Substituent Effects on the Rates of Formation of Pyridinium Ylides

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Pyridinium ylides are formed by deprotonation of the 2- and 6-positions of 3-substituted 1-methylpyridinium ions in D_2O buffer solutions at 75·0° in reactions catalysed by deuterioxide ion. The reactivity of the 2-position was determined for 10 substituted ions; eight ions gave kinetic results for the 6-position. Dual substituent parameter equations employing inductive and resonance effects correlate rate constants very well.

OUR understanding of the nature of electronic effects of substituents bonded to aromatic rings is largely derived from benzenoid systems where a reaction takes place at a side chain.[1-3] An interest in new systems is developing. One involves the formation of aryl and heteroaryl anions by deprotonation. These differ from classical systems in that the reaction involves the σ electron framework of the aromatic ring rather than the π framework.

A number of kinetic studies involving aryl and heteroaryl anion formation have been reported.[4,5] They show that substituents influence the reactivity of *ortho*-positions largely by inductive effects and the reactivity of *para*-positions by both inductive and resonance effects. However, all suffer from the same limitation. The recommended minimum basis set of substituents which allows the nature of the electronic effects to be defined precisely has not been employed.[6,7]

We report the results of hydrogen–deuterium kinetic studies involving 3-substituted 1-methylpyridinium ions in aqueous buffers. Reactive centres are situated *ortho* and *para* to the substituents. Ylides (I) and (II) are

(I)   (II)
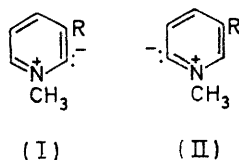
formed when the carbon acids are deprotonated by deuterioxide ion at the 2- and 6-positions. Our study involving *ortho*-substituents is the most extensive to date and the first to employ the recommended minimum basis set of substituents.

RESULTS

Rates of H–D exchange at the 2- and 6-positions of a series of 3-substituted 1-methylpyridinium ions in buffered D_2O solutions of 1·0M ionic strength were measured at

75·0 ± 0·5°. Much evidence has been presented to indicate that such reactions involve the formation of ylide intermediates.[8,9] Reactions were followed by measuring the change in the integrated area of the appropriate n.m.r. signals. The n.m.r. spectra of many of the 3-substituted pyridinium ions and 3-substituted pyridine precursors have been reported.[10] Signals for those substrates for which spectra have not been reported were assigned by analogy, and the assignments supported by the changes in appearance of the spectra during hydrogen isotope exchange. Signals for the ring protons of 3-substituted 1-methylpyridinium ions are broadened and shifted downfield to varying degrees, relative to the signals for the ring protons of the free bases. Otherwise, the spectra are similar.

In several instances signal overlap was observed. This condition generally did not prevent the accurate determination of the desired rate constants except in the case of two substrates ($R = CH_3$ and O^-). Here, the signals overlap and the 2- and 6-positions have similar reactivities.

A range of 3-substituted pyridinium ions was successfully examined. Substituents include NO_2, CN, Cl, I, SO_3^-, CH_3O, ND_2, CO_2^-, and CH_3. It was impossible to follow rates of isotope exchange for all these compounds at both the 2- and 6-positions, owing to the occurrence of side reactions. The reactivity of the less reactive 6-position of the nitro- and cyano-substrates could not be determined owing to substrate degradation. No appreciable degradation of the other substrates could be detected by n.m.r. analysis either of reaction mixtures containing D_2O or of control mixtures containing H_2O. Similarly, no degradation could be detected from pD and pH measurements made on heated samples. Under the conditions employed, no ring protons except those at the 2- or 6-positions underwent detectable exchange.

Attempts were made to determine the reactivities of 3-acetyl- and 3-methylsulphonyl-1-methylpyridinium ions. No useful data could be obtained because extensive degradation of the samples took place.

Another type of complication was encountered with the 3-O^- substituent. Owing to the reduced reactivity of this material, considerable etching of glass resulted. This brought about a reduction in the pD of the solution by 0·44. Consequently, our rate constant is only an approximate value. In order to minimize the effect of the changing base

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concentration on reactivity, an average pD value was employed to calculate the apparent activity of deuterioxide ion. Initial and final pD values were averaged.

When the base concentration remains constant and deuterium is present in large excess, rates are pseudo-first order. The rates of deprotonation are then described by equation (1) where k_ψ is the observed pseudo-first-order

$$k_\psi[\text{PyrCH}_3{}^+] = k_2[\text{PyrCH}_3{}^+]a_{\text{OD}^-} \qquad (1)$$

rate constant. The second-order rate constant k_2 may then be calculated from k_ψ and the apparent activity of deuterioxide ion as determined from pD measurements at $75\cdot0 \pm 0\cdot5°$. The apparent activity of deuterioxide ion was calculated from the expression $\text{pOD} = \text{p}K_\text{W}{}^\text{D} - \text{pD}$ where

TABLE 1

Rates of H–D exchange at the 2- and 6-positions of 3-substituted 1-methylpyridinium ions in D_2O at $75\cdot0 \pm 0\cdot5°$ and $1\cdot0\text{M}$ ionic strength

Substituent	k_ψ/s^{-1}	pD [a]	$k_2/\text{l mol}^{-1} \text{s}^{-1}$	Buffer [b]
		2-Position		
NO_2	$4\cdot84 \times 10^{-4}$	$4\cdot937$	$1\cdot87 \times 10^5$	Citrate
CN	$3\cdot18 \times 10^{-4}$	$6\cdot005$	$1\cdot05 \times 10^4$	Phosphate
Cl	$9\cdot38 \times 10^{-5}$	$6\cdot777$	$5\cdot25 \times 10^2$	Phosphate
I	$2\cdot75 \times 10^{-5}$	$7\cdot017$	$8\cdot85 \times 10$	Phosphate
SO_3^- [c]	$2\cdot88 \times 10^{-4}$	$8\cdot332$	$4\cdot49 \times 10$	Borate
	$7\cdot70 \times 10^{-5}$	$7\cdot774$	$4\cdot32 \times 10$	Borate
	$8\cdot02 \times 10^{-6}$	$6\cdot840$	$3\cdot90 \times 10$	Phosphate
		Average	$4\cdot24 \times 10$	
CH_3O	$3\cdot98 \times 10^{-4}$	$9\cdot035$	$1\cdot23 \times 10$	Borate
ND_2 [c]	$2\cdot50 \times 10^{-5}$	$9\cdot483$	$2\cdot76 \times 10^{-1}$	Borate
CO_2^- [c]	$1\cdot20 \times 10^{-4}$	$10\cdot624$	$9\cdot50 \times 10^{-2}$	Carbonate
	$1\cdot35 \times 10^{-5}$	$9\cdot641$	$1\cdot03 \times 10^{-1}$	Borate
		Average	$9\cdot90 \times 10^{-2}$	
		6-Position		
SO_3^- [c]	$7\cdot55 \times 10^{-4}$	$9\cdot954$	$2\cdot81$	Borate
	$3\cdot59 \times 10^{-4}$	$9\cdot594$	$3\cdot07$	Borate
	$1\cdot30 \times 10^{-4}$	$9\cdot277$	$2\cdot30$	Borate
	$6\cdot60 \times 10^{-5}$	$8\cdot873$	$2\cdot96$	Borate
		Average	$2\cdot79$	
Cl [c]	$1\cdot79 \times 10^{-4}$	$9\cdot419$	$2\cdot28$	Borate
	$7\cdot00 \times 10^{-5}$	$9\cdot004$	$2\cdot32$	Borate
		Average	$2\cdot30$	
I	$2\cdot25 \times 10^{-4}$	$9\cdot525$	$2\cdot25$	Borate
CO_2^- [c]	$3\cdot98 \times 10^{-4}$	$10\cdot624$	$3\cdot16 \times 10^{-1}$	Carbonate
	$4\cdot28 \times 10^{-5}$	$9\cdot641$	$3\cdot27 \times 10^{-1}$	Borate
		Average	$3\cdot22 \times 10^{-1}$	
CH_3O [c]	$3\cdot87 \times 10^{-4}$	$10\cdot896$	$1\cdot64 \times 10^{-1}$	Carbonate [d]
ND_2	$4\cdot00 \times 10^{-5}$	$11\cdot037$	$1\cdot23 \times 10^{-2}$	Carbonate [d]
		2- and 6-Positions		
CH_3 [e]	$3\cdot74 \times 10^{-4}$	$11\cdot116$	$9\cdot54 \times 10^{-2}$	Carbonate [d]
	$2\cdot35 \times 10^{-4}$	$10\cdot998$	$8\cdot19 \times 10^{-2}$	Carbonate [d]
		Average	$8\cdot87 \times 10^{-2}$	
O^- [e]	$1\cdot67 \times 10^{-7}$	$10\cdot53$ [f]	$1\cdot0 \times 10^{-4}$	Carbonate [d]

[a] pD at $75\cdot0 \pm 0\cdot5°$ measured at the end of the reaction. [b] Total buffer concentration $0\cdot05$—$0\cdot06\text{M}$. [c] Solution becomes yellow during the reaction. [d] Total buffer concentration $0\cdot10$—$0\cdot15\text{M}$. [e] 2- and 6-positions react at about the same rate. [f] Initial pD larger by $0\cdot44$.

$K_\text{W}{}^\text{D}$ is the dissociation constant for D_2O. The value $\text{p}K_\text{W}{}^\text{D}$ ($13\cdot526$ at $75\cdot0°$) was calculated from reported re-

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sults.[11,12] Table 1 lists rate constants, pD values, and the identity of the buffers employed in the study.

Several of the substrates were studied at two or more pD values; in these instances, exchange was demonstrated to be first order in deuterioxide ion. For example, a plot of log k_ψ against pD for the three kinetic runs on 1-methyl-pyridinium-3-sulphonate gave a straight line with a slope of $1\cdot05$. As expected, no buffer catalysis was detected. It has become clear from a variety of investigations that hydrogen isotope exchange reactions of the type considered here do not show significant buffer base (general base) catalysis.[4,8,13]

A first-order plot for isotope exchange of the 3-methyl carbon acid was linear over $3\cdot7$ half-lives. Because n.m.r. signals for the 2- and 6-positions overlap, this linearity indicates that both positions react at similar rates. It has been reported that the signals are resolvable at 100 MHz and that the 2-position is only 20% more reactive than the 6-position at 26°.[14] In view of this, we assume both positions have the same reactivity.

As a check, the reactivity of 1-methylpyridinium ion was redetermined. The new value, $2\cdot0 \times 10^{-1}$ l mol^{-1} s^{-1}, is only 10% smaller than our earlier value.[8]

A comparison between the reactivities of 3-substituted 1-methylpyridinium ions and the parent 1-methylpyridinium ion is given in Table 2 in the form of rate constant

TABLE 2

Rate constant ratios comparing the reactivities of the 2- and 6-positions of 3-substituted pyridinium ions at $75\cdot0°$

Substituent	2-Position k^R/k^H [a]	6-Position k^R/k^H [a]	2-Position against 6-position
H	$1\cdot0$	$1\cdot0$	$1\cdot0$
NO_2	$9\cdot4 \times 10^5$		
CN	$5\cdot3 \times 10^4$		
Cl	$2\cdot6 \times 10^3$	$1\cdot2 \times 10$	$2\cdot3 \times 10^2$
I	$4\cdot4 \times 10^2$	$1\cdot1 \times 10$	$3\cdot9 \times 10$
SO_3^-	$2\cdot1 \times 10^2$	$1\cdot4 \times 10$	$1\cdot5 \times 10$
CH_3O	$6\cdot2 \times 10$	$8\cdot2 \times 10^{-1}$	$7\cdot5 \times 10$
ND_2	$1\cdot4$	$6\cdot2 \times 10^{-2}$	$2\cdot2 \times 10$
CO_2^-	$5\cdot0 \times 10^{-1}$	$1\cdot6$	$3\cdot1 \times 10^{-1}$
CH_3	$4\cdot4 \times 10^{-1}$ [b]	$4\cdot4 \times 10^{-1}$ [b]	~ 1
O^-	(1×10^{-3}) [b,c]	(1×10^{-3}) [b,c]	~ 1

[a] Comparison of substituted ion with 1-methylpyridinium ion. [b] Values assumed to be the same due to overlap of n.m.r. signals. [c] Uncertain value.

ratios, k^R/k^H. These comparisons show that substituents can have large effects on reactivity, the 2-position generally being affected more than the 6-position. The 2-position is deactivated by O^-, CH_3, and CO_2^- substituents and activated by ND_2, CH_3O, SO_3^-, I, Cl, CN, and NO_2 groups. The 6-position is deactivated by O^-, ND_2, CH_3, and CH_3O substituents and activated by CO_2^-, I, Cl, and SO_3^- groups. This listing of substituent effects reflects increasing ease of deprotonation within each group. It is evident that all possible combinations of activation and deactivation are found (Table 2).

Substituent effects can be very large. The extremes range from a factor of $9\cdot4 \times 10^5$, reflecting activation of the

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2-position by a nitro-group, to a factor of $ca.$ 10^{-3}, due to deactivation of the 2- and 6-positions by O^-.

DISCUSSION

Reactivity of the ortho-*Position.*—The linear free energy equation (2) was found to correlate reactivity with the inductive effects of substituents as measured by σ_I.[7] When the ionic groups CO_2^-, SO_3^-, and O^- which have uncertain substituent constants are excluded from the correlation, a moderately satisfactory fit of the data was obtained. The correlation coefficient r is 0·98; a t test of ρ_I indicates a $>99\cdot9\%$ confidence level. However, the standard deviation of estimate is 0·46 and a comparison of the calculated intercept ($8\cdot1 \times 10^{-2}\,1\,mol^{-1}\,s^{-1}$), which gives the reactivity of the parent ion, with the measured reactivity ($2\cdot0 \times 10^{-1}\,1\,mol^{-1}\,s^{-1}$), shows that the calculated value is smaller by a factor of $ca.$ $2\cdot5$.[15] Clearly, the effects of the ortho-substituents are large (ρ $8\cdot9 \pm 0\cdot7$) and primarily inductive in nature. But it is likely that more than one effect influences reactivity.

$$\log k^R = \sigma\rho + \log k^H \qquad (2)$$

The three ionic substituents originally excluded from the σ_I correlation can be added to the correlation established by the basis set. The SO_3^- (σ_I 0·25[16]) and CO_2^- (σ_I $-0\cdot05$) substrates fit the correlation as well as any other. The fit indicates these groups influence reactivity primarily by means of an inductive effect. It appears that the σ_I value for CO_2^- was miscalculated in the original report;[16] recalculation changes the value from $-0\cdot35$ to $-0\cdot05$. The point for $R = O^-$ (σ_I $-0\cdot16$[16]) deviates more from the correlation line than any other point; perhaps this reflects the uncertainty in both the rate constant and the σ value.

A correlation with a multiparameter equation was attempted next. Equation (3) makes allowance for resonance effects as well as inductive effects. While it once appeared that resonance effects might be expressed

$$\log k^R = \sigma_I\rho_I + \sigma_R\sigma_R + \log k^H \qquad (3)$$

universally by the $\sigma_R{}^0$ parameter, it now appears that there is no such universal scale. Instead, four sets of substituent constants, $\sigma_R{}^0$, σ_{BA}, $\sigma_R{}^-$, and $\sigma_R{}^+$, measuring different degrees of interaction between a substituent and a reactive centre are now required.[7] Using equation (3), it was found that the best correlation results when $\sigma_R{}^-$ constants are employed to measure resonance effects; the standard deviation of the estimate is 0·23. However, correlations with the other three resonance substituent constants are not decidedly inferior. In all cases the calculated and observed reactivity of the parent ion differ by $\leqslant 10\%$, multiple correlation coefficients are $>0\cdot99$, and the confidence levels given by the t test for

ρ_I are $>99\cdot9\%$. Some variation in the confidence levels for ρ_R does result, being $>99\%$ for $\rho_R{}^-$, $>97\cdot5\%$ for $\rho_R{}^0$ and ρ_{BA}, and $>95\%$ for $\rho_R{}^+$.[15] It can be said with a high degree of confidence that a resonance effect does influence reactivity but this is small relative to the inductive effect. In no case was ρ_R $>1\cdot4$. In short, the data are very well correlated by equation (4), the indicated uncertainties representing a standard deviation. Substituents influence the reactivity of the

$$\log k^R = 7\cdot9 \pm 0\cdot4\sigma_I + 1\cdot4 \pm 0\cdot3\sigma_R{}^- - 0\cdot7 \pm 0\cdot2 \qquad (4)$$

ortho-position by both inductive and resonance effects, the inductive effect as measured by ρ values being 5·6 times larger than the resonance effect.

Reactivity of the para-*Position.*—The approach used to correlate reactivity at the position *para* to the substituent was similar to that employed for the ortho-position. Owing to a lack of tested values for SO_3^-, CO_2^-, and O^- substituents, these were omitted from correlations. First, a correlation in terms of a single substituent parameter was considered. The reactivity of the *para*-position cannot be expressed adequately in terms of a σ_I inductive parameter but a useful correlation does result with $\sigma_p{}^0$[17] [equation (2)]. These substituent constants are composed of a blend of inductive and resonance effects and are used when there is an absence of direct resonance interaction between a substituent and a reactive site. The correlation with $\sigma_p{}^0$ has $\rho_p{}^0$ $3\cdot7 \pm 0\cdot6$ and r 0·95. The t test for ρ indicates a $>99\cdot5\%$ confidence level. The standard deviation of the estimate is 0·35. The calculated rate constant for the parent ion is only 4·7% smaller than the experimental value.

Again equation (3) which considers both inductive and resonance substituent constants was employed. Because the six pyridinium ions examined do not contain strongly electron-withdrawing groups, nearly identical correlations result with $\sigma_R{}^-$ and $\sigma_R{}^0$[7] values. Correlations using σ_{BA} and $\sigma_R{}^+$[7] are inferior as evidenced by lower values for correlation coefficients, F, and t tests. Using $\sigma_R{}^-$ and $\sigma_R{}^0$ values, the calculated rate constant for the parent ion is $ca.$ 40% larger than the measured value, $\rho_I = 3\cdot7 \pm 0\cdot6$, $\rho_R = 4\cdot1 \pm 0\cdot6$, and the standard deviation of estimate is 0·28. The ρ values indicate that inductive and resonance effects influence reactivity almost equally.

Attempts to correlate ortho- and para-position reactivity using a multiparameter equation and Swain–Lupton[18] or Dewar–Grisdale[19] inductive and resonance parameters result in inferior correlations, especially for the *para*-position.

Comparison with Pyridinium Ion Acidity.—It is instructive to compare the effects of substituents on the rates of deprotonation of pyridinium ion carbon acids to give ylides (I) and (II) with the effects of substituents on

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the equilibrium acidity of pyridinium ions (III) and (IV). For both the carbon and nitrogen acids deprotonation takes place at an sp^2 hybridized centre; in both cases

(III)   (IV)
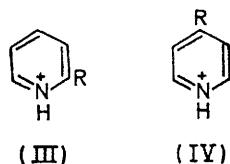
the electron pairs of the conjugate bases are part of the σ and not the π framework of the molecule.

The acidity of the *ortho*-substituted pyridinium ions shows a rough correlation with σ_I according to equation (2) (r 0·95, ρ_I 12·8, t test of ρ_I is >99·9%) but the standard deviation of estimate is large (0·80). This correlation indicates, just as with pyridinium ylide formation, that the major effect of the substituents is inductive in nature. However, acidities are better correlated with a multi-parameter equation which considers the influence of resonance as well as inductive effects. The data are best correlated with the σ_R^+ parameter which gives exalted values to strongly electron-donating groups (ρ_I 10·6, ρ_R^+ 1·4).[7]

The acidities of *para*-substituted pyridinium ions are not well correlated using an equation with a single substituent parameter reflecting a blend of inductive and resonance effects.[7] A multiparameter equation employing σ_R^+ values correlates the data very well. Just as is the case with the deprotonation of pyridinium ion carbon acids to give ylides (II), the inductive effects of the *para*-substituents are reduced and the resonance effects are enhanced (ρ_I 5·1, ρ_R^+ 2·7).[7,20]

In summary, our studies clearly show that the effects of substituents on pyridinium ylide formation can be large. The reactivity of an *ortho*-position is determined mainly by inductive effects; a small, but real, resonance effect operates as well. The sensitivity of a *para*-position to substituent effects is generally less than that of an *ortho*-position. Both resonance and inductive effects have an important influence on the reactivity of a *para*-position.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Varian A-60A instrument. Measurements of pD were made with a Beckmann model 1019 research pH meter equipped with either a Sargent–Welch (S-30070-10) or a Corning (476050) miniature combination electrode. Kinetic runs at 75·0 ± 0·5° were carried out in a constant temperature circulator. The temperature was checked with a National Bureau of Standards certified thermometer.

Chemicals and Stock Solutions.—All common laboratory chemicals were reagent grade. Deuterium oxide was 99·7%.

Pyridinium salts were dried over phosphoric anhydride at room temperature before use. Tetramethylammonium chloride (TMAC), sodium isobutyrate, and trishydroxymethylaminomethane were dried at 100° overnight and stored in a desiccator before use. These hygroscopic materials, as well as potassium hydroxide, were handled in a dry bag under nitrogen.

Deuteriated stock solutions of acetic acid, boric acid, citric acid, potassium mono- and di-hydrogen phosphate, sodium and potassium carbonate, sodium and potassium chloride, TMAC, sodium isobutyrate, and t-butyl alcohol were prepared by dissolving an appropriate weight of the analytical reagent or primary standard grade material in deuterium oxide and diluting to the mark in a volumetric flask.

Dilute DCl was prepared by diluting commercial concentrated HCl with D_2O. Stock sodium deuterioxide solution was prepared by dissolving freshly cut sodium in D_2O under nitrogen. Stock potassium deuterioxide solution was prepared by dissolving a weighed quantity of reagent grade KOH in D_2O. Solutions were standardized by potentiometric titration.

Pyridines.—Reagent grade pyridine, dried over KOH pellets, was used directly. 3-Chloropyridine was redistilled, b.p. 149—150° at 760 mmHg (lit.,[21] 148° at 744 mmHg), before use. Pyridine-3-sulphonic acid was recrystallized from water, m.p. >300° [lit.,[21] 357° (decomp.)]. Nicotinic acid was recrystallized from water, m.p. 235·5—236·0° (lit.,[21] 236—237°). 3-Aminopyridine was purified by vacuum sublimation at 59—60° and 0·1 mmHg, m.p. 63·5—65·0° (lit.,[22] 63—65°). 3-Methoxypyridine was redistilled, b.p. 80·0—80·5° at 25 mmHg (lit.,[23] 70—71° at 12 mmHg), prior to use. Methyl nicotinate, m.p. 41·0—41·5° (lit.,[24] 42·3—43·5°), was prepared from nicotinic acid. 3-Nitropyridine was prepared by the reduction of 2-chloro-3-nitropyridine.[25] Methyl 3-pyridyl sulphone was made (60%) by permanganate oxidation of 3-methylthiopyridine according to the procedure used to prepare the 2- and 4-isomers.[26] It was used directly to prepare the methiodide.

Pyridinium Iodides.—These salts were prepared by heating a solution of the 3-substituted pyridine (50 mmol) and methyl iodide (4 ml, 9·1 g, 64 mmol) in methanol or 85% aqueous methanol (10—30 ml) (Table 3) at 70° for 3—4 h. The mixture was cooled and the crystals filtered off and recrystallized from methanol, ethanol, or acetone. Compounds include 3-methoxycarbonyl-1-methyl-, m.p. 130—131·5° (lit.,[27] 129·5—130·2°), 3-chloro-1-methyl-, m.p. 138—138·5° (lit.,[28] 141—142°), 3-amino-1-methyl-, m.p. 120—121° (lit.,[29] 123°), 3-hydroxy-1-methyl-, m.p. 111·5—114·5° (lit.,[30] 114—116°), 1,3-dimethyl-, m.p. 96—97° (lit.,[14,31] 95°), 3-acetyl-1-methyl-, m.p. 165—166·5° (lit.,[31] 162°), and 1-methyl-3-nitro-pyridinium iodide, m.p. 217° (lit.,[31] 215°).

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Pyridinium Chlorides.—A solution of a 3-substituted 1-methylpyridinium iodide (45 ml) in the minimum volume of methanol or 85% aqueous methanol was heated at reflux with silver chloride (22·6 g, 158 mmol) while stirring. Silver salts then were removed. Following removal of the solvent the pyridinium chloride (Table 3) was recrystallized from ethanol or ethanol–25 ether (3 : 1).

Pyridinium Perchlorates.—The general method was adapted from that reported.[32] 1-Methylpyridinium perchlorate, m.p. 136·5—137·5° (lit.,[33] 135°), and 3-cyano-1-methylpyridinium perchlorate, m.p. 128—128·5° (lit.,[34] 135—137°), were prepared. The 3-chloro-salt is listed in Table 3.

Pyridinium Betaines.—The procedure for the preparation of 1-methylpyridinium-3-sulphonate was adapted from that reported for the synthesis of the 2- and 4-isomers.[35] The

was dictated largely by the position of its n.m.r. signal(s) relative to those of the substrate.

Periodically, the n.m.r. tube was removed, quenched in ice, and the n.m.r. spectrum of the solution recorded. Reactions were followed by measuring the change in the integrated area of the n.m.r. signal of the proton of interest with respect to that of a non-exchanging proton. The integrals of proton signals were measured in six successive sweeps, three in each direction, and the average value was taken. In favourable cases, a ring proton of the substrate served as the area reference. In others, an added standard was used. The reaction may be treated according to a pseudo-first-order method. An average of 15 points constituted each plot. Runs were followed for an average of 2·6 half-lives.

N.m.r. Spectra.—Those 3-substituted pyridinium ions having one of the substituents NO_2, CN, SO_2CH_3, SO_3^-,

TABLE 3

Properties and analyses of 3-substituted pyridinium salts [a]

Substituent	Anion	Yield (%)	M.p. (°C)	Calc. (%)			Formula	Found (%)		
				C	H	N		C	H	N
CH_3O	I^-	74	155·5—156·5	33·5	4·0	5·6	$C_7H_{10}INO$	33·7	3·95	5·55
CH_3SO_2	I^-	70	213—214	28·1	3·35	4·7	$C_7H_{10}INO_2S$	27·95	3·45	4·8
I	Cl^-	76	257·5 (decomp.)	28·2	2·75	5·5	C_6H_7ClIN	28·0	2·75	5·4
CH_3CO	Cl^-	82	197·5—198·5	56·0	5·85	8·15	$C_8H_{10}ClNO$	55·7	5·9	8·15
Cl	ClO_4^-	59	95·5—96	31·6	3·1	6·15	$C_6H_7Cl_2NO_4$	31·8	3·05	5·9

[a] Microanalyses were performed by Galbraith Laboratories, Knoxville.

pure product (42%) had m.p. >300°. Previous reports[36] about the m.p. (130°) appear to be in error (Found: C, 41·8; H, 4·15; N, 7·95. Calc. for $C_6H_7NO_3S$: C, 41·6; H, 4·05; N, 8·1%). 1-Methylpyridinium-3-carboxylate, m.p. 234·5—235·5° (lit.,[37] 230—233°), was prepared from methyl nicotinate.

Kinetic Runs.—Pyridinium salt was weighed into a volumetric flask (1—5 ml). When hygroscopic substrates were used, transfers were carried out in a dry bag filled with nitrogen. Stock solutions of buffer, internal standard, and supporting electrolyte were added by µl syringes and the solution was diluted to the mark with D_2O. Portions (*ca.* 1 ml) of the final solution were then transferred to an n.m.r. tube which was sealed immediately. The remainder of the solution was generally stored under nitrogen in a septum-stoppered test tube for later comparisons or pD measurements. The choice of anion of the pyridinium salt was determined largely by solubility. Iodides were avoided when acidic solutions were employed.

The ionic strength of the solutions was maintained at 1·0 by addition of KCl or NaCl. Sodium chloride was used with a perchlorate salt because of the low solubility of potassium perchlorate.

Except in the case of 1-methyl-3-cyanopyridinium perchlorate, where the substrate concentration employed was *ca.* 0·3M because of low solubility, all substrate concentrations were *ca.* 0·5M. The importance of charge-transfer interactions at these concentrations is not clear.[38]

Internal standards included methanol, t-butyl alcohol, TMAC, and sodium isobutyrate. The choice of a standard

CO_2^-, Cl, or I, show separate signals for 2- and 5-H and overlapped signals for 4- and 6-H. When the substituent is CH_3O or ND_2 the 2- and 6-H signals form one multiplet while those for 4- and 5-H show a second multiplet. The 3-methyl ion had overlapping 2- and 6-H signals but separated multiplets for 4- and 5-H. In the case of the 3-oxide, all the signals overlapped; methanol was employed as a standard.

Because signals overlapped, it was necessary to normalize areas to remove signal from unreactive positions. Equation (5) illustrates how this was accomplished when the rate of hydrogen exchange at 6-H was being determined. The 5-position served as the reference area and 4- and 6-H overlapped. The ratio on the right hand side was used to

$$[6\text{-H}]_0/[6\text{-H}] = [5\text{-H}]/([4\text{-H}] + [6\text{-H}] - [5\text{-H}]) \qquad (5)$$

construct the kinetic plot. The approach is similar for other patterns of signal overlap.

Product Analysis. Deuteriation of 1-Methylpyridinium-3-oxide.—Due to extensive signal overlap it is not possible to say with certainty that exchange occurs exclusively at the 2- and 6-positions. Therefore, a 0·65M sample in 0·30M-KOD was heated at 100° and the oxide was converted into its 3-methoxy-derivative. The solution was neutralized with DCl, stirred with sodium hydrogen carbonate (0·42 g, 5 mmol) and dimethyl sulphate (570 µl, 6 mmol) at room temperature for 8 h, the mixture filtered, and the n.m.r. spectrum of the filtrate recorded. That exchange had occurred exclusively at the 2- and 6-positions of the 3-oxide was evidenced by the fact that the n.m.r. spectrum of the

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methylation mixture was identical with that of a solution of 3-methoxy-1-methyl[2,6-$^2H_2$]pyridinium ion of 90% isotopic purity, obtained at the end of the kinetic run on this substrate at 75·0°.

pD Measurements.[39]—After the completion of each kinetic run at 75·0°, the pD of the solution recovered from the n.m.r. tube as well as that of a portion of the original unheated reaction mixture were determined at 75·0 ± 0·5°. Except in the case of the oxide substrate the pD values of the two solutions agreed to within 0·03, indicating that no significant change occurred.

Since the meter was standardized with protio-buffers, it is necessary to add a correction to the meter readings to convert these to pD values. For pD measurements at 25°, the pD value is reported to be obtained by adding 0·41 to the meter reading.[40] This difference was observed at 25° in the present work when 10^{-2}M-HCl and 10^{-2}M-DCl solutions of 1·0 ionic strength were employed. New readings on both solutions were obtained at 75·0 ± 0·5°, and these were found consistently to differ by 0·35 units. Therefore, for measurements at 75·0° the pD value was obtained by adding a correction of 0·35 to the meter reading.

As an additional check, the meter was standardized at pD 10·422 at 75·0 ± 0·5° against a standard deuterium carbonate buffer;[41] pD measurements on several sample solutions at 75·0 ± 0·5° were then performed. The pD

value was taken as that given by the meter reading. These values were in good agreement with those obtained on the same sample solutions by first standardizing and linearizing the meter against National Bureau of Standards protio-buffers and then adding 0·35 to the meter reading.

Control Runs.—A series of control runs in protio-buffers were performed for the following 3-substituted 1-methyl-pyridinium ions: R = SO_3^-, Cl, I, CO_2^-, OMe, and ND_2. In each case, the solutions were identical with those employed in the kinetic runs. A small amount of t-butyl alcohol internal standard was added to each solution. The n.m.r. spectra of the solutions were recorded at the time zero and after periods equivalent to three and ten half-lives. In every case, the ratio of the area of the internal standard signal to that of the signals for the ring protons of the substrate remained constant for up to 10 half-lives, and no detectable changes were apparent in the n.m.r. spectra.

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