Kinetics and Mechanism of Hydrogen–Deuterium Exchange in the Methyl Groups of Pyridines in Dilute Aqueous Acid. Factors Influencing the Degree of Catalysis

John A. Zoltewicz* and Paul E. Kandetzki[1]

Contribution from the Department of Chemistry, University of Florida, Gainesville, Florida 32601. *Received February 1, 1971*

Abstract: Rates of hydrogen–deuterium exchange in the methyl groups of 2-methyl- (II), 2,6-dimethyl- (III), and 2,6-dimethyl-4-aminopyridine (IV) in D_2O and D_2O–DCl at 164.6° were obtained by an nmr method. Substrates acted as buffers to control solution acidity. Evidence is presented for a mechanism involving specific acid–general base catalysis (kinetically equivalent to general acid catalysis). The conjugate acid of substrate is deprotonated at carbon by base. Exchange reactions of II and III are catalyzed by substrate acting as a base and by deuteroxide ion but IV shows deuteroxide ion catalysis only. A discussion of the factors influencing the relative amounts of substrate (general base) and deuteroxide ion catalysis is presented.

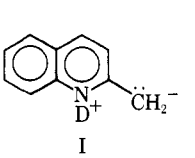
Hydrogen–deuterium exchange in the *C*-alkyl side chains of quaternized and unquaternized nitrogen-containing heterocycles has been investigated extensively.[2] Studies generally focus on base-catalyzed H–D exchange; by comparison, investigation of acid-catalyzed H–D exchange is uncommon. There are instances where the mechanism of hydrogen exchange under acidic conditions has not been established with certainty.

A good example of uncertainty in interpretation of H–D exchange results is found with 2-methylquinoline. A Russian group observed that H–D exchange in the methyl group of this molecule takes place in ethanol-*O*-*d* and in acidified ethanol-*O*-*d*. The addition of 0.5 or less of an equivalent of DCl resulted in a rate acceleration. But in the presence of more acid the rate decreased.[3] Although a mechanism was not clearly specified, it was suggested that the conjugate acid of substrate undergoes reaction when acid is present and that a hydrogen-bonded form of the free base is involved when no acid is added. Solvent and 2-methylquinoline were said to act as catalyzing bases.[3]

However, the results for 2-methylquinoline have been interpreted in terms of a mechanism involving the formation of ion pairs consisting of the conjugate acid of substrate and alkoxide (lyate) ion in equilibrium with substrate and solvent. The equilibrium step is followed by deprotonation of the carbon acid by lyate ion to give dipolar intermediate I. This intermediate on reacting with solvent gives rise to a hydrogen exchange product.[4]

The attractive feature of this second proposal is that substrate is activated by conversion to its conjugate acid, even when no acid is added. However, this mechanism does not account for the observed rate dependence on acidity.[3] Added acid can only retard the rate of the reaction.

We have determined the mechanism of H–D exchange in methyl groups of 2-methyl- (II), 2,6-dimethyl- (III), and 2,6-dimethyl-4-aminopyridine (IV). Hydrogen exchange was studied using D_2O and D_2O–DCl as solvents. In the case of II and III the kinetic effects of added acid are like those observed for 2-methylquinoline. However, added DCl only retards the rate of exchange of IV. Our results show that the conjugate acid of these substrates reacts even when no acid is added to reaction mixtures. Hydrogen exchange of II and III is catalyzed by deuteroxide (lyate) ion and also by substrate acting as a general base. Exchange of IV is catalyzed by deuteroxide ion but not by the free base form of the substrate. Our conclusions concerning the mechanism of exchange and the factors influencing the type of catalysis are likely to hold for many substrates, including nonheterocyclic systems.



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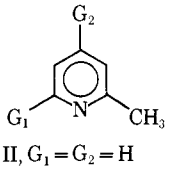


II, $G_1 = G_2 = H$
III, $G_1 = CH_3$; $G_2 = H$
IV, $G_1 = CH_3$; $G_2 = NH_2$

Results and Discussion

H–D exchange of II–IV takes place at convenient rates at 164.6 ± 0.5° in D_2O and in D_2O–DCl. Pseudo-first-order rate constants, $k\psi$, were obtained using a

(1) Taken in part from the M.S. Thesis of P. E. K., University of Florida, Gainesville, Fla., 1971.

(2) Y. Kawazoe, Y. Yoshioka, M. Yamada, and H. Igeta, *Chem. Pharm. Bull.*, **15**, 2000 (1967); Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *ibid.*, **15**, 1225 (1967); J. A. White and R. C. Anderson, *J. Heterocycl. Chem.*, **6**, 199 (1969); H. C. Brown and G. J. McDonald, *J. Amer. Chem. Soc.*, **88**, 2514 (1966); W. G. Cole, D. H. Williams, and A. N. H. Yeo, *J. Chem. Soc. B*, 1284 (1968); H. Erlenmeyer, H. M. Weber, and P. Wiessmer, *Helv. Chim. Acta*, 21, 1017 (1938); T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc. B*, 171 (1967); Sr. A. I. Gallagher, B. A. Lalinsky, and C. M. Kuper, *J. Org. Chem.*, **35**, 1176 (1970); T. Patterson and H. C. S. Wood, *Chem. Commun.*, 290 (1969); N. N. Zatsepina, I. F. Tupitsyn, A. W. Kirova, and A. J. Belashova, *Reakts. Sposobnost Org. Soedin*, **6**, 257 (1969); I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, and Yu. M. Kapustin, *ibid.*, **5**, 806 (1968); N. N. Zatsepina, I. F. Tupitsyn, Yu. L. Kaminskii, and N. S. Kolodina, *ibid.*, **6**, 766 (1969); N. N. Zatsepina, A. V. Kirova, and I. F. Tuputsyn, *ibid.*, **5**, 70 (1968); N. N. Zatsepina, Yu. L. Kaminskii, and I. F. Tuputsyn, *ibid.*, **4**, 433 (1967); N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *Dokl. Akad. Nauk SSSR*, **154**, 148 (1964); *Zh. Obshch. Khim.*, **33**, 2705 (1963); **34**, 4065, 4072 (1964); J. M. McAndless and R. Stewart, *Can. J. Chem.*, **48**, 263 (1970); T. Paterson and H. C. S. Wood, *Chem. Commun.*, 290 (1969); T. I. Abramovich, I. P. Gragerov, and V. V. Perekalin, *Dokl. Akad. Nauk SSSR*, **121**, 295 (1958); W. N. White and D. Lazdins, *J. Org. Chem.*, **34**, 2756 (1969); M. S. Kharasch, W. G. Brown, and J. McNab, *J. Org. Chem.*, **2**, 36 (1937).

(3) A. I. Shatenshtein and E. N. Zuyagintseva, *Dokl. Akad. Nauk SSSR*, 117, 852 (1957); A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, 1, 169 (1963); A. I. Shatenshtein, *Kinet. Catal. (USSR)*, 8, 907 (1967).

(4) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, pp 62–63.

standard nmr method.[5] Because it is not convenient to measure pD at the high temperature employed, the substrate was also employed as buffer. Changes in the ratio of the concentration of substrate, B, and its conjugate acid, BD^+, provide known and reproducible changes in solution acidity.[6] Equation 1 relates the ratio $[BD^+]/[B]$ to $[D^+]$ by means of the dissociation constant, K_a, of the nitrogen acid. In this way the problem of measuring and varying solution acidity at high temperatures is easily solved.

$$[D^+]/K_a = [BD^+]/[B] \quad (1)$$

Secondary hydrogen isotope effects which can give rise to curved kinetic plots[7] were not observed. Plots were linear over 2–4 half-lives. This probably results because isotope effects decrease in magnitude with increasing temperature.[8]

2-Methylpyridine. In order to determine whether B or BD^+ undergoes H–D exchange and to determine whether B and OD^- catalyze the reaction, serial dilution experiments were carried out. The buffer (substrate) ratio was held constant while varying the total buffer concentration. Under these conditions the concentration of OD^- is constant but the concentrations of B and BD^+ vary. That the exchange reaction is sensitive to the buffer concentration is seen in Figure 1; the fractional amount of conjugate acid is 0.621 (line A) and 0.250 (line B). The positive slope of the line indicates buffer catalysis by B and/or BD^+.

These results allow a distinction to be made among three different mechanisms of H–D exchange, (i) BD^+ reacting with BD^+, (ii) B reacting with B, and (iii) BD^+ reacting with B. A choice can be made by considering the slopes of the serial dilution plots and the expressions for the pseudo-first-order rate constants for the three possibilities, eq 2–4, respectively. The quantity in brackets in these equations represents the slope of a plot of $k\psi$ *vs.* $[BD^+]$.

$$k\psi = \left[\frac{k_i[BD^+]}{[B] + [BD^+]}\right] \times [BD^+] \quad (2)$$

$$k\psi = \left[\frac{k_{ii}[B]^2}{[BD^+]([B] + [BD^+])}\right] \times [BD^+] \quad (3)$$

$$k\psi = \left[\frac{k_B[B]}{[B] + [BD^+]}\right] \times [BD^+] \quad (4)$$

When the fractional amount of conjugate acid of substrate decreased from 0.621 to 0.250, the slopes of the plots in Figure 1 increased from $1.68 \times 10^{-3}\ M^{-1}\ sec^{-1}$ to $3.30 \times 10^{-3}\ M^{-1}\ sec^{-1}$, a factor 1.96. This eliminates the first possible mechanism which requires that slopes should decrease when the fractional amount of conjugate acid decreases. This mechanism involving reaction of BD^+ with BD^+ is also unlikely on purely chemical grounds. The second possibility does require the slope to increase, but by a factor of 9.74 ((3.00 × 0.750)/(0.379 × 0.610)), a significantly larger increase

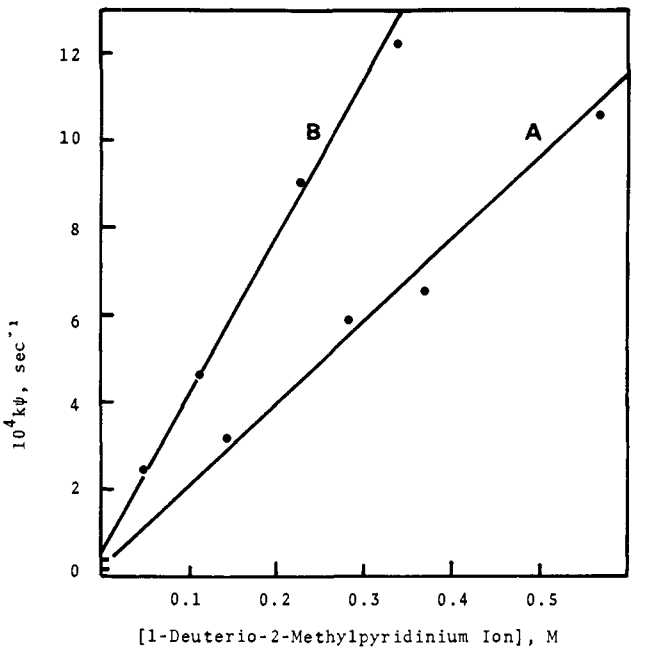
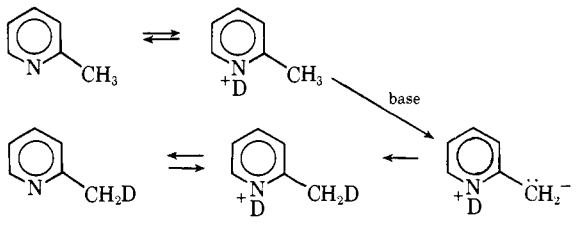


Figure 1. Plots of the pseudo-first-order rate constants for hydrogen–deuterium exchange in the methyl group of 2-methylpyridine *vs.* the concentration of conjugate acid of the substrate in D_2O at 164.6°. The ratio of added DCl to the total concentration of substrate is 0.621 (A) and 0.250 (B). The ionic strength is 0.625. Points at "zero" concentration of conjugate acid were calculated from kinetic runs in which no acid was added, see text.

than observed. The third mechanism requires an increase in the slope by a factor of 1.98 (0.750/0.379), a result in agreement with the observed increase of 1.96. Thus, the results of the serial dilution experiments establish an H–D exchange mechanism involving BD^+ reactign with B. This is likely to involve the deprotonation at carbon of the *N*-deuteriopyridinium ion by the pyridine acting as a general base catalyst to give a dipolar intermediate[9] which in a subsequent fast step incorporates deuterium, Scheme I. The value of k_B, the second-

Scheme I



order rate constant for the general base-catalyzed reaction, is $4.9 \times 10^{-3}\ M^{-1}\ sec^{-1}$.

A close examination of Figure 1 discloses that the serial dilution plots have nonzero intercepts. This indicates there is a small amount of catalysis by some other base, water and deuteroxide ion being possibilities.

The possibility of significant catalysis by D_2O acting as a general base was examined. The rate of H–D exchange was determined in the presence of excess DCl, *i.e.*, the mixture was 0.113 *M* in DCl after neutralizing II. Under these conditions the reaction of BD^+ with B is very slow and any important kinetic contribution by

(5) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969); J. A. Zoltewicz and L. S. Helmick, *ibid.*, **92**, 7547 (1970); J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(6) Changes in [B] and $[BD^+]$ by dissociation or hydrolysis are negligible for the substrates and concentrations employed.

(7) M. Bender and A. Williams, *J. Amer. Chem. Soc.*, **88**, 2502 (1966); A. Streitwieser, Jr., and D. E. Van Sickle, *ibid.*, **84**, 254 (1962).

(8) L. Melander, "Isotope Effects on Reaction Rates," The Ronald Press Co., New York, N. Y., 1960, pp 44–45.

(9) The dipolar intermediate has been named pyridone methide[10] and pyridiomethylide.[11]

(10) O. Mumm and G. Hingst, *Chem. Ber.*, **56**, 2301 (1923).

(11) D. Dodd and M. D. Johnson, *J. Chem. Soc. B*, 1337 (1970).

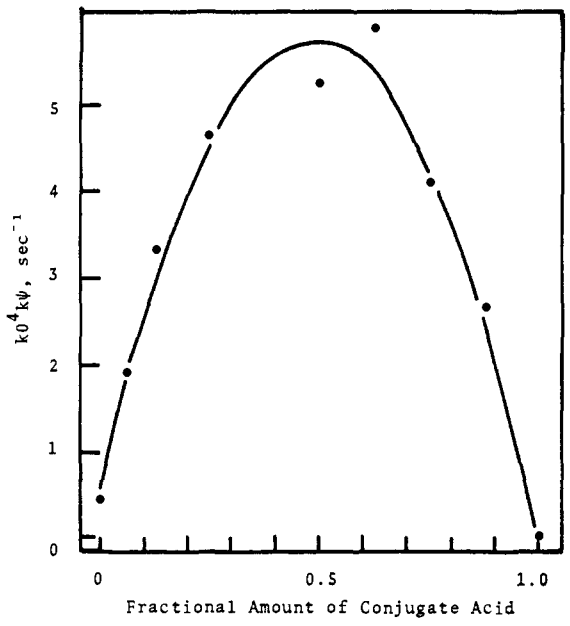


Figure 2. Plot of the pseudo-first-order rate constants for hydrogen–deuterium exchange in the methyl group of 2-methylpyridine *vs.* the fractional amount of the conjugate acid of the substrate. The total substrate concentration is 0.449 *M;* the ionic strength is 0.625. Points are experimental values and the solid line was calculated using eq 6 and the rate constants in the text.

D_2O can be determined. The value of $k\psi$ (1.3×10^{-6} sec^{-1}) is more than 10^2 times smaller than values obtained in the serial dilution studies and indicates that catalysis by D_2O in the serial dilution experiments is negligible.

In order to determine whether the H–D exchange reaction is catalyzed by OD^-, reactions were carried out in D_2O free of DCl. Under these conditions the fractional amount of substrate existing as the free base is $\sim$1. Or, in the absence of added DCl $[BD^+]/([BD^+] + [B])$ is $\sim 10^{-4}$, assuming that the pK_a for II is 4.3[12,13] and the pK_w is 11.5[16] at 165°. Duplicate experiments gave $k\psi$ values of 4.4 and 4.7 $\times 10^{-5}$ sec^{-1}, indicating that exchange does take place and that the rate is decreased in the absence of added DCl. This suggests that BD^+ does react with OD^- and that the expression for $k\psi$ must be expanded, eq 5. For subsequent discussions

$$k\psi = \frac{k_B[BD^+][B]}{[BD^+] + [B]} + \frac{k_{OD}[BD^+][OD^-]}{[BD^+] + [B]} \quad (5)$$

it is convenient to change eq 5 to its equivalent, eq 6, where the concentration of deuteroxide ion is eliminated and the only concentration terms are due to B and BD^+, readily determinable quantities. When no DCl is present, $k\psi = k_{OD}K_w/K_a$ because of the low concentration of BD^+.

$$k\psi = \frac{k_B[BD^+][B]}{[BD^+] + [B]} + \frac{k_{OD}K_w[B]}{K_a([BD^+] + [B])} \quad (6)$$

(12) R. J. L. Andon, J. D. Cox, and E. F. G. Herington, *Trans. Faraday Soc.*, 50, 918 (1954); C. T. Mortimer and K. J. Laidler, *ibid.*, 55, 1731 (1959).

(13) The estimated pK_a value at 165° is for proteo solutions. The value is expected to differ only slightly for deutero solutions.[14,15]

(14) I. R. Bellobono and P. Beltrame, *J. Chem. Soc. B*, 620 (1969).

(15) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, 70, 3820 (1966).

(16) R. E. Mesmer, C. F. Baes, Jr., and F. H. Sweeton, *ibid.*, 74, 1937 (1970).

The intercept points for the plot in Figure 1 were calculated using the results obtained from runs not employing DCl. The rate constant $k\psi = k_{OD}K_w/K_a$ obtained from these runs was corrected by the fraction $[B]/([BD^+] + [B])$ before addition to the plot. Under the conditions of the serial dilution experiments this fraction is less than one.

Additional experimental verification for catalysis by B and OD^- was obtained from a series of experiments in which the total amount of substrate is held constant while the ratio of B to BD^+ is varied. Equation 6 predicts that under these conditions a "bell-shaped" curve should result. A rate maximum occurs when $[B] = [BD^+]$ and an increasing contribution by deuteroxide ion catalysis results as [B] increases. A plot of $k\psi$ *vs.* the fractional amount of conjugate acid of substrate with the total concentration of substrate held at 0.449 *M* is shown in Figure 2. The predicted "bell" curve (solid line) was calculated using eq 6 and values of 4.9×10^{-3} M^{-1} sec^{-1} and 5.2×10^{-5} sec^{-1} for k_B and $k_{OD}K_w/K_a$, respectively. There is good agreement between the observed and predicted curves. Note that substantial catalysis by OD^- does result in the more basic solutions. For example, the $k\psi$ value associated with 6.3% acidified substrate is composed of 31% OD^- catalysis and 69% B catalysis.

A test of the proposed mechanism was made by determining whether all the data could be made to fit one plot as required by eq 6. When eq 6 is multiplied by $([BD^+] + [B])/[B]$ an equation for a straight line results. Thus, when $k\psi([BD^+] + [B])/[B]$ was plotted against $[BD^+]$ a straight line (not shown) was obtained; the slope is $k_B = 4.9 \times 10^{-3}$ M^{-1} sec^{-1} and the intercept $k_{OD} \cdot K_w/K_a = 5.0 \times 10^{-5}$ sec^{-1}. Note that while the same k_B value is obtained by treating the data in several ways, slightly different $k_{OD}K_w/K_a$ values result. The average is $4.8 \pm 0.3 \times 10^{-5}$ sec^{-1}.

The mechanism of H–D exchange of II therefore involves deprotonation of BD^+ by B and OD^-. It is an example of a specific acid–general base (general acid) catalyzed reaction.

The rate dependence on acidity of H–D exchange of II in water is similar to that reported for hydrogen exchange of 2-methylquinoline in ethanol.[3] This similar behavior indicates that both compounds react by the same kind of mechanism.

2,6-Dimethylpyridine. Similar but less extensive H–D exchange experiments were carried out on III. A serial dilution study indicated exchange is catalyzed by the buffer (substrate). Exchange was observed also when no DCl was added to D_2O mixtures. It was assumed that the mechanism operating in the case of II also holds for III. A plot of $k\psi([BD^+] + [B])/[B]$ *vs.* $[BD^+]$ is given in Figure 3; $k_B = 2.7 \times 10^{-3}$ M^{-1} sec^{-1} and intercept $k_{OD}K_w/K_a = 8.8 \times 10^{-5}$ sec^{-1}. The k_B value for III is 44% smaller than the value for II but the $k_{OD}K_w/K_a$ is 83% greater. The second methyl group has only a small effect on reactivity.

2,6-Dimethyl-4-aminopyridine.[17] H–D exchange kinetic results for IV are substantially different from

(17) 4-Aminopyridines are known to react with acids predominantly at the annular nitrogen atom and not the amino group.[18]

(18) A. R. Katritzky and J. M. Lagowski, "The Principles of Heterocyclic Chemistry," Academic Press, New York, N. Y., 1968, p 65; K. Schofield, "Hetero-Aromatic Nitrogen Compounds. Pyrroles and Pyridines," Plenum Press, New York, N. Y., 1967, pp 145–159.

those for II and III. Serial dilution experiments where $[BD^+]/([BD^+] + [B]) = 0.620$ indicate there is no detectable buffer (substrate) catalysis, Table I. Hydrogen exchange does take place in the absence of DCl and the addition of DCl does result in a rate retardation. These observations suggest that a reaction of BD^+ with B is unimportant under the conditions employed and that a reaction of BD^+ with OD^- does take place; $k\psi$ is given by eq 7. Note that the product $k\psi(([BD^+] +$

$$k\psi = \frac{k_{OD}K_w[B]}{K_a([BD^+] + [B])} \quad (7)$$

$[B])/[B])$ is satisfactorily constant, Table I. The value of $k_{OD}K_w/K_a$ for IV, 7.2×10^{-4} sec^{-1}, is 8.2 times greater than a similar term for III. A "bell-shaped" rate profile does not result for IV.

Table I. Conditions and Results of Hydrogen-Deuterium Exchange in the Methyl Groups of 2,6-Dimethyl-4-aminopyridine in D_2O-DCl[a,b]

M, $[BD^+] + [B]$	$\frac{[BD]^+}{[BD^+] + [B]}$	$10^4k\psi$, sec^{-1}	$10^4k\psi\left(\frac{[BD^+] + [B]}{[B]}\right)$
0.234	0.822	1.47	8.3
0.362	0.620	2.80	7.4
0.226	0.620	2.58	6.8
0.091	0.620	2.57	6.8
0.181	0.400	4.77	8.0
0.111	c	7.10	7.1
			Av 7.4 ± 0.5

[a] 164.6 ± 0.5°; 0.625 ionic strength. [b] All concentrations corrected for thermal expansion. [c] No acid added. Conjugate acid of substrate results from hydrolysis. Fractional amount of substrate in the conjugate acid form is estimated to be ~0.04.

Comparison of Rate Constants. The $k_{OD}K_w/K_a$ term for IV is only about ten times larger than a similar term for II and III, in spite of IV being 10^{2-3} times more basic, Table II. This means that the k_{OD} value for IV must be 10^{1-2} times smaller than that for II and III. In other words, the conjugate acid of IV is a weaker carbon acid than similar forms of II and III. A similar comparison of II and III indicates that k_{OD} for III is about five times less than k_{OD} for II.

Although no buffer catalyses were detected for IV, it is possible to derive an upper limit for k_B. If it is assumed that the data in Table I do show catalyses by B, then the second run shows it to the maximum degree.[19] The ratio from eq 6, $k_B[BD^+]/(k_{OD}K_w/K_a)$, which compares catalysis by B and OD^- is at its maximum. If it is assumed that as much as 10% catalysis by B is present in this run, then k_B is about 2×10^{-4} M^{-1} sec^{-1}.[20] This derived value is smaller than k_B values for II and III, Table II, in spite of the high basicity of IV. A similar result obtains in a comparison of II and III where k_B for III is 1.8 times smaller in spite of III being more basic.

(19) Solubility problems prevented the use of more concentrated solutions of IV.

(20) A k_B value for IV may be estimated using the rate and equilibrium constants given in Table II.[21] If $\beta = 0.6$ and the dissociation constant for water is $10^{-13.2}$ M,[16] then $k_B = 2 \times 10^{-3}$ M^{-1} sec^{-1}. This value is similar to those for II and III and is larger than the k_B value estimated from the data in Table I. This suggests that pK_a and/or β values are larger for IV.

(21) It should be recognized that the dissociation constant $10^{-13.2}$ M for water is used in the Brønsted calculations but that the ion product $10^{-11.5}$ is employed in eq 6.

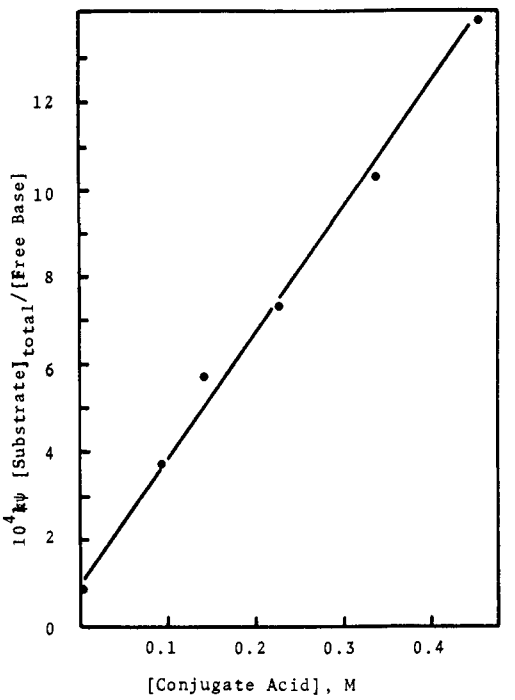


Figure 3. Plot of the product of the pseudo-first-order rate constants for hydrogen-deuterium exchange in the methyl groups of 2,6-dimethylpyridine and the inverse of the fractional amount of substrate in the free base form *vs.* the concentration of the conjugate acid of the substrate. The ionic strength is 0.785.

The decrease in k_B and k_{OD} values for IV relative to values for II and III must be associated with the strong electron-donating property of the amino group. This group must destabilize the negative charge developing in a transition state leading to carbon deprotonation.

Table II. Summary of pK_a Values and Rate Constants for Hydrogen-Deuterium Exchange of Methylated Pyridines[a]

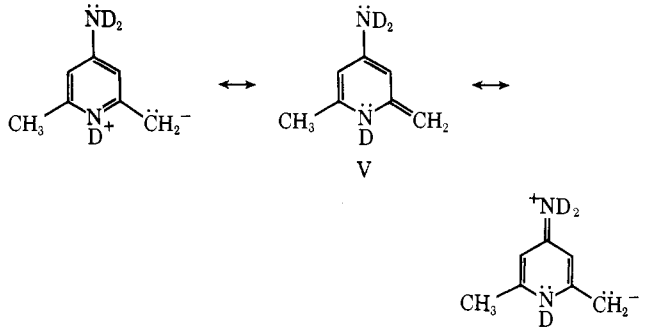
Pyridine	pK_a (25°)	pK_a (165°)	10^5k_B, M^{-1} sec^{-1}	$10^5k_{OD}K_w/K_a$, sec^{-1}
II	5.96[b]	4.3[b]	490	4.8
III	6.72[b]	5.3[b]	270	8.8
IV	10.3	7.6[c]		72

[a] pK_a values are for proteo water. No correction has been applied to obtain values for deuterium oxide. [b] From ref 12. [c] Estimated using $\Delta H = 11.27$ kcal/mol, the value for 4-aminopyridine given by R. G. Bates and H. B. Hetzer, *J. Res. Nat. Bur. Stand., Sect. A*, **64**, 427 (1960).

Although the amino group increases the basicity of the annular nitrogen atom and this effect alone is expected to increase k_B, the effect on the carbon center is greater. Resonance structures V point out the conjugation between the amino group and nitrogen and carbon centers in the conjugate base of the carbon acid. Note that decreases in rate constants for IV are not likely to be associated with significant steric factors since they are not evident in the case of III.

Factors Influencing the Magnitude of Catalysis. Two points are considered: how changes in substrate concentration and pD influence the relative amounts of catalysis by B and OD^-; how changes in the structure of the substrate influence the type of catalysis.

Equation 6 indicates that at constant pD the concentration of substrate influences the amount of catalysis.



V

This means for II and III that by decreasing the total substrate concentration it is possible to eliminate entirely catalysis by B. At low substrate concentrations $k\psi$ for II and III is given by eq 7, the same equation employed for IV.

The results for II and III indicate that at constant substrate concentration an increase in the pD of the reaction mixture causes catalysis by OD^- to increase in importance relative to catalysis by B. This reflects a property of buffer solutions: as the pD of a buffer increases the concentrations of OD^- and buffer base increase, but the concentration of lyate ion increases more. Therefore, when II and III react in D_2O–DCl catalysis by B and OD^- results but at high enough pD, only OD^- catalysis is found. Note that BD^+ and not B undergoes deprotonation at carbon under all these conditions.

From the previous consideration follows an explanation why buffer (substrate) base catalysis is unimportant for IV but important for II and III.[22] Compound IV is substantially more basic than II and III, Table II. This means the pD of mixtures of IV and DCl is higher than those for II and III containing similar amounts of substrate and DCl. Although the total concentration of substrate is about the same for II–IV, the concentration of OD^- is greater relative to the concentration of B in the case of IV. Therefore, catalysis by B becomes less important relative to catalysis by OD^-. This is a general result.[23]

From the rate and equilibrium data for II and III, Table II, an approximate Brønsted β value of 0.6 may be derived. This calculation assumes that both B and OD^- are on a common Brønsted line. The β value could be larger if, as is found,[24] OD^- deviates negatively from the Brønsted line. Moreover, the β value for IV could be larger than for II and III since it is the least reactive substrate.[25,26]

It is interesting to compare our results for alkyl group H–D exchange with those for H–D exchange at annular positions of nitrogen-containing five- and six-membered heteroaromatic molecules. In some cases the experimental conditions are very similar to those reported here.[27] The mechanism of hydrogen exchange also is similar. Exchange at annular positions takes place on the conjugate acid of the substrate and lyate ion is the catalyst. Ylide intermediates are generated. In no case has there been reported significant general base catalysis by substrate acting in its free base form, *i.e.*, $k\psi$ is not given by eq 6 but by eq 7. This lack of general base catalysis implies the Brønsted β value for deprotonation at annular positions is larger than our value for methyl group exchange. Although this dissimilarity in β values no doubt reflects differences in the acidity of the two types of carbon acids, we feel that it also reflects the difference in the type of conjugate base which results on deprotonation. The negative charge resulting from methyl group deprotonation is extensively delocalized while the charge resulting from deprotonation at an annular position is largely localized.[28]

The methods and conclusions regarding catalysis developed here may be generalized. They are expected to hold not only for other heterocyclic compounds but also for other types of compounds having both acidic and basic centers within the same molecule. Similar considerations should apply to other hydroxylic solvents as well.

Experimental Section

Reagents. 2-Methylpyridine (Matheson Coleman and Bell) was purified by distillation, bp 127–128° (lit.[29] 128°). 2,6-Dimethylpyridine (Eastman Organic Chemicals) was purified by distillation from zinc powder, bp 142–143° (lit.[29] 143°). Deuterium oxide was obtained from Columbia Organic Chemicals. DCl was prepared by adding 38% hydrochloric acid to deuterium oxide. This solution was standardized using tris(hydroxymethyl)aminomethane (Fisher Scientific Co.). Tetramethylammonium chloride (Eastman Organic Chemicals) was used after oven drying. Potassium chloride (J. T. Baker Chemicals) was used directly. 4-Amino-2,6-dimethylpyridine was prepared[30] and recrystallized from benzene, mp 190–191.5° (lit.[30] mp 191–192°).

Preparation of Reaction Mixtures. Stock solutions were prepared by adding alkylpyridine, tetramethylammonium chloride, and/or potassium chloride by weight to volumetric flasks. When appropriate, standardized deuterium chloride was added by syringe and the flask was brought to mark with deuterium oxide.

The fractional amount of conjugate acid of 2-methylpyridine was varied while keeping the total amount of substrate constant by the following method. To 0.40 ml of a stock solution of II in a dry nmr tube was added varying amounts of deuterium and potassium chloride solutions to bring the total volume to 1.00 ml. Hamilton calibrated syringes were employed. It is assumed that volumes are additive.

In serial dilution studies where the buffer ratio is held constant, a portion of the alkylpryidine stock solution was syringed into a volumetric flask (1–5 ml) already containing a weight amount of potassium chloride. Deuterium oxide was added. Using this method, two- to sevenfold dilutions were made.

The ionic strength at the reaction temperature of 2-methyl- and 2,6-dimethyl-4-aminopyridine mixtures was 0.625 and 0.785 for 2,6-dimethylpyridine.

Determination of the pK_a of 2,6-Dimethyl-4-aminopyridine. Solutions were prepared in the same manner as those used in the kinetic studies. From a knowledge of the $[B]/[BD^+]$ ratio and the pD of the solutions determined at room temperature the K_a value was calculated according to eq 1. Values (buffer ratio) are 1.14 (0.217), 1.75 (0.610), and 1.63 (1.05) $\times 10^{-11}$. The average gives pK_a = 10.82. This value after correcting for the use of a deutero rather than a proteo solvent, $10.82 - 0.50^{14} = 10.32$, may be compared with a value of 10.68 calculated using reported constants.[31]

(22) A simplifying assumption is made. The Brønsted β value is the same for all substrates being compared.

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Kinetics of Hydrogen–Deuterium Exchange. Reaction mixtures were analyzed by nmr using published methods.[5] A mesitylene vapor bath was employed to maintain constant temperature, 164.6 ± 0.5°. Tetramethylammonium chloride and/or the 3.5 positions of substrate were used as nmr reference (area) standards. The nmr signal position of methyl groups containing one or two deuterium atoms is slightly upfield relative to the original singlet.[32] This gave rise to shoulders on the original peak as the exchange proceeded.

Pseudo-first-order rate constants, $k\psi$, were obtained from plots by visually fitting the best straight line through the points. Reactions generally were followed by taking nine points over three half-lives. Only in cases where the total concentration of substrate exceeded 0.5 *M* and hydrogen exchange did not go to completion, an "infinity" method was employed.[5c] Note that $k\psi$ reflects reactivity for a single hydrogen atom, *i.e.*, results are "statistically" corrected for the number of hydrogen atoms undergoing reaction.

Constants k_B and $k_{OD}K_w/K_a$ were evaluated in several ways. (1) Serial dilution plots, Figure 1, have slopes $k_B[B]/([BD^+] + [B])$ and intercepts $k_{OD}K_w[B]/K_a([BD^+] + [B])$. Four values of $k\psi$ were used to determine each line. Concentrations are corrected for thermal expansion using a density factor of 0.905. This method gives the least reliable values of $k_{OD}K_w/K_a$. (2) Plots of $k\psi$ $([BD^+] + [B])/[B]$ *vs.* $[BD^+]$ have slopes k_B and intercepts $k_{OD}K_w/K_a$; see Figure 3. All the data obtained for a substrate were employed in constructing the plot. (3) For kinetic runs involving reaction mixtures not containing deuterium chloride, $k = k_{OD}K_w/K_a$. (4) This method was employed only for 2,6-dimethylaminopyridine. A plot of $k\psi$ *vs.* $[B]/([BD^+] + [B])$ has slope $k_{OD}K_w/K_a$ and zero intercept.

Control Runs to Determine the Stability of the Alkylpyridine. To ensure that the disappearance of nmr signal was due to the incorporation of deuterium and not to the decomposition of substrate, control runs were carried out using proteo water and hydrochloric acid and substrate approximately half converted to its conjugate acid. In all cases no decomposition was observed, as evidence by comparison with tetramethylammonium chloride internal standard. Compounds were heated at 164.6° for periods corresponding to the number of half-lives for H–D exchange indicated: 2-methylpyridine (45), 2,6-dimethylpyridine (134), and 2,6-dimethyl-4-aminopyridine (94).

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Small Charged Rings. XV.[1] Kinetics and Stereochemistry of the Ring Expansion Reaction of 2-Arylaziridinium Salts with Benzaldehyde[2]

Thomas R. Keenan[3] and Nelson J. Leonard*

Contribution from the Department of Chemistry, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801. *Received December 24, 1970*

Abstract: The preparation and isolation of 2-aryl-substituted aziridinium (ethyleniminium) salts are described for the first time. Ethyleniminium ions of this type have previously been implicated as intermediates in adrenaline blockade. Using a series of 2-aryl-1,1-dimethylaziridinium fluoroborates with benzaldehyde, the stereochemistry of the ring expansion reaction of aziridinium salts with aldehydes, ③$^+$ + 2 → ⑤$^+$, has been determined. This representative of a family of aziridinium ring expansion reactions was shown to be highly stereoselective, since only *cis*-5-aryl-3,3-dimethyl-2-phenyloxazolidinium fluoroborates were produced. The kinetics of the reaction, determined by following the nmr spectra, showed the reaction to be first order in aziridinium salt, zero order in benzaldehyde, and dependent on the substituents on the aryl ring. A Hammett correlation with σ^+, $\rho^+ = -1.25$ was observed. The stereochemical and kinetic findings preclude several mechanisms including concerted cycloaddition and favor the intermediacy of aminocarbonium ions.

In earlier reports[4] of ring expansion reactions of aziridinium salts with aldehdyes,[5] ketones,[6,7] nitriles,[7,8] and nitrones[7,9] we have drawn conclusions concerning the mechanism(s) of these reactions based on product studies alone. Although these ③$^+$ + 2 → ⑤$^+$ and ③$^+$ + 3 → ⑥$^+$ reactions[4] reveal apparent similarity, in that the heteroatom of the reacting species (aldehyde, ketone, nitrile, nitrone) generally combines with the more substituted carbon of the substituted aziridinium ring to produce what have been termed normal ring expansion products, in some cases abnormal ring expansion products have been observed.[7] We have now undertaken a detailed study of the ring expansion reaction of some 2-aryl-1,1-dimethylaziridinium fluoroborates with benzaldehyde to clarify certain features of the mechanism.

Major possible pathways are outlined in Scheme I. The first mechanism shown involves formation of an aminocarbonium ion, **2**, which would be stabilized by the aromatic ring (a). Attack of benzaldehyde would produce a second aminocarbonium ion, **3**, from which the five-membered ring compound, 5-aryl-3,3-dimethyl-

(1) For the preceding article in this series, see N. J. Leonard and J. A. Klainer, *J. Heterocycl. Chem.*, 8, 215 (1971).

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(3) National Aeronautics and Space Administration Trainee, 1966–1969; Lubrizol Foundation Fellow, 1969–1970.

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