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Transition-State Imbalance in the Deprotonation of Sulfonyl-Activated Carbon Acids in Aqueous Solution. A Quantitative Comparison of the Kinetic Acidities of Sulfones and Ketones

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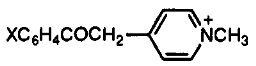
Abstract: Second-order rate constants for the deprotonation of ten *N*-methyl 4-((X-phenylsulfonyl)methyl)pyridinium cations (**4**) and eight *N*-(Y-benzyl) 4-((phenylsulfonyl)methyl)pyridinium cations (**5**) by hydroxide ion and carbonate ion have been measured in aqueous solution at 25 °C, ionic strength 0.1. Brønsted α-values for deprotonation of **4** are 0.59 and 0.45 for hydroxide ion and carbonate ion, respectively. The corresponding Brønsted α-values for **5** are 0.33 and 0.29, which clearly indicate a pronounced lag in the delocalization of π-electron density into the pyridinium ring in the transition state for deprotonation. Brønsted β-values of 0.55 and 0.52 are found for the deprotonation of **4** with X = H and **5** with Y = H, respectively, by a series of primary amine bases. Extrapolation of Brønsted relationships for the deprotonation of sulfones and ketones indicates that the intrinsic kinetic acidities of sulfones are 80-fold greater than those of structurally analogous ketones. The difference in the substituent-independent intrinsic barriers for the deprotonation of sulfones and ketones by hydroxide ion is found to be 2.85(±0.03) kcal/mol, irrespective of whether one analyzes X-substituent effects in **4** or Y-substituent effects in **5**.

The phenomenon of an imbalanced electron density distribution in the rate-determining transition-state species relative to the electron density distribution in the product species is now a well-established principle for a variety of reactions of organic molecules.[1-9] Such imbalances are the basis of Bernasconi's Principle of Non-Perfect Synchronization[9] for the stabilization of transition-state species relative to the factors which stabilize the reactant and product species of any given reaction. In recent studies in this laboratory,[7,10] it was shown that the monitoring of substituent effects in distinct regions of the ketonic carbon acids **1** and **2** indicates that the delocalization of electron density from the carbanionic atom in **3B** onto the carbonyl oxygen (as represented by the resonance contributor **3A**) and into the pyridinium ring (as represented by **3C**) in the transition state for deprotonation is not a direct reflection of the electron density distribution in the conjugate base species that is produced upon deprotonation of the methylene group of **1** and **2**.



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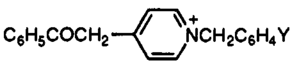

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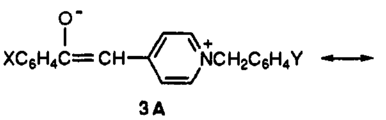

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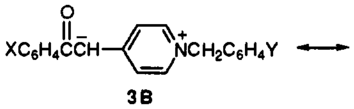

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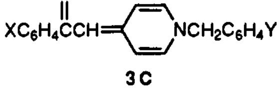
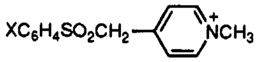


3C

In the current study we have investigated substituent effects upon the rate-equilibrium relationships for the deprotonation of two series of sulfones (**4** and **5**) which are close structural analogs of the ketonic carbon acids **1** and **2**. The electronic structures of the rate-determining transition states for the deprotonation of sulfones are of interest in their own right. Furthermore, comparisons of substituent effects and transition-state structure for the deprotonation of such closely related sulfones and ketones are of particular interest in light of the observation[11] that the kinetic acidities of sulfones are in general considerably greater than the kinetic acidities of ketones of the same thermodynamic acidity. The current study provides the most extensive quantitative comparison that is currently available of the kinetic acidities of these two important classes of carbon acids and provides a further application of the modified form of the Marcus relationship that we have recently established[12,13] for the deprotonation of carbon acids in aqueous solution.



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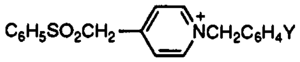

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Results

We have recently reported[14] the pK_a values for the deprotonation of the sulfones **4** ($pK_a = 11.27$ for **4** with X = H; $\rho = 1.45$) and **5** ($pK_a = 10.70$ for **5** with Y = H; $\rho = 0.65$) in aqueous solution. The substituent effects upon the pK_a values for **4** are closely correlated by the Hammett σ constants for X defined for the

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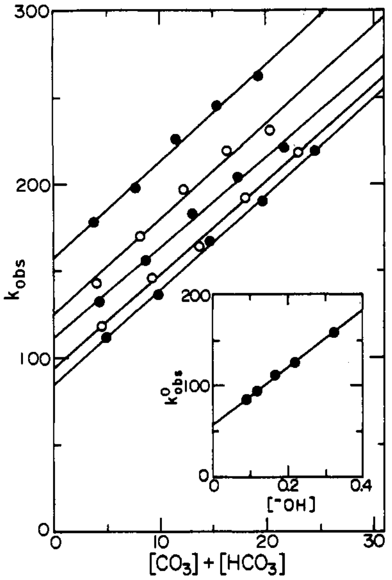


Figure 1. Pseudo-first-order rate constants (k_{obs}, s^{-1}) for the equilibration of **5** with Y = 4-NO_2 with its conjugate base in carbonate/bicarbonate buffers (mM) at 25 °C, ionic strength 0.1. The main figure represents data at pH 10.51, 10.34, 10.22, 10.07, and 9.96 (top to bottom). The inset shows k^0_{obs} (s^{-1}) extrapolated to zero buffer concentration (i.e. ordinate intercepts from the main figure) as a function of hydroxide ion concentration (mM).

deprotonation of ring-substituted benzoic acids, with no indication of any significant resonance interactions between the carbanionic center and X-substituents in the conjugate base of **4**. We have now found that the rates of equilibration of both **4** and **5** with their conjugate bases are accessible by stopped-flow spectrophotometry in basic aqueous solutions. These equilibrations are kinetically first-order in the sulfone species, and pseudo-first-order rate constants have been evaluated in carbonate buffers and potassium hydroxide solutions within the pH range 10–12 for a variety of substituents in **4** and **5**. The reactions in carbonate buffers display significant buffer catalysis (e.g. Figure 1); however, extrapolation to zero buffer concentration allows the accurate evaluation of the buffer-independent rate constants at constant pH.

The pH dependencies of the buffer-independent pseudo-first-order rate constants (k^0_{obs}) for the equilibration of these carbon acids with their conjugate bases are consistent with eq 1 and

$$k^0_{obs} = k_{OH}[^-OH] + k_{H_2O} \qquad (1)$$

allow the evaluation of the second-order rate constant (k_{OH}) for the hydroxide ion-catalyzed deprotonation of each carbon acid from the experimentally observed dependence of k_{obs} upon [$^-$OH]. The first-order rate constant for the microscopic reverse of this process (i.e. k_{H_2O} for the protonation of the conjugate base by a solvent water molecule) was most accurately calculated from $k_{H_2O} = k_{OH}K_w/K_a$. Values of k_{OH} and k_{H_2O} are summarized in Table 1 for a variety of X-substituents in **4** and Y-substituents in **5**.

The buffer dilution plots shown in Figure 1 also allow the evaluation of the second-order rate constants for the deprotonation of these cation acids by carbonate ion (k_{CO_3}) and for the protonation of the conjugate bases by bicarbonate ion (k_{HCO_3}). These data are also included in Table 1.

We have also examined the rates of equilibration of **4** with X = H and **5** with Y = H with their conjugate bases in solutions containing amine–ammonium ion buffers. We have chosen four primary amines of similar structure ($(CH_3)_nC(CH_2OH)_{3-n}NH_2$; n = 0–3) and have obtained rate data by mixing solutions of the conjugate bases of **4** and **5** with these amine buffers. The second-order rate constants defined in eq 2 for these amines and ammonium ions are listed in Table 2.

Table 1. Rate Constants for the Equilibration of ((4-Substituted-arylsulfonyl)methyl)pyridinium Cations with Their Conjugate Bases[a]

cation	X	Y	pK_a[b]	k_{OH} (10^5 M^{-1} s^{-1})	k_{H_2O}[c] (s^{-1})	k_{CO_3}[d] (M^{-1} s^{-1})	k_{HCO_3}[e] (M^{-1} s^{-1})
4	4-OCH_3		11.71	0.935	480		
	4-CH_3		11.52	1.24	410		
	H		11.27	1.55	290		
	4-Br		10.97	2.98	280	6500	33 200
	3-Cl		10.82	3.37	220	7620	24 900
	3,4-Cl_2		10.58	4.61	175	11 500	21 100
	3-NO_2		10.28	6.66	126	13 900	15 800
	3,5-Cl_2		10.27	6.26	116	13 900	15 700
	4-NO_2		10.14	7.73	107	15 900	13 600
	3-NO_2, 4-Br		10.05	9.60	108	17 100	12 700
5		4-CH_3	10.75	2.10	118	6590	5990
		3-CH_3	10.72	2.02	106	6590	5910
		H	10.70	2.13	107	6650	5820
		4-Br	10.57	2.35	94	7290	5330
		3-F	10.47	2.48	73	7830	5120
		4-CN	10.24	2.95	51	9210	4390
		3-NO_2	10.21	3.01	49	9300	4380
		4-NO_2	10.18	3.23	49	9510	4350

[a] In aqueous solution at 25 °C, ionic strength 0.1; all rate constants are within ±2%. [b] pK_a values are from ref 14. [c] Calculated from $k_{H_2O} = k_{OH}K_w/K_a$. [d] Second-order rate constant for deprotonation by carbonate dianion. [e] Second-order rate constant for protonation of conjugate base by bicarbonate ion (pK_{BH} = 10.04[7]).

Table 2. Amine Buffer Catalysis of the Equilibration of ((Phenylsulfonyl)methyl)pyridinium Cations with Their Conjugate Bases[a]

		4 with X = H		**5** with Y = H	
B	pK_{BH}	k_B (M^{-1} s^{-1})	k_{BH} (M^{-1} s^{-1})	k_B (M^{-1} s^{-1})	k_{BH} (M^{-1} s^{-1})
$(CH_3)_3CNH_2$	10.86	1260	3240	2030	1400
$(CH_3)_2C(CH_2OH)NH_2$	9.87	348	8740	601	4060
$CH_3C(CH_2OH)_2NH_2$	8.93	116	25 300	218	12 800
$(HOCH_2)_3CNH_2$	8.20	41.2	48 400	80.7	25 500

[a] In aqueous solution, ionic strength 0.1, at 25 °C; ammonium ion pK_{BH} values are from ref 15.

Table 3. Temperature Dependencies for the Deprotonation of ((Phenylsulfonyl)methyl)pyridinium Cations[a]

	4 with X = H			**5** with Y = H		
temp (°C)	pK_a	k_{OH} (10^5 M^{-1} s^{-1})	k_{H_2O} (s^{-1})	pK_a	k_{OH} (10^5 M^{-1} s^{-1})	k_{H_2O} (s^{-1})
9.3	11.87			11.34		
15.0	(11.64)[b]	1.01	200	(11.07)[b]	1.32	69
16.8	11.60			11.00		
25.0	11.27	1.55	290	10.70	2.13	107
32.6	10.93			10.42		
35.0	(10.94)[b]	2.45	450	(10.34)[b]	3.47	160
40.7	10.81			10.18		

[a] In aqueous solution, ionic strength 0.1. [b] By interpolation.

$$CH + B \underset{k_{BH}}{\overset{k_B}{\rightleftharpoons}} C^- + HB^+ \qquad (2)$$

The temperature dependencies of pK_a and k_{OH} for **4** with X = H and **5** with Y = H are given in Table 3. The derived thermodynamic and activation parameters for these reactions are presented in the following discussion and Table 8.

Discussion

Substituent effects upon k_{OH} and k_{CO_3} for the two series of sulfonyl-activated carbon acids, **4** and **5**, are summarized in Table

1. These data are described by the correlation eqs 3–6.

$$\log k_{OH}(4) = -0.59(\pm 0.02)pK_a + 11.93(\pm 0.03) \quad (r = 0.996) \quad (3)$$

$$\log k_{CO_3}(4) = -0.45(\pm 0.03)pK_a + 8.80(\pm 0.03) \quad (r = 0.988) \quad (4)$$

$$\log k_{OH}(5) = -0.33(\pm 0.02)pK_a + 8.82(\pm 0.01) \quad (r = 0.993) \quad (5)$$

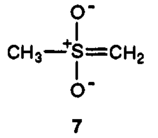
$$\log k_{CO_3}(5) = -0.29(\pm 0.01)pK_a + 6.95(\pm 0.01) \quad (r = 0.998) \quad (6)$$

The quite different Brønsted α-values indicated in eqs 3 and 4 for **4** relative to those of eqs 5 and 6 for **5** clearly indicate the imbalanced nature of charge development in the transition state for deprotonation relative to the charge delocalization in the conjugate base species. Irrespective of whether hydroxide or carbonate is the deprotonating base, α for **4** is considerably larger than α for **5**. The following discussion is presented in terms of hydroxide ion as the base; however, it appears that these considerations are independent of the nature of the deprotonating base.

It is convenient to discuss the electronic structure of the conjugate base species in terms of the stabilization of the formal carbanionic charge on the carbon atom linking the sulfonyl group and C-4 of the pyridinium ring (see 6A). The $\alpha = 0.59$ for **4** is a direct reflection of the stabilization of the developing negative charge on this carbon atom in the transition state by the substituents in the phenylsulfonyl ring relative to such stabilization in the conjugate base product. Similarly, $\alpha = 0.33$ for **5** is a measure of the importance of transition-state substituent effects upon the stabilization of the developing negative charge by π-electron delocalization into the pyridinium ring via the resonance contributor **6B** ($R = CH_2C_6H_4Y$).

6A **6B**

The question of the electronic structure of α-sulfonyl carbanions was most recently addressed in detail by Bors and Streitwieser[16] in their ab initio calculations of the structure of the anion of dimethyl sulfone. These workers concluded that d-p π-conjugation is not an important factor in stabilizing this anion. In valence bond terms, this result effectively rules out resonance contributors (such as **7**) which imply significant C═S double-bond character,


$$CH_3-\overset{+}{S}(O^-)_2=CH_2$$

7

and a similar result is also expected for the carbanions from **4** and **5**, i.e., **6A** and **6B** are the only significant resonance contributors to the electronic structure of these carbanion species. Bors and Streitwieser conclude that simple sulfonyl carbanions are stabilized predominantly by simple Coulombic interactions, although there is significant polarization which results in the two oxygen atoms and also the neutral methyl group in $CH_3SO_2CH_2^-$ bearing more electron density than is found on these same atoms in $CH_3SO_2CH_3$.

In this light, the developing transition states for the deprotonation of **4** and **5** can be described in terms of the cleavage of the C–H bond and the development of carbanionic character adjacent to the sulfonyl group (as defined by **6A**) and the π-delocalization of this carbanionic charge into the pyridinium ring as described by **6B**. The considerably smaller $\alpha = 0.33$ for **5** (eq 5) than $\alpha = 0.59$ that is found for **4** (eq 3) makes it clear that π-delocalization into the pyridinium ring lags behind the development of carbanionic character as described by **6A**. This lag produces a significant imbalance in the development of negative charge in the transition-state species relative to the final distribution of this charge density in the conjugate base product. It is also noteworthy that $\alpha = 0.33$ for **5** is quite similar to $\alpha = 0.35$ for the corresponding series of ketones, **2**.[10] Thus the lag in π-electron delocalization into the pyridinium ring is of similar magnitude irrespective of whether a carbonyl or sulfonyl group is the other activating substituent in these carbon acids.

Table 4. Comparison of Kinetic Acidities of Structurally Related Sulfones and Ketones

		sulfone ($Z = SO_2$)		ketone ($Z = CO$)	
acid	base	pK_a	$k_B^{SO_2}$	pK_a	k_B^{CO}
CH_3ZCH_3	^-OD	(30)[a]	8×10^{-3} [b]	19.16[c]	0.24[b,d]
$CH_3ZCH(CH_3)ZCH_3$	^-OH	14.56[e]	4.3×10^5 [e]	10.9[f]	130[f]
$CH_3COCH(CH_3)ZR$	OH_2	[g]	2×10^{-4} [h]	10.9[f]	8×10^{-5} [i]
$CH_3ZCH_2ZCH_3$	OH_2	12.54[j]	2.6×10^{-3} [j]	8.87[k]	3.0×10^{-4} [k]
$CH_3Py^+CH_2ZC_6H_5$	^-OH	11.27[l]	1.55×10^5 [l]	7.66[m]	3.9×10^4 [m]

[a] Estimated pK_a for aqueous solution.[14] [b] Rate data are pseudo-first-order rate constants (s^{-1}) for deuterium exchange into dimethyl sulfone[17] and into acetone[24] in 1 M NaOD in D_2O at 25 °C. [c] Reference 25. [d] $k_{OH} = 0.22\ M^{-1}\ s^{-1}$ for deprotonation in H_2O at 25 °C, ionic strength 0.1.[32] [e] Data for $C_2H_5SO_2CH(CH_3)SO_2C_2H_5$.[20] [f] Reference 26. [g] Not available. [h] Data for $CH_3CO(CH_3)SO_2C_2H_5$.[11] [i] Reference 11. [j] Reference 18. [k] Data at 27.5 °C.[27] [l] Current work. [m] Reference 10.

Kinetic Acidities of Sulfones. There have been relatively few reports of the rates of deprotonation of sulfonyl-activated carbon acids in aqueous solution. The earliest study directed specifically toward the measurement of the rate of deprotonation of a sulfone appears to be the report of Bonhoeffer and Hochberg[17] upon the rates of deuteration of dimethyl sulfone in 1 M NaOD in D_2O (see Table 4). In the first detailed comparison of the kinetic and thermodynamic acidities of carbon acids in aqueous solution, Pearson and Dillon[11] noted that "sulfones are characterized by high rates of ionization for a given acid strength", although they gave no examples of sulfonyl-activated carbon acids for which both rate and equilibium constants for deprotonation were known. Hine and co-workers[18] in 1970 appear to provide the first report of both the kinetic and thermodynamic acidity of a sulfone, in their study of proton transfer from bis(methylsulfonyl)methane ($CH_3SO_2CH_2SO_2CH_3$, $pK_a = 12.54$) to water. Consistent with the statements of Pearson and Dillon,[11] this disulfonyl-activated carbon acid undergoes deprotonation by water approximately 300-fold faster than predicted by their data for a carbonyl-activated carbon acid of the same pK_a. Several more recent investigations[19–23] of the rates of deprotonation of disulfones also report that the rates of deprotonation of these species approach the rates of "normal" proton transfer from oxygen acids.[22] This is consistent[16] with negative charge in the carbanionic conjugate base being effectively localized upon carbon with little resonance delocalization into the sulfonyl groups.

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Table 5. Comparison of the Thermodynamic and Kinetic Acidites of Sulfones and Ketones in Aqueous Solution

	sulfones[a]		ketones[b]	
parameter	**4**	**5**	**1**	**2**
$pK_a(X=H)$	11.27		7.66	
$\rho(K_a)$	1.45		1.38	
$k_{OH}(X=H)$	1.55×10^5		3.93×10^4	
$\rho(k_{OH})$	0.86		0.62	
α	0.59		0.45	
$\Delta G_0^\ddagger(X=H)$	12.17		15.21	
α_M	0.46		0.43	
A (kcal/mol)	12.62		15.49	
B	0.14		0.03	
$pK_a(Y=H)$		10.70		7.28
$\rho(K_a)$		0.65		0.47
$k_{OH}(Y=H)$		2.1×10^5		4.81×10^4
$\rho(k_{OH})$		0.21		0.16
α		0.32		0.35
$\Delta G_0^\ddagger(Y=H)$		12.34		15.31
α_M		0.45		0.43
A (kcal/mol)		11.77		14.59
B		−0.13		−0.08

[a] Data from ref 14 and current study. [b] Data from ref 10.

The most recent study of the rates of deprotonation of disulfones is the work of Aiken and co-workers,[23] who report rate and equilibrium data for the deprotonation of a series of ring-substituted phenylbis(ethylsulfonyl)methanes ($C_2H_5SO_2CHArSO_2C_2H_5$) in aqueous base at 25 °C. These species are of similar acidity ($pK_a = 12.01$ for Ar = C_6H_5) to **4** and **5** but undergo deprotonation by hydroxide ion approximately 100-fold more rapidly than **4** and **5** of similar pK_a (for **4** with X = H, $pK_a = 11.27$, $k_{OH} = 1.55 \times 10^5$ M^{-1} s^{-1}; interpolation at $pK_a = 11.27$ on the Brønsted relationship for $C_2H_5SO_2CHArSO_2C_2H_5$ reacting with hydroxide ion[23] gives $k_{OH} = 1.1 \times 10^7$ M^{-1} s^{-1}).

Sulfones and Ketones. The only literature data that we have been able to locate that allow a direct comparison of the acidities of sulfones and ketones of similar structure are collected in Table 4. In four of the entries in Table 4 it is clear that the sulfone (or disulfone) is deprotonated faster than the corresponding ketone (or diketone) despite the fact that the sulfone is the weaker acid by up to 4 pK_a units. Even dimethyl sulfone, which is approximately 11 pK_a units weaker as an acid than acetone, undergoes deprotonation only 30-fold more slowly than this ketone.

Table 5 summarizes the rate and equilibrium parameters which we have obtained in the present study for the activated sulfones **4** and **5** and compares these data with the analogous parameters that have previously been reported[10] for the corresponding two series of activated ketones, **1** and **2**. To the best of our knowledge, these data provide the most comprehensive quantitative comparison that is currently available of the kinetic and thermodynamic acidities of structurally analogous ketones and sulfones. While these results seem to firmly establish the greater kinetic acidity of sulfones than of the corresponding ketones, they leave open the question of the relative rates of deprotonation of a sulfone and a ketone of the *same* thermodynamic acidity.

We are now in a position to address this latter question by making use of the extensive linear free energy relationships that we have established for the rate and equilibrium data for the deprotonation of **1** and **2** in an earlier study[10] and of **4** and **5** in the current work. Extrapolation of the Brønsted plots of each of these carbon acids to a common pK_a value allows the direct comparison of the relative kinetic acidities of carbonyl- and sulfonyl-activated acids. However, since the Brønsted slopes vary for these series of carbon acids, the relative kinetic acidities defined in this way will depend upon the particular pK_a value that is chosen as the basis for comparison. This fact is clear from eqs 7 and 8, which are obtained by combining the Brønsted equations for **1** and **4** and for **2** and **5**, respectively.

$$\log(k_{OH}^{SO_2}/k_{OH}^{CO}) = -0.14pK_a + 3.9 \qquad (7)$$

$$\log(k_{OH}^{SO_2}/k_{OH}^{CO}) = 0.02pK_a + 1.6 \qquad (8)$$

Relative second-order rate constants for the deprotonation of sulfones and ketones by hydroxide ion are summarized in Table 6 for three pK_a values: $pK_a = 7.66$ for **1** with X = H; $pK_a = 11.27$ for **4** with X = H; and $pK_a = 14.0$, which represents the reaction of eq 9 having $\Delta G° = 0$ (i.e. $K = [C^-]/[(CH)[^-OH])= 1$, when

$$CH + {}^-OH \rightleftharpoons C^- + H_2O \qquad (9)$$

neutral water is assigned unit activity). This latter case is of most interest, since it defines the intrinsic reactivity[28] of hydroxide ion with each of the sulfone and ketone series of acids. In turn, for $pK_a = 14.0$, the $k_{OH}^{SO_2}/k_{OH}^{CO}$ ratio will represent the relative intrinsic reactivities of hydroxide ion with a sulfone and a ketone which are each activated by a 4-pyridinio substituent. It is clear from Table 6 that the $k_{OH}^{SO_2}/k_{OH}^{CO}$ ratio varies considerably with pK_a, particularly when **1** and **4** are the species under comparison; however, at $pK_a = 14.0$, these ratios are similar for the two series of sulfones and ketones. We conclude that the relative intrinsic reactivities of sulfones and ketones with hydroxide ion are close to 80:1 in favor of the sulfones.

A slightly different approach would be to ask at what pK_a value do eqs 7 and 8 predict the same $k_{OH}^{SO_2}/k_{OH}^{CO}$ ratio. Solution of eqs 7 and 8 as a pair of simultaneous equations leads to $k_{OH}^{SO_2}/k_{OH}^{CO} = 77$ at $pK_a = 14.4$, which is consistent with the result deduced above. Note that this solution for pK_a is quite sensitive to the slope of eq 8. This small slope is the difference between the similar Brønsted α-values for **2** and **5**.

The current study confidently establishes the 80-fold greater intrinsic reactivity toward deprotonation of a sulfone than of a ketone in one particular case. However, a question remains regarding the generality of this rate ratio for other series of carbon acids and for base catalysts other than hydroxide ion. Although the current ratio is only strictly applicable to series of 4-pyridinio-activated sulfones and ketones reacting with hydroxide ion, we note the following three facts which suggest that it should be a reasonably general guide to the relative *intrinsic* kinetic acidities of all structurally analogous sulfones and ketones in aqueous solution.

Firstly, despite the imbalanced nature of electron delocalization in the transition-state species which is predominantly associated with the lag of π-delocalization into the pyridinium ring, we find similar $k_{OH}^{SO_2}/k_{OH}^{CO}$ ratios at $pK_a = 14.0$ (Table 6) irrespective of whether we probe Y-substituted *N*-benzylpyridinium species in **2** and **5**, which directly reflect this lag, or X-substituted phenyl rings in **1** and **4**, which are most sensitive to the electron density on the carbanionic carbon atom.

Secondly, if we assume that the effects of multiple sulfonyl and carbonyl substituents are cumulative, then we may estimate $k_{OH}^{SO_2}/k_{OH}^{CO} = (80)^2 = 6400$ for the relative kinetic acidities of $C_2H_5SO_2CH(CH_3)SO_2C_2H_5$ and $CH_3COCH(CH_3)COCH_3$. This estimate is on the same order of magnitude as the experimentally measured ratio of $k_{OH}^{SO_2}/k_{OH}^{CO} = 3000$ for these two species (Table 4). Since k_{OH} for a diketone of $pK_a = 14.0$ should be smaller than k_{OH} for $CH_3COCH(CH_3)COCH_3$ ($pK_a = 10.9$[26]), this ratio of 3000 is a lower limit for the ratio that would be obtained upon correction of the pK_a values of $C_2H_5SO_2CH(CH_3)SO_2C_2H_5$ and $CH_3COCH(CH_3)COCH_3$ to 14.0.

Thirdly, we may compare the intrinsic kinetic acidities of **1** with X = H and **4** with X = H toward amine general base catalysts of the type $(CH_3)_nC(CH_2OH)_{3-n}NH_2$. The data of Table 2 generate the Brønsted relationships in eqs 10 and 11 with β-values

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[28] The intrinsic reactivity is the rate constant for a reaction having $\Delta G° = 0$.[29]

(29) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.

Table 6. Relative Rate Constants for the Deprotonation of Sulfones and Ketones

	$k_{OH}^{SO_2}/k_{OH}^{CO}$	
pK_a	**4** and **1**[a]	**5** and **2**[b]
7.66	670	56
11.27	210	65
14.0	87	76

[a] Calculated from eq 7. [b] Calculated from eq 8.

of 0.55 and 0.52 for **4** with X = H and **5** with Y = H, respectively. These β-values for general base catalysis of the deprotonation of these ((phenylsulfonyl)methyl)pyridinium cations are similar to values which have been reported[7] for amines in reactions with a large number of other carbon acids; in particular $\beta = 0.53$ for these same amines in the deprotonation of the 1-methyl-4-phenacylpyridinium cation (**1** with X = H).[7] Extrapolation of the Brønsted relationships that have been established for these amines reacting with **1** and with **4** (eq 10) to $pK_{BH} = pK_a$ of the appropriate carbon acid leads to $k_B^{CO} = 25$ M^{-1} s^{-1} (at $pK_{BH}^{CO} = 7.66$) for **1** and $k_B^{SO_2} = 1990$ M^{-1} s^{-1} (at $pK_{BH} = 11.27$) for **4**. Thus the relative intrinsic reactivities of sulfones and ketones with primary amines of this structural class are $k_B^{SO_2}/k_B^{CO} = 1990/25 = 80$, which is identical to the relative intrinsic reactivities of sulfones and ketones toward hydroxide ion which we have established above.

$$\log k_B(\mathbf{4}) = 0.55(\pm 0.01)pK_{BH} - 2.90(\pm 0.03) \qquad (r = 0.999) \quad (10)$$

$$\log k_B(\mathbf{5}) = 0.52(\pm 0.01)pK_{BH} - 2.33(\pm 0.03) \qquad (r = 0.999) \quad (11)$$

Why do sulfones have greater intrinsic kinetic acidities than ketones? If as discussed above there is no π-delocalization of carbanionic electron density into the sulfonyl substituent, then there will be essentially no reorganization of solvent in the vicinity of the oxygen atoms of this activating group. This contrasts with the expected extensive delocalization of electron density onto the carbonyl oxygen atom in the transition state for enolate ion formation and the resulting requirement for solvent reorganization in the vicinity of this developing oxyanion. A lag in either or both π-electron delocalization and solvent reorganization is consistent with a lower rate of deprotonation for ketones relative to sulfones.

Intrinsic Barriers for Deprotonation. For several series of carbon acids, we have recently shown[7,10,12,13,30] that the simplest form of the Marcus relationship (eq 12) is inadequate for the

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger}[1 + \Delta G^0/(4\Delta G_0^{\ddagger})]^2 \qquad (12)$$

$$\alpha_M = d(\Delta G^{\ddagger})/d(\Delta G^0) = 0.5[1 + \Delta G^0/(4\Delta G_0^{\ddagger})] \quad (13)$$

$$\Delta G^{\ddagger} = (A + B\Delta G^0)[1 + \Delta G^0/(4(A + B\Delta G^0))]^2 \quad (14)$$

description of the rate–equilibrium relationships for deprotonation. In particular, the use of eq 12 to evaluate the intrinsic barrier ($\Delta G_0^{\ddagger}$) for each member within a series of carbon acids leads to a linear dependence of $\Delta G_0^{\ddagger}$ upon ΔG^0. Such a variable intrinsic barrier can be accommodated within the modified form of the Marcus relationship of eq 14, in which A (the "true" intrinsic barrier at $\Delta G^0 = 0$) and B are empirical parameters. Figure 2 demonstrates that $\Delta G_0^{\ddagger}$ is linear in ΔG^0 and thus that the modified form of eq 12 that is expressed in eq 14 is applicable to the current data for the deprotonation of **4** and **5** by hydroxide ion; the evaluated parameters A and B are listed in Table 5.

We designate[10] α_M as the Brønsted slope defined by the simple form of the Marcus relationship. Evaluation of α_M from eq 13 for **4** with X = H and for **5** with Y = H gives values of $\alpha_M = 0.46$ and 0.45, respectively, for these two series of carbon acids. It is thus clear that the variable intrinsic barriers of Figure 2 are responsible for the enhanced experimental $\alpha = 0.59$ for **4** and the depressed experimental $\alpha = 0.33$ for **5**. As discussed above, the depressed α-value for **5** is associated with a lag of the π-delocalization of electron density into the pyridinium ring in the transition-state species. In terms of **6A** and **6B**, any lag of delocalization into the pyridinium ring must be associated with the development of excess carbanionic character adjacent to the sulfonyl substituent. This excess carbanionic character is in turn expressed in terms of an enhanced $\alpha = 0.59$ in **4**. Thus the experimental α-values for **4** and **5**, which can each be considered[13] "anomalous" in terms of simple Marcus theory, can be understood in terms of the imbalanced electron density distributions which are present in the rate-determining transition-state species.

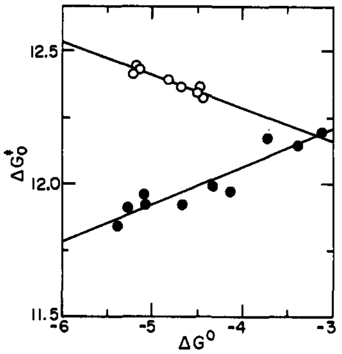

Figure 2. Variation of intrinsic barrier ($\Delta G_0^{\ddagger}$, kcal/mol) with free energy of reaction (ΔG^0, kcal/mol) for the deprotonation of **4** (filled circles) and **5** (open circles) by hydroxide ion.

Table 7. Influence of Structure upon Intrinsic Barrier (A) for Deprotonation[a]

1 and **4**	ΔA(ketone vs sulfone) = 2.87 kcal/mol
2 and **5**	ΔA(ketone vs sulfone) = 2.82 kcal/mol
1 and **2**	ΔA(N-methyl vs N-benzyl) = 0.90 kcal/mol
4 and **5**	ΔA(N-methyl vs N-benzyl) = 0.85 kcal/mol

[a] Calculated from data in Table 5.

Table 5 also includes the results of a similar analysis[10] of the data for the ketones **1** and **2** in terms of a variable intrinsic barrier of the form defined in eq 14. Structural effects upon the "true" intrinsic barriers (i.e. the A parameters) for the deprotonation of ketones and sulfones are summarized in Table 7. Note that similar differences are found in the A parameter for ketones and sulfones, irrespective of whether one probes substituent effects in the benzoyl unit of **1** and the phenylsulfonyl unit of **4** (ΔA = 2.87 kcal/mol) or alternatively between the substituted N-benzyl groups of **2** and **5** (ΔA = 2.82 kcal/mol). As mentioned above in connection with eqs 7 and 8, the similarity in these results, irrespective of which of two independent probes of substituent effects one uses, is rather remarkable. Treatment of ΔA = 2.85 kcal/mol as being equivalent to $\Delta\Delta G_0^{\ddagger}$ leads to $k_{OH}^{SO_2}/k_{OH}^{CO} = 120$ for the intrinsic reactivities of sulfones and ketones with hydroxide ion; a value of 80 for this ratio was deduced above from the direct comparison of the Brønsted relationships in eqs 7 and 8.

A similarly satisfying comparison of structural effects is found upon the intrinsic barrier for the deprotonation of N-methyl- and N-benzylpyridinium derivatives, irrespective of whether one compares ketones (for **1** and **2**, ΔA = 0.90 kcal/mol) or sulfones (for **4** and **5**, ΔA = 0.85 kcal/mol). This difference is equivalent to a 4-fold difference in the intrinsic reactivities of corresponding N-benzyl- and N-methylpyridinium-substituted carbon acids with hydroxide ion. As discussed below, we suggest that this greater reactivity of N-benzyl than of N-methyl species is associated with solvation phenomena in the vicinity of the pyridinium nitrogen atom.

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(30) Bunting, J. W.; Kanter, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 11705.

Table 8. Thermodynamic and Activation Parameters for Deprotonation of ((Phenylsulfonyl)methyl)pyridinium Cations[a]

$C_6H_5SO_2CH_2C_5H_4N^+R + {}^-OH \rightleftharpoons C_6H_5SO_2C^-HC_6H_4N^+R + H_2O$

	$R = CH_3$[b]	$R = CH_2C_6H_5$[c]	$\Delta\Delta S$
$\Delta H°$ (kcal/mol)	1.1	1.7	
$\Delta S°$ (cal/(deg mol))	+16.0	+20.5	+4.5
$\Delta H_d^{\ddagger}$ (kcal/mol)	5.7	4.8	
$\Delta S_d^{\ddagger}$ (cal/(deg mol))	−14.5	−17.8	−3.3
$\Delta H_p^{\ddagger}$ (kcal/mol)	4.6	3.1	
$\Delta S_p^{\ddagger}$ (cal/(deg mol))	−30.5	−38.3	−7.8

$(CH_3)_2NH^+R + {}^-OH \rightleftharpoons (CH_3)_2NR + H_2O$

	$R = CH_3$[d]	$R = CH_2C_6H_5$[e]	$\Delta\Delta S$
$\Delta H°$ (kcal/mol)	−4.5	−4.4	
$\Delta S°$ (cal/(deg mol))	+4.2	+7.9	+3.7

[a] Calculated from the data in Table 3, using $\Delta H° = -13.3$ kcal/mol and $\Delta S° = 19.3$ cal/(deg mol) for the ionization of water.[32] [b] Data for **4** with X = H. [c] Data for **5** with Y = H. [d] Data from ref 33. [e] Data from ref 15.

Note that the *B* parameters are negative for both the sulfones **5** and the ketones **2**, for which we have established a lag in electron density delocalization into the pyridinium ring in the transition-state species. The resonance contributors, **3C** and **6B**, indicate significant neutralization of the cationic charge on the pyridinium ring; such charge neutralization in turn implies the possibility of significant solvent reorganization in the vicinity of the formal cationic nitrogen atom of the pyridinium ring upon deprotonation. We suspect the need for such solvent reorganization is a major contributing factor to the lag in π-electron density delocalization into the pyridinium ring in the transition-state species.

Further insight into the probable importance of solvent reorganization in the vicinity of the pyridinium nitrogen atom can be obtained in the direct comparison of the parameters for the deprotonation of the *N*-methyl- and *N*-benzylpyridinium species. In particular, we note that ΔS^0 values for **4** with X = H and **5** with Y = H differ by a similar amount to the difference between ΔS^0 for the deprotonation of *N*-methyl- and *N*-benzylammonium cations (Table 8). The entropy terms for the deprotonation of ammonium ions are generally believed to be dominated by solvation phenomena.[31]

The dramatic differences between ΔS^0 and the activation energies for deprotonation ($\Delta S_d^{\ddagger}$) also imply a profound difference in the solvation of the transition-state species and the conjugate base product species. The different $\Delta\Delta S^0$ and $\Delta\Delta S_d^{\ddagger}$ values for *N*-benzyl relative to *N*-methyl cations also indicate that differences in the solvation of transition-state and product species are important in the vicinity of the pyridinium nitrogen atom.

Experimental Section

Materials. The synthesis and characterization of the pyridinium-substituted sulfones **4** and **5** are reported in our recent study[14] of the pK_a values of these species. Stock solutions of KOH and HCl were BDH prepared standard solutions (1 M or 0.1 M). Carbonate buffers (pK_a = 10.04[7]) were prepared by mixing appropriate volumes of stock solutions of sodium carbonate, sodium hydrogen carbonate, and potassium chloride (each ACS reagent grade). Amine buffer solutions were prepared by partial neutralization of an aqueous solution of the appropriate amine with standard HCl solution and the addition of an appropriate amount of KCl.

Kinetic Studies. All kinetic data were obtained in aqueous solutions of ionic strength 0.10 (KOH + KCl or buffer + KCl) on a Hi-Tech stopped-flow spectrophotometer thermostated at 25.0 °C except for the studies at other temperatures that are reported in Table 3. Reactant solutions were temperature-equilibrated in the mixing syringes for at least 15 min prior to each set of runs under each set of experimental conditions (pH, buffer concentration).

Studies of the deprotonation reactions involved the measurement of the rates of equilibration of each sulfone with its conjugate base by mixing equal volumes of a neutral aqueous solution of the substrate (0.06 mM) and a double-strength carbonate buffer or KOH solution (adjusted to ionic strength 0.2 with KCl). The time dependence of the absorbance due to the conjugate base species was monitored at λ_{max} in the electronic absorption spectrum of this species (350–360 nm).[14] All reactions were found to be accurately pseudo-first-order for >4 half-times. All pseudo-first-order rate constants (k_{obs}) under any one set of conditions were obtained as averages of at least six identical mixing experiments, in which the individual rate constants did not vary by more than 2%. The pH of each reaction solution was measured on a 1:1 mixture of the stock reactant solutions in a thermostated cell with a Radiometer PHM 82 pH meter (using a GK2401B combination electrode), which had been calibrated with BDH Colourkey 10 Buffer solution at the temperature of the experimental measurement.

Second-order rate constants for amine buffer species were evaluated by mixing solutions containing the conjugate base species (prepared by adjusting a neutral solution of the sulfone conjugate acid to pH 11.5) with amine/HCl buffers containing sufficient KCl to give ionic strength 0.2. The disappearance of the sulfone conjugate base as it was protonated to give the carbon acid was monitored at λ_{max}, and all other experimental details were as described above. Data were collected for five buffer concentrations in solutions having buffer ratio $[B]/[HB^+] = 1$.

pK_a Measurements. All pK_a values at 25 °C were reported in our earlier work.[14] Data at other temperatures (Table 3) were similarly obtained on a Perkin-Elmer Lambda 2 spectrometer with cell compartment thermostated at the temperature under study. All pH measurements were in a thermostated cell, with pH meter calibration at each temperature as described above.

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