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Computational Study of Factors Controlling the Boat and Chair Transition States of Ireland−Claisen Rearrangements

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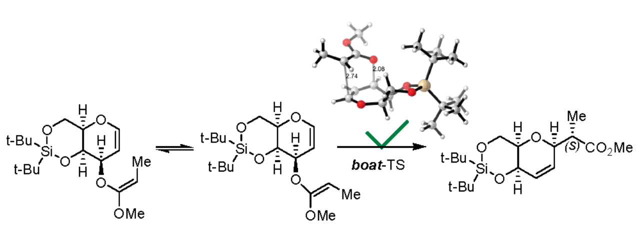

The origins of the boat transition state preference in the Ireland−Claisen rearrangements studied experimentally by Kishi and co-workers have been explored computationally with Density Functional Theory. Steric interactions in the chair transition states were identified as the principal reason for the boat transition state preference.

The Ireland−Claisen reaction[1] has found wide use in synthesis. It belongs to the class of [3,3]-sigmatropic rearrangements, involving the rearrangement of a silyl ketene acetal. It is widely accepted that chair transition states are generally preferred over the boat transition states in [3,3]-sigmatropic shifts (Figure 1). This has been demonstrated by Doering and Roth[2] and Hill and Gilman[3] for the acyclic Cope rearrangement, for instance. Their findings suggested a 6 kcal/mol preference for the chair transition state, mirroring the free energy difference between the chair and boat conformers of cyclohexane.[4] This has been confirmed by computational studies. The chair transition state in the Cope rearrangement of 1,5-hexadiene was calculated to be 11.4 kcal/mol lower than the boat transition state using (6,6)-CASPT2/6-31G(d),[5a] consistent with the corresponding experimental results (chair, $\Delta H^{\ddagger} = 33.5 \pm 0.5$ kcal/mol;[6] boat, $\Delta H^{\ddagger} = 44.7 \pm 2.0$ kcal/mol[7]). Similarly, the Claisen rearrangement of crotyl propenyl ether also prefers the chair transition state, but the preference for the chair is only 3 kcal/mol.[8,9]

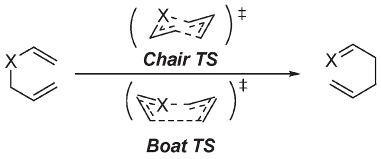

FIGURE 1. Possible transition states for Cope (X = CH_2) and Claisen (X = O) rearrangements.

In contrast to the acyclic systems described above, the preference for chair transition states in cyclic systems may be much less pronounced, and can even lead to the chair transition state being disfavored as a result of steric hindrance.[10] This has been demonstrated by several groups,[11] for instance in rearrangements of pyranoid and furanoid glucal systems.[11] The groups of Neier, Houk, and Aviyente investigated this in detail with both experimental and computational studies,[12] extending the transition state proposals by Ireland[13] (the latter are shown in Figure 2).

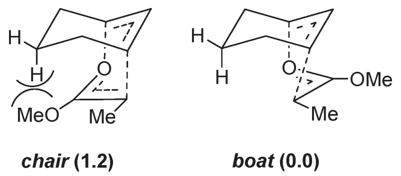

FIGURE 2. Irelands's proposed chair and boat transition state models for an Ireland−Claisen rearrangement. Relative energies (kcal/mol) are given in parentheses.[13]

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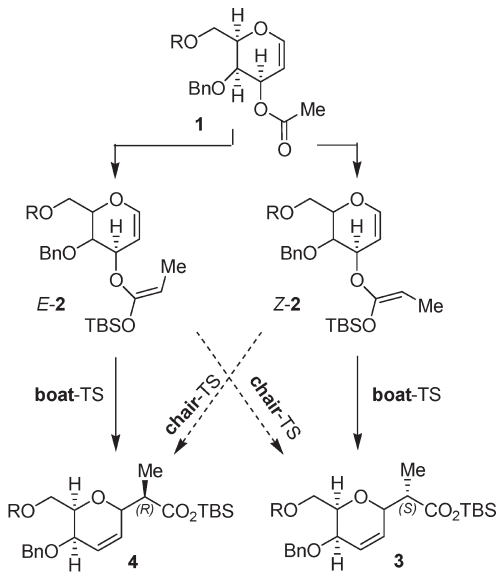
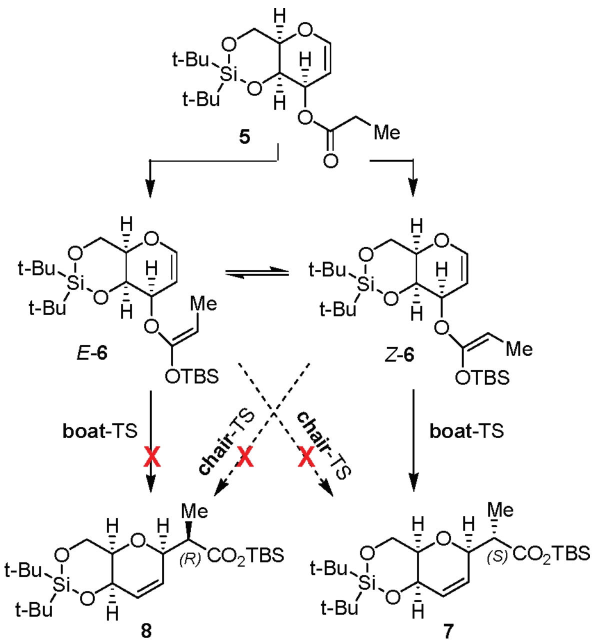
SCHEME 1. Pathways for the Conversion of 1 into 3 and 4[14]



SCHEME 2. Pathways for the Conversion of 5 into 7 and 8[14]



Some experimental studies support the existence of both chair and boat transition states; one of the most significant examples is the Ireland−Claisen rearrangement of cyclohexenyl silyl ketene acetals, which may follow either the boat or chair transition state, leading to moderate stereoselectivities.[11]

With an aim to improve the selectivity of the Ireland−Claisen rearrangement, Kishi and co-workers[14] recently performed experiments to favor further the boat transition state.[10,12] For this purpose, dihydropyran derivatives, such as **1** in Scheme 1, were synthesized and tested. The overall stereoselectivity of rearrangements was found to be largely consistent with the *E*/*Z* ratio of the produced enolate intermediate.[14] Experiments under conditions involving mainly intermediate *Z*-**2** led to **3** as the major product (8:1 ratio with **4**), where experiments via *E*-**2** gave predominantly **4** (5:1 ratio with **3**) at 80 °C.[14] This suggests that in both cases the major products arise from boat transition states (Scheme 1).

With the hypothesis that steric hindrance induced by the silyl moiety may improve selectivities, Kishi and co-workers prepared dihydropyran **5**. The corresponding silyl ketene acetal **6** reacted to form a single diastereomer **7** (see Scheme 2). Furthermore, the *E*-stereoisomer of the silyl ketene acetal (*E*-**6**) was partially recovered from the reaction mixture. The authors thus suggested that the Claisen rearrangement proceeds through *Z*-**6** but not through *E*-**6**, consistent with a mechanism that involves a boat transition state.[14]

We have performed computational studies[15,16] to examine the origins of modest stereoselectivity for the conversion of **1** to **3** and **4** (Scheme 1), and to understand the excellent stereoselectivity of the reaction of **5** to **7** (Scheme 2). For that purpose, model reactants **2′** and **6′** (models for **2** and **6**, respectively) were investigated. OR and BnO were simplified in model **2′**, and a methoxy group was used instead of the OTBS group in **6′**, shown previously to be a valid approach.[12] The Supporting Information describes additional computational models. Note, because of naming conventions, the *Z*-isomers of the experimentally investigated compounds correspond to the *E*-isomers of the computational models. For ease of comparison, we chose to use *Z**-**2′**, *E**-**2′** (for the models of *Z*-**2** and *E*-**2**) and *Z**-**6′**, *E**-**6′** (for the models of *Z*-**6** and *E*-**6**).

The lowest energy conformations[17] of the dihydropyran reactants, **2′**and **6′**, are half chairs, in which the C_1-C_2 bond is in the pseudoaxial and the C_3-O_4 bond is in the pseudoequatorial position (see Figure 3).[18] Reactant conformers that have the reverse arrangement, i.e., C_1-C_2 in the pseudoequatorial and C_3-C_4 in the pseudoaxial position, are ca. 3 kcal/mol higher in energy (see the SI).

The transition states for the rearrangements were subsequently calculated. The lowest energy conformers of chair and boat transition states for model **2′** are illustrated in Figure 4.[18] Those of model **6′** are shown in Figure 5. Table 1 summarizes the corresponding activation barriers at B3LYP/6-31+G(d).[16] The activation barriers at MO6-2X//B3LYP/6-31+G(d)[19] can be found in the Supporting Information.

Consistent with the experimental findings by Kishi and coworkers, our calculations predict the boat transition states to be preferred over the chair transition states for the rearrangements of *E**-**2′** and *Z**-**2′**. The principal reason for the boat-TS preference is the lower steric interaction between the OMe-substituents as indicated in Figure 4. To establish

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[14] Chen, C.; Namba, K.; Kishi, Y. *Org. Lett.* **2009**, *11*, 409–412.

[15] Frisch, M. J. et al. *Gaussian 03*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2004.

[16] Applying B3LYP/6-31+G(d) methodology, which was previously shown to be adequate, see: (a) Reference 12. (b) Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565. (c) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336–10337. (d) Goumans, T. P. M.; Ehlers, A. W.; Lammertsma, K.; Würthwein, E.-U.; Grimme, S. *Chem.—Eur. J.* **2004**, *10*, 6468–6475.

[17] Conformational search was done at the AM1 level of theory, using *SPARTAN*; Wavefunction, Inc. All obtained conformers within a 5 kcal/mol energy range were subsequently optimized with B3LYP/6-31+G(d) in Gaussian03.

[18] Figures created with: CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (http://www.cylview.org).

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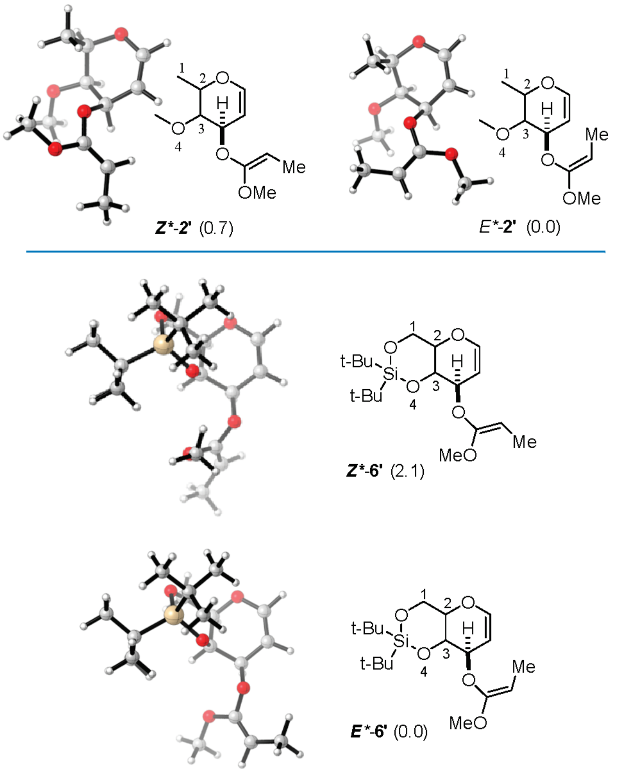

FIGURE 3. Model systems studied computationally. Relative enthalpy differences (ΔH in kcal/mol at 298 K) of *E*- and *Z*-isomers are given in parentheses, calculated with B3LYP/6-31+G(d).[17]

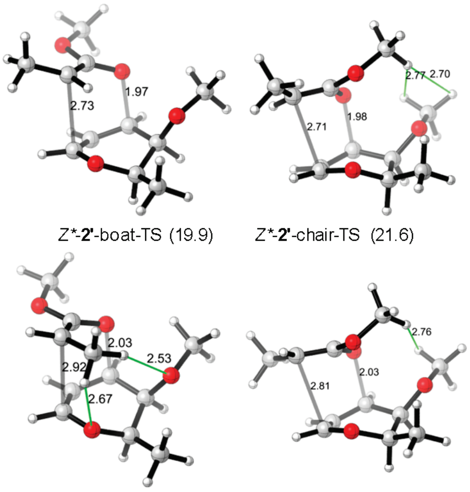

FIGURE 4. TSs for the rearrangements of **2′**. $\Delta H^{\ddagger}$ (in kcal/mol at 298 K) is given in parentheses, calculated with B3LYP/6-31+G(d).

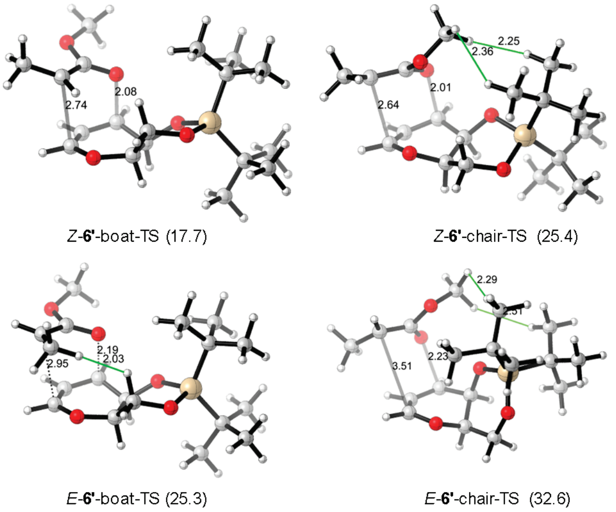

FIGURE 5. TSs for the rearrangements of **6′**. $\Delta H^{\ddagger}$ (kcal/mol) at 298 K is given in parentheses, calculated with B3LYP/6-31+G(d).

TABLE 1. Activation Parameters for Models 2′ and 6′ (in kcal/mol at 298 K) Calculated with B3LYP/6-31+G(d)[a]

TSs	$\Delta H^{\ddagger}$	$\Delta\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	$\Delta G^{\ddagger}_{sol}$
*Z**-**2**′-boat-TS	**19.9**	**0.0**	**20.5**	**0.0**	**20.6**
*Z**-**2**′-chair-TS	21.6	1.7	22.6	2.1	22.2
*E**-**2**′-boat-TS	21.6	1.7	22.6	2.1	22.4
*E**-**2**′-chair-TS	23.7	3.8	24.9	4.4	24.0
*Z**-**6**′-boat-TS	**17.7**	**0.0**	**18.2**	**0.0**	**18.2**
*Z**-**6**′-chair-TS	25.4	6.9	26.8	8.6	25.8
*E**-**6**′-boat-TS	25.3	6.8	25.7	7.5	25.2
*E**-**6**′-chair-TS	32.6	14.1	33.3	15.1	31.2

[a] $\Delta G^{\ddagger}_{sol}$ corresponds to the barriers in benzene at 353 K.

further that this repulsive interaction is crucial for the boat-TS preference, we calculated all TSs in the absence of methoxy groups. Those now resulted in a 0.8−1.3 kcal/mol preference of the chair TSs (see SI), supporting this steric hypothesis.

Turning to the sterically more encumbered model **6′**, it is apparent that the energy differences between boat and chair TSs increase substantially (Table 1). The preference for boat TSs is about 8 kcal/mol. The *tert*-butyl silyl groups increase the repulsive interaction with the methoxy group, causing structural distortions in the molecules. With the introduction of the silyl substituents, the ring C−O bonds' flexibilities are decreased (as compared to model **2′**) and forced into a more repulsive conformation. In the least favored *E**-**6′**-chair-TS the C−O ring substituents now adopt pseudoaxial positions in a twisted chair TS, which was already shown to be disfavored for the reactant conformers. This contributes further to the larger boat-chair TS energy gap.

These rearrangements are highly exergonic ($\Delta G_{rxn} = -34.6$ kcal/mol for *Z**-**6′**-chair, for example), showing that the rearrangement is irreversible.[20] Thus, the principal reason for the high stereoselectivity in the reaction of **6** is the large steric interaction in the chair-TSs and *E*-boat-TS. The *Z*-reactant isomer (*Z**-**6′**) will react via the most favorable boat-TS pathway. For the *E*-isomer, the low-energy rearrangement pathway is via the boat-TS, which is significantly disfavored compared to the *Z**-**6′**-boat-TS. However, the *E**-**6′**-boat-TS would lead to **8**—the stereoisomer opposite than observed experimentally (compare Scheme 2). This suggests that the *E* → *Z* isomerization, followed by reaction via *Z**-**6′**-boat-TS, is favored over the high-energy direct rearrangement to **8**.

This raises the question of the mechanism and facility of the *E*/*Z*-isomerization. Kishi and co-workers heated a

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(20) We calculated the silyl analogue of *E*′-6-boat-TS with OTMS instead of OMe. The activation barrier of the rearrangement is 25.8 kcal/mol and the free energy of reaction is −32.9 kcal/mol, indicating that the OMe model is adequate.

mixture of "crude" silyl ketene acetal containing *E*- and *Z*-isomers for 3 d at 80 °C. Complete isomerization to the *Z*-isomer was indeed observed.[14] Our calculation gives an unfavorable barrier of $\Delta G^{\ddagger} = 51.5$ kcal/mol ($\Delta H^{\ddagger} = 51.0$ kcal/mol) at B3LYP/6-31+G(d) for the $E \rightarrow Z$ isomerization of **6′**, suggesting that it is only feasible if catalyzed. Tanaka and Fuji[21] have previously studied the isomerization of a silyl ketene acetal derived from methyl phenylacetate. They have shown that in the presence of LiCl (which is formed during the preparation of a silyl ketene acetal), the *Z*-isomer becomes the thermodynamically preferred species. Using ^{1}H NMR spectroscopy over a course of 40 h, they established that *E*/*Z*-isomerization is a facile process at 20 °C in the presence of LiCl, but would not take place in the absence of LiCl.[21] This supports the hypothesis that $E \rightarrow Z$ isomerization of **6** occurs prior to rearrangement via the boat-TS under the "crude" reaction conditions.

For system **2**, *Z*-boat and *E*-boat-TSs are both relatively low in energy, and the pathways via those TSs are equally accessible. Selectivity in that case (substrate **2**) thus depends on the *E*/*Z* ratio of enol ethers in the reaction mixture.

Our computations thus support the hypotheses and conclusions drawn previously by Kishi and co-workers.[14]

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Supporting Information Available: Full ref 15 and Cartesian coordinates and energies of all stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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