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Secondary Deuterium Kinetic Isotope Effects in the Aqueous Claisen Rearrangement: Evidence against an Ionic Transition State

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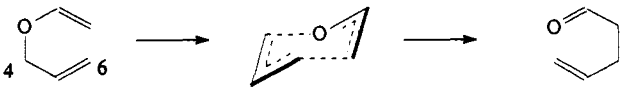
The thermally induced 3,3-shift of allyl vinyl (and phenyl) ethers, a rearrangement known as the Claisen rearrangement, provides synthetic access to γ,δ-unsaturated carbonyl compounds with transfer of double bond geometry *via* a chairlike transition state.[1] Given the importance of the reaction, both experimental and theoretical efforts have focused on the mechanistic details. In particular, the effect of solvent has been pursued. White first showed that the rate of the aromatic Claisen rearrangement responded positively to polar solvents.[2] More recently, Carpenter[3] as well as Grieco[4] showed that the reaction proceeds substantially faster in more aqueous solvent systems. Quantification of the effect was provided by Brandes, who examined the rate of rearrangement of an allyl vinyl ether with a remote ester or carboxylate function in solvents ranging from cyclohexane to water. The overall rate factor over this range is 214-fold at 60 °C, which is substantially less than what might be anticipated if bond heterolysis were important.[5]

The origin of the rate acceleration has been the subject of speculative hypotheses. Carpenter suggested that in aqueous media the transition state resembled an allyl cation–enolate ion pair.[3] More recently, Cramer and Truhlar, using an AM1 semiempirical MO approach with electric polarization of solvent and solute as well as a cavity term, suggested that the acceleration "is caused by electric polarization and first-hydration-shell hydrophilic effects".[6] They also point out that "A favorable polarization contribution is found to be associated with efficient sequestration of charges of opposite sign into separate regions of space". This also appears to be an ion pair explanation. However, most notable is that the magnitude of the aqueous solvent rate effect for the rearrangement of the parent allyl vinyl ether is calculated to be only –0.75 kcal/mol. This corresponds to a rate acceleration of no more than a factor of 3 at 100 °C.

A recently published attempt to dissect polar solvent effects in general into a dielectric term, a cohesive energy density term, and specific hydrogen bond-donating and -accepting terms revealed that the Claisen rearrangement was responding to specific hydrogen bond-donating ability of the solvent and the cohesive energy density and not to the solvent dielectric constant or hydrogen bond-accepting ability.[7] Furthermore, theoretical work by Severance and Jorgensen[8] revealed little change in dipole moment from ground state to transition state but increased hydrogen bonding to the transition state. These latter two studies therefore suggest little ion pair formation in the transition state.

Here we report the results of a determination of the secondary deuterium kinetic isotope effects (KIEs) at the C-4 and C-6 of allyl vinyl ether in the relatively nonpolar medium *m*-xylene and in 75% and 25% aqueous methanol-d_4 in D_2O at 100 °C. These reactions were studied at temperatures well below that of the gas-phase reaction, where the normal KIE at C-4 is roughly one third of the maximum value for complete bond fission and the inverse KIE at C-6 is only one eighth of the maximum value for bond making.[9] We anticipate that formation of an allyl cation–enolate ion pair would result in a much larger normal KIE at C-4 in aqueous solution than in nonpolar media and that this KIE will approach the maximum value for conversion of an sp^3 carbon which is attached to an oxygen to an sp^2 carbon of an allyl cation. A reasonable value would be 1.35 for two deuteriums at 100 °C. This is the expected ratio of equilibrium constants for the Claisen rearrangement with protio and 4,4-dideuterio-substituted allyl vinyl ether.[10] An experimental verification of this value is not available, but the secondary KIE for two deuteriums at C-1 in the ethanolysis of 3,3-dimethylallyl chloride is 1.20 at 54.2 °C with little temperature dependence.[11] Since the α-deuterium KIE for solvolysis with chloride leaving groups is usually smaller by 33% than those with oxygen leaving groups,[12] a value greater than 1.30 is possible, particularly when it is recognized that in the cases studied, the medium may not be sufficiently polar to promote rate-determining formation of a free carbocation, where the isotope effect might be maximized.



The rates of the 3,3-shifts in 25% aqueous solution (containing approximately 1% pyridine) were followed by capillary GC using a Carbowax column and direct injection of the reaction solution. The rates in 75% aqueous methanol were followed by reverse-phase liquid chromatography using 75% aqueous methanol as the mobile phase. The latter analytical system provided higher precision but was not amenable to use of more aqueous solvents. The rearrangements in *m*-xylene were followed by capillary GC on a DB-5 column. It is clear from Table 1 that the more aqueous solvents accelerate the rate by as much as a factor of 15 in 25% aqueous methanol relative to *m*-xylene. This is only a factor of one-third less than the rate ratio observed by Brandes for the rearrangements in 25% aqueous methanol versus benzene. Table 1 also makes it clear that the KIE at C-4 in 75% aqueous media is less than that in the reaction in *m*-xylene or in the gas phase (and it is reassuring that the extent of bond breaking in *m*-xylene and in the gas phase are nearly the same as measured by the ratio of the natural logarithms of the KIE and the maximum expected KIE at the temperature of the reaction). Therefore, bond breaking has not proceeded to a larger extent in the aqueous media than in *m*-xylene. Of interest is the fact that bond making has proceeded to a smaller extent in 75% aqueous methanol than in *m*-xylene, as judged by the KIE at C-6. This may also be the case in the 25% aqueous methanol experiments, but the large error makes the argument less firm. Increased hydrogen bonding to the transition state is not inconsistent with the KIEs. Also, a rate increase due to increased solvent cohesive energy density because the transition state volume is reduced relative to reactant is also not inconsistent with the KIEs.

Finally, deliberate attempts to generate the allyl cation or allyl cation–leaving group ion pair by unbuffered methanolysis of allyl mesylate-1,1-d_2 at room temperature resulted in product with no label scrambling within the limits of NMR detection (<3%). As pointed out previously by DeWolfe and Young, allyl chloride

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[1] Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2.

[2] White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196, 3585.

[3] Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

[4] Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849.

[5] Brandes, E. B.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.

[6] Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794.

[7] Gajewski, J. J. *J. Org. Chem.* **1992**, *57*, 5500.

[8] Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966.

[9] Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.

[10] Gajewski, J. J. In *Isotopes In Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, p 115.

[11] Belanic-Lipovac, V.; Borcic, S.; Sunko, D. E. *Croat. Chem. Acta* **1965**, *37*, 61.

[12] Shiner, V. J., Jr.; Rapp, M. W.; Pinnick, H. R., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 232.

0002-7863/94/1516-3165$04.50/0

Table 1. Secondary Deuterium Kinetic Isotope Effects for the 3,3-Shift of Allyl Vinyl Ether in *m*-Xylene and in 25% and 75% Aqueous Methanol[a]

compd	t, (°C)	solvent	k^H/k^{D_2}	ln KIE/ln KIE$_{max}$	k^H (10^{-6} s^{-1})
4-d_2	100	*m*-xylene	1.119 (0.019)	0.37 (0.04)	4.7
6-d_2	100	*m*-xylene	0.953 (0.015	0.155 (0.05)	
4-d_2	100	75% MeOH	1.059 (0.007)	0.191 (0.02)	46.1
6-d_2	100	75% MeOH	0.981 (0.018)	0.06 (0.06)	
4-d_2	100	25% MeOH	1.145 (0.04)	0.44 (0.09)	180.3
6-d_2	100	25% MeOH	0.958 (0.04)	0.14 (0.15)	
4-d_2	160.3	gas phase[9]	1.092 (0.005)	0.33 (0.02)	0.19 (extrapolated)
6-d_2	160.3	gas phase[9]	0.98 (0.005)	0.16 (0.05)	

[a] % refers to vol % of methanol, and the numbers in parentheses are the standard deviations.

undergoes bimolecular substitution chemistry upon solvolysis.[13] Thus, allyl cation itself cannot be generated with a good leaving group in aqueous media in competition with direct substitution chemistry. This is not inconsistent with the observations and conclusions above. Perhaps it can be argued that an intimate ion pair can be formed which results in allylic rearrangement only when the leaving group is an enolate ion. However, there is still a matter of rate to consider. The mesylate of allyl alcohol has a half-life in 25% aqueous methanol of 6 h at 25 °C. Considering the difference in pK_a of the leaving group conjugate acids (methanesulfonic acid and an enol), the ionization of allyl vinyl ether would be an exceedingly slow reaction even at 100 °C. It is not unreasonable that allylic cation-like species might be involved in Claisen rearrangements with good donor substitutents on the allyl moiety, but it certainly is not the case in the parent system. Even the 4-alkoxy-substituted allyl vinyl ether rearrangement,[14] which occurs 20–100 times faster than that of the parent allyl vinyl ethers, shows a rate increase in polar media relative to benzene solvent which represents no more than 20% of the free energy change that might be brought about on the ionization of *tert*-butyl chloride.

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(13) DeWolfe, R. H.; Young, W. G. *Chem. Rev.* **1956**, *56*, 753.

(14) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.