312. *Nucleophilic Displacement Reactions in Aromatic Systems. Part V.* Kinetics of the Reactions of Some Chloroazanaphthalenes and Related Compounds with Ethoxide Ions and with Piperidine.*

By N. B. Chapman and D. Q. Russell-Hill.

Heats and entropies of activation for the reactions in ethanol of ethoxide ion and of piperidine with a series of chloro-heterocyclic compounds (1- and 2-chloro-mono- and -di-azanaphthalenes and chloro-mono- and -di-azabenzenes) and with 5-chloroacridine and *o*-chloronitrobenzene have been determined. The results provide experimental evidence about the validity of a simplified quantum-mechanical theory of aromatic nucleophilic substitution due to Longuet-Higgins.[1] It is concluded that, while the theory leads to qualitatively correct results, it is only valid in a semiquantitative way, even over a restricted range of compounds.

There is no evidence at present of cine-substitution, or of an elimination-addition mechanism in these reactions, but additional evidence of acid-catalysis in this class of reactions is presented.

Variations of reactivity caused by the fusion of a benzene ring to 2- or 4-chloropyridine in various possible ways, and to 2-chloropyrimidine, are discussed, especially with respect to bond-fixation in the 2 : 3-position in naphthalene and similar compounds.

Our previous studies in this field have been confined to monocyclic compounds. We now turn to dicyclic compounds, with the special object of providing quantitative experimental results for comparison with a simplified quantum-mechanical theory of nucleophilic aromatic substitution due to Longuet-Higgins.[1] This theory, although apparently unsuccessful even qualitatively when applied to the reactions of azabenzene derivatives, cf. Tables 3 and 4, is much more successful qualitatively when applied to reactions of mono- and di-azanaphthalene derivatives. The present paper records chiefly studies of the reactions of 1- or 2-chloro-mono- and -di-azanaphthalenes, including quinoline, *iso*-quinoline, quinazoline, cinnoline, phthalazine, and quinoxaline derivatives. The reactions of some analogous monocyclic compounds and of 2-chloronaphthalene and 5-chloroacridine are included for comparison. Preliminary accounts of this work have already been given.[2] Some closely related reactions have been studied by Young and Amstutz,[3] and by Brower, Samuels, Way, and Amstutz,[4] and are discussed below (p. 1570).

* Part IV, *J.*, 1954, 2109.

[1] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265; *Nature*, 1950, **166**, 139; cf. Dewar, "Progress in Organic Chemistry," Butterworths, London, 1953, Vol. II, p. 1.

[2] (*a*) Chapman and Russell-Hill, *Chem. and Ind.*, 1954, 281, 1298; (*b*) Chapman, *Chem. Soc. Spec. Publ.*, No. 3, 1955, p. 155.

[3] Young and Amstutz, *J. Amer. Chem. Soc.*, 1951, **73**, 4773.

[4] Brower, Samuels, Way, and Amstutz, *J. Org. Chem.*, 1953, **18**, (*a*) 1075, (*b*) 1684; 1954, **19**, (*c*) 411, (*d*) 1830.

Experimental

Unless otherwise stated light petroleum (b. p. 40—60°) which had been dried over sodium, was used for crystallisation.

Materials.—Chloro-compounds. 2-Chloroquinoline (from British Drug Houses Ltd.) was recrystallised and had m. p. 37—38°. 4-Chloroquinoline was prepared by the method of Riegel and his co-workers,[5] and after recrystallisation had m. p. 30°. 1-Chloro*iso*quinoline was prepared by Fisher and Hamer's method [6] and freed from 1 : 4-dichloro*iso*quinoline by dissolution in hydrochloric acid, removal of the undissolved dichloro-compound, and recovery of the 1-chloro*iso*quinoline as usual. After recrystallisation it had m. p. 36—37°. 3-Chloro-*iso*quinoline, m. p. 46—48° after recrystallisation, was prepared by reduction of 1 : 3-dichloro-*iso*quinoline,[7] itself prepared by Gabriel's method [8] starting from homophthalimide.[9] 5-Chloroacridine was prepared by the method given by Albert [10] and purified by recrystallisation from slightly ammoniacal ethanol, and had m. p. 119·5—120·5°. 4-Chloroquinazoline, m. p. 98—100°, was prepared by Chapman, Gibson and Mann's method,[11] and 2-chloroquinazoline by Gabriel's method [12] to m. p. 107·5—108°. 4-Chlorocinnoline, m. p. 75—76° after crystallisation from light petroleum (b. p. 80—100°), was prepared by Leonard and Boyd's method,[13] and 1-chlorophthalazine by Gabriel's method [14]; this had m. p. 113° after crystallisation from dry ether. 2-Chloroquinoxaline (from Merck and Co., Inc.) was recrystallised and had m. p. 46·5—47°. 2-Chloropyridine (from L. Light & Co.) was purified from neutral impurities as usual and fractionated, a fraction of b. p. 168—170°/760 mm., n_D^{25} 1·5300, being collected; Rogers and Campbell [15] give n_D^{25} 1·5304. 4-Chloropyridine, which was stored at −78°, was prepared by Wibaut and Broeckman's method [16] by use of 4-hydroxypyridine [17] and had n_D^{20} 1·5313; Leis and Curran [18] give n_D^{20} 1·5315. 2-Chloropyrimidine and *o*-chloronitrobenzene were prepared as described in Parts III [19] and IV [19] respectively. 2-Chloronaphthalene prepared by a Sandmeyer reaction from 2-naphthylamine was recrystallised from aqueous ethanol and had m. p. 57°.

Amines, sodium ethoxide, and solvent. Piperidine and morpholine were purified as described in Part III.[19] Sodium ethoxide solutions were prepared by dissolving clean sodium in 99·8% ethanol, prepared as described in Part I,[20] and standardised acidimetrically. The carbonate content was also determined and this was usually negligible. 99·8% Ethanol was used as solvent throughout this investigation, unless otherwise stated (p. 1566).

Reaction Products.—These were isolated where necessary from solutions used in kinetic experiments or prepared independently under conditions very similar to those used in kinetic experiments. Selected known reaction products were characterised by their m. p.s. Most of the reactions studied had been shown by previous investigators to yield the expected products, *e.g.*, with hot ethanolic sodium ethoxide 2-chloroquinoline yields 2-ethoxyquinoline,[21] and 1-chlorophthalazine yields 1-ethoxyphthalazine.[22] 4-Chloroquinoline with hot methanolic sodium methoxide yields 4-methoxyquinoline,[23] and it is safe to assume a similar reaction with sodium ethoxide.

Procedure.—For reactions with amines in the range 20—40° this was as described in Part III,[19] save that for the reactions of 4-chloroquinazoline the procedure of Part I [20] was adopted. The essential feature was a Volhard determination of chloride ion. For reactions with amines in the range 50—160°, and for all ethoxide reactions, the method of sealed bulbs was used. All

[5] Riegel, Lappin, Adelson, Jackson, Albisetti, jun., Dodson, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1264.
[6] Fisher and Hamer, *J.*, 1933, 1904.
[7] Haworth and Robinson, *J.*, 1948, 777.
[8] Gabriel, *Ber.*, 1886, **19**, 1653.
[9] Harriman, Shelton, Van Campen, and Warren, *J. Amer. Chem. Soc.*, 1945, **67**, 1481.
[10] Albert, "The Acridines," Edward Arnold & Co., London, 1951, p. 152.
[11] Chapman, Gibson, and Mann, *J.*, 1947, 890.
[12] Gabriel, *Ber.*, 1896, **29**, 1313.
[13] Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 409.
[14] Gabriel, *Ber.*, 1893, **26**, 523.
[15] Rogers and Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 1209.
[16] Wibaut and Broekman, *Rec. Trav. chim.*, 1939, **58**, 885.
[17] König and Greiner, *Ber.*, 1931, **64**, 1052.
[18] Leis and Curran, *J. Amer. Chem. Soc.*, 1945, **67**, 79.
[19] Chapman and Rees, *J.*, 1954, 1190; Chapman, Parker, and Soanes, *J.*, 1954, 2109.
[20] Bishop, Cavell, and Chapman, *J.*, 1952, 437.
[21] Friedländer and Ostermaier, *Ber.*, 1882, **15**, 332.
[22] Von Rothenburg, *J. prakt. Chem.*, 1895, **51**, 149.
[23] Meyer, *Monatsh.*, 1906, **27**, 255, 987.

experiments were carried out in duplicate and independently determined mean values of k rarely differed by more than 1%. In certain cases the rate coefficients thus obtained were checked by determination of the consumption of ethoxide ion, by pouring reaction mixtures into an excess of standard hydrochloric acid and back-titration with standard sodium hydroxide.

Results

Detailed values for some of the reactions studied are given in Table 1 and all the results are summarised in Table 2. Evidence of order of reaction is provided for the reaction of 2-chloroquinoline with ethoxide ions, and the internal consistency of the rate coefficients together with

Table 1.

Reactions of piperidine.

1-*Chloro*isoquinoline at 110·0°. $a = 0{\cdot}4032$M, $b = 0{\cdot}1037$M.

Time (hr.)	1·00	2·25	4·00	6·05	8·00	12·00	16·00	20·00
Decompn. (%)	10·2	20·8	33·0	44·3	52·4	64·9	73·7	80·3
10^5k	8·52	8·50	8·48	8·57	8·46	8·48	8·52	8·61

Mean $k = 8{\cdot}52 \pm 0{\cdot}04 \times 10^{-5}$

2-*Chloroquinazoline at* 20·0°. $a = 0{\cdot}1928$M, $b = 0{\cdot}0514$M.

Time (min.)	30·0	55·0	80·0	110·0	150·0	215·0	250·0	310·0
Decompn. (%)	15·0	24·7	33·3	41·2	50·0	61·7	65·8	72·4
10^4k	4·86	4·79	4·85	4·78	4·73	4·82	4·74	4·77

Mean $k = 4{\cdot}79 \pm 0{\cdot}04 \times 10^{-4}$

Reactions of ethoxide ions.

2-*Chloroquinoline at* 80·0°. $a = 0{\cdot}2470$M, $b = 0{\cdot}1013$M.

Time (min.)	21·5	40·5	80·0	102·0	130·0	170·0	220·0	255·0
Decompn. (%)	13·3	23·0	39·1	45·7	53·6	61·9	71·0	75·1
10^4k	4·96	4·92	4·94	4·86	4·90	4·86	4·96	4·94

Mean $k = 4{\cdot}92 \pm 0{\cdot}03 \times 10^{-4}$. Order with respect to ethoxide ion 1·0; with respect to 2-chloroquinoline 0·97 (by differential method).

Mean $k = 4{\cdot}86 \pm 0{\cdot}03 \times 10^{-4}$, determined by ethoxide consumed ($a = 0{\cdot}2260$, b, 0·1041M).

4-*Chloroquinoline at* 80·0°. $a = 0{\cdot}2550$M, $b = 0{\cdot}1021$M.

Time (min.)	30·0	60·0	105	150	210	295	335	480	∞
Decompn. (%)	10·4	19·6	30·5	40·3	49·8	60·8	65·5	76·7	99·7
10^4k	2·60	2·66	2·60	2·64	2·60	2·60	2·64	2·66	—

Mean $k = 2{\cdot}62 \pm 0{\cdot}02 \times 10^{-4}$

3-*Chloro*isoquinoline at 130·0°. $a = 0{\cdot}1084$M, $b = 0{\cdot}0545$M.

Time (hr.)	9·75	18·0	21·25	30·0	45·0	60·0	75·0	90·0
Decompn. (%)	13·6	23·5	26·8	34·9	46·1	54·7	61·5	67·5
10^5k	(4·63)	4·74	4·72	4·72	4·72	4·70	4·67	4·76

Mean $k = 4{\cdot}72 \pm 0{\cdot}02 \times 10^{-5}$

1-*Chlorophthalazine at* 30·0°. $a = 0{\cdot}1256$M, $b = 0{\cdot}0522$M.

Time (min.)	4·0	8·0	11·0	16·0	21·0	27·5	35·0	42·0	∞
Decompn. (%)	13·0	23·6	30·6	40·2	48·5	56·9	64·4	70·9	99·8
10^3k	4·80	4·75	4·78	4·76	4·78	4·77	4·73	4·83	—

Mean $k = 4{\cdot}77 \pm 0{\cdot}02 \times 10^{-3}$

previous experience in this field is taken as sufficient evidence of second-order reactions for the remaining examples. Rate coefficients are given as l. mole^{-1} sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures in the range 20—110° are accurate to $\pm 0{\cdot}04°$ or better, and in the range 120—160° to about $\pm 0{\cdot}2°$. For the reactions of amines the second-order rate coefficient, k, is given by

$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10}\left(\frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}\right)$$

and for ethoxide ion reactions by

$$k = \frac{1}{t(a - b)} 2{\cdot}303 \log_{10}\left(\frac{b}{a} \cdot \frac{a - x}{b - x}\right)$$

TABLE 2. *Values of* 10^5k.

Reagent :	Ethoxide ion			Piperidine		
Temp. :	20·0°	30·0°	40·0°	20·0°	30·0°	40·0°
Chloro-compound	(i)	(i)	(i)	(i)	(i)	(i)
2-Chloroquinazoline	296—305	782—790	1840—1910	47·3—48·6	87·3—90·1	160—165
2-Chloroquinoxaline	821—854	1930	114—118 †	6·29—6·43	12·0—12·2	—
1-Chlorophthalazine	182—190	473—483	1080—1150	14·1—14·6 *	25·1—25·5 *	41·3—42·6 *
4-Chlorocinnoline	474—490	1140—1180	154—163 ‡	—	—	—
5-Chloroacridine	94·0—96·6 *	15·6—16·1	39·6—40·8	—	—	—
2-Chloropyrimidine	159—165	413—436	1030—1060	—	—	—
	70·0°	80·0°	90·0°	90·0°	100·0°	110·0°
2-Chloroquinoline	18·7—19·2	48·6—49·6	121—123	2·59—2·66	4·72—4·87	7·90—8·33
1-Chloro*iso*quinoline	19·2—19·7	49·8—51·0	7·34—7·54 §	2·95—3·04	4·94—5·12	8·46—8·61
4-Chloroquinoline	11·2—11·4	26·0—26·6	57·4—59·0	—	—	—
4-Chloropyridine	15·8—16·4 *	33·2—33·8 *	7·26—7·37	—	—	—
o-Chloronitrobenzene	115—118 *	18·9—19·5	48·5—49·9	—	—	—
	120·0°	130·0°	140·0°	130·0°	145·0°	160·0°
2-Chloropyridine ¶	23·0—23·6	54·2—55·6	123—126	0·569—0·597	1·41—1·50	3·18—3·36
3-Chloro*iso*quinoline	1·62—1·69	4·67—4·76	13·5—14·1	—	0·111—0·117 ‖	—

(i) Extreme values of 10^5k in l. mole^{-1} sec.$^{-1}$ for a given experiment. Values of k are usually accurate to ± 2%. Not less than 70% of the reaction was usually studied (for mean k's at 20·0° see Tables 3 and 4).

* 30° higher. † At 0·0°. ‡ At 8·85°. § At 60·0°. ‖ At 150·0°.

¶ For this compound $k_2 = 1{\cdot}00 \times 10^{-4}$ at 110·6°, and $1{\cdot}40 \times 10^{-5}$ at 90·0°, for reactions with ethoxide ion.

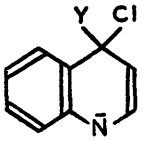
The values for the reaction of 2-chloroquinoxaline with ethoxide ion were determined by Mr. A. G. McKenna, whom we thank for unpublished results. They refer to anhydrous ethanol as solvent, but this change is only of minor importance, and is disregarded at present.

where a is the initial amine or ethoxide-ion concentration and b the initial concentration of chloro-compound. Analytically determined mean values of k were checked against values obtained by plotting t against $\log_{10}(0{\cdot}5a - x)/(b - x)$ or $\log_{10}(a - x)/(b - x)$. For all runs above 40° a correction for the expansion of ethanol was introduced into the calculation of the rate coefficients. Chloride determinations at " infinite " time (at least 30 times the half-life of the reaction) gave values of 99·7—100·1% reaction, thus confirming the purity of the chloro-compounds and indicating the absence of significant reversibility.

The courses of the reactions of 4-chloroquinoline with piperidine, and of 4-chloroquinazoline with pyridine, are displayed in Figs. 1 and 2. Analogous phenomena were observed in the reactions of morpholine with 2-chloropyridine at 160° and 2-chloroquinoline at 90° (Fig. 1, *B*); and of 4-chloropyridine at 100° and 5-chloroacridine at 40° with piperidine.

DISCUSSION

As in previous communications in this series, we assume a one-stage bimolecular mechanism for the reactions studied, since they show the kinetic, structural, and environmental properties characteristic of such a mechanism. Moreover, we have no evidence of the intervention of stable intermediates of type (I), although we have always regarded this type of structure as " providing a good guide to the nature of the transition state," as Hammond [24] recently emphasised. Furthermore, we have no evidence of " cine-substitution " [25] or of the intervention of the elimination-addition mechanism discovered by J. D. Roberts and his co-workers,[26] an example of which in the heterocyclic series has recently been brought to light in the reaction of 3-bromopyridine with sodioacetophenone.[27] The last two phenomena are most likely to be observed in the least activated substitutions, *e.g.*, reactions 1, 6, and 7, Table 3. We have isolated 2-ethoxynaphthalene from the reaction of 2-chloronaphthalene and assumed that 3-chloro*iso*quinoline gives the 3-ethoxy-compound since this reaction is a more activated substitution



(I)

[24] Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.
[25] Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 382.
[26] J. D. Roberts and co-workers, *J. Amer. Chem. Soc.*, 1953, **75**, 3290.
[27] Levine and Leeke, *Science*, 1955, **121**, 780.

than that of 2-chloronaphthalene. We hope to verify this point experimentally in due course. Cine-substitution and the elimination-addition mechanism are both to be disregarded for reactions 3, 4, 9, 13, and 14 on structural grounds. Even high-temperature solvolysis of halogenoquinolines by piperidine has been shown [4b] not to involve cine-substitution, so that it is clearly justifiable to disregard this for the reactions of piperidine in dilute solution listed in Table 4. We have also shown previously [19] that ion exchange between piperidine and ethanol is unlikely to be significant in this class of reaction.

We interpret the results displayed in Figs. 1 and 2 as providing further evidence in favour of acid catalysis of nucleophilic displacements from basic heterocyclic systems (cf. ref. 19). It is noteworthy that the reaction of 4-chloroquinoline with piperidine in dilute solution shows rising rate coefficients as the reaction proceeds, as will be clear from Fig. 1, but steady coefficients in solvolysis with piperidine,[4b] whereas 2-chloroquinoline

FIG. 1. *A, Reaction of 4-chloroquinoline* (0·1M) *with piperidine* (0·4M) *at* 90°.
B, Reaction of 2-chloroquinoline (0·1M) *with morpholine* (0·4M) *at* 90°.

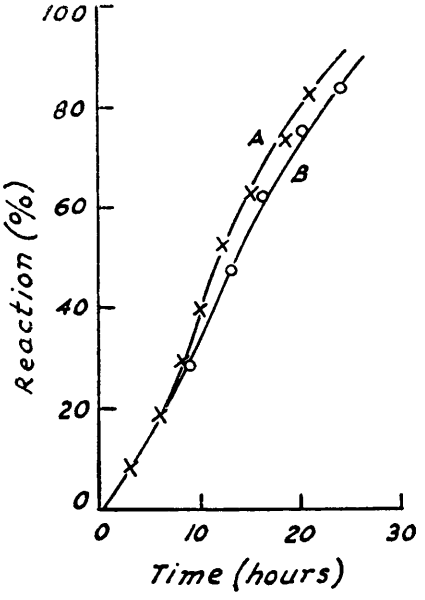
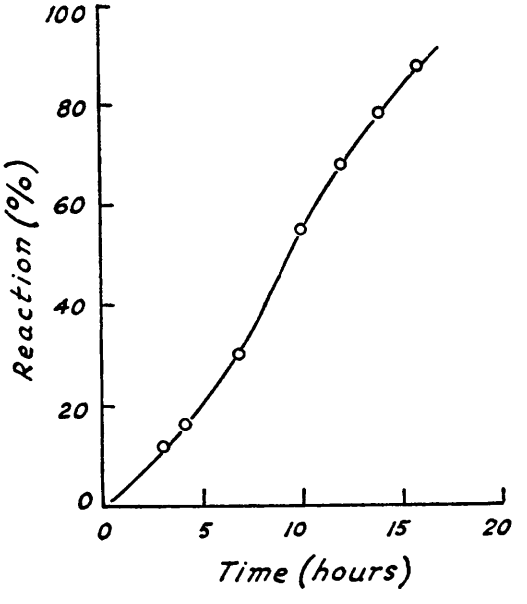


FIG. 2. *Reaction of 4-chloroquinazoline* (0·05M) *with pyridine* (0·20M) *at* 40°.



shows regular second-order kinetics in dilute solution. We relate this to a significant difference in basic strength between 2- and 4-chloroquinoline, a view confirmed by recent independent spectroscopic measurements giving for 4-chloroquinoline $K_b = 2{\cdot}6 \times 10^{-11}$. It was, however, found that " 2-chloroquinoline is such a weak base that a constant could not be determined." [28] This is to be understood on the basis of a much stronger $-I$ effect of chlorine, which is more base-weakening, in the 2-position than in the 4-position, offset by base-strengthening mesomeric effects. However, with a reagent more weakly basic than piperidine (pK_b 2·8), *viz.*, morpholine (pK_b 5·6), 2-chloroquinoline seems to be able to compete successfully for protons, as indicated by the rising rate coefficients implied in curve *B*, Fig. 1. The situation as to basic strength and resultant reactivity is almost certainly the same for 2- and 4-chloropyridine. Thus 2-chloropyridine shows regular kinetics with piperidine but not with morpholine, whereas 4-chloropyridine shows rising coefficients even with piperidine. The suggestion of Brower *et al.*[4b] that the predominating reaction here is the polymerisation of 4-chloropyridine seems to us unlikely in view of the relative " nucleophilic powers " of piperidine and pyridine. Similar phenomena are also

[28] Knight, Wallick, and Balch, *J. Amer. Chem. Soc.*, 1955, **77**, 2577.

displayed in Fig. 2, but the reactions here are further complicated by a significant ethanolysis of 4-chloroquinazoline. The formation of acid in the reaction of pyridine with 4-chloroquinazoline is ascribed, as in a similar case in Part III,[19] to solvolysis of a first formed quaternary salt, with liberation of protons. Brower *et al.*,[4b] however, obtained satisfactory second-order coefficients for the reaction of 4-chloroquinazoline with piperidine at low temperatures. In toluene solution, in which piperidine hydrochloride is very

TABLE 3.* *Reactions of ethoxide ions.*

Compound	20·0°, 10^5k	20·0°, $7 + \log_{10} k$	E (cal. mole^{-1})	$\Delta H^{\ddagger}$ (cal. mole^{-1})	$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	$\Delta U - \Delta U^0$ (cal. mole^{-1} deg.$^{-1}$)
1-Chloro-mono- and -di-azanaphthalenes.						
1. 1-Chloronaphthalene †	—	—	—	—	—	0
2. 4-Chloroquinoline	0·065	0·81	20,400	19,700	19·6	12δ/33
3. 1-Chloro*iso*quinoline ...	0·069	0·84	22,500	21,800	12·3	12δ/33
4. 1-Chlorophthalazine ...	186	4·27	16,500	15,900	16·9	20δ/33
5. 4-Chlorocinnoline	477	4·68	15,800	15,200	17·3	20δ/33
	20·0°, k	20·0°, $17 + \log_{10} k$				
2-Chloro-mono- and -di-azanaphthalenes.						
6. 2-Chloronaphthalene...	$9·1 \times 10^{-17}$	0·96	~39,000 §	~38,000 §	2·0	0
7. 3-Chloro*iso*quinoline ...	$1·2 \times 10^{-11}$	6·07	32,400	31,600	0·7	3δ/24
8. 2-Chloroquinoline	$6·3 \times 10^{-7}$	10·80	23,100	22,400	10·7	12δ/24
9. 2-Chloroquinazoline ...	$2·98 \times 10^{-3}$	14·47	16,800	16,200	15·9	15δ/24
10. 2-Chloroquinoxaline ...	$8·28 \times 10^{-3}$	14·92	15,400	14,800	18·2	15δ/24
	20·0°, k	20·0°, $9 + \log_{10} k$				
Chloro-mono- and -di-azabenzenes.						
11. 2-Chloropyridine	$2·2 \times 10^{-9}$	0·34	26,800	26,200	9·2	δ/3
12. 4-Chloropyridine	$8·7 \times 10^{-8}$	1·94	20,900	20,200	22·3	δ/3
13. 2-Chloropyrimidine ...	$1·63 \times 10^{-3}$	6·21	16,900	16,300	15·7	2δ/3
	20·0°, 10^7k	20·0°, $7 + \log_{10} k$				
Miscellaneous.						
14. 5-Chloroacridine	620	2·79	17,600	17,000	20·0	4δ/10
15. *o*-Chloronitrobenzene	1·8	0·25	23,700	23,000	10·8	—

* Values calculated from Arrhenius parameters given to 2 significant figures. Values of E and $\Delta H^{\ddagger}$ are usually accurate to ± 300 cal. mole^{-1}, and of $\Delta S^{\ddagger}$ to ± 1·1 cal. mole^{-1} deg.$^{-1}$.
† Preliminary experiments indicated irregular kinetics.
§ Accurate to ± 1000 cal.

TABLE 4.* *Reactions of piperidine.*

Compound	20·0°, k	20·0°, $7 + \log_{10} k$	E (cal. mole^{-1})	$\Delta H^{\ddagger}$ (cal. mole^{-1})	$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	$\Delta U - \Delta U^0$ (cal. mole^{-1} deg.$^{-1}$)
1-Chloro-mono- and -di-azanaphthalenes.						
1. 1-Chloro*iso*quinoline ...	$2·5 \times 10^{-7}$	0·40	14,500	13,800	41·9	12δ/33
2. 1-Chlorophthalazine ...	$2·0 \times 10^{-5}$	2·31	11,800	11,100	42·0	20δ/33
3. 4-Chloroquinazoline †...	3·1	7·49	7,000	6,600	37·5	24δ/33
2-Chloro-mono- and -di-azanaphthalenes.						
4. 2-Chloroquinoline	$1·5 \times 10^{-7}$	0·18	15,600	14,900	38·9	12δ/24
5. 2-Chloroquinoxaline ...	$6·36 \times 10^{-5}$	2·79	11,300	10,800	40·9	14δ/24
6. 2-Chloroquinazoline ...	$4·79 \times 10^{-4}$	3·68	11,100	10,500	37·8	15δ/24
Chloroazabenzenes.						
7. 2-Chloropyridine	$4·8 \times 10^{-10}$	−2·32	19,900	19,100	35·8	δ/3
8. 2-Chloropyrimidine § ...	$3·34 \times 10^{-6}$	3·52	12,400	11,800	34·3	2δ/3
9. 4-Chloropyrimidine § ...	$1·5 \times 10^{-3}$	4·2	~10,500	~9,900	~35·7	2δ/3

* Values calculated from Arrhenius parameters given to 2 significant figures. Values of E, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ are usually within the limits indicated in Table 3.
† Ref. 4*d*. § Ref. 19.

insoluble, 5-chloroacridine shows regular kinetics in reaction with piperidine,[4b] but rising coefficients when the reaction is conducted in ethanol in which the acidic piperidinium chloride is soluble.

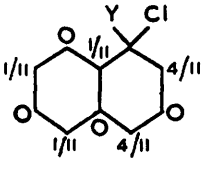
In Tables 3 and 4 are assembled results whereby the theoretical treatment of reactions of this type by Longuet-Higgins [1] may be tested quantitatively. In this treatment, which is based on the molecular-orbital method, it is assumed that the structure of the transition state is of the type shown in formula (I), *i.e.*, the localisation approximation for the study of chemical reactivity is adopted, and the carbon atom at the seat of substitution is assumed to be sp^3 hybridised. Changes in skeletal energy and in energy of interaction of the chlorine atom with the ring on formation of the transition state are neglected, so that only changes in unsaturation energy are to be determined. We consider the reactions with a given reagent under fixed conditions of a parent chlorohydrocarbon (iso-conjugate hydrocarbon), which is referred to by superscript zero, and of a chloroazahydrocarbon, and determine the difference in unsaturation energy of the initial and the transition state in each case. This gives the difference in *potential* energy of activation, *i.e.*, heat of activation referring to the absolute zero and the gas phase, for the two reactions, $(\Delta U - \Delta U^0)$.

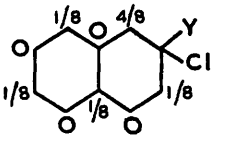
It has been shown by Longuet-Higgins [1] that if E_u and $E^0{}_u$ represent the unsaturation energies of an azahydrocarbon and the iso-electronic hydrocarbon respectively, then $E_u - E^0{}_u = \sum_r \alpha_r q^0{}_r$ where $q^0{}_r$ is the π-electronic charge at position r in the hydrocarbon and α_r is the coulomb term at position r in the azahydrocarbon. Applying this result differentially to the initial and transition states, and designating the latter by primes, we obtain :

$$\Delta U - \Delta U^0 = (E_u' - E_u) - (E^0{}_u' - E^0{}_u) = \sum_r \alpha_r (q^0{}_r' - q^0{}_r).$$

Now the initial states are even-alternant hydrocarbons or their aza-derivatives and the transition states are odd-alternant carbanions. Therefore $q^0{}_r$ is unity at every position and $q^0{}_r' = 1 + c_r^2$, where c_r is a non-bonding molecular-orbital coefficient (Longuet-Higgins [1]). Hence $\Delta U - \Delta U^0 = \sum_r \alpha_r c_r^2$. Rules for the calculation of c_r have been given by Longuet-Higgins (*loc. cit.*). We regard α_r as an energy parameter for position r of the heteromolecule, taking the value δ at the position of aza-substitution and $\delta/3$ at neighbouring positions (auxiliary inductive parameter). The calculated charge-density distribution for substitution at the α- and the β-position in naphthalene is shown in (II) and (III) respectively. On this basis the values of $(\Delta U - \Delta U^0)$ shown in Tables 3 and 4 are readily calculated, *e.g.*, for reactions of 4-chloroquinoline $(\Delta U - \Delta U^0) = (4/11)\delta + (0)\delta/3 + (0)\delta/3 = 12\delta/33$.

(II)





(III)

It is usually assumed that for a series of reactions such as those listed in Tables 3 and 4, which are very similar in character, solvation factors are more or less constant throughout the series. In the absence of experimental evidence on this point, we shall make the same assumption. Then, provided that each series of reactions is characterised by an entropy of activation constant throughout the series (cf. Hammett [29]), it is legitimate to identify the potential-energy magnitudes $(\Delta U - \Delta U^0)$ with differences in the heats of activation, $\Delta H^\ddagger$. Constancy of entropy of activation is a prime assumption of the theoretical treatment, the validity of which may be judged from the values of $\Delta S^\ddagger$ in Tables 3 and 4. It is clear that the reactions of piperidine show comparatively small variations of $\Delta S^\ddagger$, and it is regrettable that a wider range of reactions could not be studied

[29] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 118.

because of the intervention of acid catalysis (cf. p. 1567). The reactions of ethoxide ions, even if unactivated or weakly activated substitutions are neglected, show so wide a range of values of $\Delta S^{\ddagger}$ as to render the above conditions inapplicable on the whole. As to values of $\Delta H^{\ddagger}$, the theoretical predictions are not borne out precisely by experiments, as can be seen from the tabulated values, although the prediction of equality of values of $\Delta H^{\ddagger}$ for reactions 4 and 5 (Table 3) is approximately true.

Polanyi and Evans have shown [30] that, when $\Delta S^{\ddagger}$ is not constant, log k for ordinary temperatures reflects trends in heats of activation at the absolute zero, better than does $\Delta H^{\ddagger}$. Fig. 3 illustrates the applicability of this to reactions 6—10 of Table 3, and over this limited range the theory appears, on this basis, to have semiquantitative validity. For the remaining reactions correlation between $(\Delta U - \Delta U^0)$ and log k/k_0 is poor. Despite the demonstrable inadequacy of the theory quantitatively, it leads to qualitative conclusions as to reactivity well supported by experiments, *e.g.*, the following reactivity

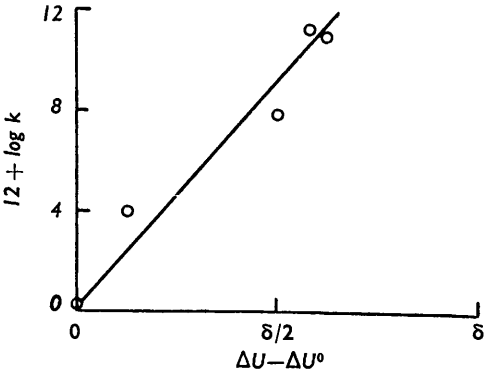


FIG. 3. *Relation between* log k *and* $(\Delta U - \Delta U^0)$ *for reactions of 2-chloro-mono- and -di-azanaphthalenes with ethanolic ethoxide.*

series: 4-chloroquinazoline > 1-chlorophthalazine ~ 4-chlorocinnoline ⩾ 4-chloroquinoline ~ 1-chloro*iso*quinoline ⩾ 1-chloronaphthalene. More elaborate treatments of the problem of reactivity in heterocyclic molecules by Brown [31] and by Dewar [32] seem to have no advantage over that at present being tested, in the first case for lack of necessary values for the parameters introduced.

Consideration of reactions 6 and 7 (Table 3) shows clearly that 3-chloro*iso*quinoline resembles 2-chloronaphthalene closely in properties and may be regarded, as the theory indicates, as virtually unactivated, in strong contrast with 1-chloro*iso*quinoline and 2-chloroquinoline.

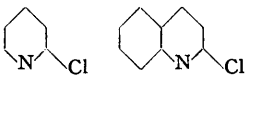
The solvolysis of 1- and 2-bromonaphthalene and all the isomeric monobromoquinolines by piperidine has been studied by Brower and Amstutz and their co-workers,[4b] and the results compared with theoretical predictions based on Longuet-Higgins's theory, which, however, has apparently been applied without taking into account the auxiliary inductive parameter. Examination of suitably revised theoretical figures and the experimental values shows that there is very fair agreement between theory and practice in the less activated cases (cf. Chapman,[2b] Table 1, p. 161).

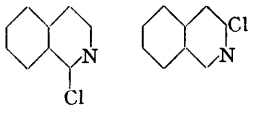
It seems true that Longuet-Higgins's theory suffers from two main weaknesses: first, the assumption of the same completely localised structure for the transition state in all cases—there are probably considerable variations depending on the character of the nucleophilic reagent and of the compound undergoing substitution; and, secondly, the assumption of constancy of entropy of activation throughout. Moreover the value assigned to the so-called auxiliary inductive parameter remains rather arbitrary. Finally, despite the possibility of minor complications due to a primary steric effect, piperidine appears to be a more suitable nucleophilic reagent than ethoxide ion for experimental studies aimed at

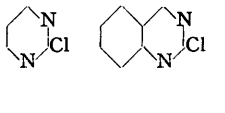
[30] Polanyi and Evans, *Trans. Faraday Soc.*, 1936, **32**, 1333.
[31] Brown, *J.*, 1951, 1955.
[32] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.

verifying the theory. It should be added that, on the whole, the localisation approximation leads to more accurate qualitative conclusions than the isolated molecule approximation, for the different charge density distributions in pyridine, quinoline, and *iso*quinoline calculated by Longuet-Higgins and Coulson [33] and by Brown and Dewar [34] both lead to conclusions unsupported by experiment.

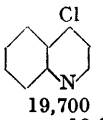
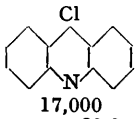
TABLE 5.







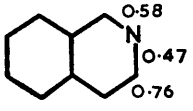
(i) $\Delta H^{\ddagger}$ (cal. mole^{-1})	26,200	22,400	21,800	31,600	16,300	16,200
(i) $-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	9·2	10·7	12·3	0·7	15·7	15·9
(i) $11 + \log_{10} k_{20}$	2·34	4·80	4·84	0·07	8·23	8·47
(ii) $\Delta H^{\ddagger}$ (cal. mole^{-1})	19,100	14,900	13,800	—	11,800 *	10,500
(ii) $-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	35·8	38·9	41·9	—	34·3 *	37·8
(ii) $10 + \log_{10} k_{20}$	0·28	3·18	3·40	—	6·47	6·63



(*a*)

(*b*)

(i) $\Delta H^{\ddagger}$ (cal. mole^{-1})	20,200	19,700	17,000
(i) $-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	22·3	19·6	20·0
(i) $9 + \log_{10} k_{20}$	1·94	2·81	4·79

(i) Reactions of ethoxide ion. (ii) Reactions of piperidine. * Part III.[19]

In Table 5 are collected results illustrating the effect of " fusing a benzene ring " (in fact, adding the system –CH:CH·CH:CH–) to the pyridine or the pyrimidine ring. This fusion can be done in the 5 : 6-, 3 : 4-, or 4 : 5-position of 2-chloropyridine and generally results in an increase in activation of the mobile halogen, which can be regarded as due to the possibility of a wider delocalisation of the charge imposed on the transition state. However, the fusion which converts 2-chloropyridine into 3-chloro*iso*quinoline results in an unmistakable decrease in reactivity. This we ascribe to bond-fixation in the 2 : 3-position of 3-chloro*iso*quinoline (as in naphthalene) with the result that the activating influence of the hetero-nitrogen atom is poorly transmitted to the 3-position in *iso*quinoline. This is supported by calculations of the mobile bond orders in *iso*quinoline,[35] as shown inset. Such an effect would not operate with 2-chloroquinoline or 1-chloro*iso*quinoline. It is probable that the comparatively low reactivity of 2-chloroquinazoline relatively to 2-chloropyrimidine is to be explained similarly, as it may be supposed that any increase of reactivity due to fusion of a benzene ring is offset by the reduction in the activating power of $N_{(3)}$ because of bond fixation. 4-Chloroquinazoline, on the other hand, where such an effect would not apply, is notably more reactive than 4-chloropyrimidine. The higher reactivity of 2-chloroquinoxaline than of 2-chloroquinazoline (Table 3) is also possibly to be understood in such terms. The powerful effect of fusion of a second benzene ring is also illustrated in Table 5 [reactions (*a*) and (*b*)]. This process of fusion or " annelation " of a benzene ring has been treated theoretically by Brown,[31] but it is questionable whether the theory is applicable to the present case, and the relevant parameters are not available.

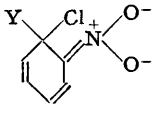
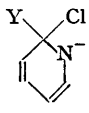
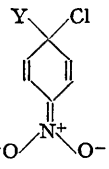
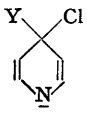


In conclusion, we provide in Table 6 further evidence for the view previously expressed [23] that a " *para* "-cyclic nitrogen atom and a *para*-exocyclic nitro-group are roughly equal in activating power, but that in the *ortho*-position the nitro-group is much more effective. Further, some of the results at present reported (Table 3, nos. 2 and 8, and 11 and 12; Table 4, nos. 3 and 6, and 8 and 9; and Table 6) support the view that a transition state

[33] Longuet-Higgins and Coulson, *J.*, 1949, 971.
[34] Brown and Dewar, *J.*, 1953, 2406.
[35] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87.

with a predominating "*para*"-resonance structure is more stable than one with a predominating "*ortho*"-resonance structure. They also establish for the examples considered a reactivity sequence: *para* > *ortho*. Application of valence-bond theory to nucleophilic aromatic substitution by Green [36] has led to the order of reactivity, *ortho* ≥ *para* > *meta*. When the results adduced by Green in support of his theoretical conclusions and the present results are considered as a whole, the balance of evidence favours the reactivity sequence, *para* > *ortho*, and the long-held view that a "*p*-quinonoid" is more stable than an "*o*-quinonoid" transition state.

TABLE 6.

				
$\Delta H^{\ddagger}$ (cal. mole^{-1})	23,000	26,200	19,400 *	20,200
$-\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$) ...	10·8	9·2	19·5 *	22·3
$10^9 k_{20}$ (l. mole^{-1} sec.$^{-1}$)	180	2·2	910	87
Predominating resonance structure in the transition state. Y = OEt				

* Bevan.[37]

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[36] Green, *J.*, 1954, 3538.
[37] Bevan, *J.*, 1951, 2340.