

The Claisen Rearrangement. Response to Solvents and Substituents: The Case for Both Hydrophobic and Hydrogen Bond Acceleration in Water and for a Variable Transition State

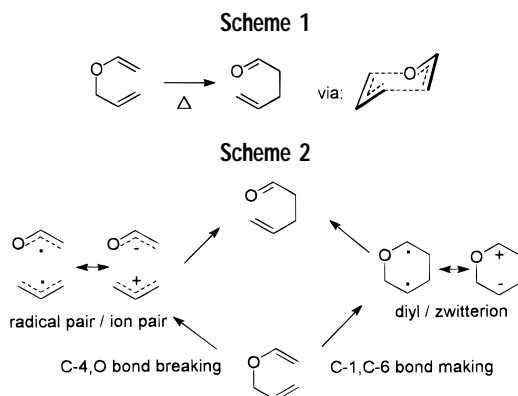
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The thermally induced 3,3-sigmatropic shift of allyl vinyl ethers to γ,δ -unsaturated carbonyl compounds, i.e., the Claisen rearrangement (Scheme 1), is an important reaction in synthetic organic chemistry and is the prototype for the conversion of chorismate to prephenate in the biosynthesis of phenylalanine.¹ Because of the simplicity of the reaction, its mechanism has been the object of numerous experimental and theoretical studies. The concern of this Account is not only how the reaction proceeds but how well theory reproduces the experimentally observed kinetic isotope effects, solvent effects, and substituent effects. It is our contention that, despite great progress, theory is lacking, particularly in the area of solvent effects where hydrophobic acceleration is an important factor. Indeed, we argue that hydrophobic effects are critically important in the Claisen rearrangement and in many other reactions, including solvolysis of *tert*-alkyl chlorides. Further, the response of the Claisen rearrangement to substituents is, in our view, predictable, not on the basis of an "aromatic" transition state of fixed geometry but rather on the basis of a transition state of variable geometry whose structure and stability respond to the nature and placement of substituents.

The Claisen rearrangement is a unimolecular process with activation parameters that suggest a cyclic transition state.² Stereochemical studies have revealed transfer of asymmetry from the double bonds to the newly formed σ bond in a manner that suggests not only a transition state with cyclic delocalization of the six electrons of the original π bonds and the C–O σ bond but a three-dimensional geometry which resembles a chairlike structure (Scheme 1).³ This would be consistent with the conservation of orbital symmetry rules.⁴ However, the observations could also be rationalized by formation of a chairlike oxacyclohexanediyl or zwitterion-like transition state or intermedi-

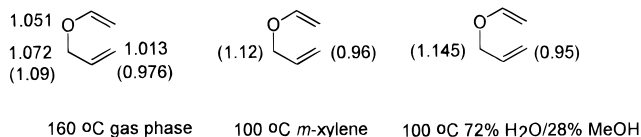


ate resulting from complete C-1–C-6 bond making (Scheme 2). Alternatively, dissociation of the C-4–O bond into an oxallyl–allyl radical pair or an enolate ion and an allyl cation pair in a chairlike relationship can also account for the stereochemistry provided that tumbling of one or the other of the three heavy atom units does not occur. While charged intermediates or transition states are unlikely for reactions occurring in the gas phase or in hydrocarbon solvents, they might be involved when the reactions are run in polar solvents. The radical-pair and diyl structures represent opposite extremes for, and not resonance structures of, a delocalized transition state. Indeed, through the use of secondary deuterium kinetic isotope effects, the all-carbon variant of the Claisen rearrangement, namely, the Cope rearrangement, has been shown to have a transition state structure which varies between these extremes in response to the placement of radical-stabilizing substituents.⁵

The mechanistic questions which will be explored in this Account are (1) the structure of the transition state in the reaction of the parent compound, allyl vinyl ether, (2) the extent of charge separation in the transition state for the parent reaction, and (3) the variation in transition state structure and charge separation upon perturbation by solvents and substituents. An experimental answer to the first question can be inferred from kinetic isotope effects since any other change of substituent or solvent might perturb the transition state structure and energy. With respect to the second question, the α secondary deuterium kinetic isotope effect (k^H/k^D) in the formation of ion pairs is known for an oxygen leaving group at room temperature,⁶ so this can be used as a measure of ion-pair formation. Whether or not the extent of charge separation in the parent system can be determined by solvent perturbations is problematic since the perturba-

Joseph J. Gajewski was born in Hammond, IN, in 1939. After receiving a B.S. degree in chemistry from Loyola (Chicago), having been "turned on" to organic chemistry by (the late) Jim Wilt, he worked with Jerome A. Berson for the Ph.D. degree (Southern California and Wisconsin). After an NSF Postdoctoral with Ronald Breslow (Columbia) he moved to Bloomington in 1966. Besides research and teaching, he enjoys serving the organic community in a variety of roles. Downhill skiing and racing a Flying Dutchman occupy some of his leisure time.

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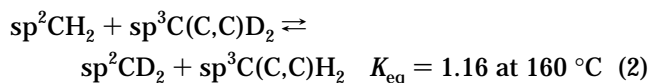
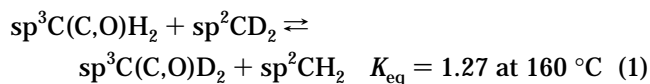
Chart 1. Experimental Heavy Atom, $^{16}\text{O}/^{18}\text{O}$, $^{12}\text{C}/^{14}\text{C}$, and (H_2/D_2) , Kinetic Isotope Effects in the Claisen Rearrangement

tion can alter the energy surface in the direction of increased polar character in more polar solvents. Nonetheless, the response of the system might provide a measure of the maximal charge separation in nonpolar solvents.

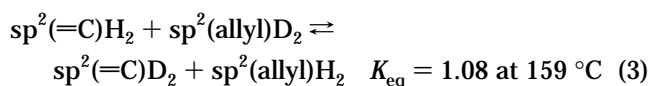
Isotope Effects in the Rearrangement of Allyl Vinyl Ether Itself

Summary: The transition state in the parent reaction is early with more C–O bond cleavage than terminal C–C bond formation.

The secondary deuterium KIEs ($k^{\text{H}}/k^{\text{D}_2}$) at C-4 and C-6 of allyl vinyl ether in the Claisen rearrangement in the gas phase at 160 °C were determined by Conrad to be 1.09 ± 0.005 and 0.976 ± 0.005 , respectively (Chart 1).⁷ These were compared with fractionation factor estimates, which are the effects of deuterium at each of the two carbons in the reactant and product in the equilibria described by eqs 1 and 2.



The equilibrium constant in eq 1 was obtained from equilibration of 1,1- and 3,3-dideuterioallyl acetate at 160 °C, and the value for the equilibrium in eq 2 was obtained from numerous equilibrium studies involving 1,3- and 3,3-sigmatropic shifts, all assuming that atoms one removed from those bonded to the isotope-bearing center have no effect on the equilibria. With these values, which are taken to represent the maximum secondary kinetic isotope effect possible, the percentage of bond breaking and making in the gas-phase Claisen rearrangement was estimated at 45% and 17%, respectively. More recent work, which found that the equilibrium fractionation factor between deuterium and hydrogen on an sp^2 olefinic carbon vs deuterium on an sp^2 allyl radical carbon favors two deuteriums on the former by 1.08 at 159 °C (eq 3),



suggests that the original fractionation factor for formation of an allylic radical by complete bond breaking was underestimated by focusing on the isotopic fractionation between the reactant and product. With revisions in the

fractionation factors, the percentages of bond breaking and making were revised to 37% and 28%, respectively.⁸

However, a Shine–Wm. Saunders collaboration determined the ^{18}O effect, and the ^{14}C effect at C-4 and C-6 at 160 °C (Chart 1),⁹ and these heavy atom effects could be reproduced by a BEBOVIB calculation with a transition state model that requires 40–50% bond breaking and 20% bond making. This calculation is more in line with the original estimates from the deuterium KIEs, suggesting that the corrections applied recently to the deuterium effects are not necessary unless bond breaking is much more advanced. Nonetheless, the deuterium and heavy atom isotope effects are not in great disagreement considering the very different basis of their interpretation (comparisons to interpolations of fractionation factors and direct force field analysis of primary effects).

An important insight can be gained from the fact that the sum of the bonding changes at the bond breaking and making sites is less than 100%, namely, that the transition state must resemble more the reactant than the product. This is not unexpected in view of the large exothermicity of the reaction. According to Hammond's postulate,¹⁰ this should result in an early transition state. It is also significant that the isotope effects indicate that the transition state resembles the radical-pair alternative more than the diyl alternative. We suggested in our original paper on the deuterium KIEs in the Claisen rearrangement that the radical-pair alternative is more stable than the 1,4-oxacyclohexanediyl species since the transition state should more resemble the more stable alternative.⁷ This behavior is consistent with Thornton's perpendicular effect, which summarizes the organic chemist's intuition on how perturbations other than those on reaction exergonicity might effect changes in mechanism.¹¹

Isotope Effects in Aqueous Media

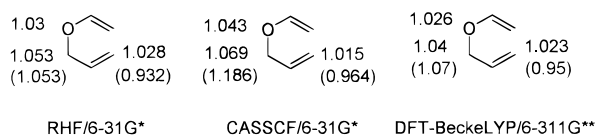
Summary: The secondary deuterium kinetic isotope effects in the Claisen rearrangement in aqueous media are within experimental error of those in nonpolar solvents.

In order to detect changes in transition state structure in response to more polar solvents, Brichford determined the deuterium kinetic isotope effects at C-4 and C-6 of allyl vinyl ether in *m*-xylene and in aqueous methanol solvents at 100 °C. The results are given in Chart 1 where the standard deviation in the effect at C-4 is 0.04 and that

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Chart 2. Calculated Heavy Atom, $^{16}\text{O}/^{18}\text{O}$, $^{12}\text{C}/^{14}\text{C}$, and (H_2/D_2) , Kinetic Isotope Effects in the Claisen Rearrangement



at C-6 is 0.02 in both solvent systems. The similarity in the KIEs is noteworthy. There appears to be no significant increase in bond breaking in more aqueous media that might be associated with formation of ion pairs or substantially greater dissociation of the two allylic moieties. Further, extrapolation of the 4,4- D_2 isotope effects to 25 °C results in a value of ca. 1.09/D, which is less than two-thirds that expected for formation of an ion pair.¹²

Theory and KIEs

Summary: Theory has been modestly successful in reproducing the KIEs and energies of 3,3-shift transition states.

Semiempirical theory applied to Claisen and Cope rearrangement transition states gives very poor agreement with experimentally determined secondary α deuterium kinetic isotope effects.¹³ This is because the diyl extreme of Scheme 2 is calculated to be the intermediate in these rearrangements. The results of *ab initio* calculations reproduce the deuterium and heavy atom KIEs better than semiempirical theory, but the fit is not superb, and different approaches give rather different results. Thus, a restricted Hartree–Fock, RHF, calculation by Houk et al. with a 6-31G* basis set gives relatively short transition state bonds (Chart 2). This results in bond breaking KIEs that are only 40–60% of those observed and gives bond making values that are roughly twice as large as those observed.¹⁴ The RHF calculation also reveals little change in charge distribution from the ground to transition state in the Claisen rearrangement. A complete active space self-consistent field, CASSCF, calculation with 6-31G* basis set by Houk¹⁴ does better with the heavy atom isotope effects but overestimates the deuterium isotope effects by a factor of 2 because it gives very long transition state σ bonds. The CASSCF calculation also reveals some charge increase in the Claisen rearrangement transition state (+0.15 at carbon and –0.23 at oxygen), and these charges indicate a 2 D change from the ground to transition state.

The best computational results appear to be from density functional theory (DFT) using the BeckeLYP functional for the 6-311G** basis set.¹⁵ The empirical nature of this approach might be of concern, but it has done well with the Cope rearrangement transition state and isotope effects.¹⁵ The DFT transition state for the Claisen rearrangement is intermediate between those from

the RHF and CASSCF calculations, and this suggests that there is roughly half the charge separation derived from the CASSCF calculation which would indicate a 1 D change in dipole moment from the reactant to the transition state.

Experimental Solvent Effects on the Claisen Rearrangement

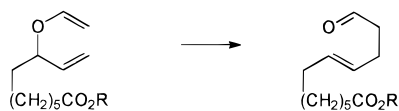
Summary: The Claisen rearrangement is more than 200 times faster in water than in cyclohexane; solvent studies suggest that both solvent self-association (hydrophobicity in the case of water) and hydrogen bond donation are important factors.

Carpenter¹⁶ was the first to note that the rate of Claisen rearrangement of allyl vinyl ether itself increased in increasingly aqueous media. This effect was utilized by Grieco¹⁷ to improve the synthetic utility of the reaction. However, the data presented by the Cornell group did not correlate with solvent $E_T(30)$ values.¹⁸ In more aqueous environments, the rates were increasingly faster than expected on the basis of a reasonable correlation with this solvent parameter in less polar media; that is, a plot of $\ln k$ vs $E_T(30)$ curved upward at higher $E_T(30)$ values. To extend the kinetic data to a wider range of solvents, Brandes attached a hydrophilic group at C-4 of allyl vinyl ether, namely, a hexamethylene chain terminating in a sodium carboxylate.¹⁹ This allowed examination of the rate in polar media, and by esterification of the acid, the rate of the reaction could also be determined in nonpolar solvents. Importantly, in those solvents where both the carboxylate and the ester were soluble, the rates were the same within a factor of 2. Thus, the response of the rearrangement could be examined over a wide variety of different solvent types. Table 1 lists the relative rate constants in various solvents along with the values of two parameters that characterize the effect of solvent on the Claisen rearrangement, namely, the cohesive energy density and the hydrogen bond donor ability of the solvent.

There is a 214-fold difference in the rate of rearrangement of this allyl vinyl ether on taking the reaction out of cyclohexane and placing it in water. Such a large rate difference is remarkable and useful, but what does it really mean in terms of mechanism? *An important clue as to the major factor in the rearrangement can be derived from the observation of the 7-fold increase of the rate in water relative to that in 2,2,2-trifluoroethanol (TFE) solvent.* The polarity of the two solvents as measured by the Kirkwood–Onsager function, $(\epsilon - 1)/(2\epsilon + 1)$,²⁰ is similar for both solvents, so dielectric effects cannot be an important factor in explaining the difference in rates. Further, 2,2,2-

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Table 1. Relative Rate Constants for a Claisen Rearrangement of a Soluble Allyl Vinyl Ether Derivative in Various Solvents^a

solvent	k_{rel} (R = Na)	k_{rel} (R = CH ₃)	CED ^b	α' ^c
water	214		0.9270	0.2582
1,2,2-trifluoroethanol	31	56	0.2314	0.2902
methanol	9.4	8.6	0.3461	0.1958
ethanol		6.1	0.2736	0.1789
isopropyl alcohol		5.0	0.2250	0.1424
dimethyl sulfoxide		3.2	0.2850	0.0685
acetonitrile		3.1	0.2326	0.0662
acetone		2.1	0.1530	0.0356
benzene		2.0	0.1414	0.0089
cyclohexane		1.0	0.1134	0.0000

^a Reference 19. ^b Cohesive energy density of solvent in units of $\text{cm}^{-3}\cdot\text{mol}^{-1}$, calculated by dividing the heat of vaporization of the solvent by its molar volume and by RT (ref 24). ^c Transfer free energies of chloride ion with the Kirkwood–Onsager dielectric contribution, $(\epsilon - 1)/(2\epsilon + 1)$, and CED contribution subtracted and then divided by $100(RT)$ (ref 12b). This represents the hydrogen bond donor ability in bulk solvents.

trifluoroethanol is a better hydrogen bond donor solvent than water as judged by a 2.5 kcal/mol preference by chloride ion for bulk TFE over bulk water.²¹ Therefore, if hydrogen bond changes between the ground state and transition state were the major factor, the reaction should proceed faster in TFE.

The most reasonable hypothesis for the increased rate of the Claisen rearrangement in water vs TFE is hydrophobic destabilization of the reactant state relative to the transition state. Importantly, the free energy of transfer of nonpolar compounds between solvents correlates well²² with the cohesive energy density (CED) of the solvent,²³ so that the destabilization of nonpolar materials in water (or more appropriately, the destabilization of the system: water–nonpolar solute) can be quantified. The extent of destabilization would appear to be a function of the volume of the solute since the solvent CED has the units of pressure.²³ The negative activation volume determined for the Claisen rearrangement²⁴ implies that the transition state would be destabilized less than the reactant in water solvent.

Hydrophobic effects have been invoked previously to account for the dramatic rate acceleration of the Diels–Alder reaction in aqueous media, particularly with cyclopentadiene.²⁵ It is noteworthy that these reactions must have a negative activation volume, which is consistent with greater destabilization of the reactant state than the transition state in water solvent.

Solvent Effect Correlations

Attempts to characterize the effect of solvent on reactions have a long history, and despite the fact that a single solvent parameter, namely, $E_T(30)$, has enjoyed some success, its origin in wavelength shift in the UV spectrum of a zwitterionic dye¹⁸ introduces the complexity of excited states into ground state behavior. Multiparameter approaches were first proposed by Koppel and Palm,²⁶ but the most extensive analysis of factors responsible for solvent effects is due to Taft.²⁷ One of the most important parameters in the Taft analysis is π^* , which is also derived from shifts in the UV absorption of dyes but with modifications due to “experience”. Therefore, any attempt to use this approach requires assessment of the π^* parameter. In an important study, Beak²⁸ replaced the π^* parameter by the Kirkwood–Onsager dielectric function²⁰ and used the Taft hydrogen bond donor and acceptor parameters, α and β , respectively, to obtain good correlation of some tautomeric equilibrium data as a function of solvent. Our attempt to assess the relative magnitude of factors contributing to solvent effects on the rate of the Claisen rearrangement used as parameters the Kirkwood–Onsager dielectric function,²⁰ the CED term,²⁴ and both chloride ion and potassium ion transfer free energies²¹ between various solvents and water (eq 4).²²

$$\ln k \text{ (or } K_{eq}) = c_1(\epsilon - 1)/(2\epsilon + 1) + c_2(\text{CED}) + c_3\alpha' + c_4\beta' + c_5 \quad (4)$$

The latter two factors, α' and β' , represent the hydrogen bond donation and solvent basicity, respectively, of solvents in eq 4 (see Table 1 for values of the solvent CED and α'). The ion transfer data between bulk solvents should be compared with the α and β parameters used by Taft.²⁷ The latter are derived from spectroscopic examination of specific hydrogen bonding interactions in nonpolar solvents and should be interpreted as characteristic of single solvent molecule interactions with a single substrate molecule rather than indicative of bulk solvent interactions. However, our α' values derived from bulk solvation of chloride ion correlate well with Taft's α values, and our β' values are reasonably correlated with Taft's β values, so both the parameters derived from transference data and from spectroscopic studies reflect the total hydrogen bond donicity or acceptor ability of bulk solvents. *This is important because it might be argued that water, due to its smaller size, might donate more hydrogen bonds than TFE in bulk, but this is not consistent with the chloride ion transfer data.*

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(23) Hildebrand, J. H.; Prousnitz, J. M.; Scott, R. L. *Regular and Related Solutions*; Van Nostrand-Reinhold: Princeton, 1970. Hildebrand, J. H.; Scott, R. L. *Regular Solutions*; Prentice-Hall: Englewood Cliffs, NJ, 1962. The solvent CED is the solvent heat of vaporization minus RT divided by the molar volume. For water the value in pressure units is 22,000 atm!

(24) ΔV (activation) from external pressure studies on the Claisen rearrangement is $-10 \text{ cm}^3/\text{mol}$: Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370.

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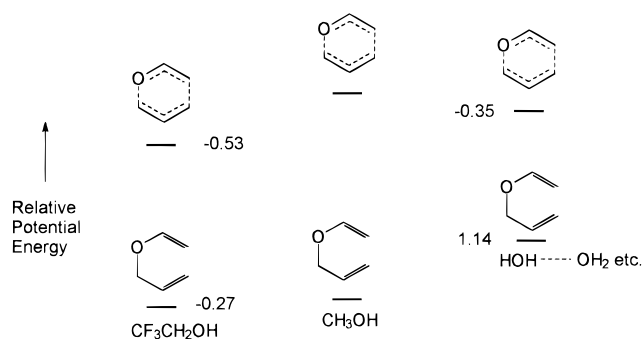


FIGURE 1. Solvent effects on the ground state and transition state in the Claisen rearrangement reaction (kcal/mol) relative to methanol from ref 12b.

More recently, the hydrogen bond and solvent basicity parameters, α' and β' , were updated by removing a small contribution of the solvent CED and the dielectric effect from the free energies of chloride ion and potassium ion transfer. Further, these parameters were extended to the gas phase since the free energies of aquation of these ions are known.^{12b} Both the original and extended parameter sets for eq 4 provided good correlations of kinetic data from the Claisen rearrangement and Diels–Alder reactions.^{12b} Remarkably, with the Claisen rearrangement rate data, the correlation requires no contribution from the Kirkwood–Onsager term nor from the solvent basicity term.^{12b} The only important factors are the solvent CED and solvent hydrogen bond donicity, α' (Table 1). In TFE solvent, the hydrogen bond donation term is most important, but in water solvent, the total CED contribution to the energy responsible for the rate acceleration is more important than the hydrogen bond contribution by a ratio of 56:44. Figure 1 provides a measure of the effect of 2,2,2-trifluoroethanol and water on the ground state and the transition state relative to methanol solvent, assuming that all of the hydrogen bond donor effect is in the transition state and the entire CED effect is on the ground state.

Hydrophobicity as a Factor in Other Organic Reactions

Results similar to those described above are obtained with the Diels–Alder reaction of naphthoquinone and cyclopentadiene and with the *tert*-butyl chloride solvolysis reaction.^{12b} The latter reaction, which is taught to thousands of undergraduates every year, is invariably described as a reaction whose rate increases in polar solvents because they stabilize a polar transition state and whose rate increases in hydrogen bond donor solvents because they stabilize the departing chloride ion in the transition state. Yet in the regime of hydroxylic solvents, the rate effect is dominated by the self-association of the solvent, a hypothesis studied and advanced by Winstein and Grunwald almost 50 years ago to explain the high rate of solvolysis of *tert*-butyl chloride in water relative to that in methanol.²⁹ Nonetheless, hydrogen bond donation to small negative ions is important in all hydroxylic solvents but is even more so in fluoroalcohol solvents where the low pK_a values suggest excellent hydrogen bond donation. Using Abraham's data on the free energy of transfer of *tert*-butyl chloride and of its S_N1 transition state between bulk solvents (ref 29c), the relative effectiveness of the

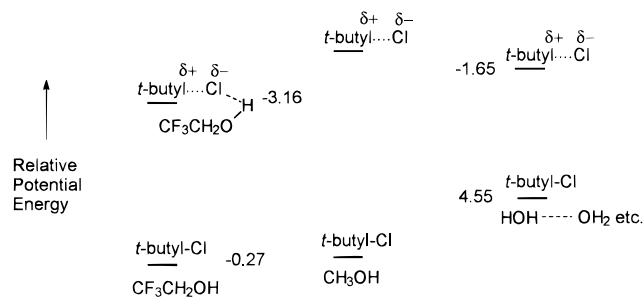


FIGURE 2. Solvent effects on the ground state and transition state in the S_N1 reaction of *tert*-butyl chloride (kcal/mol) relative to methanol from ref 29c.

various solvents to increase the rate of the S_N1 reaction can be cast in terms of two factors, hydrogen bond donation to stabilize the transition state and solvent self-association as measured by the CED to destabilize the ground state. Figure 2 displays these effects relative to the solvent methanol and makes clear the dramatic effect of water solvent on the ground state.

In general, ground state destabilization in aqueous media, probably involving destabilization of the water solvent, is an important factor in determining rates of reactions where negative volume changes occur. This also suggests that homolytic dissociation reactions, which involve increases in volume from the ground to transition state, would be inhibited in aqueous media, but there appears to be insufficient data to examine this hypothesis.

Solvent Effect Correlations: Causality or Merely Correlation?

The validity of a factor analysis of solvent effects depends first on whether the factors themselves are independent. This can only be guaranteed by a wide selection of solvents. Ideally the solvents of choice are the gas phase, a saturated hydrocarbon, a dipolar aprotic solvent like DMSO, a good hydrogen bond donor solvent like TFE, and a solvent that is highly self-associated like water or formamide. To obtain statistics, only six solvents are required for a factor analysis with four parameters and one constant provided that the solvents represent each of the four factors described above. Omission of solvents that represent a particular factor may invalidate the correlation, and if that factor is an important contributor, it is unlikely that a good correlation of the data could be obtained.

Another test of validity is whether or not the coefficients of the parameters are reasonable in light of the theory represented by each of the factors. The four factors utilized in eq 4 appear adequate to describe solvent effects in many reactions; indeed, they may even provide information about the charge, volume, and hydrogen bonding changes from the ground to transition state,^{12b} but other solvent characteristics might be involved. For instance,

(29) (a) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846. (b) Winstein, S.; Fainberg, A. H. *Ibid.* **1957**, *79*, 5937. Smith, S. G. Fainberg, A. H.; Winstein, S. *Ibid.* **1961**, *83*, 618. See also: (c) Abraham, M. H.; Grellier, P. L.; Nasehzadeh, A.; Walker, R. A. C. *J. Chem. Soc.* **1988**, 1717. For one of the few citations to the work listed in ref 29b, see also: (d) Harris, J. M.; Wamser, C. C. *Fundamentals of Organic Reaction Mechanisms*; John Wiley & Sons, Inc.: New York, 1976; p 143.

solvent polarizability has received little attention here. This factor provides a small corrective term for aromatic and halogenated solvents in the Taft scheme.²⁷ However, attempts to incorporate it as a parameter in eq 4 using the usual formulation $(3/4)(MW)(\eta^2 - 1)/(\pi RT\rho^*(\eta^2 + 2))$ where η is the refractive index of the solvent reveals that its presence does not improve the correlations cited here. Another concern is the polarization or change in structure of the solute in response to different solvents. This factor is absent in the analyses cited here as is any consideration of solvent viscosity which would be particularly important in bimolecular reactions. While future work should focus on these alternative contributions to solvent rate effects, the factors utilized in eq 4 cannot be ignored.

Theory: Charge Separation and Solvent Effects

Summary: Current theoretical approaches to solvent effects in the Claisen rearrangement appear to underestimate the importance of hydrophobicity.

The solvation of quantum-mechanically derived ground states and transition states from gas-phase calculations has been evaluated by Jorgensen by placing each in a bath of hundreds of solvent molecules.³⁰ The method involves the use of empirically derived interaction potentials between atoms of the solvent as well as between solute and solvent atoms without polarization of the solute and involves evaluation of stable states of the system by Monte-Carlo methods using Metropolis sampling procedures. With the RHF/6-31G* transition state for the Claisen rearrangement, a 3.85 kcal/mol free energy benefit was calculated³⁰ for the reaction rate in water vs the gas phase. At this calculational level there is little change in dipole moment from the ground to transition state so the energy change could not have come from a Kirkwood–Onsager dielectric effect. However, changes in geometry might lead to some contribution from monopoles and higher multipoles. The calculations did reveal two hydrogen bonds to the transition state carbonyl oxygen compared with one hydrogen bond to the oxygen in the reactant, so the entire rate effect in water was attributed to an increase in hydrogen bonding. Hydrophobic effects were given little consideration.

In a related effort, Gao³¹ started with the gas-phase reaction coordinate and performed quantum mechanical/molecular mechanical calculations in which the solute was modeled using the AM1 semiempirical Hamiltonian modified by the solvent dynamics. Thus, changes in the transition state electronic structure resulting from immersion in water could be calculated. The rate acceleration calculated between the gas phase and water was a factor of 368 at 25 °C. This corresponds to a free energy of activation change of 3.5 kcal/mol, and charge increase on the oxygen was identified as the major contributor. Other approaches by Gao have led to similar conclusions.³²

In another study, Cramer and Truhlar have pursued a combined AM1–Born solvation continuum approach to the question of water acceleration of the Claisen rear-

angement. The most recent version,³³ like its predecessors, uses an exposed surface area calculation as a way of modeling the hydrophobic effect. The results suggest that hydrophobic packing is relatively unimportant in water and that electric polarization and first-hydration-sphere hydrophilic effects dominate the calculated acceleration which provide a rate factor of 1400 when using the CASSCF/6-31G* transition state geometry calculated by Houk.

Finally, continuum solvent models derived from Kirkwood–Onsager approaches to solvation are also included in the Gaussian programs, and Hillier has used these to assess solvation in the Claisen rearrangement. In the most recent study two water molecules were placed around the oxygen of allyl vinyl ether and its transition state for formation of 4-pentenal, and all were imbedded in a cavity of high dielectric solvent and were subjected to DFT calculations with the B3LYP functional.³⁴ The transition state was lowered by 6.3 kcal/mol, and the calculated kinetic isotope effects are not dissimilar to the experimental values of Scheme 2 ($k^H/k^{C-4-D_2} = 1.158$ and $k^H/k^{C-6-D_2} = 0.942$). However, the authors indicate that the transition state is more open than in nonpolar media where the calculated secondary deuterium KIEs are 1.06 and 0.95, respectively, which are values that are not consistent with the data of Scheme 2 in xylene solvent. Thus, these calculations provide approximately twice as large an energy difference between aqueous and nonpolar media as is observed and provide an inappropriately large difference in kinetic isotope effects in aqueous and nonpolar solvents. Further, it is surprising that the differential hydrophobicity of allyl vinyl ether and its transition state for a 3,3-shift plays no role in the rate differences calculated by all of the theoretical approaches described in this section despite the fact that solubilities of weakly polar solutes in aqueous media are a function of the molecular size, and presumably shape, of the solute.³⁵

Rate Effects in the 3,3-Sigmatropic Shifts of Substituted Allyl Vinyl Ethers

Summary: The substituent rate effects can be explained by alteration in transition state structure between the two extremes of Scheme 2 in response to the nature and position of substituents.

For completeness, the effects of substituents on the Claisen rearrangement should receive some attention, particularly since they can be dramatic. The effect of electron donors and acceptors as well as radical-stabilizing groups are summarized in Chart 3.

While cyano substitution at every site has been investigated,³⁶ the interpretation of the effect is ambiguous because this group can function both as an electron-withdrawing group and as a radical-stabilizing group. As a result of examination of trifluoromethyl substitution,

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Chart 3. Rates of Claisen Rearrangement Relative to That of Allyl Vinyl Ether

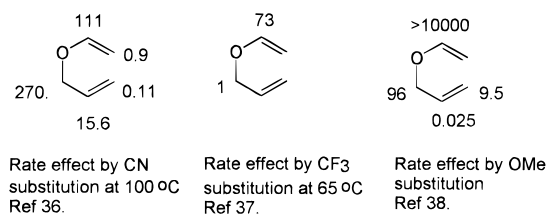
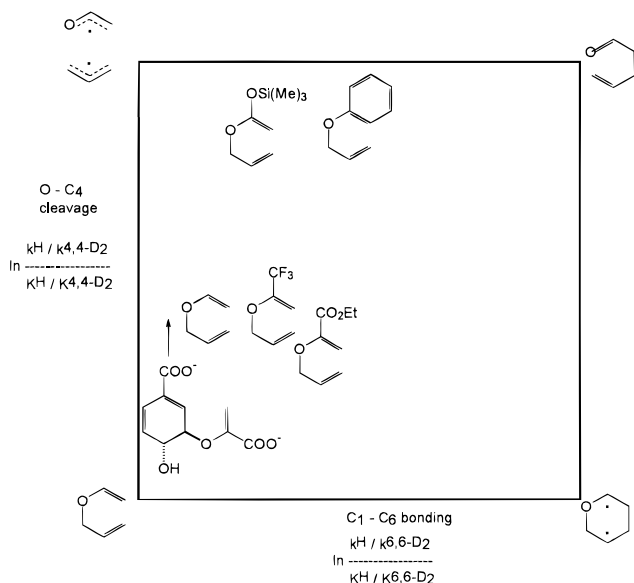


Chart 4



which has little effect on the rate, we have argued that the cyano group at C-4 (the numbering starts at the terminal carbon nearest oxygen) stabilizes radical character in the transition state.³⁷ Donor substituents like methoxy have little rate effect except at C-2 and C-4, where in the latter case some carbocationic character might be induced by the substituent in the transition state,³⁸ but in the former case³⁹ the donor substituent is not positioned to stabilize an enolate ion. Indeed, a donor substituent at C-2 would destabilize a potential enolate ion, so more detailed consideration of this type of substitution is necessary.

The case of donor substituents at C-2 as well as those of substituents at other positions requires examination of the variation in transition state structure as deduced from secondary deuterium kinetic isotope effects. This variation is as dramatic as the rate effects and provides a challenging mechanistic problem. Chart 4 provides a "bird's eye" view of a three-dimensional energy surface where the two structural coordinates are the O-C-4 bond breaking and the C-1-C-6 bond making coordinates of Scheme 2. These are characterized by the natural logarithm of the ratio of the deuterium kinetic isotope effect at the appropriate site divided by the maximum expected deuterium

isotope effect which is deduced from equilibrium fractionation of deuterium between reactants and products uncorrected for the known deuterium fractionation between sp^2 olefinic carbon and sp^2 allyl radical carbon,⁸ which apparently comes into play only when the transition state closely resembles the bond-broken alternative.

These diagrams, which were first used by More O'Ferrall⁴⁰ and popularized by Jencks,⁴¹ are derived from efforts by Kreevoy and Albery⁴² to characterize the identity reactions of Marcus theory for electron and proton transfer reactions.⁴³

Given in the scheme are the transition state positions for representative Claisen rearrangements based on the natural logarithm of the ratio of the KIE to the equilibrium isotope effects (see eqs 1 and 2). The data on the parent system and for the 2-substituted materials were determined in our laboratory.^{7,37,44} The KIEs for the aromatic Claisen rearrangement were determined by McMichael,⁴⁵ and Knowles determined the tritium kinetic isotope effects for the uncatalyzed rearrangement of chorismate to prephenate in aqueous solution.⁴⁶ The Knowles results are included in the scheme, recognizing that the isotope effect for tritium can be converted to that for deuterium from the mass effect on zero point energies. The variation observed can be explained⁴⁷ by a hypothesis similar to that utilized by us to analyze the variation of the isotope effect in the 3,3-shift of 1,5-hexadienes,⁵ namely, that Hammond's postulate¹⁰ rationalizes the position of the transition state with respect to the reactant and product and that Thornton's perpendicular effect rationalizes the position of the transition state between the two possible nonconcerted alternatives. That is, the transition state should more resemble the more stable of the two possible nonconcerted alternative structures, diyl and allylic radical pairs.⁴⁸ The relative energies of the transition states for the nonconcerted alternatives and the relative energy of the product can be used as parameters in a nonlinear free energy relationship derived from hyperbolic paraboloid energy surfaces to characterize the changes in activation free energies for the Claisen rearrangement as a function of substitution.⁴⁷

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