J. Am. Chem. Soc. **1989**, *111*, 683-692

An alternate explanation for the modest inhibition of thiazolium C(2)-proton exchange in strong acid should be considered in which acid has a direct role in the chemistry of C(2)-proton exchange, rather than the indirect role of stabilization of the C(2) ylide. Specifically, an increase in the C(2)-proton exchange rate due to acid-catalyzed exchange might not be observed because of incomplete cancellation of activity coefficient effects, rather than from a large decrease of f_{C^-} in strong acid.[8] However, acid-catalyzed exchange involving electrophilic displacement at carbon with a transition state in which the leaving and entering protons interact weakly with the C(2) ylide, as shown in Chart I, is unlikely because (1) there is no increase in the rate of exchange with increasing acidity from $D_0 = -2$ to -4 (Figure 2), (2) there is no clear precedent for such electrophilic assistance to proton exchange, and (3) the strong inhibition by acid of proton exchange of protonated amines[4] is inconsistent with this mechanism.

Supplementary Material Available: Tables showing rate constants for general-base catalysis of 3-R-4-methylthiazolium ion and N(1′)-protonated thiamin C(2)-L → D exchange, and for exchange of 3-cyanomethyl-4-methylthiazolium ion C(2)-H in aqueous LCl solutions (6 pages). Ordering information is given on any current masthead page.

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Thiazolium C(2)-Proton Exchange: Isotope Effects, Internal Return, and a Small Intrinsic Barrier[1]

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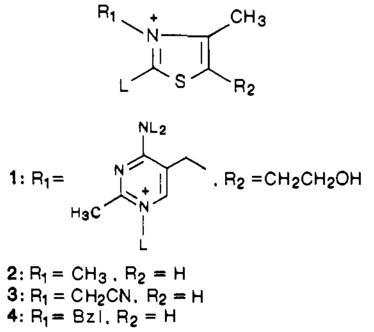
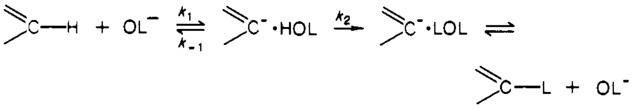
Abstract: Rate constants are reported for C(2)-hydron exchange catalyzed by lyoxide ion from thiazolium ions of pK_a 16.9–18.9 at 30 °C and ionic strength 2.0 M in aqueous solution. The reactions with deuterioxide ion, which are close to $\Delta pK = 0$, show primary kinetic isotope effects that increase over the range $(k_H/k_T)_{obsd} = 2.9$–14.7 with increasing acidity of the thiazolium ion. Deviations of $(k_D/k_T)_{obsd}$ and $(k_H/k_T)_{obsd}$ from the Swain–Schaad equation are consistent with internal return of the transferred proton to the C(2) ylide from water. This corresponds to an Eigen mechanism for proton transfer, in which both proton transfer and diffusional separation of the C(2)-ylide·water complex are partially rate limiting, and a small intrinsic barrier for C(2)-hydron exchange. A disappearance of the temperature dependence of $(k_H/k_T)_{obsd}$ with decreasing thiazolium ion acidity is also consistent with internal return. Correction of $(k_H/k_T)_{obsd}$ for internal return gives the primary isotope effect on the proton-transfer step, which increases over the range of ~9.6–18.7 as the acidity of the carbon acid increases. This is consistent with a changing structure of the transition state for proton transfer. A large decrease in the secondary solvent isotope effect for C(2)-T → L exchange from $k_{OD}/k_{OH} = 2.4$ to 1.3 provides evidence for a decrease in the amount of triton transfer to lyoxide ion in the transition state as the acidity of the carbon acid increases. The values of k_{OD}/k_{OH} and the negative deviation of deuterioxide ion from the Brønsted plot for general-base catalysis are consistent with a requirement for the removal of a solvating water molecule from lyoxide ion before abstraction of a C(2) hydron, with $K_{desolv} = 0.02$ and $pK_a = 18.1$ for the partially desolvated deuterioxide ion at 30 °C. The rate constants for C(2)-H → D exchange catalyzed by deuterioxide ion increase with decreasing ionic strength.



The preceding paper[2] describes evidence that thermodynamically unfavorable C(2)-proton transfer from N(1′)-protonated thiamin ($pK_a = 17.6$)[3] (**1**), 3,4-dimethylthiazolium ion ($pK_a = 18.9$) (**2**), and 3-(cyanomethyl)-4-methylthiazolium ion ($pK_a = 16.9$) (**3**) in aqueous solution is similar to proton transfer from "normal" acids. Proton transfer between the electronegative atoms of normal acids and bases involves diffusion-controlled separation of the products in the unfavorable direction and there is a small region near $\Delta pK = 0$ in which the proton-transfer step itself is partially rate limiting.[4-6] The Brønsted plots for such reactions follow "Eigen curves" with slopes of 0 and ±1.0 in the favorable and unfavorable directions, respectively, and have a small transition region near $\Delta pK = 0$ of slope ~0.5 where the proton-transfer step gives rise to a deuterium isotope effect.[5] Abstraction of the C(2) proton from these thiazolium ions follows almost completely

Scheme I



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[1] This research was supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 81-17816). M.W.W. was supported by a fellowship from the American Cancer Society (PF 2669).

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normal Eigen curves, with Brønsted β values of ≥0.95 for catalysis by buffer bases, and values of k_H/k_T in the range 1.2 ± 0.2 for catalysis by buffer bases are in the range expected for rate-limiting diffusional separation of buffer acids from the C(2) ylide.[2]

The goal of the work reported here was to determine whether the rate-limiting step for thermodynamically unfavorable C(2)-proton transfer from thiazolium ions to lyoxide ion involves diffusion-controlled separation of the products (k_2, Scheme I). The reactions with lyoxide ion are close to $\Delta pK = 0$ where, if thiazolium ions are normal acids, both proton transfer (k_1) and diffusional separation of the products would be partially rate limiting. When both k_1 and k_2 are partially rate limiting, k_{-1} competes with k_2 and the carbanion intermediate partitions between products and reactants. Streitwieser et al. showed[7] that for base-catalyzed C–L exchange (where L = H, D, or T),[8] the extent of internal return (k_{-1}/k_2) could be measured from the breakdown of the Swain–Schaad equation (eq 1, with $y = 3.34$)[9]

$$\log (k_H/k_T)_{obsd} = y \log (k_D/k_T)_{obsd} \qquad (1)$$

when both k_1 and k_2 are partially rate limiting. We have used this method to estimate the amount of internal return during thiazolium C(2)-proton exchange near $\Delta pK = 0$.

In this paper we describe evidence that these proton-transfer reactions proceed through a free carbanion intermediate, as expected for a normal acid. The magnitudes of isotope effects for proton transfer to lyoxide ion provide evidence for (1) significant internal return of the abstracted proton to the C(2) ylide from water, which is competitive with diffusional equilibration of the abstracted proton with solvent protons, (2) a change in the structure of the transition state for proton transfer, (3) a small intrinsic barrier for proton transfer, and (4) a requirement for the removal of a solvating water molecule from lyoxide ion before abstraction of a C(2) hydron.

Experimental Section

Materials and experimental procedures were generally as described in the preceding paper.[2] The synthesis of 3-benzyl-4-methylthiazolium chloride (**4**) was described previously.[10] C(2)-[^{2}H]thiazolium salts were prepared from unlabeled thiazolium salts by exchange in D_2O, and ^{1}H NMR examination of the exchanged thiazolium ions indicated ≥98% C(2)–D in the products. Solution pH was typically measured with an Orion Model 701A pH meter and a Radiometer GK23121C combination electrode containing a saturated solution of potassium chloride and standardized at pH 7.03 and 4.00 (19.5 ± 0.2 °C), pH 7.00 and 4.00 (25 °C), pH 6.99 and 4.01 (30 °C), pH 6.97 and 4.03 (40 °C), or pH 6.97 and 4.06 (50 °C). For solutions containing sodium perchlorate, pH was measured at 30 ± 0.2 °C by using the above combination electrode containing a saturated solution of lithium trichloroacetate and standardized at pH 6.99 and 4.01;[11] values of pH in solutions containing salts other than sodium perchlorate were found to agree with values determined with the electrode containing a saturated solution of potassium chloride. ^{1}H NMR spectra were recorded on a Varian XL-300 NMR spectrometer in D_2O.

Kinetics. Rate constants for catalysis of thiazolium C(2)–H → D and C(2)–T → L exchange by lyoxide ion were determined by ^{1}H NMR spectroscopy[3] in D_2O and detritiation[2] in L_2O as described previously. All reactions were carried out at 30 ± 0.2 °C (±1 °C in the NMR) and the ionic strength was maintained at 2.0 M with NaCl, unless indicated otherwise. The NMR probe temperature was measured by a thermocouple at the probe, which was calibrated by using the chemical shift difference of the methylene and hydroxyl protons of ethylene glycol [containing 0.03% (v/v) concentrated HCl].[12] Buffers in L_2O were either 3×10^{-4}–5×10^{-3} M LCl, 0.010 M sodium acetate buffer (pH 3.5–6, from sodium acetate and acetic acid), or 0.010 M sodium acetate-d_3 buffer (pD 3.5–6, from acetic-d_3 acid-d and NaOD). The exchange reaction was initiated by dissolving 0.0625 mmol of thiazolium salt in 0.5 mL of temperature-equilibrated buffer, to give a final concentration of 0.125 M thiazolium salt, unless stated otherwise.

Rate constants for thiazolium C(2)–D → H exchange in H_2O were determined with a discontinuous assay by measuring exchanged C(2)–H by ^{1}H NMR spectroscopy. The exchange reaction was initiated as described above in a 1.5-mL Eppendorf centrifuge tube. The reaction solution was incubated in a constant-temperature bath (30 ± 0.2 °C) and was removed for about 10 s every 1–30 min in order to obtain a 40-μL aliquot that was immediately mixed with 660 μL of 3.6 M HCl in a 1.5-mL Eppendorf centrifuge tube to quench the reaction. The solvent was removed by lyophilization, the thiazolium salt was redissolved in 700 μL of 3.6 M DCl, a ^{1}H NMR spectrum of each time point was obtained, and the integrated areas were measured for the C(2)–H signal and compared to those for the C(5)–H signal (as nonexchanging internal standard). The pseudo-first-order rate constants were obtained from semilogarithmic plots of A_2/A_5 against time, where A is the integrated area of the C(2)–H or C(5)–H signal, respectively, and from the relationship $k_{obsd} = 0.693/t_{1/2}$. These plots were linear for $>3t_{1/2}$ with 10–15 time points.

Measurements of pH were made at the reaction temperature on the buffered solutions of the thiazolium salts after exchange had occurred as described previously.[3] Measurements of pH with the KCl-saturated electrode at known concentrations of hydroxide ion at 30 °C and 0.022 and 2.0 M ionic strength, maintained with KCl or K_2SO_4, and eq 2 were

$$[OL^-] = 10^{(pL-K_w^L)}/\gamma_{OL} \qquad (2)$$

used to calculate the concentration of lyoxide ion at any pL for reactions performed at 30 °C; values of the activity coefficient for lyoxide ion, γ_{OL}, are 0.90 and 0.99 (0.022 M), 0.82 and 0.90 (0.14 M), 0.76 and 0.81 (0.50 M), 0.77 and 0.82 (1.0 M), or 0.85 and 0.94 (2.0 M) for ionic strength maintained with KCl or K_2SO_4, respectively. This equation includes the ion product of H_2O ($pK_w^H = 13.83$) or D_2O ($pK_w^D = 14.70$) at 30 °C.[13]

Second-order rate constants for lyoxide ion catalyzed exchange were obtained from the slopes of plots of k_{obsd} against lyoxide ion concentration with eight or more data points for reactions at 30 °C and $I = 0.022$–2.0 M (NaCl or Na_2SO_4) by least-squares analysis; the standard error in the slope of the least-squares line was calculated from the standard deviations of the values of k_{obsd}.[14] The slope of plots of k_{obsd} against lyoxide ion concentration typically showed 1–6% error (standard deviation/slope times 100) over typically a 100-fold range of lyoxide ion concentration. Buffer base does not significantly contribute to k_{obsd} under these reaction conditions and was neglected. Values of $(k_D/k_T)_{obsd}$ and $(k_H/k_T)_{obsd}$ for catalysis by hydroxide and deuterioxide ion, respectively, and k_{OD}/k_{OH} for C(2)–T → L exchange were calculated from these slopes according to eq 3, in which A and B are the rate constants and a and b are standard deviations (see below).[15]

$$(A \pm a)/(B \pm b) = A/B \pm [(A/B)^2[(a/A)^2 + (b/B)^2]]^{1/2} \qquad (3)$$

For studies of the temperature dependence of the observed primary kinetic isotope effect or with the ionic strength maintained with $NaClO_4$, the second-order rate constants for deuterioxide ion catalyzed exchange are activity based and were obtained from the slopes of plots of k_{obsd} against deuterioxide ion activity containing four or more data points; the deuterioxide ion activity was calculated from the observed pD (see above) with values of the ion product of deuterium oxide at the reaction temperature.[13]

Determination of the Extent of Internal Return. A steady-state treatment of Scheme I gives eq 4 for the observed rate constant for hydron exchange.

$$k_{obsd}{}^L = k_1{}^L k_2/(k_{-1}{}^L + k_2) \qquad (4)$$

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[8] The term "hydron" refers to the hydrogen cation (L^+) without regard to nuclear mass. The specific names "proton" (^{1}H), "deuteron" (^{2}H), and "triton" (^{3}H) refer to the specific isotopes (Commission on Physical Organic Chemistry, IUPAC *Pure Appl. Chem.*, in press) and are abbreviated here as: $^1H^+$, H; $^2H^+$, D; $^3H^+$, T.

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[15] Reference 14, pp 52–55.

Table I. Catalysis of 3-R-4-Methylthiazolium Ion C(2)–L Exchange by Lyoxide Ion[a]

R	$\mathrm{p}K_a$[b]	C(2)–L/ OL^-	$10^{-6}k_{\mathrm{OL}}$,[c] $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$	$(k_L/k_T)_{\mathrm{obsd}}$[d]	y[e]	k_{-1}^{H}/k_2[f,g] ((k_{-1}^{T}/k_2)[f,j])	k_1^{H}/k_1^{T}[f,h]	k_{OD}/k_{OH}[i] ((β)[k])
2 Me	18.9	$\mathrm{D/OH^-}$	0.0975 ± 0.0030	1.58 ± 0.08				
		$\mathrm{T/OH^-}$	0.0617 ± 0.0024		2.36 ± 0.30	3.3 ± 2.4 (0.31 + 0.08)		2.35 ± 0.17 (0.98 ± 0.08)
		$\mathrm{H/OD^-}$	0.427 ± 0.013	2.94 ± 0.20			9.6 ± 6.6	
		$\mathrm{T/OD^-}$	0.145 ± 0.009					
4 Bzl	18.2	$\mathrm{D/OH^-}$	0.350 ± 0.008	1.94 ± 0.06				
		$\mathrm{T/OH^-}$	0.180 ± 0.004		2.79 ± 0.14	1.1 ± 0.3 (0.078 ± 0.016)		1.87 ± 0.11 (0.72 ± 0.07)
		$\mathrm{H/OD^-}$	2.14 ± 0.07	6.37 ± 0.17			12.0 ± 2.4	
		$\mathrm{T/OD^-}$	0.336 ± 0.019					
1 thiamin	17.6	$\mathrm{D/OH^-}$	1.44 ± 0.02	2.05 ± 0.07				
		$\mathrm{T/OH^-}$	0.703 ± 0.021		2.53 ± 0.14	2.1 ± 0.9 (0.11 ± 0.02)		1.92 ± 0.10 (0.75 ± 0.06)
		$\mathrm{H/OD^-}$	8.32 ± 0.15	6.16 ± 0.30			16.9 ± 6.4	
		$\mathrm{T/OD^-}$	1.35 ± 0.06					
1 thiamin (I = 0.022 M)		$\mathrm{D/OH^-}$	5.39 ± 0.18	1.98 ± 0.11				
		$\mathrm{T/OH^-}$	2.83 ± 0.12		2.63 ± 0.23	1.6 ± 0.8 (0.10 ± 0.03)		1.95 ± 0.11 (0.76 ± 0.06)
		$\mathrm{H/OD^-}$	33.3 ± 1.3	6.02 ± 0.33			13.8 ± 5.8	
		$\mathrm{T/OD^-}$	5.53 ± 0.21					
3 $\mathrm{CH_2CN}$	16.9	$\mathrm{D/OH^-}$	5.69 ± 0.07	2.35 ± 0.06				
		$\mathrm{T/OH^-}$	2.42 ± 0.05		3.15 ± 0.11	0.29 ± 0.13 (0.014 ± 0.006)		1.30 ± 0.06 (0.30 ± 0.05)
		$\mathrm{H/OD^-}$	46.2 ± 0.8	14.7 ± 0.7			18.7 ± 2.5	
		$\mathrm{T/OD^-}$	3.15 ± 0.13					

[a] At 30 °C and ionic strength 2.0 M (NaCl) in L_2O, unless indicated otherwise. [b] $\mathrm{p}K_a$ for thiazolium C(2)–H in H_2O at 30 °C, I = 2.0 M (NaCl); calculated from the rate constant for catalysis by OD^-.[3] [c] Concentration based, $\gamma_{\mathrm{OL}} = 0.90$ (I = 0.022 M) or 0.85 (I = 2.0 M) (see Experimental Section). [d] Values of $(k_D/k_T)_{\mathrm{obsd}}$ and $(k_H/k_T)_{\mathrm{obsd}}$ were calculated from the rate constants for catalysis by OH^- and OD^-, respectively. [e] Exponent to satisfy the Swain–Schaad equation[9] defined by $\log (k_H/k_T)_{\mathrm{obsd}} = y \log (k_D/k_T)_{\mathrm{obsd}}$ (see text). [f] Defined in Scheme I for thiazolium C(2)–H → L exchange. [g] Calculated from eq 9. [h] Calculated from eq 8. [i] For thiazolium C(2)–T → L exchange. [j] Calculated from eq 7 by using $(k_D/k_T)_{\mathrm{obsd}}$ and $(k_H/k_T)_{\mathrm{obsd}}$ with $K^T/K^H = 1.10 \pm 0.08$ (see text). [k] Exponent to satisfy the equation $k_{OD}/k_{OH} = 2.4^{\beta}$ (see text).

Defining the extent of internal return a^L as k_{-1}^{L}/k_2 and the equilibrium constant $K^L = k_1^{L}/k_{-1}^{L}$ where L = H, D, or T gives eq 5–9, in which

$$A = (k_D/k_T)^{y}_{\mathrm{obsd}}/(k_H/k_T)_{\mathrm{obsd}} \tag{5}$$

$$B = (k_D/k_T)^{y}_{\mathrm{obsd}}(K^T/K^H) \tag{6}$$

$$[1 - a^T(B^{1/y} - 1)]^y = A + a^T(A - B) \tag{7}$$

$$k_1^{H}/k_1^{T} = (k_H/k_T)_{\mathrm{obsd}}[1 - a^T[(K^T/K^H)(k_H/k_T)_{\mathrm{obsd}} - 1]]^{-1} \tag{8}$$

$$a^H = a^T(K^T/K^H)(k_1^{H}/k_1^{T}) \tag{9}$$

$y = 3.34$[9] and the ratio K^T/K^H is the equilibrium constant for CT + HOH ⇄ CH + TOH.[7] All of the quantities in eq 7 are directly measurable except the extent of internal return of the triton, $a^T = k_{-1}^{T}/k_2$; although eq 7 cannot be solved explicitly for a^T, it is possible to obtain a value of a^T by trial and error that satisfies this equation. Equation 8 uses this value of a^T to correct the observed primary kinetic isotope effect, $(k_H/k_T)_{\mathrm{obsd}}$, for the effects of internal return and gives the primary kinetic isotope effect on the proton-transfer step itself, k_1^{H}/k_1^{T}. Equation 9 gives the extent of internal return of the proton, $a^H = k_{-1}^{H}/k_2$, based on the measured extent of internal return of the triton.

The equilibrium isotope effect, K^T/K^H = [TOH][CH]/[HOH][CT], was measured for 3,4-dimethylthiazolium ion (**2**) and 3-(cyanomethyl)-4-methylthiazolium ion (**3**) by determining the amount of tritium incorporation in the C(2) position at equilibrium from $[^3H]H_2O$ in H_2O at 30 °C and pH 5–6; the pH was maintained by ambient dissolved CO_2. The equilibrium for tritium incorporation at C(2) was established within 1.5 h for both compounds; in **4** tritium incorporation also occurred at the 3-methylene position during prolonged incubation. A value of $K^T/K^H = 1.10 \pm 0.08$ for both **2** and **3** was determined from four measurements (± standard deviation) as described above and we assume this same value for the equilibrium isotope effect for N(1′)-protonated thiamin (**1**) and 3-benzyl-4-methylthiazolium ion (**4**).

Calculation of Propagated Errors. Equations for calculating the propagated random error as the standard deviation in the calculated value of the Swain–Schaad exponent (y), the extent of internal return (k_{-1}^{H}/k_2), the primary isotope effect for proton transfer (k_1^{H}/k_1^{T}), and the amount of O–T bond formation in the rate-limiting transition state for catalysis of C(2)–T → D exchange by deuterioxide ion (β) were derived from eq 1, 8, 9, and 10 with the standard error formula.[15] These equations are available as supplementary material. The propagated error in a^T was estimated by using the standard deviation of the values for a^T obtained by evaluating eq 7 with the maximum and minimum values of the variables.

Results

Second-order rate constants for catalysis of C(2)–H → D, C(2)–T → D, C(2)–D → H and C(2)–T → H exchange from N(1′)-protonated thiamin (**1**), 3,4-dimethylthiazolium ion (**2**), 3-(cyanomethyl)-4-methylthiazolium ion (**3**), and 3-benzyl-4-methylthiazolium ion (**4**) by lyoxide ion in aqueous solution at 30 °C and ionic strength 2.0 M (NaCl), and also at ionic strength 0.022 M (NaCl) for **1**, were determined by ^{1}H NMR or detritiation under pseudo-first-order conditions and are reported in Table I; the rate constants for C(2)–H → D exchange[3] and C(2)–T → D exchange[2] from **1**–**3** catalyzed by deuterioxide ion at ionic strength 2.0 M were reported previously. Typical data are shown in Figure 1 for C(2)–hydron exchange from **2** and **3** catalyzed by lyoxide ion.

Primary kinetic isotope effects for C(2)-hydron exchange $(k_L/k_T)_{\mathrm{obsd}}$, and secondary solvent isotope effects for C(2)–T → L exchange, k_{OD}/k_{OH}, based on the observed second-order rate constants for catalysis by lyoxide ion, are summarized in Table I and have errors of 3–7%, calculated as described above. The reactions with lyoxide ion are close to the region of $\Delta\mathrm{p}K = 0$ and

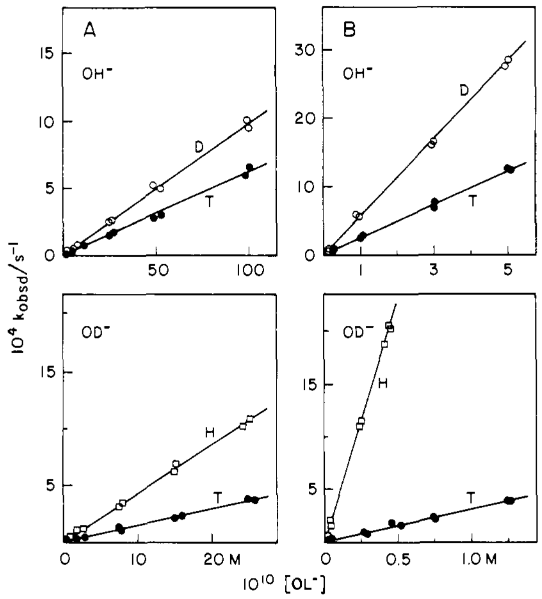

Figure 1. Catalysis by lyoxide ion of C(2)-H (□), C(2)-D (○), and C(2)-T (●) exchange from 3,4-dimethylthiazolium ion (**2**, A) and 3-(cyanomethyl)-4-methylthiazolium ion (**3**, B) in H_2O (upper panel) and D_2O (lower panel) at 30 °C, I = 2.0 M (NaCl). The experiments were carried out in LCl below pL 3.5 and in 0.010 M acetate buffers above pL 3.5; reactions with water and acetate ion do not contribute significantly to k_{obsd}. Note the difference in scale between panels A and B.

show significant primary kinetic isotope effects and secondary solvent isotope effects in aqueous solution. The values of $(k_H/k_T)_{obsd}$ for catalysis by deuterioxide ion increase in the range 2.9–14.7 with increasing thiazolium ion acidity. Similarly, the values of $(k_D/k_T)_{obsd}$ for catalysis by hydroxide ion increase in the range 1.58–2.35 with increasing thiazolium ion acidity. The values of k_{OD}/k_{OH} decrease in the range 2.35–1.3 with increasing thiazolium ion acidity.

Table I also contains several quantities that were calculated with the experimental values of $(k_L/k_T)_{obsd}$ and k_{OD}/k_{OH}. These include the following: values of the Swain–Schaad exponent, y, to satisfy the Swain–Schaad equation (eq 1) in the range 2.36–3.15; extents of internal return, $a^L = k_{-1}{}^L/k_2$, for exchange of C(2)-T and C(2)-H from eq 7 and 9, respectively, in the range of 0.014–0.31 for the triton and 0.29–3.3 for the proton; values for the primary kinetic isotope effect on the proton-transfer step itself, $k_1{}^H/k_1{}^T$, from eq 8 in the range 9.6–18.7; and values of β to satisfy eq 10[16,17] in the range 0.30–0.98. The limiting value

$$k_{OD}/k_{OH} = (2.4)^{\beta} \qquad (10)$$

of k_{OD}/k_{OH} = 2.4 was obtained from[17] $k_{OD}/k_{OH} = l^3 K_w{}^H/K_w{}^D$, the fractionation factor (l = 0.69) for the aqueous hydronium ion,[18] and the solvent isotope effect on the ionization constant of water, $K_w{}^H/K_w{}^D$ = 7.3 at 30 °C.[13]

Figure 2 shows the temperature dependence of the second-order rate constants for catalysis of C(2)-L → D exchange from **2** and **3** by deuterioxide ion, calculated from deuterioxide ion activity, and the primary kinetic isotope effect, $(k_H/k_T)_{obsd}$, at 19.4, 24.6, 26.7, 30.6, 40.5, and 50.4 °C. The results give the following parameters for deuterioxide ion catalysis, where $\ln k_{OD} = -E_a{}^L/RT + \ln A_L$ and the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are for C(2)-H → D exchange at 30 °C: for **2**, $E_a{}^T - E_a{}^H = 0.14 \pm 0.31$ kcal mol⁻¹, $A_H/A_T = 2.3$, $\Delta H^{\ddagger} = 11.7$ kcal mol⁻¹, and $\Delta S^{\ddagger} = 6.0$ cal deg⁻¹ mol⁻¹; for **3**, $E_a{}^T - E_a{}^H = 1.1 \pm 0.1$ kcal mol⁻¹, $A_H/A_T = 2.3$, $\Delta H^{\ddagger} = 7.9$ kcal mol⁻¹, and $\Delta S^{\ddagger} = 2.8$ cal deg⁻¹ mol⁻¹.

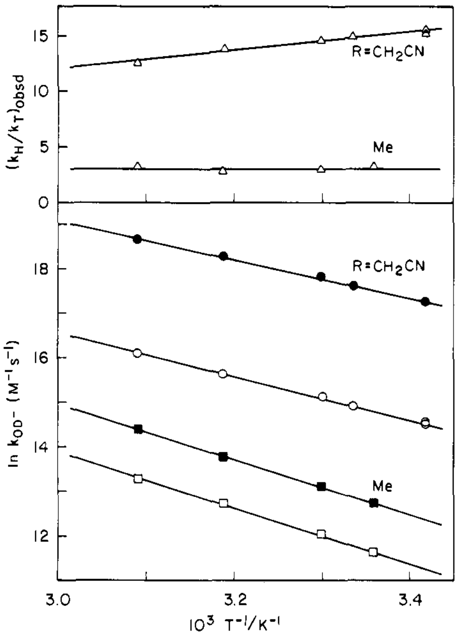

Figure 2. Temperature dependence of the activity-based second-order rate constants for C(2)-H (solid symbols) and C(2)-T (open symbols) → D exchange (lower panel) and the primary kinetic isotope effect (upper panel), $(k_H/k_T)_{obsd}$, from 3-R-4-methylthiazolium ions catalyzed by deuterioxide ion at I = 2.0 M (NaCl) in D_2O; the squares are for R = Me and circles are for R = CH_2CN. These experiments were carried out in DCl below pD 3.5 and in 0.010 M acetate-d_3 buffers above pD 3.5; reactions with D_2O and acetate ion do not contribute significantly to k_{obsd}.

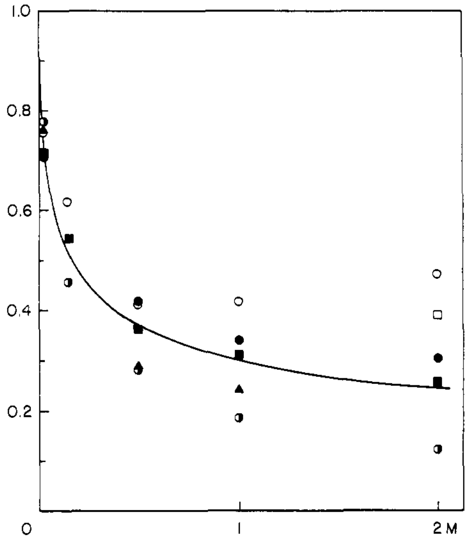

Figure 3. Dependence on ionic strength of the second-order rate constants for C(2)-H → D exchange from 3-R-4-methylthiazolium ions and N(1′)-protonated thiamin catalyzed by deuterioxide ion, for several sodium salts at 30 °C in D_2O. The experiments were carried out with 0.010 or 0.125 M thiazolium ion in the presence of 0.010 M acetate-d_3 buffer. The circles are for R = Me, squares are for R = CH_2CN, and triangles are for N(1′)-protonated thiamin. Ionic strength was maintained with NaCl (solid symbols), Na_2SO_4 (open symbols), or $NaClO_4$ (mixed symbols); the second-order rate constants are concentration-based for experiments with NaCl or Na_2SO_4 and are activity-based for experiments with $NaClO_4$. The solid line was calculated by using the Debye–Hückel equation (see text) with α = 3.0 Å, A = 0.516, and B = 0.030 Å⁻¹. The ratio k/k_0, where k_0 is the rate constant at infinite dilution, was calculated from values for k_0 of 1.4×10^6, 4.4×10^7, and 1.8×10^8 M⁻¹ s⁻¹ for R = Me, N(1′)-protonated thiamin, and R = CH_2CN, respectively.

Figure 3 shows the dependence on ionic strength of the second-order rate constants for deuterioxide ion catalyzed C(2)-H → D exchange from **1**–**3** and the effect of added salts on the exchange rate of **2**. The solid line was calculated by the Debye–Hückel equation, $\ln (k/k_0) = 2A(I)^{1/2}/(1 + B\alpha(I)^{1/2})$, with

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(18) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177–273.

$A = 0.516$, $B = 0.330$ Å^{-1}, and a value of 3.0 Å for the effective ionic radius α to fit the data;[19] k_0 is the rate constant at infinite dilution. The values of k_0 are 1.4×10^6 (**2**), 4.4×10^7 (**1**), and 1.8×10^8 M^{-1} s^{-1} (**3**).

Discussion

Primary Kinetic Isotope Effects and Internal Return. The observed primary kinetic isotope effects, $(k_H/k_T)_{obsd}$ and $(k_D/k_T)_{obsd}$, for catalysis of thiazolium ion C(2)-hydron exchange in aqueous solution by deuterioxide and hydroxide ion, respectively, increase with increasing acidity of the thiazolium ion over the range 2.9–14.7 for $(k_H/k_T)_{obsd}$ and 1.6–2.4 for $(k_D/k_T)_{obsd}$ (Table I). The small values of $(k_H/k_T)_{obsd}$ may result from an asymmetrical transition state or from the incursion of substantial internal return or both. For example, $(k_H/k_T)_{obsd} = 2.94$ for **2** may be compared with a value of ~11 that was calculated from the differences in zero-point vibrational stretching frequencies of C(2)–H and C(2)–D and the Swain–Schaad equation.[20] The isotope effects fit the Swain–Schaad equation (eq 1) with values of y in the range 2.35–3.15 (Table I); these values differ significantly from the theoretical value of $y = 3.34$ for eq 1. These results provide evidence for internal return of the transferred hydron to the C(2) ylide from water, which decreases the observed isotope effect and is more important for the more basic carbanions.

In the preceding paper we presented evidence that transfer of the C(2) hydron from N(1′)-protonated thiamin (**1**) and related N(3)-substituted thiazolium ions (**2**, **3**) is very similar to proton transfer from normal acids with electronegative atoms, although the thiazolium ions still have properties characteristics of other carbon acids.[2] The Brønsted β values of ≥ 0.95 and values of $(k_H/k_T)_{obsd}$ in the range 1.2 ± 0.2 for catalysis of thiazolium ion C(2)–L → D exchange by buffer bases suggest that diffusional separation of the conjugate buffer acid from the C(2) ylide is rate limiting for this thermodynamically unfavorable exchange reaction with $\Delta pK > 3$, as expected for normal acids.

If thiazolium ions are normal acids, a change in the rate-limiting step for C(2)-hydron exchange would occur near $\Delta pK = 0$, from rate-limiting diffusional separation of water from the C(2) ylide (k_2, Scheme I) to a situation in which both diffusional separation of the products (k_2) and proton transfer (k_1) are partially rate limiting. Such a change in rate-limiting step would give rise to a change in the observed primary kinetic isotope effect and detectable internal return, that is, partitioning of the carbanion intermediate between products and reactants. The observed increase in the primary kinetic isotope effects for the hydron-exchange reactions catalyzed by lyoxide ion as the reaction approaches thermoneutrality is consistent with such a change in the rate-limiting step near $\Delta pK = 0$.

Streitwieser and his co-workers showed[7] that when two transition states are partially rate limiting for base-catalyzed C–L exchange the amount of internal return (k_{-1}/k_2, Scheme I), or the extent that the transferred hydron L is returned to the carbanion from the protonated base before diffusional separation of the products, can be estimated from the y value of eq 1. Equation 1 describes the relationship between the primary kinetic isotope effects, $(k_H/k_T)_{obsd}$ and $(k_D/k_T)_{obsd}$; for reactions in which $k_2 \simeq k_{-1}$ and $k_{-1}{}^H > k^D{}_{-1} > k_{-1}{}^T$, internal return will contribute differently to the two isotope effects. When $k_{-1}{}^L/k_2$ is small, k_{obsd} approaches k_1 (see eq 4), and eq 11 is obeyed; when $k_{-1}{}^L/k_2$ is large, the observed isotope effects approch the equilibrium isotope effects, and eq 12 is obeyed.[21]

$$k_1{}^H/k_1{}^T = (k_1{}^D/k_1{}^T)^{3.34} \tag{11}$$

$$K^T/K^H = (K^T/K^D)^{3.34} \tag{12}$$

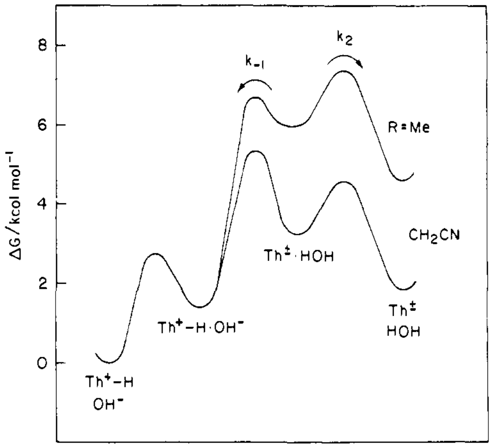

Figure 4. Gibbs free energy–reaction coordinate diagrams for thermodynamically unfavorable proton transfer to hydroxide ion from 3-R-4-methylthiazolium ions (Th$^+$–H) in H_2O at 30 °C, $I = 2.0$ M (NaCl). The values of $\Delta G^{\circ\prime}$ and $\Delta G^{\ddagger}$ are approximate and were calculated from the constants in ref 3 and Table I, respectively, for a standard state of 1 M. We assume $k_d = 3 \times 10^9$ M^{-1} s^{-1} and $k_d/k_{-d} = 0.10$ M^{-1} for the diffusion-controlled encounter complexes in the Eigen mechanism for proton transfer.[23]

The values of the internal return ratio, $k_{-1}{}^H/k_2$, that were obtained from eq 1 are in the range 0.3–3.3 (Table I) and indicate that internal return of the transferred proton to the C(2) ylide is significant. However, the extent of internal return should be interpreted conservatively because the errors are ±30% or more. These large errors arise because deviations from eq 11 as a consequence of internal return are generally small, so that high precision for measurement of rate constants is required in order to obtain useful information about the relative free energies of two transition states when both are partially rate limiting.[22] The results show the expected increase in internal return with increasing basicity of the carbanion. This brings about a progressive change from predominantly rate-limiting proton abstraction to diffusional separation of water from the ylide as the pK_a of the carbanion increases in the range pK_a 16.9–18.9, as illustrated in the energy diagram of Figure 4.

Two simplifying assumptions are required to calculate the extent of internal return from the breakdown of the Swain–Schaad equation (eq 11):[7a] (1) There is no isotope effect on the rate constant for diffusional separation of the C(2) ylide and water (k_2). This is supported by the small isotope effect ($\leq 3\%$)[24] for diffusion of HTO in H_2O and DTO in D_2O. (2) The solvent isotope effect on the primary isotope effect is negligible, which implies that $k_{-1}{}^L/k_2$ has no solvent isotope effect. The difference in ΔpK of 0.3 unit that arises from a change from DO$^-$ to HO$^-$ as the catalytic base is expected to result in a small increase in the extent of internal return, but this solvent isotope effect is less than the experimental error in the values.[25]

Data consistent with an internal return mechanism for thiazolium ion C(2)-hydron exchange was also obtained from the

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(19) Moore, J. W.; Pearson, R. G. *Kinetics and Mechanisms*; Wiley: New York, 1981; pp 272–276. Dean, J. A. *Lange's Handbook of Chemistry*, 12th ed.; McGraw-Hill: New York, 1979, pp 5-4–5-6.

(20) Primary tritium kinetic isotope effects of $k_H/k_T \sim 11$ and 15 at 30 °C for **2** and **3**, respectively, were calculated from the differences in zero-point vibrational stretching frequencies of C(2)–H and C(2)–D (ref 21, pp 130–131) by using $k_H/k_D = \exp[h(\nu_H - \nu_D)/2kT]$ and $k_H/k_T = (k_H/k_D)^{1.44}$ (ref 9); this treatment assumes that the differences in stretching vibrations upon deuteriation dominate the measured isotope effect. Although stretching vibrations contribute substantially to the total zero-point energies, contributions from other vibrational modes certainly make a significant contribution to the zero-point energies. The stretching frequencies for C(2)–H of 3020 cm^{-1} for **2** and 3080 cm^{-1} for **3** were measured in KBr pellets as described previously (ref 3); C(2)–D stretching frequencies of 2330 cm^{-1} for **2** and 2310 cm^{-1} for **3** were measured similarly.

(21) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley: New York, 1980; pp 158–162.

(22) Albery, W. J.; Knowles, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 637–638.

(23) Reference 4: see eq 3–5 in ref 2. The theoretical curves for k_{OD}/k_{OH} in Figure 5 were calculated by using eq 4 and 5 in ref 2 for proton transfer from an acid with essentially no intrinsic barrier with values of $k_p^0 = 10^{12}$ s^{-1}, $k_d = 3 \times 10^9$ M^{-1} s^{-1}, and $k_d/k_{-d} = 0.1$ M^{-1}.

(24) Weingärtner, H. *Z. Phys. Chem., Neue Folge* **1982**, *132*, 129–149.

(25) The solvent isotope effect on $k_{-1}{}^T/k_2$ was estimated from a curved plot of log $k_{-1}{}^T$ against ΔpK based on an intrinsic barrier of 1.3 kcal mol^{-1} for C(2)–T → D exchange (see text); a change in ΔpK of 0.3 unit results in a small increase in the value of log $k_{-1}{}^T$ and an increase in the extent of internal return of the triton of ~10% for **2** and ~20% for **3**.

temperature dependence of the primary kinetic isotope effect. Figure 2 shows that the value of $(k_H/k_T)_{obsd}$ for 3,4-dimethylthiazolium ion (**2**) is temperature-independent ($E_a^T - E_a^H = 0.14 \pm 0.31$ kcal mol^{-1} and $A_H/A_T = 2.3$), but is temperature-dependent for the more acidic 3-(cyanomethyl)-4-methylthiazolium ion (**3**) ($E_a^T - E_a^H = 1.1 \pm 0.1$ kcal mol^{-1} and $A_H/A_T = 2.3$) in the range 19–50 °C. This is consistent with a decrease in the extent of internal return as the reaction approaches $\Delta pK = 0$. A one-step proton-transfer reaction is expected to show a decreasing isotope effect with increasing temperature. However, a constant isotope effect could occur for a two-step proton transfer when the rate of the second step (k_2, Scheme I) increases more with temperature than the rate of collapse of the ion pair (k_{-1}), which would give less internal return and tend to increase the isotope effect; this can compensate for the decrease of the isotope effect on k_1 with increasing temperature.[26] Temperature-independent kinetic isotope effects ($\Delta E_a = 0$) and anomalous A_H/A_L ratios ($A_H/A_L > 1$) have been interpreted in terms of substantial internal return in the proton-abstraction step in E1cB elimination reactions.[26,27] A temperature-independent kinetic isotope effect and an anomalous A_H/A_L ratio cannot be used as evidence in support of a nonlinear transition state for hydron transfer.[28]

Significant internal return has been proposed to occur in several carbanion-forming reactions,[7,29] including elimination reactions,[26,27,30] according to a variety of experimental criteria. To our knowledge, this is the first instance in which internal return has been observed near $\Delta pK = 0$ for a carbanion-forming reaction.

Correction of the values of $(k_H/k_T)_{obsd}$ in the range 2.94–14.7 for the effects of internal return according to eq 8 gives values of $k_1^H/k_1^T = 9.6$–18.7 for the primary tritium kinetic isotope effect on the proton-transfer step itself. This shows that even moderate internal return markedly depresses isotope effects (Table I). The values of k_1^H/k_1^T increase 2-fold with an increase in the acidity of the thiazolium ion of 2 pK units; the propagated errors in the values of k_1^H/k_1^T are large, but the trend is significant at the 99% confidence level. This is consistent with significant asymmetry of the hydron in the transition state $[C^{\delta-}\cdots L^{\delta+}\cdots{}^{\delta-}O]^{\ddagger}$ and a considerable change in transition-state structure over a narrow range of ΔpK; it may be described as a normal Hammond effect,[31] in which the position of the hydron in the transition state for hydron transfer is closer to the carbon than the oxygen acceptor atom as the products become more stable relative to the reactants.

The increase in the value of k_1^H/k_1^T for thiazolium ions as ΔpK approaches zero is much sharper than that usually observed for hydron transfer to or from carbon.[32] However, this increase is similar to that observed for normal acids, which has been explained as resulting from the development of asymmetry in the transition state for hydron transfer. Maxima in solvent deuterium isotope effects have been observed for reactions involving proton transfer between normal acids and bases when the pK_a values of the proton donor and acceptor are similar. In most cases these maxima can be accounted for by a change in rate-limiting step to diffusion-controlled encounter or separation of the reactants.[5] However, the maxima for general-acid catalysis of the addition of methoxyamine to phenyl acetate[5b,d] and general-base catalysis by monofunctional nitrogen bases of the addition of aniline to methyl formate[5f] are consistent with a changing isotope effect on the proton-transfer step itself that is caused by a sharp change from a symmetric to an asymmetric transition state for this very rapid step, as suggested by Melander and Westheimer.[33,34]

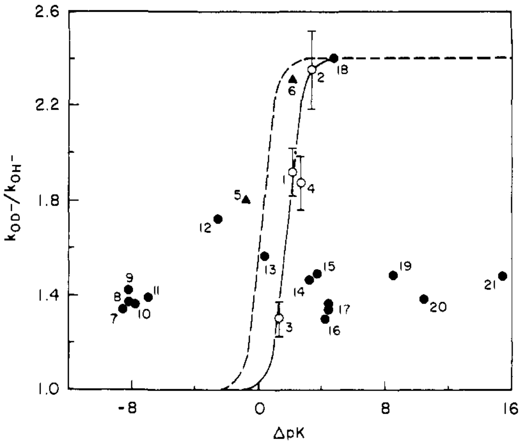

Figure 5. The dependence of the secondary solvent isotope effect, k_{OD}/k_{OH}, on ΔpK for C(2)–T → L exchange from 3-R-4-methylthiazolium ions and N(1′)-protonated thiamin at 30 °C and $I = 2.0$ M (NaCl) (○), and proton transfer from secondary amides (▲) and other carbon acids (●); values for ΔpK were calculated by using $\Delta pK = pK_a^{CH} - pK_a^{OH^-}$ and $pK_a^{OH^-} = 15.57$ at 30 °C.[13] Values[40] of k_{OD}/k_{OH} and pK_a for the secondary amides and other carbon acids are for H → L exchange at 25 °C and $I = 1.0$ M (KCl), unless stated otherwise: 4-nitrophenyl *N*-methylcarbamate (**5**), *N*-methylacetamide (**6**), 1-(3-chlorophenyl)-1-nitroethane (**7**), 1-(3-methylphenyl)-1-nitroethane (**8**), 1-phenyl-1-nitroethane (**9**), 2-nitropropane (**10**), nitroethane (**11**), *tert*-butylmalononitrile (**12**), [2-(4-nitrophenyl)ethyl]quinuclidinium ion (**13**), acetone (**14**), 9-(hydroxymethyl)fluorene (**15**), 9-[(dimethylamino)methyl]fluorene (**16**), phenylacetylene (**17**), 2,6-dinitrophenyl phenylmethanesulfonate (**18**), chloroform (**19**), 2,3-dihydro-3,3-dimethyl-5-nitro-2-benzofuranacetate (**20**), and mandelic acid (**21**). The broken and solid lines were calculated for proton transfer by the Eigen mechanism;[23] the solid line through the data for thiazolium ions is displaced 1.7 pK units from the broken line in which $\beta = 0.5$ at $\Delta pK_a = 0$.

The abrupt change in the value of k_1^H/k_1^T for thiazolium ion C(2)–L exchange as the acidity of the carbon acid is changed is consistent with a small barrier for C(2)–L transfer, which is similar to that for normal acids. A small barrier has a small curvature that allows the position of the transition state to slide easily over the energy surface as the energy of the hydron donor is changed,[35,36] which gives a change in transition-state structure and in the observed isotope effect as described by Melander and Westheimer.[33,34]

The small primary kinetic isotope effects of $k_H/k_D = 1.48$ and 2.13 for catalysis by hydroxide ion of triton transfer from chloroform ($\Delta pK \simeq -9$) and phenylacetylene ($\Delta pK \simeq -5$), respectively,[37] and $k_H/k_D = 1.17$ for triton transfer from phenylacetylene catalyzed by 1-methylimidazole ($\Delta pK \simeq -13$)[38] suggest that either

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a Melander–Westheimer effect or internal return is decreasing the observed primary kinetic isotope effect for these carbon acids. However, the hydroxide ion deviates from the Brønsted correlation of slope $\beta = 1.0$ by factors of 75 and 175 for phenylacetylene and chloroform, respectively;[39] these deviations are much larger than the deviation of ~10-fold observed for thiazolium ions at $\Delta pK \leq -2.5$ and show that the rate of triton transfer from these compounds at $\Delta pK = 0$ is significantly smaller than that for more normal carbon acids. This large deviation of hydroxide ion is inconsistent with significant internal return and suggests that triton transfer is the rate-limiting step in this ΔpK range.

Secondary Solvent Isotope Effects and Changing Transition-State Structure. The values of the secondary solvent isotope effect, k_{OD}/k_{OH}, for C(2)–T → L exchange undergo a large decrease from the maximal value of 2.4 to 1.3 in the range of $\Delta pK \simeq -3$ to -1 as the reaction approaches thermoneutrality, as shown in Figure 5. This decrease is not caused by a change in rate-limiting step, because there is little internal return of the triton to the C(2) ylide from water (Table I). This large change in k_{OD}/k_{OH} over a small range of ΔpK is similar to that observed previously for two secondary amides (**5** and **6** in Figure 5), but is much greater than has been observed for other carbon acids (**7–21**).

Values of k_{OD}/k_{OH} have been interpreted as an index of transition-state structure, based on the assumption that values of β derived from eq 10 describe the fractional extent of hydron transfer to lyoxide ion in the rate-limiting transition state for proton transfer.[16,17,44] If this quantitative interpretation of the secondary solvent isotope effect is correct, it suggests that for thiazolium ion C(2)–T → L exchange there is a remarkably large change from a very late and product-like to an early and reactant-like transition state, with a decrease in β from 0.98 for **2** to 0.30 for **3** as the proton-transfer reaction approaches $\Delta pK = 0$ (Table I; a possible explanation for this low β value will be suggested below).

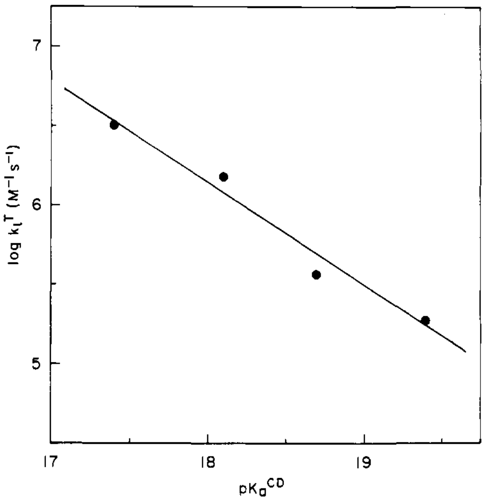

Figure 6. The dependence of log k_1^T (Scheme I) for catalysis of C(2)–T → D exchange by deuterioxide ion on the pK_a of the thiazolium ion in D_2O at 30 °C, $I = 2.0$ M (NaCl). Values of k_1^T were calculated by using eq 4 with $k_{obsd} = k_{OD}$ for C(2)–T → D exchange (Table I), which corrects the observed second-order rate constants for internal return of the triton. Values of pK_a^{CD} of 19.4 (**2**), 18.7 (**4**), 18.1 (**1**), and 17.4 (**3**) in D_2O at 30 °C and $I = 2.0$ M (NaCl) were calculated as described previously.[51]

This is also consistent with a small intrinsic barrier for C(2)-hydron transfer. Figure 5 shows that most carbon acids have values of $k_{OD}/k_{OH} \simeq 1.5$, which would suggest that proton transfer is at least partially rate limiting and that β is ~0.5 over a large range of ΔpK for catalysis by lyoxide ion.[17]

A systematic dependence of k_{OD}/k_{OH} on transition-state structure is reasonable, but the quantitative significance of the value of β obtained from k_{OD}/k_{OH} and eq 10 has been questioned.[45] There is an apparent discrepancy between the value of $\beta = 0.35$ derived from eq 10 for proton abstraction from 2-nitropropane (**10**) by lyoxide ion,[17] and the observed Brønsted slope of $\beta = 0.61$ for proton abstraction by buffer bases.[46] However, this difference does not invalidate the use of k_{OD}/k_{OH} as an index of transition-state structure[17] because catalysis by lyoxide ion is strongly favorable thermodynamically and may have a smaller value of β,[4] while the reactions with buffer bases are unfavorable. A discrepancy remains between the value of $\beta = 0.31$ derived from eq 10 for the thermodynamically unfavorable reaction of lyoxide ion with 9-[(dimethylamino)methyl]fluorene (**16**) and the Brønsted β value of ≥0.65 for general-base catalysis of this reaction, which suggests that there is a limit to the quantitative significance of values of β calculated from eq 10.[43] Nevertheless, the very large observed change in k_{OD}/k_{OH} (Figure 5) supports the conclusion that there is a large change in the structure of the transition state for thiazolium ions, which is similar to that expected for normal acids.

The changing transition-state structure for thiazolium ion C(2)–T → D exchange can be further characterized by the parallel and perpendicular effects on the transition state of substituents that change the stability of the C(2) ylide.[47] The change in the Brønsted β value for hydron removal with changing pK_a of the carbon acid may be described by the cross-interaction coefficient p_{xy} of eq 13. The values of β derived from k_{OD}/k_{OH} in eq 10

$$p_{xy} = \partial\beta/\partial pK_a^{CH} \qquad (13)$$

correspond to $p_{xy} = 0.31 \pm 0.09$ for triton abstraction from thiazolium ions by lyoxide ions. This suggests that there is significant diagonal character to the reaction coordinate that leads to movement of the transition state in a direction orthogonal to the perturbation of the stability of the C(2) ylide. The value of

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[39] Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5380–5386.

[40] Values of k_{OD}/k_{OH} and pK_a for the secondary amides and other carbon acids are as follows: **5** (Bender, M. L.; Horner, R. B., Jr. *J. Org. Chem.* **1965**, *30*, 3975–3978); $pK_a = 14.7$ was calculated (Barlin, G. B.; Perrin, D. D. *Q. Rev.* **1966**, *20*, 75–101) for R_1CONHR_2 from $pK_a = 22 - 3.1\Sigma\sigma^*$ with values of $\sigma^* = 2.36$ for $R_1CO = COO(C_6H_4\text{-}4\text{-}NO_2)$ (ref 41) and $\sigma^* = 0$ for R_2 = Me (ref 42). **6** (Molday, R. S.; Kallen, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 6739–6745); $k_{OD}/k_{OH} = 2.3$ was calculated with activity-based rate constants of $k_{OH} = 4.19 \times 10^6$ M^{-1} s^{-1} and $k_{OD} = 9.5 \times 10^6$ M^{-1} s^{-1} (Klotz, I.; Frank, B. *J. Am. Chem. Soc.* **1965**, *87*, 2721–2728). **7–9** (Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 3447–3452). **10** and **11** at 5 °C (Maron, S. H.; La Mer, V. K. *J. Am. Chem. Soc.* **1938**, *60*, 2588–2596) with $pK_a = 7.74$ (Bell, R. P.; Higginson, W. C. E. *Proc. R. Soc. London, A* **1949**, *197*, 141–159) and $pK_a = 8.6$ (Wheland, G. W.; Farr, J. *J. Am. Chem. Soc.* **1943**, *65*, 1433), respectively. **12** for T → L exchange (Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1971**, *93*, 2836–2840) and $pK_a = 13.1$ (Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829–2835). **13** (Alunni, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2052–2060) and $pK_a = 16 \pm 2$ (Keeffe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 265–279). **14** (Pocker, Y. *Chem. Ind.* (*London*) **1959**, 1383–1384) and $pK_a = 18.9$ (Tapuhi, E.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 5758–5765. Chiang, Y.; Kresge, A. J.; Tang, Y. S. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.) **15** (More O'Ferrall, R. A.; Slae, S. *J. Chem. Soc. B* **1970**, 260–268); $pK_a = 19.3$ was calculated (Bowden, K.; Cockerill, A. F.; Gilbert, J. R. *J. Chem. Soc. b* **1970**, 179–184) from $pK_a = 22.1 - 4.6\sigma^*$ with $\sigma^* = 0.62$ for CH_2OH (ref 42). **16** at $I = 0.10$ M (NaCl) (ref 43) and $pK_a = 19.8$ was calculated as described above for **15** with $\sigma^* = 0.49$ for $CH_2N(CH_3)_2$, which was calculated from $\sigma^* = (\sigma_{meta} + 0.106)/0.217$ with $\sigma_{meta} = 0$ for $CH_2N(CH_3)_2$ (ref 42). **17** and **19** for T → L exchange (Kresge, A. J.; Lin, A. C. *J. Am. Chem. Soc.* **1975**, *97*, 6257–6258) with $pK_a = 20.0$ and $pK_a = 24.1$, respectively at $I = 0.10$ M (ref 39). **18** (Davy, M. B.; Douglas, K. T.; Loran, J. S.; Steltner, A.; Williams, A. *J. Am. Chem. Soc.* **1977**, *99*, 1196–1206). **20** at 39 °C (Amyes, T. L.; Kirby, A. J. *J. Am. Chem. Soc.* **1988**, *110*, 6505–6514. **21** at 100 °C (Pocker, Y. *Chem. Ind.* (*London*) **1958**, 1117–1118) and $pK_a \geq 30$ (Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 3447–3452).

[41] The value of $\sigma^* = 2.36$ for $R_1CO = COO(C_6H_4\text{-}4\text{-}NO_2)$ was calculated from a correlation of the σ^* values for 10 substituents (R_1CO) with values of σ^* for R_1, $\sigma^*(R_1CO) = 0.168\sigma^*(R_1) + 1.871$, and $\sigma^* = 2.91$ for $R_1 = O(C_6H_4\text{-}4\text{-}NO_2)$ (ref 42).

[42] Perrin, D. D.; Dempsey, B.; Serjeant, E. P. *pK_a Prediction for Organic Acids and Bases*; Chapman and Hall: London, 1981; pp 109–126.

[43] Kelly, R. P.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1979**, 681–689.

[44] Winey, D. A.; Thornton, E. R. *J. Am. Chem. Soc.* **1975**, *97*, 3102–3108.

[45] Reference 18, pp 228–230.

[46] Dahlberg, D. B.; Kuzemko, M. A.; Chiang, Y.; Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1983**, *105*, 5387–5390.

[47] Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948–7960. Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511–527.

$\rho_{xy} = 0.31$ is much larger than a value of 0.053 for proton transfer catalyzed by amines from substituted phenylacetonitriles,[48] which are carbon acids with comparatively large intrinsic barriers, intrinsic rate constants that are 4.9–6 orders of magnitude smaller than those for thiazolium ions,[2] and resonance delocalization of negative charge upon ionization.

The change in β with changing pK_a of the catalyzing base may be described by the direct interaction coefficient p_y of eq 14. The

$$p_y = \partial\beta/-\partial\,\mathrm{p}K_a^{\mathrm{BH}^+} \qquad (14)$$

curvature in the Brønsted plot for triton abstraction from **3**, which does not involve significant internal return, corresponds to an intrinsic barrier of 1.3 ± 0.3 kcal mol^{-1} according to the Marcus equation[2] and can also be described by a value of $p_y = 0.13 \pm 0.03$.[49] This value of p_y corresponds to a large Hammond effect, or substantial movement of the transition state along, or parallel to, the reaction coordinate as the strength of the base is varied.

These large interaction coefficients are expected if there is a small intrinsic barrier for thiazolium ion C(2)-hydron transfer and a small curvature of the reaction coordinate, so that there is a large change in the position of the transition state when the stability of a reactant is varied by a small amount.

The dependence of log k_1^{T} (Scheme I) on the pK_a of the thiazolium ion gives a value of $\alpha = \partial \log k_1^{\mathrm{T}}/-\partial \mathrm{p}K_a^{\mathrm{CD}} = 0.65 \pm 0.08$, as shown in Figure 6. The values of k_1^{T} were calculated by correcting the observed second-order rate constants for catalysis of C(2)–T → D exchange by deuterioxide ion for the effects of internal return, according to eq 4. The change in α with changing pK_a of the carbon acid may be described by the direct interaction coefficient p_x of eq 15. The absence of significant curvature in Figure 6 means that p_x does not differ significantly from zero; $p_x = 0.02 \pm 0.08$.

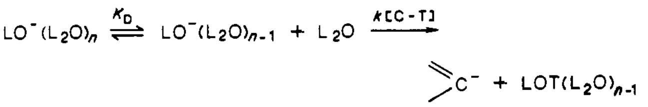
$$p_x = \partial\alpha/\partial\,\mathrm{p}K_a^{\mathrm{CD}} \qquad (15)$$

In summary, the curvature of the Brønsted correlation with increasing pK of the base catalyst that occurs near ΔpK = 0 shows that there is a large change in β with a small change in the pK of the catalyst, described by $p_y = \partial\beta/-\partial\,\mathrm{p}K_a^{\mathrm{BH}^+} = 0.13$, while the Brønsted plot for varying the carbon acid does not show a detectable curvature.

This suggests that there can be *imbalance* in the transition state because α and β will differ if α is constant and β changes. Such imbalance is well-known for the ionization of nitroalkanes and other carbon acids, in which there is resonance delocalization and strong solvation of the product,[47,52] but it would be expected to be smaller for thiazolium ions. The change in β with changing pK_a of the carbon acid, as estimated from $k_{\mathrm{OD}}/k_{\mathrm{OH}}$, is even larger. If these β values provide a quantitative measure of hydron transfer, they represent an even larger imbalance between α and β.

The changes in structure–reactivity coefficients that are defined by p_x, p_y, and p_{xy} can be described by a reaction coordinate at a saddle point on an energy surface in which α and β are the x and y coordinates, respectively.[47] The observed interaction coefficients correspond to curvatures of the surface at the saddle point of $a = 0.72$, $b = 0$, and $c = -3.33$ for the curvatures parallel to the x and y axes and the diagonal curvature, respectively. This corresponds to a reaction coordinate that is rotated slightly counterclockwise from the diagonal. It bisects two level lines of constant energy, one parallel to the y axis and the other rotated 51° counterclockwise from the x axis. The position of the transition state at the saddle point of this diagram changes with changes in the pK of the catalyst and the carbon acid according to the experimental data. If the structure–reactivity coefficients are a function of bond orders, the diagram also describes the changes in transition-state structure with changing structure of the reactants.

Scheme II



The Lyoxide Ion Anomaly. The rate constants for hydron abstraction from thiazolium ions by hydroxide (or deuterioxide) ion fall below the Brønsted plots for catalysis by alkoxide ions by factors of 6–9 for reactions with both small and large amounts of internal return.[2] It is possible to explain the negative deviations for the reactions in which hydron transfer is largely rate limiting by a requirement for partial desolvation of the lyoxide ion before reaction; however, we do not have a satisfactory explanation for deviations when diffusional separation of the products is largely rate limiting.

The secondary lyoxide isotope effect, $k_{\mathrm{OD}}/k_{\mathrm{OH}}$, for triton abstraction from thiazolium ions shows a sharp increase with increasing pK_a of the carbon acid (Figure 5) and it would be expected that the midpoint of this increase would be at or near ΔpK = 0. Instead, the β value increases sharply only when the pK_a of the thiazolium ion is more than 1 unit above the pK_a of water and the midpoint of the curve is shifted upward by 1.7 pK units from ΔpK = 0.

This result is consistent with partial desolvation of the lyoxide ion to give a more basic species that abstracts the C(2) hydron. Removal of a solvating water molecule with an equilibrium constant of $K_{\mathrm{D}} = 0.02$ would give a species that is more basic by 1.7 pK units.[53] This corresponds to pK_a = 15.6 + 1.7 = 17.3 for the partially desolvated hydroxide ion. The midpoint of the curve in Figure 5 would then represent a thermoneutral reaction.

The 6-fold negative deviation of the rate constant for catalysis of C(2)–T → D exchange by deuterioxide ion from the Brønsted correlation for **3** is in the lower range of the deviations that are well-known for other carbon acids.[50] The deviation for **3** can be accounted for by a requirement for partial desolvation of the deuterioxide ion before it reacts, with an equilibrium constant of $K_{\mathrm{D}} = 0.02$ and a pK_a of 16.4 + 1.7 = 18.1 for the desolvated base. An explanation of how such solvation effects change rate constants in a structure–reactivity correlation is not trivial because changes in the rate constant and the basicity of the ion must be related to the slope of the Brønsted correlation, which may not be linear.[53,54]

The negative deviation of the rate constants for catalysis by deuterioxide ion when hydron transfer is largely rate limiting reflects an unfavorable contribution to the equilibrium constant for formation of the encounter complex between the carbon acid and lyoxide ion, which may be described by the equilibrium constant K_{D} for partial desolvation of the lyoxide ion before reaction (Scheme II). A requirement for desolvation corresponds to an increased pK_a value and rate constant for the reactive, partially desolvated lyoxide ion. Desolvation is required because removal of the C(2) hydron proceeds through a direct, rather than through-water, mechanism.[2]

The value of K_{D} was estimated by a modification of the method described previously,[53] as shown in Figure 7. The observed

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(48) Bernasconi, C. F.; Hibdon, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 4343–4348.

(49) Reference 36. The value of $p_y = 0.13$ was calculated by using $p_y = \partial\beta/-\partial\,\mathrm{p}K_a^{\mathrm{BH}^+} = 2.303RT/8\Delta G_0^{\ddagger}$ where $\Delta G_0^{\ddagger}$ is the intrinsic barrier for the reaction: Marcus, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 7224–7225; ref 50. Interaction coefficients are defined so that a normal Hammond effect corresponds to a positive sign of the coefficient.[47]

(50) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475–503.

(51) Reference 3. The values of pK_a^{CD} were calculated from the observed rate constants for catalysis of C(2)–H → D exchange by deuterioxide ion (Table I), pK_a = 16.44 for D_2O at 30 °C, and the equation pK_a^{CD} = 16.44 − log ($8k_{\mathrm{OD}}/3 \times 10^9$ M^{-1} s^{-1}), which corrects the value of k_{OD} for an 8-fold negative deviation from the Brønsted plot of slope 1.0 that was observed for base-catalyzed proton exchange from 3,4-dimethylthiazolium ion under conditions in which diffusion-controlled separation of the products is rate-limiting.[2]

(52) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907–3911. Kresge, A. J. *Can. J. Chem.* **1974**, *52*, 1897–1903.

(53) Jencks, W. P.; Brant, S. R.; Gandler, J. R.; Fendrich, G.; Nakamura, C. *J. Am. Chem. Soc.* **1982**, *104*, 7045–7051.

(54) Jencks, W. P. *Adv. Chem.* **1987**, *215*, 155–167.

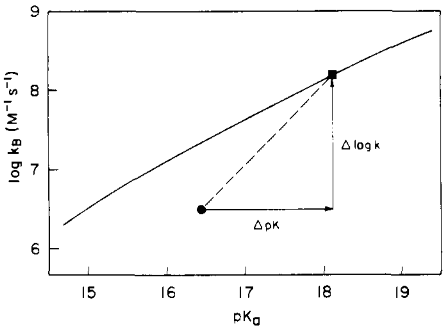

Figure 7. Eigen curve for thiazolium ion C(2)-T → D exchange to show how a requirement for partial desolvation of deuterioxide ion can cause a negative deviation from an Eigen curve by its effects on the observed pK_a (ΔpK) and reactivity ($\Delta \log k$) of solvated and desolvated deuterioxide ion. The data are for catalysis of C(2)-T → D exchange from 3-(cyanomethyl)-4-methylthiazolium ion (**3**) ($pK_a^{CD} = 17.4$) at 30 °C, $I = 2.0$ M (NaCl);[2] the observed rate constant for catalysis by deuterioxide ion is indicated by the circle.

reactivity and basicity of solvated OD^- are smaller than the reactivity and basicity of partially desolvated OD^- by the factor $1/K_D$ (when $K_D \ll 1.0$). If the rate constant for partially desolvated OD^- fits the Brønsted plot for other bases (square, Figure 7), it will be displaced horizontally and vertically from the observed rate constant and the pK_a of solvated OD^- (circle, Figure 7) by $\Delta \log k = \Delta pK = -\log K_D = 1.7$.

Although the desolvation is discussed here in terms of removal of a single water molecule, it is not unlikely that the actual situation is more complicated. There may be variable amounts of desolvation in different reactions, depending on the Brønsted slopes and the advantage that can be gained by desolvation. It is also likely that partial solvation can be retained in the transition state; a similar situation has been calculated by Jorgenson and coworkers[55] for the attack of Cl^- on methyl chloride in water.

This interpretation of the lyoxide ion anomaly is consistent with the fact that no such deviation is found for proton transfer between H_2O and H_3O^+ or H_2O and OH^- at $\Delta pK = 0$,[56] which may reflect proton transfer through solvent molecules. For reactions involving basic oxy anions as nucleophiles or as catalysts, desolvation of the oxy anion appears to be ahead of bond formation to the oxy anion in the transition state,[53,57,58] according to a variety of experimental criteria.

It is possible that the values of $-\log K_D$ and ΔpK for OL^- are underestimates because they were obtained by reference to a Brønsted line that is defined by alkoxide ions, and the alkoxide ions may also require partial desolvation before reaction.[53,57] However, it is unlikely that this effect is large because the observed rate constants for reaction of the alkoxide ions correspond to small barriers for reaction and the barriers cannot become much smaller.

Dependence on Ionic Strength. Figure 3 shows that the rate constants for catalysis of C(2)-H → D exchange by deuterioxide ion decrease 3-fold with an increase in ionic strength from 0.022 to 2.0 M (NaCl). However, there is no significant change in the primary kinetic isotope effect, $(k_L/k_T)_{obsd}$, the extent of internal return, k_{-1}^H/k_2, or the secondary solvent isotope effect, k_{OD}/k_{OH}, for catalysis of C(2)-L exchange from N(1′)-protonated thiamin (**1**) by lyoxide ion over this range of ionic strength (Table I).

The observed rate decrease with increasing ionic strength can be attributed to stabilization of the ionic reactants in solution relative to the rate-limiting transition states for proton transfer and diffusional separation of products, as shown in Figure 8. The absence of an effect of ionic strength on the observed isotope effects and the k_{-1}^H/k_2 ratio shows that the charge distribution in these two transition states does not differ enough to give a detectable effect of ionic strength.

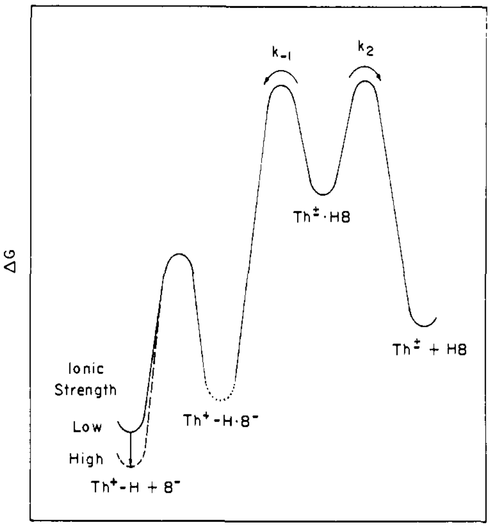

Figure 8. Gibbs free energy-reaction coordinate diagram for thermodynamically unfavorable proton transfer from a thiazolium ion (Th^+-H) to an anionic base to illustrate how an increase of ionic strength (broken line) provides a less favorable equilibrium for formation of the ionic encounter complex (Th^+-H·B^-) and a rate decrease for C(2)-proton exchange.

The solid line in Figure 3 is calculated from the Debye–Hückel equation and gives a surprisingly good fit to the data for NaCl (solid symbols) at ionic strengths up to 2 M, with a value of $\alpha = 3.0$ Å for the effective ionic radius of deuterioxide ion at 30 °C. This value of α is similar to the value of 3.5 Å taken for hydroxide ion at 25 °C by Kielland; it is at the lower limit of measured values for inorganic ions in the range 2.5–11 Å and organic ions in the range 3.5–8 Å in aqueous solution at 25 °C.[59]

The rate constants for catalysis of C(2)-H → D exchange from 3,4-dimethylthiazolium ion (**2**) by OD^- are significantly increased by Na_2SO_4 and decreased by $NaClO_4$ when compared to the rate constants obtained with NaCl above ionic strength 0.1 M, as shown in the open symbols in Figure 3; similar rate increases by SO_4^{2-} were observed for **3**. Similar anion-specific (Hofmeister) effects on the hydrolysis of an iminium ion have been observed[60] and Hofmeister effects were recently reviewed.[61] The rate increase by SO_4^{2-} cannot be explained by base catalysis by the SO_4^{2-} ion because the Brønsted plot for general-base catalysis of C(2)-L → D exchange from **2** predicts a value of $k_B = 4 \times 10^{-9}$ M^{-1} s^{-1} for SO_4^{2-},[2] based on $pK_a = 1.46$ for DSO_4^-,[62] which would not give detectable catalysis. No changes in the ultraviolet spectrum of **2** that might suggest complexation to form an unreactive ion pair between the cationic substrate and ClO_4^- were detected in 0 and 1.7 M $NaClO_4$. An effect of viscosity on the rate constant for diffusional separation also cannot explain the rate increase of ~15% with Na_2SO_4 and the rate decrease of ~18% with $NaClO_4$ for **2** at ionic strength 2.0 M, because the small changes of <10% in the viscosity of these salt solutions relative to that of 2.0 M NaCl are in the wrong direction to account for the rate effects.[63]

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(55) Chandrasekhar, J.; Smith, S. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 154–163.

(56) Meiboom, S. *J. Chem. Phys.* **1961**, *34*, 375–388. Loewenstein, A.; Szöke, A. *J. Am. Chem. Soc.* **1962**, *84*, 1151–1154.

(57) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451–464. Hupe, D. J.; Wu, D. *J. Am. Chem. Soc.* **1977**, *99*, 7653–7659. Hupe, D. J.; Wu, D.; Shepperd, P. *J. Am. Chem. Soc.* **1977**, *99*, 7659–7662. Pohl, E. R.; Wu, D.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2759–2763. Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1987**, *109*, 7115–7121.

(58) Bernasconi, C. F.; Bunnell, R. D. *Isr. J. Chem.* **1985**, *26*, 420–427. Bernasconi, C. F.; Paschalis, P. *J. Am. Chem. Soc.* **1986**, *108*, 2969–2977. Huskey, W. P.; Schowen, R. L. *Gazz. Chim. Ital.* **1987**, *117*, 409–416.

(59) Kielland, J. *J. Am. Chem. Soc.* **1937**, *59*, 1675–1678.

(60) Hogg, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5643–5645.

(61) Collins, K. D.; Washabaugh, M. W. *Q. Rev. Biophys.* **1985**, *18*, 323–422.

(62) This pK_a for DSO_4^- in D_2O was calculated from $pK_a = 1.1$ in H_2O ($I = 1.0$ M) (Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum Press: New York, 1976; Vol. 4, p 26) by adding $\Delta pK = 0.36$ for the solvent deuterium isotope effect for H_2SO_4 (Lietzke, M. H.; Stoughton, R. W. *J. Phys. Chem.* **1963**, *67*, 652–654) and assuming the same ΔpK for HSO_4^-.

Conclusion. These results indicate that the significant decrease in the Brønsted slope β that was observed[2] for catalysis of C(2)–T → D exchange by alkoxide ions and lyoxide ion as the proton-transfer reaction approaches $\Delta pK = 0$ can be explained as (1) a partial change in rate-limiting step, from diffusional separation of the products to proton abstraction by OL$^-$, (2) a change in transition-state structure with increasing acidity of the C(2) ylide and basicity of the catalyzing base, and (3) a requirement for the removal of water from HO$^-$ and DO$^-$ before reaction. The pK_a values for thiazolium C(2) ylides in the range 17–19 and the small barrier for proton transfer show that the lifetime of the carbanions in aqueous solution is very short.[3] However, the demonstration of internal return in C(2)-hydron exchange proves that the lifetime of thiazolium C(2) ylides is significant. The results provide additional evidence that thiazolium ions undergo proton loss with a small intrinsic barrier and that they are the most normal carbon acids yet identified.[2,3]

Supplementary Material Available: Equations for calculating the propagated error in the calculated values of the Swain–Schaad exponent (y), the extent of internal return (k_{-1}^{H}/k_2), the primary isotope effect for proton transfer (k_1^{H}/k_1^{T}), and the amount of O–T bond formation in the rate-limiting transition state for catalysis of C(2)–T → D exchange by deuterioxide ion (β) (2 pages). Ordering information is given on any current masthead page.

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(63) For viscosity at 25 °C, see: Stokes, R. H.; Mills, R. *Viscosity of Electrolytes and Related Properties*; Pergamon Press: New York, 1965; pp 118–123.

Anthraquinone-Based Cyclophane Hosts: Synthesis and Complexation Studies

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Abstract: Synthesis, molecular modeling, and complexation studies of the title compound, **1a–c**, are described. In striking contrast with the behavior of related hosts, they are devoid of guest-binding properties. Possible reasons for this are discussed.

Introduction and Rationale

The design of host molecules with a high specificity for guest molecules is of some current interest.[1-4] We have recently shown[1] that the meso and racemic naphthalene cyclophane-based hosts (Figure 1) show some remarkable properties as hosts: (1) Acidic guests are bound in the host's cavity by formation of a hydrogen bond between the guest's acidic site and the pyridine nitrogen. (2) The hosts are *guest specific*, binding acidic phenols (e.g. *p*-nitrophenol (pNP)) which must be unsubstituted on the C2 and C3 carbons. They are moreover specific for phenolic guests; carboxylic acids do not bind. (3) Remarkably high association constants (K_{assoc}) are observed in *nonaqueous media*. For example the meso host–pNP complex has a K_{assoc} in excess of 1.5×10^4 in chloroform. The design concept of a guest-sticky cavity[1] thus relieves one of dependence on hydrophobic effects as a force affecting guest binding.

Given the above results, we were interested in preparing similar host molecules possessing a larger cavity. Three potential hosts **1a–c** (Figure 2) based on anthraquinone cyclophanes were chosen as potential hosts for the following reasons: (1) The larger cavity size should permit binding of larger aromatic guest molecules, e.g. naphthols, with the possibility of increased K_{assoc} values arising from the increase in π-stacking interactions. (2) The anthraquinone building block would permit testing of the idea that the π-acidic quinone would increase the cavity stickiness toward π-basic guests. This was viewed with some trepidation since Shinmyozu et al.[5] found π acid–π base forces ineffective in a vaguely related cyclophane host.

Table I. Comparison of $\Delta\delta$ between the Diastereotopic CH_2N Protons of Meso and *dl* Host Cyclophanes[a]

	Δδ, ppm	
	meso	*dl*
1a	0.51	0.18
1b	0.27	0.12
1c	0.18	0.08
9[a]	1.11	0.6

[a] **9** is the naphthalene analogue of **1a**[6] (Figure 3).

Table II. Cyclization Shifts of Cyclophanes **1a–c** and **9**[a]

	Δδ, ppm			
	$H_{2,3}$	H_5	H_8	H_7
dl-**1a**	−0.27	−0.14	−0.08	+0.22
dl-**1b**	−0.17	−0.26	−0.01	+0.07
dl-**1c**	−0.18	−0.18	0.0	−0.09
9	−0.14	−0.15	+0.02	+0.39
meso-**1a**	−0.26	+0.04	−0.17	0
meso-**1b**	−0.21	−0.17	−0.14	−0.03
meso-**1c**	−0.19	−0.14	−0.14	−0.06
9	−0.17	+0.01	−0.06	+0.18

[a] δ **1** − δ precyclophane, negative values mean upfield shifts on cyclization.

Results and Discussion

Synthesis. Host **1a**, based on a bis(tosyl-*p*-phenylenediamine) spacing group, was synthesized as shown in Scheme I. Cyclization of the precyclophane **6** ($Cu(OAc)_2$, pyridine, 40 °C) gave, in 35% yield, an impure (1:1) mixture of meso and racemic isomers of

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