553. *Nucleophilic Displacement Reactions in Aromatic Systems. Part IX.*[1] *Kinetics of the Reactions of 2-, 6-, or 8-Chloro-9-methylpurine with Piperidine in Ethanol*

By G. B. Barlin and N. B. Chapman

The kinetics of the reactions of 2-, 6-, or 8-chloro-9-methylpurine with piperidine in ethanol have been measured; at 40·0°, the 6-chloro-compound is significantly more reactive than the 8-isomer, the 2-chloro-compound is far less reactive than either, and this relation persists over a wide range of temperature.

The Arrhenius parameters are discussed. Ionisation constants and ultraviolet spectra are also recorded.

Considerable confusion has existed regarding the reactivity of chloropurines towards nucleophilic substitution. Sutcliffe and Robins [2] recently suggested that cation and anion formation (in strong acid and base, respectively) are responsible for the apparent anomalies, and their experiments with 9-(tetrahydro-2-pyranyl)-2,6,8-trichloropurine are consistent with this view.

In an attempt to clarify the situation further, the kinetics of nucleophilic substitution by piperidine in 99·8% ethanol in the simple 2-, 6-, and 8-chloro-9-methylpurines (in which *N*-methylation precludes anion formation) have now been determined, and the relative reactivities of these compounds have been compared with predictions based on quantum-mechanical calculations [3,4] for purine.

Chloro-9-methylpurines react with piperidine according to the following scheme:

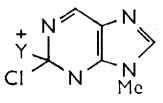
$$RCl + R'_2NH \longrightarrow RNR'_2 + HCl$$
$$HCl + R'_2NH \rightleftharpoons [R'_2NH^+_2] + Cl^-$$

The first step is rate-determining and the reaction is of the second-order (first-order with respect to each reactant). Because two moles of piperidine are consumed per mole of chloropurine, the second-order rate coefficient must be calculated from the expression:

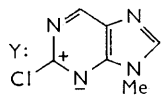
$$k = \frac{2{\cdot}303}{t(a - 2b)} \log \frac{b(a - 2x)}{a(b - x)}$$

where a is the initial concentration of amine, b the initial concentration of chloropurine, x the concentration of chloride ion produced at time t (sec.), and k the second-order rate coefficient in l. mole^{-1} sec.$^{-1}$. Table 1 gives details of some typical kinetic experiments. Table 2 summarises all the results, and Table 3 gives the energies of activation, E, and the frequency factors, log A.

We assume that the main features of reaction mechanism, almost certainly bimolecular, are common to the three reactions studied. There is no experimental evidence in this case to decide between a one-stage mechanism with a transition state represented approximately by structure (I), and a two-stage mechanism involving the formation of a complex with



(I)



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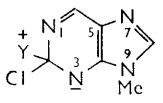

(III)

[Y represents the nucleophile, piperidine]

structure (I), the transition state for its formation having structure (II). If nucleophilic aromatic substitution in chloro-compounds, in which base-catalysis is absent is regarded

[1] Part VIII, N. B. Chapman, D. K. Chaudhury, and J. Shorter, *J.*, 1962, 1975.
[2] E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 1662.
[3] (*a*) R. C. Miller and P. G. Lykos, *Tetrahedron Letters*, 1962, 493; (*b*) R. C. Miller, P. G. Lykos, and H. N. Schmeising, *J. Amer. Chem. Soc.*, 1962, **84**, 4623; (*c*) B. Pullman, *J.*, 1959, 1621.
[4] S. F. Mason, "The Chemistry and Biology of Purines," a CIBA Foundation Symposium, ed. Wolstenholme and O'Connor, Churchill, London, 1957, p. 72.

TABLE 1

Reactions of piperidine

2-Chloro-9-methylpurine at 84·8°

Piperidine 0·0701M, chloro-compound 0·0144M

Time (min.)	30·0	60·0	90·0	130·0	168·0	216·0	280·0	370·0
Reaction (%)	12·1	23·2	31·8	41·8	48·5	56·6	63·6	72·3
10^4k	10·6	11·0	10·9	11·0	10·6	10·7	10·2	10·2

Mean $10^4k = 10{\cdot}6_5 \pm 0{\cdot}2_5$; after correction for solvent expansion, 11·4

6-Chloro-9-methylpurine at 32·6°

Piperidine 0·0757M, chloro-compound 0·0193M

Time (min.)	5·00	7·00	9·00	12·0	15·0	20·0	27·0	35·0
Reaction (%)	32·3	40·4	47·9	56·7	63·2	71·0	78·8	85·5
10^3k	18·8	18·4	18·6	18·6	18·3	17·7	17·3	17·4

Mean $10^3k = 18{\cdot}1 \pm 0{\cdot}04$; after correction for solvent expansion, 18·3

8-Chloro-9-methylpurine at 12·3°

Piperidine 0·0719M, chloro-compound 0·0145M

Time (min.)	15·0	35·0	58·0	80·0	100·0	130·5	170·0	215·0	260·0
Reaction (%)	13·4	27·7	41·7	51·5	58·4	66·5	74·4	81·3	85·3
10^4k	23·0	22·8	23·8	23·8	23·6	23·2	23·0	23·0	22·4

Mean $10^4k = 23{\cdot}2 \pm 0{\cdot}4$; after correction for solvent contraction, 23·0

TABLE 2

Kinetic results for the reactions of chloro-9-methyl purines with piperidine

Chloro-substituent	Temp.[a]	[Piperidine] [b]	[Chloro-cpd.]	10^4k [c]	$10^4k_{corr.}$ [d]	$t_{\frac{1}{2}}$ [e]	$t\,/t'_{\frac{1}{2}}$ [f]	$(t_{\frac{1}{2}}/t_{\frac{1}{2}})_{calc.}$ [g]
2-	64·1°	0·0711	0·0144	3·07	3·22	—	—	—
2-	74·0	0·0699	0·0144	5·73	6·10	—	—	—
2-	84·8	0·0701	0·0144	10·6	11·4	178	—	—
2-	84·8	0·0364	0·00722	10·5	11·3	334	1·88	1·88
2-	94·8	0·0368	0·00721	18·1	19·8	—	—	—
6-	13·5	0·0756	0·0193	54·1	54·1	—	—	—
6-	24·5	0·0727	0·0193	115	115	16·1	—	—
6-	24·5	0·0366	0·0096	122	122	30·8	1·92	1·98
6-	32·6	0·0757	0·0193	181	183	—	—	—
6-	40·4	0·0753	0·0193	291	295	—	—	—
8-	12·3	0·0719	0·0145	23·2	23·0	—	—	—
8-	22·8	0·0703	0·0145	42·3	42·3	44	—	—
8-	22·8	0·0354	0·00073	40·2	40·2	92	2·09	1·98
8-	31·2	0·0719	0·0145	65·8	66·4	—	—	—
8-	40·0	0·0688	0·0144	103	104	—	—	—

[a] ±0·1°. [b] The reactions do not appear to be significantly catalysed by amines; cf. S. D. Ross, "Progress in Physical Organic Chemistry," ed. S. G. Cohen, A. Streitwieser, and R. W. Taft, Interscience, New York, 1963, p. 31. [c] In l. mole^{-1} sec.$^{-1}$; the standard deviation was usually below 3%. [d] Corrected for solvent expansion. [e] Time for 50% reaction, in min. [f] The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations. [g] Calculated by assuming second-order reaction.

TABLE 3

Chloro-compound	10^5k * (l. mole^{-1} sec.$^{-1}$)	E ‡ (kcal. mole^{-1})	log A §	Localisation energy ¶ for nucleophilic substitution (units of β)
2-Chloro-9-methylpurine...	$6{\cdot}1_6$ †	14·4	5·8	2·323
6-Chloro-9-methylpurine...	2880 †	11·3	6·3	2·176
8-Chloro-9-methylpurine...	1040	$9{\cdot}6_4$	4·7	2·176

* At 40°. † Calculated from the Arrhenius parameters. ‡ Accurate to ±0·3 kcal. mole^{-1}. § Accurate to ±0·4 unit. ¶ Ref. 3*c*.

as pursuing the intermediate-complex mechanism, the formation of the complex is usually found to be rate-limiting. For simplicity we discuss the reaction parameters with the one-stage mechanism in mind.

The results clearly show that, in the monochloro-9-methylpurines (in which the reactivity

of the chloropurine has been modified by the effect of the 9-methyl group), nucleophilic substitution by piperidine under the conditions studied is preferred at position 6, followed closely by position 8. At both positions reactivity at 40·0° is much greater than at the 2-position, and this relation persists over a wide range of temperature. The energy of activation is less for the reaction of the 8- than for that of the 6-chloro-compound (9·64 compared with 11·3 kcal. mole^{-1}), but this is modified by a considerably smaller value of log A for the reaction of the 8-isomer so that the 6-isomer reacts more rapidly than 8-chloro-9-methylpurine at 40·0°. The energy of activation for the reaction of 2-chloro-9-methylpurine with piperidine is much greater than for the reactions of its two isomers (whereas log A is almost the same as for the reaction of the 6-isomer) so that the 2-isomer is the least reactive. The small difference between the log A values for the reactions of the 2- and 6-isomers is barely significant when compared with the estimated error, so that their difference in reactivity results almost entirely from the difference in heat of activation. This may well reflect a corresponding potential-energy difference; cf. the localisation energies for these reactions (Table 3).

Although the inductive effect of the 9-methyl group is unlikely to affect the rates of reaction of the 2- and 6-chloro-derivatives appreciably, it would be expected to increase the electron density in the imidazole ring. Hence, the reactivity of 8-chloro-9-methylpurine towards nucleophilic reagents may well be less than that of the neutral molecule of 8-chloropurine, and the reactivity of this molecule may therefore be equal to that of its 6-isomer. Calculations of electron density (and, in one case, of localisation energy [3c]) for purine in relation to nucleophilic substitution have been carried out by a number of workers [3,4] and have led to widely differing predictions of relative reactivity. Although no allowance was made for the effects of the chlorine atom, of the methyl group, and of solvation of the transition state, the calculations of localisation energy by Pullman [3c] predict an order of reactivity $6 \sim 8 > 2$ and appear to represent most nearly the position observed with chloro-9-methylpurines. However, the reaction of the 8-chloro-compound shows a significantly smaller log A than the other two reactions. There seems no reason to assume substantial differences in the solvation of the initial states of the reactions being considered. If this is true, then the reaction of the 8-chloro-compound may well be characterised by a more highly solvated transition state than those of the other two reactions, possibly corresponding to further progress along the reaction co-ordinate. The substantially reduced heat of activation may be achieved partly at the expense of a relatively highly arranged transition state, resulting in a corresponding decrease of entropy.

Annelation of the imidazole ring to the chloropyrimidine ring decreases the reactivity of the chlorine atom in the 2-chloro-compound towards nucleophilic substitution by piperidine, since it increases the energy of activation by 2·0 kcal. mole^{-1}, with little change in log A (for the reaction of 2-chloropyrimidine: [5] $E = 12{\cdot}4$ kcal. mole^{-1}, log $A = 5{\cdot}7$). For the 6-chloro-compound, the energy of activation is 0·8 kcal. mole^{-1} greater and log A is 1·3 units greater than the values estimated for 4-chloropyrimidine.[5] The deactivating effect of the annelation on the reactivity of the 2-chloro-compound may be due to bond fixation in the 4,5-position, preventing full participation of N-1 in structures contributing to the transition state, *e.g.*, structure (III). A similar effect has been claimed for 3-chloroisoquinoline.[6]

The ionisation constants and ultraviolet spectra for some chloropurines are given in Table 4. The 2- and 6-chloro-compounds are weaker bases than the 8-chloro-compound since the 2- and 6-substituents are nearer to the basic centre at N-3. Likewise the effect on the pK_a of the neutral acids is greatest when the chlorine atom is in the 8-position. Insertion of more than one chlorine atom enhances the above effects. Substitution by a methyl group at the 9-position has a small effect on the basic ionisation constants and ultraviolet spectra.

[5] N. B. Chapman and C. W. Rees, *J.*, 1954, 1190.
[6] N. B. Chapman and D. Q. Russel-Hill, *J.*, 1956, 1563.

TABLE 4

Physical properties

Purine deriv.	Ionisation (water, 20°) Charged species involved	pK_a	Spread	Concn. (M)	A.w.l.[a] (mμ)	Spectroscopy in water (shoulders and inflections in italics) $\lambda_{max.}$ (mμ)	log ε	pH [e]
—	Cation	2·39[b]	—	—	—	—	—	
	Anion	8·93[b]	—	—	—	—	—	
2-Cl	Neutral	—	—	—	—	*207*, 273	*4·31*, 3·87	5·0
	Cation	0·69	0·04	0·0001	286	*221*, 270·5	*3·52*, 3·91	−1·38
	Anion	8·21	0·01	0·0001	294	213, 278[f]	4·33, 3·89	10·5
6-Cl	Neutral	—	—	—	—	*245*, 265[g]	*3·64*, 3·95	4·0
	Cation	0·45	0·03	0·0001	276	233, *257*, 262, *269*	3·65, *3·91*, 3·97, *3·85*	−1·85
	Anion	7·88[c]	0·03	0·0001	285	210, 274[g]	4·33, 3·92	10·0
8-Cl	Neutral	—	—	—	—	*216*, 269	*4·15*, 3·98	4·0
	Cation	1·77	0·04	0·0001	230	269	3·97	−0·26
	Anion	6·02	0·02	0·0001	286	275[h]	4·02	9·0
2,6-Cl_2	Neutral	—	—	—	—	211, *249*, 275	4·35, *3·55*, 3·95	4·0
	Cation	−1·16	0·06	0·0001	290	235, *242*, 273	3·63, *3·49*, 3·98	−2·28
	Anion	7·06	0·03	0·0001	300	219, 280[f]	4·33, 3·93	9·5
2,6,8-Cl_3	Neutral	—	—	—	—	213, 248, 280, *288*[f]	4·43, 3·65, 4·11, *4·00*	1·0
	Cation	−3·1	0·1	0·00005	230	210, *227*, *245*, 279, 287	4·45, *3·76*, *3·54*, 4·11, 4·09	−5·05
	Anion	3·96	0·03	0·00005	244	220, 285[i]	4·34, 4·08	7·0
2-Cl, 9-Me	Neutral	—	—	—	—	272[j]	3·89	2·9
	Cation	0·65	0·06	0·0002	235	271, *278*	3·94, *3·72*	−1·6
6-Cl, 9-Me	Neutral	—	—	—	—	266[k]	4·05	2·4
	Cation	0·20	0·06	0·0001	280	*238*, *244*, 263, *270*	*3·66*, *3·72*, 4·01, *3·88*	−2·0
8-Cl, 9-Me	Neutral	—	—	—	—	267[j]	4·03	4·2
	Cation	2·00[d]	0·04	0·0001	290	270[i]	3·90	−0·2

[a] Analytical wavelength for spectroscopic determination of pK_a. [b] A. Albert and D. J. Brown, *J.*, 1954, 2060. [c] A. Albert and D. J. Brown, *loc. cit.*, determined the pK_a by potentiometry as 7·82. [d] Absorption due to the cation was obtained by extrapolation as the spectrum of the cation changed with time. [e] pH values < 0 have been obtained for solutions of sulphuric acid to which Hammett's acidity functions (cf. M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1) have been assigned. [f] Cf. ref. 11 for spectra at various pH values. [g] Cf. A. Bendich, P. J. Russell, jun., and J. J. Fox, *J. Amer. Chem. Soc.*, 1954, **76**, 6073. [h] Cf. ref. 13 for spectra at various pH values. [i] Cf. R. K. Robins (*J. Org. Chem.*, 1961, **26**, 447) for spectra at arbitrary pH values. [j] Cf. ref. 8 for spectra at other pH values. [k] Cf. the values given in ref. 9 for pH 11. [l] Absorption maximum taken within 2 min. of preparation of solution.

EXPERIMENTAL

Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 100° unless otherwise stated. M. p.s were taken in soda-glass capillaries. All compounds were examined for the presence of isomers and other impurities by paper chromatography on Whatman No. 1 paper with (*a*) 3% aqueous ammonium chloride, and (*b*) butan-2-ol–5N-acetic acid (7 : 3) as solvent.

Ionisation constants were determined (Mr. D. Light) by methods already described.[7] Ultraviolet spectra were measured first on a Perkin-Elmer Spectracord model 4000 recording spectrophotometer, and then $\lambda_{max.}$ and ε values were checked on a Hilger Uvispek manual instrument (Mr. Arandejelovic).

Preparation of Materials.—2- and 8-Chloro-9-methylpurine [8] were prepared by methylation of the chloropurine, followed by separation from the 7-methyl isomer. 6-Chloro-9-methylpurine [9] was prepared from 5-amino-4-chloro-6-methylaminopyrimidine. The preparation of 8-mercaptopurine from the reaction of 4,5-diaminopyrimidine and carbon disulphide in pyridine [10] has been investigated, and details are given which ensure a high, reproducible yield.

Methylation of 8-chloropurine with methyl iodide and potassium carbonate in dimethyl sulphoxide gives a poor yield (7·5%) of 8-chloro-9-methylpurine,[8] but the yield can be increased to 33% by using ethereal diazomethane.

[7] A. Albert and E. P. Serjeant, "Ionization Constants," Methuen, London, 1962.
[8] A. G. Beaman and R. K. Robins, *J. Org. Chem.*, 1963, **28**, 2310.
[9] R. K. Robins and H. H. Lin, *J. Amer. Chem. Soc.*, 1957, **79**, 490.
[10] A. G. Beaman, J. F. Gerster, and R. K. Robins, *J. Org. Chem.*, 1962, **27**, 986.

2-*Chloro*-9-*methylpurine*. 2-Chloropurine [11] was methylated with methyl iodide and potassium carbonate in dimethyl sulphoxide as described by Beaman and Robins,[8] and the mixture of 2-chloro-9-methylpurine and 2-chloro-7-methylpurine, extracted with ethyl acetate, was chromatographed in benzene on alumina. The 2-chloro-9-methylpurine was eluted first and was recrystallised from benzene–light petroleum (b. p. 60—80°). It had m. p. 132—133·5° (lit.,[8] 135—136°) (Found: C, 42·9; H, 3·1; N, 33·2. Calc. for $C_6H_5ClN_4$: C, 42·75; H, 3·0; N, 33·2%). Paper chromatography of the product in each solvent revealed no trace of the other isomer.

2-*Piperidino*-9-*methylpurine*. 2-Chloro-9-methylpurine (0·12 g.) and piperidine (0·17 ml., 2·4 mol.) in ethanol (10 ml.) were heated in a sealed tube at 100° for 48 hr. The solvent was removed, the residue shaken with benzene, and the mixture filtered to remove piperidine hydrochloride. Concentration of the filtrate gave an oily residue which was crystallised from light petroleum (b. p. 40—60°) to give 2-*piperidino*-9-*methylpurine* (0·042 g.), m. p. 135·5—136·5° (Found: C, 60·7; H, 7·0; N, 32·3. $C_{11}H_{15}N_5$ requires C, 60·8; H, 7·0; N, 32·2%).

6-*Chloro*-9-*methylpurine*. 5-Amino-4,6-dichloropyrimidine and 10% ethanolic methylamine at 125° for 6 hr. gave 5-amino-4-chloro-6-methylaminopyrimidine (95%),[12] which with ethyl orthoformate and acetic anhydride gave 6-chloro-9-methylpurine.[9] After recrystallisation from benzene–n-hexane this had m. p. 136—137·5° and showed no depression with a sample (m. p. 136—138°) kindly supplied by Professor R. K. Robins (lit.,[8] 143—144°) (Found: C, 42·8; H, 3·05; N, 33·25%).

6-*Piperidino*-9-*methylpurine* was prepared similarly to the 2-isomer (44° for 3 hr.); it crystallised from light petroleum (b. p. 40—60°), m. p. 65—66° (Found, for material dried at 20°/20 mm.: C, 60·6; H, 6·8; N, 32·45%).

8-*Mercaptopurine*. 4,5-Diaminopyrimidine (12·5 g.) was dissolved in pyridine (375 ml.), the solution was cooled, carbon disulphide (125 ml.) added, and the mixture refluxed on a steam-bath for 6 hr. The volatile materials were removed under reduced pressure and the residue was recrystallised from water (800 ml.) to give 8-mercaptopurine (16·7 g., 97%), m. p. 305° (decomp.) [lit.,[10] 310° (decomp.)].

8-*Chloro*-9-*methylpurine*. 8-Chloropurine [13] was prepared from 8-mercaptopurine through 8-methylthiopurine.[14] Ethereal diazomethane (from 6 g. of nitrosomethylurea) was added to an ice-cold solution of 8-chloropurine (0·75 g.) in methanol (22 ml.). A vigorous evolution of nitrogen took place and after 1 hr. at +1° the solvent was evaporated, the oily residue extracted with benzene, and the extract chromatographed on 4 in. of alumina. The first fractions gave 8-chloro-9-methylpurine which crystallised from n-hexane as white needles (0·27 g., 33%), m. p. 106·5—107° (lit.,[13] 106—108°) (Found, for material dried at 20°/20 min.: C, 42·9; H, 3·1; N, 33·25%). Paper chromatography of the purified product in 3% ammonium chloride and butanol–acetic acid revealed no trace of the other isomer.

8-*Piperidino*-9-*methylpurine* was prepared similarly to the 2-isomer (45° for 4 days). It crystallised from light petroleum (b. p. 60—80°), m. p. 89·5—91° (Found, for material dried at 20°/20 mm.: C, 60·95; H, 6·95; N, 32·0%).

Piperidine. AnalaR piperidine, dried over potassium hydroxide and then sodium, was fractionated through a 24 in. column packed with Fenske helices. The fraction, b. p. 103·5—104·8°/718 mm. (lit.,[5] 106·4°/760 mm.) $n_D^{22·7}$ 1·4530 (lit.,[5] n_D^{20} 1·4537) was collected.

99·8% *Ethanol*. Commercial absolute ethanol was dried by the method of Lund and Bjerrum [15] and fractionated. The water content was determined by Karl Fischer titration [16] and then adjusted to 99·8% (by weight).

Procedure.—This was generally similar to that used by Chapman and his co-workers.[1] Mixtures of chloro-9-methylpurine in 99·8% ethanol (5·00 ml.; 0·0300M) and piperidine in 99·8% ethanol (5·00 ml.; 0·140M) in stoppered tubes (sealed tubes for temperatures exceeding 80°) were placed in a thermostat bath. After the required time each tube was removed, chilled briefly, and the contents poured into 6N-nitric acid (25 ml.) which fixes the amine and stops the reaction. The chloride ions produced were determined by Volhard's method. For each run, 9 samples covering from 10—20 to 80—90% reaction were examined. In the absence of

[11] J. A. Montgomery, *J. Amer. Chem. Soc.*, 1956, **78**, 1928.
[12] D. J. Brown, *J. Appl. Chem.*, 1954, **4**, 72.
[13] A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, 1962, **12**, 432.
[14] A. Albert and D. J. Brown, *J.*, 1954, 2060.
[15] H. Lund and J. Bjerrum, *Ber.*, 1931, **64**, 210.
[16] D. M. Smith, W. M. D. Bryant, and J. Mitchell, jun., *J. Amer. Chem. Soc.*, 1939, **61**, 2407.

piperidine, chloride ions were not produced by the chloro-9-methylpurines in ethanol, and the presence of unchanged chloro-9-methylpurine did not interfere with the Volhard titration. Each reaction was studied at four temperatures, covering a 30° range. The second-order rate coefficients were calculated from the expression given on p. 3017 and were constant within the limits of experimental error. The times for 50% reaction are given in Table 2 for selected examples. Analytically determined mean values of k were checked against values obtained by plotting $1/t$ against log $(a - 2x)/(b - x)$. For most runs, a correction for the expansion of ethanol was introduced into the calculation of the rate coefficient. Chloride determinations at infinite time (at least 30 times the half-life of the reaction) gave values of 98—100% reaction, and thus indicated the absence of significant reversibility, and confirmed the purity of the chloro-compounds.

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