Organic and Biological Chemistry

Base-Catalyzed Hydrogen–Deuterium Exchange of N-Substituted Pyridinium Ions. Inductive Effects and Internal Return[1]

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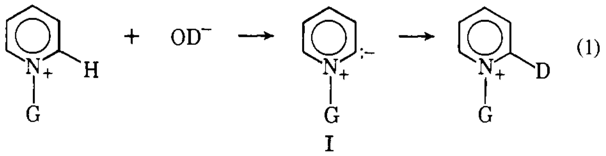
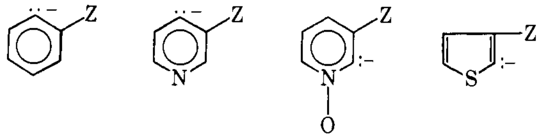
Abstract: Rates of hydrogen–deuterium exchange of N-substituted pyridinium ions in D_2O at 75.0° were obtained by the use of an nmr method. Deprotonation is catalyzed by deuteroxide ion. Catalysis by buffer bases is negligible. Relative rates of exchange for substituents O^-, $CH_2C_6H_5$, CH_3, C_6H_5, ND_2, and OCH_3 are 1.0, 1.1×10^2, 1.4×10^2, 5.3×10^2, 2.7×10^3, and 1.3×10^6, respectively. Rates show a good correlation with the Taft σ_I inductive parameter; ρ_I is 15. The substituent rate factor for positively charged nitrogen is estimated to be about 10^{14-16}. The absence of substantial buffer base catalysis for these reactions giving pyridinium ylide intermediates is consistent with internal return during exchange. Generalizations concerning the structure of carbon acids, general base catalysis, and internal return are given.

N-Alkylpyridinium ions[3–10] and pyridine *N*-oxides[8–13] undergo base-catalyzed hydrogen–deuterium exchange by simple deprotonation to give intermediates such as I (G = CH_3 and O^-). We report a study of the ability of substituents bonded to the nitrogen atom of pyridinium ions to influence the rates of pyridinium ylide formation (eq 1). This study, which provides the opportunity of determining the kinetic acidities of these aromatic carbon acids under mild conditions in water, shows that the rates of deprotonation of these acids linearly correlate with the Taft σ_I inductive parameter. Moreover, the deprotonation reactions are not significantly general base catalyzed, a result in keeping with a mechanism involving internal return.[14]



G = O^-, $CH_2C_6H_5$, CH_3, C_6H_5, ND_2, and OCH_3

Several examples of linear free energy correlations involving σ_I and rates of base-catalyzed hydrogen–deuterium exchange at annular positions of substituted aromatic or heteroaromatic rings now are available. These include exchange of monosubstituted benzenes,[15,16] pyridines,[17] pyridine *N*-oxides,[18,19] and thiophenes.[20] These correlations indicate that the inductive and not the resonance effects of substituents predominantly influence reactivity. The correlations provide further strong evidence that carbanions II–V are formed during hydrogen isotope exchange.



II III IV V

Results

Rates of deuteroxide ion-catalyzed hydrogen–deuterium exchange at the equivalent 2,6 positions of N-substituted pyridinium ions were obtained using nmr to follow the reactions. Under the conditions employed no other annular positions underwent detectable exchange. Each of the five substrates was studied at two or more pD values; in all instances exchange is first order in deuteroxide ion. The concentration of deuteroxide ion was obtained from the expression pOD = pK_W^D − pD where K_W^D is the dis-

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(2) (a) To whom correspondence should be addressed; (b) member of the 1969 National Science Foundation Summer Research Participation Program for College Teachers.

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(16) G. E. Hall, R. Piccolini, and J. D. Roberts, *J. Amer. Chem. Soc.*, 77, 4540 (1955); G. E. Hall, E. M. Libby, and E. L. James, *J. Org. Chem.*, **28**, 311 (1963).

(17) I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, and Yu. M. Kapustin, *Reakts. Sposobnost Org. Soedin.*, **5**, 601 (1968).

(18) I. F. Tupitsyn, N. N. Zatsepina, Yu. M. Kapustin, and A. V. Kirova, *ibid.*, **5**, 613 (1968).

(19) N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. J. Belashova, *ibid.*, **6**, 257 (1969).

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Table I. Rates of Hydrogen–Deuterium Exchange at the 2,6 Positions of N-Substituted Pyridinium Salts in D_2O at 75.0° and 1.0 Ionic Strength

Substituent	pD	$k\psi$, sec^{-1}	k_2, M^{-1} sec^{-1}	[DA], M^a	$[A^-]$, M^b
O^- [c]	10.74	2.10×10^{-6}	1.67×10^{-3}	0.020	0.18
	10.94	3.85×10^{-6}	1.50×10^{-3}	0.002	0.20
			Av $1.58 \pm 0.08 \times 10^{-3}$		
$CH_2C_6H_5$ [d]	10.26	9.17×10^{-5}	1.71×10^{-1}	0.010	0.11
	10.56	1.89×10^{-4}	1.77×10^{-1}	0.002	0.12
			Av $1.74 \pm 0.03 \times 10^{-1}$		
CH_3 [c]	10.06	1.10×10^{-4}	3.24×10^{-1}	0.060	0.14
	10.40	1.30×10^{-4}	1.75×10^{-1}	0.013	0.037
	10.49[e]	1.84×10^{-4}	1.99×10^{-1}	0.001	0.049
	10.50	1.54×10^{-4}	1.65×10^{-1}	0.040	0.16
	10.75	3.40×10^{-4}	2.05×10^{-1}	0.009	0.091
	10.76	4.28×10^{-4}	2.52×10^{-1}	0.020	0.18
			Av $2.20 \pm 0.51 \times 10^{-1}$		
C_6H_5 [d]	9.19	3.73×10^{-5}	8.16×10^{-1}	0.055	0.024
	9.79	1.54×10^{-4}	8.46×10^{-1}	0.039	0.059
	10.45	7.22×10^{-4}	8.69×10^{-1}	0.006	0.071
			Av $8.44 \pm 0.18 \times 10^{-1}$		
ND_2 [d]	8.86	8.90×10^{-5}	4.12	0.16	0.070
	9.17	1.92×10^{-4}	4.37	0.12	0.085
	9.32	2.82×10^{-4}	4.51	0.10	0.10
			Av 4.33		
OCH_3 [f]	6.08	7.91×10^{-5}	2.23×10^{3}	0.14	0.016
	6.82	3.61×10^{-4}	1.85×10^{3}	0.11	0.047
	7.21	9.63×10^{-4}	2.21×10^{3}	0.08	0.078
			Av $2.10 \pm 0.16 \times 10^{3}$		

[a] Buffer acid. [b] Buffer base. [c] $DCO_3^- - CO_3^{2-}$. [d] $D_3BO_3 - D_2BO_3^-$. [e] Perchlorate salt and sodium chloride electrolyte. Data of R. E. Cross. [f] $D_2PO_4^- - DPO_4^{2-}$.

sociation constant for deuterium oxide. The value of $pK_W^D = 13.526$ at 75.0° was calculated from recently reported data.[21] This pK_W^D value is uncorrected for salt effects which are expected to be small.[22] Although the value chosen for pK_W^D influences the absolute value of rate constants, it does not change their relative values.

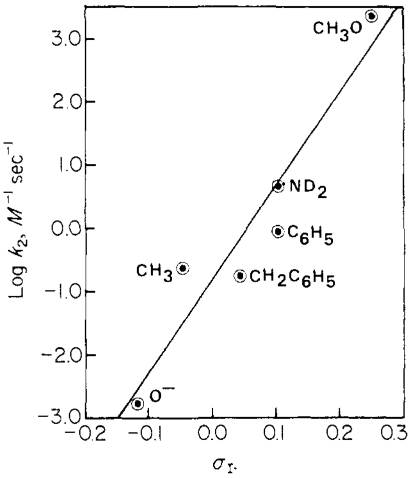

Figure 1. Linear free energy plot of the second-order rate constants for deuteroxide ion catalyzed hydrogen–deuterium exchange of N-substituted pyridinium ions *vs.* Taft's σ_I inductive constants. The 2,6 positions of substrate in deuterium oxide at 75.0° undergo exchange.

Results of the kinetic studies at 75.0° and 1.0 ionic strength are presented in Table I for pyridinium ions having as the N substituent O^-, $CH_2C_6H_5$, CH_3, C_6H_5, ND_2, and OCH_3. Note that any catalysis by buffer is marginal. This is seen from a comparison of the second-order rate constant k_2 with [DA] or $[A^-]$, the concentration of buffer acid or base. Moreover, undissociated water does not act as kinetically detectable base. The Brønsted β value for these reactions must therefore be ~1. Consequently, rates of deprotonation are described by eq 2 where $k\psi$ is the observed pseudo-first-order rate constant.

$$k\psi[NG^+] = k_2[OD^-][NG^+] \qquad (2)$$

That nitrogen substituents have a pronounced influence on reactivity is indicated by the following. Relative second-order rate constants for groups O^-, $CH_2C_6H_5$, CH_3, C_6H_5, ND_2, and OCH_3 are 1.0, 1.1×10^2, 1.4×10^2, 5.3×10^2, 2.7×10^3, and 1.3×10^6, respectively.

A correlation exists between log k_2 and the Taft inductive parameter σ_I.[23,24] This is shown in Figure 1. The least-squares slope ρ_I of this plot is 14.5 (r = 0.955)[25] with a standard deviation of 0.7.[26] Because σ_I values for some polar groups are solvent dependent, the value for oxide ion (−0.12) was obtained from a consideration of aqueous solution data.[23]

The methylated substrate deviates the most from the regression line in the Taft plot. Its reactivity appears to be higher than that expected from the plot.[27]

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(21) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, 70, 3820 (1966); G. S. Kell, *J. Chem. Eng. Data*, 12, 66 (1967).

(22) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, pp 639–643.

(23) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, 85, 709 (1963).

(24) M. Charton, *J. Org. Chem.*, 29, 1222 (1964).

(25) The correlation coefficient is symbolized by *r*.

(26) Statistics of a straight line were obtained by the methods given by W. J. Youden, "Statistical Methods for Chemists," Wiley, New York, N. Y., 1951, Chapter 5.

(27) Rates of H-2,6 exchange of *N*-methylpyridinium ion in water are independent of the anion. Both iodide and perchlorate salts were examined.[28]

(28) E. H. Gold, Ph.D. Thesis, Yale University, 1963.

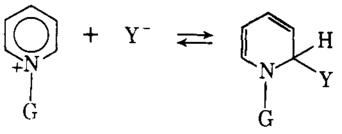
The methylated ion also is 27% more reactive than the benzylated ion. This order is contrary to that expected from the σ_I values for methyl and benzyl groups, -0.05 and 0.04, respectively. However, rate constants for these two ions actually overlap, considering the experimental uncertainty limits, which, at high pD, are essentially the uncertainty limits of the pD measurements (see Experimental Section).

An estimate of the reactivity of the parent pyridinium ion (G = D) is obtained from the plot at $\sigma_I = 0.00$. The value is 1.4×10^{-1} M^{-1} sec^{-1}. The standard deviation in log k_2 is 0.30.[26]

Since OCH_3 and OD have essentially the same σ_I values,[23] the reactivity of the *N*-methoxy- and *N*-deuterioxypyridinium ions are expected to be similar. Using our data for a comparison, *N*-deuterioxypyridinium ion is expected to be about 10^6 times more reactive than pyridine *N*-oxide, its conjugate base. This implies that, depending upon acidity, pyridine *N*-oxide can undergo hydrogen exchange at carbon either as the oxide form or as its conjugate acid. Such dual pathways for exchange have been demonstrated for pyridine and pyridinium ion.[29] Pyridine *N*-oxide should not have reacted at all as its conjugate acid in our studies. The *N*-oxide is too weakly basic (pK_a[30] at 24° is 0.8) to give kinetically significant quantities of its conjugate acid at pD 10–11. However, it should be possible to demonstrate hydrogen exchange of the conjugate acid of pyridine *N*-oxide by a carbanion mechanism by working at low pD. Temperatures >75° would be required for convenient rates.

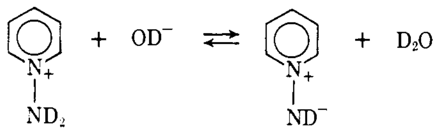
No appreciable degradation of substrate was detected during the kinetic runs using deuterium oxide and during control runs using proteo water. Moreover, substrate was recovered from these solutions and its identity verified. Note that ring opening, a possible side reaction leading to the destruction of substrate, is second order in base.[31,32] Hence such degradation is expected to be unimportant in the dilute alkaline solution employed in the deprotonation studies.

No evidence was found for the reversible formation of dihydropyridines by the addition of nucleophile Y^- to the pyridinium ion ring, eq 3.[33] If such intermediates were formed to a detectable degree, then the exchange rates could be less than first order in deuteroxide ion and the apparent order would decrease as the deuteroxide ion concentration increased. It is unlikely that dihydropyridines would undergo hydrogen exchange at the 2,6 positions under the basic conditions employed.[33]



(3)

In the case of the *N*-amino substrate there is another mechanism which is consistent with our data. This involves electrophilic aromatic substitution. Hydrogen exchange could take place between water and the ylide generated by ionization of the amino group ($pK_a = 13.5$[34]), eq 4. This possibility was eliminated using *N*-dimethylaminopyridinium iodide. This material which cannot ionize according to eq 4 undergoes hydrogen exchange at the 2,6 positions. Qualitatively, rates are similar to those for the *N*-amino substrate.



(4)

Discussion

Substituent Effects. The correlation between Taft's σ_I values and the rates of deuterioxide ion catalyzed hydrogen exchange at the 2,6 positions of N-substituted pyridinium ions (ρ_I = 15, 75°), Figure 1, provides additional strong evidence for the formation of pyridinium ylide intermediates I during hydrogen exchange. More importantly, these results indicate that substituents bonded to positively charged annular nitrogen exert inductive effects in the same way as substituents bonded to annular carbon and that the substituent effects are large.

The reactivity of the N-substituted pyridinium ions may be considered to be influenced both by the substituents on nitrogen and by the positively charged nitrogen atom itself. A measure of the activating effect of the positively charged nitrogen atom may be obtained from a comparison of the reactivity of pyridinium ion (G = D, eq 1) with benzene. Extrapolated values for methoxide ion catalyzed H–D exchange of benzene in methanol are 2×10^{-17} (40°)[35] and 6×10^{-15} (50°)[13] M^{-1} sec^{-1}. Neglecting temperature and solvent differences and using the value 1.4×10^{-1} M^{-1} sec^{-1} obtained for pyridinium-*N-d* ion from Figure 1, comparison indicates that the positively charged annular nitrogen atom activates an aromatic ring for deprotonation *via* ylide formation by an enormous factor of approximately 10^{14} to 10^{16}.

In spite of the very large activation by the positively charged nitrogen atom, substituents on this atom also exert a large influence on the rates of anion formation. The rate spread between substrates having O^- and OCH_3 substituents, the extremes of our study, is 1.3×10^6. Using pyridinium-*N-d* ion as a standard, it may be calculated that the oxide group deactivates by a factor of 88 while the benzyl, methyl, phenyl, amino, and methoxy groups activate by factors of 1.2, 1.6, 6.0, 31, and 1.5×10^4, respectively.[36] Except for the effect of a methyl group, these rate factors are similar to those found for H–D exchange reactions involving carbon centers of uncharged substrates.[15–20] For example, an *o*-phenyl group activates a benzene ring for deprotonation in NH_3 at $-33°$ by a factor of 4.7

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[29] J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3358 (1967).

[30] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, Washington, D. C., 1965, p 179.

[31] (a) A. R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965); (b) A. R. Katritzky and E. Lunt, *ibid.*, **25**, 4291 (1969).

[32] S. L. Johnson and K. A. Rumon, *Tetrahedron Lett.*, 1721 (1966).

[33] For a discussion of the factors influencing the addition of hydroxide ion to N-substituted benzopyridinium ions, see C. J. Cooksey and M. D. Johnson, *J. Chem. Soc. B*, 1191 (1968), and references cited therein.

[34] J. Epsztajn, E. Lunt, and A. R. Katritzky, *Tetrahedron*, **26**, 1665 (1970).

[35] A. Streitwieser, Jr., J. A. Hudson, and F. Mares, *J. Amer. Chem. Soc.*, **90**, 648 (1968).

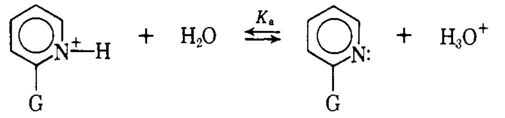
[36] Owing to the large uncertainty in the derived rate constant for pyridinium-*N-d* ion, the reference substrate, the magnitudes of substituent rate factors should only be regarded as illustrative.

and a methoxy group by a factor of 500 but a methyl group deactivates by a factor of 5;[15,16] for the benzene series $\rho_I = 11$.

The exchange rates in the pyridinium ion series are explicable in terms of a reaction involving the generation of a considerable amount of negative charge. Substituents have a large effect, essentially inductive in character, on the stability of this negative charge in transition and intermediate states. It seems likely that the substituents exert approximately a constant effect on the positive charge throughout the reaction.

The foregoing discussion of the effects of ortho substituents on the kinetic acidities of carbon centers can be placed in a larger context. The equilibrium acidities of annular nitrogen centers also are influenced primarily by the inductive effects of ortho substituents.

Consider the effects of ortho substituents on the acidity of pyridinium ions in water, eq 5. Reactions here also involve the σ electron framework and the effects of substituents also show a correlation with σ_I (ρ_I = 10.9 at 20°).[37] However, the correlation shows more scatter ($r^{25} = 0.893$) and the amino group deviates considerably.



(5)

The acidity data for pyridinium ions, eq 5, may be considered in terms of the extended Hammett equation (6) which separates the effects of substituents into their inductive ($\rho_I\sigma_I$) and resonance ($\rho_R\sigma_R{}^0$) components.[38,39]

$$\log K_G/K_H = \rho_I\sigma_I + \rho_R\sigma_R{}^0 \qquad (6)$$

This consideration reveals that an improved correlation results when a small contribution of a resonance effect of the groups is added to the analysis.[37] That is, although inductive effects are of primary importance, there is a small contribution of a resonance effect involving the substituents and the reactive center. This conclusion contrasts with that from our hydrogen exchange studies. Essentially no resonance effect involving the ortho substituents could be discerned. It is to be noted that the oxide and amino substituents have large resonance components ($\sigma_R{}^0 = -0.66$, $\sigma_I = -0.12$, $\sigma_R{}^0 = -0.48$, and $\sigma_I = +0.10$, respectively.[38]) If resonance were important in the H–D exchange series, these two substituents would reveal it.

A reasonably clear and consistent pattern of the effect of ortho substituents on the rates and equilibria of deprotonation of annular carbon and nitrogen acids has emerged. For deprotonation reactions involving the formation of essentially localized electron pairs on carbon and nitrogen which are part of the σ and not the π electron frame-work, inductive effects of adjacent substituents are of primary importance; resonance effects are small or are absent.[40]

There are some practical implications of our results which relate to the use of ylide intermediates in syntheses. When generating ylide intermediates for use in synthetic work it is customary to vary the nature of substituents bonded to the anionic center in order to achieve systems with the desired degree of stability. Generally, attempts to influence ylide stability by varying the nature of substituents bonded to the cationic center are not made.[42] In view of the large substituent effects we have observed, varying the nature of groups bonded to the cationic center may provide gratifying results in other ylide studies.

Internal Return and General-Base Catalysis. The H–D exchange reactions of the N-substituted pyridinium ions are catalyzed by deuteroxide ion. They are not significantly catalyzed by buffer bases. We will attempt to establish that this is consistent with internal return[14] and to explain why the deprotonation of other carbon acids may or may not be subject to general-base catalysis.

Rates of deprotonation of carbon acids in solvents which are considerably more acidic than the acids themselves are subject to the effects of internal return.[43] That is, the rate of back-protonation of the hydrogen-bonded carbanion (k_{-B}) may favorably compete with the rate of replacement of proton by deuteron from solvent at the carbanion site (k_H) (Scheme I). Rates of hydrogen exchange then are given by eq 7 and do not solely reflect rates of deprotonation.

Scheme I

$$\text{C–H} + \text{B} \underset{k_{-B}}{\overset{k_B}{\rightleftarrows}} \text{C}^- \cdots \text{HB} \xrightarrow[\text{DB}]{k_H} \text{C}^- \cdots \text{DB} \rightleftarrows \text{CD} + \text{B}$$

$$\text{rate} = k\psi[\text{C–H}] = \frac{k_B k_H[\text{C–H}][\text{B}]}{k_{-B} + k_H} \qquad (7)$$

The extent of buffer catalysis is related to the presence or absence of internal return in hydrogen exchange reactions. (1) If the exchange reaction clearly is general or buffer-base catalyzed and $0 < \beta < 1$, then proton transfer takes place in the rate-limiting step ($k_{-B} \ll k_H$) and there is no internal return. This means $k\psi = k_B[\text{B}]$ where B may be a variety of bases present in the reaction mixture. The rate of deprotonation of a given acid then is related to the basicity of B by the Brønsted equation, $\log k = \beta \text{p}K_A' + G$ where k is a second-order rate constant for deprotonation by B and K_A' is the acidity of the conjugate acid of B.[44,45] (2) When $\beta \sim 1$ buffer catalytic effects generally are small[46] and conclusions regarding the reaction mechanism, Scheme I, are less definite.[47] (a) Internal

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(37) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).

(38) (a) P. R. Wells, S. Ehrenson, and R. W. Taft, *Progr. Phys. Org. Chem.*, **6**, 147 (1968); (b) P. R. Wells, "Linear Free Energy Relationships," Academic Press, New York, N. Y., 1968.

(39) For a related treatment, see C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

(40) Relative rates of dehydrobromination of bromoarenes with lithium piperidide to give aryne intermediates also appear to be measures of relative rates of deprotonation. These kinetic acidity measurements show on a logarithmic scale a linear correlation with the (nitrogen) acidities of substituted pyridinium ions.[41]

(41) R. Huisgen in "Organometallic Chemistry," H. Zeiss, Ed., Reinhold, New York, N. Y., 1960, Chapter 2.

(42) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966.

(43) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).

(44) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(45) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter 3.

(46) R. P. Bell, "Acid-Base Catalysis," Oxford University Press, London, 1941, pp 93–95. It is important to note the assumption that hydroxide ion and other bases lie on the same, linear Brønsted correlation line.

(47) Even though $\beta \sim 1$, there are special instances where it is possible to demonstrate buffer base catalysis clearly. Hydroxide ion deviates negatively from the linear Brønsted relationship established by other bases.[48,49] It is possible that deprotonation of carbon acids by

return is not present. Mechanism 1 may be operating. This is an established interpretation. (b) As another possibility we suggest that internal return is present. When $k_B > k_H$ the rate-limiting step is separation of the hydrogen-bonded complex and this slow step is preceded by an equilibrium. The equilibrium concentration of hydrogen-bonded complex $C^- \cdots HB$ depends on the concentration and the basicity of B. As the concentration of this complex increases, the hydrogen exchange rate increases. Now, even though buffer base may be present in greater concentration than lyate ion, $B = OD^-$, the greater basicity of the lyate ion results in its kinetic dominance. While it is tempting to employ high concentrations of buffers to magnify effects, this is not without difficulties. Medium and salt changes can give rise to rate accelerations which appear to be the sought after effects.

Determining the magnitude of the hydrogen kinetic isotope effect provides one way to test for internal return. A large effect signifies the absence of internal return and a small effect indicates that internal return may be operating.[50,51] Note that small isotope effects are expected when $\beta \sim 1$.[53,54]

Whether the deprotonation of a carbon acid is subject to internal return is determined by k_H/k_{-B}, Scheme I. This ratio is likely to be influenced primarily by changes in k_{-B}. This rate constant will be very large when the proton removed from a carbon acid remains hydrogen bonded to the resulting carbanion and the formation of this anion requires little solvent and structural reorganization. If the charge is essentially localized on this carbanion and if there has been little restructuring of the solvent, then the energy barrier for reprotonation is almost negligible and the rate constant may be on the order of 10^{12} sec^{-1}.[43] Back-protonation then occurs much faster than the rate of replacement of HB by DB at the anionic site,[55] a process which must take place if hydrogen exchange is to result, Scheme I.

However, when a carbon acid on deprotonation gives a resonance-delocalized anion, then the rate of back-protonation of the carbanion may be reduced considerably.[43,57] In this case k_{-B} may be less than k_H. Such acids may show general base catalysis.

It follows, then, that along a series of structurally similar carbon acids of increasing acidity there should be a gradual change in k_H/k_{-B}. As this ratio increases there is a transition from internal return to rate-limiting transfer with no significant general base catalysis to hydrogen transfer with detectable general base catalysis.[58] When $\beta = 0$ deprotonation rates are independent of the identity of the bases; *i.e.*, hydrogen transfer occurs faster than the encounter rates.[43]

Deprotonation at annular carbon positions of a variety of heteroaromatic systems has been reported.[3–13,60,61] A mechanism of hydrogen exchange for these has reasonably been postulated in terms of simple deprotonation at carbon by base. In only a few cases where exchange has been carried out in aqueous solution has evidence been presented for buffer catalytic effects. The buffer effects are not large. While the substrates for which no buffer catalysis was reported may react by a mechanism involving rate-limiting proton transfer with an extreme β value, it seems more likely that these substrates giving largely localized anions do not show buffer base catalysis because internal return is operating.[62]

This situation contrasts with proton abstraction from other carbon acids,[64] including nitroalkanes,[67] and ketones.[44] For example, both nitroethane[67] and acetone[44] show significant buffer base catalysis and yet they are less reactive toward lyate ion than is *N*-methoxypyridinium ion. In other words, the rate of lyate ion catalyzed deprotonation of a carbon acid does not necessarily provide an indication of whether the substrate will show buffer catalysis.

We suggest that the rates of deprotonation of N-substituted pyridinium ions in water may be influenced by internal return. If this is so, then the linear free energy relationship found for the deprotonation of these pyridinium ions assumes added importance. The correlation shows not only the effects of substituents but also the effects of internal return on reactivity. Similarly, those substrates giving anions III–V in methanol probably also are subject to internal return. By contrast, the data on benzene compounds giving ion II in ammonia do not reflect internal return.

In the pyridinium ion series a comparison of the second-order constants for hydrogen exchange, k_2, then amounts to a comparison of the equilibrium constants for dissociation of these carbon acids along with a comparison of k_H, where $B = OD^-$, Scheme I. That is, $k_2^G/k_2^H = (K_A^G/K_A^H)(k_H^G/k_H^H)$, assuming

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hydroxide ion in water is not subject to internal return although internal return may operate for weaker bases.

(48) E. A. Walters and F. A. Long, *J. Amer. Chem. Soc.*, **91**, 3733 (1969).

(49) For examples involving oxygen reactive centers, see R. E. Barnett and W. P. Jencks, *ibid.*, **91**, 2358, 6758 (1969).

(50) A. Streitwieser, Jr., W. C. Langworthy, and D. E. VanSickle, *ibid.*, **84**, 251 (1962).

(51) Hydrogen exchange of *N*-methylpyridinium-*2-d(t)* iodide in methanol at 55° shows practically no kinetic isotope effect for catalysis by triethylamine.[52]

(52) N. N. Zatsepina, Yu. L. Kaminsky, and I. F. Tupitsyn, *Reakt. Sposobnost Org. Soedin*, 4, 177 (1967).

(53) R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, **294**, 273 (1966), and references cited therein.

(54) E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, **89**, 2322 (1967).

(55) By way of comparison, the first-order rate constant for cleavage of a hydrogen bond between water and an imidazole nitrogen atom is 1.8×10^9 sec^{-1} at 25°.[56] Notice that dissociation of the imidazolium ion is formulated in terms of an internal return mechanism.

(56) E. K. Ralph and E. Grunwald, *J. Amer. Chem. Soc.*, **91**, 2422, (1969).

(57) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953); M. E. Langmuir, L. Dogliotti, E. D. Black, and G. Wettermark, *ibid.*, **91**, 2204, (1969), and references cited therein.

(58) This view interrelates both interpretations given for the occurrence of low primary kinetic isotope effects in hydrogen exchange reactions.[14,59]

(59) J. R. Jones, *Chem. Commun.*, 710 (1967).

(60) A sampling of additional references includes T. M. Harris and J. C. Randall, *Chem. Ind. (London)*, 1728 (1965); R. A. Olofson and J. M. Landesberg, *J. Amer. Chem. Soc.*, **88**, 4263 (1966); W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, 33, 1087 (1968); P. Beak and E. McL. Monroe, *ibid.*, **34**, 589 (1969).

(61) P. Haake, L. P. Bausher, and W. B. Miller, *J. Amer. Chem. Soc.*, **91**, 1113 (1969); D. S. Kemp and J. T. O'Brien, *ibid.*, **92**, 2554 (1970).

(62) This situation is not unique to heteroaromatics. Acetylenes, for example, may fit this classification as well.[63]

(63) E. A. Halevi and F. A. Long, *J. Amer. Chem. Soc.*, **83**, 2809 (1961); C. Eaborn, G. A. Skinner, and D. R. M. Walton, *J. Chem. Soc. B*, 922, 989 (1966), and references cited therein.

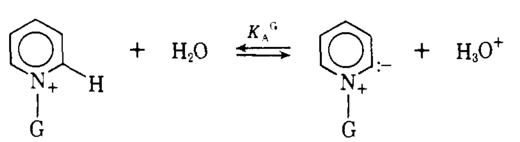
(64) Catalysis of H–D exchange by a variety of bases has been demonstrated for 1,3-dinitro-[65] and 1,3,5-trinitrobenzene[66] in 90% *N,N*-dimethylformamide–10% deuterium oxide. Notably, internal return was said to be absent.

(65) E. Buncel and A. W. Zabel, *J. Amer. Chem. Soc.*, **89**, 3082 (1967).

(66) E. Buncel and E. A. Symons, *Chem. Commun.*, 771 (1967).

(67) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967), and references cited therein.

$k_{-B} > k_H$.[68] Such dissociation in water has the form given by eq 8. If k_H is essentially constant for the



(8)

series,[35] then the hydrogen exchange rate constant ratio is the equilibrium acidity constant ratio.[69] A determination of K_A for one member of the series amounts to a determination of K_A for them all, an exciting prospect. However, an understanding of the importance of k_H for deprotonation reactions involving internal return must await future developments.[69a]

Experimental Section

Materials. Buffer solutions were prepared by mixing DCl (D_2O and concentrated HCl) or NaOD (D_2O and Na) with D_2O solutions of anhydrous, reagent grade Na_2CO_3, KH_2PO_4, or H_3PO_3. An estimate of the hydrogen content of these deuterated solvents was made before and after kinetic runs, using heterocyclic substrate as the internal standard. The amount of hydrogen was 1–4 mol %.

Pyridine *N*-oxide (Reilly Tar and Chemical Corp.) was vacuum distilled and stored under dry nitrogen. *N*-Phenylpyridinium chloride (mp 104–105°; lit.[70] mp 105–106°) was prepared from *N*-(2,4-dinitrophenyl)pyridinium chloride and aniline.[71] Alkylation of pyridine gave *N*-methylpyridinium iodide (mp 114–116°; lit.[72] mp 116–117°) and *N*-benzylpyridinium chloride[73]; pyridine *N*-oxide gave *N*-methoxylpyridinium methosulfate.[74] The benzyl and methoxy salts were more conveniently handled as their perchlorates; these were made by treating the salts with concentrated $HClO_4$[31a] (*N*-benzylpyridinium perchlorate, mp 88–89°, lit.[75] mp 89–92°; *N*-methoxypyridinium perchlorate, mp 70–71°, lit.[31a] mp 69–70°). *N*-Aminopyridinium iodide was prepared using hydroxylamino-*O*-sulfonic acid (mp 161–163°, lit.[76] mp 160–162°).

***N*-Dimethylaminopyridinium Iodide.** The purple solution obtained by adding 10 ml of methyl iodide and 2 g of sodium carbonate to 1.29 g of 1-aminopyridinium iodide in 10 ml of ethanol turned yellow on refluxing for 20 hr. The beige solid obtained by filtering and evaporating the solution to dryness under reduced pressure was recrystallized from ethanol–ethyl acetate to yield 0.958 g (66%) of slightly yellow hydroscopic needles, mp 121–123°. The expected 6 H singlet of the methyl groups is at τ 6.88 (D_2O).

Anal. Calcd for $C_7H_{11}N_2I$: C, 33.62; H, 4.43; N, 11.20. Found: C, 33.82; H, 4.46; N, 11.07.

Control Experiments. Using proteo buffers, each compound was subjected to the same reaction conditions employed in the hydrogen-exchange kinetic studies. No decomposition was detected by nmr after heating for a period corresponding to 5–10 half-lives for hydrogen exchange. Substrates were recovered from control or kinetic runs and compared with starting materials. No evidence for degradation was found. No attempt was made to recover *N*-phenylpyridinium chloride.

In order to determine whether deuterium oxide might deprotonate *N*-methoxypyridinium perchlorate, this substrate was heated in 0.03 *M* DCl at 75° for 795 min. No hydrogen exchange was detected.

Kinetic Procedure. Pyridine *N*-oxide or pyridinium salt was weighed into a 1-ml volumetric flask; buffer solution and 1.3 *M* KCl were added by syringe. After diluting to the mark with D_2O, substrate concentration was 0.2–0.5 *M* and the ionic strength was 1.0. Samples in sealed nmr tubes were placed in a constant-temperature bath set at 75.0° using a National Bureau of Standards certified thermometer. The tube was removed periodically and the reaction quenched using a cold water bath. Reactions were followed for 2–3 half-lives. Rate constants for exchange at H-2,6 were obtained in the usual way from plots of log [H-2,6]/[H-3,5] *vs.* time.[13] H-3,5 served as the nmr reference standard. No correction for approach to equilibrium hydrogen exchange was necessary, owing to the low concentration of hydrogen isotope present in mixtures. Note that rate constants reflect reactivity of a single position in the substrate.

Following a kinetic run, pD measurements were made on the reaction mixture at 75° according to the method of Bates[77] using a Beckman 1019 research pH meter and a Sargent miniature combination electrode (S-30070-10). Reproducibility of pD (pH meter reading +0.40) was ±0.02, except at the highest pD values.[78] An average of seven determinations on a carbonate buffer gave 10.28 with a standard deviation of 0.13, for example.[79] The Jena U glass electrode has no important alkaline error in the pD region employed here.[77] Using an established method,[80] it was determined that the factor necessary to convert the operational pH of buffer solutions in heavy water at 30° into pD values was essentially the same at 75°. A decrease of 0.06 pD unit was found at the higher temperature.[79]

Some hydrogen exchange was observed at the benzyl group (saturated carbon) of *N*-benzylpyridinium ion; the methyl group of *N*-methylpyridinium ion was unreactive.

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(68) $k_B/k_{-B} = K_A^G/K_W$.

(69) The converse comparison has long been known. For example, the protonation of many oxygen and nitrogen species by proton proceeds at diffusion controlled rates in water. A comparison of the dissociation constants of the conjugate acids of these anions is also a comparison of their rates of deprotonation by water.[43]

(69a) NOTE ADDED IN PROOF. Professor Marvin Charton has kindly computer analyzed our data using the extended Hammett equation of the form $\log k = \rho_I\sigma_I + \rho_R\sigma_R + \log k_H$. The following σ_R values were employed: O^-, −0.90; $CH_2C_6H_5$, −0.14; CH_3, −0.12; C_6H_5, −0.11; ND_2, −0.76; and OCH_3, −0.52. Results (standard errors) are: ρ_I = 14.84 (2.74), ρ_R = −0.07 (1.01), and $\log k_H$ = −0.88 (0.57). The standard error of the estimate is 0.789 and the *F* test for significance of the regression is 14.8 (95% confidence level). These results show that a resonance effect is not significant.

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