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Effect of Solvent on the Claisen Rearrangement of Allyl Vinyl Ether Using *ab Initio* Continuum Methods

Mark M. Davidson,[†] Ian H. Hillier,[*,†] Richard J. Hall,[†] and Neil A. Burton[‡]

Contribution from the Chemistry Department and Manchester Computing Centre, University of Manchester, Manchester M13 9PL, UK

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Abstract: A number of continuum models, combined with *ab initio* wave functions, are used to predict the effect of solvation by water and by di-*n*-butyl ether on the Claisen rearrangement of allyl vinyl ether. The polarizable continuum model (PCM) is the most successful, although the lowering of the barrier height in water is slightly underestimated. The effect of electron correlation both on the gas phase barrier and in water is predicted using the B–LYP density functional. A comparison of the molecular dipole moments from the different calculations yields a rationalization of the success of simulation calculations based upon gas phase SCF charge distributions.

Introduction

Quantum mechanical methods, both *ab initio* and semiempirical, for locating stationary points on potential energy surfaces and for following reaction pathways are now well-established[1–3] and have been widely used for studying gas phase chemical reactions. There is now increasing interest in the extension of these methods to study condensed phase reactions, which include the majority of chemical and biochemical reactions. The understanding of the effect of solvation on reaction rate is one of the most important condensed phase reactivity problems and has been tackled by two different approaches. In the first the solvent molecules (usually water) are explicitly considered and their interaction with the solute modeled by simulation methods (molecular dynamics (MD), Monte Carlo (MC)) employing suitably parametrized force fields. Recent examples of this approach are studies of the effect of hydration, by Severance and Jorgensen on the Claisen rearrangement[4] and by Peng and Merz[5] on the nucleophilic attack of OH^- on CO_2. In these studies structures along the gas phase reaction path were solvated using MD or MC methods.

An alternative approach is to model the solvent as a dielectric continuum, thus avoiding the inclusion of explicit solute–solvent interactions. The development of the reaction field approach following Onsager[6] and Kirkwood[7] has resulted in continuum models being implemented within both semiempirical and *ab initio* molecular orbital methods. The various methods differ in the description of the solute charge density and of the shape of the solvent cavity, the latter reflecting the shape of the solute molecule. The simplest self-consistent reaction field (SCRF) approach considers a spherical cavity and a single center multipole expansion of the solute charge density truncated at the dipole ($\ell = 1$) term.[8] In spite of its simplicity, this model has been successful in predicting the effect of solvation on a number of properties such as tautomeric equilibria[9,10] and barriers to rotation.[11] A more refined model, developed by Rivail and co-workers,[12] uses an ellipsoidal cavity, with dimensions based upon the solute van der Waals surface and a multipole expansion for the solute charge density beyond the dipole description. In situations when the solute molecule has polar groups, but a small net dipole moment, such a higher order multipole expansion is needed.[13] In an alternative model, the polarizable continuum model (PCM), developed by Tomasi and co-workers,[14] the solvent cavity directly reflects the molecular shape, being constructed from atomic centered spheres of appropriate radii, with the solvent polarization modeled by virtual charges on the surface of the spheres. The value of this approach has been shown in a variety of applications.[15]

In this paper we describe the use of a number of variants of the continuum model to predict the effect of solvents of varying dielectric constant on the Claisen rearrangement of allyl vinyl either (AVE) (**1**) to 4-pentenal (**2**). This reaction has been studied in the gas phase using both semiempirical[16] and *ab initio*[17] MO methods. At the *ab initio* level it has been found that correlation effects at the MP2 level cause a considerable reduction in the barrier and yield a value closer to experiment. In view of this we here investigate including electron correlation *via* a density functional (DF) method in predicting the gas phase barrier followed by the use of both Hartree–Fock and DF wave functions within continuum models to model solvation. Both continuum models within the semiempirical MO AM1 method[18] and explicit solvation along the reaction pathway using MC simulations[4] have been employed to study the effect of water on the reaction rate. Interest in this reaction is stimulated by its relationship to the enzyme-catalyzed rearrangement of chorismic acid (**3**) to

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[†] Chemistry Department.

[‡] Manchester Computing Centre.

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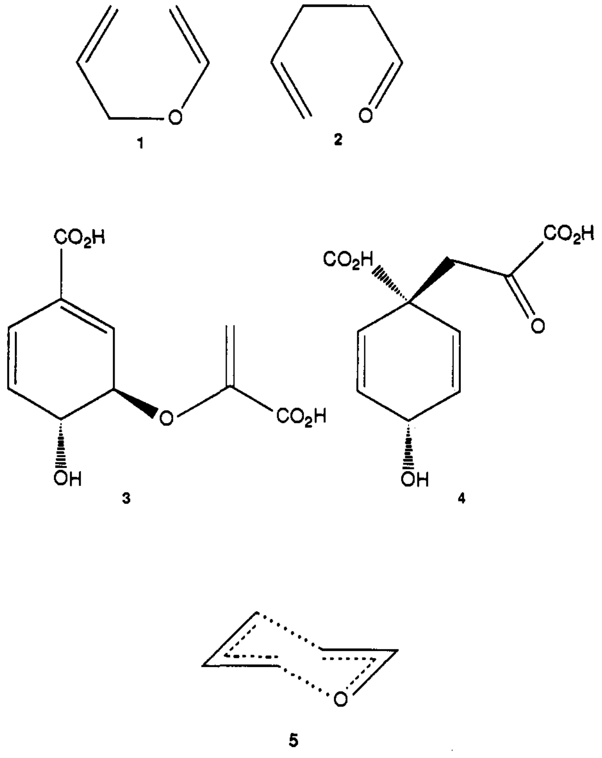
Chart 1



prephenic acid (**4**), which is a key process in the shikimate biosynthetic pathway[19] that occurs in bacteria, fungi, and higher plants.

Computational Details

The calculations were carried out using a 6-31G* basis. Geometry optimization of the isolated molecule at the SCF level yielded the global minimum energy and transition state structures reported by Vance et al.[17] The barrier involving the lower energy chair transition structure **5** (48.8 kcal mol^{-1}) is considerably larger than the experimental value (29.8 kcal mol^{-1}).[20] Vance et al. have shown that introduction of correlation effects at the MP2 level lowers the predicted barrier to 24.6 kcal mol^{-1}, using the RHF/3-21G optimized geometries. In view of the considerable interest in the larger system (**3** → **4**) where the calculation of correlation effects using conventional *ab initio* methods may be computationally prohibitive we have used a density function method (a Becke Lee–Yang–Parr functional, B-LYP[21] within a Kohn Sham treatment[22]) to calculate the barrier for the reaction (**1** → **2**). We have used our own computer code[23] implemented within the GAUSSIAN92 program. In view of the more favorable scaling of such calculations, with molecular size, compared to *ab initio* methods, the value of the density functional approach for studying the reaction (**3** → **4**) is strongly suggested.

Returning now to modeling the effect of solvation on the barrier height we adopt the strategy of solvating stationary point structures determined for the gas phase reaction. This approach is in line with that of Severance and Jorgensen[4] in their MC studies. A more complete treatment would involve consideration of the effect of solvation on the structures of the reactant and transition state, either by geometry optimization within a continuum model or by considerably more extensive MC calculations. Solvation is expected to have significant differential effects on reactant and transition state structures when extensive charge separation occurs, for example, when ionic products result. This extreme situation is not found for the reaction considered here.

Table 1. Energies of Chair Transition State (**5**) Relative to Allyl Vinyl Ether (**1**) (kcal mol^{-1})

level	ϵ	ΔE^a
RHF/6-31G*	1.0	48.9
B-LYP/6-31G*	1.0	23.3
RHF/6-31G* (ℓ = 1, sphere)	78.54	48.2 (0.7)
RHF/6-31G* (ℓ = 6, ellip)	78.54	48.1 (0.8)
RHF/6-31G* (PCM)	78.54	46.1 (2.8)
B-LYP/6-31G* (ℓ = 6, ellip)	78.54	23.0 (0.3)
RHF/6-31G* (ℓ = 6, ellip)	3.08	48.4 (0.5)
RHF/6-31G* (PCM)	3.08	47.3 (1.6)

[a] The relative electrostatic contribution to solvation is given in parentheses.

Within a Hartree–Fock model we have investigated the predictions of three continuum models on the barrier height for the reaction **1** → **2**: (i) a spherical solvent cavity with radius determined by the method implemented within GAUSSIAN92[24] based upon computing the 0.001 au electron density envelope, scaling by 1.33, and adding 0.5 Å to the resulting cavity radius[9] (this approach yielded a cavity radius of 3.93 and 3.90 Å for AVE(**1**) and the transition state, respectively; the solute charge density was truncated at the $\ell = 1$ level; (ii) an ellipsoidal cavity, with dimensions determined by the method of Rivail et al.[12] using the van der Waals surface and the solute charge distribution expanded up to $\ell = 6$ ($\ell = 6$, ellip) (iii) the polarizable continuum model (PCM), with atomic radii of 1.5, 1.875, and 1.75 Å for H, C, and O, respectively, as suggested by Orozco et al.[25]

To investigate the effect on the solvation energy of electron correlation we have included the SCRF continuum model of Rivail et al. within our implementation of the density functional method. Since the SCRF model results in modification of the one-electron terms, it can be readily incorporated into the iterative solution of the Kohn Sham equations of the density functional method.

We may write the total Fock matrix as

$$F^{\mathrm{total}} = H + G' + F^{\mathrm{XC}} + F^{\mathrm{scrf}}$$

where H is the normal one-electron kinetic energy and potential contribution and G' is the Coulomb (two-electron) contribution

$$G' = \sum_{\sigma\tau} D\sigma\tau(\mu\nu|\sigma\tau)$$

The exchange-correlation contribution is obtained from the functional $f[\rho(r), \nabla\rho(r)]$[22] and basis set ϕ.

$$F^{\mathrm{XC}}_{\mu\nu} = \left\langle \phi_\mu \left| \frac{\delta f}{\delta\rho} \right| \phi_\nu \right\rangle + \left\langle \frac{\delta f}{\delta\nabla\rho} \cdot \nabla(\phi_\mu \cdot \phi_\nu) \right\rangle$$

The solvation polarization term[12]

$$F^{\mathrm{scrf}} = \sum_{\ell=0}^{\infty} \sum_{m=-\ell}^{m=\ell} R_\ell^m \, \langle \phi_\mu | M_\ell^m | \phi_\upsilon \rangle$$

where

$$R_\ell^m = \sum_{\ell'=0}^{\infty} \sum_{m'=-\ell'}^{m'=\ell'} M_{\ell'}^{m'} f_{\ell\ell'}^{mm'}$$

The reaction field factors $f_{\ell\ell'}^{mm'}$ are dependent on the cavity size and shape and the solvent dielectric. M_ℓ^m is the mth element of the multipole operator of rank ℓ and is dependent on the (one-particle) density matrix by contraction with the relevant spherical harmonics.

We note that our Kohn Sham correlated SCRF procedure has an implicit self-consistency associated with using the exact reaction field during the energy evaluation. This is similar to the generalized method described for correlated solvation energies[11] which are obtained iteratively from energy and energy derivative (for dipole) evaluations. Since the Kohn Sham multipole can be evaluated as the expectation value of the

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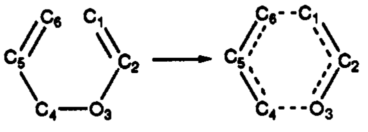
Table 2. Atomic Charges (Including Attached Hydrogens) and Dipole Moment (D) in Gas Phase and in Water



1 **5**

	ϵ	C-1	C-2	O-3	C-4	C-5	C-6	μ
reactant **1**								
RHF/6-31G*	1	–0.14	0.41	–0.61	0.31	0.07	–0.03	0.91
B-LYP/6-31G*	1	–0.12	0.27	–0.39	0.19	0.09	–0.05	0.85
RHF/6-31G* (ℓ = 6, ellip)	78.54	–0.15	0.42	–0.62	0.32	0.06	–0.03	1.05
RHF/6-31G* (PCM)	78.54	–0.13	0.41	–0.64	0.33	0.05	–0.01	1.35
B-LYP/6-31G* (ℓ = 6, ellip)	78.54	–0.12	0.27	–0.40	0.20	0.09	–0.04	0.98
chair TS **5**								
RHF/6-31G*	1	–0.11	0.40	–0.60	0.23	0.00	0.07	2.51
B-LYP/6-31G*	1	–0.04	0.27	–0.41	0.10	0.10	–0.01	1.89
RHF/6-31G* (ℓ = 6, ellip)	78.54	–0.11	0.40	–0.63	0.25	–0.01	0.10	3.08
RHF/6-31G* (PCM)	78.54	–0.10	0.41	–0.67	0.26	–0.02	0.12	3.48
B-LYP/6-31G* (ℓ = 6, ellip)	78.54	–0.03	0.26	–0.43	0.10	0.10	0.01	2.33

multipole operator, computationally expensive derivative calculations can thus be avoided. This method differs from the (MP2) double perturbation methods which obtain correlated solvation energies based upon a reaction field using the unperturbed density whereas the density functional solvent polarization term is based on a correlated density.[26]

Finally we have estimated the cavitation and dispersive energy contributions to the solvation energies of **1** and **5** in water. For the calculation of the dispersive energies we use the method of Floris and Tomasi.[27] Cavitation energies were estimated using a hard sphere diameter of 2.75 Å for water within the scaled particle theory of Pierotti.[28]

Calculations were carried out for solvation by both dibutyl ether (ϵ = 3.08) and water (ϵ = 78.54). Experimental data on the Claisen reaction involving **1** have been reported which yield estimates of the rate enhancement in both these solvents.[29,30]

Computational Results

The computational results are summarized in Table 1, showing the predicted energy differences between AVE **1** and the chair transition state structure **5**, both structures being obtain at the HF/6-31G* level. Our value for the gas phase reaction at the Hartree–Fock level, 48.9 kcal mol^{-1}, is essentially the same as that reported by Vance et al.[17] The use of the B-LYP exchange correlation functional reduces this barrier to 23.3 kcal mol^{-1}, a value close to that (24.6 kcal mol^{-1}) obtained at the MP2 level.[17] The corresponding Mulliken charge distributions and calculated dipole moments (Table 2) show the expected decrease in polarity on including correlation effects, particularly for the transition state. The relatively large charge reorganization associated with electron correlation is clearly responsible for the considerable lowering of the barrier.

For solvation in water at the RHF level, a clear trend emerges from the results for the three continuum models (Table 1). When the multipole expansion is truncated at the ℓ = 1 level, the **relative** solvation energy is essentially the same as that found when terms up to ℓ = 6 are included in the expansion. However, this is not to say that terms beyond ℓ = 1 are insignificant in determining the absolute electrostatic contribution to the solvation energy. Thus, in water the electrostatic terms for AVE **1** and the TS **5** are 0.1 and 0.8 kcal mol^{-1}, respectively, at the ℓ = 1 level and 2.4 and 3.2 kcal mol^{-1}, respectively, at the ℓ = 6 level. In this case, as was observed in a study of a range of applications of the continuum model, the **relative** contribution of terms beyond ℓ = 1 is often small.[31] However, when the PCM treatment is used, a significant increase in both the absolute and relative solvation energies is found. Thus for **1** and **5**, the solvation energies are found to be 3.5 and 6.3 kcal mol^{-1}. A similar trend is found for solvation in dibutyl ether, with the SCRF method giving a relative solvation energy of 0.5 kcal mol^{-1} and the PCM approach giving 1.6 kcal mol^{-1}. For solvation in water, our estimates of the cavitation and dispersion energy contributions lead to an additional lowering of the barrier by 0.6 kcal mol^{-1}. We now compare our predicted changes in the activation barrier, upon solvation, with experiment. Analysis of the experimental data[4,29,30] suggests a rate enhancement (at 75 °C) in di-*n*-butyl ether of ~9 and in water of ~10^3, compared to the gas phase, leading to a barrier lowering of 1.5 and 4.7 kcal mol^{-1}, respectively, if classical transition state theory is used. Thus, at the Hartree–Fock level, it can be seen (Table 1) that the PCM approach is closest to the experimental data. For solvation in di-*n*-butyl ether this model yields an excellent prediction of the experimental data. For solvation in water, when cavitation and dispersion contributions are included, the PCM model yields a barrier lowering of 3.4 kcal mol^{-1}, an underestimate of the experimental value by ~1 kcal mol^{-1}. The greater solvation energy predicted by the PCM approach is not unexpected when the charge distributions (Table 2) are examined. For all models there is considerably more electron polarization in the transition state (**5**) than in the ground state (**1**) as shown by both the formal atomic charges and the dipole moment. However, this polarization is significantly greater for the PCM method.

Turning now to our calculations that include electron correlation, we see (Table 1) that the lowering of the barrier in water is somewhat less than that predicted at the SCF level. This effect can be attributed to the reduction in the polarity occurring upon including correlation. Thus, although the degree of polarization due to the solvent occurring at the correlation level is similar to that found at the SCF level, there is a far greater reduction in the dipole moment of the transition state than of the ground state when correlation effects are included.

Conclusions

In this paper we have critically examined the value of continuum models, combined with *ab initio* wave functions, to predict the change in barrier height of the Claisen reaction, due to solvation effects. At the SCF level, the polarizable continuum model, which includes a more complete description of both the molecular shape and the molecular charge distribution, results in better agreement with experiment than those models using spherical or elliptical

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cavities and single-center, truncated multipole expansions. Indeed for di-*n*-butyl ether the PCM description is in excellent agreement with experiment. For solvation in water, the experimental barrier height reduction may be somewhat underestimated. A rather greater underestimate of the barrier height reduction was found by Cramer and Truhlar[18] using their semiempirical effective-Hamiltonian SCF approach for modeling aqueous solvation and by our SCRF treatments (Table 1).

The MC simulations of Severance and Jorgensen[4] yield a barrier reduction of 3.9 kcal mol^{-1}, a value larger than that given by both semiempirical[18] and our *ab initio* continuum models. This difference can be attributed to the explicit consideration of hydrogen bonding effects in the MC simulations, important for hydration, but presumably not so for solvation in di-*n*-butyl ether.

Our use of a density functional approach within the SCRF model identifies a potentially powerful way of including electron correlation within *ab initio* continuum models. The greater effect of electron correlation on the transition state, compared to ground state energy, is predicted by this method, and results in improved agreement of the calculated barrier with gas phase experimental data. Such barrier lowering is reflected in the considerably reduced polarity of the transition state, compared to that of the ground state, and leads to a reduction in the calculated differential solvation energy. In view of the large effect that electron correlation has on the charge distribution, particularly of the transition state, it is of value to seek a rationalization of the success of the simulation approach based upon charge distributions obtained at the SCF level.[4] We see (Table 2) that solute polarization and electron correlation act in opposite directions so that their **net** effect is to yield a molecular dipole moment (though not individual atomic charges) in water for both the reactant and the transition state that is very close to the corresponding values predicted at the SCF level for the gas phase species. Hence intermolecular potentials obtained from gas phase SCF calculations may be appropriate for actual condensed phase simulations.

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