Transition Structure and Substituent Effects on Aqueous Acceleration of the Claisen Rearrangement

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Abstract: A combined quantum mechanical and statistical mechanical approach is used to assess the transition structure and substituent effects on the rate acceleration of Claisen rearrangements in aqueous solution. It is demonstrated that the computed aqueous solvent effect depends critically on the nature of the transition structure, and a correlation between transition state stabilization and dipole moment in water is obtained. In addition, transition structures for a series of substituted allyl vinyl ether compounds have been optimized at the RHF/6-31G(d) level. The results indicate that transition structures are less tight for donor substitutions on the allyl fragment and acceptor groups on the oxallyl unit than the parent AVE. This leads to increased aqueous rate acceleration, accompanying enhanced ionic characters at the transition state for the Claisen rearrangement. Substituted R_2-cyano and R_6 = methoxy allyl vinyl ether is predicted to have a synergetic effect with a solvent-induced rate increase of 6×10^5.

The mechanism and transition structures of [3,3] sigmatropic shifts have been extensively explored experimentally and theoretically.[1,2] Among these processes, the Claisen rearrangement continues to fascinate chemists because of its synthetic and mechanistic importance in organic and biological chemistry.[3,4] Of particular interest is the finding of substantial rate acceleration in aqueous solution. For example, the reaction rate is about 1000 times faster for the rearrangement of allyl vinyl ether (AVE) in water than in the gas phase at 75 °C.[4,5] The origin of the solvent effect has been attributed to enhanced hydrogen bonding to the transition state (TS)[5] and solvent-induced electronic polarization within the oxallyl fragment rather than oxallyl–allyl interfragment charge separation.[6,7] In addition, the transition structure for AVE rearrangement is interpreted to be consistent with a diradical pair in the gas phase as well as in solution.[8] More recently, Storer et al. observed that the computed solvent effect is sensitive to the TS geometry used in these calculations, and pronounced solvent effect is accompanied by loose transition structures.[7b]

There are still several issues of fundamental interest: (1) Is there a simple correlation of the solvent rate acceleration with the transition state geometry in the Claisen rearrangement? (2) What are the substituent effects on the aqueous rate acceleration, and how can it be utilized in catalyst design? (3) Will the putative enolate/allylic cation ion-pair character in the TS be enhanced by polar solvents for substituted AVE? To answer these questions, we have carried out a combined quantum mechanical and statistical mechanical investigation and provide computational evidence of substitution patterns that can amplify the solvent effect on Claisen rearrangements in water.

Computational Procedure

Following a procedure established previously,[6,9] we employ a combined quantum mechanical and molecular mechanical (QM/MM) potential by treating the allyl vinyl ether system quantum mechanically with the Austin model 1 (AM1) method in statistical Monte Carlo simulations.[10] Details of the combined QM/MM method have been reviewed; interested readers are directed to ref 9. In short, the combined QM/MM approach takes advantage of both the accuracy of quantum mechanical methods for the reactive species and the computational efficiency of the empirical force field for the bulk solution system. The method is particularly suited for systems that cannot be adequately modeled by force fields such as chemical reactions considered here but are too large to be entirely treated by quantum mechanical methods. In the present study, the solute molecule is embedded in a box of 506 water molecules represented by a simple 3-point charge (TIP3P) model.[11] Solute–solvent interaction energies are determined by Hartree–Fock molecular orbital calculations during the fluid simulation.[9] Such a combined quantum mechanical and molecular mechanical (QM/MM) approach has been used to study several chemical reactions

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in solution and was found to provide valuable insight into specific solute–solvent interactions.[12]

Two types of simulations are carried out in this study. To begin, we examine the dependence of solvent effects and TS geometry using Monte Carlo methods. Starting with the chair transition state structure obtained at the RHF/6-31G(d) level for the Claisen rearrangement of AVE,[5a] the distance between the oxallyl and allyl fragments is parallelly reduced and elongated as the geometry of the two fragments is held rigid in a series of 11 free energy perturbation calculations.[13,14] Thus, the change in free energy of hydration (ΔG_{hyd}) for the transition state is determined as a function of the TS geometry. This is followed by investigation of the effect of substitution on the transition state structure for the Claisen rearrangement through ab initio molecular orbital calculations using the 6-31G(d) basis set. We note that previous studies have demonstrated that HF/6-31G(d) calculations can yield excellent geometrical results for the Claisen rearrangement in comparison with the MCSCF data.[2a,8b] Here, a series of substituents including cyano, fluoro, and methoxy groups at various positions of AVE are considered. Both ground and transition state structures are optimized, which are subsequently used in Monte Carlo simulations to evaluate the solvent effect. For the ground state calculations, there are many stable conformers with similar energies due to the flexibility of these molecules. A thorough search of all possible conformers was not carried out here, though the lowest energy conformers in the methoxy-substituted cases are obtained for the methoxy dihedral rotations. Since there is no intramolecular hydrogen bonding, the extended (all-trans conformer) structures are chosen in other systems. Of course, to accurately reflect the energetics of these ground state conformers, conformational averaging should be performed in computing the activation free energy for these reactions. This problem has been recently addressed by Severance and Jorgensen for the AVE system.[5b] They found that the total conformationally-averaged solvent effect is virually identical to the result obtained with a single ground state geometry from the reaction path calculation.[5b]

All Monte Carlo simulations were executed in the isothermal–isobaric (NPT) ensemble at 1 atm and 25 °C with preferential sampling and periodic boundary conditions. A spherical cutoff distance of 10 Å between the water oxygen and any solute atoms was used to evaluate the interaction energy. The MCQUB/BOSS program, which is coupled to the MOPAC package, is used on IBM RS6000/370 workstations.[14] Each simulation involved 10^6 configurations of equilibration, followed by 1.5×10^6 to 2×10^6 configurations of averaging.

Results and Discussion

Figure 1 illustrates the change in $\Delta\Delta G^{\ddagger}_{\mathrm{hyd}}$ as a function of the oxallyl and allyl fragment separation (R_f), which is defined by the average of the breaking (O–C_4) and forming (C_1–C_6) bonds. Consequently, a small R_f value represents a tight transition structure, whereas a large R_f indicates a loose geometry for the Claisen rearrangement. In Figure 1, the difference in ΔG_{hyd} between the TS and reactant determined previously for the 6-31G(d) reaction path is used to anchor the relative free energies.[6] The results reveal that solvent effects on the Claisen rearrangement depend critically on the nature of the TS structure. Greater solvent effects are found for loose TS resembling separate oxallyl/allyl fragments.[7b] For comparison, Storer et al. considered transition structures obtained from the AM1, RHF/6-31G(d), and MCSCF/6-31G(d) optimizations, corresponding to R_f's of 1.7, 2.1, and 2.3 Å for the Claisen rearrangement of AVE.[7b] Based on a continuum solvation model, SM4-SRP, Storer et al. predicted rate accelerations (gas phase to solution) of 3.4, 46, and 1400 at 25 °C for the three TS, respectively.[7b] This may be compared with our prediction of 22, 368, and 2500 for the three R_f's. In these calculations, the results for $R_f = 1.7$ Å were predicted using eq 1 (see below) based on the computed dipole moment from a simulation with the structure corresponding to $R_f = 1.7$ Å, whereas the other two values are obtained directly from Monte Carlo calculations. It is interesting to note the increasing agreement between the SM4-SRP and our simulation results as the TS gets looser. Since the computed TS for the Claisen rearrangement is very sensitive to the theoretical models used,[7b,8b] it is critical to choose an appropriate TS structure in condensed phase simulations.[5a,6] Recent experimental and theoretical kinetic isotope effect studies suggest that the TS for the AVE rearrangement may lie between the RHF/6-31G(d) and MCSCF/6-31G(d) structures.[4b,8]

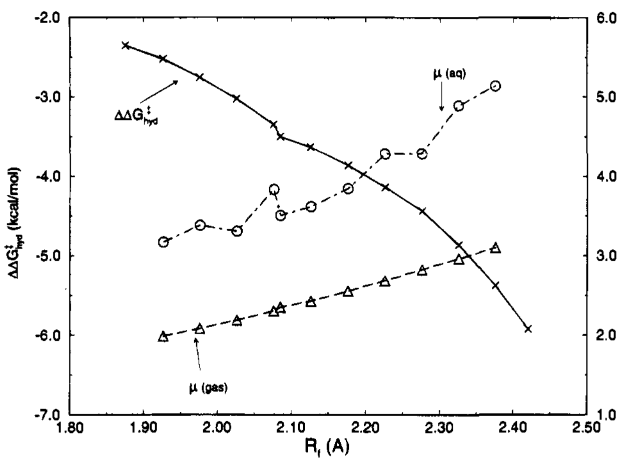

Figure 1. Computed change in free energy of hydration (solid line) and dipole moment in the gas phase (dashed line) and aqueous solution (dot-dashed line) for the transition state structure. Average distance for the breaking and forming bonds is give in angstroms.

The ionic character of the TS is undoubtedly enhanced as the distance between the oxallyl and allyl fragments increases. Figure 1 also shows the variation of dipole moment in the gas phase and in water. Charge separation is progressively enlarged as the TS becomes looser in the gas phase, evidenced by an increase in dipole moment as R_f elongates. Hydration effects provide further enhancement of the ionic character of the oxallyl–allyl pair in water. To provide a rough estimate of the qualitative trend, Mulliken population charges have been averaged in Monte Carlo simulations using the AM1 wave function for the stretched TS at $R_f = 2.3$. The interfragment separation in this structure is similar to that of the MCSCF transition structure. An interfragment charge separation of 0.43 e is found for this stretched-out TS in water, identical to that predicted by Storer et al. for the MCSCF structure using the SM4-SRP model.[7b] This represents a solvent enhanced ionic character of 0.14 e, and a solvent-induced dipole moment ($\Delta\mu_{\mathrm{ind}}$) of 1.92 D. Within the oxallyl unit, the atomic charge on oxygen concomitantly increases from −0.35 e in the gas phase to −0.51 e in water using the AM1 wave function. Thus, intrafragment electronic polarization is critical even in regions where ionic character of the TS is enhanced.[6,7a,b]

Cramer and Truhlar found a rough correlation between the aqueous solvent effect and molecular dipole moment for the Claisen rearrangement of methoxy-substituted compounds.[7a] However, quantitative prediction was hampered by the underestimated $\Delta\Delta G^{\ddagger}_{\mathrm{hyd}}$ using the too tight AM1 TS structures.[7a] In Figure 2, our computed $\Delta\Delta G^{\ddagger}_{\mathrm{hyd}}$ can be correlated with the difference in dipole moment between the TS and reactant in water ($\Delta\mu_{\mathrm{aq}}$), eq 1. This equation is subsequently used to estimate the solvent effect for other Claisen rearrangements.

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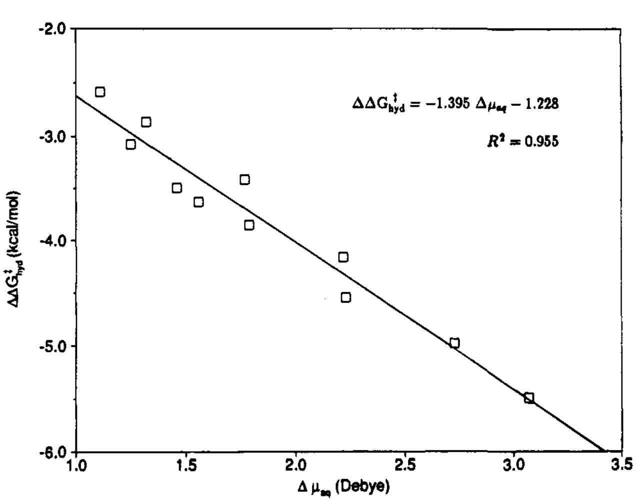


Figure 2. Correlation of the computed difference in solvation free energy versus change in dipole moment between the transition state and the reactant in water.

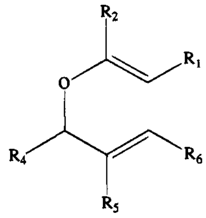
$$\Delta\Delta G^{\ddagger}_{\text{hyd}} = -1.395[\mu_{\text{aq}}(\text{TS}) - \mu_{\text{aq}}(\text{R})] - 1.228 \quad (1)$$

Here, μ_{aq}(TS) and μ_{aq}(R) are average dipole moments of the transition structure and reactant in aqueous solution, respectively. They are determined in Monte Carlo simulations with the combined AM1/TIP3P potential.

Finally, we turn our attention to the substituent effects on the rate acceleration in Claisen rearrangements. Experimentally, substituent effects have been extensively investigated, including substituted silyloxy, alkoxy, amino, carbanion, oxyanion, fluoro, and cyano systems.[1,15] A rate-accelerating effect is generally observed for these reactions, except for the substituted R_5 = alkoxy case which shows rate retardation.[4b] Furthermore, enhanced solvent effects on substituted AVE have been documented.[4] For example, the rates of rearrangement of methoxy-substituted AVE at R_4 and R_6 positions are respectively 18 and 68 times faster in methanol than in benzene at 65 and 80 °C, whereas the change for the parent AVE is only 1.7-fold at 134 °C.[4b] The difference in water is expected to be even larger. These findings appear to be consistent with pronounced dipolar character in the TS for substituted AVE. Since our simulation results relate the solvent effects to the TS geometry and $\Delta\mu_{aq}$, it would be informative to examine the structural trend upon substitution. Consequently, we have located transition structures for a series of substituted AVE at the RHF/6-31G(d) level.[16]

Table 1 lists key geometrical variables and gas phase activation energies from 6-31G(d) optimizations and $\Delta\mu_{aq}$ along with the predicted aqueous rate accleration based on $\Delta\Delta G^{\ddagger}_{hyd}$ from the correlation shown in Figure 2 and eq 1. Clearly, all substitutions lead to a lowering of the barrier height for the Claisen rearrangement in the gas phase with the exception of R_5-substituted methoxy AVE, in accord with experimental observations.[4b] However, it is not straightforward to compare the computed and experimental solvent effects because experimental rate measurements were conducted at different temperatures.[4,15] Thus, only trends may be inferred. Our simulations suggest that R_6 = alkoxy substitution gives rise to substantial solvent-induced rate increase over the parent AVE system, consistent with findings by Coates et al.[4b] However, solvent effects for the reaction of substituted R_2 = methoxy AVE were found to be minimal in water, contrary to the experimental data. Acceptor groups on the oxallyl unit, e.g., substituted R_2 = cyano AVE, yield significant rate enhancement. The most dramatic, synergetic effect results from combined donor–acceptor substitutions. The reaction rate of substituted R_2 = cyano and R_6 = methoxy allyl vinyl ether is estimated to be accelerated by (6 × 10^5)-fold on going from the gas phase into aqueous solution—the effect is 1700 times the rate acceleration for AVE in water. Interestingly, the rate enhancement is accompanied by development of substantial ionic character in the TS with a charge separation of 0.62 e (from Mulliken population analysis) between the oxallyl and allyl fragments in water. This is 0.15 e more than that in the gas phase. The charge separation leads to a computed dipole moment of 8.36 D for the TS, an increase ($\Delta\mu_{ind}$) of 2.44 D over the gas phase value. Intrafragment polarization is also significant: the O partial charge increases from −0.35 e in the gas phase to −0.50 e in water based on AM1 population analysis.

Table 1. Key Geometrical Parameters of the Optimized Transition Structures for the Claisen Rearrangement of Substituted Allyl Vinyl Ethers at the RHF/6-31G* Level and Predicted Aqueous Rate Accelerations[a]



molecule	R(O−C_4)	R(C_1−C_6)	ΔE_a	$\Delta\mu$(aq)[b]	rate increase[c]
parent AVE	1.918	2.266	48.8	1.46	368[d] (1.0)
R_1 = F	1.914	2.243	46.0	0.28	15 (0.04)
R_2 = F	1.924	2.371	37.9	2.42	2400 (6)
R_2 = MeO	1.873	2.330	39.7	−0.26	4 (0.01)
R_4 = MeO	2.034	2.371	44.1	0.91	68 (0.2)
R_5 = MeO	1.900	2.245	52.8	1.14	115 (0.3)
R_6 = MeO	2.046	2.359	47.6	2.18	1350 (4)
R_2 = CN	1.973	2.288	43.8	2.87	6800 (18)
R_4 = CN, R_6 = MeO	2.014	2.397	45.7	3.49	3 × 10^4 (80)
R_2 = CN, R_6 = MeO	2.167	2.482	41.7	4.79	6 × 10^6 (1700)

[a] Units for distances are in Å, energies in kcal/mol, and dipole moments in D. [b] $\Delta\mu$(aq) = μ_{aq}(TS) − μ_{aq}(reactant), where μ_{aq}(TS) and μ_{aq}(reactant) are determined from separate QM/MM simulations of the transition state and reactant in water. [c] Predicted aqueous rate acceleration over the gas phase process from the relationship shown in Figure 2 is given first, followed in parentheses by rate enhancement by substitution relative to AVE in water. [d] Reference 6.

It should be noted that the prediction of the drastic rate acceleration for the substituted systems is based on the correlation of $\Delta\Delta G^{\ddagger}_{hyd}$ and $\Delta\mu_{aq}$ (eq 1, Figure 2) for the parent molecule. A direct application of eq 1 to the substituted cases may lead to errors, while the computed $\Delta\mu_{aq}$ by the combined QM/MM simulations also has an uncertainty of about 0.2−0.5 D from different simulations. Nevertheless, in view of the magnitude of the computed dipole moments for the substituted systems which are similar to the parent AVE, the qualitative trend of the predicted rate increase and substitution patterns for

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the Claisen rearrangement in water is unlikely to be significantly altered due to these computational uncertainties.

Conclusions

The present study examines the relationship between aqueous rate acceleration and the transition state geometry for the Claisen rearrangement. Consistent with early findings by Storer et al.,[7b] our combined QM/MM Monte Carlo simulations showed that the computed solvent effect depends critically on the transition geometries used in these calculations. A loose transition structure, which is obtained from high-level ab initio calculations, leads to substantial transition state stabilization by the solvent and a huge rate increase. On the other hand, a tight TS as predicted by the AM1 method gives marginal solvent effects. Thus, it is of interest to further investigate the change of transition state structure by aqueous solvent effects. A linear relationship was obtained between the solvation free energy and the difference in dipole moment between the transition state and reactant in water. Substituted allyl vinyl ethers are preidcted to have lower activation barrier than the parent species except for the R_5 = methoxy substitution. Furthermore, the aqueous rate acceleration is significantly enhanced in several cases, particularly with the electron-withdrawing group on the oxallyl unit and the electron-donating group on the allyl fragment, respectively. The largest, synergetic effect is found in substituted R_2 = cyano and R_6 = methoxy allyl vinyl ether, for which the aqueous rate acceleration is predicted to be 6×10^5 on going from the gas phase into water. Experimental verification of these predictions would be interesting, and will provide a test of the computational results. These findings may be utilized in future simulation studies of enzymatic and antibody catalysis of the Claisen rearrangement of chorismate to prehenate.[17]

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Supporting Information Available: Listing of 6-31G* geometries and simulation results (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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