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Transition-State Imbalance in the General-Base Catalysis of the Deprotonation of 4-Phenacylpyridinium Cations

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Abstract: Second-order rate constants (k_B) have been measured in aqueous solution at ionic strength 0.1 and 25 °C for the general-base-catalyzed deprotonation of eight 1-methyl-4-(X-phenacyl)pyridinium cations (**1**), eight 1-(X-benzyl)-4-phenacylpyridinium cations (**2**), and five 1-benzyl-4-(X-phenacyl)pyridinium cations (**3**) by a variety of primary amines and also *N*-methyl- and *N*,*N*-dimethylbenzylamine. Brønsted plots for the deprotonation of **1a** (X = H) by these amine bases show considerable scatter. However, there are close linear correlations between log k_B for **1a** (and **2a**) and log k_B for the deprotonation of the 1-methyl-4-(phenylacetyl)pyridinium cation (**4**) by these same amine bases. This observation indicates that the solvation phenomena that have previously been established as the reasons for scattered Brønsted plots for the deprotonation of **4** are general phenomena for the deprotonation of ketonic carbon acids by amine bases. Brønsted α values for the deprotonation of **1**–**3** by individual amine bases indicate significant transition-state imbalances between the developing cationic charge on the ammonium ion conjugate acids and the delocalization of electron density in the developing enolate ion conjugate bases. Comparisons of Brønsted α values for **1** and **2** reacting with the same amine base also indicate transition-state imbalance within the developing enolate ion conjugate base species. The Brønsted α values for the reaction of **2** with benzylamine and its *N*-methyl and *N*,*N*-dimethyl derivatives are particularly small (α = 0.14–0.18) and suggest an interaction between the aromatic ring of these amine bases and the pyridinium ring of **2**. This interaction results in delayed delocalization of electron density into the pyridinium ring in the transition-state species. All of these data can be analyzed in terms of Marcus theory by use of a variable intrinsic barrier, in a manner similar to that described previously for related base-catalyzed deprotonation reactions.

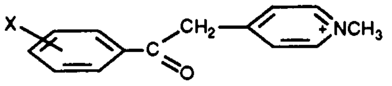
We have recently shown[1] that rate–equilibrium analyses of substituent effects[2] in **1**–**3** can be used as sensitive probes of charge imbalances that develop in the transition-state species during the deprotonation of these ketonic carbon acids by hydroxide ion. We have now extended these studies to the general-base-catalyzed deprotonation of these same carbon acids by a series of amine bases. These studies demonstrate that such charge imbalances can be significantly influenced by the nature of the general-base catalyst. The current data also allow a detailed comparison of the influence of the structure of the general-base catalyst upon deviations from the Brønsted plots for the deprotonation of **1** (X = H) with analogous deviations that we have reported[3] for the deprotonation of **4**. These considerations demonstrate that the solvation effects that were shown[3] to be the source of such deviations in the deprotonation of **4** are accurately reproduced in the case of **1**–**3**.

Experimental Section

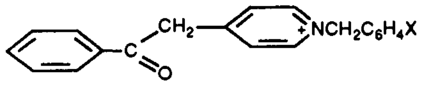
The bromide salts of **1**–**3** were available from our recent study[1,2] of these phenacylpyridinium cations. All experimental methods in the kinetic studies closely followed the descriptions that we have given of our previous studies in this area.[1,3] In general, the equilibrium of the carbon acid with its enolate ion conjugate base was investigated in solutions containing a 1:1 ratio of the amine base (B) and its conjugate acid (BH^+) over a 5-fold variation in amine concentration. Pseudo-first-order rate constants (k_d) for deprotonation were calculated in each experiment and were then corrected for a minor contribution from the hydroxide ion catalyzed deprotonation (e.g., Figure 1). All kinetic data are in aqueous solutions of ionic strength 0.1 at 25 °C.

Results

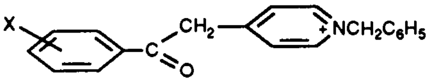
Pseudo-first-order rate constants for the deprotonation of **1**–**3** by amine buffers are strictly linear in buffer base concentration in all cases (e.g., Figure 1). Second-order rate constants (k_B) for these general-base-catalyzed deprotonations of **1a** and **2a** are summarized in Table I.



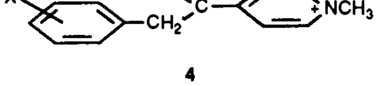
1a: X = H
b: X = 4-OCH$_3$
d: X = 4-Cl
e: X = 3-Cl
f: X = 4-CF$_3$
g: X = 3-NO$_2$
h: X = 3-NO$_2$, 4-Cl
i: X = 4-NO$_2$



2a: X = H
b: X = 3-CH$_3$
c: X = 4-CH$_3$
d: X = 3-Cl
e: X = 4-Br
f: X = 3-NO$_2$
g: X = 4-NO$_2$
h: X = 3,5-(NO$_2$)$_2$



3a: X = H
d: X = 4-Cl
e: X = 3-Cl
f: X = 4-CF$_3$
g: X = 3-NO$_2$



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Second-order rate constants for the deprotonation of **1**–**3** by selected amine bases are summarized in Table II, and Brønsted plots for some of these data are shown in Figures 2 and 3. The Brønsted slopes (α) for all the deprotonation reactions studied in the current work are listed in Table III. In general, the data points for the 4-nitro and 4-methoxy substituents show deviations in the Brønsted plots for **1** and **3** as described previously[1] for the hydroxide ion catalyzed deprotonations. These two substituents have been ignored in the calculation of the α values in Table III.

Discussion

The Brønsted plot for the general-base-catalyzed deprotonation of **1a** is shown in Figure 4. The scatter in the data in this figure

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(1) Stefanidis, D.; Bunting, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 3163.

(2) Note that cation series 1–3 of the current study refer to the series **6**, **8**, and **7**, respectively, of our previous work.[1] The substituent indicators (**a**–**i**) are the same in the current work and in ref 1.

(3) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1990**, *112*, 779.

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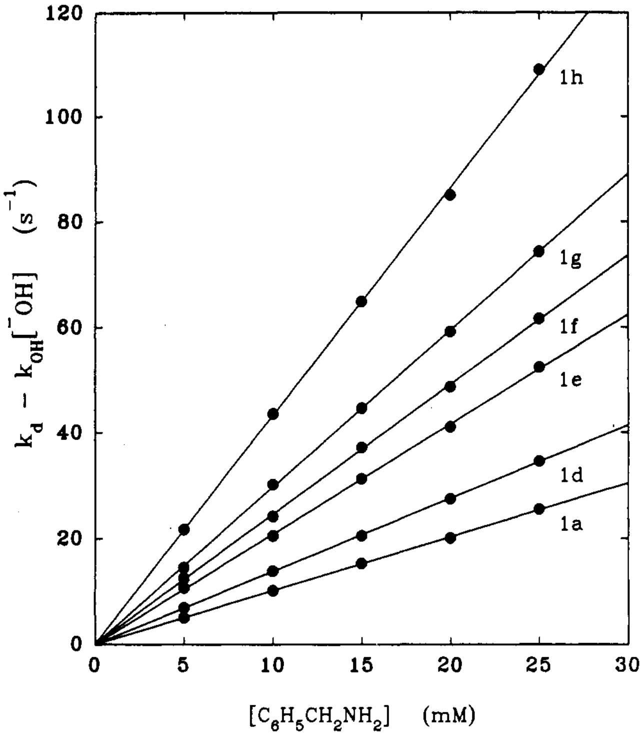

Figure 1. Pseudo-first-order rate constants as a function of benzylamine concentration for the deprotonation of selected **1** in aqueous solution at pH 9.54, ionic strength 0.1, 25 °C.

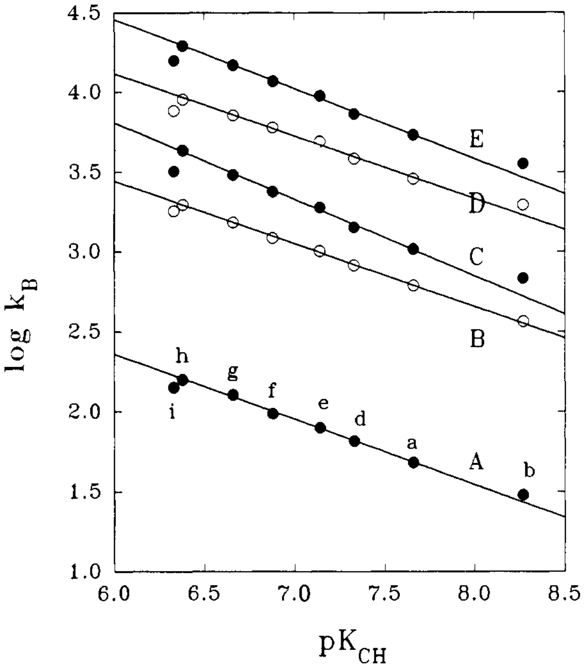

Figure 2. Brønsted plots for the deprotonation of **1a**–**i** by various amine bases: A, $(HOCH_2)_3CNH_2$; B, $^-O_2CCH_2NH_2$; C, $C_6H_5CH_2NH_2$; D, $C_6H_5CH_2N(CH_3)_3$; E, $C_6H_5CH_2NHCH_3$.

is similar to what we have recently reported[3] in our study of the general-base-catalyzed deprotonation of **4** by many of these amine bases. Again, one may select limited subsets of closely structurally related bases, which give linear Brønsted plots of slope $\beta = 0.53$ for $(HOCH_2)_nC(CH_3)_{3-n}NH_2$ (n = 1–3) (bases 7, 13, and 14 in Figure 4) and $\beta = 0.55$ for $CH_3(CH_2)_2NH_2$ and $HO(CH_2)_nNH_2$ (n = 2, 3) (bases 4, 5, and 10). These β values are essentially identical with the β values for these same amines reacting with **4** and similar to the β values reported for amine bases reacting with a variety of other carbon acids in aqueous solution.[4]

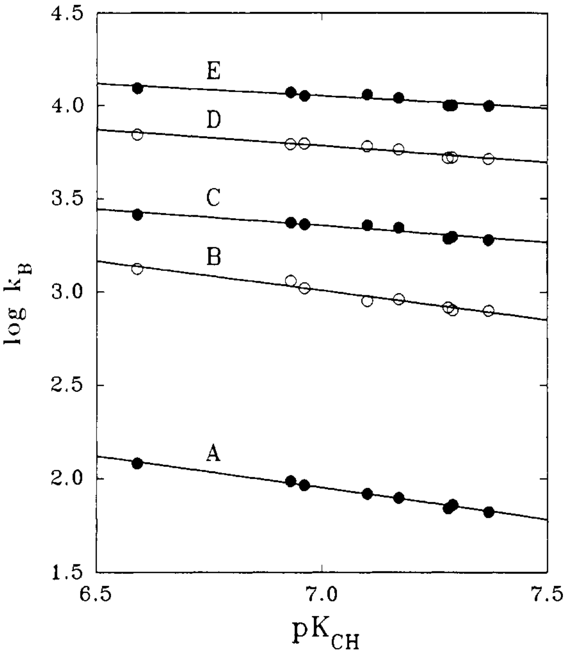

Figure 3. Brønsted plots for the deprotonation of **2a**–**h** by various amine bases (A–E) as indicated in the legend to Figure 2.

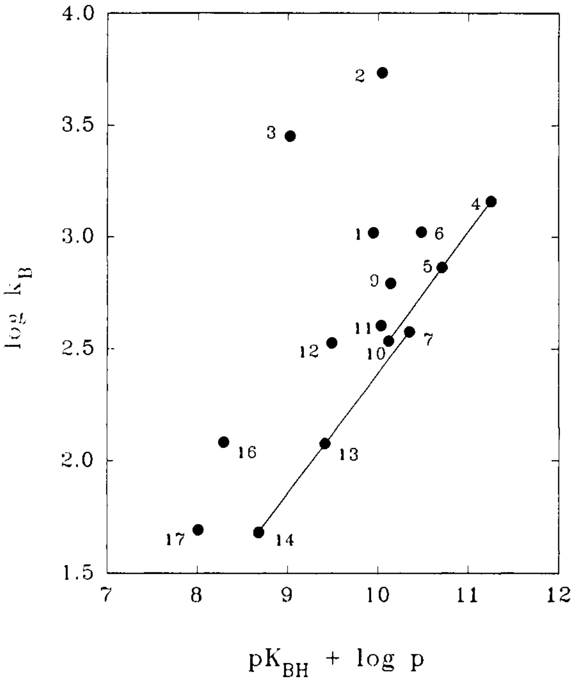

Figure 4. Brønsted plot for the deprotonation of **1a** by various amine bases as indicated by numbers from Table I.

In Figure 5 we present a direct comparison of k_B for the deprotonation of **1a** and k_B for the deprotonation of **4**. The data in Figure 5 define a close linear relationship (eq 1), and it is clear that the same transition-state phenomena must influence the scatter in the Brønsted plots for the deprotonation of **1a** and **4**. We have demonstrated[3] from comparisons of entropies of activation and entropies of protonation that solvation effects are probably the major cause of such scatter in the deprotonation of

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(4) (a) Bordwell, F. G.; Boyle, W. J., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 3907. (b) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1972**, *94*, 2647. (c) Dahlberg, D. B.; Kuzemko, M. A.; Chiang, Y.; Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1983**, *105*, 5387. (d) Bruice, P. Y. *J. Am. Chem. Soc.* **1984**, *106*, 5959. (e) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1985**, *107*, 4737.

Table I. Second-Order Rate Constants for the Deprotonation of **1a** and **2a** by Amine Bases[a]

base no.	base (B)	pK_{BH}	k_B^{1a} (M^{-1} s^{-1})	k_B^{2a} (M^{-1} s^{-1})	k_B^{2a}/k_B^{1a}
1	$C_6H_5CH_2NH_2$	9.47	1050	1920	1.83
2	$C_6H_5CH_2NHCH_3$	9.75	5390	9960	1.85
3	$C_6H_5CH_2N(CH_3)_2$	9.03	2830	5210	1.84
4	$CH_3(CH_2)_3NH_2$	10.77	1450	2160	1.49
5	$HO(CH_2)_3NH_2$	10.23	730	990	1.36
6	$C_6H_5(CH_2)_2NH_2$	10.00	1050	1590	1.51
7	$HOCH_2C(CH_3)_2NH_2$	9.87	377		
8	$(CH_3)_2NC_5H_4N$[b]	9.68		935	
9	$^-O_2CCH_2NH_2$	9.66	620	826	1.33
10	$HO(CH_2)_2NH_2$	9.64	343	495	1.44
11	$CH_3O(CH_2)_2NH_2$	9.55	401		
12	$^-O_3S(CH_2)_2NH_2$	9.01	337	449	1.33
13	$(HOCH_2)_2C(CH_3)NH_2$	8.93	119	171	1.44
14	$(HOCH_2)_3CNH_2$	8.20	48.2	69.3	1.44
15	$H_2NCOCH_2NH_2$	8.07		150	
16	$CH_3CH_2O_2CCH_2NH_2$	7.81	121		
17	$BrCH_2CH_2NH_2$	7.53	49.4		
18	CO_3^{2-}	10.04	1230		
19	^-OH[c]	15.74	3.93×10^4	4.81×10^4	1.22

[a] In aqueous solution, ionic strength 0.1, at 25 °C. pK_{BH} from ref 3. Standard deviations in k_B are $<\pm 2\%$. [b] 4-(Dimethylamino)pyridine. [c] Data from ref 1.

Table II. Second-Order Rate Constants for the Deprotonation of **1–3** by Selected Amine Bases[a,b]

		k_B (10^3 M^{-1} s^{-1})							
acid	pK_{CH}	1	2	3	6	8	9	14	15
1b[c]	8.27	0.68	3.56	1.97	0.71		0.365	0.0302	
1d	7.33	1.43	7.29	3.85	1.30		0.824	0.0655	
1e	7.14	1.90	9.49	4.90	1.63		1.01	0.0793	
1f	6.88	2.39	11.7	6.01	1.99		1.22	0.0969	
1g	6.66	3.04	14.8	7.18	2.34		1.53	0.127	
1h	6.38	4.31	19.5	9.01	2.99		1.98	0.159	
1i	6.33	3.22	15.8	7.63	2.74		1.80	0.142	
2b[c]	7.29	1.98	10.0	5.28	1.65		0.798	0.0722	0.142
2c	7.37	1.90	9.91	5.16	1.65		0.795	0.0666	0.142
2d	7.10	2.27	11.5	6.04	1.81		0.899	0.0831	0.168
2e	7.17	2.20	11.0	5.80	1.87		0.918	0.0788	0.161
2f	6.96	2.30	11.3	6.25	2.05		1.05	0.0923	0.187
2g	6.93	2.35	11.8	6.21	2.19		1.15	0.0967	0.192
2h	6.59	2.59	12.4	6.98	2.57	1.53	1.33	0.120	0.232
3d[d]	6.96	2.59						0.0978	
3e	6.70	3.35						0.123	
3f	6.50	4.09						0.141	
3g	6.27	4.94						0.169	

[a] In aqueous solution, ionic strength 0.1, at 25 °C. pK_{CH} from ref 1. [b] Base no. from Table I. [c] Data for **1a** (pK_{CH} = 7.66) and **2a** (pK_{CH} = 7.28) are in Table I. [d] **3a** ≡ **2a** (Table I).

Table III. Brønsted α Values for the General-Base-Catalyzed Deprotonation of **1–3**

acid	base	α	n[a]	r[a]
1	$C_6H_5CH_2NH_2$	0.48 (±0.01)	6	0.9984
	$C_6H_5CH_2NHCH_3$	0.44 (±0.01)	6	0.9987
	$C_6H_5CH_2N(CH_3)_2$	0.39 (±0.01)	6	0.9973
	$C_6H_5(CH_2)_2NH_2$	0.36 (±0.01)	6	0.9980
	$^-O_2CCH_2NH_2$	0.39 (±0.01)	6	0.9993
	$(HOCH_2)_3CNH_2$	0.41 (±0.01)	6	0.9988
	^-OH[b]	0.45		
2	$C_6H_5CH_2NH_2$	0.18 (±0.02)	8	0.9515
	$C_6H_5CH_2NHCH_3$	0.14 (±0.02)	8	0.9246
	$C_6H_5CH_2N(CH_3)_2$	0.18 (±0.02)	8	0.9698
	$C_6H_5(CH_2)_2NH_2$	0.27 (±0.03)	8	0.9743
	$(CH_3)_2NC_5H_4N$	0.31[c]	2	
	$^-O_2CCH_2NH_2$	0.31 (±0.03)	8	0.9782
	$(HOCH_2)_3CNH_2$	0.34 (±0.01)	8	0.9950
	$H_2NCOCH_2NH_2$	0.29 (±0.01)	8	0.9931
	^-OH[b]	0.35		
3	$C_6H_5CH_2NH_2$	0.41 (±0.01)	5	0.9996
	$(HOCH_2)_3CNH_2$	0.38 (±0.02)	5	0.9960
	^-OH[b]	0.42		

[a] n is the number of substituted acids in the correlation; data points for **1b** (4-OCH_3) and **1i** (4-NO_2) are not used in the correlations, since these substituents always systematically deviate from the correlation lines due to resonance interactions; r = correlation coefficient. [b] Data from ref 1. [c] Based on only two substituents (**2a** and **2h**).

4, and the close linear relationship of Figure 5 suggests that such is also the case for the amine-catalyzed deprotonation of **1a**. A similar comparison (not shown) of the data for **2a** and **4** is also linear (eq 2). Note that hydroxide ion, although it has not been included in the correlation equations (1 and 2), does fall close to these correlation lines.

$$\log k_B^{1a} = 0.96(\pm 0.04) \log k_B^{4} + 1.96(\pm 0.07) \qquad r = 0.992 \tag{1}$$

$$\log k_B^{2a} = 1.00(\pm 0.05) \log k_B^{4} + 2.1(\pm 0.1) \qquad r = 0.987 \tag{2}$$

The Brønsted α values in Table III for the deprotonation of **1** by the various amine catalysts cluster in a range from 0.36 to 0.48, which encompasses $\alpha = 0.45$ for the hydroxide ion catalyzed deprotonation[1] of **1**. This range of α values for **1** is quite distinct from the range of α = 0.14–0.34 that is found for these same amine bases as catalysts for the deprotonation of **2**, for which α = 0.35 for deprotonation by hydroxide ion.[1] It is clear that the lower α for deprotonation of **2** than for **1**, which we have also reported[1] for hydroxide ion, is a phenomenon that is independent of the base catalyst. The X-substituents in **1** reflect quite a different aspect of electronic structure in the transition-state species than do the X-substituents in **2**. Whereas substituents in **1** reflect mainly the electron density on the oxygen and carbon atoms in

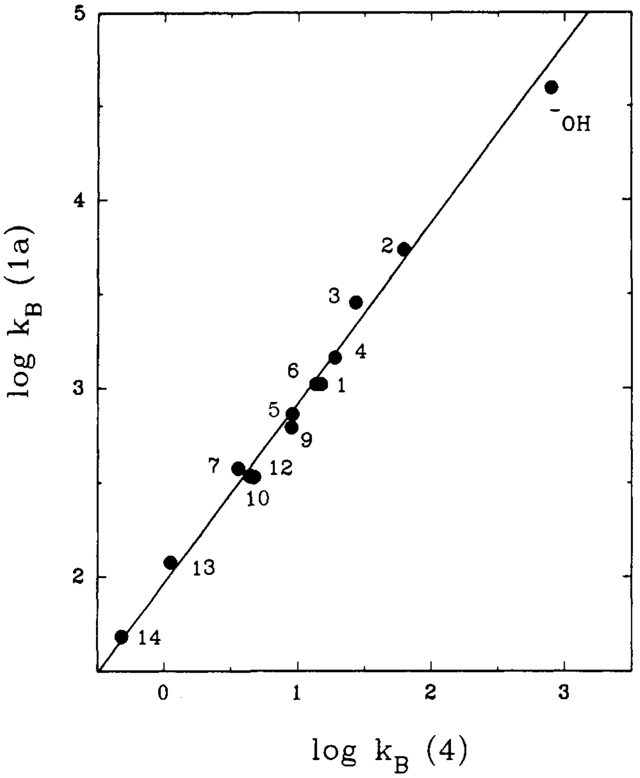

Figure 5. Comparison of the second-order rate constants for the deprotonation of **1a** and **4** by amine bases (indicated by numbers from Table I). Data for **4** are from ref 3.

the developing enolate ion, substituents in **2** predominantly sample electron density delocalization into the pyridinium ring. The different α values for **1** and **2** are then a reflection of the lack of synchronization in the progress of these various events in the transition-state species relative to their role in the stabilization of the conjugate base product species. Thus, the amount ($\Delta\alpha = \alpha(\mathbf{1}) - \alpha(\mathbf{2})$) by which α differs between **1** and **2** is a quantitative measure of imbalance within the transition-state species.

It is also important to note that $\Delta\alpha$ is quite dependent upon the structure of the base in question. Thus, 2-phenylethylamine (0.09), glycine (0.08), and tris(hydroxymethyl)aminomethane (0.07) have $\Delta\alpha$ values similar to one another and also to hydroxide ion (0.10). On the other hand, benzylamine and its *N*-methyl and *N,N*-dimethyl derivatives have $\Delta\alpha$ in the range 0.21–0.30. This dramatic difference in $\Delta\alpha$ for these benzylamine derivatives in comparison with other amines suggests an important difference in the transition-state interactions between the general-base catalyst and these pyridinium carbon acids for these two empirically distinct classes of amines. The geometric relationship between the aromatic ring and the basic nitrogen atom of these benzylamines seems to be important since 2-phenylethylamine appears to be a "normal" amine catalyst. Since the α values for the benzylamines interacting with **1** appear to be similar to those for other amines, it is clear that it is the unusually low α values for the benzylamines reacting with **2** that require specific consideration.

We have argued previously[1] that the major influence of substituents in the *N*-benzyl groups upon the pK_a values of **2** (Hammett $\rho = 0.47$)[1] is upon the stabilization of resonance contributors such as **5**. The magnitudes of the α values for **2** are then an expression of the relative importance of transition-state resonance interactions similar to **5** with various base catalysts. The lower α for **2** reacting with benzylamines than with other amines suggests that resonance delocalization from the developing carbanionic center into the pyridinium ring is less important in the transition-state species with the benzylamine catalysts than with other amine catalysts.

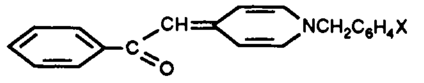

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Table IV. Marcus Parameters for the General-Base-Catalyzed Deprotonation of **1**–**3**[a]

acid	base	ΔG_0^*	α_M	*A*	*B*
1	$C_6H_5CH_2NH_2$	14.55	0.48	14.57	0.01
	$C_6H_5CH_2NHCH_3$	13.76	0.47	13.68	−0.03
	$C_6H_5CH_2N(CH_3)_2$	13.67	0.48	13.50	−0.08
	$C_6H_5(CH_2)_2NH_2$	14.89	0.47	14.56	−0.11
	$^-O_2CCH_2NH_2$	14.98	0.47	14.78	−0.08
	$(HOCH_2)_3CNH_2$	15.53	0.50	15.48	−0.08
	^-OH[b]	15.21	0.43	15.49	0.03
2	$C_6H_5CH_2NH_2$	14.44	0.47	13.53	−0.29
	$C_6H_5CH_2NHCH_3$	13.64	0.47	12.50	−0.33
	$C_6H_5CH_2N(CH_3)_2$	13.56	0.48	12.82	−0.30
	$C_6H_5(CH_2)_2NH_2$	14.89	0.47	14.15	−0.19
	$^-O_2CCH_2NH_2$	15.06	0.47	14.54	−0.16
	$(HOCH_2)_3CNH_2$	15.57	0.49	15.36	−0.15
	$H_2NCOCH_2NH_2$	15.03	0.49	14.82	−0.20
	^-OH[b]	15.31	0.43	14.59	−0.08
3	$C_6H_5CH_2NH_2$	14.44	0.47	14.27	−0.06
	$(HOCH_2)_3CNH_2$	15.57	0.49	15.42	−0.11
	^-OH[b]	15.31	0.43	15.29	−0.00

[a] Calculated as described in text. ΔG_0^* and *A* in kilocalories per mole; standard deviations in *A* are ±0.02; standard deviations in *B* are in the range ±0.01–±0.03. [b] Data from ref 1.

It should be noted that the α values for X-substituents in the benzoyl group are similar for **1** and **3** in reactions with benzylamine, Tris, and hydroxide ion (Table III). Thus, the unusually small α values for **2** reacting with benzylamine derivatives cannot simply be a matter of an overall difference between *N*-methyl- and *N*-benzylpyridinium carbon acids. Rather, there seems to be a specific interaction between the benzylamine base and the pyridinium unit of **2**, and this interaction significantly reduces electron density flow into the pyridinium ring in the transition-state species relative to that which occurs with other amine bases. We tentatively suggest that in the transition-state species the phenyl ring of the benzylamine (and its *N*-methyl and *N,N*-dimethyl derivatives) is involved in a π–π interaction with the pyridinium ring of the carbon acid. Such an interaction would be expected to hinder electron density delocalization from the developing carbanionic center into the pyridinium ring, which is consistent with the experimental observation of unusually small α values for benzylamine deprotonation of **2**.

In Table IV, we present the Brønsted α (denoted as α_M) predicted from Marcus theory assuming a constant intrinsic barrier (ΔG_0^*) for each base. Each of these α_M should be compared with the corresponding experimentally observed α value in Table III. Each α_M is calculated by solving the Marcus equation (eq 3) for ΔG_0^* for the case X = H and insertion of this value into eq 4.

$$\Delta G^* = \Delta G_0^*(1 + \Delta G^\circ/4\Delta G_0^*)^2 \qquad (3)$$

$$\alpha_M = 0.5(1 + \Delta G^\circ/4\Delta G_0^*) \qquad (4)$$

In general, the experimentally observed α values of Table III are considerably smaller than predicted in Table IV. We have shown[5] that such "abnormal" α values can be reconciled by the introduction of a variable intrinsic barrier that has a linear dependence upon the free energy of reaction (eq 5).

$$\Delta G_0^* = A + B\Delta G^\circ \qquad (5)$$

Application of eq 5 to the current experimental data generates the *A* and *B* parameters that are included in Table IV. Note that while the *A* parameters (the "true" intrinsic barriers) for deprotonation of **2** by 2-phenylethylamine, glycine, and tris(hydroxymethyl)aminomethane are only 0.1–0.5 kcal/mol lower than for the deprotonation of **1** by these same bases, for the benzylamine

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(5) (a) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1988**, *110*, 4008. (b) Bunting, J. W.; Stefanidis, D. *J. Am. Chem. Soc.* **1989**, *111*, 5834.

Table V. Relative Reactivities of Benzylamines in the Deprotonation of **1a** and **2a**[a]

acid	base	$k_B{}^n$ (M^{-1} s^{-1})	rel $k_B{}^n$
1a	$C_6H_5CH_2NH_2$	330	(1)
	$C_6H_5CH_2NHCH_3$	1480	4.5
	$C_6H_5CH_2N(CH_3)_2$	2830	8.6
2a	$C_6H_5CH_2NH_2$	600	(1)
	$C_6H_5CH_2NHCH_3$	2740	4.6
	$C_6H_5CH_2N(CH_3)_2$	5210	8.7

[a] $k_B{}^n$ is calculated by extrapolation to (pK_{BH} + log p) = 9.03 with β = 0.55. *N*,*N*-Dimethylbenzylamine has pK_{BH} = 9.03.

derivatives *A* is 0.8–1.2 kcal/mol smaller for **2** than for **1**. This result again indicates that for benzylamines interacting with these carbon acids there is an important transition-state stabilization effect that is not available to the other bases that were investigated in this study. The dramatically smaller α values for benzylamine derivatives reacting with **2** also result in significantly more negative *B* value for these bases than for the other amine bases reacting with **2**.

In general, the *B* parameters in Table IV are more negative for amines than for hydroxide ion and further dramatically reflect the importance of transition-state imbalance of electron density distribution within the developing carbanionic species in comparison with the conjugate base product. Note that while k_B for hydroxide ion is much larger than for any of the amine bases (Table I), this does *not* lead to a lower intrinsic barrier for hydroxide ion than for these amine bases. In fact, both $\Delta G_0{}^{\ddagger}$ and *A* are significantly smaller for the benzylamines than for hydroxide ion, and these barriers are of similar magnitude for hydroxide ion and the other amine bases in Table IV. These observations again stress the importance of the *B* parameters, and thus the concept of a variable intrinsic barrier, in determining the overall observed reactivities. We have previously shown[5b] that these *B* parameters are intimately related to the work terms that are required for a complete description of rate–equilibrium relationships by the Marcus theory.

Although we have interpreted the phenomena associated with the benzylamines in terms of an interaction of the phenyl ring of these bases with the pyridinium ring of 1–3, there are several subtle indications in the experimental data that suggest that some interaction between the benzylamines and the *N*-benzyl substituents of **2** and **3** may also be present in the transition-state species. For instance, note the enhanced $k_B{}^{2a}/k_B{}^{1a}$ ratios in Table I for the benzylamines relative to the other amines and hydroxide ion. Also, there is considerably more scatter in the Brønsted plots for the benzylamines reacting with **2** than for these same amines reacting with **1** (see the correlation coefficients in Table III). This scatter is quite reproducible; it is not simply experimental error in the rate measurements. Note that the scatter is absent for benzylamine reacting with **3** in which a constant *N*-benzyl substituent is present. Furthermore, the Brønsted α for benzylamine with **3** appears to be slightly smaller than for the corresponding *N*-methyl cation series (**1**). We realize that all of these effects are quite small, but they do appear to be real, and they make their presence felt in a variety of ways that are suggestive of an interaction of the benzylamines with the *N*-benzyl substituents of **2** and **3**.

Despite the unusual reactivity phenomena that are discussed earlier for the benzylamines, it should be noted that these bases do show the usual order of reactivity (tertiary > secondary > primary) that is commonly found for amines as general-base catalysts. This result is clear from the data in Table V, where a Brønsted β = 0.55 has been assumed to allow the extrapolation of the data for these three amines to a common basicity. Thus, the effects discussed previously appear to be superimposed over the usual solvation phenomena that influence the reactivities of these amine bases.[3]

The close correlation of the data for the benzylamines with the data for other amines in Figure 5 suggests that similar transition-state interactions between benzylamines and the aromatic rings of **4** may also be important. None of the data that we have reported[1,3] for **4** have directly tested this possibility in the way described in the current study. We did report, however, that the Brønsted plot for the deprotonation of **4** by ring-substituted benzylamines does show a significant amount of scatter,[3] and this may be an indication of such an interaction between the aromatic rings of this series of bases and one of the rings of **4**.

One might have expected[4c] that the reaction of the anionic amines, glycine, and 2-aminoethanesulfonate with these cationic carbon acids may possibly result in important transition-state phenomena. While these two bases are slightly more reactive than the simple aliphatic amines in Figure 4, glycine appears to be quite "normal" in all of the data in Tables III and IV. In fact, the somewhat enhanced reactivities for these anionic bases are similar to those found for glycinamide and glycine ethyl ester, and there is no indication of any particular influence from an electrostatic interaction between anionic amine base and cationic carbon acid.

The difference between the β values (~0.55) for base catalysts and the various α values reported in the current work represents transition-state imbalances $I = \alpha_{CH} - \beta_B$ of the type that Bernasconi[6] has extensively investigated in a variety of reactions involving carbanionic species. The data in the current study indicate that *I* may be as large as −0.4 in the amine-catalyzed deprotonation of these cationic ketones. Note that such an *I* and the $\Delta\alpha$ defined above represent quite different probes, and quite different aspects, of imbalance within the same transition-state species. Whereas *I* represents an imbalance between the developing positive charge on the ammonium ion (BH^+) and the delocalization of the developing negative charge on the conjugate base of the carbon acid, $\Delta\alpha$ represents a direct measure of the asynchronicity of charge delocalization within the developing conjugate base species. The fact that both α(**1**) and α(**2**) are smaller than β seems to imply that excess negative charge develops on the benzylic carbon atom in the transition-state species. Most of this carbanionic charge is delocalized onto the enolate oxygen atom and onto the nitrogen atom of the pyridinium ring in the product species. Such charge delocalization is expected to be accompanied by significant solvational reorganization in the vicinity of the oxygen and nitrogen atoms. Thus, these imbalanced α and β values point toward a lag in solvation changes relative to the proton-transfer process.

The current work demonstrates how cautious one must be in extrapolating experimental rate–equilibrium correlations when complex resonance delocalization and solvation effects are involved in the stabilization of the transition-state species. Even what appear to be quite similar species (e.g., benzylamine and 2-phenylethylamine of the current study) can lead to unexpected additional complications. Whatever the source of the unusual α values that we find for benzylamine bases reacting with **2**, we feel that the current study demonstrates the need for very careful systematic explorations of structural dependences in rate–equilibrium correlations. Given such data, it is clear that such correlations do allow significant quantitative insight into the structures of rate-determining transition-state species. The fact that apparently chaotic plots such as Figure 4 can be readily transformed into clean linear correlations such as Figure 5 is particularly reassuring. In this light, it is clear that Jencks' 20-year-old comment[7] is still quite appropriate: "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."

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(7) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969; p 180.