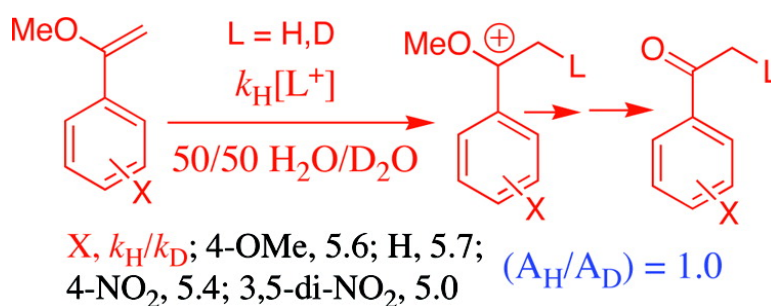## Communication

A Simple Method To Determine Kinetic Deuterium Isotope Effects Provides Evidence that Proton Transfer to Carbon Proceeds over and Not through the Reaction Barrier

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A Simple Method To Determine Kinetic Deuterium Isotope Effects Provides Evidence that Proton Transfer to Carbon Proceeds over and Not through the Reaction Barrier

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We report a fast, simple, and general method to determine primary kinetic isotope effects (KIEs) on proton transfer in hydroxylic solvents, and its application to obtain primary deuterium isotope effects on protonation of ring-substituted α-methoxystyrenes X-**1** (Scheme 1) over a broad range of temperature and thermodynamic driving force. These data provide evidence that hydron transfer at X-**1** proceeds by passing over a reaction barrier, as opposed to tunneling through the barrier and insight into the relationship between the primary kinetic isotope effect and the transition state structure.

Proton transfer at carbon is an apparently simple reaction, whose profound importance in chemistry and biology has led to interest in providing a theoretical description of the reaction coordinate profile.[1] Kinetic isotope effects on proton transfer at carbon can be predicted by theory and determined by experiment. Advances in theory and computational power have been incorporated into recent theoretical studies on KIEs,[2] but there has been little effort to extend classic experimental studies using modern experimental methods. Studies of this type are needed to provide a *reality check* for theory.

Ratios of second-order rate constants, k_H/k_D, have been reported for lyonium-ion-catalyzed protonation of a broad series of vinyl ethers in H$_2$O and in D$_2$O.[3] This ratio decreases with decreasing vinyl ether reactivity from $k_H/k_D = 4.1$ for protonation of ethyl cyclooctenyl ether ($k_H = 623$ M^{-1} s^{-1} at 25°) to $k_H/k_D = 2.4$ for protonation of phenyl vinyl ether ($k_H = 0.00328$ M^{-1} s^{-1}). These data may be explained either by a model in which there is increasing zero-point-energy (zpe) of the O–L bond maintained in the transition state for proton transfer as the reaction becomes strongly thermodynamically favorable or unfavorable[4] or by including a correction for quantum mechanical tunneling through the reaction barrier, which is largest when $\Delta G_o = 0$.[5] A similar correlation between the KIE and thermodynamic driving force has been reported for deprotonation of H- and D-labeled carbon acids.[5]

The correlation between reaction driving force and k_H/k_D for the effectively irreversible protonation of vinyl ethers to form oxocarbenium ions—the first step in their hydrolysis reactions—is poor.[3] This is because of the broad range of the structures of the reacting carbon bases examined. Further, the absolute thermodynamic driving force for vinyl ether protonation is generally not known nor can the experimental rate constant ratio k_H/k_D for these reactions in H$_2$O and in D$_2$O be easily partitioned into the contribution of the primary KIE and the secondary solvent deuterium isotope effect.[3]

We have determined the product isotope effect (PIE) on the specific acid-catalyzed protonation of X-**1** in 50/50 (v/v) H$_2$O/D$_2$O ($I = 1.0$, KCl) at 25 °C by ^{1}H NMR analyses (eq 1),[6] where A_{CH_3} and A_{CH_2D} are, respectively, the peak areas for the singlet for the -CH$_3$ group at (2.56–2.78) ppm and for the 0.012 ppm upfield shifted triplet for the -CH$_2$D group of X-**3** (Scheme 1).[7a–8] PIEs from competition experiments, where -H and -D labeled products form in a single reaction vessel, are more precise and easier to interpret than KIEs determined for separate reactions in H$_2$O and

Scheme 1

X = 4-OMe, H, 4-NO$_2$, 3,5-di-NO$_2$
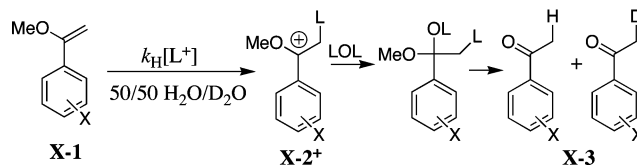
D$_2$O because (1) there are no errors from differences in the conditions for reactions in H$_2$O and D$_2$O, such as temperature and [L$^+$]; (2) there is no need to correct for the secondary solvent KIE when the H- and D-labeled products form in the same solvent.

$$\text{PIE} = \frac{[A_{CH_3}]}{1.5\,[A_{CH_2D}]} \qquad (1)$$

Values of the PIE for protonation of X-**1** by L$_3$O$^+$ (Scheme 1), determined in five reactions at different [L$^+$], are shown in Figure 1A. The variation in the values of the PIE determined for reactions in solutions that contain different [L$^+$] is less than ±2%. The PIEs for the lyonium ion-catalyzed reactions were calculated as the average of these five determinations and range from PIE = 8.1 for protonation of 4-MeO-**1** (●, Figure 1A) to 7.3 for protonation of 3,5-di-NO$_2$-**1** (▼). Figure 1B (●) shows a plot of log PIE for protonation of X-**1** against the recently reported values of $\Delta G°$ for proton transfer from H$_3$O$^+$ to X-**1** to form X-**2**$^+$.[9]

The PIEs for protonation of X-**1** in 50/50 (v/v) H$_2$O/D$_2$O that contains L$_3$O$^+$ provide a measure of the fractionation of H and D between L$_2$O and the transition state for this proton-transfer reaction, while the KIEs for protonation by L$_3$O$^+$ measures the fractionation of H and D between L$_3$O$^+$ and this same transition state.[10] Values of the KIE = 5.6 and 5.0 for protonation of 4-MeO-**1** and 3,5-di-NO$_2$-**1**, respectively, were calculated as $(k_H/k_D) = 0.69$(PIE), where $\varphi_H = 0.69$ corrects for the more favorable fractionation of hydrogen compared to deuterium from L$_2$O to L$_3$O$^+$ that has the effect of enriching L$_3$O$^+$ in hydrogen (Figure 1B, ▼).[10] Also shown in Figure 1B are values of the Brønsted coefficients α determined for protonation of X-**1** by substituted alkane carboxylic acids.[9]

PIEs were determined at $T = 25–86$ °C and at $T = 5–70$ °C, respectively, for protonation of 3,5-di-NO$_2$-**1** and 4-MeO-**1** in 50/50 (v/v) H$_2$O/D$_2$O that contains L$_3$O$^+$.[7b] Figure 2 shows linear Arrhenius plots of these data. The slopes and intercepts of these correlations give $[(E_a)_H - (E_a)_D] = -1.25$ and -1.17 kcal/mol for the difference in the activation barriers for the reaction of the different isotopes and $(A_H/A_D) = 1.00$ and 0.95 for protonation of 4-MeO-**1** and 3,5-di-NO$_2$-**1**, respectively.[11]

The results from Figure 1B are consistent with the maximum KIE observed for thermoneutral proton transfer at carbon,[4,5] but show that there is not a large change from this maximum as the driving force for proton transfer is changed by ca. 9 kcal/mol.[9] The values of $[(E_a)_H - (E_a)_D] \approx -1.2$ kcal/mol are consistent with the
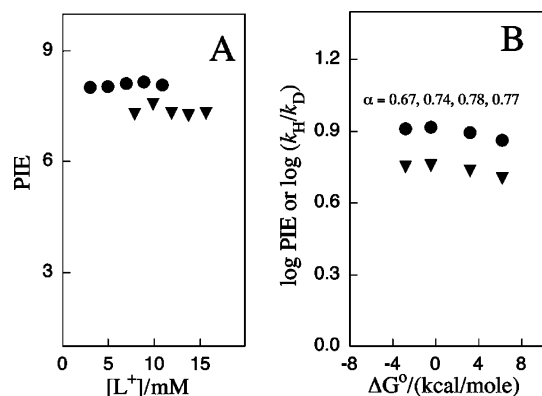
Figure 1. (A) The PIE for protonation of X-**1** (Scheme 1) in acidic solutions of 50/50 (v/v) H_2O/D_2O: (●) 4-MeO-**1**; (▼) 3,5-di-NO_2-**1**. (B) The change in the PIE and KIE with changing $\Delta G°$ for protonation of X-**1** by L_3O^+: (●) PIE; (▼) KIE. The Brønsted coefficients α for protonation of the respective X-**1** are shown directly above the isotope effects.[9]
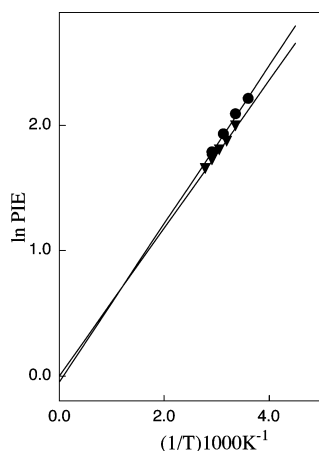

Figure 2. Arrhenius-type plots of PIEs for the reactions of 4-MeO-**1** (●) and 3,5-di-NO_2-**1** (▼) in 50/50 (v/v) H_2O/D_2O at $I = 1.0$ (KCl).

conclusion that most or all of the zpe of the LO−L bond ($v = 3400$ cm^{-1} for L = H) is lost at the transition state for protonation of X-**1** by L_3O^+. The ratios $(A_H/A_D) = 1.0$ for nearly thermoneutral protonation of 4-MeO-**1** and for endothermic protonation of 3,5-di-NO_2-**1** are consistent with a semiclassical model for proton transfer in which there is minimal tunneling of the hydron through the reaction barrier at $T = 278-359$ K.[12]

One explanation for the isotope effect maximum observed for thermoneutral proton transfer is that there are equal force constants for the partial C−H and O−H bonds at the reaction transition state, so that the proton remains stationary and there are no residual zpe associated with the symmetric transition-state stretching mode.[4] However, this explanation for the KIE maximum cannot be simply reconciled with the Brønsted coefficients of ca. 0.6 for thermoneutral protonation of X-**1**.[9] These coefficients are consistent with a transition state [X-**1**]‡ in which there is more than 50% transfer of the proton from the Brønsted acid catalyst to the carbon base X-**1**, and a stronger partial C−H bond compared with the partial O−H bond.

[X-1]‡
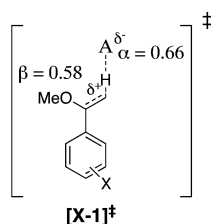
Brønsted coefficients provide a measure of the change in apparent charge at the reacting atoms on proceeding to the transition state, compared with the unit change in charge for the reference equilibrium reaction.[13] It is possible that these Brønsted parameters overestimate the extent of formal proton transfer to X-**1**, which is measured as the apparent change in charge at the reaction center, because of a lag in the "neutralization" of charge by aqueous solvation.[14] Theoretical calculations that reproduce Brønsted parameters and KIEs determined by experiment have the potential to provide a more realistic description of the transition state for these proton reactions and solidify or suggest alternative interpretations of these experimental data.

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(7) (a) Reactions were initiated by making a 1/100 dilution of the substrate in acetonitrile into 50/50 (v/v) H_2O/D_2O ($I = 1.0$, KCl) to give the following final concentrations and reaction volumes: 4-MeO-**1**, 0.3 mM in 25 mL; **1**, 0.8 mM in 10 mL; 4-NO_2-**1**, 0.09 mM in 50 mL; and, 3,5-di-NO_2-**1**, 0.06 mM in 50 mL. After 5−7 reaction halftimes, the organic product was extracted into CDCl$_3$. The organic layer was dried by filtration through a short column of MgSO$_4$ directly into an NMR tube, and the samples were stored at − 15 °C until being analyzed for deuterium content by ^{1}H NMR. Control experiments with 3,5-di-NO_2-**1** were performed to show that the ketone reaction product is stable to base-catalyzed deuterium exchange of the α-methyl protons during acid-catalyzed hydrolysis of 3,5-di-NO_2-**1**. (b) Each PIE is the average of PIEs determined in five experiments at different acid concentrations.

(8) ^{1}H-NMR spectra at 500 MHz were recorded in CDCl$_3$ on a Varian UNITY INOVA 500 MHz spectrometer as described in earlier work.[6] The following relaxation times T_1 were determined for the α-CH$_2$L protons of the product ring substituted acetophenones: 3,5-dinitroacetophenone, 3 s; 4-methoxyacetophenone, 3 s; 4-nitroacetophenone, 3 s; and, acetophenone, 4 s. Spectra (32−64 transients) were recorded with a pulse angle of 90°, an acquisition time of 7−10 s, and a relaxation delay between pulses of ≥7 T_1. All spectra were referenced to CHCl$_3$ at 7.27 ppm, and base lines were drift-corrected before integration of the signals for the α-CH$_3$ and α-CH$_2$D groups.

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(11) The following slopes and intercepts were determined by linear least squares analysis of data (Figure 2) for protonation of 4-MeO-**1** and 3,5-di-NO_2-**1**, respectively: Slope ($-[(E_a)_H − (E_a)_D]/R$), 630 ± 30 and 590 ± 19 K. Intercept, $\ln(A_H/A_D) = -0.048 ± 0.11$ and $-0.001 ± 0.06$. The quoted errors are standard deviations.

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