000	0.180	48	1	1	1	0.170	0.270	0.093
47	48	49	5	0.000	0.000	0.000	47	48	49	1	0.000	0.000	0.000
47	48	1	5	0.000	0.000	−0.240	47	48	1	1	−0.440	0.240	0.060
47	46	3	7	0.000	10.379	0.303	47	46	3	6	0.000	16.250	0.000
47	46	1	5	0.000	0.000	−0.240	47	46	1	1	−0.440	0.240	0.060
47	1	6	21	0.000	0.000	0.090	47	1	6	20	0.000	0.000	0.000
47	1	1	6	0.000	0.000	0.180	47	1	1	5	0.000	0.000	0.500
47	1	1	1	0.170	0.270	0.093	46	47	48	5	0.000	0.000	0.000
46	47	48	1	0.000	0.000	0.000	46	47	1	6	0.000	0.000	0.000
46	47	1	5	0.000	0.000	−0.240	46	47	1	1	−0.440	0.240	0.060
46	45	50	5	0.000	0.000	0.000	46	45	50	3	0.000	0.000	0.000
46	45	50	1	0.000	0.000	0.000	46	3	6	1	3.530	2.300	−3.530
45	50	49	5	0.000	0.000	0.000	45	50	49	1	0.000	0.000	0.000
45	50	3	7	−0.167	0.000	−0.100	45	50	3	1	0.000	0.000	0.130
45	46	47	5	0.000	0.000	0.000	45	46	47	1	0.000	0.000	0.000
45	46	3	7	0.000	10.379	0.000	45	46	3	6	0.000	16.250	0.000
5	50	49	5	0.000	0.000	0.000	5	50	49	1	0.000	0.000	0.000
5	50	3	7	−0.167	0.000	−0.100	5	50	3	1	0.000	0.000	0.130
5	49	50	3	0.000	0.000	0.000	5	49	48	5	0.000	0.000	0.000
5	49	48	1	0.000	0.000	0.000	5	48	49	1	0.000	0.000	0.000
5	48	47	5	0.000	0.000	0.000	5	48	47	1	0.000	0.000	0.000
5	48	1	5	0.000	0.000	0.520	5	48	1	1	0.000	0.000	0.010
5	47	48	1	0.000	0.000	0.000	5	47	46	5	0.000	0.000	0.000
5	47	46	3	0.000	0.000	0.000	5	47	46	1	0.000	0.000	0.000
5	47	1	6	0.000	0.000	0.000	5	47	1	5	0.000	0.000	0.520
5	47	1	1	0.000	0.000	0.010	5	46	47	1	0.000	0.000	0.000
5	46	3	7	0.000	10.379	0.000	5	46	3	6	0.000	16.250	0.000
5	1	48	1	0.000	0.000	0.540	3	46	47	1	0.000	15.000	0.000
3	46	3	7	0.000	10.379	0.303	3	46	3	6	0.000	16.250	0.000
1	49	48	1	−0.100	15.000	0.000	1	48	47	1	0.200	0.270	0.093
1	47	46	1	−0.100	15.000	0.000	1	48	1	5	0.000	0.000	0.540
1	48	1	1	0.400	0.030	0.500							

stretching parameters

bond		K_S	L	bond		K_S	L
50	49	0.00	1.4024	50	45	0.00	1.3493
50	5	0.00	1.0785	50	3	4.40	1.5090
50	1	4.40	1.5230	49	48	0.00	1.3740
49	5	0.00	1.0760	49	1	4.40	1.4970
48	47	0.00	2.1095	48	5	0.00	1.0745
48	1	4.40	1.4970	47	46	0.00	1.3966
47	5	0.00	1.0730	47	3	9.60	1.3370
47	1	4.40	1.4970	46	45	0.00	1.4473
46	5	0.00	1.0770	46	3	9.60	1.3370
46	1	4.40	1.4970				

bending parameters

angle			K_B	θ	angle			K_B	θ
50	49	48	0.00	119.30	48	47	5	0.00	93.10
50	49	1	0.45	118.60	48	1	5	0.36	110.00
50	3	7	0.46	122.50	47	48	5	0.00	97.00
49	50	45	0.00	96.20	47	46	45	0.00	103.20
49	50	3	0.47	110.20	47	46	3	0.60	118.55
49	48	5	0.00	119.50	47	1	5	0.36	110.00
49	1	5	0.36	110.00	46	47	5	0.00	119.10
48	49	1	0.55	118.70	46	3	7	0.50	124.50

Table VIII (Continued)

bending parameters

angle			K_B	θ	angle			K_B	θ
45	50	5	0.00	102.70	48	47	1	0.55	93.10
45	46	5	0.00	97.80	48	1	1	0.45	109.50
5	50	5	0.32	113.70	47	48	1	0.55	97.00
5	48	5	0.24	114.80	47	46	5	0.00	118.55
5	47	5	0.00	114.20	47	1	6	0.70	109.50
5	46	5	0.00	114.60	47	1	1	0.45	110.50
3	46	3	0.60	114.60	46	47	1	0.45	119.10
	3	35	0.80		46	3	6	0.70	124.30
50	49	5	0.00	118.60	45	50	3	0.37	109.49
50	45	46	0.00	156.60	45	46	3	0.24	97.80
50	3	1	0.40	115.00	5	50	3	0.37	113.70
49	50	5	0.00	118.30	5	48	1	0.36	114.80
49	48	47	0.00	100.60	5	47	1	0.38	114.20
49	48	1	0.55	119.50	5	46	3	0.24	114.60
48	49	5	0.00	118.70	1	48	1	0.45	114.80
48	47	46	0.00	110.60					

van der Waals parameters

atom	EPS	R	atom	EPS	R	atom	EPS	R
50	0.044	1.90	49	0.044	1.94	48	0.044	1.94
47	0.044	1.94	46	0.044	1.94	45	0.047	1.50

dipole parameters

bond		μ	bond		μ	bond		μ	bond		μ
50	49	0.30	50	45	0.00	50	5	0.00	50	3	0.30
50	1	0.00	49	48	0.00	49	5	0.00	49	1	−0.30
48	47	0.00	48	5	0.00	48	1	−0.30	47	46	0.00
47	5	0.00	47	3	0.00	47	1	−0.30	46	45	0.00
46	5	0.00	46	3	0.00	46	1	−0.30			

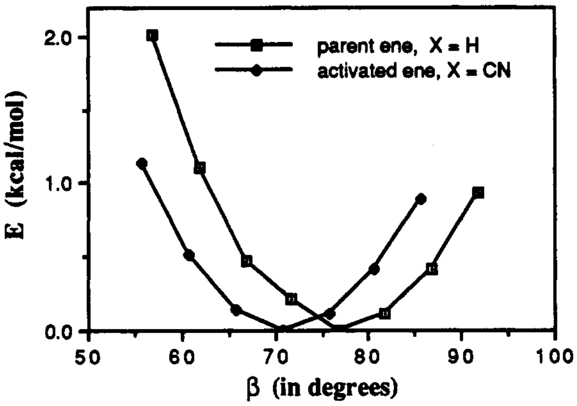


Figure 7. Potential energy curves for rotation about the forming CC bond in the parent and activated ene transition structures.

cases will have to be a flexible model.

Returning to ene reactions of unactivated substrates, very few cases of intramolecular ene reactions of 1,7-dienes have been reported, particularly with unactivated enophiles.[28] We have examined several 1,7-diene ene reactions in order to predict the effect of substituents on the stereochemical outcome of these reactions. The results are given in Tables V and VI. We find that the trans-disubstituted products are almost exclusively the major products, in accordance with our previous work.[6] The stereoselectivity of these reactions is directed by the position(s) of the substituent(s) in the forming ring with the preferred transition structure being that which has the largest substituent in an equatorial position, as was the case with the 1,6-dienes.

One of the most interesting cases is *trans*-1,7-nonadiene. This is the only example where the force field predicts the cis product to be preferred over the trans product for 1,7-dienes. This result arises because only two transition structures (XC and NT) are available for the trans diene. NT is such a high energy transition structure for 1,6-dienes and 1,7-dienes that the cis product should be formed exclusively.

Conclusion

The use of the rigid transition-state approximation for the modeling of organic reactions is a simple and useful way of predicting the stereochemistries of reactions as long as only the reaction type for which it is developed is studied. This type of modeling is easily applicable to many organic reactions.

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Appendix

The parameters used in this study, determined as described in the paper, are listed in Table VIII. Atom types 45–50 were used for the transition state atoms. The numbering scheme is given in Figure 1.

atom	new atom type
carbon 1	46
carbon 2	47
carbon 3	48
carbon 4	49
carbon 5	50
transferring hydrogen	45

Registry No. *trans*-1,6-Octadiene, 19036-81-8; *cis*-1,6-octadiene, 74392-39-5; 7-methyl-1,6-octadiene, 42152-47-6; (3*S*)-3,7-

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dimethyl-1,6-octadiene, 10281-55-7; (3*R*)-3,7-dimethyl-1,6-octadiene, 10281-56-8; (*R*)-3-hydroxy-3,7-dimethyl-1,6-octadiene, 126-91-0; (3*R*,4*S*)-4-hydroxy-3,7-dimethyl-1,6-octadiene, 138332-65-7; (*E*)-8-methyl-2,7-nonadienoic acid methyl ester, 68654-11-5; (*Z*)-8-methyl-2,7-nonadienoic acid methyl ester, 68654-13-7; (*E*)-5,5,8-trimethyl-2,7-nonadienoic acid methyl ester, 104315-11-9; (*Z*)-5,5,8-trimethyl-2,7-nonadienoic acid methyl ester, 104315-12-0; *trans*-1,7-nonadiene, 13150-98-6; *cis*-1,7-nonadiene, 92230-16-5; 8-methyl-1,7-nonadiene, 90975-99-8; (3*R*)-3,8-dimethyl-1,7-nonadiene, 138260-68-1; (*S*)-3-hydroxy-3,8-dimethyl-1,7-nonadiene, 138260-69-2; (3*S*,4*R*)-4-hydroxy-3,8-dimethyl-1,7-nonadiene, 138260-70-5; (3*R*,6*R*)-3,6,8-trimethyl-1,7-nonadiene, 138260-71-6.

Supplementary Material Available: Archive entries of the ab initio calculations (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A New Model for the Stereoselectivities of Dihydroxylations of Alkenes by Chiral Diamine Complexes of Osmium Tetraoxide

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A symmetrical five-membered transition structure model for the dihydroxylations of alkenes by chiral diamine complexes of osmium tetraoxide has been developed based on X-ray crystal structures of OsO_4–amine complexes and osmate esters and ab initio transition structures of analogous reactions. The MM2 calculations based upon this model reproduce the stereoselectivities observed with a variety of chiral diamine ligands. Some predictions are also made using this force field.

Introduction

Highly enantioselective hydroxylations of alkenes by osmium tetraoxide, in the presence of chiral amines, have been discovered by several research groups. Examples of the chiral amine ligands are shown in Figure 1.[1-5] The presence of amine ligands accelerates the reaction rate in each case, but only Sharpless' ligand **1** leads to true catalysis. These reactions are important practically and serve as prototypes of a highly sought reaction type: enantioselective catalytic oxidations of hydrocarbons without functional groups.[6] Several different qualitative models have been proposed to explain the degree and sense of stereoselectivities obtained with various amines.[2,3] Sharpless and Gutierrez have recently used force-field calculations to support a two-step mechanism in which the rearrangement of a reversibly formed metallocyclic intermediate determines the stereoselectivity.[7] We have developed a new working model based upon considerations of crystal structures of reactants and products, as well as knowledge of calculated transition structures of related compounds. The model is qualitative, but we have nevertheless shown that a simple molecular mechanics force field provides semiquantitative predictions in accordance with available experimental results. While these results do not prove the mechanism of the reaction or of stereocontrol, they do give a transition state consistent with all of the available data and predictions to test the model. As a more varied set of alkenes is studied, more demanding challenges of the model will be offered, and the model can be further refined.

Background

Two mechanisms have been proposed for the reaction of OsO_4 with alkenes (Figure 2).[8] One is direct addition of both oxygens to the termini of an alkene double bond via a concerted five-membered cyclic transition state **5**. Jorgensen and Hoffmann's molecular orbital analysis indicated that such a reaction is an allowed process.[9] The other mechanism, proposed by Sharpless and co-workers,[10] involves a fast reversible [2 + 2] cycloaddition of the alkene C=C to a Os=O bond to form a four-membered metallocyclic intermediate **7**; this subsequently undergoes rate-determining rearrangement to form the osmate product **6**.

Either mechanism can rationalize the rate acceleration caused by amines; amine coordination causes distortion

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