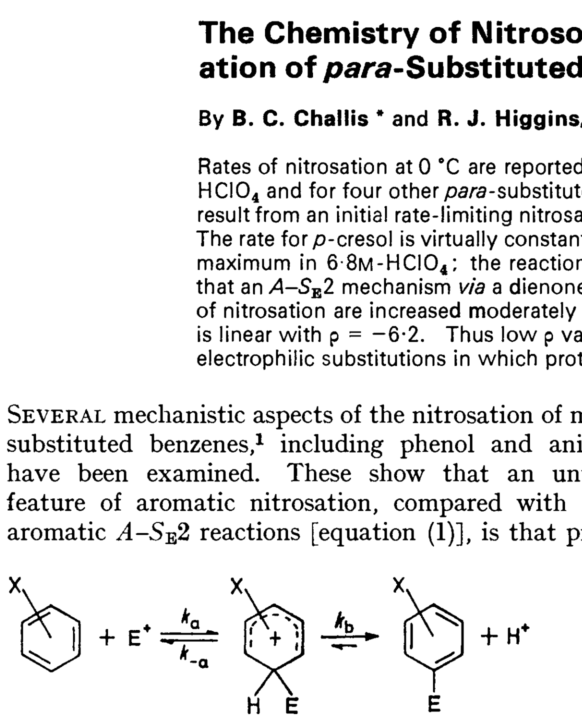
The Chemistry of Nitroso-compounds. Part IV.[1] Acid-catalysed Nitrosation of *para*-Substituted Phenols

By **B. C. Challis** * and **R. J. Higgins**, Department of Organic Chemistry, Imperial College, London SW7 2AY

Rates of nitrosation at 0 °C are reported for *p*-cresol in 0·01—9·3M-$HClO_4$, for [2,6-$^2H_2$]-*p*-cresol in 0·01—5·7M-$HClO_4$ and for four other *para*-substituted phenols in 6·8M-$HClO_4$. Only 2-nitro-products are obtained and these result from an initial rate-limiting nitrosation followed by rapid oxidation rather than from a direct nitration reaction. The rate for *p*-cresol is virtually constant below 0·5M-$HClO_4$, but thereafter increases rapidly with acidity to reach a maximum in 6·8M-$HClO_4$; the reaction also shows a substantial deuterium isotope effect. These facts suggest that an A–S_E2 mechanism *via* a dienone intermediate is involved, in which expulsion of the proton is slow. Rates of nitrosation are increased moderately by electron-donating *para*-substituents. The Hammett plot for these data is linear with $\rho = -6{\cdot}2$. Thus low ρ values appear to be characteristic of aromatic nitrosation and other aromatic electrophilic substitutions in which proton loss from the Wheland intermediate is slow.

SEVERAL mechanistic aspects of the nitrosation of monosubstituted benzenes,[1] including phenol and anisole,[2] have been examined. These show that an unusual feature of aromatic nitrosation, compared with other aromatic A–S_E2 reactions [equation (1)], is that proton loss from the Wheland intermediate (step k_b) is invariably rate-limiting. This difference appears to result mainly from the relatively high stability of electrophilic nitrosating species such as the nitrosonium ion (NO^+) in acidic solutions [3] promoting the k_{-a} step, and the outcome is that most nitrosating agents are relatively ineffective. Studies with benzene,[1] for example, indicate that NO^+ is at least 10^{14} times less effective than the nitronium ion (NO_2^+).



(1)

Rate-limiting proton loss produces several kinetic consequences for nitrosation, such as the incidence of general-acid catalysis even in strong acid solutions,[1,4] and substantial primary deuterium isotope effects.[1,2] It also reduces the magnitude of the Hammett ρ reaction constant.[1] This effect has not been generally anticipated,[5] although it is clearly expected from the opposite electronic demands of Wheland intermediate formation and the rate-limiting step. Assessment of reagent reactivity from the magnitude of ρ therefore requires circumspection, as is evident from the similar reaction constants obtained for nitrosation by NO^+ ($\rho = -6{\cdot}9$) [1] and for nitration by NO_2^+ ($\rho = -6{\cdot}2$).[6]

Because of the low reactivity of NO^+, the ρ value referred to above was obtained from examination of monosubstituted substrates more reactive than benzene itself. To reaffirm its low magnitude, we have extended our studies to the *ortho*-nitrosation of *para*-substituted phenols, for which a wider range of substituents can be examined. The initial products, *o*-nitrosophenols, are usually synthesized *via* the Baudisch reaction,[7] but direct *o*-nitrosation is known qualitatively to occur[8] and, indeed, may be expected from product studies with phenol itself.[9] Nitrosation of the *ortho*- rather than the normal *para*-position of phenol should not induce a major change of mechanism, but to establish this fact we have examined the nitrosation of *p*-cresol in detail.

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EXPERIMENTAL

Substrates and Reagents.—Since relatively small amounts of unsubstituted phenol as impurity would have an inordinate effect on the kinetic data, special care was taken to remove it when purifying the substrates by conventional methods. Reagent grade *p*-cresol and *p*-chlorophenol were twice fractionally distilled under high vacuum and the middle 20% fraction was taken each time and finally vacuum-dried over P_2O_5. For *p*-fluoro, *p*-cyano-, and *p*-nitro-phenol, reagent grade material was recrystallized repeatedly from either light petroleum or water, and the product again vacuum-dried over P_2O_5. M.p.s of purified compounds agreed closely with literature values[10] and spectroscopic examination showed the purity of these compounds to be in excess of 99·8%.

$[2,6\text{-}^2H_2]$-*p*-Cresol was prepared by heating the normal compound, dissolved in D_2O (Koch–Light; 99·7%) at pH 9, in a sealed tube at 100 °C for nine days. After neutralization, and extraction with ether, the *p*-cresol was purified as before; $n_D^{30} = 1{\cdot}5310$ (lit.,[11] $n_D^{30} = 1{\cdot}5311$). Mass spectral examination showed 69% deuterium incorporation in the 2,6-positions.

AnalaR $NaNO_2$ (vacuum-dried) and $HClO_4$ were used without further purification.

Products.—Spectral analysis of the reaction solutions after 10 half-lives showed the presence of 2-nitro-derivatives only. For all but *p*-cyanophenol, products were isolated from scaled-up reactions under otherwise identical conditions to those used for kinetic studies. Comparison with authentic materials showed that in each case the only product after purification was the 4-substituted 2-nitrophenol.

The formation of these products is discussed further below, where it is shown that several factors point to an initial formation of the 2-nitrosophenol, which is then rapidly oxidized by the solvent $HClO_4$. This oxidation is well-known[1,7b] and was confirmed under our conditions by examination of 4-methyl-2-nitrosophenol and 4-chloro-2-nitrosophenol, prepared independently by Cronheim's[7b] method. The former was oxidized appreciably even on dissolution in distilled H_2O, and both were completely oxidized to their nitro-counterparts on brief contact with dilute $HClO_4$.

Some compounds proved to be unsatisfactory for kinetic studies because of rapid displacement of the *para*-substituent by nitrous acid. Thus *p*-bromophenol on reacting with HNO_2 in 5·8M-$HClO_4$ rapidly gave a brown colour and substantial amounts of *p*-nitrophenol were isolated from the reaction mixture. Displacement of the methoxy-group from *p*-methoxyphenol by HNO_2 has recently been reported,[12] but was much more extensive under our conditions. Thus at 0 °C in 2—5M-$HClO_4$, *p*-benzoquinone was obtained in quantitative yield with excess of HNO_2; at lower acidities (pH = 2—3), *p*-benzoquinone is still the major product, but increasing amounts (up to 30%) of the 4-methoxy-2-nitrophenol were also obtained.

Kinetics.—Rates of nitrosation were obtained by measurement of the concentration of unchanged HNO_2 at timed intervals. Details of the method have been fully described.[1,2] All the kinetic experiments were carried out at 0 °C in an ice–water bath. As a large excess of the substrate was always present, the reactions followed a pseudo-first-order relationship (2). Values of k_0 obtained were reasonably constant to at least 90% reaction, as

$$\text{Rate} = k_0[HNO_2] \qquad (2)$$

is evident from the results for a typical experiment with *p*-cresol in 4·06M-$HClO_4$ given in Table 1.

TABLE 1

Nitrosation of *p*-cresol in 4·06M-$HClO_4$ at 0 °C

Initial [*p*-cresol] = $1{\cdot}04 \times 10^{-2}$M; initial [$NaNO_2$] = $1{\cdot}25 \times 10^{-4}$M

t/min	*A* at 541 nm	Reaction (%)	$10^5k_1/s^{-1}$
2	0·423		Taken as t_0
13	0·373	12	8·2
38	0·296	30	7·2
56	0·236	44	7·8
73	0·198	53	7·7
103	0·138	67	8·0
138	0·099	77	8·0
223	0·033	90	8·0
∞	0	100	

Some spontaneous decomposition of HNO_2 is evident even at 0 °C, and it is necessary to allow for this factor in computing rate coefficients for the nitrosation of substrates other than *p*-cresol. This unproductive loss was ascertained by independent concurrent measurement of [HNO_2] in flasks containing 6·8M-$HClO_4$ but no substrate. Numerical details are given in the Results section.

At the completion of kinetic measurements, the acidity of each reaction solution was checked by titration against B.D.H. standard alkali.

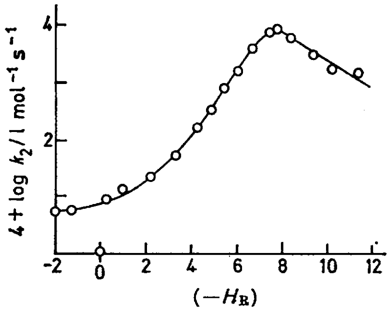

FIGURE 1 Acidity-dependence for the nitrosation of *p*-cresol in $HClO_4$ at 0 °C

RESULTS

p-*Cresol.*—To establish the kinetic form for *ortho*-nitrosation, this compound was subjected to detailed examination. Evidence for a first-order dependence on substrate concentration is collected in Table 2. Thus at any given acidity the reaction rate may be specified by equation (3), which is entirely consistent with previous studies of aromatic

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

nitrosation.[1,2] The variation of k_2 with acidity is listed in Table 3, and, as for phenol itself,[2] three distinct regions of acid catalysis are evident. These features are more easily seen from the plot of log k_2 against the $(-H_R)$ acidity function[13] in Figure 1. (i) Below 0·5M-$HClO_4$, k_2 = *ca.* 5·5 ×

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[10] See ' Dictionary of Organic Compounds,' 4th edn., Heilbron–Bunbury, Eyre and Spottiswoode, London, 1965.

[11] Ref. 10, vol. 2, p. 751.

[12] D. H. R. Barton, P. G. Gordon, and D. G. Hewitt, *J. Chem. Soc.* (*C*), 1971, 1206.

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10^{-4} l mol^{-1} s^{-1} and is virtually independent of solvent acidity. (ii) From *ca.* 2M- to 7M-HClO$_4$, k_2 increases rapidly with acidity. The slope of Figure 1 in this region is +0·53. (iii) Above 8M-HClO$_4$, k_2 decreases with increasing acidity, and the slope of log k_2 against $(-H_R)$ is *ca.* −0·22.

TABLE 2

Kinetic order for the nitrosation of *p*-cresol in HClO$_4$ at 0 °C; initial [NaNO$_2$] = *ca.* 10^{-4}M

[HClO$_4$]/M	10^2[*p*-Cresol]/M	10^3k_1/s^{-1}	k_2/l mol^{-1} s^{-1}
4·06	1·03	0·170	0·0165
4·06	2·06	0·350	0·0170
4·57	0·518	0·182	0·033
4·57	1·036	0·333	0·031
6·10	0·126	0·44	0·35
6·10	0·503	2·07	0·41
6·10	1·01	3·84	0·38

TABLE 3

Variation of k_2 with acidity for the nitrosation of *p*-cresol at 0 °C

[HClO$_4$]/M	$(-H_R)$ [a]	10^4k_2/l mol^{-1} s^{-1}
0·0097	−2·0	5·29
0·048	−1·3	5·64
0·508	0·23	9·03
1·02	0·99	12·8
2·03	2·20	21·6
3·05	3·30	52·2
4·06	4·31	160
4·57	4·88	332
5·08	5·48	798
5·59	6·08	1630
6·12	6·72	4090
6·70	7·49	7640
6·90	7·78	8750
7·32	8·39	6000
7·96	9·34	3130
8·54	10·22	1850
9·28	11·41	1520

[a] From ref. 13.

[2,6-^{2}H$_2$]-p-*Cresol*.—Measurements were made under conditions comparable with those for *p*-cresol and k_2 at 0 °C is listed in Table 4 for [HClO$_4$] up to 5·68M. This upper limit arose from the onset of appreciable exchange of the deuterium label with the solvent. Table 4 also records isotopic rate ratios ($k_2^H : k_2^D$) derived from interpolated values of k_2^H. It being borne in mind that the extent of isotopic substitution is *ca.* 69%, the reaction is subject to an appreciable primary deuterium isotope effect. This fixes the k_b step of the A–S_E2 mechanism [equation (1)] as rate-limiting. There appears to be little difference between the magnitudes of the deuterium isotope effect for the acid-independent and catalysed pathways. The average observed value corresponds to a calculated $k_2^H : k_2^D$ = *ca.* 1·9 ∓ 0·6 for the fully deuteriated substrate, a linear dependence on the deuterium concentration being assumed.

TABLE 4

Deuterium isotope effects for the nitrosation of *p*-cresol in HClO$_4$ at 0 °C

[HClO$_4$]/M	$10^4k_2^H$ [a]/l mol^{-1} s^{-1}	$10^4k_2^D$ [b]/l mol^{-1} s^{-1}	$k_2^H : k_2^D$
0·0097	5·29	4·06	1·40
0·048	5·64	4·02	1·30
4·30	234	139	1·70
5·10	724	560	1·29
5·68	1740	1070	1·63

[a] Interpolated from Table 3. [b] For [2,6-^{2}H$_2$]-*p*-cresol containing 69% deuterium.

Other Substrates.—Four other *para*-substituted compounds were examined to investigate the sensitivity of aromatic nitrosation to substituent effects. To obviate complications arising from reaction *via* several nitrosating reagents, these measurements were made at 0 °C in 6·8M-HClO$_4$, where the maximum rate is observed for *p*-cresol and where the major species is thought to be the nitrosonium ion (NO$^+$).[3] Under these conditions, spontaneous decomposition of the nitrous acid solutions is quite slow, but it is, nonetheless, of similar order to the rate of nitrosation of the most deactivated substrates. This decomposition is known to have a first-order dependence on [HNO$_2$][3] and our results are confirmatory. Thus, with an excess of substrate concentration, the observed rate of disappearence of nitrous acid will continue to follow equation (2), but k_0 will be the sum of the spontaneous decomposition rate (k') and the nitrosation rate ($v = k_1$[HNO$_2$]), *i.e.*, equation (4). Values of k' (obtained

$$k_0 = k' + k_1 \qquad (4)$$

from concurrent measurements in the absence of substrate), k_0, and k_1 are in Table 5. The second order coefficients, k_2, also in Table 5, show that these reactions follow equation (3) as expected.

TABLE 5

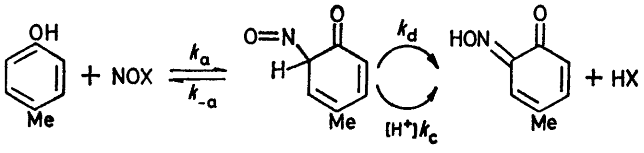
Experimental rate coefficients (k_0, k_1, and k_2) for nitrosation of *para*-substituted phenols in 6·8M-HClO$_4$ at 0 °C; initial [NaNO$_2$] = *ca.* 10^{-4}M; $10^5k'$ = 0·60 s^{-1} throughout

10^2[Substrate]/M	10^5k_0/s^{-1}	10^5k_1/s^{-1}	10^5k_2/l mol^{-1} s^{-1}
1-Fluorophenol			
0·530	2·57	1·97	372
0·530	2·62	2·02	381
0·530	2·78	2·18	411
1·06	4·84	4·24	400
p-Chlorophenol			
1·02	3·45	2·85	279
1·02	3·27	2·67	262
1·01	3·37	2·77	274
2·02	6·29	5·69	282
p-Cyanophenol			
5·51	1·78	1·18	21·4
5·51	1·86	1·26	22·9
5·51	1·90	1·30	23·6
p-Nitrophenol			
5·50	0·73	0·13	2·4
5·50	0·72	0·12	2·2
5·50	0·71	0·11	2·0

DISCUSSION

Striking similarities between the kinetic acidity-dependence and the deuterium isotope effect for *p*-cresol and for phenol[2] suggest a common reaction mechanism for these compounds. Thus the nitrosation of *p*-cresol must occur by two pathways (Scheme), both involving rapid, reversible formation of a dienone intermediate (I), which slowly transforms into products either spontaneously (step k_d) or by an acid-catalysed process (step k_c). Attempts to isolate (I), or to detect it spectrophotometrically, were unsuccessful, so this structure must be formed in a rapid, reversible step (*i.e.*, $k_{-a} \gg k_a > k_d$ or k_c). Spontaneous decomposition of (I) to products accounts for the acid-independent reaction at low acidities. The acid-catalysis could involve protonation of either the phenolic- or the nitroso-oxygen atoms and studies with phenol implicate the latter.[2] The rate maximum is consistent with conversion of HNO_2 completely into NO^+ at about this acidity,[3] and the subsequent fall-off in reaction rate with increasing acidity arises mainly from the diminishing concentration of H_2O, the strongest base available for removal of the proton.

As noted,[2] the incidence of slow proton transfer from (I) prohibits explicit identification of the nitrosating agent(s) effective at any given acidity up to *ca.* 5M-$HClO_4$. Beyond this concentration, it is probable that reaction proceeds *via* the nitrosonium ion (NO^+).[2]



(I)

SCHEME Spontaneous and acid-catalysed pathways for the nitrosation of *p*-cresol

For this reason, substituent effects have been studied at an acidity corresponding to the rate maximum for the nitrosation of *p*-cresol. Mean values of the second-order coefficients (k_2) in 6·8M-$HClO_4$ at 0 °C, derived from equation (3) by use of stoicheiometric reactant concentrations are summarized in Table 6. Under these conditions, none of the substrates is appreciably protonated and nitrous acid exists mainly (>97%) [3] as NO^+. Thus the k_2 values in Table 6 are, to a good approximation, equivalent to molecular rate coefficients for reaction by NO^+.

Figure 2 shows the plot of log k_2 against Hammett σ substituent parameters:[14] this is linear, with a slope (ρ = −6·2), which confirms satisfactorily the low value (ρ = −6·9) obtained earlier for the nitrosation of monosubstituted benzenes.[1] The linearity of the plot suggests no change of rate-determining step or mechanism occurs with changing *para*-substituents. It also rules out the possibility that π-complex formation between the aromatic substrate and NO^+ is kinetically significant. This deduction is important because π-complexes appear to form in concentrated sulphuric acid, when the substrate and nitrous acid concentrations are relatively high.[15] Detailed spectral examination has given no positive evidence for their formation under our conditions.

The isolation of only 2-nitro-products again brings up the question of whether our studies refer to an initial nitrosation followed by oxidation, or to a direct nitration by nitric acid formed *in situ*. We believe that all the available evidence points strongly towards the former explanation. There can be no question in the case of *p*-cresol, as direct nitration is known to proceed without a primary deuterium isotope effect (*i.e.*, step k_a is rate-limiting).[5b] The linearity of the Hammett ρσ plot in Figure 2 leaves little possibility of a change of mechanism or rate-limiting step over the range of substrates examined. Further, recent studies in concentrated $HClO_4$ suggest that compounds more reactive than benzene, which includes, of course, all the phenols used in our investigation, undergo nitration at an encounter rate.[16] Thus the marked difference in reactivity that we observed in our experiments is wholly inconsistent with a direct nitration.

TABLE 6

Mean values of k_2 for the nitrosation of *para*-substituted phenols in 6·8M-$HClO_4$ at 0 °C

Substituent	σ_m	$\frac{10^5 k_2}{\text{l mol}^{-1}\text{ s}^{-1}}$
Me	−0·066	91,000 [a]
F	0·352	390
Cl	0·399	270
CN	0·562	23
NO_2	0·674	2·2

[a] Interpolated from the data of Table 3.

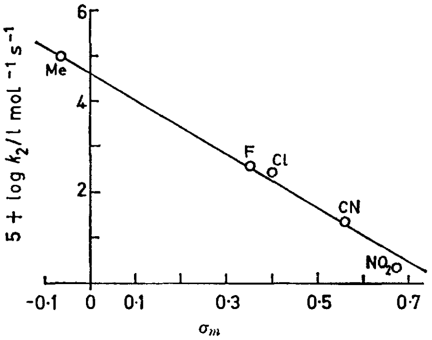


FIGURE 2 Linear free-energy plot for the nitrosation of *para*-substituted phenols in 6·8M-$HClO_4$ at 0 °C

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