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Laboratories and Demonstrations

Modeling the Asymmetric Diels–Alder Reaction: Using a Combination Wet Lab/ Computer Lab Approach to Examining Organic Reactions

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Within the framework of a laboratory experiment, students can begin to envision the excitement and demands of true chemical research.

Molecular modeling is rapidly becoming a standard analysis tool for the synthetic chemist. It is appropriate that students be exposed to modeling in conjunction with wet chemistry and instrumental analysis. The Diels–Alder reaction between cyclopentadiene and *l*-menthyl acrylate leads to the production of four diastereomers. Both the *endo*/*exo* ratio and (R/S) ratio (referring to the stereochemistry of the newly generated stereocenter at the ring 2 position) are dependent upon reaction conditions. Simple examination of the calculated geometries and frontier orbitals of the starting reagents offers explanations for the observed selectivities. More detailed modeling of the transition states leading to the various products suggests that the cyclization reaction is asychronous and gives insight into the relative importance of molecular features on the energies of the available reaction pathways. This exercise lets undergraduates investigate a problem of current chemical interest. As in a

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research project, they are required not only to think about the chemistry being investigated, but to also examine the assumptions and limitations of their analysis tools.

Introduction

Molecular modeling is taking on an increasingly important role in chemical education [1–3], just as it is in chemical research. In each case the combination of vivid graphics, versatile data generation, and (relatively) rapid response to chemical questions provides a powerful complement to other types of analysis. For the educator modeling provides both challenge and opportunity. For example, graphical displays of complex information can help students to visualize molecular properties and spatial relationships, but it is important to ensure that they understand the meaning behind the figures [4].

Educators have also used various computational methods to enable students to investigate molecular features and reaction pathways [5–10]. In such experiments it is common to consider well-understood systems in which the computer model is known to give the “correct” answer. It is also possible to attack chemical problems of current theoretical research interest [11–12]. In these less obvious cases, it may not be possible to reach closure on all questions. By wrestling with such problems, however, students become involved in real scientific inquiry and extremely valuable lessons can be learned. Students discover that all of the answers are *not* known and that the tools at our disposal are *not* perfect. They also learn to test the results of one experiment against other experiments as well as against chemical intuition. It is our firm belief that students, even as undergraduates, are ready and able to learn from complex, subtle chemical questions.

In this paper we describe the development of a complementary wet laboratory/computer modeling experiment involving the Diels–Alder reaction. This experiment is designed to be used at the intermediate (Sophomore/Junior) level, with students who have had organic chemistry, but not necessarily physical chemistry. The laboratory is accompanied by a review of basic molecular orbital theory as well as an introduction to molecular modeling techniques. The modeling portion works very well at a qualitative level, but shows weaknesses when pushed to quantitatively explain reaction subtleties. The deliberately open-ended design of the experiment allows more aggressive students to refine the modeling protocol based upon recent literature reports and to discover the

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limitations of computer models. The effort gives students a better understanding of not only the Diels–Alder reaction, but also of the computation techniques themselves.

Experimental

General

All reagents were purchased from Aldrich and used as received with the exception of menthyl acrylate, which was prepared by condensation from menthol and acryloyl chloride under dry nitrogen [13]. The full synthesis procedure, safety, and disposal information are fully described in the reference.

Neat Reaction

l-Menthyl acrylate **1** (50 mg, 0.24 mmol) was mixed with freshly cracked cyclopentadiene (44 µL, 0.53 mmol). The solution was sonicated for 3 min and left at room temperature. The solution was then sonicated for an additional 3 min and left to react for 24 h. The *endo/exo* product ratio was determined from the crude reaction mixture by gas chromatography. The Diels–Alder adducts were separated by silica gel chromatography (0–2% EtOAc:hexane) and isolated as oils.

Endo adducts **2** yield: 42.4 mg (64%). ^{1}H NMR ($CDCl_{3,}$ resolved signals) for the major diastereomer (2R) δ 6.20 (dd, J = 3.0, 5.7, 1H), 5.87 (dd, J = 2.7, 5.4, 1H), 4.58 (dt, J = 6.2, 12.3, 1H); for the minor diastereomer (2S) δ 6.18, 5.92 and 4.60. IR (neat) 3063, 3956, 2870. 2360, 1738, 1571, 1462, 1455, 1386, 1371, 1336, 1271, 1178, 1110, 1065, 1036, 1014 cm^{-1}. D.e.= 5.1 ± 4% (^{1}H integration of peaks in the δ = 5.8-6.3 range).

Exo adducts **3** yield: 15.1 mg (23%). ^{1}H NMR ($CDCl_3$) δ 6.09 (dd, J = 3.0, 5.6, 1H), 4.73 (dt, J = 4.3, 10.8, 1H), 4.58. IR (neat) 3440, 2956, 2870, 1732, 1633, 1456, 1370, 1334, 1262, 1233, 1171, 1071, 1097, 1038 cm^{-1}.

CH_2Cl_2 Reaction

To a solution of *l*-Menthyl acrylate **1** (see Figure 1), (74.6 mg, 0.35 mmol) in dry CH_2Cl_2 (1 mL) freshly cracked cyclopentadiene (70 µL, 0.85 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The solvent was then removed and the residue purified on silica gel (0–2% EtOAc:hexane) to give the Diels–Alder adducts **2** and **3** as clear oils. Total yield *endo* product **2**: 33.1 mg, 34%. D.e. = 9.0 ± 4% (2R) diastereomer (^{1}H integration of peaks in the δ 5.8–6.3 range).

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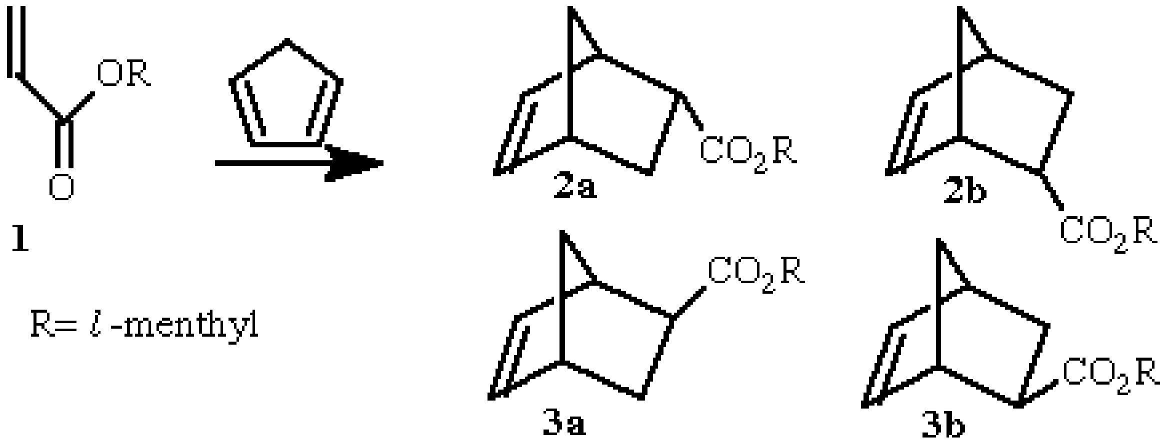

FIGURE 1. DIELS–ALDER REACTION OF MENTHYL ACRYLATE AND CYCLOPENTADIENE.

Gas Chromatographic Analysis

Endo/exo ratios (ratio of **2** to **3**) were determined on a Hewlett Packard 5890 gas chromatograph equipped with a flame ionization detector and using a cross-linked methylsilicone gum column (25 m × 0.32 mm i.d.). Nitrogen was used as a carrier gas (15 psi). The injector and detector temperatures were maintained at 230 and 250 °C respectively, while the oven was held at 190 °C for 1 min, then cooled (2 °C/min) to 180 °C and then at 1 °C/min to 170 °C. The final oven temperature was maintained for the rest of the experiment (24 min). Ratios were determined by electronic integration of peaks from the crude reaction mixtures. The peaks cleanly resolved and were identified by comparison to the individual purified products isolated by column chromatography. Retention times: *exo*, 27.5 min; *endo*, 28.5 min.

Molecular Modeling

All calculations were carried out on an Apple Power PC 9500 with 32 MB RAM and running the CAChe[1] suite of molecular modeling software (version 3.8). Standard Allinger MMX parameters [14] were used in all force field calculations. Semi-empirical calculations were performed using the CAChe implementation of MOPAC 6.0 using the PM3 method. Initial geometries were generated by searching conformational space of the starting materials and products with MMX. Minimum energy conformations were

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[1] Oxford Molecular Group, P. O. Box 500 M/S 13-400, Beaverton, OR 97077.

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then refined with MOPAC. Initial transition states were generated by placing the starting diene and dienophile 5 Å apart and running a MOPAC SADDLE calculation. The transition-state structure was then refined by a MINIMIZE GRADIENT calculation, using sequentially the eigenvector following method and the nonlinear least squares optimization method. A second set of transition states was generated by previously reported bond angles and distances for the six carbon atoms directly participating in the reaction. These values come from *ab initio* calculations of the reaction between cyclopentadiene and methyl acrylate [15]. The heats of formation of all transition states were calculated by MOPAC PM3 calculations and steric energies by MMX calculations.

Results and Discussion

The Diels–Alder reaction remains one of the fundamental reactions in organic chemistry, both because of its valuable role in synthesis and for its conceptual challenge. The early work of Woodward and Hoffmann [16] has made this reaction a natural vehicle for introducing and expanding student understanding of the orbital approach to describing reactions. While the fundamentals of the reaction are straightforward, numerous subtleties remain. The *endo/exo* product distribution in the reaction of cyclic dienes is very sensitive to substrates and reaction conditions as are the diastereomeric ratios obtained from either asymmetric dienes or dienophiles.

We have recently described an exercise which takes advantage of Lewis acid catalysts to give high yields and good selectivities in the reaction between cyclopentadiene and chiral acrylates [13]. We have shown that this system can be nicely modeled in a qualitative way. In this paper, we will consider the uncatalyzed reaction in addition to the titanium-catalyzed reaction discussed previously. This system displays very poor selectivity, but is far easier to model. By examining the uncatalyzed reaction in detail, we are able to offer some explanations for the differences between the two systems as well as gain some insights into the origin of the selectivities.

Reaction Conditions and Product Distributions

The Diels–Alder reaction is easily carried out and analyzed using microscale glassware. The reaction can also be carried out in a variety of other solvents, with more polar

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solvents giving both greater *endo/exo* ratios and diastereomeric excess (d.e.). Gas chromatography with a cross-linked methysilicone gum column gave good separation of the *endo* and *exo* products (identified by comparison to resolved products), which could be reproducibly integrated to give the product ratios (Table 1). Diastereomeric excesses of the *endo* isomers could be obtained by integrating the olefinic signals at 5.87 (major isomer) and 5.92 ppm. The minor fraction *exo* isomers were not further examined, since there is no easily resolved signal in the spectrum.

The CH_2Cl_2 reaction gives lower yields and a slightly lower *endo/exo* ratio than does the neat reaction. The d.e. of the CH_2Cl_2 reaction however, is larger, consistent with previous reports [17].

Basic Molecular Modeling Exercises

Following the completion of their wet laboratory work, students are asked to use molecular modeling to show which of the *endo* diastereomers is preferred and why. In order to do this, it is necessary for them to understand the strengths and limitations of the computational techniques available to them. They first use the MMX force field to explore the possible conformations of the starting materials. Cyclopentadiene is rather straightforward, but menthyl acrylate has several possible local minima. For example, one common mistake is to build the cyclohexyl ring so that the substituents are in the axial positions, rather than equatorial.

A more serious question is the orientation of the alkene relative to the carbonyl. Both MMX (Figure 2) and PM3 predict the *s-cis* conformation to be lower in energy than the *s-trans*, although this difference is very small. Calculations on methyl acrylate at the *ab initio* level also show the cisoid geometry to be preferred in vacuum [18]. Solvation appears to stabilize the *s-trans* orientation more than the *s-cis* [19]. This issue is an interesting one, because the less sterically hindered approach to the *s-cis* conformer results in the formation of the *endo* product having the (2S) conformation, the minor product in all cases. Given the small energy difference between the rotomers and the low barrier for interconversion, it is reasonable to conclude that both geometries are present under either the CH_2Cl_2 solution or neat reaction conditions. In addition, there is the possibility for rotation about the bond between the cyclohexyl ring and the ester. Again, we find that a number of low energy orientations are possible.

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TABLE 1. Diels–Alder Reactions of *l*-Menthyl Acrylate with Cyclopentadiene.

Conditions	%Yield, *endo* isomers	endo/exo ratio	d.e. of endo isomer (±4%)
Neat, rt, 24 hr	64	2.8:1	5.1[a]
CH2Cl2, rt, 24 hr	34	2.5:1	9.0

[a]The major diastereomer has the (2*R*) absolute configuration in all cases. See reference 15 for representative spectra.

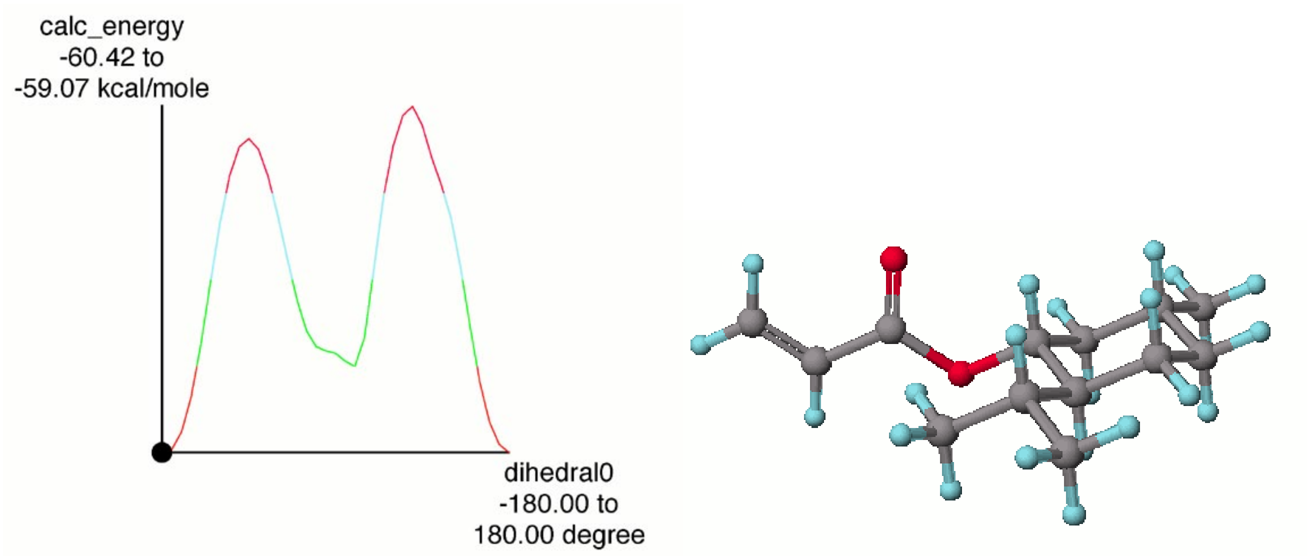

FIGURE 2. CONFORMATIONAL ENERGY CHANGES UPON ROTATING MENTHYL ACRYLATE FROM THE *S-CIS* TO *S-TRANS* GEOMETRY.

Since the Lewis acid catalyzed reaction gives the same major product, but with much greater specificity, it is useful to examine the conformational preference in this system. The $TiCl_4$ adduct can be modeled using x-ray crystal data to define the location of the metal [20]. By locking the Ti-O bond distance and related bond angles, important dihedral angles may be driven as shown in Figure 3. It is clear that the *s-trans* conformation is highly preferred in this case and that the *endo* (2R) product should be formed, as is experimentally observed. Thus, students can reason that the *s-trans*

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geometry is actually slightly preferred in the non-catalyzed reaction and that at least part of the reason for the poor selectivity is competition from the *s-cis* geometry. Figure 3 also shows that rotation about the titanium-acrylate bond is essentially unhindered. Finally, the titanium prevents rotation about the bond between the ester and the cyclohexyl ring, locking in the steric effects of the ring substituents on the approaches to the alkene.

Another issue is that of *endo* vs *exo* selectivity. To investigate this question, students generate the frontier orbitals of the diene and dienophile using the PM3 method. Comparing the HOMO of the diene with the LUMO of the dienophile clearly shows that a [4+2] cycloaddition can be expected. Figure 4 shows that the observed *endo* selectivity cannot be accounted for by steric interactions, since the preferred product is actually the more congested one. This is true for both the major (R) isomer as well as the minor (S) isomer (shown). A closer examination of the molecular orbitals, however, shows that there can be secondary orbital overlap between the carbonyl carbon and the diene. This interaction may stabilize the incipient transition state and accounts for the experimentally observed behavior. Note that the secondary orbital argument holds for both the catalyzed and uncatalyzed systems and also for both the *cisoid* and *transoid* geometries of the carbonyl and alkene. Thus, good *endo* selectivity is observed in both systems.

Advanced Modeling Exercises

If we assume kinetic control of the reaction, an analysis of competing transition states is the best way to understand the distribution of products. This level of modeling is beyond that which we felt could be required of all students, but something that could be attempted by those with the time and inclination to do so. The following results were obtained by one of the authors (B.S.) as a special project conducted during the term following the wet laboratory work. During this term, he also took a physical chemistry course that included a discussion of quantum mechanics and of the mathematical details upon which the computational methods are based.

In order to keep our calculations at a manageable level, several simplifications are required. First, we did not attempt to find transition states in the more selective Lewis-acid-catalyzed systems, focusing instead on the all organic reaction. Next, we chose not to consider solvation. Recent *ab initio* calculations on the reaction of methyl acrylate and cyclopentadiene suggest that these effects are substantial, particularly for polar

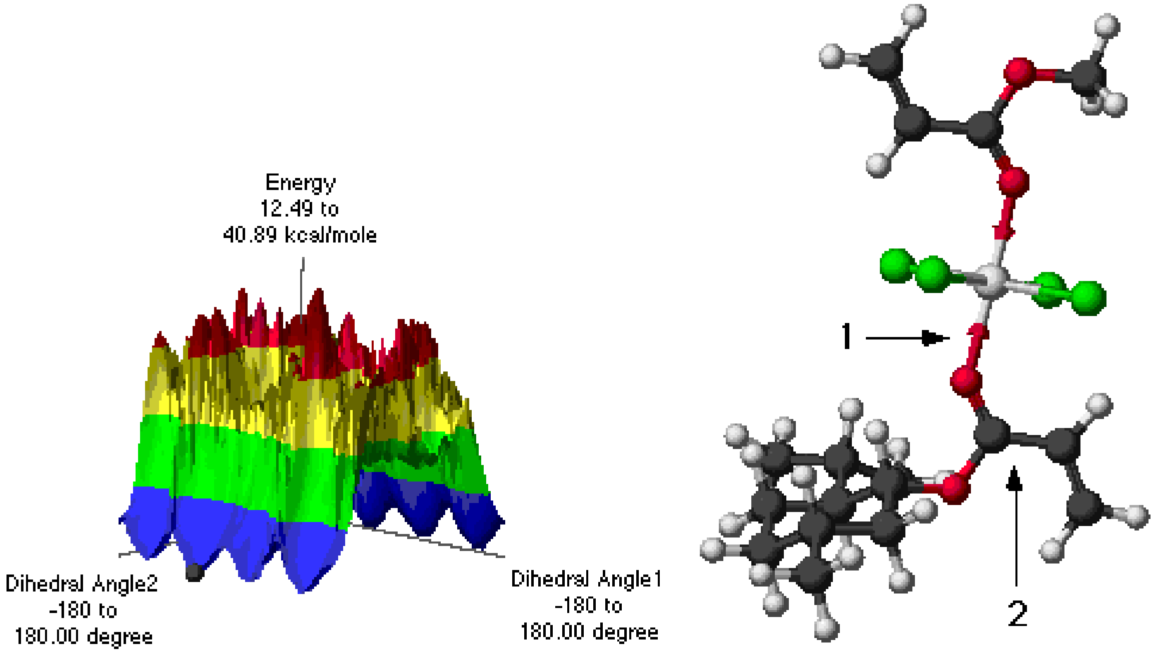

FIGURE 3. CONFORMATIONAL ENERGY CHANGES UPON ROTATING THE $TICL_4$-MENTHYL ACRYLATE COMPLEX FROM THE *S-TRANS* TO *S-CIS* GEOMETRY (*X*-AXIS) AND IN ROTATING ABOUT THE ACRYLATE-LEWIS ACID BOND (*Y* AXIS).

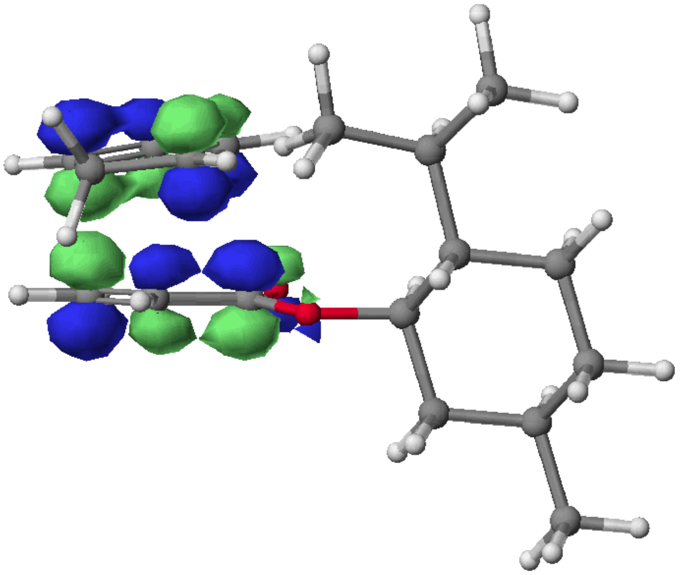

FIGURE 4. LUMO OF MENTHYL ACRYLATE AND THE HOMO OF CYCLOPENTADIENE.

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solvents [18]. Because of the neglect of solvent and the low level of theory that we are applying, we did not expect to generate accurate absolute activation energies, but we did hope to come up with reasonable relative energies. Next, our calculations of the free acrylate indicate considerable fluxionality. It is probable that there are an ensemble of transition states of similar energy, but differing in the orientation of the cyclohexyl ring or the carbonyl-alkene geometry. We chose to address the second of these directly, because either of the planar orientations is strongly preferred over the nonconjugated rotomers. The rotation of the cyclohexyl ring is more of a problem. It is likely that there are a large number of transition states of similar energy that differ only in the orientation of the ring, yet that orientation is the asymmetry which determines the (R) or (S) selectivity in the system. In order to simplify the system, we began our transition state searches using the ring orientation found to be the minimum energy geometry of the titanium catalyzed structure where the ring is relatively fixed. The reasoning was that we could learn something about the steric effect of the menthyl group and then extrapolate our results to the very rigid, catalyzed system and to the very fluxional, uncatalyzed system.

Transition states were generated by performing MOPAC SADDLE calculations beginning with starting materials located 5 Å apart and ending with the appropriate geometry optimized products. Transition states were optimized with a MINIMIZE GRADIENT calculation and single point energies were calculated by both the PM3 and MMX methods. The results are shown in Table 2.

The PM3 derived transition states were highly sensitive to the starting geometry of the reagents. A considerable amount of effort was put into searching conformational space for the lowest energy reaction coordinate. Previous workers have found that low-level *ab initio* approaches often give good geometries for the transition states, but poor values for the energies of those states [18, 21]. We found fairly wide ranges of energies for the PM3 transition states, which appeared qualitatively to be very similar. The results shown in Table 2 for this method predict almost exactly the opposite product preferences as is observed experimentally! Interestingly enough, single point MMX calculations on exactly the same transition states give far more reasonable results. Mechanics predicts that products arising from a transoid acrylate geometry should be favored; that *endo* products **2** should be favored over *exo* **3** and that the (2R) diastereomer should be preferred over the (2S). These results are consistent with the experimental data shown in Figure 1 and in reference 13.

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TABLE 2. Relative energies (kcal mol^{-1}) of calculated transition state structures in the reaction of menthyl acrylate and cyclopentadiene.

Transition State	PM3 Transition State[a]		ab initio Transition State[b]	
	PM3	MMX	PM3	MMX
trans, 2a	0.0	0.0	0.0	0.0
trans, 2b	-1.58	1.86	0.09	1.19
trans, 3a	2.96	1.47	0.18	1.27
trans, 3b	6.10	1.43	0.37	5.01
cis, 2a	5.07	3.49	-0.37	5.65
cis, 2b	-0.57	2.81	-0.72	4.59
cis, 3a	-2.05	3.03	-2.48	10.82
cis, 3b	-4.23	3.46	-0.41	11.45

[a] Transition states were generated by PM3 saddle calculations. Relative energies were obtained by single point energy calculations.
[b] Bond distances and angles for the six carbon atoms directly involved in the cyclization were obtained from *ab initio* calculations [15]. These values were locked and the rest of the molecule minimized by the indicated method.
[c] Transition states are designated by the orientation of the starting dienophile followed by the product which is produced.

Houk and coworkers recently described a combination *ab initio*-molecular mechanics method, called “transition state modeling,” for analyzing Lewis-acid-catalyzed Diels–Alder reactions [15, 21]. In this approach, the transition states of simple model systems are treated by high level *ab initio* methods. The resulting geometry is then applied to more complex systems, either directly or by introducing new atom and bond parameters into the MMX force field.

The data from Houk’s RHF/3-21G-optimized transition state for the BF_3-catalyzed reaction of methyl acrylate and cyclopentadiene was used to define the second set of transition states shown in Table 2 [15]. The bond lengths and angles about the six carbon atoms directly involved in the cycloaddition process (the four diene carbons and

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two dienophile carbons) were locked. Then the remainder of the molecule was allowed to relax using the PM3 method and an unmodified MMX force field.

The mechanics results are very similar to those found with the PM3-derived transition states. The geometries resulting from a cisoid acrylate are more highly disfavored than the PM3 states, as are those resulting from *endo* attack. The PM3 energies are also more stable due to the more consistent approach vectors. The *s-cis* acrylate geometry is still favored (probably as a result of neglecting the solvent, see above), but within the *s-trans* transition states, the ordering of the energies mirror those of the mechanics calculations. The magnitude of the energy differences are small, however.

Another interesting feature of these transition states, predicted by both approaches, is that the process is not concerted. Figure 5 shows that the σ-bond to the terminal carbon of the alkene is formed before the second σ-bond. These results are in agreement with very recent *ab initio* calculations performed on related systems [22].

Conclusions

Furman University’s unusual academic calendar lends itself well to involved laboratory exercises such as this one, but this experiment can easily be carried out in a set of two to three standard laboratory periods and one or two lecture hours. The synthesis and isolation of the Diels–Alder adducts is straightforward and similar to experiments described in many organic laboratory texts. Analysis of product ratios requires a gas chromatograph and a superconducting NMR spectrometer, while the modeling portion of the experiment can be carried out with a number of commercially available modeling packages.

The combination of force field and semi-empirical computational methodologies provides an effective way to qualitatively investigate mechanistic details of the asymmetric Diels–Alder reaction. It is possible to extend the modeling investigation beyond a simplistic consideration of the starting materials. MOPAC calculations can give transition state geometries that are very close to those produced by much higher level techniques, effectively illustrating the details such as the asynchronous formation of the new σ-bonds. Orbital calculations offer an explanation of the *endo/exo* selectivity, while an exploration of transition state conformational space helps to explain the selectivity enhancement of the Lewis acid system. By discovering these reaction

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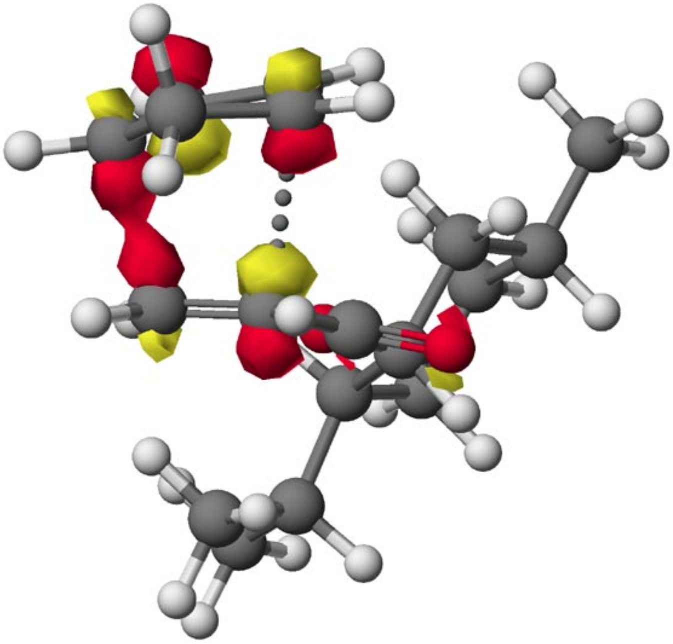

FIGURE 5. HOMO OF A TRANSITION STATE LEADING TO THE FORMATION OF 2B.

features, students naturally begin designing new systems which test their theories and give better selectivities.

Undergraduate students at the Sophomore or Junior level can participate fully in exploring computational problems of this sort. In doing so, they begin to realize the purpose and power of conceptual models of structure and reactivity. Within the framework of a laboratory experiment, students can begin to envision the excitement and demands of true chemical research. Molecular modeling is an excellent venue for encouraging this process.

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