The Chemistry of Nitroso-compounds. Part VII.[1] The First 'Fast' Proton Transfer for an Aromatic Nitrosation

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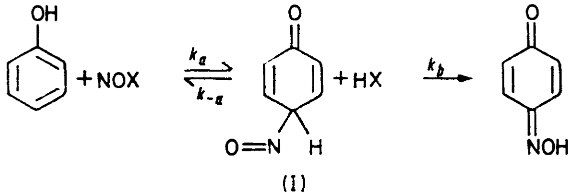
Rates of nitrosation are reported for phenol and 2-naphthol in aqueous carboxylic acid buffers over the pH range 1—*ca.* 5·5 at 25 °C. Substitution of phenol occurs predominantly at the *para*-position at rates which are pH independent, but general-base catalysed, below pH *ca.* 4·5, and comparative experiments with [4-^{2}H]phenol show the existence of a substantial primary hydrogen isotope effect (k^H/k^D = 3·5). Above pH *ca.* 4·5, however, the kinetic dependences for phenol show significant changes. These differences are more easily seen with 2-naphthol, which undergoes nitrosation exclusively at the 1-position. Here reaction rates are pH independent, subject to general-base catalysis, and to substantial primary hydrogen isotope effects (k^H/k^D = 4·0) only below pH *ca.* 2. At higher pH, the rate is proportional to [H_3O^+], and both base catalysis and isotope effects diminish substantially. All these observations are consistent with a common A–S_E2 reaction mechanism in which proton expulsion from a dienone intermediate is rate limiting for phenol at pH < *ca.* 4·5 and for 2-naphthol at pH < *ca.* 2·0. Formation of the dienone intermediate is rate limiting, however, for 2-naphthol at pH > *ca.* 4·0, so this is the first-known aromatic nitrosation for which proton expulsion is rapid. Neither nitrous anhydride (N_2O_3) nor nitrosyl acetate (NOOAc) is sufficiently reactive to substitute the nucleus of phenol or 2-naphthol and reaction at pH 1—*ca.* 5 probably involves the nitrous acidium ion ($H_2NO_2^+$); with halide ions present, additional reaction *via* nitrosyl halides occurs. The pH dependent rate for 2-naphthol excludes significant nitrosation of the 2-naphtholate ion up to pH *ca.* 5, but this species may preferentially interact at oxygen to form an unstable aryl nitrite. The implications of this deduction on the ambident nucleophilic properties of phenolic compounds, and the incursion of free radical substitution pathways, are also discussed.

OUR recent studies have shown that proton loss from the Wheland intermediate on the A–S_E2 pathway is usually rate limiting for aromatic nitrosation.[2] Different behaviour has been noted, however, for some heteroaromatic compounds which appear to be so reactive towards some nitrosating agents in aqueous solution that diffusion of the reactants becomes the rate-limiting process.[3] In these cases, it is not possible to deduce the relative rates of subsequent steps on the reaction path. Thus far, aromatic nitrosation has not been observed under conditions where formation of the Wheland intermediate is slow and it has therefore been impossible, by and large, to deduce from kinetic studies the structure of nitrosating agents involved in these reactions.

Application of steady-state kinetic approximations to the A–S_E2 pathway (Scheme 1) shows that the rate-limiting step for reactivity controlled reactions is determined by the relative magnitude of the k_{-a} and k_b steps.



(I)

SCHEME 1 A–S_E2 Mechanism for the nitrosation of phenol.

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[1] Part VI, B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526.

[2] (*a*) B. C. Challis and R. J. Higgins, *J.C.S. Perkin II*, 1972, 2365; (*b*) B. C. Challis, R. J. Higgins, and A. J. Lawson, *ibid.*, p. 1972.

[3] B. C. Challis and A. J. Lawson, *J.C.S. Perkin II*, 1973, 918.

Evidently for most aromatic nitrosations $k_{-a} > k_b$ and the observed rate approximates to $k_0 \simeq k_a k_b / k_{-a}$. Various observations have intimated that this inequality arises mainly from the relatively high stability of NOX reagents (which promote the k_{-a} step) rather than the low acidity of the leaving proton.[2,3]

Previous observations of an acidity-independent pathway for the nitrosation of phenol from pH 2 to 1M-$HClO_4$ imply that the intermediate on the A–S_E2 pathway is the neutral dienone structure (I).[4] Thus the k_{-a} step for phenol under these conditions must be acid-catalysed. Although no indication of a shift in the rate-limiting step was evident in these earlier studies,[4] it follows that at some higher pH $k_{-a} < k_b$ and formation of (I) should then be slow. In this event the rate equation should give direct information on the structure of the nitrosating agent. We have therefore extended our investigation of phenol to higher pH and, because this reaction becomes very slow under these conditions, have also examined the more reactive 2-naphthol. Both substrates are known to undergo nitrosation predominantly (>90%) at the 4- and 1-positions, respectively, in dilute acidic media.[5]

EXPERIMENTAL

Substrates and Reagents.—AnalaR phenol was fractionally distilled under reduced pressure and then vacuum-dried over P_2O_5, f.p. 40·5 °C, (lit.,[6] f.p. 40·5—41·5 °C). [4-^{2}H]-Phenol was prepared from *p*-bromophenol by a Grignard reaction and purified as for phenol. Mass spectrometric analysis showed 80% deuterium incorporation at the *para*-position. Reagent grade 2-naphthol was recrystallised repeatedly from water and then vacuum-dried over P_2O_5, m.p. 124 °C (lit.,[7] m.p. 123—124 °C). [1-^{2}H]-2-Naphthol was prepared by heating the normal compound in D_2O (Koch-Light 99·7% D) at pH 12 in a sealed tube at 200 °C for 9 days. After neutralisation and filtration of the precipitated naphthol, the solid was recrystallised from boiling water and then vacuum-dried over P_2O_5. Mass spectrometric analysis revealed extensive deuteriation of all four reactive sites of the 2-naphthol, but complete absence of a molecular ion corresponding to undeuteriated nuclear sites. It was therefore assumed that the substrate was 100% deuteriated in the 1-position.

AnalaR sodium nitrite, sodium acetate, sodium chloride, sodium perchlorate, and reagent grade chloracetic acid were used without purification other than vacuum-drying over P_2O_5. AnalaR acetic acid was also used without further purification. Standard solutions were prepared by dilution.

Products.—The nitrosation of phenol in 0·2M-H_2SO_4 yields at least 95% *p*-nitrosophenol, the remainder being the *ortho*-isomer.[5a] T.l.c. analysis of the reaction solutions after 10 half-lives showed only these two products, and the product ratio appeared to be pH independent: comparative u.v. assay with authentic material showed a yield of *p*-nitrosophenol >90% throughout the pH range examined kinetically.

The nitrosation of 2-naphthol in HOAc gives quantitative amounts of 1-nitroso-2-naphthol.[5b] This result was confirmed for the pH range of our investigation by comparative t.l.c. and u.v. assay with an authentic sample. Infinity absorptions of the reaction solutions from pH 1 to 5 gave $\lambda_{max.}$ (H_2O) 380 nm (log ε 3·7), based on the stoicheiometry of added $NaNO_2$ [lit.,[8] $\lambda_{max.}$ (H_2O) 380 nm (log ε 3·7)]. A similar result was also obtained for the product isolated from reaction at pH 5 with excess of $NaNO_2$. This eliminates the possibility of polysubstitution under these conditions.

Kinetics.—Rates of nitrosation were usually obtained by measurement of the concentration of unreacted HNO_2 at timed intervals. Details of this method have been fully described in earlier papers.[2,4] All the kinetic experiments were carried out in a thermostatted bath at 25 ± 0·1 °C. Spontaneous decomposition of nitrous acid under our conditions was very much slower than the rates of nitrosation and no correction was therefore applied. On completion of the kinetic run, the pH of the reaction solution was measured with a Radiometer model 26 instrument.

Nitrosation rates of 2-naphthol at pH <3, and at pH 4·34 with a stoicheiometric excess of $NaNO_2$, were ascertained by direct monitoring at 380 nm of the solution contained in a jacketted cuvette (maintained at 25 ± 0·1 °C by circulating water) in the cell compartment of a Unicam SP 1800 spectrophotometer. Rates measured by the two methods were completely compatible.

RESULTS AND DISCUSSION

Kinetic Orders.—Both substrates were examined at 25 °C in aqueous carboxylic acid buffer solutions of pH 1·7—5·5. Because nitrous acid (pK_A 3·29)[9] is largely dissociated at the higher pH, these reactions were quite slow and, to ensure reasonably short half-lives, a large excess of substrate had to be employed. Under these conditions, the reaction rates followed equation (1) with

$$\text{Rate} = \bar{k}_1(\text{Sodium nitrite}) \qquad (1)$$

a first-order dependence on the stoicheiometric amount of sodium nitrite.* The consistency of $\bar{k}_1$ throughout a kinetic run for 2-naphthol in acetic acid buffer solution at pH 3·97 is listed in Table 1.

As expected, reactions of both phenol and 2-naphthol showed a first-order dependence on the substrate concentration. This dependence was checked over the pH range and the results are listed in Table 2. Even at the highest pH examined, neither phenol (pK_A 9·99)[10] nor

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* To distinguish between various kinetic expressions, stoicheiometric reactant concentrations are denoted by parentheses and stoicheiometric rate coefficients by a superscript bar. Actual reactant concentrations are written as chemical formulae within the usual square brackets.

[4] B. C. Challis and A. J. Lawson, *J. Chem. Soc. (B)*, 1971, 770.

[5] (*a*) S. Veibel, *Ber.*, 1930, **63**, 1577; (*b*) W. Dettwyler, U.S.P. 3,051,750/1963; E. Kremos, N. Wakeman, and R. Hixon, *Org. Synth.*, 1941, **1**, 511.

[6] 'Dictionary of Organic Compounds,' eds. J. R. A. Pollock and R. Stevens, Eyre and Spottiswoode, London, 1955, 4th edn., vol. 4, p. 2660.

[7] Ref. 6, p. 2378.

[8] 'Organic Electronic Spectral Data,' ed. H. E. Ungnade, Interscience, New York, 1960, vol. 2, p. 199.

[9] 'Dissociation Constants of Inorganic Acids and Bases in Aqueous Solution,' ed. D. D. Perrin, Butterworths, London, 1969, p. 185.

[10] 'Dissociation Constants of Organic Acids in Aqueous Solution,' eds. G. Kortüm, W. Vogel, and K. Andrussow, Butterworths, London, 1961, p. 428.

2-naphthol (pK_A 9·57)[11] is appreciably ionised, so the substrate term in equation (2) refers to actual concentrations of the neutral species.

$$\text{Rate} = \bar{k}_2(\text{Sodium nitrite})[\text{Substrate}] \qquad (2)$$

The $\bar{k}_2$ coefficient is dependent on acidity (see Table 2) partly because sodium nitrite is only partially converted to nitrous acid at the pH of the reaction solutions. To allow for this, second-order coefficients (k_2) based on actual concentrations of both substrate and nitrous acid [equation (3)] have been calculated from the experimental data.

$$\text{Rate} = k_2[\text{HNO}_2][\text{Substrate}] \qquad (3)$$

The relationship between $\bar{k}_2$ and k_2 is given by equation (4), where the acid dissociation constant for nitrous acid, $K_{\text{HNO}_2} = 4{\cdot}6 \times 10^{-3}$ mol l^{-1} at 25 °C.[9]

$$k_2 = \bar{k}_2\{1 + K_{\text{HNO}_2}/[\text{H}_3\text{O}^+]\} \qquad (4)$$

For brevity the dependence of nitrosation rates on pH and buffer composition is discussed below in terms of k_2, calculated as described above from equation (4).

TABLE 1

Nitrosation of 2-naphthol in acetic acid buffers (pH 3·97) at 25 °C; initial [2-Naphthol] = 2·84 × 10^{-3}M, initial (Sodium nitrite) = 8·00 × 10^{-5}M

t/min	O.D. at 541 nm	Reaction (%)	10^4k_1/s^{-1}
2	0·821	0	t_0
12	0·720	11·0	2·19
39	0·520	36·6	2·05
57	0·419	48·9	2·04
77	0·332	59·7	2·01
102	0·244	70·3	2·03
137	0·156	81·1	2·05
172	0·105	87·3	2·02
202	0·073	91·2	2·02
∞	0·001		

TABLE 2

Kinetic order in substrate for the nitrosation of phenol and 2-naphthol at 25 °C

pH	10^2[Substrate]/M	10^5k_1/s^{-1}	$10^3\bar{k}_2$/l mol^{-1} s^{-1}
Phenol			
[NaOAc] = 0·15M, initial (Sodium nitrite) = 10^{-4}M			
3·72	3·78	21·4	5·66
3·72	1·26	6·94	5·61
4·19	3·94	9·09	2·31
4·19	1·97	4·50	2·29
5·13	7·98	1·13	0·142
5·13	3·94	0·57	0·144
5·54	7·98	0·206	0·026
5·54	3·94	0·104	0·026
2-Naphthol			
[NaOAc] = 0·2M, initial (Sodium nitrite) = 5 × 10^{-5}M			
2·99	0·284	420	1,490
2·99	0·142	218	1,530
2·99	0·071	109	1,530
4·50	0·213	2·84	13·6
4·50	0·107	1·45	13·3
4·92	0·249	0·355	1·4
4·92	0·142	0·186	1·3

Acid and Base Catalysis

Phenol.—Acidity dependence. The variation of k_2 [equation (3)] with pH for reaction at 25 °C in acetic acid buffer solutions containing a constant amount (0·15N) of sodium acetate is given in Table 3. The cited pH values are experimental but they are consistent with pK_{HOAc} 4·6, close to the value reported for dissociation in aqueous solutions containing 0·1M-salt.[12] Table 3 shows that k_2 is virtually constant up to pH *ca.* 4·5, but thereafter decreases significantly: the diminution observed is well outside possible experimental error. The pH-independent rate is consistent with earlier investigations of the reaction in dilute mineral acid, both aqueous HClO$_4$[4] and HCl.[13] The incidence of a pH-dependent rate, however, has not previously been reported.

TABLE 3

Acidity dependence of k_2 [equation (3)] for the nitrosation of phenol at 25 °C; [NaOAc] = 0·15M

pH	[HOAc]/M	10^2k_2/l mol^{-1} s^{-1}
3·61	1·47	1·80
3·72	1·22	1·83
3·88	0·85	1·82
3·87$_5$	0·85	1·82
4·06	0·563	1·75
4·62	0·150	1·53
5·12$_5$	0·058	0·898
5·54	0·020	0·424

Acetate ion catalysis. Results listed in Table 4 show that k_2 [equation (3)] also depends on [AcO$^-$]. These experiments were not conducted at constant ionic strength, but the negligible influence of added NaClO$_4$ (see Table 4) eliminates the possibility of a large salt effect. Acetate ion must therefore act as a base catalyst

TABLE 4

Acetate ion catalysis and salt effects for the nitrosation of phenol at 25 °C

pH	[HOAc]/M	[NaOAc]/M	[NaClO$_4$]/M	10^2k_2/ l mol^{-1} s^{-1}
4·06	0·282	0·075		1·35
4·06	0·563	0·15		1·75
3·91	0·800	0·20		1·89
4·05	1·32	0·30		2·46
3·91	1·60	0·40		2·82
3·92	2·00	0·50		3·37
3·91	0·282	0·075	0·50	1·25
4·54	0·135	0·10		1·32
4·53	0·270	0·20		1·78
4·53	0·405	0·30		2·08
4·54	0·540	0·40		2·61
4·49	0·675	0·50		2·94
4·49	0·135	0·10	0·40	1·20
4·65	0·05	0·05		1·01
4·62	0·15	0·15		1·33
4·61	0·25	0·25		1·67
4·62	0·50	0·50		2·54
4·61	0·50	0·50		2·50

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[11] Ref. 10, p. 437.

[12] M. Kilpatrick and R. D. Eanes, *J. Amer. Chem. Soc.*, 1953, **75**, 586.

[13] H. Schmid, G. Muhr, and P. Riedl, *Monatsh.*, 1966, **97**, 781.

and this conclusion is in line with expectations for rate-limiting proton transfer from the Wheland intermediate[4] and with earlier examination of the nitrosation of 2,6-dibromophenol.[14]

Closer scrutiny shows that the degree of acetate ion catalysis depends on the pH of the reaction solution: plots of k_2 *versus* [NaOAc] shown in Figure 1 are linear, but show diminishing slope with increasing pH and a significant, but varying, intercept. Thus the reaction under these conditions follows equation (5), where k_{H_2O}

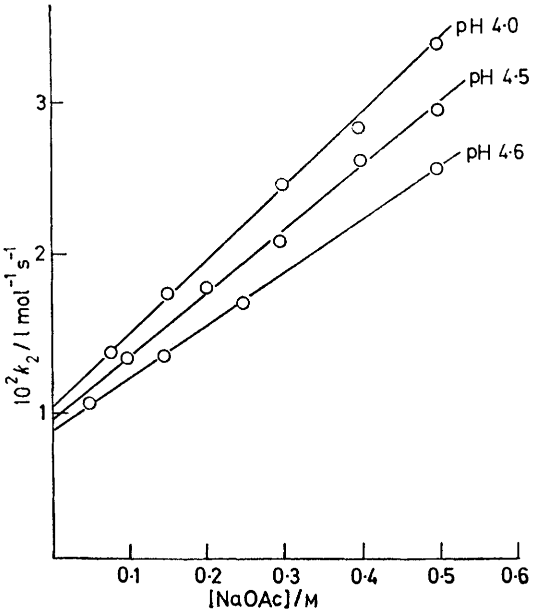

FIGURE 1 Dependence of k_2 on [NaOAc] for the nitrosation of phenol at 25 °C

$$k_2 = k_{H_2O} + k_{A^-}[AcO^-] \qquad (5)$$

relates to catalysis by the solvent and k_{A^-} represents the catalytic rate coefficient for the acetate ion. Values of both k_{A^-} and k_{H_2O} are summarised in Table 5 and changes in both coefficients appear to be linked to the onset of the pH-dependent pathway noted above. Thus k_{H_2O} and k_{A^-} decrease by about 6 and 14%, respectively, on increasing the pH from 4·0 to 4·5, but by further increments of 12 and 15%, respectively, with the smaller pH change from 4·5 to 4·6.

TABLE 5

Catalytic rate coefficients [equation (5)] for the nitrosation of phenol and 2-naphthol at 25 °C

Catalyst	pH	$10^2k_{H_2O}$/l mol^{-1} s^{-1}	$10^2k_{A^-}$/l^2 mol^{-2} s^{-1}
		Phenol	
AcO^-	4·0	1·02	4·7
AcO^-	4·5	0·96	4·0
AcO^-	4·6	0·84	3·4
		2-Naphthol	
a	1·13	427	
a	2·23	368	
$ClCH_2CO_2^-$	2·70	304	1310
AcO^-	2·91	222	710
AcO^-	3·51	105	430
AcO^-	3·95	35	260
AcO^-	4·51	15	50

[a] In dil. $HClO_4$ (see text).

The solvent term (k_{H_2O}) of equation (5) must refer to base catalysis by H_2O. By assuming $[H_2O] = 55·5$M, the Brønsted coefficient derived from the catalytic coefficients for H_2O and AcO^- at pH 4·0 becomes $\beta = 0·37$. This value lies sensibly between the theoretical limits, $0 < \beta < 1$, and is therefore consistent with a rate-limiting proton transfer.

2-Naphthol.—Base catalysis. 2-Naphthol was examined in both acetic acid and chloroacetic acid buffer solutions at pH 2·7—4·5. These measurements were not made at constant ionic strength, but the negligible effect of added $NaClO_4$ at constant pH showed the absence of any significant primary salt effect. Reaction rates for 2-naphthol, however, were dependent on pH (much more so than for phenol) as is shown below and the experimental data have therefore been adjusted for secondary salt effects (variation of pH with ionic strength) empirically from the variation of k_2 [equation (3)] with pH. Details of this adjustment are available elsewhere[15] and normalised values of k_2 are plotted against the buffer anion concentration in Figure 2 for several pH. Their linearity shows that the reaction rate has a first-order dependence on the buffer base concentration, whereas their positive intercepts imply significant catalysis by the solvent. Thus, as for phenol, the variation of k_2 for 2-naphthol at a constant pH is defined by equation (5). The slight reduction of both AcO^- and H_2O catalysis with increasing pH noted above for phenol is much more marked in the case

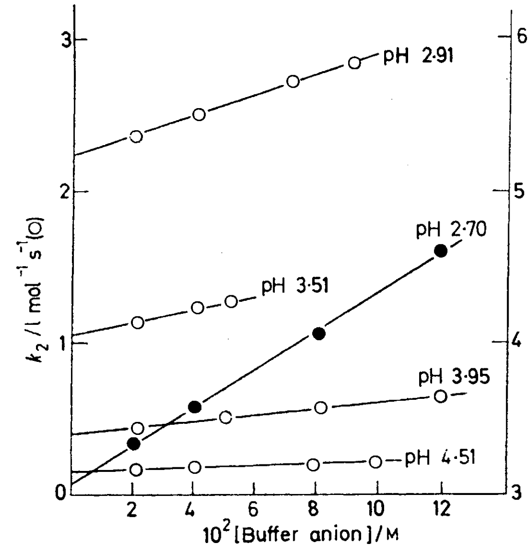

FIGURE 2 Dependence of k_2 on [Buffer anion] for the nitrosation of 2-naphthol at 25 °C: ○ HOAc buffers; ● $ClCH_2CO_2H$ buffers

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[14] K. M. Ibne Rasa, *J. Amer. Chem. Soc.*, 1962, **84**, 4962.

[15] R. J. Higgins, Ph.D. Thesis, London, 1972.

of 2-naphthol. This is evident both from the slopes of the plots in Figure 2 and from the derived values of $k_{\mathrm{A^-}}$ and $k_{\mathrm{H_2O}}$ summarised in Table 5. Both catalytic coefficients decrease by a factor of *ca.* 14 as the pH increases from 2·91 to 4·5.

Acidity dependence. Nitrosation rates for 2-naphthol were also measured in dilute $HClO_4$ at pH 1·13 and 2·23 and values of k_2 = 4·27 and 3·68 l mol^{-1} s^{-1}, respectively, were found. Since added $NaClO_4$ does not catalyse the reaction, the observed values of k_2 correspond to $k_{\mathrm{H_2O}}$ obtained from the measurements in buffer solutions.

The variation of $k_{\mathrm{H_2O}}$ with pH is plotted in Figure 3.

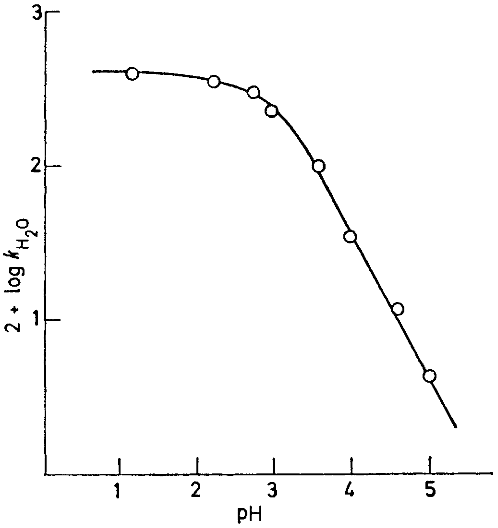

FIGURE 3 Variation of log $k_{\mathrm{H_2O}}$ with pH for the nitrosation of 2-naphthol at 25 °C

Clearly at pH <2, the rate is virtually acidity independent as found for the nitrosation of phenol. At pH >2, however, the slope of Figure 3 is 1·0, indicating a first-order dependence of $k_{\mathrm{H_2O}}$ on $[H_3O^+]$. The same trend is apparent from the variation of $k_{\mathrm{A^-}}$ with acidity.*

Hydrogen Isotope Effects

Substantial primary hydrogen isotope effects were reported previously for the nitrosation of phenol in dilute mineral acid.[4] We have examined them again to establish whether any change of mechanism or rate-limiting step occurs in acetic acid buffers. These experiments were carried out with high concentrations of the buffer components, to accelerate proton expulsion as much as possible, at various pH. Values of the second-order rate coefficient obtained from equation (3) for [4-^{2}H]phenol (k_2^{D}) and for the undeuteriated substrate (k_2^{H}) under identical conditions are listed in Table 6, together with the experimental pH of the reaction solutions. Since mass spectrometric analysis showed 81% *para*-deuteriation of the phenol, the experimental $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ ratio has been normalised by assuming a linear dependence of k_2^{D} on the % deuteriation. Only the normalised ratios are listed in Table 6 from which it is evident that up to pH *ca.* 4·5 even high concentrations (*ca.* 3·6M) of AcO^- do not significantly reduce the primary isotope effect from that observed in dilute $HClO_4$. We therefore conclude that base catalysis by AcO^- must be insufficient to induce a shift in the rate-limiting step. However, the $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ ratio does decrease from 3·3 to 2·3 on increasing the pH from 4·3 to 5·3. Since these reactions were carried out with buffers of similar $[AcO^-]$ *ca.* 2M, and independent mass spectrometric analyses showed that insignificant exchange of the deuterium label with the solvent occurred during the course of the reaction, the reduction of the primary isotope effect must relate to the pH change. It is linked, presumably, with the onset of the acidity-dependent reaction at pH *ca.* 4·5 noted above, and with the concurrent reduced dependence on $[AcO^-]$.

TABLE 6

Kinetic deuterium isotope effects for the nitrosation of phenol and 2-naphthol at 25 °C; k_2 in l mol^{-1} s^{-1} throughout

pH	[AcOH]/M	[NaOAc]/M	$10^2k_2^{\mathrm{H}}$	$10^2k_2^{\mathrm{D}}$	$k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$
		Phenol			
1·0 [a]			0·80	0·21	3·9
1·70	7·00	0·006	1·09	0·39	3·5 [b]
4·32	6·87	2·40	8·02	3·03	3·3 [b]
4·44	10·31	3·60	9·90	4·32	3·0 [b]
5·31	2·80	2·10	5·70	3·23	2·3 [b]
		2-Naphthol			
2·15			371	88	4·2
2·98	1·125	0·02	222	88	2·5
3·51	0·356	0·02	113	55	2·0
3·97	0·113	0·02	38	26	1·45
4·51	0·036	0·02	13·5	9·8	1·40

[a] For reaction in dilute $HClO_4$ at 0 °C, from ref. 4. [b] Obtained from experimental $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ assuming linear dependence of k_2^{D} on % deuteriation (see text).

The data of Table 6 also show that acetic acid, itself, does not catalyse the reaction. Thus the value of $k_2^{\mathrm{H}} = 1{\cdot}09 \times 10^{-2}$ l mol^{-1} s^{-1} in 7·0M-HOAc (pH 1·69$_5$) where the $[AcO^-]$ is estimated to be 0·006M is closely similar to the values of both $k_{\mathrm{H_2O}} = 0{\cdot}96 \times 10^{-2}$ l mol^{-1} s^{-1} at pH 4·5 (see Table 5) and $k_2 = 0{\cdot}8 \times 10^{-2}$ l mol^{-1} s^{-1} obtained previously[4] for the nitrosation of phenol in dilute $HClO_4$ (pH *ca.* 1·0).

The corresponding isotope effect for 2-naphthol was measured in both acetic acid buffers and dilute $HClO_4$. Values of the second-order coefficient for [1-^{2}H]-2-naphthol (k_2^{D}) and the normal compound (k_2^{H}) are also listed in Table 6. Since deuteriation of the 1-position was presumed to be complete (*vide supra*), and independent experiments established that deuterium exchange with the solvent was negligible, the observed $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ ratios listed in Table 6 directly represent the primary isotope effect. Their variation with pH is much more marked than that with phenol. Thus $k_2^{\mathrm{H}}/k_2^{\mathrm{D}}$ drops from 4·2 at pH 2·15 to 1·4 at pH >3·5

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* A similar pH profile has recently been reported for the nitrosation of resorcinol (J. Jahelka, V. Sterba, and K. Valter, *Coll. Czech. Chem. Comm.*, 1973, **38**, 877).

and parallels the change in acidity dependence and base catalysis for this substrate.

Mechanism

In dilute mineral acid, the nitrosation of phenol is believed to proceed by an A–S_E2 mechanism (Scheme 1) involving a neutral dienone structure (I) from which proton expulsion (step k_b) is rate-limiting.[4] Two distinctive features of this pathway are an acid-independent rate with a substantial kinetic isotope effect. Thus the present results extend this mechanism and rate-limiting step to solutions of pH <4 at least. Because of their structural similarities, a common mechanism would be expected for phenol and 2-naphthol under equivalent conditions. So the diminution of the kinetic isotope effect so clearly observed for 2-naphthol must be considered in the context of an A–S_E2 mechanism. This implies that the low k_2^H/k_2^D ratios for 2-naphthol at high pH arise because proton expulsion from the intermediate is no longer rate-limiting.

Several alternative rate-limiting steps for the A–S_E2 pathway can be envisaged from our experience with other aromatic nitrosation reactions, but fortunately most can be eliminated by other experimental observations. There is no likelihood, for example, that formation of the nitrosating species is slow although this phenomenon has been observed for diazotisation [16] and the nitrosation of 1,2-dimethylindole.[3] On the contrary, this possibility is eliminated for phenol and 2-naphthol by the first-order dependence on substrate concentration throughout the pH range of interest. Similarly, diffusion of the reactants (which may then combine on encounter) cannot be rate controlling, although, here again, this process is known to be slow for the nitrosation of very reactive non-benzenoid aromatic and hetero-aromatic hydrocarbons.[3] The arguments behind this conclusion will be amplified later and at this point it is sufficient to note that 2-naphthol, itself, obviously cannot react on encounter at lower pH because $k_2^H/k_2^D > 1$ and that any reaction, encounter or otherwise, of the 2-naphtholate ion is excluded by the dependence of k_2 on $[H_3O^+]$ at pH $>3{\cdot}5$. Thus by negative deduction, we conclude that, on increasing the pH, formation of the dienone intermediate (step k_a of Scheme 1) becomes progressively rate limiting for 2-naphthol and probably for phenol, too.

Realisation of this rate-limiting step is important because the reagents involved can now be identified unambiguously from the kinetic form of the reaction. We have already deduced that the observed acidity dependence at pH $>3{\cdot}5$ excludes any reaction of the naphtholate ion. As far as the nitrosating agent is concerned, several potentially reactive species are present under our conditions. Nitrous anhydride (N_2O_3), although an effective reagent towards aromatic amines at pH 2—4,[16] can be ruled out immediately because of the first-order dependence on sodium nitrite concentration [equation (1)] noted above. We have checked this point further, however, by examining the reaction of 2-naphthol at high pH with high sodium nitrite concentrations, conditions which favour the formation of N_2O_3. These data are given in Table 7 for acetic acid buffer at pH 4·34 with a stoicheiometric excess of $NaNO_2$. Under these conditions there is little general base catalysis (*vide supra*) and the reaction follows equation (6). The values of $\bar{k}_2$ [$= \bar{k}_1'$/(Sodium nitrite)] listed in Table 7 are virtually independent of (Sodium nitrite),

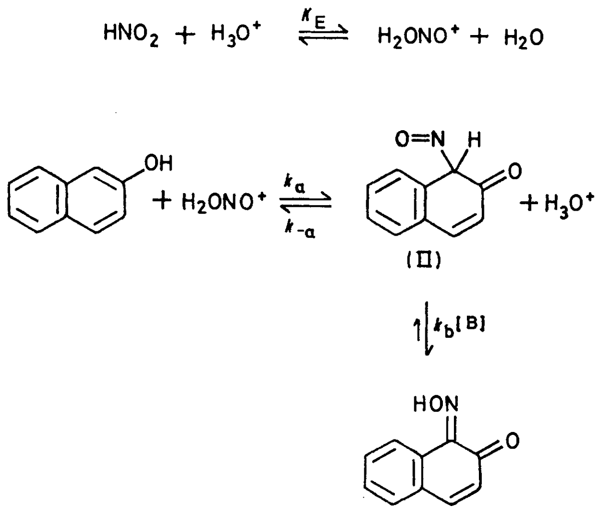
$$\text{Rate} = \bar{k}_1'[\text{2-Naphthol}] \qquad (6)$$

which confirms the absence of any significant reaction by N_2O_3. Presumably this reagent is too weak to substitute the nucleus of 2-naphthol, and therefore of phenol, too. The absence of significant base catalysis at high pH noted above also rules out any reaction *via* covalent nitrosyl species derived from the buffer, such as nitrosyl acetate. Further, interaction between HNO_2, itself, and 2-naphthol can also be discounted because this is inconsistent with the acid catalysis observed at pH $>3{\cdot}5$. These arguments therefore imply that in the absence of strongly nucleophilic species such as halide ion, only the nitrous acidium ion (H_2ONO^+) is sufficiently reactive and available in solutions of low acidity to attack the nucleus of phenol and 2-naphthol.

TABLE 7

Kinetic order in sodium nitrite for the nitrosation of 2-naphthol in acetic acid buffers (pH 4·34) at 25 °C; [NaOAc] = 0·1M, initial [2-Naphthol] = $1{\cdot}71 \times 10^{-4}$M

$[NaClO_4]$/M	(Sodium nitrite)/M	$10^4\bar{k}_1/s^{-1}$	$10^2\bar{k}_2$/l mol^{-1} s^{-1}
0·080	0·020	9·15	4·6
0·090	0·010	3·79	3·8
0·095	0·005	2·09	4·2



SCHEME 2 A–S_E2 Mechanism for the nitrosation of 2-naphthol by the nitrous acidium ion

The A–S_E2 mechanism for substitution by H_2ONO^+ (formed in a fast pre-equilibrium step) of the neutral naphthol is detailed in Scheme 2. If the intermediate

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[16] E. D. Hughes, C. K. Ingold, and J. H. Ridd, *J. Chem. Soc.*, 1958, **65**, 88.

is a neutral dienone (II) as shown then its collapse to reactants (step k_{-a}) must be acid-catalysed, whereas transmission to products (step k_b) is catalysed by basic species (B). Application of steady state kinetic approximations show that the dependence of k_2 [equation (3)] on kinetic coefficients for the individual steps of Scheme 2 is given by equation (7), which transforms to equation (8) if allowance is made for the pre-equilibrium associated with H_2ONO^+ ($K_E = [H_2ONO^+]/[HNO_2][H_3O^+]$). Equation (8) also defines the dependence of k_2 on both

$$k_2[HNO_2] = \frac{k_a k_b [H_2ONO^+][B]}{k_{-a}[H_3O^+] + k_b[B]} \qquad (7)$$

$$k_2 = \frac{k_a k_b K_E [B][H_3O^+]}{k_{-a}[H_3O^+] + k_b[B]} \qquad (8)$$

the pH and the buffer composition and its ability to account for the experimental behaviour of k_2 is therefore a critical test of our mechanistic proposals.

At high acidity, when $k_{-a}[H_3O^+] > k_b[B]$, equation (8) reduces to $k_2 \simeq k_a k_b K_E [B]/k_{-a}$. Thus the experimental rate should be pH independent, but subject to both base catalysis and a substantial primary hydrogen isotope effect. This behaviour is observed for phenol at pH $<4{\cdot}5$ and for 2-naphthol at pH $<2{\cdot}5$. At low acidity, however, $k_{-a}[H_3O^+] < k_b[B]$ and $k_2 \simeq k_a K_E [H_3O^+]$, so the experimental rate should be acidity dependent but show neither base catalysis nor an isotope effect. This behaviour is apparent for 2-naphthol at pH $>3{\cdot}6$. Transition between the limiting conditions defined above would be expected for 2-naphthol from pH 2·5—3·5. As the pH increases, $k_{-a}[H_3O^+]$ must approach the magnitude of k_b, so the experimental coefficient (k_2) becomes progressively less dependent on k_b. Accordingly, the k_2^H/k_2^D ratio decreases and the degree of buffer base catalysis also diminishes.

Partition of Intermediate (II).—We have suggested previously [2,3] that the incidence of primary hydrogen isotope effects for aromatic nitrosations must stem from the facile loss of NO^+ from the Wheland intermediate rather than from any other factor. It is therefore of great interest to ascertain the relative magnitude of k_{-a} for these reactions. A direct measurement is not possible, but correlation of k_2 with the steady state rate expression [equation (8)] for 2-naphthol allows the partition of the intermediate (II) to reactants and to product (k_{-a}/k_b) to be estimated. Thus at pH 2, $k_{-a}[H_3O^+] > k_b$ whereas at pH 4, $k_{-a}[H_3O^+] < k_b$: since each limit must represent a 'threshold,' it follows that k_{-a}/k_b is of the order of 100 if k_b is independent of pH as might reasonably be expected. From the present results, a similar estimate is not possible for phenol. However, in this case the inequality $k_{-a}[H_3O^+] < k_b[B]$ cannot be realised at pH <5 and it follows that, relative to 2-naphthol, either k_{-a} is larger and/or k_b is smaller. Both changes are consistent with the lower reactivity of phenol and either one would tend to increase k_{-a}/k_b. Thus for even less reactive compounds, such as benzene, k_{-a}/k_b must be very much larger than 100.[2b]

Chloride Ion Catalysis.—Previous studies of phenol [4,13] showed complete absence of halide ion catalysis where the rate was pH independent and this observation was important additional evidence for rapid formation of the neutral intermediate (I). The pH-dependent pathway for 2-naphthol, however, is catalysed by added Cl^-, which nicely confirms our deduction about the rate-limiting step at high pH. Data listed in Table 8 show that added NaCl produces a significantly larger rate enhancement than added $NaClO_4$, which presumably acts only by a secondary salt effect. Since basic species such as AcO^- are feebly catalytic at pH 4 (*vide supra*), nitrosation must proceed by an additional pathway involving NOCl in the presence of Cl^-.

TABLE 8

Cl^- Catalysis and salt effects for the nitrosation of 2-naphthol at 25 °C in acetic acid buffers

pH	$[NaClO_4]$/M	[NaCl]/M	k_2/l mol^{-1} s^{-1}
3·85			0·50
3·85	0·08		0·46
3·85		0·08	0·70
4·38			0·165
4·38	0·08		0·160
4·38		0·08	0·29

Reagents and Reactants for Aromatic Nitrosation.—These results appear to resolve many of the previous uncertainties about the kind of nitrosating agents that are able to react with aromatic substrates in dilute acid. As far as neutral reagents are concerned, nitrosyl chloride does react readily and this is in line with its behaviour in aromatic diazotisation.[17] Nitrous anhydride and nitrosyl acetate, however, are clearly too feeble to substitute phenol or 2-naphthol and they must be similarly ineffectual for less reactive substrates. In the absence of powerful nucleophilic species, therefore, nitrosation of most benzene derivatives must proceed *via* either the nitrous acidium or the nitrosonium ions. We deduced from indirect evidence in Part II that the latter was important in concentrated acid (>5M-$HClO_4$),[4] but the question of whether an additional reagent is required in dilute acid remains.

Because the equilibrium constant for its formation is known (pK_{NO^+} $-6{\cdot}12$ on the H_R scale),[18] the $[NO^+]$ can be readily estimated for any acidity. Thus at pH 4·0, $[NO^+]/[HNO_2]$ *ca.* 10^{-10}, and the molecular rate coefficient for reaction by NO^+ required to account for the observed rate comes out at 4×10^9 l mol^{-1} s^{-1} at 25 °C, which is indicative of an encounter-controlled process.[19] All the other evidence, however, suggests the nitrosation of 2-naphthol at pH 4 is *not* encounter controlled. Thus, high positional selectivity prevails with a quantitative yield of the 1-nitroso-product: at pH 2, the reaction cannot be encounter controlled because $k_2^H/k_2^D > 1$ and

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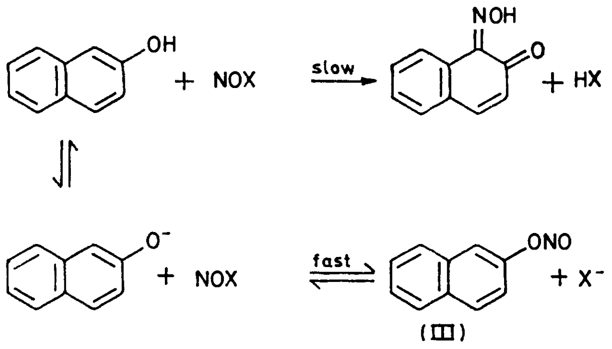
[17] See B. C. Challis and A. R. Butler, 'Chemistry of the Amino Group,' ed. S. Patai, Wiley, London, 1968, p. 308.

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

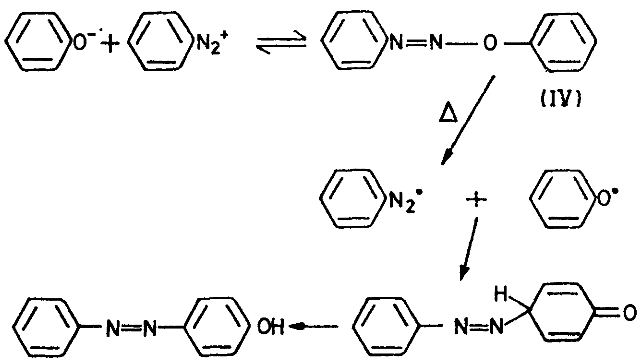
[19] P. Debye, *Trans. Electrochem. Soc.*, 1942, **82**, 265.

there is no possibility that changes in solvent basicity in going from pH 2 to 4 could effect a shift in the rate-limiting step: finally, other studies [3] have demonstrated that compounds less reactive than 2-methyl-5-nitroindole (pK_{BH^+} −3·58),[20] which includes 2-naphthol, itself, do not react on encounter with nitrosating agents present in dilute acid. We therefore conclude that nitrosation proceeds *via* an additional reagent to NO^+ under these conditions, whose concentration is pH dependent. This species is likely to be the nitrous acidium ion.

The observation of a pH-dependent rate also excludes the possibility of significant aromatic nitrosation of the 2-naphtholate ion. This is surprising in view of the powerful activation expected for an O^- substituent towards electrophilic reagents. One reasonable explanation is that nitrosation of the 2-naphtholate ion under our conditions must proceed entirely at the O^- atom to form an unstable aryl nitrite (III), which readily dissociates to regenerate reactants (Scheme 3). The tendency for electrophilic reagents to react preferentially at carbon of neutral phenolic compounds but at the oxygen atom of their conjugate bases may be a general phenomenon, and direct experiments to test this hypothesis are being carried out. Examination of the ambident nucleophilic properties by Kornblum and his colleagues [21] show clearly that *C*-alkylation is favoured in hydroxylic solvents, which has been attributed to hydrogen-bonding between the solvent and O^- atom. Extrapolation of these findings implies that neutral phenolic compounds should also undergo extensive *C*-alkylation. This hypothesis may also explain the incidence of an electron transfer process reported recently [22] for diazo-coupling. Thus preferential interaction of the diazonium ion with oxygen of the phenolate ion would produce an *O*-diazotate (IV). Depending on the temperature and other experimental conditions, (IV) may undergo (Scheme 4) either heterolytic fission to regenerate the reactants or homolytic fission to a radical pair. The latter could then combine to produce the usual azo-product, as well as transformations similar to the Gomberg [23] reaction.



SCHEME 3 Reversible *O*-nitrosation of the 2-naphtholate ion



SCHEME 4 Free radical pathway for diazo-coupling

[3/568 *Received*, 19*th March*, 1973]

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[20] R. J. Hinman and J. Lang, *J. Amer. Chem. Soc.*, 1964, **86**, 3796.

[21] N. Kornblum, P. J. Berrigan, and W. J. Le Noble, *J. Amer. Chem. Soc.*, 1963, **85**, 1141; N. Kornblum, R. Seltzer, and P. Haberfeld, *ibid.*, p. 1148.

[22] N. N. Bubnov, K. A. Bilevitch, L. A. Poljakova, and O. Yu. Okhlbystin, *Chem. Comm.*, 1972, 1058.

[23] See D. R. Augood and G. H. Williams, *Chem. Rev.*, 1957, **57**, 129.