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Combined QM/MM Simulation Study of the Claisen Rearrangement of Allyl Vinyl Ether in Aqueous Solution

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The solvent effects on the rates of Claisen rearrangement have been extensively investigated experimentally and theoretically.[1-6] The interest in this reaction stems from its synthetic and mechanistic importance in organic chemistry and biochemistry.[2,7] A fundamental issue is the dipolar versus radical nature of the transition state (TS) structure;[2,6] however, it is difficult to sequester specific contributions experimentally. Two recent theoretical studies, employing a self-consistent reaction field (SCRF) model and Monte Carlo simulations,[5,6] suggest that enhanced hydrogen bonding and electric polarization at the TS provide an alternative explanation. The present results, obtained from a combined quantum mechanical and molecular mechanical (QM/MM) approach in Monte Carlo simulations, reinforce this notion and provide additional insights on the interplay of intermolecular interactions and electric polarization in the Claisen rearrangement of allyl vinyl ether (AVE) in aqueous solution.

The present approach is an updated version of our efforts on the use of a combined QM/MM potential for simulations of chemical reactions in solution.[8] The first step in this approach is to determine the reaction path in the gas phase through ab initio molecular orbital calculations. For the Claisen rearrangement of AVE, the intrinsic reaction path (IRC) determined by Severance and Jorgensen at the RHF/6-31G(d) level was adopted,[6,9] which contained a "movie" of 143 frames transforming the reactant AVE through the TS to the product 4-pentenal. This is followed by computing the profile of free energy of hydration ($\Delta G_{\rm hyd}$) along the IRC path using a combined QM/MM potential in Monte Carlo simulations.[8] The procedure is, in essence, similar to the method employed by Jorgensen and co-workers.[6,10] However, the major difference here is that it is no longer necessary to parametrize the empirical potential functions for the reactant system since solute–solvent interactions are evaluated by quantum mechanical calculations during the fluid simulation.[8] In addition, it has the advantage of both allowing solute electronic structure relaxation, which is not included in the empirical potential approach,[6] and considering specific solute–solvent interactions, which is treated as a continuum dielectric in the SCRF method.[5]

The combined QM/MM potential involves a partitioning of the condensed-phase system into a QM region consisting of the solute and an MM region of the surrounding solvent molecules.[11] The total effective Hamiltonian of the system is as follows:

$$\hat{H}_{\rm eff} = \hat{H}^{\circ} + \hat{H}_{\rm QM/MM} + \hat{H}_{\rm MM} \qquad (1)$$

where $\hat{H}^{\circ}$ is the Hamiltonian for the isolated QM solute, $\hat{H}_{\rm QM/MM}$ is the QM/MM interaction Hamiltonian,[11] and $\hat{H}_{\rm MM}$ is the solvent interaction energy determined empirically by the TIP3P model for water.[12] Because electronic degrees of freedom are explicitly included in the fluid simulations, a computationally efficient quantum mechanical method must be used. We have adopted the semiempirical Austin Model 1 (AM1) theory developed by Dewar and co-workers to form the present AM1/TIP3P model.[13] The good performance of this hybrid AM1/TIP3P method has been demonstrated through evaluation of the solute electric polarization and estimation of solvation free energies for amino acids and nucleotide bases.[14]

The Monte Carlo simulations were carried out in the NPT ensemble at 25 °C and 1 atm with Metropolis sampling. A cubic cell containing 506 water molecules plus the reactant was used in all calculations. Periodic boundary conditions along with a cutoff distance of 10.5 Å were employed to evaluate the interaction energies. In the fluid simulation, solute–solvent interaction energies were obtained by SCF calculations including $\hat{H}_{\rm QM/MM}$ to allow full solute electronic structure relaxation in the presence of the solvent electric fields.[5,11,14] Sixty-nine of the 143 frames along the reaction path were used, which required a total of 34 simulations with the double-wide sampling technique to span the entire reaction coordinate (RC).[15] The van der Waals radius for oxygen was scaled from sp^3 to sp^2 hybridizations between RC of -2 and 2.[14] The changes in $\Delta G_{\rm hyd}$ between adjacent frames were computed using statistical perturbation theory[16] with the MCQUB/BOSS program, in which the QM energies are evaluated by MOPAC.[17] Each simulation involved $(0.5-1.0) \times 10^6$ configurations for equilibration followed by an additional 1.5×10^6 configurations of averaging.

Figure 1 shows the key results of the present study. The TS corresponding to an IRC value of 0 is the best hydrated species along the reaction path, which has a $\Delta\Delta G_{\rm hyd}$ of -3.5 ± 0.1 kcal/mol relative to the reactant AVE. Consequently, the Claisen rearrangement is predicted to be accelerated by a factor of 368 in water over the rate in the gas phase at 25 °C. For comparison, our prediction is in good agreement with the computed $\Delta\Delta G_{\rm hyd}$ of -3.85 ± 0.16 kcal/mol by Severance and Jorgensen from a Monte Carlo calculation with the OPLS potential.[6] Analyzing the available data,[1-3] these authors concluded that the experimental rate acceleration for AVE is about 10^3 at 75 °C from the gas phase into aqueous solution. Thus, our computed results appear to be consistent with experimental findings. Cramer and Truhlar reported a rate acceleration of 16, or a $\Delta\Delta G_{\rm hyd}$ of -1.6 kcal/mol, for AVE at 25 °C using the AM1-SM2 model at the 6-31G(d) geometry.[5] They concluded that the solute electric polarization and the hydrophilic effects in the first solvation shell account for the rate acceleration of the Claisen rearrangement.

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(1) (a) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196; 3585. (b) Goering, H. L.; Jacobsen, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 3277.

(2) (a) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1060. (b) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. (c) Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500.

(3) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.

(4) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511.

(5) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794.

(6) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966.

(7) (a) Grieco, P. A. *Aldrichim. Acta* **1991**, *24*, 59. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (c) Pawlak, J. L.; Padykula, R. E.; Kronis, J. D.; Aleksejczyk, R. A.; Berchtold, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 3374. (d) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008.

(8) (a) Gao, J. *J. Am. Chem. Soc.* **1991**, *113*, 7796. (b) Gao, J.; Pavelites, J. J. *J. Am. Chem. Soc.* **1992**, *114*, 1912. (c) Gao, J. *J. Am. Chem. Soc.* **1993**, *115*, 2930. (d) Gao, J.; Xia, X. *J. Am. Chem. Soc.* **1993**, *115*, 9667. (e) Gao, J.; Chou, L. W.; Auerbach, A. *Biophys. J.* **1993**, *65*, 43.

(9) Vance, R. L.; Rondan, R. N.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

(10) Jorgensen, W. L. *Adv. Chem. Phys., Part II* **1988**, *70*, 469.

(11) For reviews, see: (a) Warshel, A. *Computer Modeling of Chemical Reactions in Enzymes and Solutions*; Wiley: New York, 1991. (b) Luzhkov, V.; Warshel, A. *J. Comput. Chem.* **1992**, *13*, 199. (c) Field, M. J.; Bash, P. A.; Karplus, M. *J. Comput. Chem.* **1990**, *11*, 700. (d) Gao, J. *J. Phys. Chem.* **1992**, *96*, 537. (e) For continuum models, see, for example: Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305.

(12) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, *79*, 926.

(13) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(14) Gao, J.; Xia, X. *Science* **1992**, *258*, 631.

(15) Jorgensen, W. J.; Ravimohan, C. *J. Chem. Phys.* **1985**, *83*, 3050.

(16) Zwanzig, R. W. *J. Chem. Phys.* **1954**, *22*, 1420.

(17) (a) Gao, J. *MCQUB (Monte Carlo QM/MM at the University at Buffalo)*; SUNY at Buffalo, 1993. (b) Jorgensen, W. L. *BOSS 2.9*; Yale University, 1990. (c) Stewart, J. J. P. *MOPAC, Version 5.0*; QCPE 455, 1986.

0002-7863/94/1516-1563$04.50/0

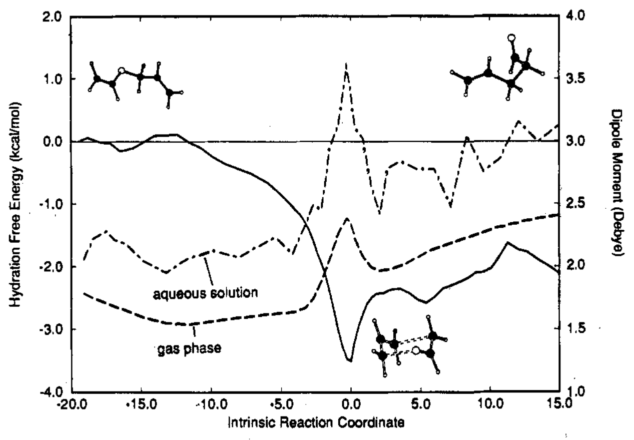

Figure 1. Computed changes in free energies of hydration (solid curve) and the AM1 dipole moments in the gas phase (dashed curve) and in aqueous solution (dash-dotted curve) along the 6-31G(d) intrinsic reaction coordinate (arbitrary unit).

Their qualitative explanation is consistent with the analyses of our results (*vide infra*).[5] Finally, the difference in ΔG_{hyd} between 4-pentenal and AVE (-2.1 ± 0.2 kcal/mol, Figure 1) is in accord with the experimental trend that aldehydes are better hydrated than ethers by 1-2 kcal/mol.[6]

To characterize the origin of the solvent effects on the rate acceleration of the Claisen rearrangement, the solute electric polarization contribution has been evaluated. We have determined the "polarization free energies" of hydration, $\Delta G_{h,pol}$, for the reactant AVE and the TS by perturbing the fully-relaxed solute wave function in water to the gas-phase wave function in the presence of the same solvent configurations using statistical perturbation theory. The computed $\Delta G_{h,pol}$ is -0.55 ± 0.04 kcal/mol for AVE and -1.77 ± 0.08 kcal/mol for the TS. Consequently, the difference in solute polarization contributes up to 1.2 kcal/mol, or 35%, to the total $\Delta\Delta G_{hyd}$. Interestingly, $\Delta G_{h,pol}$ values are nicely mirrored by the computed induced dipole moments, $\Delta\mu_{ind}$, for the starting material and the TS. The AM1 dipole moments for AVE and the TS in the gas phase are 1.8 and 2.3 D (Figure 1), respectively, in good accord with the 6-31G(d) values used in ref 6 (1.9 and 2.5 D). However, in addition, there is a computed $\Delta\mu_{ind}$ of 0.3 ± 0.1 D for AVE and 1.0 ± 0.1 D for the TS in water (the largest aqueous dipole moment is 3.6 D for a structure near the TS at an IRC of -0.03). Clearly, solvent polarization of the solute electronic structure significantly enhances the magnitude of the molecular dipole moment, particularly at the TS. The large, unbalanced polarization effects between the starting material and the TS are the basis for the predicted polarization contribution to aqueous acceleration, which further demonstrates the need for specific representation of these terms in empirical force fields for fluid simulations.[8] Consistent with previous analyses,[5,6] our calculation indicates that there is insignificant change in charge transfer between the allyl and $H_2C{=}CHO$ fragments as a result of hydration. The difference in charge transfer on going from the ground state (AVE) to the TS in water is found to exceed the difference in the gas phase by only 0.03 e based on Mulliken population analysis. However, the hydration effect on charge distribution within the $H_2C{=}CHO$ unit is significant. In aqueous solution, the partial charge on oxygen increases by 0.17 e on going from AVE (-0.25 e) to the TS (-0.42 e), whereas in the gas phase, the increase is only 0.10 e. Thus, it is important to differentiate between a solvent-induced polarization and a solvent-induced heterolytic cleavage.[2b,18] This solvent polarization effect would be consistent with enhanced hydrogen bonding to the oxygen in the TS.[6]

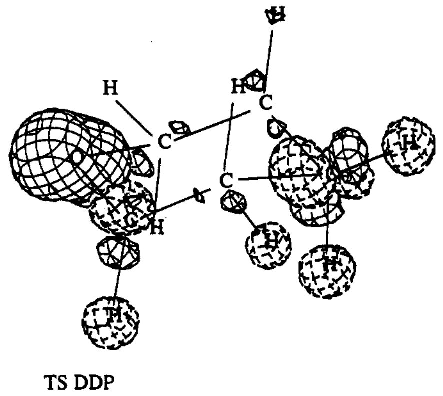

Figure 2. Electron density difference (EDD) plot for the transition state in water. Dotted contours represent regions where there is a depletion in electron density, and solid curves indicate regions with a gain in electron density, on transferring the TS from the gas phase into aqueous solution.

The qualitative picture of the solute electric polarization is depicted in Figure 2, which shows the difference between electron densities for the TS in the gas phase and in aqueous solution.[14,19] Clearly, the most apparent change is a gain in electron density on the oxygen atom (*vide ante*), a feature stressed by Cramer and Truhlar in their SCRF calculations.[5] This observation supports the suggestion of catalyst designs to incorporate specific hydrogen bonds to the oxygen in the TS.[6]

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(18) I thank an anonymous referee for suggestions to make this clearer.

(19) Severance, D. L.; Jorgensen, W. L. *Psi/88*; Yale University, 1990.