Two-step Conversion of Pyridines into their Ylides. Compensatory Effects of Substituents on Reactivity

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Rates of hydrogen–deuterium exchange at the 2- and 6-positions of pyridine and 3-substituted pyridines were obtained in neutral D_2O generally at 217·9 ∓ 0·5°. The rate constant for pyridine under these conditions is $1{\cdot}84 \times 10^{-4}$ s^{-1}. Rate constant ratios for the substituted molecules relative to pyridine are as follows: 2-position, Cl (8·6), CO_2^- (0·39), SO_3^- (1·8), CH_3O (13), and ND_2 (7·3); 6-position, Cl (0·13), CO_2^- (1·2), SO_3^- (0·42), CH_3O (*ca.* 0·4), and ND_2 (0·31). Evidence is presented to show that the compounds react by a two-step conversion of the pyridines into pyridinium ions and then into pyridinium ylides. The small effect of substituents on overall reactivity is rationalized in terms of compensatory effects on the two steps.

HETEROCYCLIC molecules containing a ring nitrogen atom are known to form ylides by a two-step protonation–deprotonation process. The pathway is illustrated in the Scheme for pyridine.[1] The reaction involves as a first step the formation of a pyridinium ion from the pyridine. In the second step base-catalysed deprotonation of the carbon acid at a position adjacent to the highly activating, positively charged nitrogen centre takes place to give ylide (I). When such an ylide forms from a protio-substrate in a deuteriated solvent, hydrogen–deuterium exchange at carbon results. This H–D exchange process offers a convenient way to study the ylide-forming reaction.

Although it is clear from the many known examples involving five- and six-membered heteroaromatic compounds that the two-step route to ylides is highly general and constitutes a useful way to introduce specifically hydrogen isotopes into positions adjacent to a ring nitrogen atom,[1-10] very little is known about the influence of substituents on the rates of the overall process.

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[2] For a review see J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *Adv. Heterocyclic Chem.*, 1974, **16**, 1.

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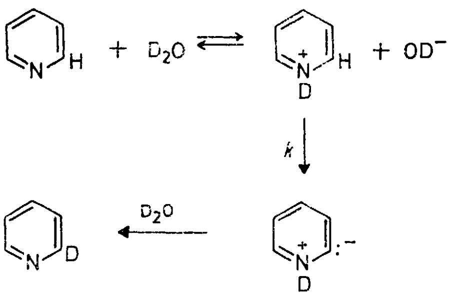
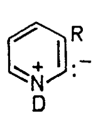
We now report the results of a study dealing with the effects of 3-substitution on the rates of hydrogen–deuterium exchange at the 2- and 6-positions of pyridine.



(I)

SCHEME

Pyridinium ylides (II) and (III) are believed to be intermediates in the isotope exchange reactions. The results



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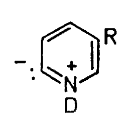

(III)

of this study along with those presented in the accompanying paper allow us to generalize about the effects of substituents on the rates of ylide formation by the two-step route.

RESULTS

All hydrogen–deuterium exchange reactions were followed by n.m.r. spectroscopy. The n.m.r. spectra of substituted pyridines have been studied so extensively that signal assignments can be made unambiguously.[11] Isotope exchange took place at the 2- and 6-positions.

3-Chloropyridine was studied thoroughly so that the mechanism of H–D exchange could be established. Because this compound has low solubility in deuterium oxide under the conditions employed to make n.m.r. measurements, rate constants were obtained using dioxan–D$_2$O (3 : 17 v/v) solutions. Convenient rates were found at 197·5 ± 0·5°. Pyridine also was studied under identical conditions for comparison purposes. Repetitive measurements on three different samples show that rate constants are highly reproducible, the average deviation for the chloro-substrate being no greater than 12%. Thus, the rate constants for the 2- and 6-positions of 3-chloropyridine are $2{\cdot}7 \pm 0{\cdot}3 \times 10^{-4}$ and $4{\cdot}2 \pm 0{\cdot}5 \times 10^{-6}$ s^{-1}, respectively. For the equivalent 2- and 6-positions of pyridine the value is $3{\cdot}2 \times 10^{-5}$ s^{-1}, duplicate runs giving identical values.

A comparison of the pseudo-first-order rate constants k_ψ reveals that the chlorine atom in the 3-position increases the reactivity of the 2-position by a factor of 8·5, relative to the 2-position in pyridine. The 6-position is deactivated by a factor of 7·6. The 2-position of 3-chloropyridine undergoes H–D exchange 64 times faster than the 6-position.

The effect of acid on the reactivity of 3-chloropyridine was also determined. By examining extracts of reaction mixtures, it was unnecessary to employ a co-solvent. Since the isotope exchange at the 6-position is inconveniently slow, limited studies of this reaction were carried out. Rates of isotope exchange were measured at 197·5 ± 0·5° in D$_2$O containing DCl.

In estimating the extent of conversion of the pyridine into its conjugate acid by DCl, it was assumed that all the acid reacted with the pyridine which was present in excess. The amount of 3-chloropyridine not so converted into its conjugate acid is indicated in Table 1; this is expressed as the inverse of the fractional amount of heterocycle present in the free base form. Although such an expression is uncommon, it is employed because it facilitates subsequent discussion of the reaction mechanism. The results given in Table 1 show that acid decreases the reactivity of both the 2- and 6-position, retardation increasing as the amount of added acid increases. Although added acid decreases the reactivity of both positions, the ratio of the rate constants for the 2- and 6-positions is essentially the same, being 83 and 76 for the two runs having the same value for the inverse of the fraction of free base. These values are similar to that (64) obtained using dioxan–water as solvent. Note that the maximum value of the pseudo-first-order rate constant is obtained when no acid is added, *i.e.* the solution consists only of substrate and water.

TABLE 1

Rate constants for H–D exchange at the 2- and 6-positions of 3-chloropyridine in D$_2$O–DCl at 197·5 ± 0·5°

Position	10^6k_ψ/s^{-1}	$\frac{1}{\text{(Fraction free base)}}$	$10^6kK\text{w}(K_a)^{-1}$ /s^{-1} [a]
2	580	1·0 [b]	580
	340	1·5	510
	220	2·0	440
	130	4·0	520
	46	10·0	460
		Average	502 ± 42
6	7·0	1·0 [b]	7·0
	2·9	2·0	5·8
		Average	6·4 ± 0·6

[a] Product of k_ψ and 1/(fraction free base). [b] No DCl added.

Since it was expected that 3-chloropyridine would undergo H–D exchange by the ylide route, the reactivity of a derivative, 3-chloro-1-methylpyridinium ion was examined. Because this derivative already is in the ionic form, the first step of the two-step ylide scheme cannot operate. It therefore is of interest to compare the rate constant ratio for the 2- and 6-positions of both chloro-compounds. The isotope exchange reaction was carried out in 0·03M-DCl at 197·5°. The rate constant ratio for the 2- and 6-positions of 3-chloro-1-methylpyridinium ion under these conditions is 60, the 2-position being more reactive. This value is very similar to those found for 3-chloropyridine at the same temperature.

The rates of H–D exchange at the 2- and 6-positions of several 3-substituted pyridines (R = CO$_2^-$, SO$_3^-$, ND$_2$, and CH$_3$O) were measured in D$_2$O solution at 217·9 ± 0·5°. Results are given in Table 2.

In the case of pyridine-3-carboxylic acid and -3-sulphonic acid, sodium carbonate was added to ensure that the substituents existed in the anionic form. The use of an

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[11] T. J. Batterham, ' N.M.R. Spectra of Simple Heterocycles,' Wiley-Interscience, London, 1973, ch. 2.

excess of sodium carbonate was found not to influence the reactivity of pyridine-3-carboxylate ion. No variation in the rate constant was observed when the pD of the medium measured at 25° was changed from 7 to 10 by adding carbonate ion.

The reactivity of pyridine-3-sulphonic acid was also determined in the absence of added sodium carbonate. In the absence of base the molecule exists largely as the betaine, pyridinium-3-sulphonate, *i.e.*, the sulpho-group converts the pyridine into its conjugate acid.[12] As expected, isotope exchange is retarded; the 2-position is 14 times and the 6-position is 9 times less reactive when sodium carbonate is not added. The kinetic effect is similar to that found for mixtures of 3-chloropyridine and DCl and differs only in terms of the source of the acid.

TABLE 2

Rate constants and rate constant ratios for H–D exchange at the 2- and 6-positions of 3-substituted pyridines in D_2O at 217·9 ± 0·5°

Substituent	2-Position k_ψ/s^{-1}	6-Position k_ψ/s^{-1}	2-Position against 6-position [a]
CO_2^- [b]	$7\cdot5 \times 10^{-5}$	$2\cdot3 \times 10^{-4}$	0·33
	$7\cdot0 \times 10^{-5}$	$2\cdot1 \times 10^{-4}$	0·31
	$7\cdot2 \times 10^{-5}$	$2\cdot3 \times 10^{-4}$	0·31
Average	$7\cdot2 \pm 0\cdot2 \times 10^{-5}$	$2\cdot2 \pm 0\cdot1 \times 10^{-4}$	0·32
SO_3^-	$3\cdot4 \times 10^{-4}$ [c]	$7\cdot7 \times 10^{-5}$ [c]	4·4
	$2\cdot5 \times 10^{-5}$ [d]	$8\cdot5 \times 10^{-6}$ [d]	2·9
ND_2	$1\cdot4 \times 10^{-3}$	$5\cdot7 \times 10^{-5}$	25
	$2\cdot4 \times 10^{-4}$ [e,f]		
CH_3O	$2\cdot3 \times 10^{-3}$	($8\cdot2 \times 10^{-5}$ [g])	(28 [g])
	$4\cdot4 \times 10^{-4}$ [e,h]		

[a] Ratio of rate constants. [b] pD (25°) *ca.* 7, 9·8, and 10·3 for the three solutions indicated. [c] Na_2CO_3 added. [d] No Na_2CO_3 added. [e] 197·5 ± 0·5°. [f] E_a 39·6 kcal mol^{-1}. [g] Uncertain value. [h] E_a 37·3 kcal mol^{-1}.

The kinetics of H–D exchange at the 6-position of 3-methoxypyridine are complicated by several side reactions. One of these was identified as cleavage of the ether group resulting in the formation of methanol. The heated solution was found to be 10-fold more acidic than the original unheated mixture. Although the pseudo-first-order rate plot was linear over 2·5 half-lives, the reported rate constant for the slower 6-position must therefore be only an approximation.

The ionic strengths of various sample solutions were not held constant, since, in many cases, the limited solubility of the substrate precluded the addition of supporting electrolytes. However, several studies were carried out using pyridine to determine whether rates of isotope exchange are highly dependent on medium polarity. The rate constant for H–D exchange of pyridine in 1M-NaCl at 217·9 ± 0·5° is only 41% larger than that ($1\cdot8 \pm 0\cdot3 \times 10^{-4}$ s^{-1}) for pyridine in salt-free D_2O, indicating a negligible kinetic salt effect. Moreover, the reactivity of pyridine in D_2O free of salt and in the less polar dioxan–D_2O (3 : 17 v/v) at 197·5° differs by only 6%. The reactivity of pyridine in D_2O was found to be somewhat larger than our earlier reported value;[1] therefore, all comparisons involving pyridine reacting at 217·9° are based on the average of the former and newly determined values with an average deviation of 17%. The reactivity of 3-chloropyridine in dioxan–D_2O is less than that in D_2O by a factor of *ca.* 2. In view of these results it is assumed that the rates of H–D exchange of the 3-substituted pyridines do not depend markedly on salt effects.

The effect of a substituent bonded to the 3-position of a pyridine ring on the reactivity of the 2- relative to the 6-position is given in Table 2 in the form of ratios of pseudo-first-order rate constants. These values as well as those for the chloro-group indicate that the chloro-, amino-, and sulphonato-groups cause the 2-position to be more reactive than the 6-position, the ratios of the rate constant being 64—83, 25, and 3·6, respectively. Several values are found for the chloro-group under different conditions. The same pattern appears to result in the case of a methoxy-group but owing to substrate decomposition the reactivity of the 6-position is uncertain. Only the carboxylato-group caused a reverse order, the 6-position being 3·2 times more reactive than the 2-position. Note that the two ionic groups do not give the same pattern of reactivity.

Comparisons of the reactivity of a 3-substituted pyridine with that of pyridine at the 2- and 6-positions are given in Table 3. These rate constant ratios show that the range of activation or deactivation by the substituent is small. 13-Fold is the maximum increase; this is found for the 2-position of the 3-methoxy-compound. The 6-position of the 3-chloro-compound is deactivated the most, by a factor of 7·6. In all cases one position (either 2 or 6) of the 3-substituted compound is activated while the other is deactivated.

TABLE 3

Rate constant ratios comparing the effects of substituents on the reactivities of 3-substituted pyridines relative to pyridine in H–D exchange reactions at 217·9° in D_2O [a]

Substituent	2-Position [b]	6-Position [b]
Cl [c]	8·6 (10·4)	0·13 (0·05)
CO_2^-	0·39 (0·20)	1·2 (0·64)
SO_3^-	1·8 (0·84)	0·42 (0·06)
OCH_3	13 (28)	0·4 [d] (0·37)
ND_2	7·8 (8·4)	0·31 (0·37)

[a] Predicted values are in parentheses; see Discussion section. [b] Relative to the equivalent 2- and 6-positions of pyridine under the same conditions. [c] 197·5° in dioxan–D_2O (3 : 17 v/v). [d] Uncertain value.

DISCUSSION

Mechanism.—Evidence that the observed H–D exchange reactions involving 3-substituted pyridines do proceed by a two-step ylide mechanism similar to that given in the Scheme for pyridine[1] is considered first. Most of the attempts to establish a mechanism involve 3-chloropyridine.

Consider the requirements of the ylide mechanism. The rate of H–D exchange at a 2- or 6-position is given by equation (1) and the pseudo-first-order constant by equation (2), where $[\mathrm{Pyr}]_\mathrm{T} = [\mathrm{Pyr}] + [\mathrm{PyrD}^+]$ and k is a

$$k_\psi[\mathrm{Pyr}]_\mathrm{T} = k[\mathrm{PyrD}^+][\mathrm{OD}^-] \qquad (1)$$

$$k_\psi = \frac{kK_\mathrm{w}}{K_\mathrm{a}} \cdot \frac{[\mathrm{Pyr}]}{[\mathrm{Pyr}] + [\mathrm{PyrD}^+]} \qquad (2)$$

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[12] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.

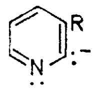
second-order rate constant for deprotonation of the pyridinium ion PyrD$^+$ to give the ylide. The dissociation constant of the ion is K_a and K_w is the ion product for water. This mechanism requires that k_ψ *decreases* as acid is added to the reaction mixture and the fractional amount of free pyridine decreases. It also requires that the product of k_ψ and the inverse of the fractional amount of free pyridine be a constant [kK_w/K_a, equation (2)]. This is exactly what is observed for the rates of H–D exchange at both the 2- and 6-positions of 3-chloropyridine (Table 1). The average values for the 2- and 6-positions are 502 and 6·4 s^{-1}, respectively.

According to equations (1) and (2) the ratio of pseudo-first-order rate constants for the 2- and 6-positions should be a constant. This constant is a ratio of second-order rate constants for deprotonation of the pyridinium ion to give ylides (II) and (III), *i.e.*, $k^2{}_\psi/k^6{}_\psi = k^2/k^6$, the superscripts indicating positions. In other words, the positional reactivity ratio is independent of the degree of conversion of the pyridine into its conjugate acid and is independent of the concentration of deuterioxide ion. The results given in Table 1 are in agreement with this requirement.

In further support of the ylide mechanism is the observation that the rate constant ratio for the 2- and 6-positions of 3-chloropyridine is essentially the same as that for 3-chloro-1-methylpyridinium ion. Clearly, the reactive form of 3-chloropyridine is its conjugate acid, 3-chloro-1-deuteriopyridinium ion.

There is no evidence in the results for 3-chloropyridine to indicate that the carbon deprotonation reaction is general base catalysed. That is, free 3-chloropyridine does not act as a base to deprotonate 3-chloro-1-deuteriopyridinium ion. If free 3-chloropyridine were acting as a general base, then k_ψ would have its maximum value when the substrate is half converted to its conjugate base [13] (third entry in Table 1). This clearly is not the case. For a kinetic analysis and a thorough discussion of this possibility, a study of H–D exchange at the methyl group of 2-methylpyridine in D_2O–DCl should be consulted; general base catalysis is observed for this carbon acid.[13] It should be noted that significant general base catalysis has not been reported for deprotonation reactions at ring positions of pyridinium ions or other closely related substrates, even though considerable effort has been expended to detect it.[14–16]

Still another mechanism must be considered. This involves deprotonation by deuterioxide ion of the pyridine in its free base form to give a pyridyl anion such as (IV) instead of a pyridinium ylide. Such a mechanism could not have been important under the conditions of our study. The deuterioxide ion concentrations were not large enough to make this pathway important. Moreover, according to this mechanism deprotonation at positions adjacent to the ring nitrogen atom is disfavoured. Instead, more distant positions such as 4 and 5 are favoured, owing to the unusual effect of the nitrogen atom on the reactivity of an adjacent position.[2] Exchange only at the 2- and 6-positions was detected. The carbanion mechanism is directly eliminated for pyridine-3-carboxylate anion. Increasing the pD of solutions containing this ion does not change k_ψ; increasing k_ψ with increasing pD is a requirement of the anion mechanism.



(IV)

In view of evidence supporting an ylide mechanism of H–D exchange for pyridine,[1] 4-aminopyridine,[17] 3-chloropyridine, and pyridine-3-carboxylate ion, it seems reasonable to conclude that this mechanism applies to all the pyridines employed in the present study.

Neutral water was employed in most of the hydrogen exchange reactions. With this solvent, conversion of the pyridines into their conjugate acids takes place to the extent of $<1\%$ at the reaction temperature. Under these conditions the pseudo-first-order rate constant for hydrogen isotope exchange is a true constant, *i.e.* $k_\psi = kK_w/K_a$ [equation (2)] and k_ψ has its maximum value. This value reflects the rate constant k for deprotonation to give the ylide and the dissociation constant K_a of the intermediate pyridinium ion. Although only a small fraction of the substrate is converted into its conjugate acid under these conditions, the enormous activating effect of a positively charged nitrogen atom offsets the kinetic effect of the low concentration, and thus, ylides rather than anions are responsible for hydrogen exchange. A similar mechanism is expected to apply to many other heteroaromatic compounds reacting at ring positions in neutral water.

Substituent Effects.—Two types of substituent effects need to be considered. The first involves the effect of a substituent on the reactivity of the 2- relative to the 6-position. The second considers the effects of the substituents on the reactivities of these same positions relative to the equivalent 2- and 6-positions of the parent compound pyridine.

The effects of a substituent on the reactivity of the 2- relative to the 6-position are discernible from the rate constant ratios given in the right hand column of Table 2. These substituent effects, as expected for an ylide mechanism, are similar to those found in our companion study dealing with the formation of pyridinium ylides from 3-substituted 1-methylpyridinium ions and require no additional comment.[18]

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[13] J. A. Zoltewicz and P. E. Kandetzki, *J. Amer. Chem. Soc.*, 1971, **93**, 6562.

[14] J. A. Zoltewics, C. L. Smith, and G. M. Kauffman, *J. Heterocyclic Chem.*, 1971, **8**, 337.

[15] J. A. Zoltewicz and V. W. Cantwell, *J. Org. Chem.*, 1973, **38**, 829.

[16] D. S. Kemp and J. T. O'Brien, *J. Amer. Chem. Soc.*, 1970, **92**, 2554.

[17] J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Letters*, 1964, 1577.

[18] J. A. Zoltewicz and R. L. Cross, preceding paper.

Our study provides considerable insight into the effects of substituents on the formation of ylides by the two-step protonation–deprotonation process. Thus, the overall effect of a substituent on the reactivity of the 3-substituted compound relative to pyridine (Table 2) can be understood if the effect of the substituent on each of the two steps is considered separately. A chloro-group, for example, changes pyridinium ion into a stronger nitrogen acid.[12] The increased nitrogen acidity in the substituted compound serves to decrease H–D exchange reactivity because a smaller fraction of the substrate is converted in neutral water into the precursor of the ylide, the pyridinium ion. But the chloro-group also increases the acidity of the two carbon acids, the 2-position being more activated than the 6-position because it is closer. This serves to increase H–D exchange reactivity. Thus, the chloro-group exerts opposing effects on the two reaction steps. It suppresses the formation of the pyridinium ion, relative to the parent substrate, but facilitates the formation of the ylide. The opposing effects nearly balance. The overall effect is activation (8·5) at the 2-position and deactivation (0·13) at the 6-position.

A mathematically equivalent statement is obtained when a ratio of pseudo-first-order rate constants for the 2- and 6-positions is constructed from equation (2) to give (3). This new equation makes it clear that such a ratio involves a comparison of rate constants for carbon acid deprotonation, k^R/k^H, as well as equilibrium constants for nitrogen acid dissociation, $K_a{}^H/K_a{}^R$. Moreover, because these two ratios have an inverse relationship involving the substituted and parent compounds, the effects of the substituent on the two steps are largely compensatory.

$$k_\psi{}^R/k_\psi{}^H = k^R K_a{}^H/k^H K_a{}^R \qquad (3)$$

In order to test the relationship given by equation (3) the rate constant ratio $k_\psi{}^R/k_\psi{}^H$ was calculated from available data. In making the calculations the ratios k^R/k^H were taken from our study of H–D exchange reactions of 3-substituted 1-methylpyridinium ions in D_2O at 75·0°.[18] The $K_a{}^H/K_a{}^R$ values were taken from tabulated data for pyridinium ions at ambient temperatures.[12] Table 3 lists ten experimental and ten calculated values, those enclosed in parentheses being predicted using equation (3). In spite of very large temperature differences (as much as 195°) calculated and observed values are in reasonable agreement. In the worst case ($R = SO_3{}^-$, 6-position) they differ by a large factor of seven; in four instances differences are negligible. This agreement again points to compensatory substituent effects. Clearly, calculated rate constant ratios are only semi-quantitative in nature.

It is to be expected that predicted rate constant ratios, $k_\psi{}^R/k_\psi{}^H$, calculated with the aid of equation (3) will not be highly sensitive to temperature changes. Since ratios are employed, equation (3) deals with differences in energy terms, *e.g.* $\Delta\Delta H^\ddagger$ for k^R/k^H and $-\Delta\Delta H^0$ for $K_a{}^H/K_a{}^R$. Although rate constants are likely to be more sensitive to temperature changes than equilibrium constants[19] because $\Delta H^\ddagger$ is expected to be greater than ΔH^0, $\Delta\Delta H^\ddagger$ may be about the same in magnitude but opposite in sign to $\Delta\Delta H^0$. Compensatory energy changes are likely to result.

EXPERIMENTAL

See the preceding paper for additional details.[18] Except for the extraction method, reactions were followed for 2—3 half-lives; *ca.* 10 points were taken during a run.

Deoxygenated solutions were prepared by heating D_2O and dioxan at reflux for 30 min under a continuous stream of dry nitrogen. The cooled solvents, stored under nitrogen, were used to prepare stock solutions. All sample solutions were *ca.* 0·5M in substrate. Temperatures were maintained by immersing the n.m.r. tube in a refluxing vapour bath. Ethylene glycol was used for reactions at 197·5 ± 0·5° and naphthalene for those at 217·9 ± 0·5°. The variations in temperatures of the baths occasionally exceeded those reported above. In no case, however, did individual variations exceed ±1·5°, even over extended periods. All pD measurements were made at 25°.[20]

The n.m.r. spectra of 3-chloro-, 3-methoxy-, and 3-amino-pyridine consist of overlapped peaks for 2- and 6-H at the lowest fields.[11] The entire multiplet was integrated when following hydrogen exchange. The difference in reactivity of these two positions is so large that exchange at 2-H is effectively complete before significant exchange at 6-H commences. In the absence of added base the signals for 4- and 6-H of pyridine-3-sulphonic acid overlap; again the entire multiplet was integrated. Internal (area) standards employed in kinetic runs include methanol and tetramethylammonium and isobutyrate ions.

Kinetics using an Extraction Method.—Owing to the limited solubility of 3-chloropyridine in water and to signal broadening in solutions containing DCl an extraction method was employed. After addition of NaCl (Na_2CO_3 in the case of DCl solutions) to a cooled reaction mixture, substrate was removed by extraction with CCl_4. Extracts were dried (Na_2SO_4) and n.m.r. spectra recorded. Only two heating periods covering *ca.* 60—70% reaction were employed to measure hydrogen exchange at the 2- or 6-position. Rate plots therefore consist of three points, including the origin.

Control Experiments.—Comparison of n.m.r. areas of internal standard with those of unreactive positions of all substrates except 3-methoxypyridine showed there was insignificant degradation of the substrates during kinetic runs. Preliminary experiments with 3-chloropyridine indicated instability of the substrate but deoxygenation of solutions eliminated this complication.

A preliminary run on 3-chloro-1-methylpyridinium ion indicated that methanol was being formed by solvolysis of the substrate on a time scale comparable with that for H–D exchange at the 6-position. Addition of 0·32M-methanol had the effect of successfully suppressing this solvolysis.

A solution of 0·03M-DCl, *ca.* 0·5M in KCl and containing isobutyric acid and methanol internal standards, was prepared to simulate the solution of 3-chloro-1-methylpyridinium chloride employed in the kinetic run at 197·5 ± 0·5°,

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[19] D. D. Perrin, *Austral. J. Chem.*, 1964, **17**, 484.

[20] R. Bates, 'Determination of pH. Theory and Practice,' Wiley, New York, 1964.

and then pD measurements at 25° were made on portions of unheated and recovered solution. The recovered solution was found to be 0·31 pD units more basic than the original solution. Although such a variation is expected to increase the value of a pseudo-first-order rate constant for H–D exchange by a maximum of a factor of two, the rate constant ratio for the 2- and 6-positions is likely to be affected to a smaller degree. The heating period corresponds to *ca.* 2·2 half-lives for H–D exchange at the slower 6-position of 3-chloro-1-methylpyridinium chloride.

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