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C(α)-Proton Transfer from 2-(1-Hydroxybenzyl)oxythiamin: The Unit Brønsted Slope Overestimates the Amount of Bond Formation to the Base Catalyst in the Transition State[1]

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Abstract: Rate constants for C(α)-hydron transfer from racemic 2-(1-hydroxybenzyl)oxythiamin (HBOT) in oxygen-containing (cacodylate, phosphate, or alcohol) and primary amine buffers are reported. Thermodynamically unfavorable C(α)-H transfer from HBOT ($pK_a = 15 \pm 1$) shows general-base catalysis with a Brønsted β value of ≥ 0.95, which suggests rate-limiting diffusional separation of the conjugate buffer acid from the C(α)-carbanion/enamine. The calculated rate constant for the reverse protonation of the C(α)-carbanion/enamine by buffer acids, $k_{BH} = 10^{4\pm1}$ M^{-1} s^{-1}, is independent of pK_a^{BH} with $\alpha \leq 0.05$, but is far below the diffusion-controlled limit. The primary kinetic isotope effects for cacodylate catalysis, $k_H/k_T = 1.8 \pm 0.1$ and $k_H/k_D = 1.5 \pm 0.1$ in H$_2$O, obey the Swain–Schaad relation and require incomplete proton transfer in the rate-limiting transition state. These results are consistent with the suggestion that a value of $\alpha_d \approx -0.2$ for desolvation of the buffer acid offsets $\alpha = 0.2$ for protonation to give $\alpha_{obsd} = 0$ for some carbanions. General-base catalysis is detectable because there is a $10^{2.9}$-fold negative deviation from the Brønsted correlation for hydroxide ion.

Transfer of the C(α)-proton of thiamin carbinols (**1a**) (Scheme 1) gives a resonance-stabilized conjugate base (**2**) that has been implicated in addition–elimination reactions catalyzed by several thiamin diphosphate-dependent enzymes.[2] This has generated interest in the factors that contribute to the kinetic barriers for C(α)-proton transfer and the stability of **2**.[3] Abstraction of the C(α)-proton from 2-(1-hydroxyethyl)thiamin (**1a**, R_1 = Me) exhibits "normal" acid behavior in aqueous solution (pK_a = 18.4–19.8):[3a] the reaction follows a normal Eigen curve,[4] with a Brønsted β value of ≥ 0.9 for catalysis by buffer bases, and values of $(k_H/k_D)_{obsd}$ in the range 1.0 ± 0.1 for catalysis by buffer bases are in the range expected for rate-limiting diffusional separation of buffer acids from the discrete C(α)-carbanion/enamine (**2a**).

We report here evidence that the Brønsted β value of ≥ 0.95 for C(α)-proton transfer from another thiazolium carbinol, racemic 2-(1-hydroxybenzyl)oxythiamin (**1b**), overestimates the amount of bond formation to the base catalyst in the rate-limiting transition state: this requires that α ($= 1 - \beta$) ≤ 0.05 for the reverse protonation reaction underestimates the degree of proton transfer from an acid catalyst. The magnitudes of isotope effects for C(α)-proton transfer provide evidence against the rate-limiting transition state involving diffusion-controlled separation of the buffer acid from **2b**. Similar evidence for deprotonation of a sulfonium salt has been reported and attributed to significant effects of solvation of the base catalyst (desolvation of the buffer acid in the protonation direction) on the value of β (α).[5]

Experimental Section

Materials. All chemicals were of analytical or reagent grade and were used without purification unless otherwise stated. Water was prepared on a four-bowl Milli-Q water system including an Organex-Q cartridge (Millipore). [^{3}H]H$_2$O (1 Ci/mL) was purchased from New England Nuclear. Catalysts were purified by redistillation or by recrystallization as the hydrochloride or potassium salt except for 2,2,2-trifluoroethanol (Aldrich, 99.5+%), which was used without further purification. 4-Oxo-5-(aminomethyl)-2-methylpyrimidine dihydrochloride was synthesized as described previously.[6] In a manner similar to that shown for the synthesis of 2-(1-hydroxyethyl)oxythiamin chloride hydrochloride,[3a] 1.1 g (80%) of racemic **1b** was obtained from racemic **1a** (R_1 = Ph, R_2 = NH$_2$) as a hygroscopic white solid: ^{1}H NMR (Me$_2$SO-d_6) δ 2.37 (s, 3H), 2.47 (s, 3H), 2.99 (t, 2H), 3.61 (t, 2H), 5.40 (q, 2H), 6.64 (s, 1H), 7.29–7.76 (m, 9H). The synthesis of **1a** with ^{2}H (D)[7] in the C(α) position was accomplished using benzaldehyde-d_1 (ICN) instead of benzaldehyde-h_1.[8] The synthesis of **1b** with ^{3}H (T) in the C(α) position was accomplished by exchange with [^{3}H]H$_2$O in H$_2$O at 25 °C for >24 h and pH 4; the pH was adjusted with KOH. The solvent was removed by evaporation under a water aspirator vacuum in a Savant Speed-Vac centrifugal concentrator; all operations were performed in a fume hood. The 2-([1-^{3}H]-1-hydroxybenzyl)oxythiamin, which was typically 0.3–0.5 mCi/mol, was stored *in vacuo* over P$_2$O$_5$ at ambient temperature in a fume hood. Parallel experiments in deuterium oxide (Aldrich) and ^{1}H NMR examination of the exchanged thiazolium ion showed that isotopic labeling under these conditions occurs exclusively by exchange at C(α)-H.

Methods. Solution pH was measured at 25 °C with an Orion Model SA 720 pH meter and a Radiometer GK2321C combination electrode

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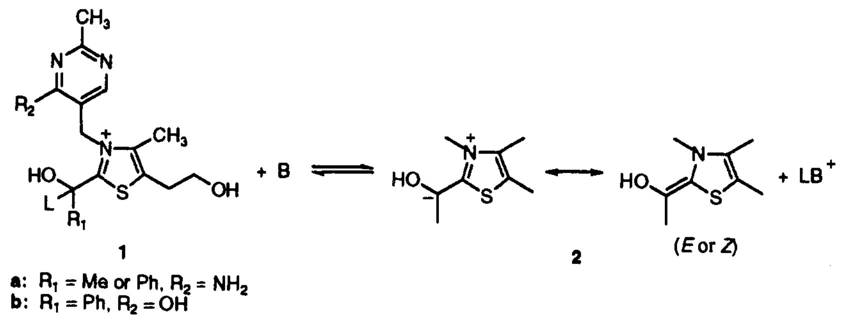
Scheme 1



1

2

(*E* or *Z*)

a: R_1 = Me or Ph, R_2 = NH_2
b: R_1 = Ph, R_2 = OH

standardized at pH 7.00 and 4.00 or 10.00. ^1H NMR spectra were recorded on a Bruker AMX-300 NMR spectrometer using sodium 3-(trimethylsilyl)propanesulfonate as an internal standard. Radioactivity was measured with a Beckman LS 7500 liquid scintillation counter.

Kinetics. Rate constants for C(α)-H transfer in H_2O at 25 °C were determined by iodination from initial rate measurements, in which the reaction had proceeded ≤5% to completion, as described previously.[3a,c] The ionic strength was maintained at 1.0 M with potassium nitrate. Rate constants for C(α)-D → H exchange catalyzed by cacodylate in H_2O at 25 °C and 1 M ionic strength (KNO_3) were determined either by iodination[3a,c] or by quenching aliquots in acid, lyophilizing, redissolving in 0.05 M DCl, and monitoring the relative areas of C(α)-H to nonexchanging C(6′)-H by NMR, as described previously.[9] Rate constants for C(α)-T → H exchange in H_2O at 25 °C and 1 M ionic strength (KNO_3) were determined as described previously[9] with several modifications: aliquots of the reaction solution were quenched with acid, absorbed onto SP-Sephadex C-25, washed with water to remove [^3H]-H_2O, eluted with 6 M HCl, and lyophilized, and the nonvolatile radioactivity of 2-([1-^3H]-1-hydroxybenzyl)oxythiamin was measured.[10] When duplicate determinations of k_{obsd} were made, they agreed within ≤±5% of the average value.

Measurements of pH were made at 25 ± 0.2 °C on the buffered solutions of **1b** after exchange had occurred. From measurements of pH at known concentrations of hydroxide ion at 25 °C and 1.0 M ionic strength, maintained with potassium nitrate, eq 1 was used to calculate the concentration of hydroxide ion at any pH. This equation includes the ion product of water at 25 °C.[11]

$$[HO^-] = 1.56 \times 10^{(pH-13.997)} \qquad (1)$$

Experiments to measure general-base catalysis were performed as described previously.[3a,c] Second-order rate constants for catalysis by buffer bases, water, and hydroxide ion were determined graphically[3c] from plots of ≥4 values of k_{obsd} against buffer concentration, corrected for the fraction free base of the buffer (20, 30, 50, 70, 80% free base), and are concentration-based. We estimate that the second-order rate constants are accurate to within ≤±17% on the basis of the maximum and minimum slopes that could be drawn in these plots.

Determination of Catalyst pK_a′ Values. Values of pK_a′ for the buffer catalysts were typically determined from the pH values of gravimetrically prepared buffer solutions containing the acid and base form at a 1:1 ratio. Errors in the pK_a′ values in H_2O were ≤±0.04. Values of pK_a′ = 7.62 ± 0.03 and 10.56 ± 0.05 for 1,2-diaminoethane dihydrochloride were determined by potentiometric titration at 25 °C and ionic strength 1.0 M (KNO_3): data were analyzed by assuming overlapping ionization steps.[12-15]

Results

The kinetics of general-base-catalyzed C(α)-hydron transfer (L = H, D, or T)[7] from 2-(1-hydroxybenzyl)oxythiamin (**1b**) in the pH range 4.5–10 at 25 °C and ionic strength 1.0 M, maintained with potassium nitrate, in H_2O were followed by a combination of ^1H NMR, detritiation, and iodination methods under pseudo-first-order and initial rate conditions. The C(α)-hydron-transfer reaction obeys the rate law described by eq 2, as observed

$$k_{obsd}\,(s^{-1}) = k'_{H_2O} + k_{HO^-}[HO^-] + k_{B_1}[Base_1] + k_{B_2}[Base_2] \qquad (2)$$

previously for **1a** (R_1 = Me):[3a] no catalysis by the acid component of the buffer was observed. A second term for catalysis by buffer bases ($k_{B2}[Base_2]$) is required in the rate law when dibasic buffer catalysts are used.[3c] The rate constants for base catalysis of C(α)-hydron transfer were determined as described in the Experimental Section. The second-order rate constants, k_B, for general-base catalysis of C(α)-hydron transfer from **1b** are summarized in Table 1. Rate increases from general-base catalysis were typically large (≤400%) at total buffer concentrations ≤ 0.4 M. Changing the concentration of the acid component of the buffer or substituting potassium trifluoroacetate for potassium nitrate had no effect on k_B, which indicates that medium and specific salt effects are small. The absence of significant curvature at high buffer concentrations in plots of k_{obsd} against [buffer] (data not shown) also suggests that medium effects are small.

Table 1. General-Base-Catalyzed C(α)-L Transfer from 2-(1-Hydroxybenzyl)oxythiamin[a]

catalyst	C(α)-L	pK_a′ [b]	*p*	*q*	pK_a′ + log(*p*/*q*)	k_B (M^{-1} s^{-1})	log(k_B/*q*)
H_2O[c]	H	−1.74	3	1	−1.26	(1.67 ± 0.28) × 10^{-8}	−7.78
	T					(1.08 ± 0.06) × 10^{-8}	
$F_3CCH_2NH_2$	H	5.66	3	1	6.14	≤7.94 × 10^{-7}	≤−6.10
$(CH_3)_2AsO_2^-$	H					(6.32 ± 0.33) × 10^{-7}	−6.50
	D	6.20	1	2	5.90	(4.21 ± 0.21) × 10^{-7}	
	T					(3.51 ± 0.17) × 10^{-7}	
HPO_4^{2-}	H	6.49	2	3	6.31	1.14 × 10^{-5}	−5.42
$^+H_3NCH_2CH_2NH_2$	H	7.62	3	1	8.10	1.62 × 10^{-5}	−4.79
$(HOCH_2)_3CNH_2$	H	8.31	3	1	8.79	9.77 × 10^{-4}	−3.01
$(CF_3)_2CHO^-$	H	9.3[d]	1	1	9.3	8.91 × 10^{-4}	−3.05
$H_2NCH_2CH_2NH_2$	H	10.56	3	1	11.04	3.39 × 10^{-2}	−1.47
PO_4^{3-}	H	11.3	1	3	10.82	9.27 × 10^{-2}	−1.51
$F_3CCH_2O^-$ [e]	H	12.3[f]	1	1	12.3	0.40	−0.40
HO^- [g]	H	15.74	2	1	16.04	2.9	0.46

[a] At 25 °C and ionic strength 1.0 M (KNO_3) in H_2O. Statistical corrections of the values of pK_a′ and k_B were made according to Bell and Evans.[13] [b] Apparent pK_a of the conjugate acid at 25 °C and ionic strength 1.0 M (KNO_3) in H_2O (see text). [c] The second-order rate constant was calculated using a standard state of 55.4 M for pure H_2O at 25 °C. [d] Reference 14. [e] 2,2,2-Trifluoroethylamine buffer present. [f] Estimated from the pK_a′ value at low ionic strength in H_2O.[15] [g] The rate constant for catalysis by HO^- is concentration-based, γ_{HO^-} = 0.64.

Identical values of k_{obsd} for C(α)-D → H exchange from **1b** were determined using the iodine assay and by ^{1}H NMR in the pH range 4.5–10. The usual zero-order kinetics in iodine[3a,c] was obtained in the pH range 4.5–10, and no changes in the ultraviolet or ^{1}H NMR spectrum of **1b** that might suggest a side reaction were detected in the presence or absence of iodine. No significant consumption of iodine by 4-oxo-5-(aminomethyl)-2-methylpyrimidine that might suggest iodination of the N(3)-substituent of **1b** was detected in the pH range 4.5–10. These results confirm previous conclusions that the iodine reaction is following C(α)-hydron transfer, that the reaction with iodine is not rate limiting, that the iodination reaction is not readily reversible, and that the stoichiometry of the reaction with iodine involves one molecule of iodine.[3a,c]

We do not have a satisfactory explanation for different values of k_{HO^-} for hydroxide ion-catalyzed C(α)-proton transfer from different thiazolium carbinols. For example, the value of k_{HO^-} = 2.9 M^{-1} s^{-1} reported here for C(α)-proton transfer from **1b** (Table 1) cannot be directly compared with a value of k_{HO^-} = 20 M^{-1} s^{-1} for C(α)-proton transfer from a 2-[(1-methoxyphenyl)-methyl]-3,4-dimethylthiazolium ion,[3b] in part, because of a poorly understood N(3)-substituent-dependent "hydroxide ion anomaly".[3a]

Discussion

Figure 1 shows that the Brønsted plot for C(α)-proton transfer from **1b** in H_2O has a slope of $\beta \geq 0.95$ for catalysis by water, buffer bases, and hydroxide ion.[16] The calculated rate constant[18] for protonation of **2b** by buffer acids, $k_{BH} = 10^{4\pm1}$ M^{-1} s^{-1}, is independent of pK_a^{BH}, but is far below the diffusion-controlled limit.[19–21] The observed primary kinetic isotope effects for cacodylate-catalyzed C(α)-proton transfer ($\Delta pK_a \approx 9$), k_H/k_T = 1.8 ± 0.1 and k_H/k_D = 1.5 ± 0.1 in H_2O, satisfy the Swain–Schaad relation, $\log(k_H/k_T)_{obsd} = y \log(k_H/k_D)_{obsd}$,[22] with a value of y = 1.5 ± 0.2, and are consistent with chiefly rate-limiting proton transfer.[23] These small isotope effects are qualitatively consistent with an asymmetric transition state as proposed by Westheimer[24] and observed for thiazolium C(2)-proton transfer.[25] Catalysis is detectable because the rate constant for hydroxide ion falls below the Brønsted line: because of the large β value in this reaction, catalysis by hydroxide ion would overwhelm general-base catalysis if hydroxide ion also obeyed the Brønsted correlation.

These results can be explained by direct protonation of **2b** by a buffer acid that is initially hydrogen bonded to water.[5] Proton transfers to and from carbon occur directly so that an acid catalyst must break a hydrogen bond to water before it can protonate a carbanion.[9,26] The Brønsted $\alpha \leq 0.05$ and value of $k_{BH} = 10^{4\pm1}$ M^{-1} s^{-1} reflect the equilibrium constant for breaking the $BH^+ \cdot OH_2$ hydrogen bond and the rate constant for direct proton transfer from BH^+ to **2b**. For comparison, a value of $k_{BH} = 10^{7.3}$ M^{-1} s^{-1} was calculated for protonation of a sulfonium ylide by BH^+.[5] The $10^{2.9}$-fold negative deviation for hydroxide ion in Figure 1 is consistent with a requirement for partial desolvation of hydroxide ion before reaction,[3a,26b] and the positive deviation for water probably results from the ability of H_3O^+ to undergo facilitated diffusion.[26a]

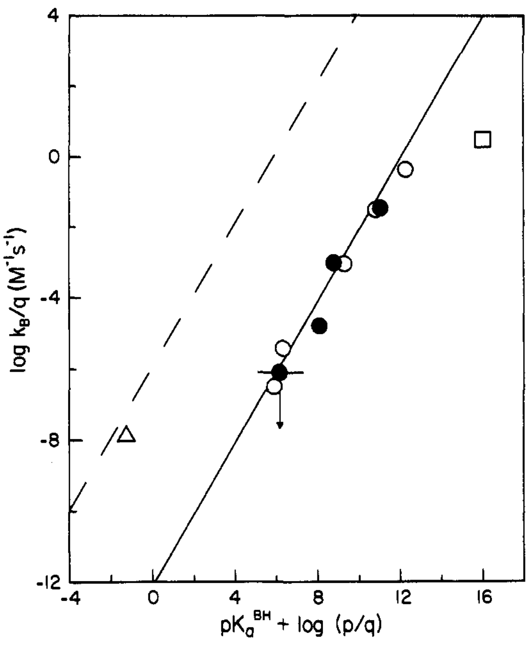


Figure 1. Brønsted plot for general-base catalysis of C(α)-proton transfer from 2-(1-hydroxybenzyl)oxythiamin (**1b**) catalyzed by water (△), oxygen-containing buffer bases (cacodylate, phosphate, or alkoxide) (○), primary amines (●), and hydroxide ion (□) in aqueous solution at 25 °C, I = 1.0 M (KNO_3). Values of k_B are summarized in Table 1. Statistical corrections were made according to Bell and Evans.[13] The upper limit for catalysis by 2,2,2-trifluoroethylamine is indicated. The solid line of slope β = 1.0 is drawn through the points for buffer base-catalyzed C(α)-proton transfer. The upper broken line is a limiting theoretical Eigen curve[4] with $k_{BH} = 10^{9.5}$ M^{-1} s^{-1} for diffusion-controlled encounter of the reactants.

Consequently, to obtain an estimate of the amount of bond formation to the base catalyst in the transition state for C(α)-proton transfer from **1b**, the observed value of β must be corrected for the solvation step according to $\beta_{corr} = 0.8\beta_{obsd}$ and $\alpha_{corr} = 0.2 + 0.8\alpha_{obsd}$, as suggested previously for deprotonation of a sulfonium salt.[5] The correction of $\alpha_d \approx -0.2$ appears reasonable on the basis of indirect evidence that the equilibrium constant for desolvation (K_D) is smaller for stronger acids, which corresponds to $\partial \log K_D / \partial \log K_a = \alpha_d$;[5,27] the correction will be largest when the observed Brønsted β value approaches 1.0 and is applicable

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(16) We estimate a value of pK_a^{CH} = 15 ± 1 for **1b** in H_2O at 25 °C, I = 1.0 M (KNO_3). An upper limit of $pK_a^{CH} \leq 16.3$ was calculated according to $pK_a^{CH} = pK_a^{H_2O} - \log(k_{H_2O}/k_{H_3O^+})$ with $pK_a^{H_2O} = -1.74$ and $k_{H_2O} = 1.67 \times 10^{-8}$ M^{-1} s^{-1} for catalysis by H_2O (Table 1): an upper limit of $k_{H_3O^+} \leq 10^{10.3}$ M^{-1} s^{-1} was assumed for protonation of **2b** by H_3O^+.[3a] A lower limit of $pK_a^{CH} \geq 13.7 = 15.5 - \leq 1.8$ was calculated with the spectrophotometrically measured value of pK_a^{CH} = 15.5 in H_2O at 25 °C, $I \geq 0.3$ M, for 2-[(methoxyphenyl)methyl]-3,4-dimethylthiazolium ion.[17] The factor ≤1.8 = (≤22)(0.07 – (–0.01)) corrects for the dependence of the C(α)-proton-transfer rate on an electron-withdrawing inductive effect by substituents on the nitrogen atom of the thiazolium ring, which follow Hammett correlations with the inductive substituent constant σ_I with a slope of $\rho_I \leq 22$:[3a] $\sigma_I = -0.01$ for N(3)–CH_3; $\sigma_I = 0.07$ for the N(3)-substituent in **1b**.[6]

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(18) Calculated from pK_a^{CH} = 15 ± 1 in H_2O for **1b**[16] according to $pK_a^{CH} = pK_a^{BH} - \log(k_B/k_{BH})$.[3a] Values of k_B and pK_a^{BH} are summarized in Table 1.

(19) A value of $k_{BH} = 10^{9.2\pm0.5}$ M^{-1} s^{-1} has been suggested for diffusional encounter of unsymmetrical reagents.[20] To our knowledge, the smallest rate constant reported for diffusion-controlled protonation of a base by a buffer acid in aqueous solution is $10^{6.6}$ M^{-1} s^{-1}.[21]

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to oxygen-containing (carboxylate, cacodylate, phosphate, or alkoxide) or amine bases.

These results represent another example in which solvation of ionic and neutral species can effect observed structure–reactivity parameters in aqueous solution.[5,28] Although the desolvation is discussed here for 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 C(α)-proton-transfer reactions, which would give different calculated values of k_{BH} for different carbon acids. An explanation of how such solvation effects change rate constants in a structure–reactivity correlation is not trivial[29] because changes in the rate constant and the basicity must be related to the slope of the Brønsted correlation, which may not be linear.[26b,28]

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