795. *The Kinetics and Mechanism of Heteroaromatic Nitration.*
Part I. Quinoline.

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The kinetics of nitration of quinoline in concentrated sulphuric acid show that the nitronium ion first interacts with the protonated quinoline molecule and that the proton is still present in the transition state. The σ-bond and π-bond geometry of the transition state are therefore considered to be similar to those for the nitration of naphthalene. From a step-wise comparison of reaction rates, the 5- and the 8-position of the quinolinium ion are shown to be less reactive than the corresponding 1-position of naphthalene by a factor of 10^{10}

ALTHOUGH the orientation of heteroaromatic nitration has been studied in some detail,[1] there is much less information on the rate of these reactions and the results available have usually been obtained by competition experiments,[1,2] a method which gives no information on the individual rate coefficients or on the reaction mechanism. The work to be reported in this series of papers is intended to permit a more extensive set of comparisons between the reactivity of heteroaromatic structures, including, where appropriate, the reactivity of the corresponding homoaromatic structures. For these comparisons to be significant, it is necessary to know the mechanisms of the reactions concerned and the kinetic forms have therefore been determined. The mechanistic problems have been simplified by using aqueous sulphuric acid as the solvent; this medium enables a wide range of reactivities to be studied under conditions where the effective nitrating agent is the nitronium ion.[3]

The comparison of benzene with the pyridinium ion provides the simplest example of deactivation by an $-^+NH=$ group in a heteroaromatic system, but the nitration of pyridine occurs too slowly to be convenient for kinetic analysis (cf. Section 3). Quinoline is nitrated much more readily and at a rate similar to that of nitrobenzene. The stages of mono- and di-nitration can be separated easily and the composition of the mononitro-fraction for nitration in 98% sulphuric acid at 0° has been reported[1] as 5-nitro 47·7% and 8-nitro 52·3%. However, the optical density of the crude reaction mixture over the range 2450—2750 Å is about 8% above that expected for this ratio of mononitroquinolines and the crude product has a faint yellow colour (quinoline and pure samples of 5- and 8-nitro-quinoline are colourless). Small samples of a yellow product have been isolated from the reaction mixture and appear to arise from oxidative side-reactions (see Experimental section).

We have not taken explicit account of these side reactions in the kinetic analysis,

[1] Cf. Dewar and Maitlis, *J.*, 1957, 2521, and references there quoted.
[2] Dewar and Urch, *J.*, 1958, 3079.
[3] (a) Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 269; (b) de la Mare and Ridd, " Aromatic Substitution," Butterworths, London, 1959, Chapter 5.

partly because their extent must be small (the mononitroquinolines can be isolated in yields exceeding 90%) and partly because the ultraviolet spectrum of the reaction mixture does not vary significantly with acidity over the range 87·5—100% H_2SO_4. The constancy of the spectrum indicates that the extent of the side-reaction and the relative amounts of 5- and 8-substitution do not depend markedly on the acidity. Mechanistic arguments based on the rate profile are therefore independent of assumptions concerning the composition of the mononitro-fraction.

(1) *Kinetic Form.*—The reaction rate has been determined spectrophotometrically by using aliquot parts of the reaction mixture after dilution with water. At a given concentration of sulphuric acid as solvent, the reaction essentially follows equation (1), where the concentration terms refer to the stoicheiometric concentrations of the reactants:

$$\text{Rate} = k_2[\text{Quinoline}][\text{Nitric acid}] \qquad (1)$$
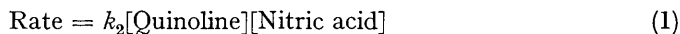
The results in Table 1 show a small systematic variation of k_2 with the concentration of nitric acid, but this can be understood because the nitric acid was added as concentrated nitric acid (d 1·42); this reagent contains some water, and more water is formed by the reaction of the nitric acid with the sulphuric acid, giving nitronium hydrogen sulphate.

TABLE 1.

Dependence of the rate of nitration at 25·27° on the concentration of the reactants.

H_2SO_4 (%) (solvent)	H_2SO_4 (%) (corr.)	10^2[Quinoline] (M)	10^2[Nitric acid] (M)	$10^2 k_2$ (l. mole⁻¹ sec.⁻¹)
98·00	97·96	10·4	2·47	0·953
,,	97·96	5·21	2·47	0·931
,,	97·96	2·60	2·47	0·947
98·07	97·85	1·21	15·3	1·11
,,	97·98	1·01	6·12	1·00
,,	98·05	1·20	1·53	0·985
85·77	85·50	1·56	16·3	0·892
,,	85·66	1·56	8·17	1·14
,,	85·77	1·56	0·31	1·21

As expected from the rate profile (see below), the rate coefficient increases with the concentration of nitric acid when the medium contains more than 90% sulphuric acid and decreases with the concentration of nitric acid when the percentage of sulphuric acid is below this value. Corrected values of the % H_2SO_4 are included in Table 1 to allow for the water introduced with the nitric acid (but not for water accompanying the formation of nitronium hydrogen sulphate). The variation of the rate coefficient with the concentration of quinoline is much less marked. Apart from minor medium effects, equation (1) appears to be accurately obeyed, even for large excesses of either reagent.

The variation of the rate coefficient with the acidity of the medium is given in Table 2 in terms of the same " corrected " concentrations of sulphuric acid. These results,

TABLE 2.

Dependence of the rate of nitration at 25·27° on the composition of the medium
(k_2 in l. mole⁻¹ sec.⁻¹).

H_2SO_4 (%) (corr.)	$10^2 k_2$	H_2SO_4 (%) (corr.)	$10^2 k_2$	H_2SO_4 (%) (corr.)	$10^2 k_2$
77·45	0·0010	91·02	4·35	95·67	1·99
87·49	3·35	91·87	4·08	97·95	0·944
89·50	5·03	93·65	3·00	98·90	0·822
90·18	5·14	94·87	2·45	1·53% SO_3	1·07

together with those for the variation of the concentration of nitric acid in Table 1, are plotted logarithmically against the corrected concentrations of sulphuric acid in Fig. 1. All results then fall on a smooth curve. One of the rate coefficients in Table 2 refers to

TABLE 3.

Dependence of the rate of nitration on the temperature.

H_2SO_4 (corr.) $= 97.95 \pm 0.02\%$.*

Temp.	$10^2 k_2$ (l. mole^{-1} sec.$^{-1}$)	E (cal.)	$\log_{10} A$	$\Delta S\ddagger$ (cal. deg.$^{-1}$)
25.27°	0.944			
31.12	2.13	15,000	9.00	−19.3
45.05	4.53			

* This range is quoted because slightly different concentrations of nitric acid were used at the different temperatures.

nitration in dilute oleum, but this value is not as accurate as the others (see Experimental section) and the expected limits are indicated by a line in Fig. 1.

The variation of the rate coefficients with temperature and the corresponding Arrhenius parameters are given in Table 3.

(2) *Mechanism.*—The overall rate of nitration is sufficient to show that the nitronium ion interacts first with the quinolinium ion, not with the neutral quinoline molecule. In 98% sulphuric acid, the concentration of the nitronium ion is effectively equal to the stoicheiometric concentration of nitric acid and the concentration of quinoline molecules can be calculated from the pK_a of the quinolinium ion [4] (4.94) and the H_0 value of the medium [5] (−9.34). The maximum contribution of nitration through the neutral quinoline
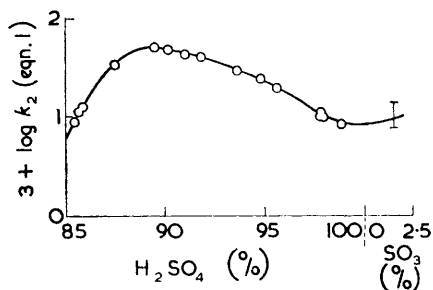

FIG. 1. Variation of the rate of nitration of quinoline with the composition of the medium.
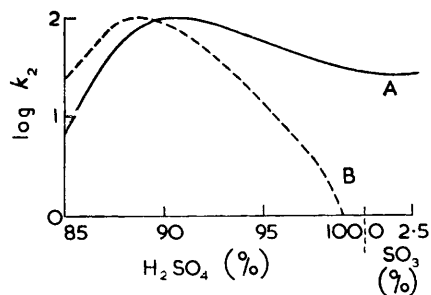

FIG. 2. Expected rate profiles for the nitration of the quinolinium ion (A) and the quinoline molecule (B).

molecule can then be calculated on the assumption that this nitration is a diffusion-controlled process with the appropriate * encounter rate coefficient of 2.5×10^8 l. mole^{-1} sec.$^{-1}$. From the above concentrations, the corresponding stoicheiometric second-order rate coefficient is then 10^{-6} l. mole^{-1} sec.$^{-1}$, a value about 0.01% of that observed. The actual contribution of nitration through the neutral quinoline molecule should be considerably less than this since C-nitration of a quinoline molecule would be expected to require some energy of activation.

However, this argument does not prove that the quinoline molecule is necessarily protonated in the rate-determining step. It is possible to write several reaction paths in which a nitronium ion reacts with a quinolinium ion with the loss of a proton to form a small equilibrium concentration of some complex (*e.g.*, a N-nitroquinolinium ion) which

* This value is calculated from the approximate equation: k_2 (encounter) $= 8RT/3000\eta$, where η is the coefficient of viscosity for the medium. Marked differences in the effective sizes of the reactants should increase the encounter rate but, for the nitration of quinoline, this correction is probably less than a factor of two.[6]

[4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[5] Paul and Long, *Chem. Rev.*, 1957, **57**, 1.
[6] Debye, *Trans. Electrochem. Soc.*, 1942, **82**, 265.

then slowly undergoes *C*-nitration. Evidence on this matter should come from the dependence of the reaction rate on the acidity of the medium.

If the N–H bond of the quinolinium ion does not undergo heterolysis before or during the rate-determining step, the rate profile should be similar to that for the nitration of such positive ions as the trimethylanilinium ion.[7] This rate profile is shown in Fig. 2, curve A (with the maximum rate coefficient arbitrarily set at 100 units). If the N–H proton of the quinolinium ion is lost before the rate-determining step, the transition state is formally composed of a nitronium ion and a neutral quinoline molecule and, to a first approximation, the rate profile should be the same as that for a direct reaction between these species. Since medium effects on the nitration of neutral molecules are at least as great as those on the nitration of positive ions,[7] the rate profile obtained by dividing the rate coefficients in curve A by h_0 should not overestimate the anticatalysis by acids. The result is then curve B, again with the maximum rate coefficient set at 100 units. Comparison of Figs. 1 and 2 indicates that the experimental results more closely follow curve A, both at low acidities (~86% H_2SO_4) and over the range 95—99% H_2SO_4; the quinoline molecule is therefore still protonated in the rate-determining step. Medium effects on the nitration of the quinolinium ion over the range 90—99% H_2SO_4 appear somewhat greater than those for the nitration of the trimethylanilinium ion (the quotient k_2^{90}/k_2^{99} is 5·9 and 3·5, respectively), but this difference is probably not mechanistically significant for this rate ratio is known to vary somewhat with the nature of the substrate and may depend in part on the extent of charge spreading in the transition state.[7] The ratio predicted from curve B for the reaction of the quinoline molecule is ~100.

The Arrhenius parameters (Table 3) accord with the nitration of the quinolinium ion. The activation energy (15,000 cal. mole⁻¹) is a little less than that for the nitration of the *p*-chlorotrimethylanilinium ion at a similar acidity (17,400 cal. mole⁻¹),[7] but the *A* factors are within a power of ten and the entropy of activation (−19·3 cal. deg.⁻¹) is consistent with a reaction between unipositive ions.[8]

Since the nitrogen atom of quinoline is protonated during the initial interaction with the nitronium ion and apparently remains protonated in the transition state, it is reasonable to regard the difference between the apparent reactivity of quinoline and naphthalene towards the nitronium ion as a measure of the effect of replacing one =CH– group in naphthalene by the isoelectronic –⁺NH= group. The quantitative evaluation of this effect requires a knowledge of the partial rate factors for substitution in the quinolinium ion.

TABLE 4.

Rate coefficients used in calculating the partial rate factors.

H_2SO_4 (%)	Substrates		k_A/k_B	Ref.
	A	B		
67·96	Benzene	Bromobenzene	16	a
71·98	Bromobenzene	*p*-Tolyl-NMe₃⁺	4100 *	a, b
~85	*p*-Tolyl-NMe₃⁺	Phenyl-NMe₃⁺	870	c
90·22	Phenyl-NMe₃⁺	Quinolinium ion	0·71	d

* Based on an extrapolation from rate coefficients obtained by using 75—85% H_2SO_4. The dependence of log k_2 on % of H_2SO_4 is linear.

References: (*a*) Deno and Stein, *J. Amer. Chem. Soc.*, 1956, **78**, 578. (*b*) Williams and Lowen, *J.*, 1950, 3312. (*c*) Lowen, Murray, and Williams, *J.*, 1950, 3318. (*d*) Ref. 7 and this paper.

(3) *Partial Rate Factors.*—The reactivities of benzene and the quinolinium ion towards the nitronium ion differ too greatly for comparison by direct competition, but an indirect comparison is still possible by the use of compounds of intermediate reactivity. The necessary information is available in the literature and is collected in Table 4. The overall

[7] Gillespie and Norton, *J.*, 1953, 971.
[8] Frost and Pearson, " Kinetics and Mechanism," John Wiley, New York, 1953, p. 132.

reaction rates of benzene and the quinolinium ion appear to differ by a factor * of 4×10^7; this leads to partial rate factors of 7.5×10^{-8} at the 5- and the 8-position of the quinolinium ion.

Since the above argument involves the product of rate comparisons at different acidities, it includes the assumption that relative reaction rates are independent of the acidity. Over the range of medium compositions considered (68—90% H_2SO_4), and if specific interaction with the medium is excluded, this is probably a fairly good approximation. For different nitration reactions at a given acidity, the maximum difference reported between the slopes of log k_2 against % H_2SO_4 is 0.03 unit;[9] this corresponds to a variation in relative reaction rates by a factor of ~5 over the range 68—90% H_2SO_4. The partial rate factors for the quinolinium ion are, therefore, probably correct within an order of magnitude. They are also significant, in that the rate comparisons involved almost certainly refer to the same mechanism of nitration, for Bunton, Halevi, and Stedman[10] have shown that the nitronium ion remains the effective nitrating agent in aqueous solutions of mineral acids.

The partial rate factors for the nitration of naphthalene are known only in acetic anhydride as solvent; the factors are 470 at the 1-position and 50 at the 2-position.[11] Recent work[12] has thrown some doubt on the mechanism of nitration in this solvent, but there is probably no great error in ascribing these partial rate factors to nitration by the nitronium ion; for the nitrating agent shows the expected lack of discrimination (compare chlorination[13]). These partial rate factors can then be combined with those calculated above to show that, for nitration by the nitronium ion, the 5- and the 8-position of the quinolinium ion are deactivated by a factor of ~10^{10} with respect to the 1-position of naphthalene. For the 4-position of the quinolinium ion, the deactivation must be greater by at least a factor of 10^2.

Some experiments were carried out in an attempt to determine partial rate factors for the nitration of the pyridinium ion. Unfortunately, no nitration could be detected in mixtures of nitric and sulphuric acid, even after several days at 100°. This suggests that the reactivity of the pyridinium ion towards nitration is at least 10^5 less than that of the quinolinium ion; the partial rate factor for the 3-nitration of the pyridinium ion should then be below 10^{-12}. This strong deactivation is consistent with the partial rate factor of 10^{-19} recently estimated by Katritzky and Ridgewell[14] for hydrogen isotope exchange at the 3-position in the pyridinium ion.

The derivation of these partial rate factors and the comparison of the $-CH=$ and $-^+NH=$ groups have been discussed in some detail because the results differ considerably from those calculated from the relative localisation energies. The localisation energy for substitution in the α-position of naphthalene[15] is 2.30β and the corresponding values for electrophilic substitution in the 5- and the 8-position of the quinolinium ion have been given as[16] 2.44β and 2.35β, respectively (these values are based on $\alpha_N = \alpha + 2\beta$, and with the auxiliary inductive parameter set at zero). If the value of β is taken as -20 kcal., these localisation energies suggest that the 5- and the 8-positions of the quinolinium ion are less reactive than one α-position in naphthalene by factors of about 5 and 100,

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* An alternative method of calculation would be to use the J_0 (= C_0) function to estimate the rate of nitration of benzene in 90% sulphuric acid. However, the medium-dependence of rates of nitration is rather greater than would be expected from the J_0 function; hence this method should underestimate the reactivity of benzene and overestimate the partial rate factors of unreactive substrates.

[9] Deno and Stein, *J. Amer. Chem. Soc.*, 1956, **78**, 578.
[10] Bunton and Halevi, *J.*, 1952, 4917; Bunton and Stedman, *J.*, 1958, 2420.
[11] Dewar, Mole, and Warford, *J.*, 1956, 3581.
[12] Bordwell and Garbisch, *J. Amer. Chem. Soc.*, 1960, **82**, 3588.
[13] Dewar and Mole, *J.*, 1957, 342.
[14] Katritzky and Ridgewell, *J.*, 1963, 3753.
[15] Burkitt, Coulson, and Longuet-Higgins, *Trans. Faraday Soc.*, 1951, **47**, 553.
[16] Brown and Harcourt, *J.*, 1959, 3451.

respectively. Other discrepancies of this kind have recently been discussed elsewhere.[17] The discrepancies are large enough to illustrate that other factors besides localisation energies can be very important in determining the reactivity of these heteroaromatic ions.

EXPERIMENTAL

Materials.—Kodak synthetic quinoline was dried over magnesium sulphate and distilled twice, the second time under reduced pressure. The sulphuric acid, oleum (Judex), and nitric acid were "AnalaR" materials. The concentration of the sulphuric acid and of the nitric acid were determined by dilution and titration of weighed samples; some of the results were checked by gravimetric analyses on the acids with barium chloride and nitron, respectively. Commercial samples of 5- and 8-nitroquinoline were repeatedly recrystallised until the ultraviolet and infrared spectra and the m. p. were constant.

Products.—In agreement with previous workers we found that the mononitroquinolines could be isolated under preparative conditions in >90% yield. However, a small amount of an impurity was detected spectroscopically and considered to give rise to the slight yellow colour of the crude product. This yellow material was separated by ether extraction of an acidic aqueous solution (pH ~1) after the bulk of the nitroquinolines had been removed by neutralisation and filtration. After evaporation of the ether, the product contained some nitroquinolines but these were removed by ether-extraction of an aqueous solution and the yellow material was then isolated by evaporation of the aqueous layer. Unfortunately the properties and composition of the material which crystallised varied somewhat in different experiments and proved difficult to purify, but combustion always indicated a high proportion of oxygen (by difference); the result $C_5H_7N_2O_{6-7}$ is typical. The nitration of quinoline is therefore probably accompanied by a slight amount of ring opening, leading to these oxygenated products.

Kinetics.—Weighed quantities of quinoline and nitric acid in separate volumes of sulphuric acid of the required strength were brought to the required temperature in a Landolt tube and mixed. At suitable times, samples (2 ml.) were extracted by a calibrated pipette, run into about 250 ml. of water, and examined in a Unicam S.P. 500 spectrophotometer. The extent of reaction was determined mainly from measurement of the optical density at 2640 Å, where the absorption spectrum of the nitroquinolines is much more intense than that of the quinolinium ion; measurements at other wavelengths gave very similar results. Details of the integrated rate coefficients throughout a typical kinetic run are given in Table 5. The combined concentration of 5- and 8-nitroquinoline (x) was calculated from the following equation:

$$x = a(D_t - D_0)/(D_\infty - D_0), \qquad (2)$$

where a is the lower of the two initial concentrations of the reactants, and D_0, D_t, D_∞ are the optical densities at the beginning of the run, during the run, and at the end of the

TABLE 5.

The nitration of quinoline in 90·18% sulphuric acid at 25·27°.

Nitric acid = 0·0263M.   Quinoline = 0·0162M.

Time (min.)	Optical density (2640 Å)	10^2x (eqn. 2)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)	Time (min.)	Optical density (2640 Å)	10^2x (eqn. 2)	10^2k_2 (l. mole^{-1} sec.$^{-1}$)
0	0·064 (calc.)	—	—	16·00	0·392	1·01	5·05
1·83	0·146	0·253	(6·22)	29·93	0·488	1·31	5·05
4·18	0·204	0·433	5·16	∞ ⎰6½ hr.	0·583		
7·10	0·269	0·632	5·08	⎱22 hr.	0·601	Mean 5·14	
10·38	0·327	0·810	5·15	(calc.)	0·549		

Dilution factor before measurement of optical density = 129·5.

run, respectively. Values of D_0 and D_∞ were calculated from the appropriate extinction coefficients but, as mentioned above, the observed values of D_∞ slightly exceeded the calculated values (cf. Table 5); the observed values were used in equation (2). The following extinction

17 Austin, Brickman, Ridd, and Smith, *Chem. and Ind.*, 1962, 1057; Ridd in "Physical Methods in Heterocyclic Chemistry," ed. Katritzky, Academic Press, New York, 1963, Vol. I, Chapter 2.

coefficients, ε_{2640}, were used in the calculations: quinoline $5 \cdot 08 \times 10^2$; 5-nitroquinoline $3 \cdot 49 \times 10^3$; 8-nitroquinoline $5 \cdot 34 \times 10^3$. these values refer to ($\sim 0 \cdot 3$M)-solutions in dilute sulphuric acid, where all three species are largely present as their conjugate acids.

This method had to be modified for the kinetic runs in oleum since the observed values of D_∞ were only about 70% of the calculated values; this discrepancy precludes the calculation of integrated rate coefficients throughout the kinetic runs. However, the absorption at 2640 Å after reaction must still come essentially from a mixture of 5- and 8-nitroquinoline since these products can be isolated in about 60% yield. Values of x were therefore obtained from equation (2) by using the calculated value of D_∞ and were plotted as a function of time. The rate coefficient (k_2) was then calculated by dividing the initial reaction rate by the initial reactant concentration. The value listed in Table 2 is the mean of those obtained in two kinetic runs with different initial concentrations; the corresponding rate coefficients agreed within 4%.

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