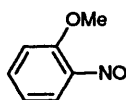# Protonation and Acid Catalysed Hydrolysis of Nitrosoaryl Ethers
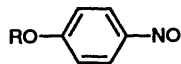
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Studies of the equilibrium protonation and kinetics of acid catalysed hydrolysis of 4-nitrosoanisole, 4-nitrosophenyl phenyl ether and related compounds in dilute aqueous acid and in concentrated aqueous trifluoroacetic acid are reported. Hydrolysis is remarkably facile and occurs by nucleophilic attack of water at the ring carbon bearing the alkoxy or aryloxy substituent of the protonated nitroso aromatic. Direct and indirect pK_a determinations for nitroso protonation are reported.

It has been reported[1-3] that the nitrosations of anisole and diphenyl ether in aqueous acid media give rise to nitrosophenol, because the initial products, nitrosoaryl ethers, are readily hydrolysed. There has been no investigation of the kinetics and mechanism of the hydrolysis reaction. We were interested because of its relevance to our present studies of the preparation of nitrosoaryl ethers. Its extraordinary facility, compared with other acid catalysed aryl ether hydrolyses which require much more forcing conditions,[4-6] was intriguing.


```
        OMe
                                    RO—⟨  ⟩—NO
   ⟨  ⟩—NO
                                    2  R = Me
    1                               3  R = Et
                                    4  R = Ph
                                    5  R = 4-NO₂C₆H₄
```

We report here on the kinetics of the hydrolysis of 2- nitrosoanisole, **1**, 4-nitrosoanisole, **2**, 4-nitrosophenetole, **3**, 4-nitrosophenyl phenyl ether, **4**, and 4-nitrophenyl 4′-nitrosophenyl ether, **5**, in dilute aqueous acid. The hydrolysis of **2**, **4** and **5** has also been investigated in concentrated (90–98%) aqueous trifluoroacetic acid solution.

The investigations have also yielded information on the basicity of **2–4**. The pK_a values of their conjugate acids are compared through a Hammett plot with those reported for other nitrosoarenes.[7]

Results and Discussion

Hydrolysis in Dilute Aqueous Acid.—In each case repeated scans of the UV–VIS spectrum revealed a cleanly first-order reaction with good isosbestic points. With **2** and **3** the final spectrum corresponded closely to that of the equilibrium mixture **6** of 4-nitrosophenol and its tautomer benzoquinone monoxime, and with **4** and **5** similarly the final spectra were consistent with quantitative conversion to **6**, plus phenol (from **4**) or 4-nitrophenol (from **5**). The final spectrum from the reaction of **1** corresponded closely to that previously determined for 2-nitrosophenol and its tautomer in acidic solution.[8]

First-order rate constants k_{obs} were determined for the hydrolyses at 25 °C of **1–4** in ten solutions of different acidity covering the range 0.1–1.0 mol dm⁻³ aqueous HCl, all adjusted to an ionic strength of 1.0 mol dm⁻³ with sodium chloride (Table 1). The value of k_{obs} is proportional to $[H^+]$ within experimental error for compounds **1** and **4**. For compounds **2** and **3** there is evidence for saturation in the $[H^+]$ catalysis. Thus plots of $1/k_{obs}$ vs. $1/[H^+]$ are linear, with a non-zero intercept (Fig. 1). Compound **5** reacted rather slowly and there were

Table 1 Observed first-order rate constants k_{obs}[a] for acid hydrolysis of alkoxy- and aryloxy-nitrosobenzenes in dilute aqueous HCl at 25 °C and ionic strength 1 mol dm⁻³[b]
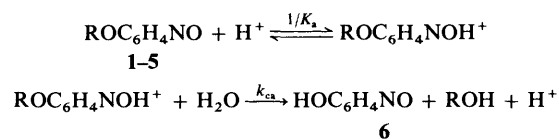
	$k_{obs}/10^{-3}\ s^{-1}$				
$[H^+]$/mol dm⁻³	1	2	3	4	5
0.10	3.22	5.16	6.90	0.277	
0.20	6.88	10.4	14.2	0.597	
0.30	9.18	14.9	20.7	0.819	
0.40	11.5	18.9	26.1	1.19	
0.50	15.0	23.5	32.4	1.42	
0.60	18.5	26.9	36.4	1.83	
0.70	22.6	32.2	44.8	1.92	
0.80	25.0	36.5	53.2	2.15	0.27
0.90		39.5	56.5	2.52	
1.00	28.7	47.1	60.0	2.81	0.28

[a] Quoted values are the mean of at least two determinations. [b] Maintained with NaCl.

indications, increasingly as acidity decreased below 0.6 mol dm⁻³ $[H^+]$, of competing side-reactions. These were not investigated.

We conclude that hydrolysis occurs through the protonated form (Scheme 1). This Scheme leads to the following relation

$$ROC_6H_4NO + H^+ \underset{1-5}{\overset{1/K_a}{\rightleftharpoons}} ROC_6H_4NOH^+$$

$$ROC_6H_4NOH^+ + H_2O \xrightarrow{k_{ca}} HOC_6H_4NO + ROH + H^+$$
$$\mathbf{6}$$

Scheme 1

(1) between the specific first-order rate constant for reaction with solvent water of the conjugate acid of the substrate, k_{ca}, the acidity constant K_a of the conjugate acid of the substrate, and k_{obs}. The intercept and slope of the double reciprocal plots for

$$k_{obs} = k_{ca}\{[H^+]/(K_a + [H^+])\} \qquad (1)$$

compounds **2** and **3** can be identified respectively with $1/k_{ca}$ and $1/k_H$ where k_H ($=k_{ca}/K_a$) is the specific second-order rate constant for the acid catalysed reaction of the neutral substrate. For compounds **1**, **4** and **5**, $K_a \gg [H^+]$ and eqn. (1) approximates to eqn. (2).

$$k_{obs} = k_H[H^+] \qquad (2)$$

Table 2 gives values of k_H, k_{ca} and pK_a. For compounds **2** and **3**, k_{ca} and pK_a were derived from the double reciprocal plots. It
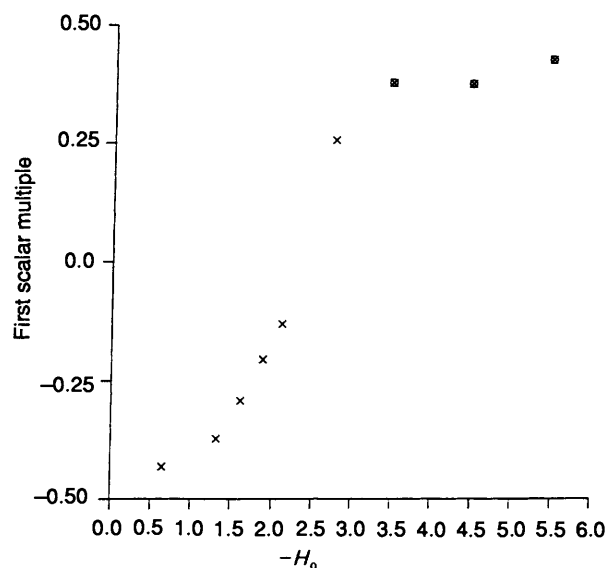
Table 2 Derived rate and acidity constants

Compd.	$k_H/10^{-3}$ dm^3 mol^{-1} s^{-1}	k_{ca}/s^{-1}	pK_a
1	33 ± 1		
2	53 ± 1	0.26 ± 0.04	−0.69 ± 0.07
3	71 ± 1	0.43 ± 0.09	−0.78 ± 0.09
4	3.0 ± 0.1	0.50 ± 0.20	−2.22 ± 0.2
5	0.3 ± 0.3		(ca. −3)
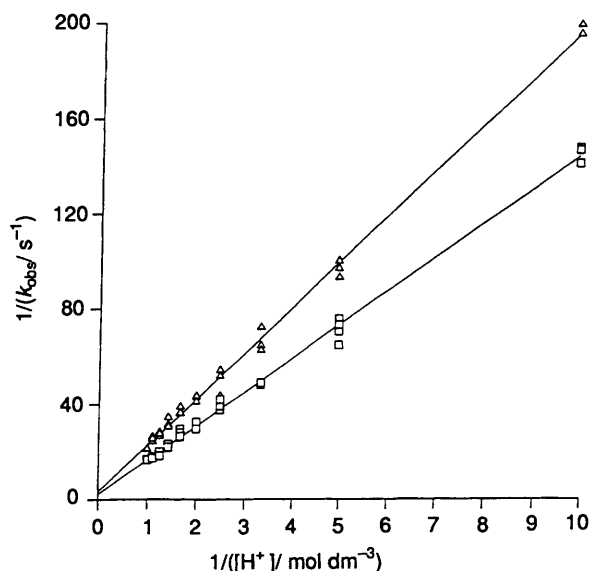
Fig. 1 Kinetics of hydrolysis of 2 and 3 in dilute aq. HCl at 25 °C. Double reciprocal plots of $1/(k_{obs}/s^{-1})$ vs. $1/([H^+]/mol\ dm^{-3})$. 2, △; 3, □.

Fig. 2 Change of initial UV spectrum of 4 with H_0 of 50–100% aq. trifluoroacetic acid, ×; and trifluoroacetic–trifluoromethanesulfonic acid, ⊠. The ordinate is the first scalar multiple derived by characteristic vector analysis of the whole spectrum.

Fig. 3 Change of initial UV spectrum of 5 with composition, 96–100% aqueous trifluoroacetic acid, ×; and in trifluoroacetic acid containing small amounts of H_2SO_4, ⊠. The ordinate is the first scalar multiple derived by characteristic vector analysis of the whole spectrum.

is clear that there is greater precision in the slopes than the intercepts and that is reflected in the errors, derived by weighted least squares analysis, in Table 2. For compound 4, the value of pK_a was determined directly as described below (a procedure not possible with 1–3 because of the rapidity of the hydrolysis) and the value of k_{ca} deduced from it and k_H.

Protonation and Hydrolysis in Aqueous Trifluoroacetic Acid.—The initial spectra of 4 changed with acidity in the range 50–98% trifluoroacetic acid in a way that suggested that protonation was occurring. The method of characteristic vector analysis[9] was used to investigate the whole spectral change and the sigmoid shape of the plot of the first scalar multiple, Fig. 2, indicates that changes due to protonation have been successfully separated from solvent shifts. The sigmoid curve was completed by using small additions of trifluoromethanesulfonic acid to enhance the acidity. Values of H_0 for these mixtures are known.[10] The curve implies that half-protonation occurs at an H_0 value of −2.22, corresponding to 88.8% trifluoroacetic acid. The protonation of nitroso-compounds is reported[7] to follow the acidity function H_0 and we therefore interpret our slope of 1.16 for the plot of log I vs. −H_0 as close to unity, so that the best estimate of the value of the pK_a of 4 is −2.22.

Similar results were obtained for 5 but the interpretation is more difficult for two reasons. First, the curve in Fig. 3 indicates that the extent of protonation is very small in 99% but substantial in 100% trifluoroacetic acid, which implies a very steep increase in acidity in this very narrow range of composition and secondly there are two reports in the literature that the value of H_0 increases[11,12] rather than decreases over this range of acidity, having reached a minimum value of −2.80 in 98% trifluoroacetic acid. We are unable to resolve these puzzles at the moment and accept that the pK_a value (ca. −3)
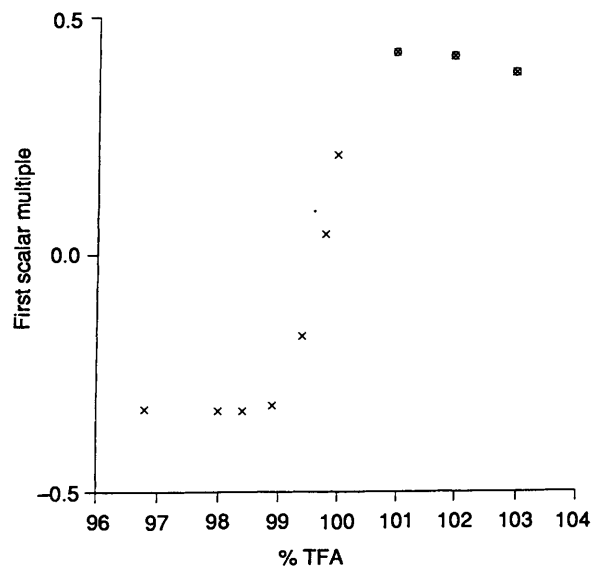
must be treated with caution. It is clear, however, from comparison of the initial spectra of the substrates in these media compared with their spectra in dilute aqueous acid where all three are in their free base forms that 5 remains predominantly unprotonated even in 90–98% trifluoroacetic acid whereas 2 is predominantly protonated and 4 is partially protonated in this region.

This accounts for the different profiles of the variation with the logarithm of the activity of water of the first-order rate constants for hydrolysis of 2, 4 and 5 in 92–98% trifluoroacetic acid (Table 3 and Fig. 4). When the observed rate constants for hydrolysis of 4 are divided by the measured fraction protonated to give specific rate constants for reaction of the conjugate acid (Table 3) the profile for 4 (pecked line in Fig. 4) is closer to that for 2. Both have slopes approaching unity, indicating very similar reactivity of the conjugate acids of 2 and 4 and a transition state formed with one additional water molecule.
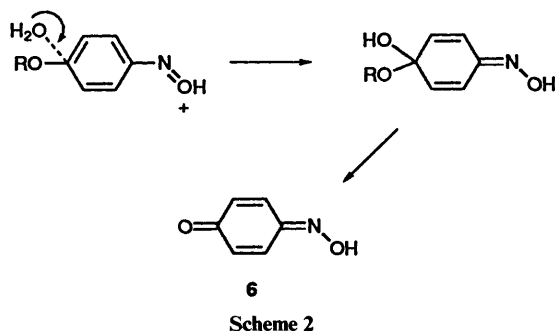
Table 3 Observed first-order rate constants k_{obs}[a] for acid hydrolysis of alkoxy- and aryloxy-nitrosobenzenes in concentrated aquous trifluoroacetic acid (TFA)[c]

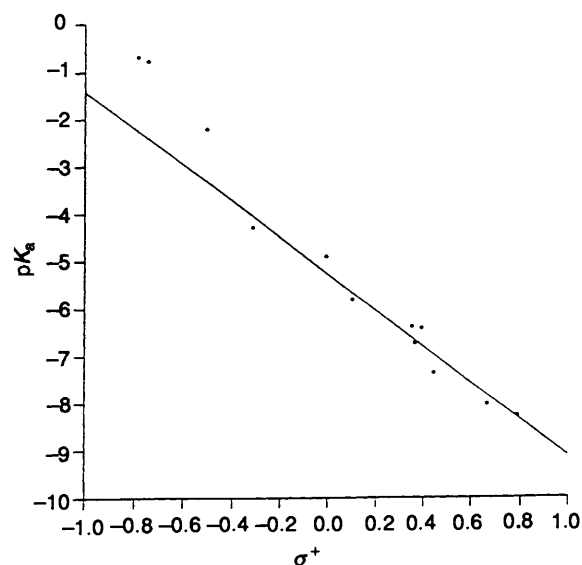|			$k_{obs}/10^{-3}$ s^{-1}		
TFA (%)	$-H_o$	log a_w	2	4	5
92.0	2.50	−1.18	2.52	1.56 (2.31)[b]	0.242
94.2	2.69	−1.40	1.45	1.01 (1.30)[b]	0.297
98.1	2.80	−2.37	0.200	0.188 (0.230)[b]	0.119

[a] Quoted values are the mean of at least two determinations. [b] Figures in parentheses are for $k_{ca}/10^{-3}$ s^{-1} calculated by dividing the value of $k_{obs}/10^{-3}$ s^{-1} by the measured fraction protonated. [c] Values of H_o and log a_w (where a_w is the activity of water) from refs. 12 and 13, respectively.
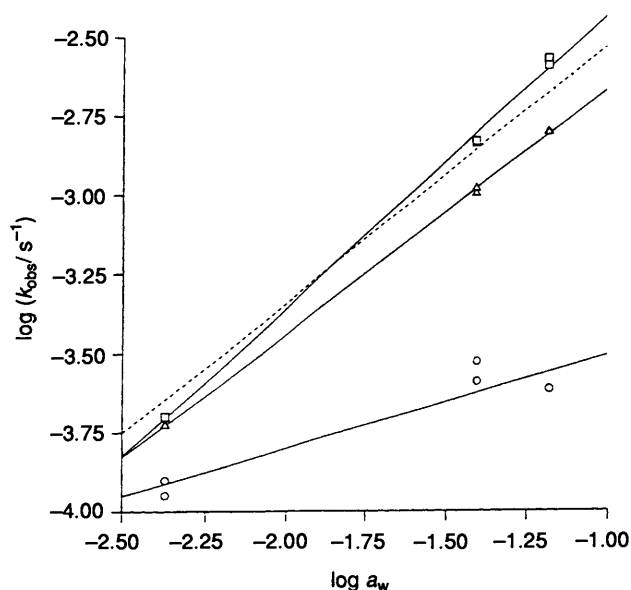
Fig. 4 Kinetics of hydrolysis of **2**, **4** and **5** in 92–98% trifluoroacetic acid. Variation of log (k_{obs}/s^{-1}) with log a_w. **2**, □; **4**, △; **5**, ○. For pecked line see text.

Fig. 5 Values of pK_a of protonated *m*- and *p*-substituted nitrosobenzenes plotted against σ^+ constants. The line is the best straight line through the previous data; the three points at the top left are results reported in this paper for **2–4**.

The similar reactivity of the conjugate acids of **1–3** on the one hand and **4** on the other suggests strongly that the reactions do not occur by S_N2 substitution at the alkyl group, because such a pathway is not available to **4**. The reaction appears to be a nucleophilic aromatic substitution, with water attacking the aryl carbon bearing the alkoxy or aryloxy group in the protonated nitroso compound, Scheme 2. This is in accord with

ter of the nitroso substituent has been noted previously[14] $(\sigma_p^- = 1.63)$ and of course this will be further enhanced to a considerable extent by protonation. One can compare for instance the failure of 4-methoxypyridinium ion to undergo hydrolysis at ambient temperatures, despite the strongly electron withdrawing protonated nitrogen in the aromatic ring $(\sigma = 2.3–2.6)$.[15] The exocyclic protonated nitroso group appears to be much more powerfully electron withdrawing.

Further evidence for the unusual nature of the protonated nitroso group as an aryl substituent comes from Hammett correlation of the values of pK_a of some protonated nitrosoarenes.[7] The ρ value when σ^+ constants are used is reported to be $−3.86$. When the present data (Table 2) are included on the Hammett plot (Fig. 5) it is seen that even σ^+ values underestimate the resonance interaction between the protonated nitroso group and the alkoxy and phenoxy substituents. If the Yukawa–Tsuno equation[16] is used with our data and the previous data, the best correlation is obtained with $\rho = −3.82$ and a high value, $r = 1.69$, for the resonance parameter.

$$pK_a = -3.82 [\sigma + 1.69 (\sigma^+ - \sigma)] - 5.34$$

The correlation coefficient between observed and calculated pK_a values using this formula is 0.993.

6

Scheme 2

conclusions reached concerning other aryl ether solvolyses,[4–6] where aryl–oxygen rather than alkyl–oxygen bond fission has been demonstrated. A surprising feature is the relative facility of the present reactions. It appears that the protonated nitroso substituent very strongly activates *ortho* and *para* positions towards nucleophilic attack. The electron withdrawing charac-

Experimental

Materials.—Commercial grade trifluoroacetic acid was fractionally distilled from 10% v/v concentrated sulfuric acid prior to use. 4-Nitrosoanisole, 2-nitrosoanisole, 4-nitrosophenetole and 4-nitrosophenyl phenyl ether were prepared from the corresponding nitro compounds by reduction to the hydroxylamine with zinc and oxidation to the nitroso with iron(III) chloride.[17] Bis(4-nitrophenyl) ether was prepared by the reaction of 4-fluoro-1-nitrobenzene with potassium carbonate in the presence of copper(I) chloride.[18] All other materials were used as supplied.

4-Aminophenyl 4'-nitrophenyl ether.[19] Bis(4-nitrophenyl) ether (10.16 g, 0.039 mol), cyclohexene (25.68 g, 0.31 mol) and 10% palladium on carbon (0.88 g) were refluxed in 135 cm^3 absolute ethanol for 1 h. On cooling, the mixture was filtered through Celite and the solvent removed from the filtrate under reduced pressure. The resulting solid was purified by column

chromatography. Unreacted bis(4-nitrophenyl) ether (0.75 g, 1.2%) was eluted with 20% ethyl acetate in light petroleum (bp 60–80 °C). 4-Aminophenyl 4′-nitrophenyl ether (3.17 g, 35%) was eluted with 50% ethyl acetate in light petroleum: mp 137.4–137.8 °C (from EtOH–CHCl$_3$) (Found: C, 62.85; H, 4.3; N, 11.9%. C$_{12}$H$_{10}$N$_2$O$_3$ required C, 62.6; H, 4.4; N, 12.2%); λ_{max}(EtOH)/nm 301.0 (ε/dm^3 mol^{-1} cm^{-1} 10 390); ν_{max}(CHCl$_3$)/cm^{-1} 3696, 3628 (NH$_2$), 1595 (N–H), 1490, 1345 (NO$_2$) and 1244 (C–O–C); δ_H(250 MHz; CDCl$_3$) 3.63 (2 H, br s, NH$_2$), 6.68 (2 H, d, 3-, 5-H), 6.89 (2 H, d, 2-, 5-H), 6.95 (2 H, d, 2′-, 6′-H) and 8.18 (2 H, d, 5′-, 3′-H); δ_C(69.2 MHz; CDCl$_3$) 116.24 (C-2, -6), 116.32 (C-2′, -6′), 121.80 (C-3, -5), 125.85 (C-3′, -5′), 144.25 (C-1, -1′), 146.40 (C-4) and 164.53 (C-4′).

4-*Nitrophenyl* 4′-*nitrosophenyl ether.* 4-Aminophenyl 4′-nitrophenyl ether (1.22 g, 0.053 mol) in 20 cm^3 dry dichloromethane was added to a suspension of 80% 3-chloroperoxybenzoic acid (2.34 g, 0.137 mol) in 30 cm^3 dry dichloromethane and stirred under nitrogen at 0 °C for 50 min. An immediate colour change from yellow to green was observed. The solution was then washed with saturated aq. potassium carbonate and twice with water, dried (magnesium sulfate), filtered and the solvent removed by evaporation. The crude residue was purified by column chromatography using 15% dichloromethane in light petroleum (bp 60–80 °C) as an eluent. The product was recovered as a pale blue solid in a yield of 0.353 g, 26%; mp 126.2–128.0 °C (from CH$_2$Cl$_2$ light petroleum) (Found: C, 58.6; H, 3.3; N, 11.4. C$_{12}$H$_8$N$_2$O$_4$ requires C, 59.0; H, 3.3; N, 11.5%); λ_{max}(H$_2$O)/nm 339 (ε/dm^3 mol^{-1} cm^{-1} 15 750); ν_{max}(CDCl$_3$)/cm^{-1} 1505 (NO), 1490, 1459, 1345 (NO$_2$) and 1245 (C–O–C); δ_H(250 MHz; CDCl$_3$) 7.20 (2 H, dt, 2-, 6-H), 7.22 (2 H, dt, 2′-, 6′-H), 7.90 (2 H, dt, 3′-, 5′-H) and 8.30 (2 H, dt, 3-, 5-H); δ_C(69.2 MHz) 163.54, 161.39, 160.59 (C-1, -4, -1′, -4′), 126.26 (C-2′, -6′), 123.89 (C-2, -6), 119.59 (C-3′, -5′) and 119.01 (C-3, -5).

Kinetic Experiments.—Trifluoroacetic acid solutions of the required concentrations were made up and titrated with sodium hydroxide to determine their acidity. Solutions containing hydrochloric acid and sodium chloride were prepared from analytical standards such that the concentration of HCl ranged from 0.1 to 1.0 mol dm^{-3} and the ionic strength was maintained at 1.0 mol dm^{-3}. A small volume (*ca.* 15 μl) (1 μl = 1 mm^3) of a solution of the nitroso ether in HPLC grade acetonitrile was transferred by syringe at zero time to an optical cell of path length 10 mm containing 3.0 cm^3 acid solution at 25 °C in the thermostatted compartment of a Perkin-Elmer Lambda 5 Spectrophotometer. The change in absorbance at a suitable wavelength (usually 300 nm) over time was monitored.

Calculation of pK_a *of* 4-*nitrosophenyl phenyl ether.* A small volume of a solution of the substrate in acetonitrile was transferred at zero time to an optical cell containing a solution of trifluoroacetic acid (in the concentration range 56–97%) as described above. The spectrum of the solution was measured between 280 and 500 nm at 2 min intervals. By measuring the change in absorbance at several wavelengths it was possible to construct an 'initial spectrum' of absorbances at zero time. Characteristic vector analysis of these 'initial spectra' at different acidities was used to calculate the pK_a of 4-nitrosophenyl phenyl ether.

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