Kinetics of Displacement Reactions with Pyridines as both Leaving Group and Nucleophile [1]

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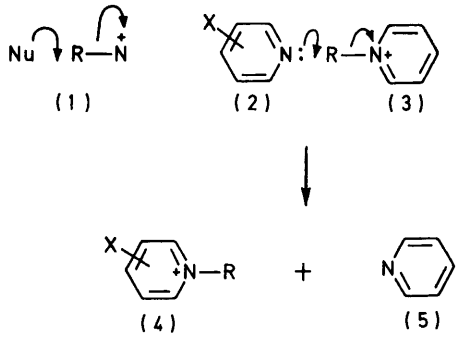
Kinetic rates are determined for the transfer of *N*-benzyl, methyl, and ethyl groups from a pyridinium cation to a substituted pyridine. Rates (and equilibrium constants) vary significantly with alkyl group, nucleophilicity of the substituted pyridine, and with solvent. Transfer rates for methyl and ethyl depend on the anion showing that the corresponding alkyl iodides and bromides are intermediates. Exploratory experiments designed to catalyse electrophilic substitution in substituted heteroaromatics are described.

NUCLEOPHILIC displacements of a group attached to quaternary nitrogen [2] [see (1)] are of current interest in two contexts: (i) they can be synthetically important when more conventional alkylating or arylating agents of type R–X are unstable;[3] (ii) in attempts to catalyse electrophilic substitution of heterocycles involving reversible attack at pyridine-like nitrogen atoms (see below). We have therefore investigated reactions of type (2) + (3) ⟶ (4) + (5). Such reactions in which a substituted pyridine displaced another pyridine molecule have apparently not previously been investigated, either preparatively or kinetically. However the transfer of



1-substituents from a pyridinium cation to a variety of nucleophiles has been extensively studied (for a review see ref. 4). Among these the following examples involve an amine as nucleophile: styryl to piperidine,[5] diethylaminoethyl to aminoquinoline,[6] each of 2,4-dinitrophenyl,[7] 2,4-dinitro-6-carboxyphenyl [8] and pteridinylmethyl to aniline,[9] and benzyl groups to mono-, di-, and tri-n-butylamine.[10] Other workers have investigated the transfer of *N*-benzyl groups from *N*-benzyl-*N*-methylpiperidinium halides to form *N*-benzylpyridinium salts and *N*-methylpiperidine.[11]

Transfer of 1-*Substituents of Pyridinium Cations to Pyridines under Preparative Conditions* (Table 1).—The tabulated examples show that an *N*-methyl group is transferred from the pyridine nitrogen at $T > 140$ °C, in good yield if a large excess of pyridine used as nucleophile is present (Table 1; Nos. 1 and 2). *N*-Benzyl groups are transferred somewhat more readily (Table 1; Nos. 3 and 4), and the 2,4-dinitrophenyl group quite rapidly at 115 °C although in the latter case (Table 1; No. 5) considerable decomposition occurred which resulted in reduced yield.

Kinetic Investigation of Transfer of 1-*Substituents from Pyridinium Cations to Pyridines* (Table 2).—To gain further insight into the qualitative aspects of these reactions, kinetic determinations were undertaken. Trials with 1-(2,4-dinitrophenyl) or 1-(5-nitro-2-pyridyl) as the *N*-substituent indicated that the significant decomposition under the kinetic conditions could complicate the interpretation, but that the utilisation of *N*-methyl, *N*-ethyl, and *N*-benzyl groups should provide clean kinetics.

1-Benzylpyridinium salts were treated with 3- or 4-picoline under second-order conditions. Equilibrium constants were determined by the n.m.r. method by integrating specific peaks characteristic of the products and reactants (Table 3), and these same peaks were used to follow the kinetic rates. For the reaction of 1-benzylpyridinium bromide with 4-picoline, kinetics were obtained at five temperatures over the range 110—150 °C (Table 2; Nos. 1a—e) and the activation enthalpies for the forward and the reverse reaction are respectively $\Delta H^{\ddagger}_{373}$ (f) = 27 ± 6 kcal mol^{-1} and $\Delta H^{\ddagger}_{373}$ (r) = 25 ± 6 kcal mol^{-1} while the corresponding value for the equili

TABLE 1

Pyridine displacements of 1-substituted pyridinium cations

	Pyridinium quaternary salt			Pyridine				Product			
	Substs.	Anion	Wt. (g)	Subst.	Vol. (ml)	*T* (°C)	Time (h)	%	M.p. (°C)	Lit. m.p. (°C)	Ref.
1	1-Methyl	I⁻	0.51	4-Methyl	15	144	5	94	157—158	157—158	15
2	1,4-Dimethyl	I⁻	0.5	(none)	5	155 [a]	24	60 [b]	*c*		
3	1-Benzyl	Br⁻	2.1	4-Methyl	5 [d]	150	3	71 [e]	159—161	*f*	
4	1-Benzyl-4-methyl	Br⁻	1.5	(none)	5	115	24	*g*			
5	1-(2,4-Dinitrophenyl)-3-methyl	Cl⁻	0.5	(none)	15	115	4	65	206—209	190—191	23

[a] Reaction in sealed tube. [b] By n.m.r. analysis. [c] Product not isolated. [d] Reaction carried out in $HCONMe_2$ (20 ml). [e] Isolated yields. N.m.r. analysis of reaction mixtures showed 90% conversion into products. [f] Product has not been reported. [g] ^{1}H N.m.r. analysis showed 90% conversion into the product.

TABLE 2

Exchange reactions of pyridinium salts

No.	Reactants: Pyridinium salt (A) Cation	Anion	Pyridine nucleophile (B)	Molar ratio (A : B)	Solvent	Temp. (°C)	K equilib.	$k_{f(2)}$ ($\times 10^5$) / l mol^{-1} s^{-1}	$k_{f(1)}$ ($\times 10^5$) / s^{-1}	Corr. coeff. for k_f	k_f ($\times 10^5$) / l mol^{-1} s^{-1}
1a	1-Benzyl	Br^-	4-Methyl	1 : 1	PhCN	110	2.07	1.67		0.999 0	0.81
b				1 : 1	PhCN	120	2.13	3.51		0.998	1.66
c				1 : 1	PhCN	130	2.28	13.35		0.999 8	5.91
d				1 : 1	PhCN	140	2.33	26.99		0.999 7	11.59
e				1 : 1	PhCN	150	2.56	42.10		0.999	15.33
f				1 : 1	$HCONMe_2$	130	5.14	22.60		0.999 6	4.41
2	1-Benzyl	Cl^-	4-Methyl	1 : 1	$HCONMe_2$	130	4.28	22.90		0.996 8	5.35
3	1-Benzyl	Br^-	3-Methyl	1 : 1	PhCN	120	1.33	2.83		0.997 5	2.13
4	1-Methyl	TsO^-	4-Methyl	1 : 10	$HCONMe_2$	140			0.42	0.999 6	
5	1-Methyl	I^-	4-Methyl	1 : 10	$HCONMe_2$	140			3.10	0.997	
6	1-Ethyl	I^-	4-Methyl	1 : 10	$HCONMe_2$	160			2.20	0.999	
7	1-Ethyl	Br^-	4-Methyl	1 : 10	$HCONMe_2$	160			3.76	0.998 5	

TABLE 3

N.m.r. analysis for equilibrium constants and kinetics [a]

Reaction no.[b]	Solvent	Reactants: Peak used	Mult.	J	δ	Products: Peak used	Mult.	J	δ
(1a—e)	PhCN	4-Me	1		1.50	4-Me	1		1.90
(1f), (2)	$HCONMe_2$	2,6-H	2	6	9.65	2,6-H	2	6	9.45
(3)	PhCN	3-Me	1		2.23	3-Me	1		2.48
(4), (5)	$HCONMe_2$	1-Me	1		4.20	1-Me	1		4.10
(6), (7)	$HCONMe_2$	2,6-H	2	6	8.80	2,6-H	2	6	8.60

[a] 2,6-H refers in all cases to the quaternised ring. [b] See Table 2.

brium is ΔH_{373} (eq) $= 1.6 \pm 0.5$ kcal mol^{-1}.* As would be expected, the enthalpy difference for the equilibrium is small but favours the right-hand side of the equilibrium presumably owing to the stabilising effect of the 4-methyl substituent in the pyridinium ring.

In dimethylformamide as solvent, the rate constants for the forward reaction (k_f) and the equilibrium constants (K) for the reaction of 1-benzylpyridinium bromides and chloride were identical within experimental error (Table 2; Nos. 1f and 2) showing that the anion has negligible influence. However comparison of Table 2; Nos. 1c and 1f discloses appreciable solvent effects on both rate and equilibrium constants: the more highly polar dimethylformamide increased both k_f and K for the reaction, while leaving the rate constant for the reverse reaction (k_r) almost unchanged. It is curious that K should be so much altered. A single experiment with nitrobenzene as solvent indicated that it behaved very similarly to benzonitrile, whereas the rate was very slow in protic solvents such as water or phenol.[4] Similar solvent effects have been reported for the reaction between 1-benzylpyridinium halides and aliphatic amines.[11] The 4-methyl group considerably stabilises the pyridinium cation, but a 3-methyl group has much less effect as shown by the comparison of Nos. 1b with 3 (Table 2): both k_f and K are much less, while k_r is somewhat increased.

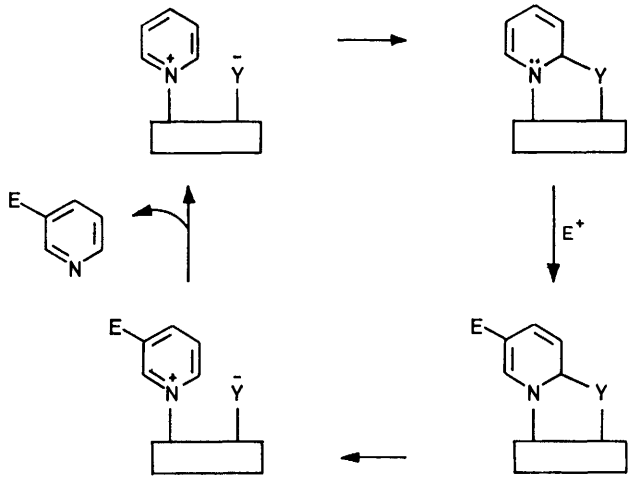
The less reactive 1-methyl- and 1-ethyl-pyridinium cations were treated with 4-picoline under pseudo first-order conditions (Table 2; Nos. 4—7). The kinetics were again followed by the n.m.r. method (Table 3). Good first-order rate plots were obtained.[4] Preliminary work [4] had indicated that the anion was playing a role in these reactions and the kinetic rate constants confirm this. 1-Methylpyridinium iodide reacts some 7 times as fast as the tosylate. For the 1-ethyl analogue, the bromide reacted significantly more rapidly than the iodide and no reaction was detected for the tosylate or tetrafluoroborate unless the temperature was raised.[4] We postulate that the halide anions react by intermediate formation of alkyl halides: the more rapid reaction of bromide is unexpected but may be due to a reduction in the nucleophilicity of the iodide (*cf.* ref. 12) as a result of charge-transfer complex formation.

Attempted Catalysis of Electrophilic Substitution of Pyridine.—Our results on the transfer of 1-substituents of pyridinium cations to pyridines led us to consider the possibility of utilising this type of displacement to design a catalyst which would facilitate the electrophilic substitution of pyridines. In particular we envisaged a system in which (i) pyridine initially formed a pyridinium salt with a catalyst molecule; (ii) a strategically placed functional group in the catalyst activates the pyridine ring by addition at the 2-position; (iii) electrophilic substitution of the resulting dienamine occurs; (iv) the substituted pyridine is displaced by a new pyridine molecule and the process is repeated. This type of sequence is summarised in the Scheme.

We have investigated four simple molecules which might function as catalysts in the manner depicted in the Scheme. These are 8-chloro-5,7-dinitroquinoline (6),[13] quinoline-8-sulphonyl chloride (7) and 10-chloro-1,7-phenanthroline (8),[14] and its 4-piperidino-derivative (9). In each case the anticipated mode of action is easy to envisage, *i.e.* displacement of the chlorine by pyridine followed by activation by the quinoline or phenan-

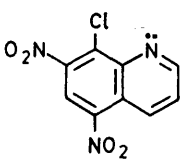
* Significant entropy values cannot be obtained owing to uncertainty in the intercept of the regression line $\log k = f(1/T)$.

throline nitrogen atom. Attempts to isolate pyridinium salts from the molecules (6)—(9) were not successful, although the sulphonyl chloride undoubtedly formed a salt in solution. Neither were any attempts to catalyse pyridine substitution using these molecules (6)—(9)

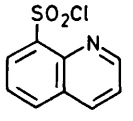


SCHEME

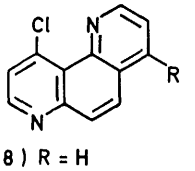
successful. Typically compound (9) and pyridine under several conditions with bromine, acetic anhydride, or acetyl chloride gave no trace of 3-substituted pyridines (see Experimental section). We conclude that the geometry and reactivity of the molecules (6)—(9) are not suitable for activating the pyridine molecule.



(6)



(7)



(8) R = H
(9) R = Piperidino

EXPERIMENTAL

I.r. spectra were recorded with Perkin-Elmer 237 and 257 spectrophotometers, and n.m.r. spectra with Varian HA-100 and Perkin-Elmer R12 instruments. A Hitachi–Perkin-Elmer RMU6E mass spectrometer was used to record mass spectra. G.l.c. analyses were performed using a Perkin-Elmer F11 gas chromatograph equipped with flame-ionisation detectors. A stationary phase of Apiezon-L on Chromosorb P (15 : 85) was used: oven temperatures were in the range 200—220 °C.

Preparation of Pyridinium Salts.—The quaternary salts for the present investigation were prepared by the following general method. A mixture of the pyridine (0.11 mol) and the alkylating or arylating agent (0.1 mol) was refluxed for 2—6 h in MeCN (50 ml). After removal of the MeCN, the residue was crystallised several times from a suitable solvent.

The compounds prepared by this method were 1-methylpyridinium iodide, m.p. 123—125 °C [lit.,[15] 123—125 °C], 1-methylpyridinium tosylate, m.p. 137—138 °C [lit.,[16] 138—139 °C], 1,4-dimethylpyridinium iodide, m.p. 157—158 °C [lit.,[15] 157—158 °C], 1-benzylpyridinium bromide, m.p. 97—99 °C [lit.,[17] 98—100 °C], 1-benzylpyridinium chloride, m.p. 102—104 °C [lit.,[18] 105—106 °C], 1-benzyl-4-methylpyridinium bromide, m.p. 159—161 °C [Found: C, 59.0; H, 5.4; N, 5.3. $C_{13}H_{14}BrN$ requires C, 59.1; H, 5.3; N, 5.3%], 1-benzyl-4-methylpyridinium chloride, m.p. 78 °C [lit.,[19] 78 °C], 1-ethylpyridinium bromide, m.p. 119—121 °C [lit.,[20] m.p. 111—112 °C], 1-ethylpyridinium iodide, m.p. 89—90 °C [lit.,[21] 90 °C], 1-ethylpyridinium toluene-*p*-sulphonate, m.p. 75 °C, 1-ethylpyridinium fluoroborate, m.p. 59 °C [lit.,[22] 58.5—59.5 °C], 1-(2,4-dinitrophenyl)-pyridinium chloride, m.p. 206—209 °C [lit.,[23] 190—210 °C], 1-(2,4-dinitrophenyl)-3-methylpyridinium chloride, m.p. 212—213 °C [lit.,[23] 208—209 °C], and 1-(5-nitro-2-pyridyl)-pyridinium chloride (as picrate), m.p. 181 °C [lit.,[24] 181.5 °C].

Pyridine Displacements of 1-Substituted Pyridinium Cations.—The pyridinium halide and the pyridine nucleophile were heated either at reflux temperature or in a sealed tube (see Table 1). Evaporation gave either pure products or mixtures whose composition was examined by n.m.r. spectroscopy. In most cases pure products were obtained from the mixtures by recrystallisation. See Table 1 for details. 10-Chloro-1,7-phenanthroline was prepared according to ref. 14.

10-*Hydroxy*-4-*piperidino*-1,7-*phenanthroline.*— 4-Chloro-10-hydroxy-1,7-phenanthroline, m.p. 200—201 °C [lit.,[25] 196—196.5 °C], prepared according to the method of Surrey and Cutler,[25] (200 mg, 8.7×10^{-4} mol) was refluxed in anhydrous piperidine (2 ml) for 1 h. After removal of the piperidine, the residue was treated with 6—7 ml NH_3 solution (6M), and the mixture extracted with $CHCl_3$ (4×4 ml). The residue, obtained on evaporation of the $CHCl_3$, was crystallised from benzene–light petroleum (b.p. 60—80 °C) to give yellow microcrystals, m.p. 118—119 °C (225 mg, 93%) of 10-*hydroxy*-4-*piperidino*-1,7-*phenanthroline* (Found: C, 72.6; H, 6.2; N, 14.7. $C_{17}H_{17}N_3O$ requires C, 73.1; H, 6.1; N, 15.0%).

10-*Chloro*-4-*piperidino*-1,7-*phenanthroline* (9).—10-Hydroxy-4-piperidino-1,7-phenanthroline (3.38 g, 1.21×10^{-2} mol) was refluxed for 1.5 h in freshly distilled phosphoryl chloride (15 ml) to which 5—6 drops of water had been added. The reaction mixture was poured into ice (100 g), the mixture basified with NH_3 solution and extracted with $CHCl_3$ (5×50 ml). The $CHCl_3$ extract was chromatographed over silica gel. 10-*Chloro*-4-*piperidino*-1,7-*phenanthroline* migrated out in the benzene–EtOAc (4 : 1 and 1 : 1) eluates. Crystallisation from benzene–cyclohexane (1 : 1) gave needles, m.p. 101—102 °C (2.0 g, 63%) (Found: N, 13.7; Cl, 11.5%; M^+ 297. $C_{17}H_{16}ClN_3$ requires N, 14.1; Cl, 11.9%; M^+ 297); $\nu_{max.}$ (Nujol) 1 613, 1 575, 1 563, and 1 552 cm^{-1}; $\delta(CDCl_3)$ 8.85 (1 H, d, *J* 6 Hz, H-8), 8.78 (1 H, d, *J* 5 Hz, H-2), 8.23 (1 H, d, *J* 10 Hz, H-5 or H-6), 7.97 (1 H, d, *J* 10 Hz, H-6 or H-5), 7.64 (1 H, d, *J* 5 Hz, H-3), 7.05 (1 H, d, *J* 6 Hz, H-9), 3.10—3.35 [4 H, m, $-N-(CH_2)_2$], and 1.60—2.10 (6 H, m).

Kinetic Studies.—The solvents used for kinetic studies were purified by fractional distillation. Pyridine and 4-methylpyridine were distilled over KOH, and stored over BaO.

The required amounts of the reactants dissolved in the appropriate solvent were placed in glass tubes (internal diameter 5 mm, wall thickness 1 mm) which were then sealed and placed in a thermostatically controlled heating block. The tubes were removed after appropriate intervals of time, cooled quickly, and the contents analysed by n.m.r. spectroscopy. A Perkin-Elmer R12 60 MHz instrument was used for the n.m.r. measurements.

The concentrations of the reactants were 0.5—1 mol l^{-1}.

For the reactions of the 1-benzylpyridinium salts, the reactants were taken in 1 : 1 ratio and the rate constant determined by equation (1). The rate constant in the forward direction k_f was determined from plots of the logarithmic function on the r.h.s. of equation (1) [26] *vs.* t: good straight line plots were obtained,[4] confirming the second-order nature of the reaction. In equation (1) the initial contribution of each of the reactants (2) and (3) = a; the equilibrium concentration of each of the products (4) and (5) = x, and the concentration of each of the products after time t = y.

$$k_f t = \frac{x}{2a(a - x)} \ln \frac{y(a - 2x) + ax}{a(x - y)} \quad (1)$$

The determinations for the 1-methyl- and 1-ethyl-pyridinium salts were made under pseudo first-order conditions, a 10 times excess of the displacing nucleophile being taken. The pseudo first-order rate constants (k) were determined by using equation (2) where a_0 is the initial concentration of the pyridinium salt.

$$k = \frac{1}{t} \ln \frac{a_0}{a_0 - y} \quad (2)$$

The equilibrium constants K were calculated from the ratio of concentrations of products and reactants at equilibrium (after 24 h).

Second-order rate constants for the reverse reaction were calculated from the relation $k_r = k_f/K$.

Experiments Carried Out to test Catalytic Activity of (9).—Mixtures of pyridine, the appropriate reagent, and compound (9) were subjected to the reaction conditions shown in Table 4. The general work-up procedure was as follows: the reaction mixture was diluted with water (10 ml) and

TABLE 4

Attempts to use compound (9) as a catalyst for electrophilic substitution of pyridine

	Amounts of reactants (g)				Reaction
No.	Pyridine	Reagent	Compound (9)	Temp. (°C)	time (h)
1	2.0	Br_2; 0.8	0.3	25	1
2	2.0	Br_2; 0.8	0.3	25	18
3	2.0	Br_2; 0.8	0.3	25	168
4	1.0	Br_2; 0.3	0.05	115	1
5	1.0	Br_2; 0.3	0.05	115	6
6	1.0	Ac_2O; 0.3	0.05	115	4
7	2.0	AcCl; 0.4	0.05	115	4

neutralised by the addition of Na_2CO_3 solution (for bromination experiments $NaHSO_3$ was added before neutralisation to destroy any bromine present). The mixture was then extracted with $CHCl_3$ (10 × 5 ml). The dried extract was concentrated (10 ml) and examined by t.l.c. silica gel GF 254; EtOAc–EtOH (5 : 1) as eluant and g.l.c. In none of the experiments were any of the 3-substituted products, 3-bromo- or 3-acetyl-pyridine detected.

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