The effect of water on the Claisen rearrangement of allyl vinyl ether: theoretical methods including explicit solvent and electron correlation

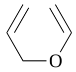
Jonathan M. Guest, J. Simon Craw, Mark A. Vincent and Ian H. Hillier*

Department of Chemistry, University of Manchester, Manchester, UK M13 9PL

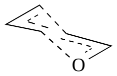
The effect of water on the Claisen rearrangement of allyl vinyl ether is modelled using both *ab initio* continuum and Monte Carlo simulation techniques. The effect of electron correlation and electronic polarisation of the solute is included in both treatments. In the continuum calculations these effects are included directly in the quantum mechanical treatment, whilst in the classical simulations solute atomic charges that reflect both correlation and polarisation are employed. The results of the calculations are used to predict both the barrier lowering and the kinetic isotope effects in aqueous solution. The role of both electron correlation, solute polarisation and the need to include explicit solvent molecules are all clearly identified by the results presented.

Introduction

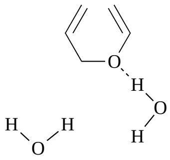
The effect of solvent, particularly water, on the mechanism and rate of chemical reactions is one of the central areas of condensed phase chemistry. Many prototype organic reactions have been studied using a variety of theoretical models with particular interest in the change in the structure and energetics of the transition state induced by the polar aqueous environment. One such reaction, the Claisen rearrangement of allyl vinyl ether **1** to pent-4-enal has been the subject of a number of theoretical studies, both in the gas phase[1–5] and in solution.[6–11] These have centred on the gas phase structure of the chair transition state **2** and how it is influenced by electron correlation,[2,4] the prediction of the gas phase kinetic isotope effects (KIE) at different levels of theory,[2,5] and the contributions to the observed lowering of the barrier height upon hydration.[6,8,9] Electron correlation (beyond MP2) is needed to predict a gas phase barrier close to the experimental value, whilst a density functional theory (DFT) treatment using the Becke3LYP (B3LYP) functional gives a transition state structure close to the best *ab initio* one.[2,4]



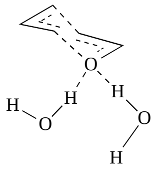
1



2



3



4

To study the reaction in an aqueous environment both *ab initio* continuum models[7,8] and those that include explicit water molecules[6,9] have been used. Two approaches to model the effect of explicit water molecules have been reported. First, a classical force-field within a Monte Carlo (MC) free energy perturbation (FEP) method has been used[9] to solvate structures along the reaction pathway obtained from *ab initio* electronic structure calculations of the gas phase reaction. A second approach includes explicit water molecules hydrogen bonded to the oxygen atom of the reactant and transition state as suggested from MC calculations, the composite systems being treated *via* an *ab initio* supermolecule method.[6] These treatments are generally successful in predicting the observed experimental barrier lowering of *ca.* 4 kcal mol^{-1} (1 cal = 4.184 J) arising from hydration, in spite of the various simplifications that they all employ, although the continuum models tend to underestimate the effect. For the gas phase reaction, the prediction of the KIEs has been used to judge the quality of predicted transition state structures and has given support to a DFT structure obtained using a B3LYP functional.[2,3] For the reaction in aqueous solution, the measured KIEs lead to the conclusion that bond breaking has not proceeded to a larger extent in the aqueous media than in non-polar *m*-xylene,[12] a conclusion at variance with transition state structures obtained using *ab initio* supermolecule[6] and continuum models.[4] In this paper we report results using models that employ fewer approximations than those previously described in order to understand the origin of the observed solvation effects. We focus on the role of electron correlation on the Claisen rearrangement of **1** occurring in aqueous media, within both continuum and explicit water models and use these models to predict both the change in the barrier due to solvation and the KIEs.

Computational details

Electronic structure calculations

Conventional *ab initio*[1] and density functional (DFT)[2] calculations of the gas phase structures of the reactant (AVE) and transition state (TS) using a 6-31G* basis set have previously been reported. Our calculations at the RHF level and using a B3LYP functional confirm these structures. We have included the effect of solvation firstly by using the polarisable continuum model (PCM)[13] at both the RHF and B3LYP levels, as implemented in GAUSSIAN94.[14] This method has been shown to be successful in predicting the effect of solvation on a wide variety of molecular structure and energetic features. The variant we use here (SCIPCM) employs an isodensity surface, determined self-consistently, to describe the solvent cavity, and allows both geometry optimisation, and characterisation of the nature of the stationary structures to be determined *via* calculation of the harmonic frequencies. The 0.0004 au isodensity surface and a relative permittivity of 78.4 were employed. Explicit solvent–solute interactions were modelled at the quantum mechanical level by studying a supermolecule in which two water molecules are hydrogen bonded to the oxygen atom of both **1** and **2** giving structures **3** and **4** respectively, which are similar to those found from classical simulation studies.[9] These supermolecule calculations were carried out at the B3LYP level.

The harmonic frequencies, calculated for the predicted stationary structures, were used to estimate the KIEs from tran-

Table 1 Calculated barrier (kcal mol^{-1}), transition state bond lengths (Å) and secondary kinetic isotope effects for Claisen rearrangement of allyl vinyl ether

					KIE	
Level		ΔE^a	r(C4–O)^b	r(C1–C6)	4,4-$^2H_2$	6,6-$^2H_2$
Expt.	$\varepsilon = 1$				1.092[19]	0.976[19]
	$\varepsilon = 78.4$				1.059[12]	0.981[12]
RHF	$\varepsilon = 1$	47.6	1.918 (1.406)	2.266	1.071	0.919
	$\varepsilon = 78.4$	45.7	1.969 (1.412)	2.320	1.173	0.898
B3LYP	$\varepsilon = 1$	27.7	1.902 (1.430)	2.312	1.058	0.938
	$\varepsilon = 78.4$	27.1	1.928 (1.436)	2.351	1.154	0.925
B3LYP(2H_2O)	$\varepsilon = 1$	21.4	1.974 (1.451)	2.457	1.158	0.942

[a] Zero-point energy included. [b] The values in parentheses are for the reactant **1**.

sition state theory within the ideal gas, rigid rotor, harmonic oscillator approximation. At the RHF level, the frequencies were scaled by the usual factor of 0.91, whilst at the DFT level, no scaling was employed. The values of the KIEs (k_H/k_D) are quoted with no correction for tunnelling.

In all cases, the formal atomic charges for the solutes to be used in the MC simulations were determined *via* a fit of the electrostatic potential surface using the Merz-Kollman (MK) method.[15] Electron correlation and solute polarisation is thus included implicitly in the MC simulations by the use of atomic charges obtained from the appropriate wavefunction.

Monte Carlo calculations

The MC simulations were performed with the BOSS program[16] employing isothermal–isobaric (NPT) ensembles with one solute molecule (with the internal degrees of freedom constrained at the appropriate geometry obtained from the electronic structure calculation) solvated by 740 TIP4P water molecules.[17] The intermolecular potential function comprised Coulomb and Lennard Jones (L-J) terms. The formal atomic charges for the solute were the MK values derived from the calculated electronic charge distributions. OPLS all-atom L-J parameters (σ,ε) were taken,[18] with geometric combining rules. Simulations were carried out at 25 °C and 1 atm pressure. Equilibration runs were performed for typically 1–2 × 10^6 configurations, followed by data collection for 2–4 × 10^6 configurations. The free energy perturbation (FEP) simulations were carried out both in the forward and backward directions using increments of 0.1 for the coupling parameter. The following FEP calculations were carried out employing molecular structures and associated atomic charges derived from different levels of electronic structure (RHF, B3LYP) and corresponding to the gas phase ($\varepsilon = 1.0$) and water ($\varepsilon = 78.4$) modelled at the SCIPCM level.

(*i*) The conversion of the reactant (RHF, $\varepsilon = 1.0$) to transition state at (RHF, $\varepsilon = 1.0$).

(*ii*) The conversion of the reactant initially at the (RHF, $\varepsilon = 1.0$) and (B3LYP, $\varepsilon = 1.0$) level to the reactant at the (RHF, $\varepsilon = 78.4$; B3LYP, $\varepsilon = 1.0$) and (B3LYP, $\varepsilon = 78.4$) levels respectively.

(*iii*) As (*ii*) for the transition state.

By construction of the appropriate cycle, these simulations enable the contribution of water to the free energy of activation to be estimated using structures and charge distributions obtained at the four levels of theory employed (RHF, $\varepsilon = 1.0$; RHF, $\varepsilon = 78.4$; B3LYP, $\varepsilon = 1.0$; B3LYP, $\varepsilon = 78.4$). For both the reactant and transition state described at the Hartree–Fock or B3LYP level the free energy of polarisation ΔG_{pol} was calculated from the free energy of the transformation eqn. (1),

$$\mathrm{A}^{\text{gas phase charges}}_{\text{solvated}} \xrightarrow{\Delta G_1} \mathrm{A}^{\text{solvated charges}}_{\text{solvated}} \qquad (1)$$

together with the distortion free energy (ΔG_{dist}), being the energy associated with changing the geometry and electron density of species A from the optimal gas phase values to those in the aqueous environment, obtained by the SCIPCM method at the appropriate level of theory. Thus eqn. (2) holds.

$$\Delta G_{pol} = \Delta G_1 + \Delta G_{dist} \qquad (2)$$

These calculations thus allow the effect of solute electron correlation and electron polarisation on the solvation free energy to be studied within an explicit solvent model.

Results and discussion

Structure and energetics from electronic structure calculations

The effect of hydration as modelled by the continuum approach is to produce a more open transition state with both the breaking and forming bonds, C4−O and C1−C6 respectively (see Table 2), being lengthened compared to the gas phase values (Table 1). This effect is evident at both the RHF and correlated (B3LYP) levels, although it is considerably greater at the Hartree–Fock level. When compared to the corresponding RHF calculations, the inclusion of electron correlation results in a shorter C−O and longer C−C length, thus predicting an earlier transition state. This effect is accentuated when the role of electron correlation on the reactant geometry is considered, when an increase in the C−O bond length is predicted, in contrast to the transition state results. The model that includes two explicit water molecules is seen to produce a considerably more open transition state when compared to the continuum results. The effect of both solvation and electron correlation are evident in the MK atomic charges shown in Table 2. For the transition state, the increased C−O bond polarity in the polar environment and the corresponding reduced polarity upon inclusion of electron correlation are both important effects which will influence the nature of the solvent–solute interactions. As far as the predicted barrier is concerned, the lowering due to solvation given by the continuum model is greater at the RHF than at the B3LYP level, in line with the greater change in the transition state structure at the RHF level.

When compared with the experimental barrier lowering of 3.5–4.7 kcal mol^{-1} [19,20] we have previously noted[7] that a PCM model at the RHF level with fixed atomic radii results in quite good agreement with experiment. The SCIPCM results reported here give a somewhat smaller barrier lowering at the RHF level (1.9 kcal mol^{-1}) which is further reduced (to 0.6 kcal mol^{-1}) at the B3LYP level. However, the inclusion of two explicit water molecules results in a substantially greater solvation effect, with a barrier lowering of 6.3 kcal mol^{-1}. Thus, there are indications that the continuum model underestimates the effect of solvation, whilst the explicit water model overestimates the rate acceleration due to hydration. It is of interest to note that the calculation involving explicit water molecules predicts a net charge transfer of 0.03e to each water molecule in the transition state structure, whilst in the reactant structure, there is essentially no charge transfer involving one water

Table 2 Potential derived charges for allyl vinyl ether

	RHF/6-31G*				B3LYP/6-31G*			
Structure	**1**	**1**	**2**	**2**	**1**	**1**	**2**	**2**
ε	1.0	78.4	1.0	78.4	1.0	78.4	1.0	78.4
C1	−0.621	−0.640	−0.487	−0.502	−0.559	−0.580	−0.386	−0.389
C2	0.172	0.172	0.241	0.200	0.146	0.149	0.176	0.134
O3	−0.375	−0.408	−0.436	−0.479	−0.313	−0.343	−0.345	−0.381
C4	0.370	0.383	−0.081	−0.064	0.300	0.311	−0.169	−0.161
C5	−0.245	−0.267	−0.352	−0.378	−0.191	−0.209	−0.178	−0.190
C6	−0.392	−0.403	−0.190	−0.178	−0.354	−0.365	−0.264	−0.263
H1	0.200	0.211	0.221	0.227	0.174	0.185	0.190	0.196
H1′	0.205	0.214	0.145	0.159	0.185	0.192	0.133	0.146
H2	0.123	0.131	0.074	0.099	0.105	0.111	0.058	0.080
H4	0.008	0.019	0.164	0.163	0.013	0.023	0.153	0.152
H4′	0.036	0.042	0.161	0.174	0.039	0.045	0.155	0.164
H5	0.166	0.173	0.207	0.215	0.142	0.150	0.163	0.171
H6	0.170	0.182	0.176	0.193	0.149	0.159	0.168	0.183
H6′	0.183	0.191	0.157	0.171	0.164	0.172	0.146	0.158

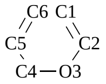


Table 3 Changes in free energies (kcal mol^{-1}) for perturbations indicated

AVE[a] $\varepsilon = 78.4$ B3LYP		AVE $\varepsilon = 78.4$ RHF		TS $\varepsilon = 78.4$ RHF		TS $\varepsilon = 78.4$ B3LYP
↑−0.38 ± 0.08[b] (0.20)		↑−0.30 ± 0.12 (0.24)		↑−2.42 ± 0.10 (1.06)		↑−1.14 ± 0.15 (0.63)
AVE $\varepsilon = 1.0$ B3LYP	← 0.74 ±0.09	AVE $\varepsilon = 1.0$ RHF	→ −3.81 ± 0.18	TS $\varepsilon = 1.0$ RHF	→ 2.18 ±0.10	TS $\varepsilon = 1.0$ B3LYP

[a] RHF and B3LYP represent respectively the RHF/6-31G* and Becke 3LYP/6-31G* optimised geometries and charges. [b] ΔG_{pol} and, in parentheses, ΔG_{dist}.

molecule, and the electron transfer to the other (0.01e) is much less than in the transition state.

The calculated KIEs (Table 1) largely follow the predicted structures, with an increase in the value at the 4-position, upon hydration. Indeed for the continuum calculations there is a monatonic increase in this calculated value with increase in the C–O length. The calculated value of the KIE at the 6-position is greater for the correlated than for the Hartree–Fock wavefunctions in line with the longer C–C distances. However, for both levels of wavefunction employed there is not the expected increase of the KIE accompanying the increase in C–C distance upon solvation as modelled by the continuum approach, although such an effect is seen for the explicit water calculation. Thus, none of the models are in agreement with experiment[12] which yields a reduced KIE at the 4-position when compared to the gas phase and hence suggests a less polar transition state. The somewhat larger value compared to the gas phase, reported experimentally at the 6-position, is predicted by the explicit water model, but not by the continuum treatments.

Results of the FEP simulations

The results of the various FEP simulations carried out are summarised in Table 3. The effect of polarisation of the solute is reflected in both the change in the molecular geometry from the continuum model (Table 1) and in the polarisation energies calculated from the FEP method (Table 3). Thus, at both the RHF and B3LYP levels solvation results in small and comparable increases in the C–O bond length of the reactant **1** with corresponding small and similar values of ΔG_{pol} (Table 3). For the transition state there is a considerably greater increase in the C–O length due to solvation, particularly at the RHF level, with correspondingly larger values of ΔG_{pol}. For all the species studied, the distortion energy (ΔG_{dist}) follows the trend in the values of ΔG_{pol}.

The use of these values of ΔG_{pol}, together with the free energy changes associated with the other transformations shown in Table 3 leads to the barrier lowering shown in Table 4. Both the reduced C–O bond polarity of the transition state arising from the inclusion of electron correlation and the increased polarity due to the effect of solvation, as previously discussed and witnessed by the atomic charges (Table 2), are clearly evident. Thus, using gas phase charges, the barrier lowering is reduced from 3.8 kcal mol^{-1} at the RHF level, to 2.4 kcal mol^{-1} when correlation effects are included (Table 4). The use of solvent polarised charges results in an increase in the barrier lowering at both the RHF and B3LYP levels, this effect being greater at the RHF than at the B3LYP level. Again using solvent polarised charges, correlation reduces the barrier lowering from approximately 6 to 3 kcal mol^{-1}. Thus, the effects of electron correlation and solvation act in opposite directions as far as the barrier lowering is concerned and it is of interest that the barrier lowering using RHF gas phase charges and B3LYP continuum charges are quite close (3.8 and 3.1 kcal mol^{-1}) due to the near cancellation of polarisation and correlation effects, as suggested in our previous study[7] of this reaction. Indeed as far as correlation with experimental data is concerned it is these two calculations that are closest to the experimental barrier lowering.

Conclusions

The effect of water on the Claisen rearrangement of allyl vinyl

Table 4 Contribution of water to the free energy of activation (kcal mol^{-1})

Level[a]	MC/FEP	PCM	Oxygen charge in TS
RHF, $\varepsilon = 1.0$	−3.8		−0.44
RHF, $\varepsilon = 78.4$	−5.9	−1.9	−0.48
B3LYP, $\varepsilon = 1.0$	−2.4		−0.35
B3LYP, $\varepsilon = 78.4$	−3.1	−0.6	−0.38

[a] RHF and B3LYP represent respectively the RHF/6-31G* and Becke 3LYP/6-31G* optimised geometries and charges.

ether has been much studied theoretically since it provides a system ideally suited to test models of solvation. The much-used models of solvation, employing either simulation studies with explicit water molecules, but with classical force-fields, or quantum continuum models which lack explicit solvent, may both be inadequate to study chemical reactions where both explicit solvent–solute interactions and solute polarisation are important, and may require the inclusion of electron correlation effects. The models we have used have clearly shown the importance of both these effects and show that an acceptable way of including these may be *via* the use of atomic charges derived from correlated wavefunctions in which solute polarisation is included by a continuum description. A study of this reaction using a combined semi-empirical quantum mechanical and molecular mechanical (QM/MM) approach in Monte Carlo simulations[11] has also identified the importance of differential solute polarization. Our calculations show that the opposing effects of electron polarisation and correlation of the solute can result in simulations using charges derived from gas phase, RHF wavefunctions, that are in good agreement with experiment, as found previously by Severance and Jorgensen[9] for the reaction studied in this paper. A model that includes a limited number of explicit water molecules modelled quantum mechanically suggests that charge transfer to the first solvation shell of solvent is more important in the transition state than in the reactant and results in a further lowering of the barrier. There is thus clearly a role for developing computationally feasible models that model the solvent quantum mechanically. Finally, we note that although the barrier lowering due to solvation is now quite well understood, the disagreement between the calculated and experimental change in the KIEs at the 4-position, previously noted, is still unresolved.

Acknowledgements

We thank the EPSRC for support of this research and Professor W. L. Jorgensen for the use of the BOSS program.

References

1 R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki and E. Wimmer, *J. Am. Chem. Soc.*, 1988, **110**, 2314.
2 O. Wiest, K. A. Black and K. N. Houk, *J. Am. Chem. Soc.*, 1994, **116**, 10336.
3 H. Y. Yoo and K. N. Houk, *J. Am. Chem. Soc.*, 1994, **116**, 12047.
4 M. M. Davidson, I. H. Hillier and M. A. Vincent, *Chem. Phys. Lett.*, 1995, **246**, 536.
5 M. M. Davidson and I. H. Hillier, *Chem. Phys. Lett.*, 1994, **225**, 293.
6 M. M. Davidson and I. H. Hillier, *J. Phys. Chem.*, 1995, **99**, 6748.
7 M. M. Davidson, I. H. Hillier, R. J. Hall and N. A. Burton, *J. Am. Chem. Soc.*, 1994, **116**, 9294.
8 R. J. Hall, M. M. Davidson, N. A. Burton and I. H. Hillier, *J. Phys. Chem.*, 1995, **99**, 921.
9 D. L. Severance and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1992, **114**, 10966.
10 C. J. Cramer and D. G. Truhlar, *J. Am. Chem. Soc.*, 1992, **114**, 8794.
11 J. Gao, *J. Am. Chem. Soc.*, 1994, **116**, 1563.
12 J. J. Gajewski and N. L. Brichford, *J. Am. Chem. Soc.*, 1994, **116**, 3165.
13 S. Miertus, E. Scrocco and J. Tomasi, *Chem. Phys.*, 1981, **55**, 117.
14 M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, GAUSSIAN 94, Revision A.1, Gaussian, Inc., Pittsburgh, PA, 1995.
15 B. H. Besler, K. M. Merz and P. A. Kollman, *J. Comput. Chem.*, 1990, **11**, 431.
16 W. L. Jorgensen, BOSS, Version 3.5, Yale University, New Haven, CT, 1994.
17 W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey and M. L. Klein, *J. Chem. Phys.*, 1983, **79**, 926.
18 W. L. Jorgensen and J. Tirado-Rives, *J. Am. Chem. Soc.*, 1988, **110**, 1657; W. L. Jorgensen and D. L. Severance, *J. Am. Chem. Soc.*, 1990, **112**, 4768.
19 J. J. Gajewski and N. D. Conrad, *J. Am. Chem. Soc.*, 1979, **101**, 6693.
20 E. B. Brandes, P. A. Grieco and J. J. Gajewski, *J. Org. Chem.*, 1989, **54**, 515.

Paper 6/04379H
Received 24*th June* 1996
Accepted 2*nd September* 1996