The Chemistry of Nitroso-compounds. Part V.[1] Encounter Control for the Nitrosation of Indoles in Dilute Acid

By **Brian C. Challis,*** Department of Chemistry, Imperial College, London SW7 2AY
Alexander J. Lawson, Department of Chemistry, St. Salvators College, St. Andrews, Fife

Rates of nitrosation of 1,2-dimethyl-, 2-phenyl-, 2-methyl-, 2-methyl-5-nitro-, 5-cyano-, 5-nitro-, and 1-methyl-5-nitro-indole in dilute aqueous acid under various conditions are reported. Reaction to form the 3-nitroso-product may be brought about by various reagents, including nitrous anhydride, the nitrous acidium ion, and nitrosyl chloride, depending on the conditions. Examination of kinetic hydrogen isotope effects and chloride ion catalysis shows that these reactions follow the expected A–S_E2 pathway characteristic of aromatic electrophilic substitution, but that the rate-limiting step depends on the basicity of the substrate. For basic compounds ($pK_A \geqslant -3{\cdot}5$) either formation of the reagent (in the case of nitrous anhydride) or diffusion of the reactants is rate limiting: molecular rate coefficients for the reaction of nitrosyl chloride with the neutral substrate are of the order of 10^{10} l mol^{-1} min^{-1} at 0 °C. For less basic compounds ($pK_A \leqslant -6{\cdot}0$), proton expulsion from the Wheland-type intermediate is slow as is usual for aromatic nitrosation. Generally, indole compounds are much more reactive than aromatic amines (diazotisation) towards these nitrosating agents, and this suggests that nitrosation of the former may involve initial substitution of the heterocyclic N atom, with rearrangement to the 3-nitroso-product.

IN common with other electrophilic substitutions, aromatic nitrosation proceeds *via* a two-step A–S_E2 mechanism [equation (1)].[2] Its distinctive feature is that proton expulsion from the Wheland intermediate

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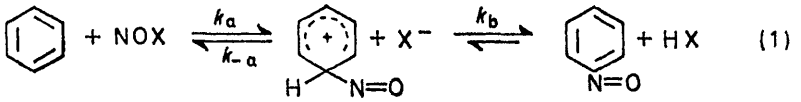
[1] Part IV, B. C. Challis and R. J. Higgins, *J.C.S. Perkin II*, 1972, 2365.

[2] B. C. Challis, R. J. Higgins, and A. J. Lawson, *J.C.S. Perkin II*, 1972, 1831.

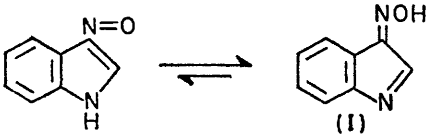
(step k_b) is usually slow and all the reactions examined so far have shown substantial deuterium isotope effects.[1-3]



This characteristic appears to relate to the relatively high stabilities of the NOX reagents, which promote the k_{-a} step, rather than the low acidity of the leaving proton.[2]

These deductions are founded mainly on studies of substituted benzenes in concentrated solutions of strong acids, where nitrous acid is converted to the reactive nitrosonium ion (NO^+).[4] Under milder conditions, several other species such as nitrous anhydride (N_2O_3), the nitrous acidium ion (H_2ONO^+), and nitrosyl halides (NOHal) may exist in equilibrium with nitrous acid. All have been implicated [5] in the nitrosation of aromatic amines (diazotisation) with varying facility depending on the reaction conditions. It has also been suggested [5,6] that their reactivity towards nucleophilic centres diminishes along the series $NO^+ > H_2ONO^+ > NOHal > N_2O_3$. Little is known about the properties of these reagents in aromatic nitrosation. Only phenols have been examined [1,3] in dilute acidic media, but the incidence of slow proton transfer prohibits identification of the reagent from the kinetic equations.

To examine the mechanism of aromatic nitrosation under mild acid conditions, we have extended our investigations to some very reactive heteroaromatic (indole) compounds. All are considerably more basic ($pK_A = +0{\cdot}3$ to $-7{\cdot}0$) [7] than the substituted benzenes examined previously, and some are known to undergo nitrosation readily [8] and to give an isomeric 3-monoxime product (I), if the heterocyclic nitrogen is unsubstituted.[9]



(I)

Otherwise, little is known about these reactions, but two mechanistic changes might be anticipated. The first is that *N*-nitrosation could be important, reflecting the secondary amine structure of indoles, but this is likely to be reversible. The second is that, if the magnitude of the primary hydrogen isotope effect for aromatic substitution is related to the acidity of the leaving proton, as widely predicted,[10] large isotopic rate ratios should be observed with the basic indole substrates.

A preliminary account of some of these findings has been published.[11]

EXPERIMENTAL

Substrates and Reagents.—1,2-Dimethyl-, 2-methyl-, 2-phenyl-, 5-nitro-, and 5-cyano-indole were supplied by Aldrich, and 2-methyl-5-nitroindole was obtained from Regis. All were purified by recrystallisation or vacuum sublimation just prior to use and their m.p.s and spectral properties agreed with the literature values. 1-*Methyl*-5-*nitroindole* was synthesised by nitration of 1-methylindole using $NaNO_3$ in 98% H_2SO_4 at 0 °C.[12] Purification was effected by steam distillation, followed by recrystallisation from ligroin. The compound, a yellow crystalline solid, had m.p. 169 °C (Found: C, 61·3; H, 4·5; N, 15·8. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·55; N, 15·9%). Assignment of the nitro-group to the 5-position was substantiated by n.m.r. spectroscopy. [3-$^2H_1$]-5-Cyanoindole was prepared by exchange with D_2O as described elsewhere.[13]

AnalaR NaCl, $NaNO_2$ (both vacuum-dried), and $HClO_4$, and reagent grade $NaClO_4$, were used without further purification. D_2O (Koch–Light; 99·7% D) was redistilled from alkaline permanganate.

Products.—Authentic products were independently synthesised for compounds whose rate of nitrosation was ascertained by u.v. assay of the reaction product (see below). Thus both 2-methyl-3-nitroso- and 2-phenyl-3-nitroso-indole were prepared by reaction of $NaNO_2$ on the appropriate indole in glacial acetic acid at 0 °C.[8] Purification by repeated vacuum sublimation gave 2-methyl-3-nitrosoindole, m.p. 198 °C (lit.,[12] m.p. 198—199 °C). Repeated washing of the crude 2-phenyl-3-nitrosoindole with hot ethanol gave a yellow solid, m.p. 282 °C (lit.,[14] m.p. 280 °C). 1,2-*Dimethyl*-3-*nitrosoindole* was prepared by dissolving 1,2-dimethylindole (0·24 g) in 10M-$HClO_4$ (50 ml) at 0 °C and then adding $NaNO_2$ (0·12 g in 5 ml H_2O) dropwise to the stirred indole solution over 5 min. The mixture at 0 °C was stirred for a further 10 min and then poured into H_2O (200 ml). After neutralisation with Na_2CO_3 followed by ether extraction, the residue, on vacuum sublimation (100 °C; 0·1 mmHg), gave a chromatographically homogeneous, green, crystalline solid (0·015 g), m.p. 156—158 °C (Found: C, 68·95; H, 5·8; N, 15·8. $C_{10}H_{10}N_2O$ requires C, 68·9; H, 5·75; N, 16·1%). Treatment of 1,2-dimethylindole with excess $NaNO_2$ in acetic acid gives a dinitroso-product.[15]

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[3] (*a*) B. C. Challis and A. J. Lawson, *J. Chem. Soc.* (*B*), 1971, 770; (*b*) K. M. Ibne-Rasa, *J. Amer. Chem. Soc.*, 1962, **84**, 4962.

[4] N. S. Bayliss, R. Dingle, D. W. Watts, and R. J. Wilkie, *Austral. J. Chem.*, 1963, **16**, 933 and references therein.

[5] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J. Chem. Soc.*, 1958, 88.

[6] See J. H. Ridd, *Quart. Rev.*, 1961, **15**, 418; B. C. Challis and A. R. Butler, 'Chemistry of the Amino Group,' ed. S. Patai, Wiley, New York, 1968, p. 277.

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[9] A. Angeli and F. Angelico, *Gazzetta*, 1900, **30**, II, 268.

[10] E. Berliner, *Progr. Phys. Org. Chem.*, 1964, **2**, 253; H. Zollinger, *Adv. Phys. Org. Chem.*, 1964, **2**, 163.

[11] B. C. Challis, R. J. Higgins, and A. J. Lawson, *Chem. Comm.*, 1970, 1223.

[12] See W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, 1965, **30**, 3457.

[13] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1618.

[14] W. E. Noland, K. R. Rush, and L. R. Smith, *J. Org. Chem.*, 1966, **31**, 65.

[15] F. G. Mann and R. Haworth, *J. Chem. Soc.*, 1944, 670.

Kinetics.—Rates of nitrosation of 1,2-dimethyl-, 2-methyl-, and 2-phenyl-indole were determined from the increase in product concentration with respect to time. These products, the conjugate acids of the corresponding 3-nitroso-derivatives in each case, were assayed by u.v. spectrophotometry of the reaction solutions at the following predetermined wavelengths (logarithmic molecular extinction coefficients in parentheses refer to values obtained from authentic compounds in aqueous $[HClO_4] = 10^{-1}$—10^{-2}M): 1,2-dimethyl- $\lambda_{max.}$ 250 (log ε 4·18), 267 (4·18), and 345 nm (3·77); 2-methyl- $\lambda_{max.}$ 249 (log ε 4·18), 263 (4·17), and 347 nm (3·76); 2-phenyl- $\lambda_{max.}$ 272 nm (log ε 4·49). Independent checks established that the absorbance of each product obeyed the Beer–Lambert law.

The reaction mixture was prepared in a volumetric flask at the required temperature by the addition of aqueous $NaNO_2$ to the acidic indole solution. After mixing and adjustment of the volume, a portion was transferred quickly to a jacketted 1 or 10 cm cell maintained at the required temperature by circulating water in a Unicam SP 700 spectrophotometer. Dry nitrogen was passed over the cell windows to prevent atmospheric condensation and a similar cell containing the reaction solution without reactants was used as a reference. The reaction was followed until no further change in the absorbance of the reaction solution was apparent. In every case, this final absorbance agreed to within ±2% of the value expected for 100% reaction computed from the extinction coefficients of authentic products and excess of reactants. Finally, the acidity of each kinetic run was determined by titration of the reaction solution against B.D.H. standard alkali using Methyl Red as indicator.

Independent checks of product stability in acid and in the presence of excess of reagents were made. Significant instability was found only for 2-methyl-3-nitrosoindole in the presence of excess of $NaNO_2$ and these reactions were therefore carried out with an excess of substrate concentration.

Rates of nitrosation of all the other substrates were ascertained by measurements of the unreacted $[HNO_2]$ at timed intervals. Details of the method have been described earlier.[2]

RESULTS

1,2-Dimethylindole.—In very dilute $HClO_4$ (*ca.* 10^{-3}M) with an excess of nitrous acid over substrate, zeroth-order reaction–time curves were obtained for much of the run (Figure 1). Deviations observed towards completion of reaction probably result from the onset of a different pathway with a reduced dependence on nitrous acid concentration. This process becomes more important as the solvent acidity is raised, and it is discussed further below in this context. Apart from this qualification, the rate is independent of the 1,2-dimethylindole concentration. The kinetic order with respect to nitrous acid under these conditions can be readily obtained from the initial rate (v_0), *i.e.* the initial slopes of the plots in Figure 1. These v_0 values are summarised in Table 1: doubling the nitrous acid concentration increases v_0 fourfold, and the reaction must therefore follow equation (2). The consistency of the k_1

$$\text{Rate} = k_1[HNO_2]^2 \qquad (2)$$

values also listed in Table 1 confirms this deduction. The mean value of k_1 is 53·9 l mol^{-1} min^{-1}.

As the concentration of $HClO_4$ is raised above 10^{-2}M, the zeroth-order process becomes unimportant and reaction proceeds by a new pathway with a first-order dependence on the stoicheiometric concentration of both reactants [equation (3)]. Evidence for the kinetic dependences in this

$$\text{Rate} = k_2[\text{Substrate}][HNO_2] \qquad (3)$$

case has also been obtained from the variation of initial rates (v_0) with reactant concentrations. This information, together with k_2 values, for $[HClO_4]$ = 0·4M at 3 °C, is given in Table 2. The mean value of k_2 = 7700 l mol^{-1} min^{-1}.

TABLE 1

Nitrosation of 1,2-dimethylindole under zeroth-order conditions at 3 °C. Initial [Substrate] = 1·13 × 10^{-5}M throughout

Run	$10^4[HClO_4]$/M	$10^5[HNO_2]$/M	$10^8 v_0$/l^{-1} mol min	k_1/l mol^{-1} min^{-1}
1	14·5	3·1	5·93	61·8
2	14·5	5·0	13·0	51·4
3	14·5	10·0	51·4	51·4
4	14·5	15·6	125	51·4
5	5·8	10·0	53·6	53·6

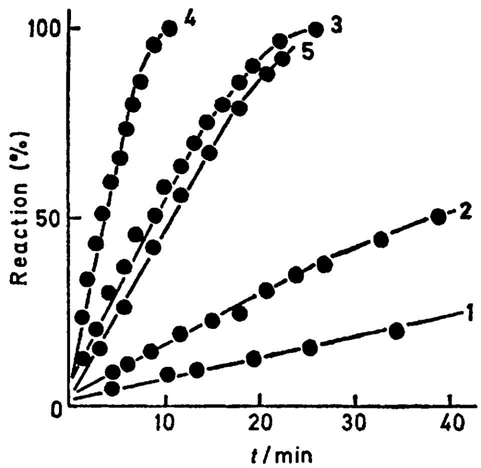

FIGURE 1 Zeroth-order plots for the nitrosation of 1,2-dimethylindole in $HClO_4$ at 3 °C. Initial [1,2-Dimethylindole] = 1·13 × 10^{-5}M; the numbers refer to the kinetic runs in Table 1

TABLE 2

Nitrosation of 1,2-dimethylindole in 0·4M-$HClO_4$ at 3 °C

10^6[1,2-Dimethylindole]/M	$10^5[HNO_2]$/M	$10^7 v_0$/l^{-1} mol min	k_2/l mol^{-1} min^{-1}
10·6	3·10	28·6	8700
10·6	1·04	8·5	7400
7·1	2·06	10·8	7700
11·3	2·06	16·2	6940
18·8	2·06	30·0	7750

This pathway is also acid catalysed. At low acidities, where the 1,2-dimethylindole is largely unprotonated (pK_A = +0·3),[7] there is a linear dependence of k_2 on $[HClO_4]$ (Figure 2) and the reaction follows equation (4). At higher acidities, a more complex relationship requiring acidity functions prevails and these results will be reported subsequently.[16]

$$\text{Rate} = k_3[\text{Substrate}][HNO_2][H^+] \qquad (4)$$

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[16] B. C. Challis and A. J. Lawson, to be published.

1,2-*Dimethyl*[3-$^2H_1$]*indole*.—The solvent isotope effect for the nitrosation of 1,2-dimethylindole has also been examined and the results are listed in Table 3. Because exchange of 3-H with the solvent is rapid under the experimental conditions,[17] the reaction in D_2O refers to 1,2-dimethyl[3-$^2H_1$]indole. The observed solvent isotope effect is inverse ($k_2^{H_2O}/k_2^{D_2O}$ *ca.* 0·61). Apart from any primary isotope effect associated with displacement of deuterium relative to hydrogen, the experimental ratio contains contributions from pre-equilibrium steps associated with protonation of the substrate and formation of the nitrosating agent. Allowance for these contributions will be made later, when the nature of the nitrosating agent is known.

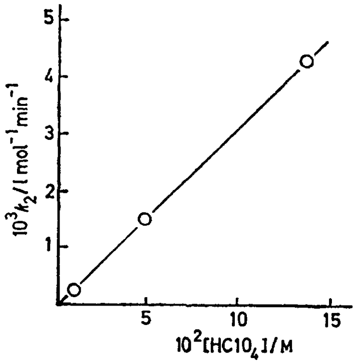

FIGURE 2 Acid catalysis for the nitrosation of 1,2-dimethylindole by equation (3) at 3 °C. Initial [1,2-dimethylindole] = 7·9—4·1 × 10^{-5}M, [NaNO$_2$] = 3·5—1·1 × 10^{-5}M

TABLE 3

Solvent isotope effect for the nitrosation of 1,2-dimethylindole at 3 °C

10^2[Acid]/M	10^5[1,2-Dimethylindole]/M	10^6[NaNO$_2$]/M	k_2/l mol^{-1} min^{-1}
1·03 HClO$_4$	4·1	11·2	253
1·02 DClO$_4$	3·6	9·4	416

2-*Phenylindole*.—The aqueous solubility of 2-phenylindole is low and these reactions were examined with an excess of nitrous acid. Accordingly, pseudo-first-order rate coefficients [equation (5)] were obtained from the experimental data. Table 4 gives details of a typical experiment in 0·024M-HClO$_4$ at 3 °C. In dilute HClO$_4$ (*ca.* 10^{-2}M), the apparent order for nitrous acid, ascertained by the variation of k_0 with [NaNO$_2$], is about 1·3. A sensible interpretation of this finding is that nitrosation occurs by two concurrent pathways with a first- and second-order dependence on nitrous acid concentration, respectively. In this event, the observed rate would be given by equation (6), and it follows that the dependence of k_0 [equation (5)] on the stoicheiometric nitrous acid concentration is then given by equation (7), from which equation (8) is obtained by dividing through with [HNO$_2$].

$$\text{Rate} = k_0[\text{2-Phenylindole}] \qquad (5)$$

$$\text{Rate} = (k_2[\text{HNO}_2] + k_4[\text{HNO}_2]^2)[\text{2-Phenylindole}] \qquad (6)$$

$$k_0 = k_2[\text{HNO}_2] + k_4[\text{HNO}_2]^2 \qquad (7)$$

$$k_0/[\text{HNO}_2] = k_2 + k_4[\text{HNO}_2] \qquad (8)$$

The plot of k_0/[HNO$_2$] against [HNO$_2$], for reaction where [HClO$_4$] = 0·024M at 3 °C, is shown in Figure 3. Its linearity sustains the hypothesis of two concurrent pathways; from the intercept and slope, respectively, k_2 = 950 l mol^{-1} min^{-1} and k_4 = 1·1 × 10^7 l^2 mol^{-2} min^{-1}.

TABLE 4

Experimental values of k_0 [equation (5)] for nitrosation of 2-phenylindole in 0·024M-HClO$_4$ at 3 °C. Initial [2-Phenylindole] = 1·76 × 10^{-6}M, [NaNO$_2$] = 8·0 × 10^{-5}M

t/min	Reaction (%)	10^2k_0/min^{-1}
1·50	19·9	14·9
2·25	29·6	15·5
3·0	37·0	15·4
4·5	48·4	14·5
6·0	58·5	14·6
9·0	74·5	15·1
12·0	82·5	14·4
15·0	88·1	14·2

Simpler kinetics prevail when the reaction with 2-phenylindole is studied at higher acidity and with a low initial nitrite concentration (<10^{-5}M). Under these conditions the contribution to the overall rate from the second-order nitrous acid pathway is negligible and the rate follows the first term of equation (6), *i.e.* Rate = k_2[2-Phenylindole][HNO$_2$]. The data given in Table 5 show that, as for 1,2-dimethylindole, the k_2 coefficient has a first-order dependence on [HClO$_4$], and the full kinetic equation for this pathway is therefore equation (4). Values of k_3 [equation (4)] for 2-phenylindole are also listed in Table 5: the average value (k_3 = 3·93 × 10^4 l^2 mol^{-2} min^{-1}) agrees well with the intercept value ($k_3 = k_2/[\text{H}^+]$ = 3·96 × 10^4 l^2 mol^{-2} min^{-1}) obtained from Figure 3. Thus the full kinetic expression for the mixed order reaction is given by equation (9).

$$\text{Rate} = (k_3[\text{HNO}_2][\text{H}^+] + k_4[\text{HNO}_2]^2)[\text{2-Phenylindole}] \qquad (9)$$

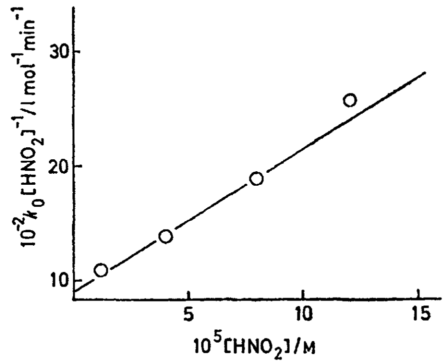

FIGURE 3 Test of equation (8) for the nitrosation of 2-phenylindole in 0·24M-HClO$_4$ at 3 °C

TABLE 5

Variation of k_2 [equation (6)] with [HClO$_4$] for the nitrosation of 2-phenylindole at 3 °C. Initial [2-Phenylindole] = 1·76 × 10^{-6}M, [HNO$_2$] = 1·2 × 10^{-5}M

10^2[HClO$_4$]/M	k_2/l mol^{-1} min^{-1}	10^4k_3/l^2 mol^{-2} min^{-1}
2·4	950 [a]	3·96
6·7	2420	3·61
20·0	8450	4·23

[a] From the intercept of Figure 3.

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[17] B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, 1963, **85**, 2524.

5-Cyanoindole.—Examination of this compound in 10^{-1}—10^{-2}M-$HClO_4$, mainly at 0·5 °C, was made with a large excess of substrate over nitrous acid to effect reasonably rapid reactions. Thus pseudo-first-order coefficients [equation (10)] were obtained from the experimental data and these

$$\text{Rate} = k_0'[HNO_2] \qquad (10)$$

were constant for reaction in excess of 90%. In view of the findings for other indoles, the reaction order with respect to substrate concentration was not examined in detail, but values of $k_0' = 5{\cdot}37 \times 10^{-2}$ min^{-1} and $k_0' = 2{\cdot}77 \times 10^{-2}$ min^{-1} for nitrosation at 25 °C in 0·012M-$HClO_4$ with [5-cyanoindole] = $8{\cdot}0 \times 10^{-4}$M and $4{\cdot}0 \times 10^{-4}$M, respectively, show that this reaction, as expected, also follows equation (3). Likewise, a first-order dependence on [$HClO_4$] may be expected, too, and this is confirmed nicely by the data given in Table 6. Thus the complete kinetic expression is given by equation (4), and the mean value of $k_3 = 1{\cdot}23 \times 10^3$ l^2 mol^{-2} min^{-1}.

TABLE 6

Acid catalysis for the nitrosation of 5-cyanoindole in $HClO_4$ at 0·5 °C. Initial [HNO_2] = 6×10^{-5}—6×10^{-6}M

[$HClO_4$]/M	10^4[5-Cyanoindole]/M	$10^2k_0'$/ min^{-1}	k_2 / l mol^{-1} min^{-1}	10^3k_3 / l^2 mol^{-2} min^{-1}
0·010	16·3	2·07	12·7	1·27
0·049	4·6	2·72	59·0	1·20
0·10	1·76	2·21	126	1·26

[3-$^2H_1$]-5-*Cyanoindole*.—The existence of a primary deuterium isotope effect for 5-cyanoindole was established by examination of the 3-deuteriated isomer. Unlike 1,2-dimethylindole (see above), these measurements could be made in solvent H_2O because exchange of isotopic hydrogen in dilute $HClO_4$ is much slower than nitrosation.[13] In practice, comparative experiments with labelled and unlabelled substrate were carried out in 0·12M-$HClO_4$ at both 0 and 25 °C, and the results, computed in accordance with equation (4), are given in Table 7. A significant difference in rates is evident ($k_3^H/k_3^D = 1{\cdot}8 \pm 0{\cdot}1$) suggesting that proton loss from the Wheland intermediate is rate limiting.

TABLE 7

Primary deuterium isotope effect for the nitrosation of 5-cyanoindole in 0·012M-$HClO_4$. Initial [HNO_2] = $1{\cdot}25 \times 10^{-4}$M

3-Substituent	T/°C	k_2/l mol^{-1} min^{-1}	$k_2^H/k_2^D = k_3^H/k_3^D$
[$^1H_1$]	0·5	14·9 [a]	1·86
[$^2H_1$]	0·5	8·0	
[$^1H_1$]	25·0	66·5	1·75
[$^2H_1$]	25·0	38·1	

[a] Interpolated from Table 6.

Other Compounds.—Acid-catalysed nitrosation of four other indole compounds, the 2-methyl-, the 1-methyl-5-nitro-, the 2-methyl-5-nitro-, and the 5-nitro-derivatives, were also examined briefly. Reaction orders were not determined rigorously, but conditions and reactant concentrations were adjusted to favour the pathway defined by equation (4) and the experimental results show no significant deviation from a first-order dependence on the stoicheiometric concentrations of substrate and nitrous acid. Values of k_2 [equation (3)] are listed in Table 8. As acidity function correlations become necessary at higher acidities, values of k_3 (= k_2[H$^+$]) have been computed only for the lowest $HClO_4$ concentrations (*ca.* 10^{-1}M) in each case.

TABLE 8

Acid-catalysed nitrosation of various indoles in $HClO_4$ at 0·5 °C

[$HClO_4$]/ M	10^6 [Substrate]/ M	10^6 [HNO_2]/ M	k_2 l mol^{-1} min^{-1}	$10^{-2}k_3$ l^2 mol^{-2} min^{-1}
5-Nitroindole				
0·119	60	6·0	35	2·9
1·20	60	6·0	1100	
1-Methyl-5-nitroindole				
0·10	28·6	6·0	70	7·0
0·20	28·6	19	195	
2-Methyl-5-nitroindole				
0·113	20·8	11·2	1700	150
0·119	7·8	10·0	1800	151
2-Methylindole				
0·0052	600	60	138	276
0·0104	600	60	338	325
0·0205	600	60	545	266

Chloride Ion Catalysis.—Addition of NaCl to the $HClO_4$ solutions strongly accelerates the nitrosation rate of 1,2-dimethylindole, 2-phenylindole, and 2-methyl-5-nitroindole.

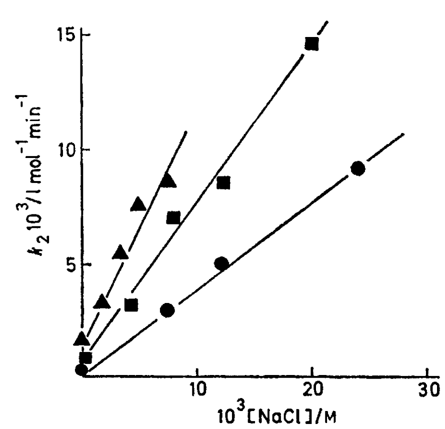

FIGURE 4 Chloride ion catalysis for the nitrosation of basic indoles: ▲, 2-methyl-5-nitroindole in 0·1M-$HClO_4$ at 0·5 °C; ■, 2-Phenylindole in 0·024M-$HClO_4$ at 3 °C; ●, 1,2-dimethylindole in 0·0103M-$HClO_4$ at 3 °C

This catalysis was examined under conditions where a first-order dependence on nitrous acid and substrate concentrations prevails, and where the reaction is acid catalysed. At a constant acidity, however, the plots in Figure 4 show that the second-order coefficient, k_2 [equation (3)], varies linearly with [NaCl], but there is a finite rate in the absence of added NaCl. It follows that the dependence of k_2 on solvent composition is given by equation (11), and that the complete kinetic expression for the reaction is given by equation (12).

$$k_2 = (k_3 + k_5[Cl^-])[H^+] \qquad (11)$$

The first term of equation (12) is identical to equation (4)

$$\text{Rate} = k_3[\text{Substrate}][HNO_2][H^+] + k_5[\text{Substrate}][HNO_2][H^+][Cl^-] \qquad (12)$$

and both refer to the same pathway as values of k_3 computed from the intercepts of Figure 4 and equation (4) itself are in excellent agreement. The second term of equation (12), however, refers to an additional pathway for nitrosation involving catalysis by Cl$^-$.

In contrast to the above findings, addition of NaCl has negligible effect on the nitrosation rate of 5-cyano-, 5-nitro-, and 1-methyl-5-nitro-indole in $HClO_4$. For example, 0·005M-NaCl induces a five-fold increase in the rate of nitrosation of 2-methyl-5-nitroindole, whereas 0·75M-NaCl just doubles the rate for 5-cyanoindole. Furthermore, information in Table 9 shows that NaCl is no more catalytically effective for these compounds than $NaClO_4$, which is believed to influence nitrosation reactions only by a salt effect.[18] In any event, it is clear that the catalytic coefficients, k_5 [equation (12)], for the less basic indole substrates are substantially less than 1·0 $l^3\ mol^{-3}\ min^{-1}$.

TABLE 9

Effect of added NaCl and $NaClO_4$ on the nitrosation of 5-cyanoindole, 5-nitroindole, and 1-methyl-5-nitroindole at 0·5 °C

$[HClO_4]$/M	$[NaClO_4]$/M	[NaCl]/M	k_2[equation (3)] / $l\ mol^{-1}\ min^{-1}$
5-Cyanoindole			
0·10			126
0·10	0·4		226
0·10	0·8		350
0·10		0·1	170
0·10		0·75	314
5-Nitroindole			
0·2			195
0·2		0·1	221
1-Methyl-5-nitroindole			
0·119			35
0·10		0·1	24

DISCUSSION

Depending on both experimental conditions and substrate reactivity four rate expressions [equation (2), k_1; equation (4), k_3; equation (6), k_4; and equation (12), k_3 and k_5] have been found for the nitrosation of indoles. All have counterparts in the diazotisation of aromatic amines, where they have been attributed [5,6] to nitrosation by a series of carriers of the nitrosonium ion (NO^+). Thus k_1 then refers to rate-limiting formation of N_2O_3, and k_3, k_4, and k_5 to rate-limiting attack on the substrate by H_2ONO^+, N_2O_3, and NOCl, respectively.[5,6] Any extension of this interpretation to the indole reactions as far as k_3, k_4, and k_5 are concerned requires that proton expulsion from the Wheland intermediate is rapid. This event is not usually found for aromatic nitrosation,[1-3] and the observation, or otherwise, of a primary hydrogen isotope effect for these reactions is therefore fundamental to any mechanistic interpretation of the results.

TABLE 10

Average k_1, k_3, k_4, and k_5 coefficients for nitrosation at 0 °C of indoles and anilines (diazotisation)

Substrate	pK_A	k_1 / $l\ mol^{-1}\ min^{-1}$	$10^{-2}k_3$ / $l^2\ mol^{-2}\ min^{-1}$	$10^{-7}k_4$ / $l^2\ mol^{-2}\ min^{-1}$	$10^{-7}k_5$ / $l^3\ mol^{-3}\ min^{-1}$	$10^{-10}k_{NOCL}$ / $l\ mol^{-1}\ min^{-1}$
Indoles						
1,2-Dimethyl	0·30[a]	53·9[d]	320[d]		3·67[d]	3·23[d]
2-Methyl	−0·28[a]		290[d]			
2-Phenyl	−1·85[b]		390[d]	1·1[d]	2·85[d]	2·51[d]
2-Methyl-5-nitro	−3·58[a]		150		1·10	0·97
5-Cyano	−6·0[a]		12·4		Salt effect only	
1-Methyl-5-nitro	−6·6[b]		7·0			
5-Nitro	−7·4[a]		2·7			
Anilines[c]						
H	4·6	51·0		1·9		15·7[e]
4-Chloro	4·1			0·55		11·3[e]
2-Chloro	2·65		105	0·28[e]		7·0[e]
4-Nitro	0·99		97			
2,4-Dinitro	−4·53		2·2			

[a] From ref. 7. [b] From ref. 21. [c] From ref. 6. [d] At 3 °C. [e] At 25 °C.

Average values of these four coefficients are summarised in Table 10, together with the basicity (pK_A) of the compounds to which they relate. For comparison, equivalent literature [6] data for several representative diazotisation reactions of primary aromatic amines are also listed.

Second to the kinetic isotope effects, the most significant mechanistic information derives from the effect of added NaCl on the reaction rate. From the values of k_5 in Table 10, it is evident that significant catalysis is observed only for indole compounds more basic than 2-methyl-5-nitroindole ($pK_A = -3{\cdot}6$).[7] Because Cl^- is a weak base, this catalysis is unlikely to relate to proton expulsion from the Wheland intermediate and must therefore be associated, as in diazotisation, with reaction *via* NOCl, formed in a rapid pre-equilibrium step [equation (13)].[6] In this instance, molecular rate

$$HCl + HNO_2 \rightleftharpoons H_2ONO^+ + Cl^- \rightleftharpoons NOCl + H_2O \qquad (13)$$

coefficients (k_{NOCl}) defined by equation (14) in terms of actual reactant concentrations can be computed readily

$$\text{Rate} = k_{NOCl}[\text{Substrate}][\text{NOCl}] \qquad (14)$$

(*i.e.* $k_{NOCl} = k_5/K_{NOCl}$) because the equilibrium constant for equation (13) is known $\{K_{NOCl} = [NOCl]/([HNO_2][H^+][Cl^-]) = 1{\cdot}14 \times 10^3\ l^2\ mol^{-2}$ at 0 °C$\}$.[19] These molecular coefficients, also listed in Table 10, are large. They are, in fact, of similar magnitude to the calculated encounter rate of two neutral species in aqueous solution ($k_{en} = 3 \times 10^{11}\ l\ mol^{-1}\ min^{-1}$ at 3 °C) [20] and we therefore conclude that Cl^- catalysis is only

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[18] B. C. Challis and J. H. Ridd, *J. Chem. Soc.*, 1962, 5197.

[19] H. Schmid and J. Maschka, *Z. phys. Chem.*, 1941, *B*, **49**, 171.

[20] P. Debye, *Trans. Electrochem. Soc.*, 1942, **82**, 265.

observed in the context of a diffusion-controlled reaction. This explanation would also account for the insensitivity of k_5 (and therefore k_{NOCl}) to substrate reactivity for the more basic set of compounds. In sharp contrast to this, however, there is a rapid decrease of k_5 (by a factor of *ca.* 10^{-4}) in going from 2-methyl-5-nitroindole to 5-cyanoindole ($\Delta pK_A = -2\cdot5$).[7] This fall-off is much too rapid to relate to the reactivity difference of the two compounds and suggests a change to a new rate-limiting step that is not catalysed by Cl^-. This deduction is consistent with the comparative effect of added NaCl and $NaClO_4$ for 5-cyanoindole. We therefore suggest that proton loss from the Wheland intermediate must be rate limiting for the less basic indole ($pK_A \leqslant -6\cdot0$) and that catalysis by Cl^- is not observed because of its feebly basic properties.

In the absence of added NaCl, the nitrosation of indoles in dilute $HClO_4$ follows equation (4). In diazotisation, this expression has been associated with reaction *via* H_2ONO^+, which is believed to be more reactive than NOCl.[5,6] Thus for the more basic indoles, at least, equation (4) should refer to an encounter-controlled reaction between H_2ONO^+ and the neutral substrate. It is not possible to compute molecular rate coefficients for this process because the equilibrium constant for the formation of H_2ONO^+ is not known, but the variation of k_3 with substrate basicity is remarkably similar to that of k_5 for the NOCl reaction. Thus k_3 is virtually constant for the four most basic indoles (a span of almost 4 pK units)[7] but thereafter decreases significantly for less reactive compounds. The trend is more readily seen in the plot of log k_3 *versus* pK_A in Figure 5: the sudden change of slope about $pK_A = -4\cdot0$, suggests a change in the rate-limiting step at this point.

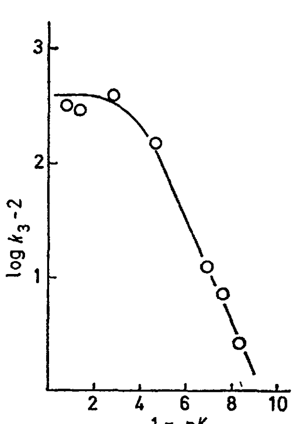

FIGURE 5 Variation of log k_3 [equation (4)] with pK_A for the low temperature nitrosation of indoles

Examination of the kinetic hydrogen isotope effect for 5-cyanoindole and 1,2-dimethylindole confirms this hypothesis. The datum for 5-cyanoindole is clear-cut, with $k^H{}_3/k^D{}_3 = 1\cdot8 \pm 0\cdot1$ indicative of slow proton-transfer from the Wheland intermediate, as is normal for aromatic nitrosation.[1-3] Studies with 1,2-dimethylindole, however, were carried out in H_2O and D_2O because exchange of 3-H in dilute acid is rapid.[17] The observed solvent isotope effect ($k_2{}^{H_2O}/k_2{}^{D_2O} = 0\cdot61$) is therefore comprised of any primary isotope effect for nitrosation plus solvent effects for pre-equilibria associated with protonation of both substrate and nitrous acid. 1,2-Dimethylindole is sufficiently basic to undergo significant protonation in dilute acid, but to different extents in H_2O and D_2O. If the neutral substrate is the reactant, this has to be allowed for, in our case, by independent measurement of the basicity in H_2O ($pK_A{}^{H_2O} = +0\cdot30$)[7] and D_2O ($pK_A{}^{D_2O} = +0\cdot8$).[21] No direct information on the basicity of nitrous acid is available, but earlier kinetic studies of diazotisation by the nitrous acidium ion (the likely reagent under our conditions) suggest that $[D_2ONO^+]/[H_2ONO^+] = 2\cdot2$.[22] Assuming that the acid-catalysed pathway [equation (4)] refers to reaction between the nitrous acidium ion and neutral 1,2-dimethylindole (*i.e.* Rate = k^L[1,2-Dimethyl-3-L_1-indole][L_2ONO^+] *), it can readily be shown that the relationship between k^L and $k_2{}^{L_2O}$ is given by equation (15) and that the isotopic rate ratio (*i.e.* the kinetic hydrogen isotope effect after correction for solvent effects on both reactants) is therefore expressed by equation (16). On substituting the right hand side

$$k^L = k_2{}^{L_2O}\left\{1 + \frac{[L^+]}{K_A{}^{L_2O}}\right\}\frac{[LNO_2]}{[L_2ONO^+]} \qquad (15)$$

$$\frac{k^H}{k^D} = \frac{k_2{}^{H_2O}}{k_2{}^{D_2O}}\cdot\frac{\left\{1 + \dfrac{[H^+]}{K_A{}^{H_2O}}\right\}}{\left\{1 + \dfrac{[D^+]}{K_A{}^{D_2O}}\right\}}\cdot\frac{[D_2ONO^+]}{[H_2ONO^+]} \qquad (16)$$

of equation (16) with values cited above $k^H/k^D = 1\cdot26 \pm 0\cdot2$ for 1,2-dimethylindole in 0·0102M-$HClO_4$ at 3 °C. If the magnitude of the primary isotope effect for aromatic substitution is related to the acidity of the leaving proton, as widely predicted,[10] this ratio is unreasonably low in relation to those observed for 5-cyanoindole and other aromatic nitrosations.[1-3] If nitrosation of 1,2-dimethylindole were diffusion controlled, however, $k^H/k^D = 1\cdot26 \pm 0\cdot2$ would be associated with the different viscosity for H_2O and D_2O, a factor of *ca.* 1·25 at 25 °C.[23] We therefore infer from these isotopic rate ratios that proton loss from the Wheland intermediate is rate limiting for 5-cyanoindole, but not for 1,2-dimethylindole, and this agrees with the hypothesis based on the variation of k_3 with substrate basicity.

Nitrosation by nitrous anhydride (N_2O_3), one of the weakest reagents,[5,6] would be expected only for the most reactive indoles. There is no doubt about the involvement of this reagent with 1,2-dimethylindole in very dilute $HClO_4$ because the zeroth-order reaction path

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* The symbol L throughout the text refers to isotopic hydrogen, *i.e.* L = D in D_2O and H in H_2O.

[21] A. J. Lawson, Ph.D. Thesis, London, 1969.

[22] B. C. Challis, L. F. Larkworthy, and J. H. Ridd, *J. Chem. Soc.*, 1962, 5203.

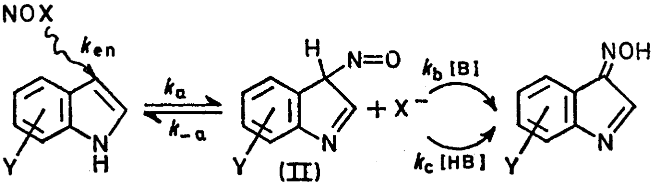
[23] R. Vaillard, ' Nouveau Traite de Chimie Minerale,' ed. P. Pascal, Masson, Paris, 1956, vol. 1, p. 818.

[equation (2)] implies that the formation of N_2O_3 is rate limiting [equation (17)] and that its interaction with

$$2HNO_2 \rightleftharpoons H_2ONO^+ + NO_2^- \rightleftharpoons N_2O_3 + H_2O \quad (17)$$

substrate is accordingly rapid. Since a comparable situation for diazotisation is found only with much more basic amines (Table 10), this result is unexpected, but the close agreement between k_1 obtained independently from the 1,2-dimethylindole and aniline studies[5] confirms the interpretation of equation (2).

Mechanism.—All these findings are accommodated by the recently established[1-3] A–S_E2 mechanism (Scheme) for aromatic nitrosation, with the added proviso that diffusion of the reactants (k_{en}), or formation of the nitrosating agent, may be rate limiting under certain circumstances.

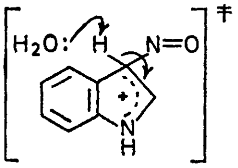


SCHEME A–S_E2 Mechanism for the nitrosation of indoles

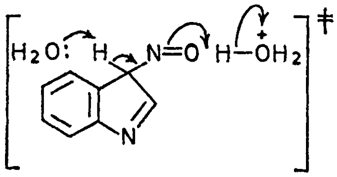
Thus, when substrate reactivity controls the reaction rate [pK_A(Substrate) $\leqslant -6{\cdot}0$], both the kinetic isotope effect and the absence of significant nucleophilic (Cl^-) catalysis imply that breakdown of the Wheland intermediate (II) to products is slow, and this agrees nicely with the results for other aromatic nitrosations.[1-3] Depending on whether step k_b or k_c (Scheme) is the pathway to products, catalysis by either Brønsted bases or acids might therefore be anticipated.

Our results provide no evidence for base-catalysis of k_b apart from the low acidity kinetics of 2-phenylindole [equation (6)], where the dependence of k_4 on $[HNO_2]^2$ may derive either from reaction by N_2O_3 or from NO_2^- catalysis. The former explanation requires that either N_2O_3 reacts with 2-phenylindole on encounter or that k_a is rate limiting: the first option is apparently excluded by the relatively low molecular rate coefficient for this reaction ($k_{N_2O_3} = 5 \times 10^7$ l mol^{-1} min^{-1} at 3 °C assuming $K_{N_2O_3} = [N_2O_3]/[HNO_2]^2 = 0{\cdot}2$),[24] and the second seems inconsistent with the mechanism for other indoles. We therefore tentatively conclude that k_4 does refer to NO_2^--catalysed proton removal from the Wheland intermediate (*i.e.* path k_b), but confirmation awaits measurement of the deuterium isotope effect.

The preferred pathway to products for most of the less reactive indoles appears to be acid-catalysed breakdown of the Wheland intermediate (k_c). Thus k_3 [equations (4) and (12)] for these compounds refers to either removal of 3-H from the Wheland intermediate (III) or protonation of the nitroso oxygen atom as in (IV). The present results fail to distinguish between these alternatives. An interesting point, however, is that k_c is rate limiting even for those reactions approaching the limiting encounter rate, which demonstrates forcibly that low reagent reactivity is not responsible for the incidence of primary hydrogen isotope effects in aromatic nitrosation. On the contrary, the major factor, as deduced previously,[2] must be the ready decomposition (step k_{-a}) of the intermediate to regenerate reactants, which is consistent with the relatively high stability of nitrous species (*e.g.* NO^+) in aqueous acidic solvents.



(III)



(IV)

The large magnitude of the molecular rate coefficients (k_{NOCl}) leaves no doubt that reaction of NOCl with the more basic indoles (p$K_A \geqslant -3{\cdot}6$) is controlled by diffusion of the reactants and it follows that the more reactive H_2ONO^+ reagent behaves likewise. This finding is unexpected in that aromatic nitrosation has long been regarded as a difficult reaction because of the low electrophilic reactivity of many nitrosating agents. There is substantial evidence from diazotisations, however, that both H_2ONO^+ and NOCl combine with primary aromatic amines (p$K_A > 0$) on encounter[6] and the observation that 1,2-dimethylindole combines with N_2O_3 as fast as it forms in solution (*i.e.* formation of N_2O_3 is rate limiting) underlines the high reactivity of indole substrates.

The kinetic expressions for the diffusion-controlled reactions give no information as to subsequent steps on the reaction path, but it seems reasonable to suppose in the first instance that the usual A–S_E2 process is followed. The only experimental observation bearing on this matter concerns the greater reactivity for a given pK_A of indole compounds relative to primary aromatic amines (see Table 10). This implies either that substrate basicity is a poor comparative index of nucleophilic reactivity in this instance or that nitrosation of indoles occurs initially at the heterocyclic nitrogen, thereby reflecting their secondary amine properties. Some observations, such as rapid isotopic hydrogen exchange,[25] point to the high 'kinetic basicity' of the indole N atom. If initial nitrosation proceeds at this site, however, our kinetic observations still require that rearrangement to the 3-nitroso-intermediate (II) is relatively fast, both for the encounter-controlled and reactivity-controlled reactions.

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[2/2635 *Received*, 21*st November*, 1972]

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[24] T. A. Turney, *J. Chem. Soc.*, 1960, 4263; C. A. Bunton and G. Stedman, *ibid.*, 1958, 2440.

[25] B. C. Challis and E. M. Millar, *J.C.S. Perkin II*, 1972, 1116; M. Koizumi, *Bull. Chem. Soc. Japan*, 1939, **14**, 453, 491.