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Origins of Stereoselectivity in Intramolecular Diels−Alder Cycloadditions of Dienes and Dienophiles Linked by Ester and Amide Tethers

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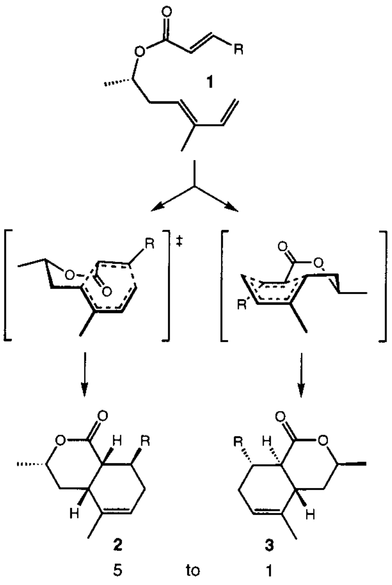
B3LYP/6-31+G(d) calculations of structures and relative energies for competing transition states for intramolecular Diels−Alder reactions of substituted 3,5-hexadienyl acrylates and acrylamides show that boatlike conformations are sometimes favored in the forming ring that includes the tether.

The intramolecular Diels−Alder (IMDA) reaction has been applied to the stereocontrolled synthesis of many complex natural products.[1] Recent investigations of IMDA-based routes to the novel diterpene eleutherobin showed that IMDA reactions of substituted 3,5-hexadienyl acrylates (**1**, Scheme 1) display a preference for products derived from transition states in which the tether-containing ring system prefers a boatlike conformation.[2,3] It was proposed that this preference results from relatively poor orbital overlap in the ester functionality of the alternative chairlike transition states.[2] The competing boat- and chairlike transition states for this process were therefore examined computationally.

All calculations were performed with the GAUSSIAN 98 program.[4] Geometries were optimized at the B3LYP/6-31+G(d) level, which has been shown to be extremely effective for describing structures and energetics for pericyclic reactions.[5] All structures were characterized by frequency calculations at the B3LYP/6-31+G(d) level, and zero-point energy corrections (unscaled) from these calculations are included in the reported enthalpies. Free energies were also computed at 423 K, the temperature at which the experiments in ref 2 were performed, and these are included in Figures 1, 2, 4, and 5.

Scheme 1



Geometries of the four diastereomeric transition states for the IMDA reaction of ester **1** (R = Me) are shown in Figure 1. Each of these four transition states is asynchronous with bond formation at the β-position of the enone preceding that at the α-position. The average forming bond length is 2.3 Å, with the α bond 0.3−0.7 Å longer than the β bond. Overall, the computed forming and breaking bond lengths are reasonable for Diels−Alder reactions.[5a]

Relative enthalpies and free energies for these transition states are also shown in Figure 1. Endo geometries are favored over exo geometries, and boatlike conformations are favored over chairlike conformations. The preference for the boatlike conformation is somewhat greater than the endo preference.[6] These results correlate nicely with the experimentally observed distribution of products arising from IMDA reaction of **1** (Scheme 1, R

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(2) Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett.* **2000**, *2*, 1835−1837.

(3) Similar systems have been studied experimentally and reported in the course of this work: (a) Kim, P.; Nantz, M. H.; Kurth, M. J.; Olmstead, M. M. *Org. Lett.* **2000**, *2*, 1831−1834. (b) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, ASAP.

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(6) Preliminary calculations at the B3LYP/3-21G level overestimated the stabilization afforded the endo transition states due to secondary orbital overlap (this effect was apparent in C(carbonyl)−C(3-position of diene) distances that were approximately 0.3 Å shorter than in the corresponding B3LYP/6-31+G(d) structures) and were therefore unable to reproduce the experimentally determined product distribution.

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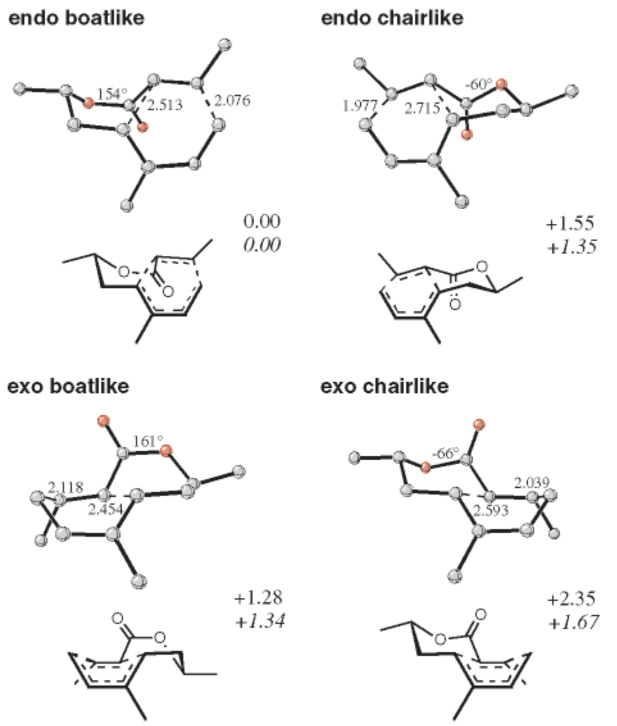

Figure 1. Computed geometries (B3LYP/6-31+G(d)), relative enthalpies (normal type), and free energies (italics), both in kcal/mol, for transition states for competing intramolecular Diels−Alder cycloadditions. Forming carbon−carbon bond distances (Å) and ester (O=C−O−C) dihedral angles are shown for each. Hydrogen atoms have been removed for clarity.

= ^{i}Pr): a 5 to 1 mixture of the products arising from the preferred endo boatlike transition state (**2**) and the exo boatlike transition state (**3**) is observed.[2] A small amount of a third product was also observed, and the identity of this product can be assigned as arising from the endo chairlike transition state. No products of the exo chairlike pathway were observed, consistent with the fact that this transition state is considerably higher in energy than the endo boatlike transition state.

The selectivity for boatlike transition states can be traced to several factors. First, as noted earlier,[2] the ester moieties in the boatlike transition states are considerably closer to the preferred planar s-cis conformation (26° and 19° from planarity; see Figure 1) than are those of the chairlike transition states (60° and 66° from planarity). The orbital overlap between the carbonyl and the oxygen p-type lone pair of the ester group is maximized in the planar conformation. Rotation to a perpendicular conformation requires approximately 10−13 kcal/mol. For comparison, the difference between boat and chair cyclohexane is 5−6 kcal/mol,[7] so it is possible that distorting the ester moiety from planarity is energetically more costly than assuming a boatlike conformation, depending on the degree of nonplanarity of the ester.

As a model for these interactions, the conformational preference of tetrahydropyrone was examined (Figure 2). A half-chair conformation is preferred over a boat conformation, but the energy difference between the two is only 1 kcal/mol. The energy difference between the half-chair and boat cyclohexene (the transition state for

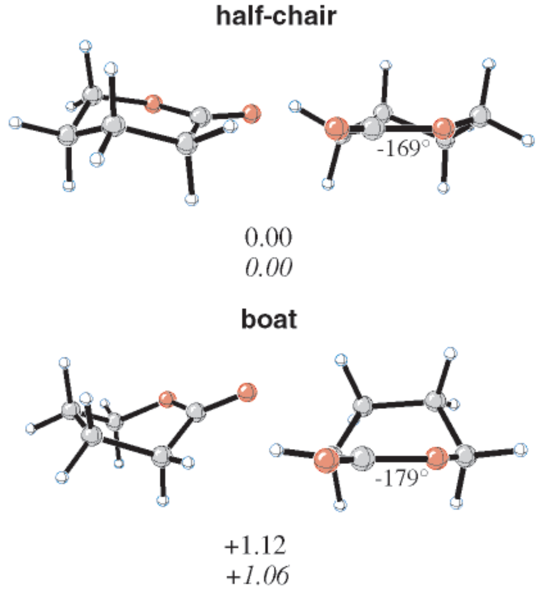

Figure 2. Computed geometries (B3LYP/6-31+G(d)), relative enthalpies (normal type), and free energies (italics) for half-chair and boat conformers of tetrahydropyrone. Two views of each are shown. O=C−O−C dihedral angles are shown explicitly.

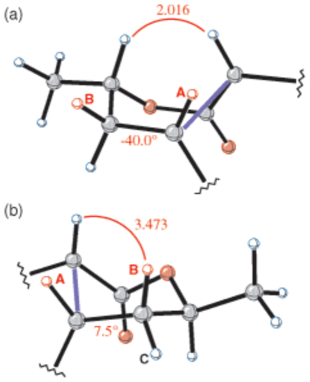

Figure 3. Tether-containing rings of the endo boatlike (a) and endo chairlike (b) transition states. Selected H−H distances (Å) and H−C−C−H dihedral angles are labeled.

interconversion of half-chairs) is computed to be 1.1 kcal/mol;[8] it appears that increased ester planarity (1° from planarity in the boat versus 11° from planarity in the half-chair; see Figure 2) can indeed compensate, at least in part, for the eclipsing interactions that destabilize the boat conformation of the unsaturated six-membered ring.

In addition, the energetic penalty associated with the flagpole interactions present in the boatlike transition states may be at least partly equaled by different unfavorable steric interactions in the chairlike transition states. The tether-containing rings of the endo boatlike and endo chairlike transition states are shown in Figure 3. While the boatlike transition state (Figure 3a) does possess a hydrogen−hydrogen flagpole interaction, the $C-H_A$ and $C-H_B$ bonds are almost perfectly staggered. In the chairlike transition state (Figure 3b) these C−H bonds are nearly eclipsed. This arrangement also leads to closer contacts between H_C and the remainder of the

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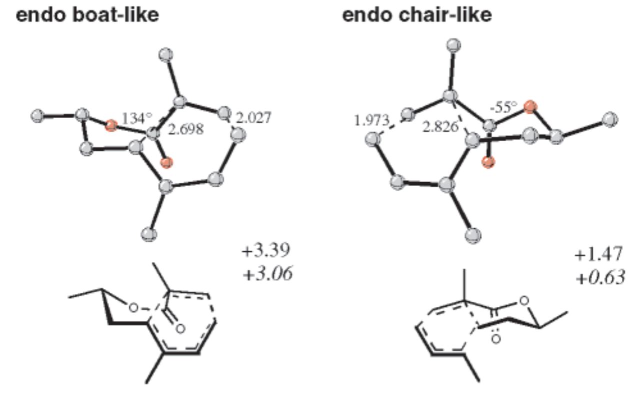

Figure 4. Computed geometries (B3LYP/6-31+G(d)), enthalpies (normal type), and free energies (italics) for transition states with internal methyl substituents. Forming carbon−carbon bond distances (Å) and ester (O═C−O−C) dihedral angles are shown for each. Hydrogen atoms have been removed for clarity.

ring system for the chairlike transition state compared to the boatlike transition state. The chairlike transition state also has a relatively weak 1,3-diaxial interaction.

To better quantitate the importance of ester overlap to the preference for boatlike transition states, several additional model systems were examined. Optimizations of methyl formate in which the ester dihedral angle was constrained to be 154° (boatlike) or −60° (chairlike) showed that the ester with the boatlike dihedral angle is 3 kcal/mol more stable than the one with the chairlike dihedral angle. However, analogous calculations on methyl propenoate—which preserves the hydrogen−hydrogen flagpole interaction present in the actual transition states—showed that the structure with the boatlike dihedral angle is actually disfavored by 0.8 kcal/mol over the chairlike alternative in this system. These results suggest that while improved ester overlap is responsible for much of the boatlike preferences in the IMDA transition states, other factors, such as the steric interactions described above and related interactions discussed previously by Roush[8] and Reissig[9] for 1,7,9-decatrien-3-ones, are operating here as well. Roush previously noted that ketones prefer an eclipsed conformation of the O═C−C−C unit, to a lesser extent, however, than the O═C−O−C eclipsed preference in esters.[8]

Not surprisingly, the preference for boatlike transition states is dependent on the nature of the substituent at the α-position of the ester. Computations on the endo boatlike and endo chairlike transition states with a methyl group at the α-position (these transition states are regioisomers of those discussed above; see Figure 4) show that the increased flagpole interaction caused by this methyl group abolishes the preference for the boatlike structure.[10]

Enhanced selectivity is predicted for amide tethers. The barriers to rotation about peptide bonds are generally 18−22 kcal/mol.[7] In the endo chairlike transition state for the amide tethered IMDA (Figure 5), the amide is rotated 59° out of planarity compared to 31° out of planarity in the endo boatlike transition state. The boatlike transition state is favored in this case by approximately 8 kcal/mol over the chairlike transition state, compared to a preference of only 1.5 kcal/mol for the corresponding esters.

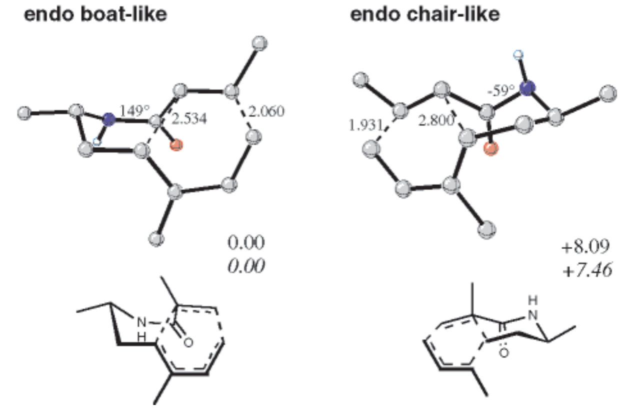

Figure 5. Computed geometries (B3LYP/6-31G(d)), enthalpies (normal type), and free energies (italics) for intramolecular Diels−Alder reactions with amide tethers.

Martin et al. reported a synthetic strategy for alkaloids that depends on an intramolecular hetero-Diels−Alder reaction with an amide tether.[11] Their AM1 and MM2 calculations showed that boat transition states are favored and that a major reason is that the amide group can maintain near-planarity.[11] B3LYP/3-21G single point energy calculations on geometries obtained from an MM2 force field we developed have also predicted preferences for boatlike transition states in related systems.[3b,12]

In conclusion, we have examined the structures of competing chairlike and boatlike transition states for IMDA reactions of substituted 3,5-hexadienyl acrylates and acrylamides. The expected flagpole interactions are observed in the boatlike transition states, but these interactions are counterbalanced by alternative steric repulsions and poorer orbital overlap in the ester and amide moieties of the chairlike transition states. The selectivity favoring products derived from boatlike transition states is predicted to be considerably larger for cases with amide rather than ester tethers. This prediction will be tested experimentally.

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[10] The endo chairlike transition state with an α-methyl group (Figure 4) is lower in energy than the isomeric transition state with a *β*-methyl group (Figure 1). This is likely a result of a combination of subtle steric and electronic effects and is consistent with the experimentally determined rates of methyl-substituted acrylates and acrylonitriles; see: Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16−33.

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