J. Am. Chem. Soc. **1990**, *112*, 779–786

5.40 (d, J = 1.5 Hz, 1 H), 4.70 (br s, 1 H), 4.40 (d, J = 9.5 Hz, 1 H), 4.37 (d, J = 9.5 Hz, 1 H), 3.36 (s, 3 H), 3.32 (s, 3 H), 2.91 (ddd, J = 7.3, 8.8, 12.5 Hz, 1 H), 2.61 (br t, J = 8.8 Hz, 1 H), 2.01 (dd, J = 6.6, 12.5 Hz, 1 H), 1.88 (dd, J = 8.8, 13.2 Hz, 1 H), 1.37 (dd, J = 3.7, 13.2 Hz, 1 H), 1.27 (s, 2 H), 1.12 (t, J = 12.5 Hz, 1 H), 1.04 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1765, 1355, 1080, 1060 cm^{-1}; MS *m/e* (rel intensity) 292 (M^+, 41), 261 (70), 260 (56), 75 (100).

The above crude **21** was treated with methanolic NaOH as described for **20** to give 44 mg (94%) of **23**: ^1H NMR ($CDCl_3$) δ 5.43 (dd, J = 1.5, 2.5 Hz, 1 H), 5.32 (br s, 1 H), 4.23 (d, J = 9.3 Hz, 1 H), 4.11 (d, J = 9.3 Hz, 1 H), 3.68 (s, 3 H), 3.40 (s, 3 H), 2.86 (ddd, J = 6.8, 6.8, 12.2 Hz, 1 H), 2.57 (br t, J = ca. 7 Hz, 1 H), 1.91 (dd, J = 6.4, 12.2 Hz, 1 H), 1.80 (dd, J = 7.8, 13.2 Hz, 1 H), 1.45 (dd, J = 1.0, 13.2 Hz, 1 H), 1.40 (d, J = 3.9 Hz, 1 H), 1.35 (d, J = 3.4 Hz, 1 H), 1.25 (t, J = 12.2 Hz, 1 H), 1.06 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1720, 1290, 1240, 1155, 1140, 1015, 1005 cm^{-1}; MS *m/e* (rel intensity) 292 (M^+, 12), 260 (72), 201 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 70.08; H, 8.28.

Hydrolysis of 18. Hydrolysis of 364 mg (1.6 mmol) of **18** was carried out as described for **20** to give 380 mg (92%) of hydroxy ester **24** after flash chromatography (elution with petroleum ether/ether, 7:3) as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.98 (br s, 1 H), 4.26 (t, J = 12.1 Hz, 1 H), 3.75 (s, 3 H), 3.09 (dd, J = 3.4, 12.7 Hz, 1 H), 2.90 (dd, J = 2.9, 11.2 Hz, 1 H), 2.76 (ddd, J = 7.8, 7.8, 11.2 Hz, 1 H), 2.45 (m, 1 H), 1.96 (dd, J = 1.5, 3.1 Hz, 3 H), 1.74 (dd, J = 8.3, 13.2 Hz, 1 H), 1.49 (dd, J = 7.8, 11.9 Hz, 1 H), 1.33 (dd, J = 2.4, 13.2 Hz, 1 H), 1.11 (d, J = 4.4 Hz, 1 H), 1.08 (d, J = 4.4 Hz, 1 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.98 (t, J = 11.9 Hz, 1 H); IR (neat) 3500, 1720, 1270, 1140, 1020 cm^{-1}; MS *m/e* (rel intensity) 264 (M^+, 13), 232 (26), 187 (100). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 9.17.

Swern Oxidation of 24. To a solution of 0.1 mL (0.78 mmol) of oxalyl chloride in 1.0 mL of CH_2Cl_2 at −60 °C was added 0.12 mL (1.7 mmol) of DMSO in 0.4 mL of CH_2Cl_2, and the mixture was stirred for 10 min. To this suspension was added 186 mg (0.76 mmol) of **24** in 0.8 mL of CH_2Cl_2, and the mixture was stirred for 15 min before 0.5 mL (3.6 mmol) of triethylamine was added. The mixture was allowed to warm to room temperature, diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Flash chromatography (elution with petroleum ether/ether, 4:1) of the crude product gave 172 mg (93%) of aldehyde **25** as a colorless oil: ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 5.06 (br s, 1 H), 3.68 (s, 3 H), 2.83 (dt, J = 12.2, 7.3 Hz, 1 H), 2.50 (m, 1 H), 2.12 (d, J = 4.4 Hz, 1 H), 1.96 (dd, J = 1.5, 2.4 Hz, 3 H), 1.76 (dd, J = 8.3, 13.2 Hz, 1 H), 1.61 (dd, J = 6.3, 12.2 Hz, 1 H), 1.49 (t, J = 12.2 Hz, 1 H), 1.42 (d, J = 4.4 Hz, 1 H), 1.37 (dd, J = 2.0, 13.2 Hz, 1 H), 1.03 (s, 3 H), 1.01 (s, 3 H); IR (neat) 1730, 1720, 1260, 1140 cm^{-1}; MS *m/e* (rel intensity) 262 (M^+, 32), 247 (69), 203 (75), 202 (100), 187 (86), 173 (90). All attempts to convert **25** to methyl marasmate (**5**) were unsuccessful.

Methyl Marasmate (5). To a solution of *tert*-butyl hydroperoxide (79 mg, 0.7 mmol) in 0.1 mL of CH_2Cl_2 was added 19 mg (0.17 mmol) of SeO_2, and the mixture was stirred for 10 min. Then 87 mg (0.33 mmol) of **24** in 0.15 mL of CH_2Cl_2 was added, and the mixture was stirred overnight. The mixture was diluted with water, extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Since an attempt to isolate diol **26** by chromatography was not successful, the crude product was subjected directly to Swern oxidation as described for **24**. Methyl marasmate (**5**) (18 mg, 19%) was isolated by flash chromatography (elution with petroleum ether/ether, 7:3), which was spectroscopically (IR, ^1H NMR, and ^{13}C NMR) identical with an authentic sample: ^1H NMR ($CDCl_3$) δ 9.85 (s, 1 H), 9.47 (s, 1 H), 6.50 (d, J = 2.7 Hz, 1 H), 3.67 (s, 3 H), 3.00 (ddd, J = 7.0, 8.0, 12.4 Hz, 1 H), 2.78 (br t, J = 8.6 Hz, 1 H), 2.35 (d, J = 4.8 Hz, 1 H), 2.00 (dd, J = 9.1, 13.4 Hz, 1 H), 1.69 (dd, J = 7.0, 12.9 Hz, 1 H), 1.58 (dd, J = 3.2, 13.4 Hz, 1 H), 1.44 (t, J = 12.9 Hz, 1 H), 1.17 (d, J = 4.8 Hz, 1 H), 1.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 197.0, 191.5, 170.9, 152.7, 139.2, 52.5, 46.7, 45.4, 40.9, 39.3, 37.9, 37.0, 33.4, 31.2, 30.6, 24.4.

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Registry No. (±)-**1**, 61216-74-8; (±)-**5**, 75918-37-5; (±)-**6**, 123675-62-7; (±)-**6** methyl epimer, 123750-17-4; (±)-**7**, 123675-63-8; (±)-**8**, 123675-64-9; (±)-**8** acid, 123675-80-9; (±)-**9**, 60064-71-3; (±)-**10**, 123675-65-0; (±)-**10** ketone, 123675-81-0; (±)-**11**, 123675-66-1; (±)-**12**, 123675-67-2; **13**, 1073-13-8; (±)-**14**, 123675-68-3; (±)-**15**, 123675-69-4; (±)-**16**, 123675-70-7; (±)-**17** isomer 1, 123675-71-8; (±)-**17** isomer 2, 123750-16-3; (±)-**18**, 123675-72-9; (±)-**19**, 123675-73-0; (±)-**20**, 123750-15-2; (±)-**21**, 123675-74-1; (±)-**22**, 123675-75-2; **23**, 123675-76-3; (±)-**24**, 123675-77-4; (±)-**25**, 123675-78-5; (±)-**26**, 123675-79-6.

A Systematic Entropy Relationship for the General-Base Catalysis of the Deprotonation of a Carbon Acid. A Quantitative Probe of Transition-State Solvation

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Abstract: The general-base-catalyzed deprotonation of a carbon acid, the 1-methyl-4-(phenylacetyl)pyridinium cation (pK_a = 9.02 at 25 °C), has been investigated for 32 general-base catalysts (25 amines and seven phenoxide ions) in aqueous solution. Amines give a generally scattered Brønsted plot; ring-substituted benzylamines have β = 0.52, and ring-substituted phenoxides have β = 0.60, with the phenoxides being more reactive than amines of similar basicity. The temperature dependences of the general-base-catalyzed deprotonation of this carbon acid have been measured over the range 15–45 °C for 12 base catalysts (eight primary, secondary, and tertiary amines; 4-(dimethylamino)pyridine; two phenoxide ions; hydroxide ion). The entropies of activation for these deprotonations show a clean curvilinear dependence upon the entropies of protonation of these base species, with the hydroxide ion being the only significant deviant from this relationship. This observation quantitatively establishes the importance of solvation effects as the major source of deviations that are commonly observed in Brønsted relationships for general-base-catalyzed processes.

The Brønsted relationship is commonly used to describe the efficiency of general-base catalysis in a wide range of reactions in organic chemistry.[1-4] However, it is also recognized that this relationship is less general than one might expect for a relatively simple free energy relationship that relates rate and equilibrium constants. Even for the general-base-catalyzed deprotonation of carbon acids (eq 1), in which proton transfer is not coupled to

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any other covalent-bond formation or fission processes, it is usual to require different correlation equations (log k_B vs pK_{BH}) for series of oxygen, nitrogen, and sulfur bases.[5-9] It is also frequently necessary to construct different Brønsted relationships to accommodate the experimentally observed differences in the catalytic efficiencies of primary, secondary, and tertiary amine bases in the same general-base-catalyzed process.[7,8,10-14]

$$CH + B \underset{k_{BH}}{\overset{k_B}{\rightleftharpoons}} C^- + BH^+ \quad (1)$$

$$CH \overset{K_{CH}}{\rightleftharpoons} C^- + H^+ \quad (2)$$

$$BH^+ \overset{K_{BH}}{\rightleftharpoons} B + H^+ \quad (3)$$

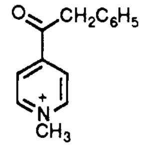
$$K = k_B/k_{BH} = K_{CH}/K_{BH} \quad (4)$$

These requirements for different Brønsted correlations for structurally different classes of general-base catalysts are usually attributed to differential solvation effects.[4] Such solvation effects are widely accepted as significant influences upon the basicities of primary, secondary, and tertiary amine bases in aqueous solution.[15-20] It is clear that if the solvation changes between the base and the transition-state species in a general-base-catalyzed process are not a simple function of the solvation change between the base (B) and its conjugate acid (BH), then there will be no unique linear free energy relationship describing log k_B as a function of pK_{BH}. Some types of curvature in Brønsted plots have also been attributed to solvation effects.[21-24]

The requirements for different Brønsted relationships for different classes of bases, and also the commonly encountered scatter in the data even within a series of apparently closely structurally related bases, are usually attributed in a qualitative way to variations in transition state solvation phenomena. Twenty years ago Jencks[25] commented, "The nature of deviations from the Brønsted relationship for different classes of general acid–base catalyzed reactions deserves more complete and systematic examination because these deviations may provide a method for approaching such difficult problems as the detailed structure of the transition state, ..., and the extent to which surrounding solvent molecules have been able to undergo arrangement to provide favourable solvation for the transition state during the time in which the transition state is reached." However, it is difficult to find an example of a truly extensive systematic study that might be regarded as an attempt to address this problem.

Furthermore, there does not appear to have been any attempt to *quantitatively* investigate these solvation processes as a function of base structure. The most directly experimentally accessible quantitative expression of solvation changes lies in the activation parameters of these general-base-catalyzed processes,[26] with the activation entropies in particular being expected to be profoundly influenced by solvation phenomena.[16,27,28] Despite the above-noted widespread acceptance of the importance of solvation effects upon general-base catalysis, there does not appear to have been any comprehensive attempt to quantitate such effects through a comparison of activation entropies for a general-base-catalyzed process and the entropies of reaction for the protonation of a variety of bases. The only such study of this type that we have located in the literature are the data of Pearson[29] for the deprotonation of nitroethane by ammonia and the mono-, di-, and trimethylamines. However, this study was limited to only four amine bases, and furthermore, the activation parameters were evaluated from rate data at only two temperatures (0 and 5.2 °C).

We have recently reported[30,31] a study of the hydroxide ion catalyzed deprotonation of several series of benzylic ketones in aqueous solution. We have now measured the temperature dependence of the general-base-catalyzed deprotonation of one of these ketones (**1**) in aqueous solution and have found an extensive systematic relationship between the entropies of activation for eq 1 and the entropies of this overall reaction which, for a common carbon acid, are determined by variations in the entropies of protonation of the bases B.



1

Experimental Section

1-Methyl-4-(phenylacetyl)pyridinium bromide (**1**·Br⁻) was prepared as previously described.[30] All amines and phenols were purchased as the purest grades commercially available from Aldrich Chemical Co., Milwaukee, WI, or BDH Chemicals, Toronto, Ontario. All liquid amines were treated with solid KOH and distilled, usually under vacuum. *tert*-Butylamine was converted to its hydrochloride to allow accurate weighing of this volatile base. Solids were recrystallized from appropriate solvents. Nitrilotriacetic acid (99.9%) was used as received. All phenols were recrystallized several times from hexane.

pK_a values of all buffer species were measured by potentiometric titration (at 10 mM) at constant temperatures (±0.1 °C) in the presence of 0.095 M KCl, which gave ionic strength 0.1 at the midpoint of the titration. Appropriate adjustments to KCl concentration were made in the case of the amino acid titrations. All pH measurements were made with a Radiometer PHM82 pH meter, equipped with a GK2401B combination electrode, and calibrated with BDH Colourkey standard buffer solutions (pH 7 and 10) at the temperature of measurement.

All buffer solutions for kinetic studies were made up by dissolving in water a carefully weighed sample of the organic buffer species and by adding a predetermined volume of standard 1 M HCl (to amines) or 1 M KOH (to phenols). Individual stock solutions were made up at each buffer concentration in the buffer dilution studies. These solutions usually contained at least five different concentrations of the buffer base species in the range 10–50 mM, and $[B]/[BH^+] = 0.5$ (for $pK_{BH} > 10$), $[B]/[BH^+] = 1$ (for $9 < pK_{BH} < 10$) and $[B]/[BH^+] = 2$ (for $pK_{BH} < 9$). Catalysis by aniline was studied in a carbonate buffer (pH = 9.8) containing aniline concentrations in the range 20–100 mM. All solutions were adjusted to total ionic strength 0.2 with the appropriate concentration of KCl. Thus a final ionic strength 0.1 was obtained upon dilution in the stopped-flow spectrophotometer with an aqueous solution of **1**·Br⁻ (0.04 mM).

All kinetic data were obtained on the Durrum–Gibson stopped-flow spectrophotometer, using an analytical wavelength of 445 nm, which is λ_{max} in the electronic absorption spectrum of the enolate ion conjugate base of **1**. All solutions were equilibrated in the reaction syringes for at

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Table I. Temperature Dependences of the Acidities of Buffer Species[a]

BH	temp, °C	pK_{BH}	$\Delta H°$, kcal/mol	$\Delta S°$, (cal deg^{-1} mol^{-1})
$C_6H_5CH_2NH_3^+$	15	9.72		
	25	9.43		
	35	9.12		
	45	8.77	13.2 ± 0.7	+1.3 ± 0.2
$C_6H_5CH_2NH_2CH_3^+$	15	9.98		
	25	9.73		
	35	9.42		
	45	9.18	11.4 ± 0.4	−6.3 ± 0.1
$C_6H_5CH_2NH(CH_3)_2^+$	15	9.21		
	25	9.03		
	35	8.80		
	45	8.58	8.9 ± 0.5	−11.4 ± 0.1
$^-O_2CCH_2NH_3^+$	15	9.96		
	25	9.68		
	35	9.41		
	45	9.18	11.0 ± 0.1	−7.5 ± 0.1
$^-O_2CCH_2NH_2CH_3^+$	15	10.30		
	25	10.05		
	35	9.79		
	45	9.62	9.7 ± 0.4	−13.6 ± 0.1
$^-O_2CCH_2NH(CH_3)_2^+$	15	9.97		
	25	9.80		
	35	9.60		
	45	9.43		
	55	9.25	7.8 ± 0.2	−18.5 ± 0.1
$(^-O_2CCH_2)_3NH^+$	15	9.95		
	20	9.88		
	25	9.83		
	35	9.74		
	45	9.65	4.1 ± 0.1	−31.3 ± 0.1
$C_5H_4N(CH_2)_3NH_3^{2+}$[b]	15	9.16		
	20	9.03		
	25	8.85		
	35	8.53		
	45	8.28	12.6 ± 0.3	+1.8 ± 0.1
$(CH_3)_2NC_5H_4NH^+$[c]	15	9.96		
	25	9.68		
	35	9.37		
	45	9.12	11.9 ± 0.3	−4.4 ± 0.1
C_6H_5OH	15	9.99		
	25	9.86		
	35	9.73		
	45	9.62		
	55	9.52	5.1 ± 0.1	−28.0 ± 0.1
$4\text{-}ClC_6H_4OH$	15	9.44		
	25	9.30		
	35	9.18		
	45	9.08		
	55	8.97	5.0 ± 0.1	−25.7 ± 0.1

[a] In aqueous solution, ionic strength 0.1. Standard deviations in $pK_{BH} \leq \pm 0.02$. $\Delta H°$ and $\Delta S°$ are calculated from least-squares fits to the van't Hoff equation. [b] 1-(3-Ammoniopropyl)pyridinium dication. [c] 4-(Dimethylamino)pyridinium cation.

Table II. Thermodynamic Parameters for Deprotonation of **1** by Buffer Species (Eq 1)[a]

B	K	$\Delta G°$, kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$, cal deg^{-1} mol^{-1}
$C_6H_5CH_2NH_2$	2.6	−0.6	−6.9 ± 0.9	−21.3 ± 0.8
$C_6H_5CH_2NHCH_3$	5.1	−1.0	−5.1 ± 0.6	−13.7 ± 0.7
$C_6H_5CH_2N(CH_3)_2$	1.0	0.0	−2.6 ± 0.7	−9.6 ± 0.7
$^-O_2CCH_2NH_2$	4.6	−0.9	−4.7 ± 0.3	−12.5 ± 0.7
$^-O_2CCH_2NHCH_3$	10.7	−1.4	−3.4 ± 0.6	−6.4 ± 0.7
$^-O_2CCH_2N(CH_3)_2$	6.0	−1.1	−1.5 ± 0.4	−1.5 ± 0.7
$(^-O_2CCH_2)_3N$	6.5	−1.1	+2.2 ± 0.3	+11.3 ± 0.7
$C_5H_4N(CH_2)_3NH_2^+$	0.68	+0.2	−6.3 ± 0.5	−21.8 ± 0.7
$(CH_3)_2NC_5H_4N$	4.6	−0.9	−5.6 ± 0.5	−15.6 ± 0.7
$C_6H_5O^-$	6.9	−1.1	−1.2 ± 0.3	+8.0 ± 0.7
$4\text{-}ClC_6H_4O^-$	1.9	−0.4	−1.3 ± 0.3	+5.7 ± 0.7
HO^-[b]	9.5×10^4[c]	−6.8	−6.9	−0.7

[a] In aqueous solution, ionic strength 0.1. K and $\Delta G°$ are calcd. for 25 °C. [b] From ref 31. [c] $\log K = pK_w - pK_a$.

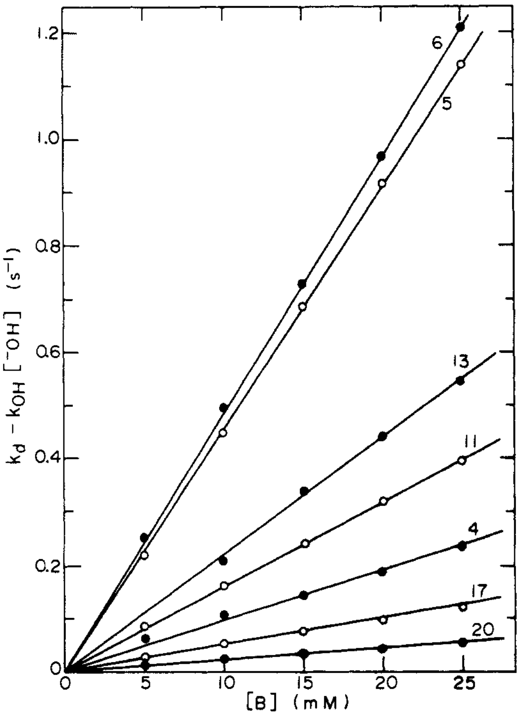

Figure 1. Pseudo-first-order rate constants for the general-base-catalyzed deprotonation of **1** by several bases (indicated by numbers from Tables III and V) at 25 °C and ionic strength 0.1.

least 20 min at the temperature under study prior to initiating mixing experiments. All data processing and rate constant evaluations were as previously described.[30] All pseudo-first-order rate constants were averaged over at least six identical experiments in which the reproducibility in k_{obs} was always better than ±1%. Plots of k_{obs} vs [B] were linear in all cases.

Plots of ln k_B vs T^{-1} were checked for linearity, and activation parameters were evaluated by fitting k_B as a function of temperature to the Eyring equation with use of a curve-fitting program that is based upon the Marquardt algorithm.

Results

The temperature dependence of the pK_a values for the conjugate acids (BH^+) of the general-base catalysts considered in the current studies are listed in Table I. Values of $\Delta H°$ and $\Delta S°$ calculated for the equilibrium of eq 3 are also included in this table.

The temperature dependence of the pK_a of **1** has recently been reported,[31] and $\Delta H° = +6.3$ (±0.2) kcal/mol and $\Delta S° = -20.0$ (±0.6) cal deg^{-1} mol^{-1} have been obtained for the ionization of **1** according to eq 2. These data may be combined with the thermodynamic parameters of Table I to calculate $\Delta H°$ and $\Delta S°$ for the equilibrium of eq 1 for each base (B). These data are collected in Table II.

Buffer catalysis for the equilibration of CH with C^- is illustrated in Figure 1 for several bases. The observed pseudo-first-order rate constant for the equilibration of CH and C^- in each experiment is the sum of the individual pseudo-first-order rate constants for deprotonation (k_d) and protonation (k_p) as defined by the following equations:

$$k_{obs} = k_d + k_p$$

$$k_d = k_{obs}/(1 + [H^+]/K_{CH})$$

$$k_d = k_B[B] + k_{OH}[^-OH] \qquad (5)$$

Values of k_B were evaluated from eq 5 and are collected in Table III, for 11 buffer species at several temperatures. This table also includes values for k_{BH} which were evaluated from $\log k_{BH} = \log k_B + pK_{CH} - pK_{BH}$. Activation parameters for k_B and k_{BH} as defined by eq 1 are listed in Table IV.

Table V lists further data for the general-base-catalyzed deprotonation of **1** by a number of bases that were only investigated at 25 °C. These bases include a series of seven substituted

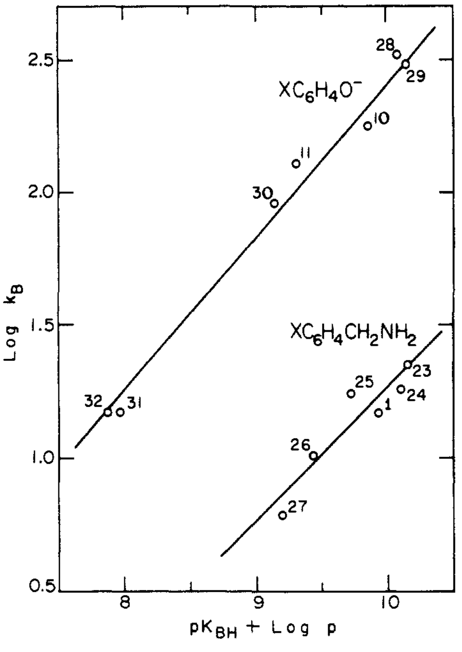

Figure 2. Brønsted plots for the general-base-catalyzed deprotonation of **1** by benzylamines (1, 23–27) and phenoxides (10, 11, 28–32). Numbers correspond to the bases in Tables III and V.

phenoxides ($XC_6H_4O^-$) and six substituted benzylamines ($XC_6H_4CH_2NH_2$) for which Brønsted plots are shown in Figure 2. The least-squares correlation lines for these two series of general-base catalysts are described by eq 6 and 7.

phenoxides:

$$\log k_B = 0.60\ (\pm 0.03)\mathrm{p}K_{BH} - 3.53\ (\pm 0.07) \qquad r = 0.993 \tag{6}$$

benzylamines:

$$\log k_B = 0.52\ (\pm 0.09)(\mathrm{p}K_{BH} + \log p) - 3.95\ (\pm 0.08) \qquad r = 0.937 \tag{7}$$

It will be noted that the data in Figure 2 show considerably more scatter for the benzylamines than for the phenoxides. This scatter appears to be real; it is not simply a matter of experimental error in the rate constant measurements. The data points in Figure 2 have been reproduced to within ±4% on several occasions over a period of several months with different synthetic batches of **1**·Br^- and after repurification of the amine bases.

Discussion

The amines and phenoxides investigated in the present study proved to be efficient general-base catalysts for the deprotonation of benzylic ketone **1**. The phenoxide ions and benzylamines in Figure 2 clearly describe two quite different Brønsted correlation lines, with the phenoxides being approximately 10-fold more reactive than benzylamines of the same basicity. This observation is somewhat unusual, since nitrogen bases are usually more reactive than oxygen bases of similar basicity.[6,7] However exceptions to this order of reactivity are known, with phenoxides being more reactive than amines of the same basicity for the deprotonation of HCN.[32] The phenoxide ion ($\mathrm{p}K_{BH} = 9.86$), itself, is only 4.5-fold less reactive than hydroxide ion ($k_{OH} = 801$ M^{-1} s^{-1}, $\mathrm{p}K_{BH} = 15.74$), even though the latter is much more basic. The hydroxide ion is 1000-fold less reactive than predicted by the extrapolation of eq 6 to $\mathrm{p}K_{BH} = 15.74$ ($k_B = 8 \times 10^5$ M^{-1} s^{-1}) and, thus, displays the usual negative deviation that is commonly observed for the hydroxide ion in Brønsted correlations.[3]

Table III. Kinetic Parameters for the General-Base-Catalyzed Deprotonation of **1**[a]

no.	base	temp, °C	k_B, M^{-1} s^{-1}	k_{BH}, M^{-1} s^{-1}
1	$C_6H_5CH_2NH_2$	15	7.74	2.4
		25	14.9	5.8
		35	22.0	13
		45	34.6	32
2	$C_6H_5CH_2NHCH_3$	15	30.6	5.2
		25	62.2	12
		35	100	30
		45	174	63
3	$C_6H_5CH_2N(CH_3)_2$	15	11.1	11
		25	26.8	26
		35	43.6	54
		45	85.6	120
4	$^-O_2CCH_2NH_2$	15	4.48	0.80
		25	8.97	2.0
		35	17.2	5.2
		45	31.7	11.5
5	$^-O_2CCH_2NHCH_3$	15	22.5	1.8
		25	45.5	4.2
		35	85.4	10.8
6	$^-O_2CCH_2N(CH_3)_2$	15	23.5	4.1
		25	47.5	7.9
		35	99.3	19
7	$(^-O_2CCH_2)_3N$	20	1.37	0.24
		25	2.10	0.33
		30	3.20	0.46
		35	4.66	0.66
8	$C_5H_4N(CH_2)_3NH_2^+$	20	2.33	2.9
		25	3.08	4.6
		35	5.23	12
		45	8.60	25
9	$(CH_3)_2NC_5H_4N$	15	5.07	0.90
		25	9.23	2.0
		35	16.8	5.6
		45	29.5	12
10	$C_6H_5O^-$	15	89.6	16
		25	179	26
		35	356	51
		45	618	81
11	$4\text{-}ClC_6H_4O^-$	15	66.1	39
		25	130	68
		35	272	140
		45	530	240

[a] In aqueous solution at 25 °C, ionic strength 0.1. k_B and k_{BH} are defined by eq 1. Standard deviations in k_B are less than ±4%. k_{BH} is callculated from $\log k_{BH} = \log k_B + \mathrm{p}K_{CH} - \mathrm{p}K_{BH}$.

The Brønsted β values of 0.60 and 0.52 in eq 5 and 6 are quite similar to those reported for general-base catalysis of the deprotonation of a variety of other carbon acids by amine and phenoxide ion bases in aqueous solution.[5,7,33-35] However, a Brønsted plot (Figure 3) of the data for all amines in the current work shows no simple correlation of $\log k_B$ with ($\mathrm{p}K_{BH} + \log p$), where $\log p$ is the appropriate statistical correction for the number of protons (p) in the ammonium ion conjugate acids for each of these bases. We have drawn two correlation lines in Figure 3 for what we feel can be considered as two series of closely related bases. These lines have $\beta = 0.51$ (±0.01) for $(HOCH_2)_nC(NH_2)(CH_3)_{3-n}$ (for $n = 0$–3) and $\beta = 0.56$ (±0.01) for $HO(CH_2)_nNH_2$ ($n = 2$ and 3) and $CH_3(CH_2)_3NH_2$. The former more hindered primary amine bases are approximately 45% less reactive than predicted by the data for the latter group of bases.

Both cationic and anionic base catalysts in Figure 3 show positive deviations from the lines defined for neutral amines. This result contrasts with the positive deviations for cationic amines but negative deviations for anionic amines that were found in the general-base-catalyzed deprotonation of 2-nitropropane.[35] The positive charge on **1** is probably influencing the electrostatic effects of the current study. Of even more interest is the fact that aromatic amines also show large positive deviations in Figure 3.

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(34) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1972**, *94*, 2647.

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Table IV. Activation Parameters for the General-Base-Catalyzed Deprotonation of 1[a]

B	$\Delta G_B^{\ddagger}$	$\Delta H_B^{\ddagger}$	$\Delta S_B^{\ddagger}$	$\Delta G_{BH}^{\ddagger}$	$\Delta H_{BH}^{\ddagger}$	$\Delta S_{BH}^{\ddagger}$
$C_6H_5CH_2NH_2$	15.9	7.9 ± 0.3	-26.7 ± 0.9	16.4	14.8	-5.4
$C_6H_5CH_2NHCH_3$	15.0	9.6 ± 0.2	-18.2 ± 0.8	16.0	14.7	-4.5
$C_6H_5CH_2N(CH_3)_2$	15.5	11.7 ± 0.4	-13.1 ± 1.4	15.5	14.3	-3.5
$^-O_2CCH_2NH_2$	16.2	11.3 ± 0.1	-16.4 ± 0.1	17.0	16.0	-3.9
$^-O_2CCH_2NHCH_3$	15.2	11.1 ± 0.1	-13.8 ± 0.4	16.6	14.5	-7.2
$^-O_2CCH_2N(CH_3)_2$	15.2	12.2 ± 0.3	-10.0 ± 1.0	16.2	13.7	-8.5
$(^-O_2CCH_2)_3N$	17.0	14.0 ± 0.1	-10.3 ± 0.5	18.1	11.8	-19.0
$C_5H_4N(CH_2)_3NH_2^+$	16.8	9.1 ± 0.1	-25.9 ± 0.1	16.5	15.4	-4.1
$(CH_3)_2NC_5H_4N$	16.1	10.1 ± 0.1	-20.1 ± 0.2	17.0	15.7	-4.5
$C_6H_5O^-$	14.4	10.8 ± 0.2	-11.9 ± 0.6	15.5	12.0	-19.9
$4\text{-}ClC_6H_4O^-$	14.6	12.1 ± 0.1	-8.2 ± 0.5	15.0	10.8	-13.9
HO^- [b]	13.5	11.6	-6.3	20.3	18.6	-5.6

[a] All $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are in kcal/mol; $\Delta S^{\ddagger}$ in cal deg^{-1} mol^{-1} $\Delta G_B^{\ddagger}$ and $\Delta G_{BH}^{\ddagger}$ are calculated from the Eyring equation at 25 °C; $\Delta H_B^{\ddagger}$ and $\Delta S_B^{\ddagger}$ are calculated from the data in Table III; $\Delta H_{BH}^{\ddagger} = \Delta H_B^{\ddagger} - \Delta H^{\circ}$; $\Delta S_{BH}^{\ddagger} = \Delta S_B^{\ddagger} - \Delta S^{\circ}$. [b] Data from ref 31.

Table V. Kinetic Data for the General-Base-Catalyzed Deprotonation of **1** (Eq 1)[a]

no.	base	pK_{BH}	k_B, $M^{-1}\,s^{-1}$	k_{BH}, $M^{-1}\,s^{-1}$
12	$(CH_3)_3CNH_2$	10.86	11.1	0.16
13	$CH_3(CH_2)_3NH_2$	10.77	18.9	0.34
14	$HO(CH_2)_3NH_2$	10.23	9.13	0.56
15	$C_6H_5(CH_2)_2NH_2$	10.00	13.6	1.4
16	$(HOCH_2)C(CH_3)_2NH_2$	9.87	3.60	0.51
17	$HO(CH_2)_2NH_2$	9.64	4.41	1.06
18	$^-O_3S(CH_2)_2NH_2$	9.01	4.72	4.8
19	$(HOCH_2)_2C(CH_3)NH_2$	8.93	1.12	1.4
20	$(HOCH_2)_3CNH_2$	8.20	0.484	3.2
21	$H_2NCOCH_2NH_2$	8.07	1.04	9.3
22	$C_6H_5NH_2$	4.72	0.454	9.1×10^3
23	$4\text{-}CH_3OC_6H_4CH_2NH_2$	9.67	22.4	5.0
24	$4\text{-}CH_3C_6H_4CH_2NH_2$	9.62	18.4	4.6
25	$4\text{-}ClC_6H_4CH_2NH_2$	9.24	17.5	10.5
26	$4\text{-}CF_3C_6H_4CH_2NH_2$	8.95	10.2	12
27	$4\text{-}NCC_6H_4CH_2NH_2$	8.72	5.96	12
28	$4\text{-}CH_3OC_6H_4O^-$	10.07	328	29
29	$4\text{-}CH_3C_6H_4O^-$	10.14	310	24
30	$4\text{-}{}^-O_2CC_6H_4O^-$	9.14	91.8	70
31	$4\text{-}CH_3COC_6H_4O^-$	7.96	14.9	170
32	$4\text{-}NCC_6H_4O^-$	7.88	14.9	206

[a] At 25 °C, and ionic strength 0.1. Data for bases 1–11 are given in Table III. Standard deviations are ±0.02 in pK_{BH} and less than ±4% in k_B. k_{BH} is calculated from $\log k_{BH} = \log k_B + pK_{CH} - pK_{BH}$.

This possibly reflects a specific transition-state interaction between these aromatic amines and one or both of the aromatic rings of **1**. Such an interaction may also be the source of the scatter that is observed for ring-substituted benzylamines in Figure 2.

In passing, we note that $\beta \approx 0.55$ for these several series of general-base catalysts is slightly greater than the $\beta = 0.5$ that is predicted by Marcus theory for a reaction having $\Delta G^{\circ} \approx 0$ and less than the Brønsted $\alpha = 0.76$ that was found[30] for the deprotonation of **1** bearing substituents in the phenyl ring. Classical Marcus theory, with a constant intrinsic barrier, predicts that α (in CH) = β (in B) for a reaction of the type shown by eq 1. The currently observed $\alpha_{CH} > \beta_B$ is typical of the transition-state imbalances that have been discussed by Bernasconi[36] in a variety of general-base-catalyzed-deprotonation reactions.

On the assumption that $\beta = 0.55$ should be applicable to all amine catalysts in this work, we have calculated the intrinsic reactivity[37] (k_B^i) of each of the primary, secondary, and tertiary benzylamine and glycine general-base catalysts by extrapolating to ($pK_{BH} + \log p$) = 9.32, which is the statistically corrected pK_a of ketone **1**. These data are listed in Table VI. The k_B^i for the nitrogen bases vary over a range of 13-fold, and all are smaller than $k_B^i = 115$ M^{-1} s^{-1} (from eq 6) for phenoxide ions. Note, however, that these intrinsic reactivities do display the commonly encountered variations in reactivity (tertiary > secondary > primary) upon successive N-methylations within both the benzylamine and glycine series of bases.

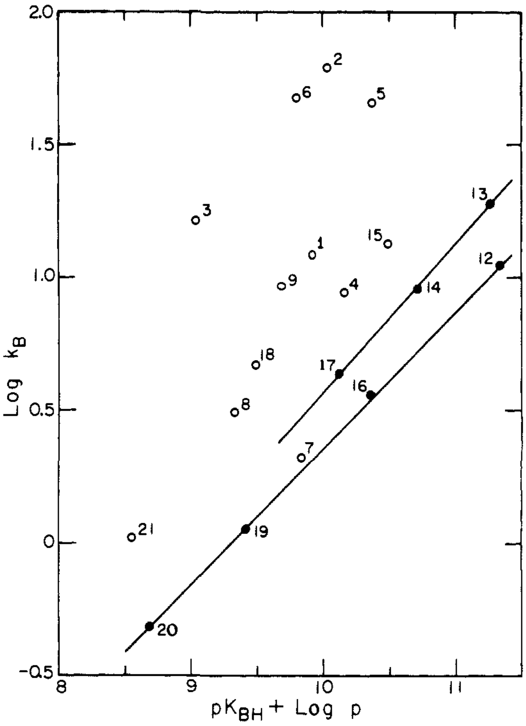

Figure 3. Brønsted plot of the data for the general-base-catalyzed deprotonation of **1** by amines. Numbers correspond to the bases in Tables III and V. The lines are drawn through the data for structurally related bases as described in the text.

Table VI. Intrinsic Reactivities of General-Base Catalysts for the Deprotonation of 1[a]

base	pK_{BH} + log p	k_B^i, $M^{-1}\,s^{-1}$	rel k_B^i
$C_6H_5CH_2NH_2$	9.91	7.1	(1)
$C_6H_5CH_2NHCH_3$	10.03	25	3.6
$C_6H_5CH_2N(CH_3)_2$	9.03	39	5.5
$^-O_2CCH_2NH_2$	10.16	3.1	(1)
$^-O_2CCH_2NHCH_3$	10.35	12	3.9
$^-O_2CCH_2N(CH_3)_2$	9.80	26	8.4

[a] At 25 °C, ionic strength 0.1. Calculated by extrapolation to (pK_{BH} + log p) = 9.32 using $\beta = 0.55$ (see text).

We conclude that the general-base-catalyzed deprotonation of **1** appears to be typical of many other general-base-catalyzed processes in displaying differential reactivities between structurally different series of bases (phenoxides vs amines; primary vs secondary vs tertiary amines). It therefore seems reasonable that any conclusions that we are able to reach regarding the scatter that is obvious in Figure 3 should also be applicable to other general-base-catalyzed processes. We have therefore measured activation parameters in an attempt to test the usual assumption

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(36) Bernasconi, C. F.; Killion, R. B., Jr. *J. Org. Chem.* **1989**, *54*, 2878 and references therein.

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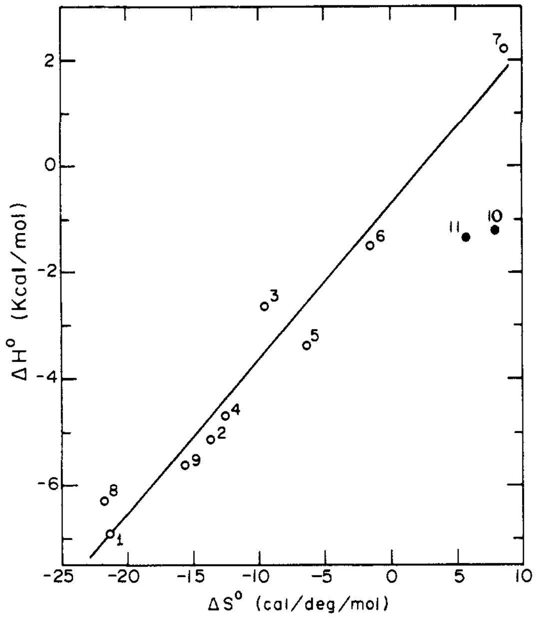

Figure 4. Enthalpy–entropy relationship for the equilibrium of eq 1. Numbers identify the bases from Table III.

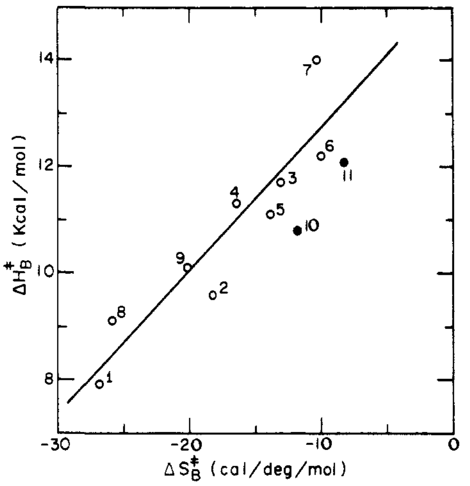

Figure 5. Enthalpy–entropy relationship for the activation parameters for the deprotonation of 1 by the general-base catalysts of Table III.

that such scatter is a solvation phenomenon.

We have chosen general-base catalysts that are of quite similar basicity to one another (pH_{BH} = 9.4 ± 0.6) and also of similar basicity to the enolate ion conjugate base of 1 (pK_{CH} = 9.02 at 25 °C). These similarities should minimize any influence from thermodynamic effects upon our comparisons of reactivity. We have, however, been able to include a wide range of structural types. Our choices of bases for study have been most heavily influenced by considerations of obtaining a wide variation in $\Delta S°$ for protonation,[38-40] since such entropic effects are believed to most directly reflect differential-solvation effects upon the stabilization of the bases and their conjugate acids.

The relationships between the activation and reaction parameters that have been measured for the reaction of eq 1 in the current study are displayed in Figures 4–7.

Figure 4 shows the well-known compensation effect between enthalpy and entropy in acid–base reactions.[38-40] Although $\Delta G°$ varies only over a range of 1.6 kcal/mol for the amine and phenoxide ion bases in Table II, $\Delta H°$ and $T\Delta S°$ each vary over greater than 9 kcal/mol. The data in Figure 4 can be fitted by the least-squares correlation of eq 8 for the amine bases and are consistent with an average $\Delta G°$ = −0.8 kcal/mol for eq 1 with these amine bases.

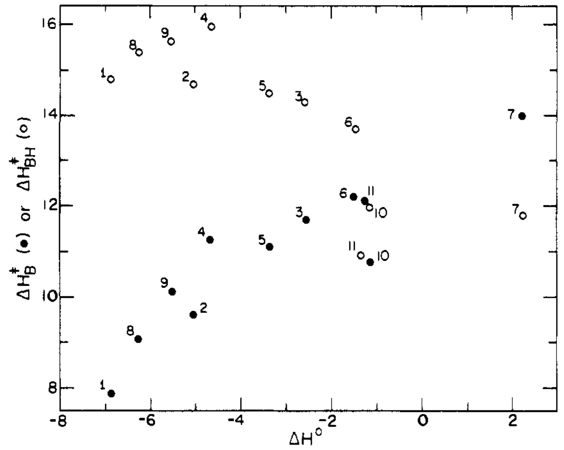

Figure 6. Dependence of $\Delta H_B^\ddagger$ and $\Delta H_{BH}^\ddagger$ on $\Delta H°$ for the general-base-catalyzed deprotonation of 1 ($\Delta H_B^\ddagger$) (and general-acid-catalyzed protonation of its conjugate base ($\Delta H_{BH}^\ddagger$)) by the bases (B) (and their conjugate acids (BH)) listed in Table III. (All ΔH units are in kcal/mol.) Data refer to the reaction of eq 1.

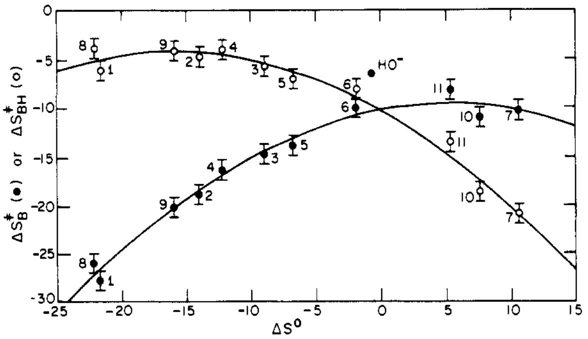

Figure 7. Dependence of $\Delta S_B^\ddagger$ and $\Delta S_{BH}^\ddagger$ upon $\Delta S°$ for the general-base-catalyzed deprotonation of 1 ($\Delta S_B^\ddagger$) (and general-acid-catalyzed protonation of its conjugate base ($\Delta S_{BH}^\ddagger$)) by the bases (B) (and their conjugate acids (BH)) listed in Table III. (All ΔS units are in cal deg^{-1} mol^{-1}). Data refer to the reaction of eq 1. The curves are described by eq 8 and 9.

$$\Delta H° = 0.29\ (\pm 0.02)\Delta S° - 0.8\ (\pm 0.6)$$

$$r = 0.978 \qquad (8)$$

The activation parameters for k_B show a similar, although more scattered, relationship (eq 9 for amines) between $\Delta H_B^\ddagger$ and $\Delta S_B^\ddagger$ (Figure 5). While $\Delta G_B^\ddagger$ varies over a range of only 2.6 kcal/mol, $\Delta H_B^\ddagger$ and $T\Delta S_B^\ddagger$ each vary over a range of 6 kcal/mol.

$$\Delta H_B^\ddagger = 0.27\ (\pm 0.04)\Delta S_B^\ddagger + 15.5\ (\pm 0.8)$$

$$r = 0.922 \qquad (9)$$

Figures 6 and 7 show the dependence of $\Delta H^\ddagger$ upon $\Delta H°$ and of $\Delta S^\ddagger$ upon $\Delta S°$ for both k_B and k_{BH} of eq 1. Figure 7, in particular, displays clear systematic relationships between entropies of activation of both the forward and reverse reactions and the overall entropy of reaction. For $\Delta S_B^\ddagger$, this relationship is approximately linear when $\Delta S°$ is quite negative, but it appears to reach a limiting value of $\Delta S_B^\ddagger \approx -10$ cal deg^{-1} mol^{-1} for $\Delta S° > 0$. On the other hand, $\Delta S_{BH}^\ddagger$ is essentially constant (≈ -5 cal deg^{-1} mol^{-1}) for negative $\Delta S°$ but shows an approximately linear trend for $\Delta S° > 0$. Note that the phenoxide ions appear to fit the same entropy relationship as the various amine bases that were investigated. It is unfortunate that we have been unable to find any readily available amine having $\Delta S°$ of an appropriate magnitude to fill the gap between nitrilotriacetate acid and the remaining amine bases of this study. The phenoxide ions do give

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[40] Jones, F. M., III; Arnett, E. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 263.

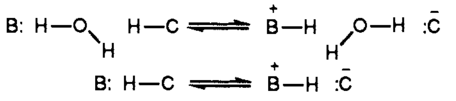
data in this area, but since these are oxyanion bases, the appropriateness of their inclusion with the amine bases is not clear. Hydroxide ion shows a small deviation from the lines drawn for the other bases. For what it is worth, the curves in Figure 7 are defined by the quadratic relationships of eq 10 and 11. Although it seems unlikely that these relationships have any physical significance, they do fit the experimental data with an average deviation of 0.8 cal deg^{-1} mol^{-1} and a maximum deviation of 1.7 cal deg^{-1} mol^{-1} (for $4\text{-}ClC_6H_4O^-$).

$$\Delta S_B^{\ddagger} = -0.027\ (\pm 0.004)(\Delta S^\circ)^2 + 0.19\ (\pm 0.06)\Delta S^\circ - 10.1\ (\pm 0.5) \quad (10)$$

$$\Delta S_{BH}^{\ddagger} = -0.027\ (\pm 0.004)(\Delta S^\circ)^2 - 0.81\ (\pm 0.06)\Delta S^\circ - 10.1\ (\pm 0.5) \quad (11)$$

A substantially similar picture is seen in Figure 6 for the enthalpy data, although in this case the data for the phenoxides do not fit well with the amine data points. We will concentrate the subsequent discussion upon the entropy relationship of Figure 7, since solvation effects are most commonly considered as entropy phenomena. However, it is clear from Figures 4 and 5 that to a large extent the enthalpy and entropy changes are compensating effects of similar magnitudes.

The interpretation of macroscopic entropy measurements in terms of solvation phenomena at the molecular level is one of the most difficult areas of physical organic chemistry. Thus, despite the smooth relation that is presented between $\Delta S^{\ddagger}$ and ΔS° in Figure 7, a simple physical interpretation of this relationship is not immediately obvious. The nonlinear form of the dependence in Figure 7 further complicates any attempt at a physical interpretation. A major problem in attempting a molecular interpretation lies in the uncertainty that surrounds the mechanism of the proton transfer from the carbon acid to the general-base catalyst. Two competing mechanisms are usually considered in all discussions of proton-transfer reactions.[41-43] These are the transfer of the proton via a bridging water molecule (A), and direct proton transfer from the acid to the base without a bridging water molecule (B).



(A)

(B)

Both of these mechanisms have been observed for proton transfer from ammonium ions to amines,[43,44] and rate constants for each mechanism have been obtained as a function of amine structure. It is not difficult to find statements in the literature[41,42] to the effect that mechanism B is most likely for proton transfer from carbon acids. However, most of these statements seem to be based upon observations regarding proton transfer to water as the abstracting base, although it should be noted that a variation on mechanism A has been established[45] recently for proton transfer from malononitriles to water. The comment is also usually made that hydrogen bonding from a carbon acid to a water molecule is unlikely, and this rules out mechanism A. However, it seems to us that hydrogen bonding from the carbon acid to the base species in mechanism B would also be very weak, and so this argument should not be used in favor of either mechanism A or B. The only case we have been able to locate of a definitive study of the mechanism of proton transfer from a carbon acid to an amine base is the study of the deprotonation of HCN. Bednar and Jencks[46] have concluded that mechanism B is overwhelmingly dominant in the proton transfer from HCN to amines. However, for a number of reasons (discussed below), it is not clear that this conclusion for HCN should be assumed to also be applicable to other carbon acids such as **1**.

One would predict that mechanism A would be far less susceptible to steric hindrance from interactions between the acid and base species than mechanism B in which the reactants have to essentially come into van der Waals contact in order to allow proton transfer to occur. This prediction is nicely confirmed by the data of Grunwald and Ku[47] for proton transfer from the ammonium ion to either ammonia or trimethylamine. For direct transfer via mechanism B, trimethylamine is over 30-fold less reactive than ammonia; via mechanism A, proton transfer to trimethylamine occurs 15-fold faster than to ammonia, despite the fact that trimethylamine is only 4-fold more basic than ammonia. Furthermore, degenerate proton transfers between ammonium ions and amines occur via mechanism A at similar rates for primary, secondary, and tertiary amines; via mechanism B, the rates of such degenerate proton transfers decrease rapidly in the order $NH_3 > CH_3NH_2 > (CH_3)_2NH > (CH_3)_3N$. These data make it quite clear that the commonly observed order of reactivity of tertiary amines > secondary amines > primary amines as general-base catalysts is not consistent with mechanism B for the deprotonation of **1** by amines. This order is clearly established for amine catalysts in the current study on the basis of the intrinsic reactivities given in Table VI, and we conclude that mechanism A, via a binding water molecule, is most likely for the deprotonation of ketone **1**.

Mechanism B requires desolvation of the base B (eq 12) as a preliminary step. The available data[43,44] indicate that the rates of such desolvation processes decrease in the order ammonia > primary amines > secondary amines > tertiary amines. These data make it even more difficult to rationalize the intrinsic reactivity order of Table VI in terms of mechanism B.

$$\text{B:}\ H{-}O{-}H \longrightarrow \text{B:} + H_2O \quad (12)$$

We note the following factors in reaching the conclusion that mechanism A is most likely for the deprotonation of **1**, in the face of the demonstration[46] of mechanism B for the deprotonation of HCN, which has similar thermodynamic acidity to **1**. Rates of deprotonation of HCN are 10^7-fold faster than for **1** by both hydroxide ion and amine bases. These rapid rates of deprotonation, and several other observations, led Bednar and Jencks to conclude[46] that HCN is "an almost normal acid" with a Brønsted plot that is a characteristic Eigen curve in the vicinity of $\Delta pK_a = 0$. Such Eigen curves are not typical of "abnormal" carbon acids such as **1** which undergo deprotonation at dramatically lower rates than normal acids. It should also be noted that in the deprotonation of HCN, tertiary amines of $pK_{BH} \approx 9$ do not show the enhanced reactivity relative to primary amines of the same basicity that is characteristic of **1**.

Grunwald concludes[44] that the process of eq 8 occurs via a mechanism in which the water molecule jumps to an adjacent "hole" in the solvent lattice. When another water molecule jumps into the vacant "hole" next to the amine nitrogen atom (i.e. the microscopic reverse of eq 12), a net exchange of the water molecule solvating the basic site through hydrogen bonding has occurred. Mechanism B requires the carbon acid to occupy the "hole" vacated by the leaving water molecule in eq 12. While it is quite reasonable to consider an HCN molecule occupying such a "hole," it seems far-fetched to expect a large carbon acid such as **1** to be able to occupy such a vacant site without further dramatic solvational reorganization in the vicinity of the general-base species.

While none of these observations, either singly or together, "prove" mechanism A for the deprotonation of **1**, we feel that they are significant indicators of a somewhat different mechanism for **1** than for HCN. We also feel that mechanism A does allow a reasonable rationalization for the $\Delta S_B^{\ddagger}$ vs ΔS° correlation, at least in the approximately linear region that is apparent for $\Delta S^\circ < 0$ in Figure 7. If we write the equilibrium for the protonation of

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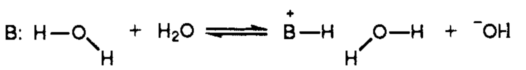
the base species as indicated in eq 13, then the relationship between $\Delta S°$ for eq 13 and $\Delta S_B^\ddagger$ for mechanism A becomes fairly clear.


(13)

When $\Delta S°$ is quite negative, the differential structural effects upon the equilibrium protonation of B are well-modeled in the transition state for $\Delta S_B^\ddagger$ of mechanism A. However, as $\Delta S°$ becomes positive, all of the solvational changes that occur during the protonation equilibrium do not take place upon attaining the transition-state species in mechanism A. Since the positive (and less negative) $\Delta S°$ occur with the more highly hindered amine bases, it is not too surprising that these hindered bases do not follow $\Delta S_B^\ddagger$ described by the less hindered bases. We suggest that the levelling off in $\Delta S_B^\ddagger$ that occurs for positive $\Delta S°$ is due to steric hindrance to solvation of the developing ammonium ion with hindered amine bases. This can be seen in the reactivity that is found for nitrilotriacetate which is lower than for the other tertiary amine bases in Table III.

If one assumes that mechanism A is reasonably accurate in depicting a carbanionic transition state species, then considerable electronic delocalization must occur following the attainment of the rate-determining transition state species. Such electronic delocalization will have consequences in solvational reorganization for the enolate ion species. Such reorganization must precede the attainment of this transition state in the microscopic reverse of mechanism A, and consequently, $\Delta S_{BH}^\ddagger$ will not be as readily interpretable via a straightforward comparison of mechanism A and eq 13 as was possible for $\Delta S_B^\ddagger$. We note that the limiting value for $\Delta S_{BH}^\ddagger \approx -5$ cal deg^{-1} mol^{-1} is similar to the value observed[31] for the entropy of activation for the protonation by water of the conjugate bases of a number of carbon acids, but it is not clear whether this observation has any physical significance.

There seem to have been very few attempts to explore rate and equilibrium entropic effects in a systematic manner. Evans and Hamann[28] compared Pearson's limited data for deprotonation of nitroethane by amines[29] and several nucleophilic substitution reactions of the same amines and reported an entropic rate-equilibrium relationship similar to the linear region of Figure 7. Arnett and Reich[48] have also used a similar comparison in their studies of the alkylation of substituted pyridines, although in this case there is little variation in either $\Delta S^\ddagger$ or $\Delta S°$ for different substituents. Figure 7 seems to be the most extensive relationship of this type that is currently known, and we feel that this relationship is particularly impressive when one notes that it is found despite the apparent chaos in the Brønsted plot of Figure 3. While the generality of such relationships remains to be established, we feel that we have quantitatively established, for at least one reaction, that the usual qualitative interpretations of diverse phenomena in general-base catalysis in terms of solvation effects are indeed soundly based.

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Outer-Sphere and Inner-Sphere Processes in Organic Chemistry. Reaction of Trifluoromethyl Bromide with Electrochemically Generated Aromatic Anion Radicals and Sulfur Dioxide Anion Radicals

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Abstract: The reduction of CF_3Br by electrochemically generated aromatic anion radicals gives rise to purely catalytic currents. An activation–driving force relationship characterizing outer-sphere electron donors can thus be established. Electrochemically generated sulfur dioxide anion radicals do not give rise to catalytic currents upon reaction with CF_3Br but rather produce trifluoromethyl sulfinate according to an overall two electron per molecule stoichiometry. The rate constant of the rate-determining step of the the reaction is at least 4 orders of magnitude larger than that of an aromatic anion radical of the same standard potential, unambiguously showing that $SO_2^{\bullet -}$ does not react as an outer-sphere electron donor. Among the various possible inner-sphere processes, bromine atom abstraction appears as the most likely.

The discovery of substitution reactions proceeding via radical-anion intermediates (S_RN1 reaction)[1] as well as the development of mechanistic studies in organic electrochemistry has triggered a growing interest for the role of single-electron transfer in organic processes. Besides its synthetic interest, the main features of the mechanism of the S_RN1 reaction at aliphatic and aromatic carbon centers are now reasonably well understood.[2] It is a chain process in which electrons play the role of a catalyst. Of different nature is the possible involvement of single-electron transfer in S_N2-substitution reactions. An essential question is

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