

Substituent Effects on Torquoselectivity. Computational Investigations of the Thermal Ring Openings of Cyclobutenes Fused to Substituted Cyclohexenes

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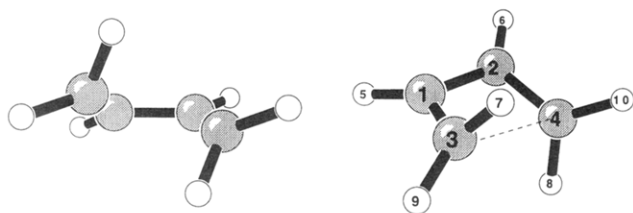
Received August 16, 1994[®]

Ab initio (RHF/3-21G to MP2/6-31G*) and force field (MacroModel/MM2*, MM3*) calculations were carried out to investigate the torquoselectivity of ring openings of cyclobutenes with substituents which sterically influence the selectivity (Piers *et al.* *J. Org. Chem.* **1989**, *54*, 2267; *Tetrahedron Lett.* **1993**, *34*, 1875). Transition state modeling gave a good correlation with experimental selectivity, while relative product stabilities did not correlate with selectivities. The difference between *ab initio* and force field relative activation energies of monosubstituted cyclobutene systems gave the electronic preference for inward or outward substituent rotation. By adding this electronic preference to the relative activation energies of highly substituted systems calculated with MM3*, a reasonable approximation for the torquoselectivity of these systems was made.

Introduction

We have studied intensively the torquoselectivity of thermal electrocyclic ring opening of 3-substituted cyclobutenes from both theoretical¹ and experimental^{2,3} points of view. Our studies have established how substituents at the 3 or 4 position of cyclobutene influence the activation energies and stereoselectivities of electrocyclic ring openings. Experiments have provided strong support for theoretical predictions.² In a polysubstituted molecule, there are other more subtle substituent effects which we investigate in this paper, inspired by the recent experimental reports by Piers and co-workers.⁴

The transition state for cyclobutene conrotatory electrocyclic opening is shown below.



The 1–5 and 2–6 bonds are not in the same plane in the transition state, although they are coplanar in both reactant and product. Substituents such as a fused cycloalkane which twist these bonds in one sense (right- or left-hand helical) should influence the direction of electrocyclic ring opening. Secondly, the substituents at C-1 and C-2 might interact directly with those at C-3 and

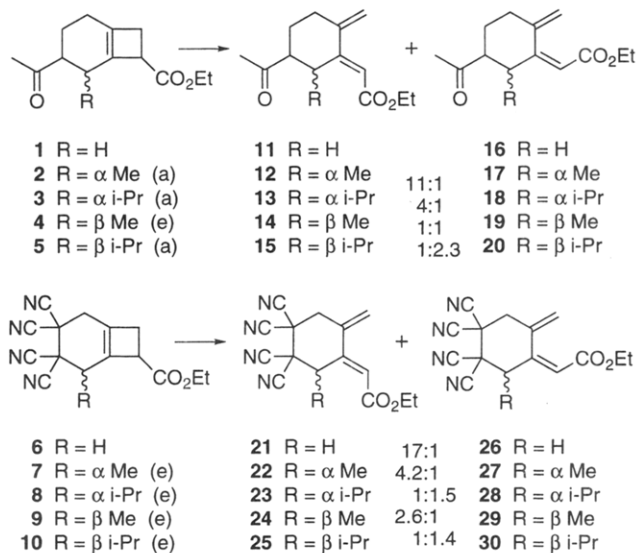


Figure 1. Thermal ring opening of bicyclo[4.2.0]octenes. Observed conformations of reactants ((a) pseudoaxial, (e) pseudo-equatorial) and the product ratios (ref 4b).

C-4 and influence the activation energy of the reaction. In such a case, the torquoselectivity is determined by a balance of both steric and electronic effects. We describe methods to understand and to predict the stereoselectivities of such systems.

Recently, Piers and Ellis reported an experimental study of the stereoselectivity of the ring openings of 3-substituted cyclobutenes fused to substituted cyclohexanes at the 1- and 2-positions of the cyclobutene (1, 7-(ethoxycarbonyl)bicyclo[4.2.0]oct-1(6)-enes).⁴ The results obtained by Piers and Ellis are summarized in Figure 1.

We have undertaken a study designed to reproduce the experimental results by using quantum mechanical calculations and a transition state force-field model.⁵ Force field calculations were carried out by using the MacroModel program.⁶ MM2* and MM3* force fields implemented in the program were used. These resemble

[®] Abstract published in *Advance ACS Abstracts*, January 1, 1995.

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Table 1. MM2* Energies (kcal/mol) and Relative Energies (Boldface, Positive Numbers Show Outward Rotation Preference) of All Possible Conformers of Reactants and Products

2 R=Me	R-ax.: 57.72 0.8 R-eq.: 58.52	t-boat: 37.72 chair: 33.25	35.8 -2.5 39.8
3 R=i-Pr	eq.: 61.21 0.4 ax.: 61.63	t-boat: 41.21 chair: 37.13	38.03 -1.0 43.05
4 R=Me	ax.: 58.16 -0.4 eq.: 57.76	t-boat: 37.80 chair: 33.79	35.15 -2.5 32.72
5 R=i-Pr	ax.: 61.99 -1.0 eq.: 61.00	t-boat: 39.46 chair: 40.22	37.97 4.8 34.78
7 R=Me	ax.: 37.57 -1.3 eq.: 36.23	t-boat: 15.00 chair: 13.15	15.33 -2.1 18.79
8 R=i-Pr	ax.: 43.63 -2.8 eq.: 40.83	t-boat: 18.54 chair: 17.00	19.91 -2.9 25.65
9 R=Me	ax.: 37.29 -1.61 eq.: 35.68	t-boat: 17.45 chair: 13.01	13.95 0.8 12.22
10 R=i-Pr	ax.: 46.71 -6.59 eq.: 40.12	t-boat: 22.78 chair: 19.96	19.35 3.6 16.33

Table 2. Energetics of the Ring Opening of Bicyclo[4.2.0]octene (Energies Relative to Reactant Energies (in kcal/mol), Numbers in Parentheses Are Relative Energies of Chair and Twist-Boat Conformers)

	TS (chair)	TS (t-boat)	chair product	boat product
HF/STO-3G	81.3 (0.0)	81.3 (0.0)	15.1 (0.0)	18.9 (3.8)
HF/3-21G	44.1 (0.0)	43.5 (-0.6)	-15.0 (0.0)	-10.1 (4.9)
HF/6-31G*	49.6 (0.0)	49.0 (-0.6)	-8.5 (0.0)	-3.4 (5.1)
MP2/6-31G*//HF/6-31G*	38.5 (0.0)	37.8 (-0.7)		
MM3/HF/3-21G	(0.0)	(-0.6)	(0.0)	(3.5)

the Allinger MM2 and MM3 force fields, but electrostatic effects and improper torsions are treated differently in the MacroModel versions. *Ab initio* molecular orbital calculations were carried out with the GAUSSIAN 92 programs.⁷

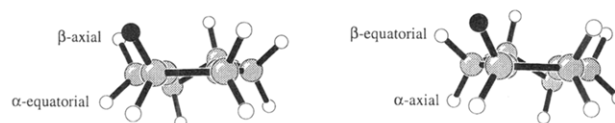
The cyclohexene moiety of the reactant has a half-chair conformation. Both β - (above plane) and α - (below plane)

Table 3. Cyclobutene Ring Opening Transition State Modeling (kcal/mol)

				ΔE_s MM3	ΔE <i>ab initio</i>	ΔE_e
Me		79.8	77.6	2.2	4.0	1.8
F		87.3	88.0	0.9	-0.7	-1.6
Cl		89.9	80.1	9.9	9.0	-0.9
CHO syn		88.3	82.0	6.3	1.7	-4.6
anti		84.8	80.4	4.4	-4.6	-8.9
COOH syn		82.3	70.1	6.3	2.3	-4.0
anti		80.4	75.2	5.2	0.7	-4.5
COOMe syn		87.9	81.6	6.3	1.7	-4.6
anti		86.1	80.8	5.3	2.3	-3.0
CN		95.3	88.0	7.3	4.3	-3.0
OMe		93.6	86.1	7.5	14.0	6.5

^a Positive ΔE represents the preference for the outward rotation. *ab initio* calculations were done at RHF/3-21G

R groups can take quasi-axial or quasi-equatorial positions in the half-chair reactants.



Piers found that the α -R groups in **2** and **3** and the β -R group in **5** are quasi-axial (R-a), while the β -R group in **4** is quasi-equatorial (R-e), from ¹H NMR experiments with NOE measurements.⁴ The orientation of the acetyl group depends on the conformation of the R-group: with the quasi-axial orientation of the R group (**5**), the acetyl group also takes axial orientation. Piers also assumed that the R groups in **7**, **8**, **9**, and **10** have quasi equatorial (R-e) conformations, although unambiguous spectroscopic evidence was not obtained.

The products and transition states of the reaction have two possible conformations, chair and twist-boat, for the six-membered ring. Inward and outward rotation of the substituent at the 3-position of the cyclobutene ring leads to one of each conformation; hence, the relative stability of these two conformations may also affect the direction of rotation.

Results and Discussion

Reactant Conformations. We optimized each reactant structure (**1–10**) with the MM2* force field to see which conformation is more stable. To confirm that the conformations obtained by the calculation are global minima, a multiconformational search with respect to noncyclic torsional angles on substituents was carried out. The steric energy of each conformer is shown in the left column of Table 1. The left boldface numbers indicate which conformer (quasi-axial or quasi-equatorial orientations of R-group) is preferred, and by how much. Positive numbers indicate the quasi-axial conformer is more stable, whereas the negative number indicates the quasi-equatorial conformer is more stable. The compu-

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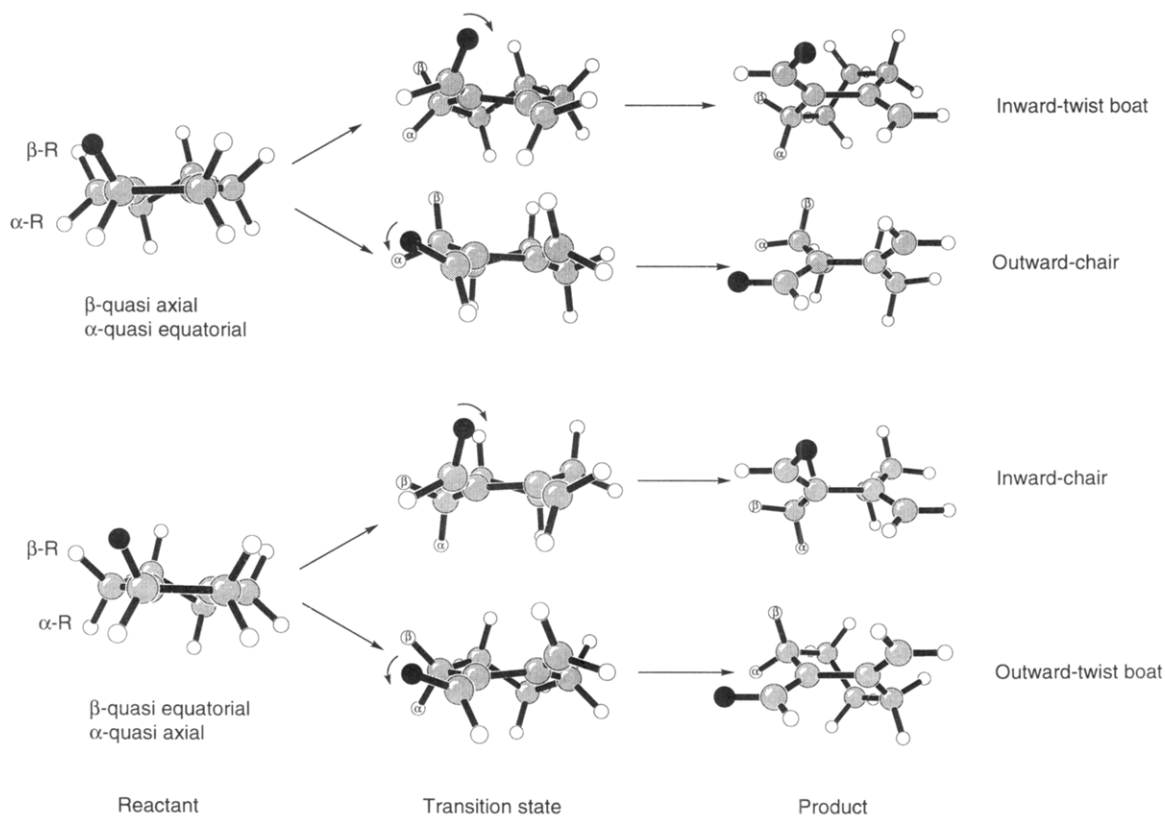


Figure 2. Four possible pathways of ring opening of bicyclo[4.2.0]octene.

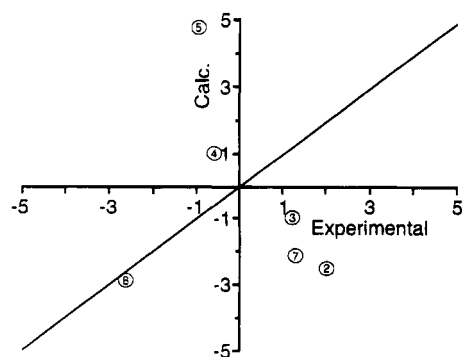
tational results indicate that for substrates **2** and **3**, the R-quasi-axial (R-a) conformation is favored, while for the other substrates (**4**, **5**, **7**, **8**, **9**, and **10**), the R-quasi-equatorial (R-e) conformations are found to be more stable.

The experimental results described earlier and the computational results agree well except in the case of **5**, for which calculations predict quasi-equatorial conformations, while experiment shows that the quasi-axial orientation is favored. For the quasi-axial conformation of **5**, the acetyl group also takes the axial position. We do not have a clear explanation for the experimental conformational preference. Probably the axial conformation of the isopropyl group is not sterically disfavored very much, since it has only one 1,3-diaxial hydrogen-hydrogen repulsion. The steric repulsion with the neighboring group at the quasi-equatorial conformation could make the axial conformer relatively more stable. However, the reactant conformations are interconvertible and do not directly affect the course of the ring opening.

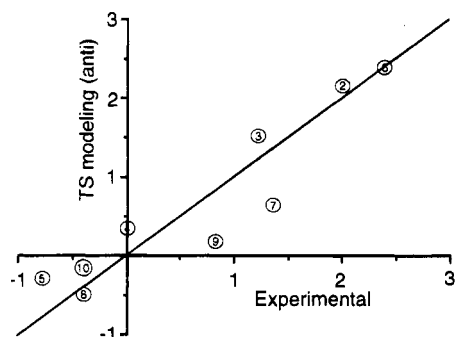
Steric Effects on Torquoselectivity. Piers found that the thermal opening of **1** occurs torquoselectively, and steric effects have little influence. The substrate **6** has no steric repulsion upon outward rotation, which is preferred by 2.4 kcal/mol (17:1 ratio). All other substrates show a lower preference for outward rotation, since the presence of the alkyl (R) group is an obstacle to outward rotation of the ethoxycarbonyl group at the 3-position regardless of whether it is α or β . The inward rotation preference also increases as the size of the R-group increases from the methyl group (**2**, **3**, **7**, **9**) to the isopropyl group (**3**, **5**, **8**, **10**). To investigate if we could reproduce the effect of the steric interaction between the ethoxycarbonyl group and the alkyl group on the torquoselectivity, we first carried out the optimization of all possible products.

Product Conformations. There are two possible conformations, chair and twist-boat, for the ring-opening product of the parent system. Quasi-axial and quasi-equatorial conformers of the reactant can afford both inward and outward rotation of the cyclobutene-C3 substituent. These can lead to chair or twist-boat conformations. Figure 2 gives all these possibilities. A MM2* multiconformational search was carried out. The energies of the product conformations are shown in Table 1. Lower energy conformers between chair and twist-boat are taken and underlined. Differences between inward and outward of those numbers are shown as bold numbers in the right side of the table, which show the relative energies of possible products. Positive numbers indicate that outward products are lower in energy, while negative numbers indicate that inward products are lower in energy. A plot of the experimental ratios of inward and outward rotation pathways with the relative stabilities of inward and outward products is shown in Figure 3a. Each point on the diagram would lie on the diagonal line of slope 1 shown on the graph, if the experimental and theoretical results correlated perfectly. However, the diagram shows no correlation. This result suggests that it is not appropriate to estimate the selectivity from the relative stabilities of the products. Hence, transition state modeling analysis was undertaken to evaluate the interaction properly.

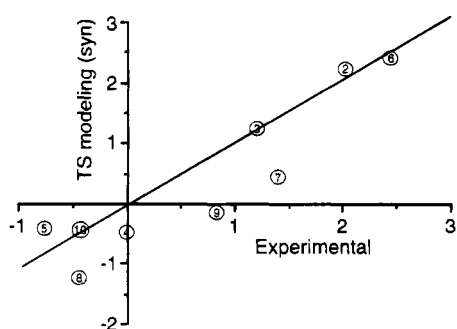
Transition State Modeling. To carry out the transition state modeling analysis, we first optimized the geometry of the reactant and chair and twist-boat conformations of both transition states and products for bicyclo[4.2.0]oct-1(6)-ene (**1**) by using *ab initio* molecular orbital calculations with the 3-21G basis set. The energies of each structure relative to the reactant are summarized in Table 2.



(a) Calculated Product Stability vs. Experimental Torquoselectivities



(b) Transition State Modeling (anti) vs. Experimental Torquoselectivities



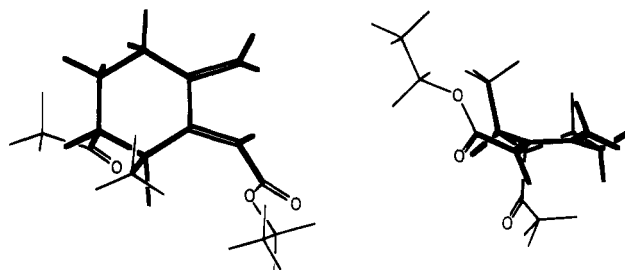
(c) Transition State Modeling (syn) vs. Experimental Torquoselectivities

Figure 3. Correlation of selectivity between experimental and various computational results (kcal/mol).

The energies depend upon the level of theory employed, but the relative energies of the chair and twist-boat conformations (numbers in parentheses) are insensitive to the theoretical level. The chair conformer is preferred for the product by 4–5 kcal/mol, while the twist-boat

conformer is slightly (0.6 kcal/mol) more stable at the transition state. The single point MM3* force field calculation at the *ab initio* transition state geometry afforded a good estimate of the relative activation energies of the two pathways. In subsequent calculations, the transition state structure was fixed at the *ab initio* geometry, and MM3* calculations were used to evaluate steric interactions. Transition states of the ring openings of bicyclo[4.2.0]oct-1-(6)ene (transition states in Figure 3) were fully optimized at the HF/3-21G level of theory. This was used as a template for the skeleton of the substituted systems. The higher level geometries (RHF/6-31G*) were obtained later in the investigation and were found to be very close to those obtained with RHF/3-21G calculations.

The transition state modeling calculation was carried out in the following manner. First, substituents (–COOEt, –R, –C≡N) were substituted for hydrogen with an arbitrary orientation on the parent *ab initio* transition state structure. Then the geometry was optimized with the MM3* force field with a fixed parent transition state skeleton (marked with heavy lines in the structures below). The constraints were maintained by assigning



1000 kcal/mol·Å² harmonic functions to fix the Cartesian coordinates of each constrained atom. Multiconformational searches involving all free torsional angles of substituents were carried out to make sure the conformations obtained is the most stable as a transition state.

Before describing the results of the transition state modeling, we note a problem with estimation of the relative activation energies obtained with these force field calculations. Torquoselectivity arises from the interaction between the σ and σ^* orbitals of the breaking C–C bond and the p or π orbitals of the substituent at the 7-position (3-position of cyclobutene). For example, the preference of inward rotation of the electron-withdrawing formyl group can be explained by the stabilizing interaction between the π^* -orbital on the carbonyl carbon and

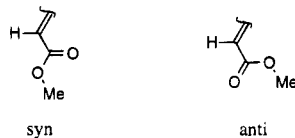
Table 4. Relative Energies (kcal/mol) between All Possible Conformers of Transition States by TS Modeling^a

substrate	exptl $E^*(in) - E^*(out)$	anti				theory (anti) $E^*(in) - E^*(out)$	syn				theory (syn) $E^*(in) - E^*(out)$
		inward		outward			inward		outward		
		chair	t-boat	chair	t-boat		chair	t-boat	chair	t-boat	
1		7.5	8.4	0.0	0.0	3.0	8.7	8.4	0.0	0.0	2.7
2	2.0	<u>6.7</u>	10.5	3.7	0.0	2.2	<u>8.2</u>	11.7	3.8	0.0	2.2
3	1.2	<u>6.0</u>	7.7	4.5	0.0	1.5	<u>7.3</u>	9.1	4.0	0.0	1.3
4	0.0	<u>4.7</u>	6.5	1.2	0.0	0.3	<u>5.5</u>	7.4	0.0	0.1	-0.5
5	-0.8	<u>4.2</u>	5.5	3.4	0.0	-0.3	<u>5.7</u>	6.7	2.5	0.0	-0.4
6	2.4	<u>7.27</u>	6.9	0.1	0.0	2.4	<u>8.8</u>	8.4	0.2	0.0	2.4
7	1.3	11.4	<u>5.2</u>	0.0	5.1	0.7	12.6	<u>4.7</u>	0.0	3.8	0.4
8	-0.4	11.8	<u>4.0</u>	0.0	4.2	-0.5	12.7	<u>4.7</u>	0.0	3.8	-1.3
9	0.8	<u>4.7</u>	8.8	3.5	0.0	0.2	<u>5.9</u>	11.6	3.4	0.0	-0.1
10	-0.4	<u>4.3</u>	8.5	6.6	0.0	-0.2	<u>5.6</u>	15.0	11.0	0.0	-0.4

^a The lower energy conformer between chair and twist-boat is underlined. The differences between these numbers, plus the correction parameters (–4.5 kcal/mol for anti, –6.0 kcal/mol for syn), give the theoretical preference (bold numbers). Experimental values are calculated from the product ratio.

Table 5. Relative Activation Energies (kcal/mol) of the Ring Opening of 3-(Methoxycarbonyl)cyclobutene (RHF/3-21G; Values in Parentheses Are Relative Energies)^a

inward		outward	
syn	anti	syn	anti
40.3	41.5	38.6	39.2
(1.7)	(2.9)	(0.0)	(0.6)

^a Key:**Table 6. Change in Preference for Change from Methyl to Isopropyl Group or from α to β Conformation**

substrate	experimental		calcd anti		calcd syn	
	α to β	Me to i-Pr	α to β	Me to i-Pr	α to β	Me to i-Pr
2		2.0	2.2		2.2	
3	-2.0	1.2	-2.0	1.5	-2.7	1.3
4	-2.0	0.0	-1.8	0.2	-1.7	-0.5
5		-0.8		-0.3		-0.4
7		1.3	0.7		0.4	
8	-0.5	-0.4	-0.5	-0.5	-0.5	-1.3
9	0.0	0.8	0.3	0.2	0.9	-0.1
10		-0.4		-0.2		-0.4

the high-lying σ -orbital of the breaking C–C bond. This kind of electronic interaction is not included in the force field calculations, unless some empirical parameter is included to account for this electronic effect. In Table 3, we tabulate the relative activation energies of inward and outward rotation in various 3-substituted cyclobutenes according to *ab initio* calculations ($\Delta E_{ab\text{ initio}}$) and by MM3* transition state modeling calculations (ΔE_{steric}). The MM3* calculations include no special in/out electronic torquoselectivity parameter and predict that all substituents which are larger than hydrogen sterically prefer the outward rotation. The difference between *ab initio* (ΔE) and force field (ΔE_s) energies is shown in Table 3 as $\Delta E_e = \Delta E - \Delta E_s$. This represents the intrinsic electronic preference for the torquoselectivity which is not included in the force field calculations. It clearly shows that all electron-withdrawing groups i.e., formyl (CHO), carboxyl (COOH), and cyano (CN) groups, electronically prefer inward rotation, while electron-donating groups (methyl and methoxy) electronically prefer outward rotation. This is in good accordance with our explanation of torquoselectivity.^{1,2} The inward rotation preference of F is different from expectations based on our previous work. Here we will utilize the value, ΔE_e , as a transferable factor to estimate the torquoselectivity (ΔE). The ΔE_e for each substituent can be added to the relative force field energies of transition states (ΔE_s) of substituted systems to add the electronic preference to the result of force field calculation.

There are four possible conformations of the transition state of each reaction. Each of these is related to a product geometry as illustrated in Figure 2. In addition, either the syn or anti orientation of ethoxycarbonyl group is possible for each transition state. Consequently, there are eight possible transition state conformations for each reactant. We estimated the steric energy of each conformation with the MM3* force field with the fixed transition state skeleton. All four carbon atoms in the cyclobutene moiety of the reactant were treated as sp^2 carbons. The results obtained are shown in Table 4.

The relative energies of eight possible conformations for inward and outward rotations with both anti and syn orientations of the ethoxycarbonyl group and chair and twist-boat conformers are given. The lower energy conformation between chair and twist-boat is underlined to compare whether inward or outward rotation is preferred for anti or syn orientation of the methoxycarbonyl group. For example, for the parent system (substrate 1), if the ring opening occurs with anti orientation of methoxycarbonyl group, the inward rotation (chair) is preferred over the outward rotation (chair) by 7.5 kcal/mol, and if the methoxycarbonyl group has syn orientation, the energy difference between inward and outward is 8.7 kcal/mol. This comparison does not include the electronic contribution to torquoselectivity. To take the electronic factor into account, the correction parameter (ΔE_e is added to the energy difference. The values for the methoxycarbonyl group in Table 2, -4.6 kcal/mol for syn and -3.0 kcal/mol for anti, make the total preference of outward rotation 3.5 kcal/mol for anti and 4.1 kcal/mol for syn. The values obtained with this method systematically overestimate the preference for outward rotation. Instead of conducting further *ab initio* calculations to obtain a better correlation value, we used the simplest system (substrate 6) as a standard and calculated the correction parameter necessary to reproduce the experimental value (2.4 kcal/mol). The resulting correction parameters, ΔE_e , are -4.5 kcal/mol for anti and -6.0 kcal/mol for syn. The resulting relative energy between inward and outward rotations for both anti and syn orientations of the ethoxycarbonyl group is shown for each substrate in boldface type together with experimental values. Positive values predict outward rotation, while negative values predict inward rotation. The correlation between experimental preference and the calculated value is shown in Figure 3b,c. The results show a good correlation between calculation and experiment. The maximum deviation from experimental result was found to be 0.6 kcal/mol for anti and 0.9 kcal/mol for syn. The results for anti conformers show better agreement with experimental results, although *ab initio* calculations have shown that the syn orientation is favored for both inward and outward rotation for the ring opening of 3-(methoxycarbonyl)cyclobutene (Table 5).

Another interesting aspect of steric effects on torquoselectivity is shown in Table 6. The table contains both experimental and calculated relative activation energies from Table 4 and summarizes the change in preference upon replacing the methyl group with an isopropyl group and upon switching the orientation of the alkyl group from α to β . Experimentally, changing the alkyl group from methyl to isopropyl decreases the outward rotation preference by 0.8–1.7 kcal/mol. This tendency is easily understood and is reproduced computationally. The outward preference is altered by switching the R group from the α to the β configuration; there is a 2 kcal/mol

decrease in the substrates which have an acetyl substituent on the cyclohexane ring (**2**–**5**) but only a 0–0.5 kcal/mol decrease in substrates without an acetyl group (**7**–**10**). This tendency is reproduced by the calculations. The calculations also clearly show why they give different trends. From **7** and **8** to **9** and **10**, the conformation of the outward transition state switches from chair to twist-boat. These are the most stable conformations for each transition state when there are no other steric effects. However, from **2** and **3** to **4** and **5**, all have twist-boat conformations. This is mainly because the acetyl group moiety must be in an axial conformation with the chair outward rotation transition state. The presence of the acetyl group makes the torquoselectivity more sensitive to the orientation of the alkyl group.

For some substrates with high steric strain in the transition state, the ethoxycarbonyl group adopts neither syn nor anti orientation, but adopts a partially rotated conformation. This might contribute to deviations in Figure 3b and c, since such orientations might have altered electronic effects on torquoselectivity.

Even though recent computer advances make it possible to calculate large organic molecules, it is still difficult to carry out a conformational search involving more than 100 conformations with *ab initio* or semiempirical calculations. The present calculations demonstrate a method to separate the electronic and steric contributions to the selectivity of a reaction. The good correlation between the experiment and calculation indicates the model is adequate to estimate the selectivity in such systems. Such rigid transition state models can be used for reactions with relatively constant transition state geometries, although subtle effects often require full geometry optimizations by quantum mechanical methods.^{1b}

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research and to Professor E. Piers for helpful discussions.

JO941423K