*Xmn*I, *Bam*HI, and *Pst*I or *Pvu*II. The reactions were ethanol precipitated, counted, and diluted to the same concentration (cpm/μL), and equal volumes were combined with the same cpm of intact pBR322.

Cleavage of Linear pBR322. Solutions were prepared containing 0.75 μL/tube 20X TA buffer, 1.5 μL 1 mM bp calf thymus DNA, radiolabeled pBR322, and water to make 9 μL. 3 μL of a 5X solution of compound·Fe(II) was added, and the solutions were incubated at 37 °C for 30 min in the dark. 3 μL of a 5 mM sodium ascorbate solution was added, and the reactions were incubated at 37 °C for 2 h. Final concentrations were 40 mM pH 7.9 Tris acetate, 5 mM sodium acetate, 100 μM bp DNA, and 1 mM sodium ascorbate, in a total volume of 15 μL. The reactions were diluted with Ficoll loading buffer and electrophoresed on a 1% vertical agarose gel.

Densitometry. Footprinting and affinity cleaving autoradiograms were scanned on a LKB XL laser densitometer. The scans were output to an IBM printer, and footprints were determined by comparison to the MPE·Fe(II) standard lane. A horizontal line was drawn from the top of the unprotected band nearest the footprint, and the distance in absorbance units from this line to the maximum peak height was determined for each band and plotted as a histogram. Affinity cleavage patterns were measured in similar fashion, using peak heights of sites without specific cleavage as a baseline. To determine the sites of cleavage in the double strand cleavage assay, the cleavage lanes were scanned as above and output to the Hoeffer program GS370 through an analog to digital converter. Cleavage band molecular weights were determined by comparison to the molecular weight standard lane, and positions on pBR322 were calculated. The positions were averaged between labels and used, along with the average relative area of the peaks, to generate histograms.

Acknowledgment. We are grateful to the National Institutes of Health (GM-27681) and to Burroughs Wellcome for research support, to the National Science Foundation for a predoctoral fellowship to W.S.W., and to the National Institutes of Health for a Research Service Award to M.M.

What Causes Aqueous Acceleration of the Claisen Rearrangement?

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Abstract: We report the results of applying a new self-consistent-field solvation model to the Claisen rearrangement of allyl vinyl ether, all possible methoxy-substituted derivatives, two alkylated derivatives, and one carboxymethylated derivative in order to understand the effects of aqueous solvation on the reaction rates. We have employed the AM1–SM2 version of the model to calculate the changes in free energies of solvation in passing from the lowest-energy conformations of the starting materials to both chair and boat transition states. The hydrophobic effect is always accelerative but always small and not very structure sensitive. Other first-hydration-shell effects attributable to hydrophilic parts of the reagents are more sensitive to the substitution pattern. The polarization contributions to the activation energies are usually larger. A favorable polarization contribution is found to be associated with efficient sequestration of charges of opposite sign into separated regions of space. We conclude that aqueous acceleration of the Claisen rearrangement is caused by electric polarization and first-hydration-shell hydrophilic effects, with the relative magnitudes and even the signs of these effects being quite sensitive to substitution pattern.

Introduction

Pericyclic reactions in aqueous solution can exhibit both rate acceleration and improved diastereoselection.[1] Increased rates have been in part attributed to hydrophobic interactions of nonpolar solutes with each other and with water. However, Blake and Jorgensen have suggested that improved solvation of a more polar transition state (TS) relative to starting material may also play a significant role in one particular class of pericyclic processes, Diels–Alder reactions.[2]

The Claisen rearrangement (Chart I) is a different example of a pericyclic reaction, a [3,3] sigmatropic shift, which also shows considerable acceleration on going from nonpolar to aqueous solvents.[3–6] By its very nature as an oxa-Cope rearrangement, even for the rearrangement of the prototype allyl vinyl ether, it is clear that both polar and hydrophobic (or hydrophilic) effects may readily contribute to the overall observed acceleration. Experimentally, it is difficult to discern the relative contributions to transition-state lowering from these effects.

We have recently described[7,8] a semiempirical, effective-Hamiltonian SCF approach[9] for modeling aqueous solvation. The method incorporates solvent-induced polarization[10] and structural relaxation[11] of the solute (whether equilibrium structure or

Chart I

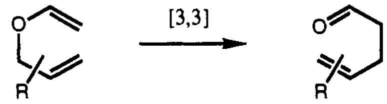

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Table I. Polarization and Surface Tension Components of the Solvation Contributions to the Free Energies of Activation (kcal) for the Claisen Rearrangement in Water at 298 K for Chair Transition State[a]

compd	C-1	C-2	O-3	C-4	C-5	C-6	O-7[b]	C-8[b]	sum	$\Delta G_{S,act}$
P	0.19[c]	−0.04	−0.51	0.14	−0.26	0.00			−0.50[c]	
	−0.11[d]	−0.01	−0.09	−0.06	0.07	−0.19			−0.25[d]	**−0.75**
1a	0.20	0.14	−0.91	−0.25	−0.10	−0.02	−0.19	−0.07	−1.24	
	−0.07	−0.01	−0.03	0.13	0.03	−0.20	−0.01	0.01	−0.16	**−1.40**
1e	0.39	−0.08	−0.71	0.24	−0.43	0.33	0.72	−0.23	0.20	
	−0.01	−0.01	−0.08	0.07	0.09	−0.26	0.28	−0.01	0.08	**0.28**
2	0.46	−0.08	−0.58	0.42	−0.58	0.20	0.29	−0.02	0.11	
	−0.10	0.00	−0.18	0.04	0.07	−0.21	0.11	0.00	−0.27	**−0.16**
4a	0.02	0.15	−0.64	0.36	−0.53	0.11	−0.10	0.01	−0.59	
	−0.06	−0.03	−0.06	0.02	0.07	−0.18	−0.21	0.00	−0.43	**−1.02**[e]
4e	0.08	−0.10	−0.65	0.34	−0.36	−0.11	−0.58	0.17	−1.20	
	−0.06	0.00	0.08	0.01	0.04	−0.15	−0.41	0.00	−0.49	**−1.69**[e]
5	0.34	−0.39	−0.41	0.09	−0.18	0.15	0.44	−0.26	−0.20	
	−0.15	0.00	−0.29	0.04	0.01	−0.15	−0.19	−0.02	−0.73	**−0.93**
6a	0.15	0.32	−1.02	−0.04	−0.25	0.13	0.16	−0.07	−0.61	
	−0.15	−0.05	−0.10	0.10	0.06	−0.09	0.21	−0.03	−0.03	**−0.64**
6e	0.53	−0.11	−0.50	0.04	−0.23	0.24	0.32	−0.08	0.08	
	−0.19	0.00	−0.12	0.08	0.05	−0.06	0.20	−0.03	−0.07	**0.01**

[a] Rounding of heavy atom ΔG values may lead to differences between the sum of the rounded atomic contributions and the actual rounded sums in the last two columns. [b] Methoxy. [c] Top entry: $\Delta G_{ENP,act}$. [d] Lower entry: $\Delta G^{\circ}_{CDS,act}$. [e] Relative energies for **4a** and **4b** are with respect to the same minimum energy conformation of 1-methoxyallyl vinyl ether.

Table II. Polarization and Surface Tension Components of the Solvation Contributions to the Free Energies of Activation (kcal) for the Claisen Rearrangement in Water at 298 K for Boat Transition State[a]

compd	C-1	C-2	O-3	C-4	C-5	C-6	O-7[b]	C-8[b]	sum	$\Delta G^{\circ}_{S,act}$
P	0.13[c]	0.10	−0.31	0.21	−0.38	0.06			−0.22[c]	
	−0.11[d]	−0.01	−0.10	0.07	0.07	−0.19			−0.27[d]	**−0.49**
1a	0.08	0.48	−1.43	−0.03	−0.23	0.04	−0.01	−0.18	−1.28	
	−0.06	−0.02	−0.05	0.14	0.06	−0.21	−0.02	0.01	−0.19	**−1.47**
1e	0.15	0.31	−1.27	0.21	−0.34	0.29	0.63	−0.18	−0.30	
	0.00	−0.01	−0.12	0.08	0.08	−0.24	0.30	0.00	0.08	**−0.22**
2	0.36	0.06	−0.38	0.36	−0.56	0.15	0.26	0.07	0.30	
	−0.09	0.00	−0.16	0.06	0.05	−0.19	0.11	0.00	−0.23	**0.07**
4a	−0.03	0.41	−1.09	0.33	−0.53	0.18	0.00	−0.03	−0.82	
	−0.07	−0.01	−0.04	0.03	0.06	−0.16	−0.20	−0.01	−0.39	**1.21**[e]
4e	−0.14	0.56	−1.83	0.36	−0.30	−0.24	−0.52	0.05	−1.99	
	−0.04	−0.01	0.02	0.02	0.03	−0.13	−0.40	−0.01	−0.52	**−2.51**[e]
5	0.22	−0.07	−0.27	0.11	−0.31	0.17	0.29	−0.17	−0.01	
	−0.13	−0.02	−0.31	0.04	0.01	−0.16	−0.13	−0.01	−0.68	**−0.69**
6a	−0.03	0.55	−1.68	0.04	−0.19	0.03	0.33	−0.19	−1.13	
	−0.17	−0.02	−0.13	0.11	0.05	−0.08	0.10	−0.04	−0.17	**−1.30**
6e	−0.06	0.67	−1.67	0.17	−0.23	0.15	0.61	−0.31	−0.66	
	−0.16	−0.02	−0.16	0.09	0.05	−0.05	0.20	−0.04	−0.11	**−0.77**

[a-e] See footnotes for Table I.

transition state) by including solvent interactions in the Fock operator of neglect-of-diatomic-differential-overlap (NDDO)[12] molecular orbital theory. The solvent is modeled as a dielectric continuum with solute–solvent interfacial tension[13] depending on the local nature of the solvent-accessible[14] surface of the solute. In this approach the free energy of solvation ΔG°_{S} is a sum of two terms. One, ΔG_{ENP}, is the effect of electric polarization of the solvent and electronic polarization of the solute. The other, G°_{CDS}, is the effect of the first hydration shell and includes the physical effects of cavitation, dispersion interactions, and solvent structural changes, which are conventionally associated with the hydrophobic effect for CH_n groups, and which are dominated by hydrophilic effects for oxygen. In this contribution, we report the first results of applying this model to the Claisen rearrangement of allyl vinyl ether, denoted **P** for parent, and all possible methoxy-substituted derivatives, denoted **1a**–**6e** on the basis of the position of methoxy substitution, shown in Figure 1 for reactant, chair transition state (TS), and boat TS. We also present results for two other Claisen substrates for which some experimental data are available in order to assess the quantitative aspects of the solvation model.

Solvation Trends in Parent and Methoxy-Substituted Reactants

We have employed the AM1[15]-SM2[8] version of the model to calculate the changes in free energies of solvation, i.e. the solvation effect $\Delta G^{\circ}_{S,act}$ on the free energy of activation for passing from the lowest-energy conformations of the starting materials to the chair and boat transition states for Claisen rearrangement in water at 298 K.[16,17] The AM1 calculations predict that the chair transition states are generally 5 to 6 kcal/mol lower in energy than the boats before solvation.[16] This difference is consistent with ab initio HF/6-31G* calculations[18] and is a bit larger than values

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(16) **P**, **1e**, **2**, **4a**, **5**, and **6e** were calculated previously in the gas phase. Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511. In several instances we found lower energy starting conformations (0–2 kcal/mol) than were reported previously. All gas-phase structures were characterized by numerical frequency calculations and solvated structures derived therefrom involved only small geometrical changes.

(17) All calculations were carried out using the computer program AMSOL Version 3.0 (Cramer, C. J.; Lynch, G. C.; Truhlar, D. G.; Quantum Chemistry Program Exchange, Program 606. *QCPE Bull.* **1992**, *12*, 62), based on AMPAC Version 2.1 (Liotard, D. L.; Healy, E. F.; Ruiz, J. M.; Dewar, M. J. S. *QCPE Bull.* **1989**, *9*, 123).

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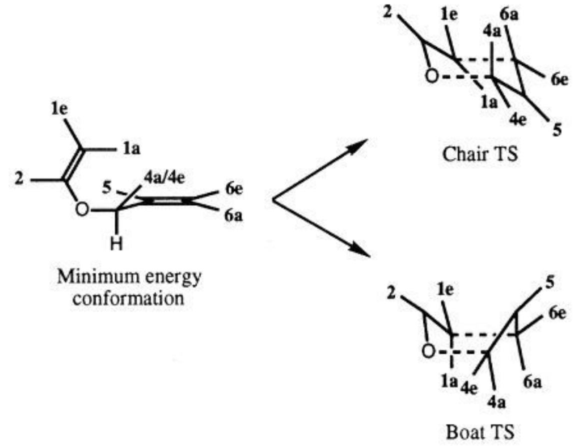

Figure 1. Substitution pattern for the methoxy group in compounds **1a**, **1e**, **2**, **4a**, **4e**, **5**, **6a**, and **6e** for the equilibrium geometries of the reactants and the chair and boat Claisen rearrangement transition states.

derived from thermochemical group contributions.[18,19] The $\Delta G^\circ_{\mathrm{S,act}}$ values are sums of $\Delta G_{\mathrm{ENP,act}}$ and $G^\circ_{\mathrm{CDS,act}}$, and these in turn are easily separated (using method I presented in detail elsewhere[20]) into contributions associated with each nonhydrogenic atom and its directly bonded hydrogens. These results are in Tables I and II.

Chair Transition States. For the chair transition states, seven cases show aqueous acceleration (negative value in last column), with the largest of these, compound **4e**, corresponding to a rate enhancement of a factor of 17. Five of the enhancements are dominated by polarization and two by hydrophilic effects at oxygen.

The hydrophobic effect is most noticeable in the 0.2–0.3 kcal net decrease of G°_{CDS} for the C-1 and C-6 methylene groups when they are brought into close proximity in the TS. The net hydrophobic effect, i.e., the sum of the contributions of the six C columns to $G^\circ_{\mathrm{CDS,act}}$, varies from −0.12 kcal for **1a** and **1e** to −0.25 kcal for **5**. Thus it is always accelerative but always small and not very structure sensitive.

For the breaking C–O bond, effects from the increased exposure of the hydrophilic O-3 and hydrophobic C-4 methylene largely cancel. Due primarily to hydrophilic effects the overall $G^\circ_{\mathrm{CDS,act}}$ is sensitive to the substitution pattern. In **1e**, for instance, the hydrophilic methoxy oxygen is better exposed in the starting conformation, contributing to a *positive* net $G^\circ_{\mathrm{CDS,act}}$.[21] On the other hand, both the hydrophilic oxygen atoms in **5** are much better exposed in the TS, leading to a significantly more negative $G^\circ_{\mathrm{CDS,act}}$.

The polarization contributions to the activation energies are usually larger. In general, the polarization of the surrounding dielectric is dominated by the smaller (in a van der Waals sense) oxygen atoms, on which moderate negative partial charges are localized. That is to say, the solvent polarization tends to respond most strongly to charges which are either large in magnitude, localized in a small volume, or both. Thus, all other factors being equal, remaining fragments within the molecule which become *more* negative in the TS (or which remain negative but become less shielded from solvent) become better solvated and deliver negative (favorable) ENP contributions to the free energy of activation. The reverse is true for groups which become more positive (or which remain positive but become less shielded from solvent); these latter may be thought of as disrupting the solvent polarization, which has been pre-organized by the negative oxygen atoms. Inspection of Mulliken charges for the various groups in the TS shows a uniform accumulation of negative charge on the O-3 atom and the C-5 methine and positive charge on the C-4 methylene. This is consistent with the resonance hybrid view of the TS as an enolate anion and an allyl cation. In each case these considerations rationalize the $\Delta G_{\mathrm{ENP,act}}$ value, with the effect of the O-3 atom usually dominating.

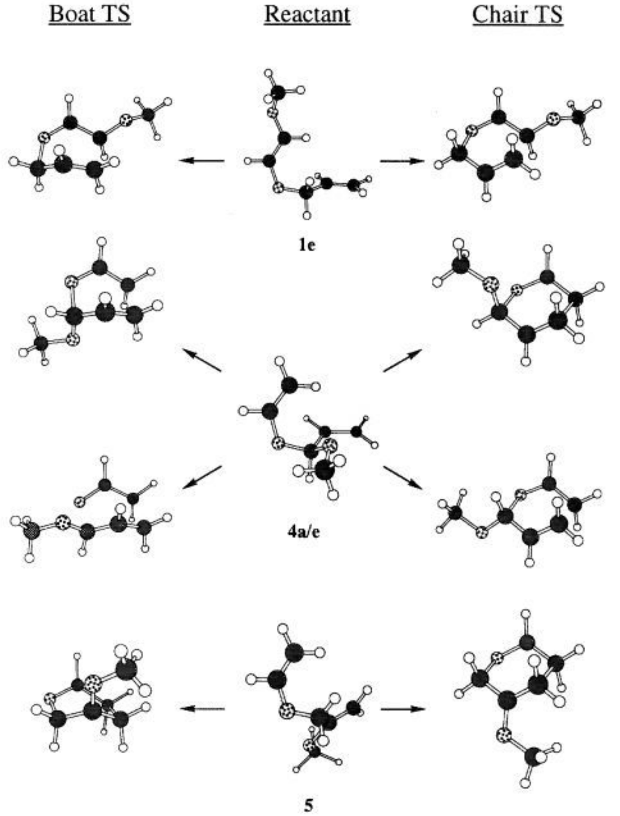

Figure 2. Starting geometries and chair and boat transition states for solvated **1e**, **4a/e**, and **5**. For the sake of consistency in the drawings, the absolute stereochemistry of the stereogenic center in **4a/e** may be shown as either *R* or *S*.

The polarization contributions are also sensitive to the substitution pattern. If two fragments bearing opposite partial charges are brought into close proximity, the disrupted polarization of the surrounding dielectric can be quite unfavorable. This is observed, for instance, in the chair TS for **1e**, where the positive C-6 methylene at the terminus of the "cationic" allyl group approaches the negative O-7 atom attached to C-1. This is in contrast to the equilibrium reactant geometry, where these two groups are far apart; the net difference in effect for these structures contributes +1.05 kcal to $\Delta G_{\mathrm{ENP,act}}$. Similarly, separating two charges of like sign has a destabilizing effect, as illustrated for **5**. In this instance, the equilibrium reactant geometry has the two oxygens relatively close to one another, while in the chair they are further apart. As a result, the contribution to $\Delta G_{\mathrm{ENP,act}}$ from O-3 is the smallest of the nine cases (it remains negative because of the increase in negative charge at O-3), and for O-7 it is the most positive of any but the already discussed **1e**. Figure 2 illustrates each of these cases to assist in visualization.

A favorable polarization contribution to $\Delta G^\circ_{\mathrm{S,act}}$ is thus associated with efficient sequestration of charges of opposite sign into separated regions of space. A frequently invoked measure of TS–solvent interaction is the dipole moment.[22] Although not always true, for the nine cases studied here the solute molecular dipole moment is a good indicator of the degree to which this

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(19) Benson, S. W. *Thermochemical Kinetics*, 2nd ed.; Wiley: New York, 1976.

(20) Cramer, C. J.; Truhlar, D. G. *Chem. Phys. Lett.*, in press.

(21) Note that if the methoxy oxygen atom were to be replaced with a methylene in this instance, the latter's *positive* surface tension would serve to further *accelerate* the reaction via the hydrophobic effect. In fact the corresponding allyl (*E*)-1-butenyl ether shows $\Delta G^\circ_{\mathrm{S,act}} = -0.31$ kcal.

(22) E.g.; Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. Pardo, L.; Branchadell, V.; Oliva, A.; Bertrân, J. *J. Mol. Struct.* (*Theochem*) **1983**, *93*, 255.

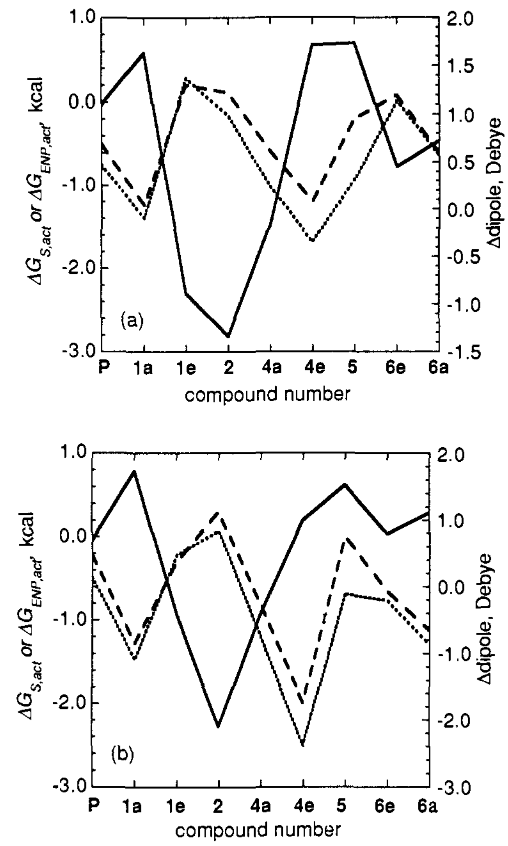


Figure 3. Changes in the solute molecular dipole moment (in aqueous solution) upon going from the minimum energy conformation of the ether to the transition state for the Claisen rearrangement (solid line, right scale), the contribution to the free energy of activation from electronic and nuclear relaxation and polarization (long dashed line, left scale), and the total solvation contribution to the free energy of activation (short dashed line, left scale): (a) chair transition states; (b) boat transition states.

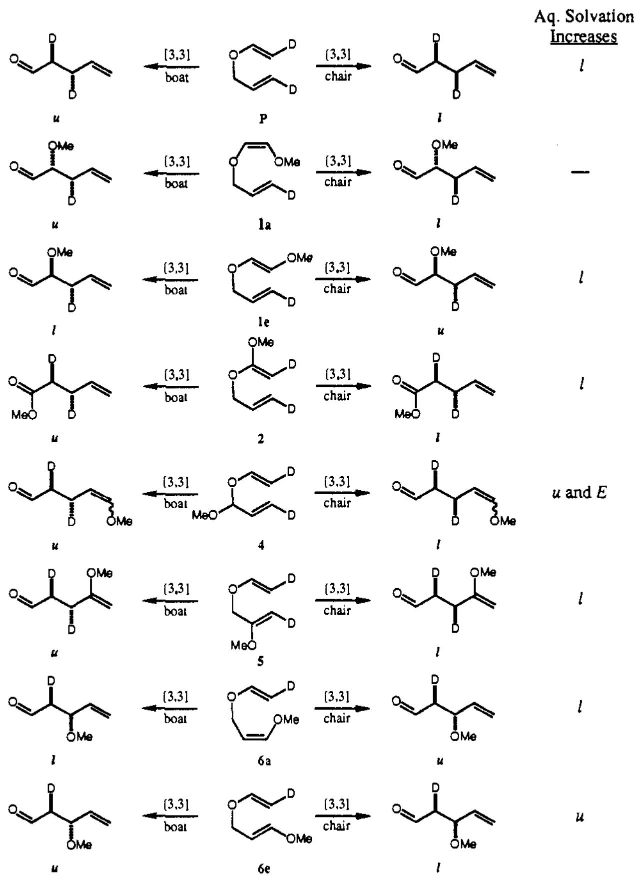
charge separation takes place. Figure 3a shows a comparison of $\Delta G_{\mathrm{ENP,act}}$ and solute dipole moment for these cases. For the most part, improved solvation of the TS is correlated with an increase in dipole moment and vice versa, but dipole correlations alone do not explain all trends, e.g., the difference of **4e** from **5**. The trends in $\Delta G^{\circ}_{\mathrm{S,aci}}$, also shown in the figure, are dominated by $\Delta G_{\mathrm{ENP,act}}$.

Boat Transition States. The boat transition states exhibit trends very similar to the chairs with respect to $G^{\circ}_{\mathrm{CDS,aci}}$, i.e., the hydrophobic effect is on the order of –0.1 to –0.3 kcal/mol and fairly insensitive to substitution pattern, while the hydrophilic effect from the oxygen atoms may play a more sizable role. The $\Delta G_{\mathrm{ENP,aci}}$ term, however, exhibits some unique behavior in the boats in comparison to the chairs. In general, the boat transition states for the present reactions are somewhat looser, and as a result develop greater charge separation. This is most noticeable in the effect on $\Delta G_{\mathrm{ENP,aci}}$ from C-1 and O-3; the increased negative charges on these portions of the "enolate" fragment cause them to dramatically increase their contribution to the overall acceleration by comparison to the chair for **1a**, **1e**, **4a**, **4e**, **6a**, and **6e**. In the remaining instances, the boat TS for **P** is not appreciably more charge separated than the chair, while for **2** and **5** the appearance of the methoxy substituent at one of the boat flagpole positions perturbs the molecule too much to make such a simple analysis straightforward.

The greater charge separation in the boats by comparison to the chairs is countered to some extent by the unique proximity of C-2 and C-5 in the boats. Since these two methines are always of opposite charge, the net effect is destabilizing: in every case the sum of the two associated $\Delta G_{\mathrm{ENP,act}}$ terms is more positive for the boats than for the chairs.

For these systems, the effects detailed above are again to some extent a microscopic dissection of overall dipole moment. Thus,

Scheme I



for the boats $\Delta G_{\mathrm{ENP,act}}$ again tracks reasonably well as a function of overall dipole moment (see Figure 3b), although higher order moments should not be ignored.

The different effect of aqueous solvation on the chair and the boat transition states will give rise, in the event the C-1 and C-6 groups each bear two non-identical substituents, to experimentally testable changes in the ratios of *l* to *u* products, that is, in the ratio of products differing in the relative topicity of bond formation at the two terminal sp^2 centers. In order to compare the calculations, one might substitute a deuterium if the methylene bears no methoxy substituent to induce prostereogenicity. The predicted effects are illustrated in Scheme I. Given the large energy differences between the chair and boat transition states for these reactions, identification of the minor isomer may be quite challenging. A more tractable experiment is suggested by **4**, where in both the boat and the chair transition states the stereochemistry of the resulting γ,δ-double bond is dependent on the axial–equatorial ratio of the methoxy substituent in the transition states. Since the energies of the two competing chairs are much closer in this instance, about 1 kcal, it should be simple to test the calculated greater solvation acceleration for the reaction delivering *E* product, i.e. the reaction should become increasingly diastereoselective. When these effects become large enough, or when steric constraints such as inclusion in a ring system cause the chair and boat transition states to be inherently closer in energy before consideration of solvation, one might well expect new stereochemical routes to open in water,[1b] a subject for a future study.

Other Reactants and Absolute Rate Accelerations. A direct comparison of the predicted rate accelerations for compounds **P** and **1–9** with experiment is difficult for three reasons. First, the standard state for the SM2 model assumes a temperature of 298 K; at this temperature, most of these rearrangements are prohibitively slow and solvent effects have not been studied. In addition, gas-phase data[23] are rarely available, and the reactants

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[23] Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155.

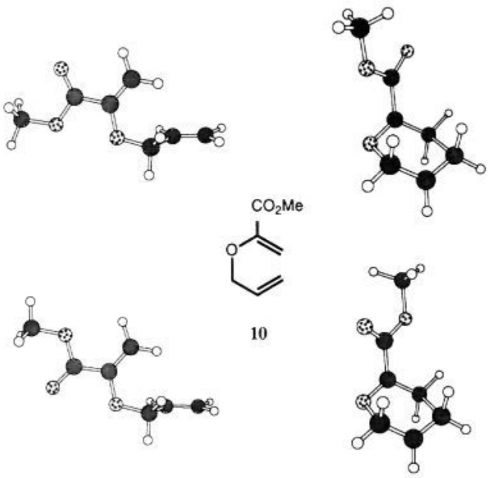


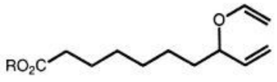
Figure 4. Solvated starting geometries and chair transition states for the *s-cis* and *s-trans* conformers of **10**.

and products have low solubility in pure water.

Coates et al.[4] have provided relative rates of rearrangement for **P**, **4**, **5**, and **6** in solvents ranging in electric permittivity from benzene to methanol. Their results show a weak acceleration (less than a factor of 2) with increasing dielectric constant for **P** and **5** at 407–412 K, a 14-fold acceleration for **4** at 338 K, and a 68-fold acceleration for **6e** at 353 K. The temperature differences make it hard to compare even trends to our results (sizable variation in activation enthalpies and entropies were measured for these substrates at 353 K in benzene), and moreover it is not at all clear that the base rates measured in benzene are an adequate surrogate for the gas phase.

To provide a more definitive assessment of the quantitative abilities of the SM2 model, we have investigated methyl 2-((prop-2′-enyl)oxy)propenoate, **10**. Gajewski et al.[5] measured a 14-fold rate acceleration for rearrangement on going from cyclohexane solvent to a 33% mixture of water in methanol at 335 K for this compound. The acceleration on going from the gas phase to pure water would therefore be expected to be considerably larger. Figure 4 illustrates the rearrangement of **10** for the *s–cis* and *s–trans* conformations of the ester. Since we find the conformational isomers of the reactants and transition states to be close in energy, both in the gas phase and in solution, a Boltzmann weighting of the solvation energies for the two dominant conformers in each case was applied. Our SM2 calculations predict that the rate is accelerated by a factor of 13 on going from the gas phase to aqueous solution at 298 K. If we can compare the acceleration factors despite the different temperatures, we conclude that AM1-SM2 quantitatively underestimates the rate acceleration.

Brandes, Grieco, and Gajewski[6] have also considered the rearrangements of the sodium salt and methyl ester of 8-(ethenyloxy)dec-9-enoic acid, **11**. In solvents where both substrates are soluble at 373 K, the absolute rate constants for rearrangement are quite similar, allowing them to assign a total acceleration of 214 on going from cyclohexane to water. The gas-phase-to-water effect would be even larger. While **11** itself is too large and floppy to lend itself readily to calculation, we have investigated the analogous systems where **P** is substituted with either a methyl group (**12**) or an ethyl group (**13**) at the C-4 position (Figure 5). For **12**, AM1-SM2 predicts a rate acceleration of a factor of 5.[24] For **13**, where again a Boltzmann distribution of low-energy conformers must be considered, the calculated acceleration factor is 4. Lengthening the alkyl chain is not expected to have much additional effect, suggesting a quantitative error factor on the order of 10^2 for this system. While this is a larger error than for **10**, this system is perhaps less appropriate for comparison, since **11** is potentially prone to nonhomogeneous effects in aqueous solution, such as formation of micelles or less organized aggregates.



11

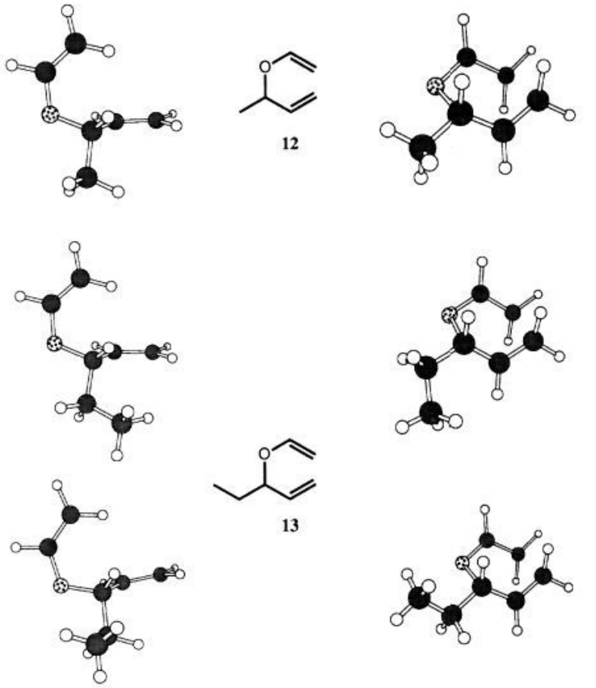


Figure 5. Solvated starting geometries and chair transition states for **12** and the two low-energy rotational isomers of **13**. These two molecules serve as analogs to **11**.

The above considerations indicate that the AM1-SM2 model underestimates the rate accelerations for Claisen reactions. The reason for this is probably that it underestimates the quantitative amount of charge separation in the reagents and transition states. On the average it is unimportant to the performance of the SM2 model whether or not the AM1 charges are "accurate", because the semiempirical adjustment of parameters in SM2 makes up for systematic errors in charges. However, even for the classes of solutes for which AM1-SM2 was parametrized, its performance shows larger errors for some substrates than others, with the larger errors presumably due mainly to the difficulty in modeling the solute charge distribution in specific cases. Continuum solvation models and explicit molecular solvation models are alike in being very sensitive to atomic charges. Within the generalized Born formalism[9] employed in the AM1-SM2 model,[8] the single center contribution to the overall polarization free energy for an atom is $-328q^2/\alpha$ kcal/mol where q is the Mulliken atomic charge and α is the effective atomic radius (in Å). Consider an atom like O-3 in the Claisen rearrangement. Since α is about 2 Å, a change in the atomic charge from -0.25 to -0.30 (both well within the range of observed charges for this atom across all of the substrates) would result in a change in its contribution to the overall polarization free energy of about 4 kcal/mol. Of course, other terms, both one-center and two-center, would change as well, and some would be of opposite sign, but the point is that small changes in charge can lead to large energetic effects.

Since the AM1-SM2 model appears to underestimate the absolute rate accelerations, we conclude that the underlying AM1 charges in the Claisen transition states are too small. Independent evidence that this is true is provided by comparing the AM1 Mulliken charges to those calculated[18] at the HF/6-31G* level.

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(24) We have also examined the methyl-substituted system using the PM3-SM3 model [Cramer, C. J.; Truhlar, D. G. *J. Comp. Chem.*, in press], which employs the PM3 gas-phase Hamiltonian of Stewart [Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209, 221. Stewart, J. J. P. *J. Comput.-Aided Mol. Des.* **1990**, *4*, 1]. In this case the acceleration is also a factor of 5.

Table III. Gas-Phase Charges (Including Attached Hydrogens) in Compound **P**

		C-1	C-2	O-3	C-4	C-5	C-6
reactant	AM1	−0.07	0.15	−0.22	0.21	−0.05	0.01
	HF/6-31G*	−0.14	0.41	−0.61	0.34	0.00	0.00
chair transition state	AM1	0.01	0.10	−0.25	0.20	−0.17	0.10
	HF/6-31G*	−0.12	0.42	−0.59	0.20	−0.17	0.10

This comparison is given in Table III for the parent compound. Clearly there is much more charge separation at C-2 and O-3 in the ab initio results than in the AM1 results. Although the HF/6-31G* level systematically overestimates dipole moments (by about 30% for ethers[25]), it is probably more realistic than AM1 in the present case. We recall that the Claisen rearrangement was a subject of earlier controversy because semiempirical studies at the MNDO level predicted a biradical-like chair TS with little C–O bond breaking.[26] At the AM1 level, this tendency is reduced, and when the SM2 model is self-consistently employed in the SCF equations the C–O bond is further lengthened; however, it remains 0.34 Å shorter than is found in the gas-phase chair TS calculated[18] at the HF/6-31G* level. If one employs the AM1-SM2 model at the HF/6-31G* geometry, the predicted acceleration for the parent compound increases from a factor of 3.5 to a factor of 16, in the correct direction but still apparently too small.[27] Another indication that the AM1 model underestimates the extent of charge separation is that Jorgensen has calculated a much larger aqueous rate acceleration for the parent reaction using the HF/6-31G* solute charge distribution.[27] (Additional unpublished calculations we have performed also show less polar transition states and smaller aqueous acceleration of Diels–Alder reactions by AM1-SM2 than found[2] in HF/6-31G* calculations. A similar lack of significant aqueous acceleration has been found in a continuum solvation model in which the substrates are described at the HF/STO-3G level.[28])

Of course, as long as the underestimation of atomic charge is consistent with respect to substitution, qualitative trends and the factors that dominate these trends may still be identified. Analogous trends in charge play an important role in determining the solvation free energies of equilibrium structures, and the AM1-SM2 model performs very well for trends in those quantities.[8] We assume that the present calculations correctly incorporate the physical factors leading to aqueous rate acceleration and their variation with respect to substitution pattern and transition state ring conformation; in fact we conclude that the trends noted here would be amplified by a more realistic treatment of the transition state charge distribution.

Summary

Aqueous acceleration of the Claisen rearrangement can be accounted for by electric polarization and first-hydration-shell hydrophilic effects. We conclude that polarization generally dominates, especially given the probable underestimation of atomic charges by the AM1-SM2 model in the transition states, and that the relative magnitudes and even the signs of these effects are quite sensitive to the substrate substitution pattern. Our calculations indicate that solvent polarization in the parent and methoxy-substituted systems tends to be most responsive to the oxygen atoms because of their smaller volume and moderately large charges. Geometrical changes on going from the reactant conformation to the transition state which sequester charges of opposite sign into well-separated regions of space contribute to rate acceleration, while the converse is true when charges of opposite sign are forced into proximity. This effect is related to the increase or decrease in overall dipole moment on progressing to the transition state, but consideration of only the dipole moment is insufficient to reproduce the distributed-monopole results of the SM2 model. Because competing axial and equatorial substitution patterns and competing chair and boat transition states involve different spatial arrangements of the critical charges, energetic discrimination between reaction routes delivering stereochemically different products may be substantially changed in water in comparison to the gas phase or to nonpolar solvents.

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