Origins of Boat or Chair Preferences in the Ireland−Claisen Rearrangements of Cyclohexenyl Esters: A Theoretical Study

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The relative energies of the chair and boat transition states of a variety of Ireland−Claisen rearrangements were obtained by B3LYP/6-31G* calculations. Theoretical results are in good agreement with experimental data and provide a quantitative analysis of the origins of boat preferences that are observed in some of these reactions.

Introduction

The energetic preference for chair transition states (TSs) in [3,3]-sigmatropic shifts is one of the bedrocks of stereoselectivity predictions (Figure 1). Doering and Roth[1] and Hill and Gilman[2] elegantly demonstrated that the preference for a chairlike transition state in the acyclic Cope rearrangement is similar in magnitude to the chair−boat free energy difference in cyclohexane, about 6 kcal/mol.[3] The Claisen rearrangement also exhibits a well-established, but smaller, preference for chairlike transition states. For example, the stereoselectivity of the Claisen rearrangement of crotyl propenyl ether indicates that the energies of the chair and boat transition states differ by only 3 kcal/mol.[4]

Computational evidence corroborates these experimental measurements. The Cope rearrangement of 1,5-hexadiene was calculated to have an 11.4 kcal/mol preference for the chair transition state (using (6,6)-CASPT2/6-31G*).[5] This value is in excellent agreement with the measured difference of 11 kcal/mol for the activation enthalpy of the Cope rearrangement of 1,1-dideuterio-1,5-hexadiene (chair, $\Delta H^{\ddagger} = 33.5 \pm 0.5$ kcal/mol, $\Delta S^{\ddagger} = -13.8 \pm 1$ eu[6]) and that found indirectly for
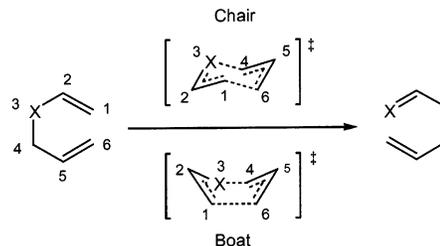
FIGURE 1. Chair and boat transition states of the Cope (X = CH₂) and Claisen (X = O) rearrangements.

the boat ($\Delta H^{\ddagger} = 44.7 \pm 2.0$ kcal/mol, $\Delta S^{\ddagger} = -3.0 \pm 3.6$ eu[7]). Woodward and Hoffmann proposed that the preference for chairlike geometries over boatlike geometries in [3,3]-sigmatropic shifts results from unfavorable secondary orbital interactions between orbitals on atoms 2 and 5 in the boat transition state.[8]

Despite the overwhelming evidence in favor of the chair transition state, occasional reports have surfaced of reaction stereoselectivities that are best explained by a boat transition state. One significant example is the Ireland−Claisen rearrangement of silyl ketene acetal systems, a particularly useful variation of the Claisen rearrangement. While the acyclic reactants show a small preference for the formation of products that are consistent with a chair transition state[9] (Figure 2), rearrangements of cyclohexenyl silyl ketene acetals appear to

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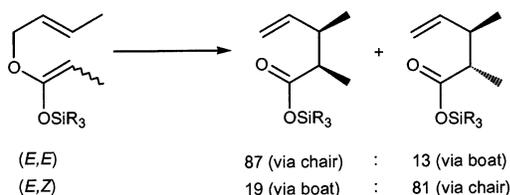(5) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2001**, *123*, 4069−4072.

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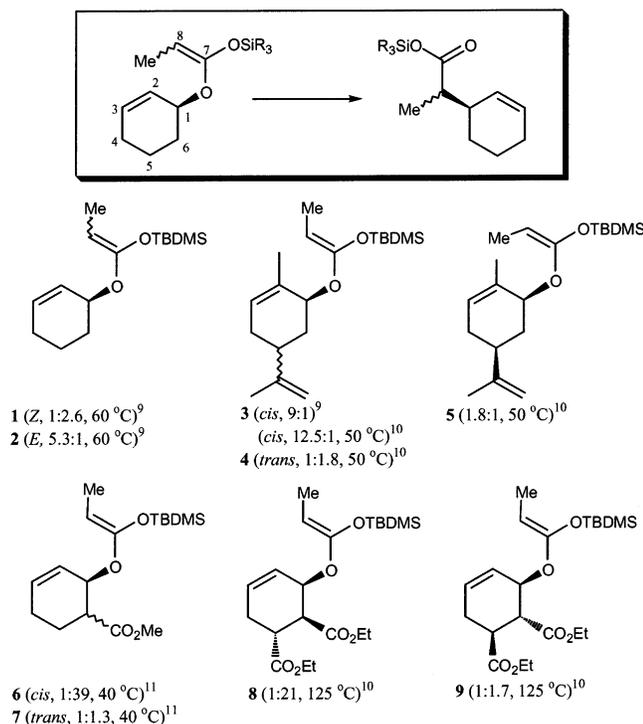(7) (a) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 5119. (b) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7147.
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FIGURE 2. Stereochemistries of Ireland–Claisen rearrangements of acyclic substrates.

FIGURE 3. Chair:boat stereoselectivities of Ireland–Claisen rearrangements of cyclohexenyl silyl ketene acetals. TBDMS = *tert*-butyldimethylsilyl.

involve either chair or boat transition states. Figure 3 summarizes results from the Ireland and Neier laboratories involving cyclohexenyl vinyl ethers. Throughout the discussion, the experimentally determined diastereoselectivities are interpreted as having a direct correlation with the relative stabilities of chair versus boat transition states in the Claisen rearrangement. Some cases are interpreted to favor boat transition states (**1** and **6**), others favor the chair (**2** and **3**), and others give no selectivity (**4** and **7**).

The chair and boat transition-state models proposed by Ireland and Neier are illustrated in essentially their original form, in Figure 4.[9,10] For compounds **1** and **2**, Ireland proposed that the cyclohexenyl moiety adopts a chair conformation (shown in **10** and **11**) that is related to what we refer to later as "*syn*" since calculations show this chair to be flattened nearly to a half-chair conformation. In the *syn*-chair transition states of both **1** and **2**, an unfavorable interaction between the silyloxy group and the axial C_5H of the six-membered ring is present (**10**). The *syn*-boat transition state (**11**) relieves the steric interaction between the silyloxy and axial CH, but this

is replaced by a destabilizing repulsive interaction between the (*E*)-allylic methyl group and the axial ring proton. On the other hand, no repulsive interactions are present in the *syn*-boat TS of the *Z* isomer (not shown here). Experimentally, a chair transition state is preferred (5.3:1) for (*E*)-**2**, while a boat transition state is preferred (chair:boat = 1:2.6) for (*Z*)-**1**.

Ireland and Neier also studied more complex derivatives (**3**–**5**, Figure 3) that have an isopropenyl substituent on the cyclohexene ring. According to Ireland, when the isopropenyl group is *cis* to the vinyl ether, the cyclohexenyl moiety is forced to adopt a boat conformation that we refer to later as "*anti*" (shown in **12** and **13**). The *anti* conformation is favored for compounds **3** and **5** because it avoids severe interaction of an axially oriented isopropenyl group that would be present in a *syn* conformation. Experimentally, it was found that the *cis* isomers **3** and **5** prefer to undergo [3,3] shifts via chair transition states (12.5:1 and 1.8:1, respectively) while the *trans* isomer **4** prefers to react via a boat transition state (1:1.8).[10]

Neier also developed a new tandem Diels–Alder reaction/[3,3]-sigmatropic shift sequence involving butadienyl-substituted ketene acetals.[10,11] Compounds **6** and **7** are the corresponding intermediates formed from *endo* and *exo* Diels–Alder reactions. The *endo* isomer **6** shows a large preference for a boat transition state (chair:boat =1:39). The *exo* Diels–Alder product **7** rearranges unselectively (1:1.3). Neier proposed that, for the *endo* reactants such as **6**, a half-chair arrangement is preferred for the cyclohexenyl moiety (**14** and **15** in Figure 4). For the boat transition state, there is no repulsion between the ring proton of the cyclohexene and the bulky TBDMSO group, while there is severe repulsion between these in the chair transition state.[11]

These models and rationalizations raised interesting questions about the details of the transition structures of these reactions, and the quantitative significance of the interactions proposed. We have employed quantum mechanical methods to elucidate the effects of substituents on the chair and boat transition states, and specifically to understand the conformation of the cyclohexenyl moiety and its role in controlling stereoselectivity.
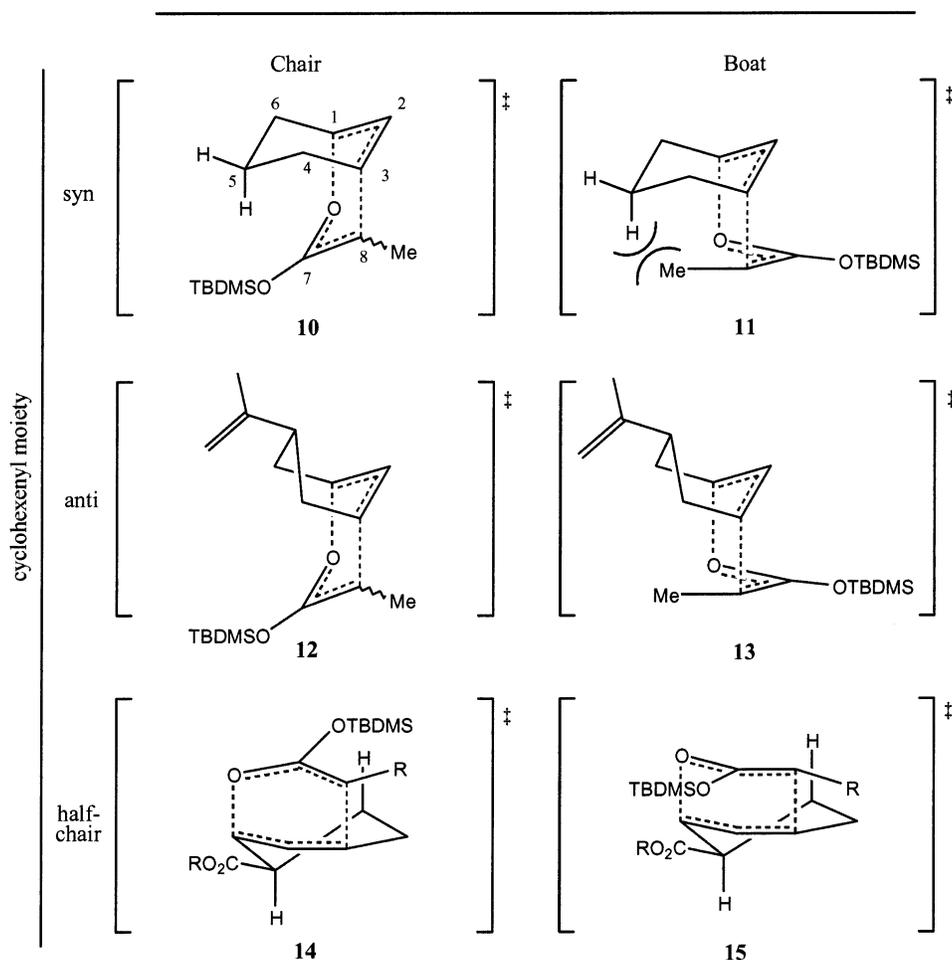
Results and Discussion

Calculations were carried out with Gaussian98[12] using the RB3LYP functional and the 6-31G* basis set. Vibrational analysis was performed at each stationary point to establish its identity as an energy minimum or a transition structure, and to obtain zero-point energy

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Transition State

FIGURE 4. Previously proposed chair and boat transition-state models for the Ireland–Claisen rearrangements of cyclohexenyl silyl enol ethers.

corrections. This method has been found to give activation energies close to experimental results for [3,3]-sigmatropic shifts such as the parent Claisen rearrangement and a variety of Cope rearrangements.[13]

Table 1 presents the computed energies of the four transition states (*syn*-chair, *syn*-boat, *anti*-chair, *anti*-boat) for several Claisen rearrangements relevant to those studied by Ireland and Neier. The calculated transition states for cyclohexenyl ketene acetal (**19**; see Figure 5) serve as representative examples of the four possible conformations for the Claisen rearrangement. The B3LYP geometries are given along with line drawings in the conventional representation of chair and boat Claisen transition states. A methyl group is substituted for the TBDMS group that is generally used in the experiments. The optimized geometries in Figure 5 closely resemble the conformations proposed earlier by Ireland, **10**–**13** shown in Figure 4; the most notable exception is that only the CH$_2$ is significantly out of the approximate plane of the other five carbons in the flattened six-membered chair. This moiety resembles the

half-chair transition state for a cyclohexane chair-to-boat ring flip; consequently, we use *syn* and *anti* to designate the position of the out-of-plane CH$_2$ with respect to the Claisen transition-state moiety. The geometries of the cyclohexenyl moiety in Figure 5 involve a different half-chair conformation than the conformations that Neier proposed earlier (**14** and **15**).

For compound **19**, the *syn*-boat transition state is lowest in energy (see Table 1 and Figure 5). The steric repulsion between the methoxy group and the axial CH at C$_5$ is avoided in the *syn*-boat. There is repulsion between the methoxy group and the axial C$_5$H in the *syn*-chair or axial C$_4$H and C$_6$H in the *anti*-chair; both transition states are 0.9 kcal/mol higher in energy than the *syn*-boat.

Figure 6 shows the lowest energy transition states for model systems **20**–**24**. Compound **20** is a simplified model for **1** and other reactants with a methyl group *cis* to the trialkylsiloxy in experimentally studied systems. Methoxy is substituted in the computational models. The conformation of the methoxy was explored for 13 of the transition states; in each case the conformer corresponding to the favored *syn* conformer of the ester product is usually ~2 kcal/mol lower in energy than the conformer corresponding to the *anti*-ester.

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TABLE 1. Computed Activation Barriers for Ireland–Claisen Rearrangements[a]

			ΔH (ΔH_{rel}) (kcal/mol)			
compd	substituent	model for	**chair**		**boat**	
16	X = H		**26.6 (0.0)**		36.9 (10.3)	
17	X = OMe		**18.0 (0.0)**		20.3 (2.3)	
			syn-chair	*anti*-chair	*syn*-boat	*anti*-boat
18	R = H		28.9 (0.6)	**28.3 (0.0)**	29.8 (1.5)	31.2 (2.9)
19	R_7 = OMe		22.9 (0.9)	22.9 (0.9)	**22.0 (0.0)**	23.7 (1.7)
20	R_7 = OMe, R_{8E} = Me	1, 3, 4, 6, 9	21.8 (1.0)	22.0 (1.2)	**20.8 (0.0)**	22.2 (1.4)
21	R_7 = OMe, R_{8Z} = Me	2, 5	24.2 (1.3)	**22.9 (0.0)**	25.1 (2.2)	24.3 (1.4)
22	R_2 = Me, R_7 = OMe	3, 5	**23.4 (0.0)**	23.5 (0.1)	23.5 (0.1)	25.0 (1.6)
23	R_{5C} = Me, R_7 = OMe	3, 5, 9		**23.4 (0.0)**	27.4 (4.0)	24.0 (0.6)
24	R_{5T} = Me, R_7 = OMe	4, 8	23.1 (1.0)	24.9 (2.8)	**22.1 (0.0)**	25.5 (3.4)
25	R_{6C} = CO_2Me, R_7 = OMe	6, 8	24.4 (2.0)	25.8 (3.4)	**22.4 (0.0)**	24.2 (1.8)
26	R_{6T} = CO_2Me, R_7 = OMe	7, 9	23.8 (1.1)	24.0 (1.3)	**22.7 (0.0)**	24.2 (1.5)
27	R_2 = R_{5C} = R_{8E} = Me, R_7 = OMe	3		**(0.0)**		(1.5)
28	R_2 = R_{5T} = R_{8E} = Me, R_7 = OMe	4	**(0.0)**		**(0.0)**	

[a] Relative energies for each reaction are given in parentheses. The lowest energy transition state is shown in bold.
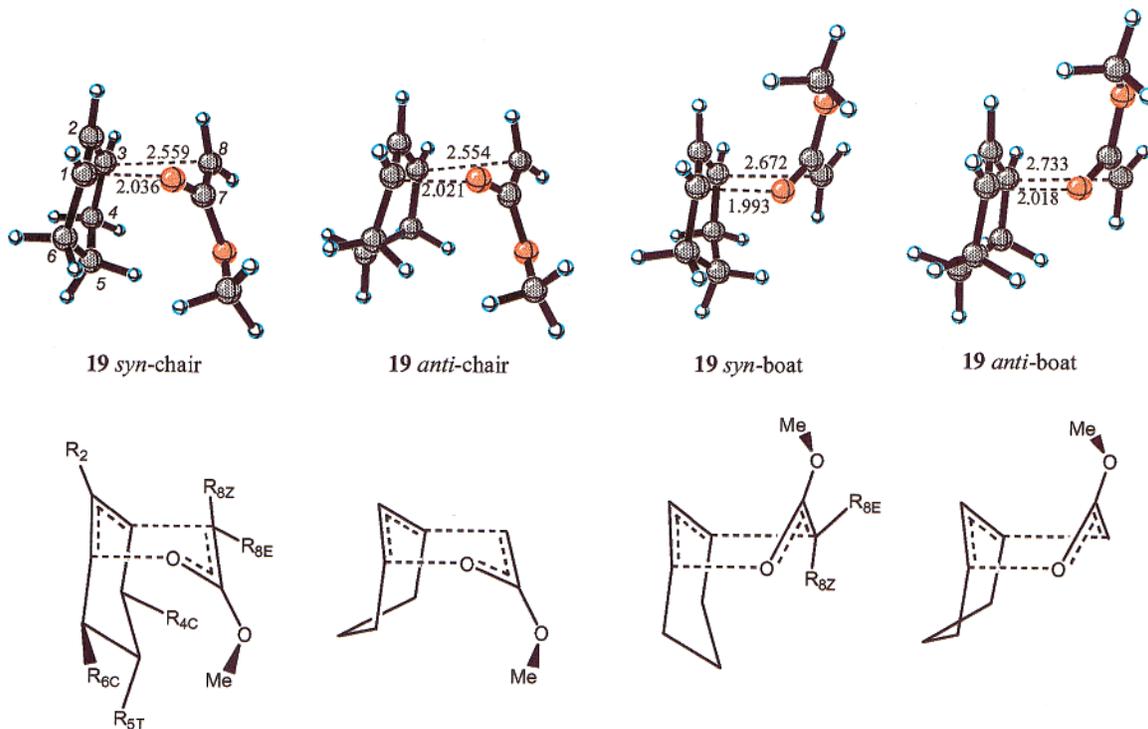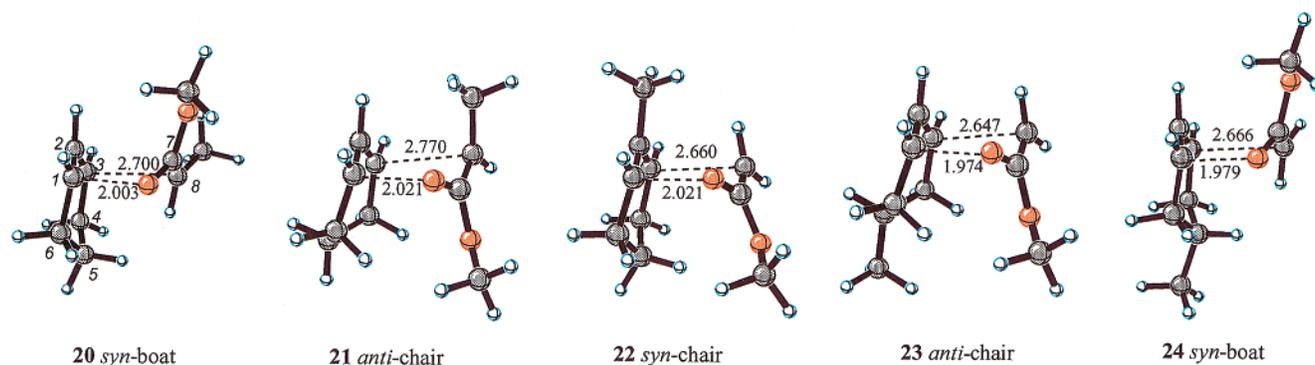

FIGURE 5. B3LYP/6-31G* transition states for Claisen rearrangements of cyclohexenyl methyl enol ether **19**. Partial bond lengths in Angstroms.

Calculations support Ireland's original proposal to explain why **1** exhibits a preference for a boat transition state. The *syn*-boat transition state of **20** avoids the destabilizing interactions between the cyclohexenyl ring hydrogens and both the R_7-OMe and R_{8E}-Me groups. The *syn*-boat is favored over the *syn*-chair and *anti*-chair transition states by 1.0 and 1.2 kcal/mol, respectively. By shifting the R_{8E}-Me group to the R_{8Z} position (as in

compound **21**), the boat versus chair preference is reversed. The *syn*-boat transition state is destabilized by repulsion between the R_{8Z}-Me and C_5H; consequently, the *anti*-chair transition state is 1.4 and 2.2 kcal/mol lower in energy than the *anti*-boat and *syn*-boat transition states. The preference of **21** for a chair transition state matches Ireland's observation that **2** primarily undergoes the Claisen rearrangement via a chair conformation.

FIGURE 6. Preferred B3LYP/6-31G* transition states for systems **20**−**24**.

Ireland's and Neier's experimental results for **3** are consistent with chair:boat transition state ratios of 9:1 and 12.5:1, respectively.[9,10] Compound **3**, which is substituted at R_2, R_{5C}, and R_{8E}, is significantly more complicated than **1** or **2**, because two additional substituents have been added to the cyclohexenyl ring. To clarify the relative importance of these substituents on the preference for a chair transition state, we performed calculations on individual model systems that included only one substituent. The relevant model systems for **3** are **20** (R_{8E}-Me, discussed above), **22** (R_2-Me), and **23** (R_{5C}-Me).

For **23**, a methyl group was used to model the effect of the isopropenyl substituent at R_{5C}. With a *cis*-C_5-methyl, both *syn* conformations are dramatically disfavored because the methyl group is forced to adopt an axial orientation. In fact, the *syn*-chair transition state cannot be located, because the axial C_5-methyl is too close to the methoxy substituent. On the other hand, the *anti*-chair and *anti*-boat conformations relieve the strain introduced by an axial methyl group and differ by only 0.6 kcal/mol. For model system **22** (in which a C_2-Me is present on the cyclohexenyl ring), the *anti*-boat transition state is approximately 1.5 kcal/mol higher in energy than the remaining three transition states. Now, combining the substituent information provided by systems **20**, **22**, and **23**, we conclude that the R_2-Me leads to a strong preference for a chair conformation, outweighing the small preference for the boat produced by the R_{8E}-Me. This supports the experimental observation that **3** undergoes the Claisen rearrangement preferably via a chair transition state. The prediction that the *anti*-chair conformation should be the most favorable is further confirmed by **27**, in which all three substituents are present in the same system.

In the case of compound **4**, Neier showed that the reaction is relatively unselective; a boat transition state is preferred by a ratio of only 1.8:1. The only difference between **3** and **4** is the placement of the C_5-methyl group. For this system, C_5-methyl is in the *trans* position, and the relevant substituent effects are modeled by **20** (R_{8E}-Me), **22** (R_2-Me), and **24** (R_{5T}-Me). The R_{5C}-Me group strongly favors *anti* conformations because the axial methyl orientation can be avoided, and the R_{5T}-Me strongly favors *syn* conformations for the same reason. Consequently, the R_{5T}-Me reinforces the R_{8E}-Me substituent effect in favoring the *syn*-boat transition state. When all three substituent effects are combined in

system **28**, the *syn*-chair and *syn*-boat transition states are nearly isoenergetic, in accord with the lack of selectivity seen in the experimental example.

In analyzing the results for **5**, the model systems **21** (R_{8Z}), **22**, and **23** should be considered. Both **21** and **23** prefer the *anti*-chair conformation, while **22** has nearly equal preference for the *syn*-chair, *anti*-chair, and *anti*-boat conformations. Experimentally, **5** is found to be unselective; the experimentally observed ratio (1.8:1) is interpreted as a slight preference for a chair relative to a boat transition state. Although the calculations on the model systems do correctly predict the preference for a chair transition state, they do not fully account for the lack of selectivity observed in this system.

Model systems **20** (R_{8E}-Me) and **25** (R_{6C}-CO$_2$Me) are relevant to compound **6**. Results for **25** illustrate that *syn* conformations of the cyclohexenyl ring allow the methoxycarbonyl group to adopt an equatorial position. The *syn*-boat transition state of **25** is 2.0 kcal/mol lower in energy than the *syn*-chair because the R_7-OMe group avoids steric interference with the axial hydrogens (C_5H) of the cyclohexenyl moiety. The additional effect of the R_{8E}-Me group (see **20**) further enhances the preference for the *syn*-boat conformation, confirming the experimental observation that **6** has a large preference for rearrangement by a boat transition state (chair:boat = 1:39).

Compound **7**, which is the least selective of the compounds studied experimentally, is modeled by **20** and **26**. Both **20** and **26** favor the *syn*-boat transition state. Similar to **5**, the calculations on the model systems do correctly predict the preference for a boat transition state, but do not fully account for the lack of selectivity observed in this system.

In **8**, model systems **20**, **24**, and **25** show that there is a significant additive preference for the *syn*-boat transition state. The *syn* conformation of the cyclohexenyl ring allows the R_{5T}-CO$_2$Et and R_{6C}-CO$_2$Et to be oriented in an equatorial fashion. As in many of the examples discussed above, the boat conformation effectively minimizes steric crowding of the R_7-OMe and R_{8E}-Me with the cyclohexenyl ring substituents. The large preference for the *syn*-boat transition state matches the high chair:boat selectivity (1:21) observed experimentally for **8**.

For **9**, our models (**20**, **23**, and **26**) predict a slight preference for the *syn*-chair transition state relative to
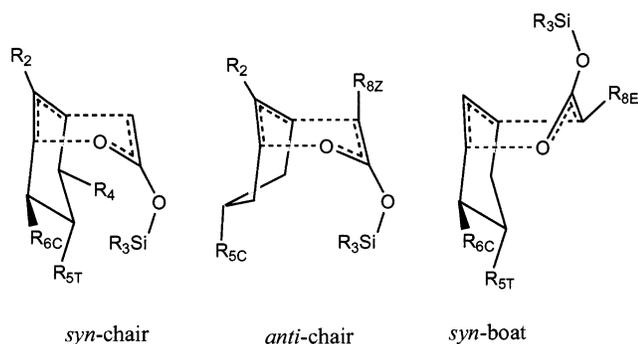
FIGURE 7. Substituents that favor various transition states.

the *syn*-boat or *anti*-boat, whereas a slight preference for the boat is experimentally observed (1:1.7).

The model that emerges from these calculations is a hybrid of that proposed by Ireland and by Neier. Figure 7 shows idealized transition-state models and the substituent patterns that favor a particular transition-state geometry. The cyclohexenyl system inherently favors the *anti*-chair, and in the absence of a substituent at C_2, the *anti*-chair and *syn*-boat tend to be the lowest energy transition states. Addition of a C_2 substituent imposes a chair preference, and selectivity becomes especially high when the *anti*-chair is favored by a *cis* C_5 group. With a *trans* C_5 group, the *syn* conformation becomes more favorable, which destabilizes the chair transition state

and leads to low selectivity among the *syn*-chair and *syn*-boat transition states.

Conclusion

The quantum mechanical calculations on model systems have provided explanations of the stereoselectivities of Ireland−Claisen rearrangements of cyclohexenyl silyl enol ethers. Four transition states are generally found, with chair or boat conformations involving the allyl and allyloxy moieties of the transition state, and either *syn* or *anti* arrangements of the half-chair cyclohexenyl moiety. Substituents on the cyclohexenyl ring may alter the preference for *syn* or *anti* transition states; steric interactions between groups on the allyloxy moiety and the cyclohexenyl ring influence whether the inherently preferred chair, or a sterically favored boat, is favored.

Supporting Information Available: Computer printout. This material is available free of charge via the Internet at http://pubs.acs.org.

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