Proton Transfer Reactions of 2-Alkyl-4-(4-nitrophenylazo)resorcinol Monoanions with Hydroxide Ion in Me$_2$SO–H$_2$O Mixtures

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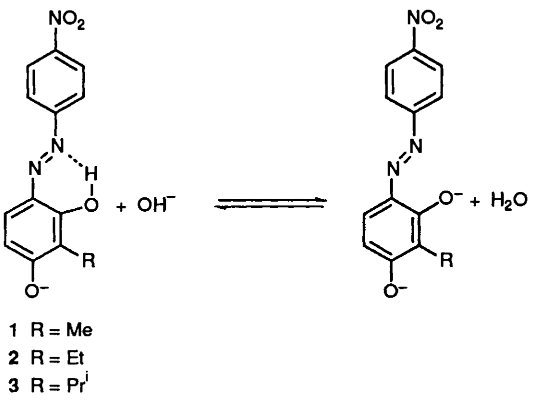
The kinetic behaviour observed for removal of the hydrogen-bonded O ··· H ··· N proton from 2-alkyl-4-(4-nitrophenylazo)resorcinol monoanions by hydroxide ion in Me$_2$SO–H$_2$O mixtures depends on the solvent ratio and on the 2-alkyl substituent (methyl, ethyl or isopropyl). For example, for 2-isopropyl-4-(4-nitrophenylazo)resorcinol monoanion in aqueous solution and in 30% (v/v) Me$_2$SO–H$_2$O the rate goes through a minimum as the hydroxide-ion concentration is increased. In 60 and 80% (v/v) Me$_2$SO–H$_2$O a practically linear dependence of rate on hydroxide-ion concentration is observed whereas in 90% (v/v) Me$_2$SO–H$_2$O the rate increases to a limiting value. The dependence of rate on hydroxide-ion concentration is determined by the relative values of the rate coefficients for attack of hydroxide ion on the hydrogen-bonded and non-hydrogen-bonded forms of the monoanion and the rate coefficients for their interconversion. The effects of the solvent and the 2-alkyl substituent are discussed.

Ionisation of the proton from the intramolecular hydrogen bond present in substituted phenylazoresorcinol monoanions shows complex kinetics. For some phenylazoresorcinols a minimum in the dependence of rate on hydroxide-ion concentration has been found [1] for the approach to equilibrium between ionised and unionised forms in aqueous solution. This has been interpreted in terms of attack of hydroxide ion on the hydrogen-bonded proton as well as on a low concentration of an open form. It is necessary to assume that the interconversion of the closed and open forms occurs slowly in comparison with the rate of proton transfer from the open form. For other phenylazoresorcinols in 70% (v/v) Me$_2$SO–H$_2$O in the presence of buffers, the rate increases with buffer concentration to a limiting value.[2] These results are explained by assuming that the open form undergoes proton transfer to buffer but that the closed form is relatively unreactive towards proton removal. At low buffer concentrations the closed and open forms interconvert rapidly in comparison with the rate at which a proton is removed from the open form and proton transfer is rate limiting. At high buffer concentrations proton transfer from the open form is rapid and opening of the hydrogen bond is rate limiting so that the overall rate becomes independent of buffer concentration.

We now report kinetic studies, in Me$_2$SO–H$_2$O mixtures, of the reaction of 2-alkyl-4-(4-nitrophenylazo)resorcinol monoanions with hydroxide ion, eqn. (1). For the first time both types of kinetic behaviour described above have been found for this single reaction. The type of behaviour is determined by the solvent ratio.



(1)

1 R = Me
2 R = Et
3 R = Pr^i

Experimental

Materials.—A sample of 2-methyl-4-(4-nitrophenylazo)resorcinol prepared from 2-methylresorcinol and 4-nitroaniline was available from a previous study.[3] In the case of 2-ethyl- and 2-isopropyl-4-(4-nitrophenylazo)resorcinols it was necessary to prepare samples of 2-ethyl- and 2-isopropyl-resorcinol from cyclohexane-1,3-dione. Cyclohexane-1,3-dione (0.178 mol) was converted into the 2-ethyl and 2-isopropyl derivatives by reaction with a mixture of aqueous 0.6 mol dm^{-3} potassium carbonate (150 cm^3) and a solution of ethyl iodide or isopropyl iodide in tetrahydrofuran (0.178 mol in 75 cm^3) at 80 °C; reaction times of 17 and 80 h, respectively were required. After removal of tetrahydrofuran, the solution was acidified and the solid product was collected and recrystallised from 95% ethanol. 2-Ethyl- and 2-isopropyl-cyclohexane-1,3-diones were obtained as white crystals of m.p. 182 and 100 °C, respectively, and were identified from their NMR spectra. The diones were aromatised to 2-ethyl- and 2-isopropyl-resorcinol by being heated with concentrated sulphuric acid in acetic acid/acetic anhydride.[4] The resorcinols were purified by sublimation and characterised by their NMR spectra. Reaction of 2-ethylresorcinol with 4-nitrophenyldiazonium chloride under alkaline conditions gave 2-ethyl-4-(4-nitrophenylazo)resorcinol as a red solid which was recrystallised from ethanol–water and purified by column chromatography on silica gel using 1:9 ethyl acetate–light petroleum (b.p. 60–80 °C) as the eluent. The product had m.p. 210 °C and δ(360 MHz; [^{2}H$_6$]Me$_2$SO) 13.60 (1 H, s, 3-OH), 10.91 (1 H, s, 1-OH), 8.37 (2 H, d, 3′- and 5′-H),* 8.07 (2 H, d, 2′- and 6′-H), 7.58 (1 H, d, 5-H), 6.66 (1 H, d, 6-H), 2.61 (2 H, q, Et) and 1.09 (3 H, t, Et).

2-Isopropyl-4-(4-nitrophenylazo)resorcinol was obtained in a similar way as a red solid with m.p. 213 °C and δ(360 MHz; [^{2}H$_6$]Me$_2$SO) 13.43 (1 H, s, 3-OH), 10.91 (1 H, s, 1-OH), 8.36 (2 H, d, 3′- and 5′-H), 8.05 (2 H, d, 2′- and 6′-H), 7.55 (1 H, d, 5-H), 6.64 (1 H, d, 6-H), 3.54 (1 H, septet, Pr^i) and 1.31 (6 H, d, Pr^i).

The Me$_2$SO–H$_2$O solvents used for these studies were made up by volume from doubly distilled water and Analar Me$_2$SO. Solutions of tetramethylammonium hydroxide were prepared from the solid pentahydrate and standardised with hydrochloric acid. Constant ionic strength was maintained by addition of tetramethylammonium chloride which had been

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* Primed numbers refer to positions in the nitrophenyl ring.

Table 1 Equilibrium constants for dissociation of the hydrogen-bonded proton from 2-alkyl-4-(4-nitrophenylazo)resorcinol monoanions[a]

	K/mol dm^{-3}					
	0%	20%	30%	40%	60%	80% v/v Me_2SO–H_2O
1 R = Me	33.6 ± 1	66.5 ± 5		113 ± 15	450 ± 15	>2000
2 R = Et	24.8 ± 1				266 ± 5	>2000
3 R = Pr^i	*ca.* 8		*ca.* 9		87.1 ± 2	>2000

[a] Temperature 15 °C and ionic strength 0.1 mol dm^{-3}.

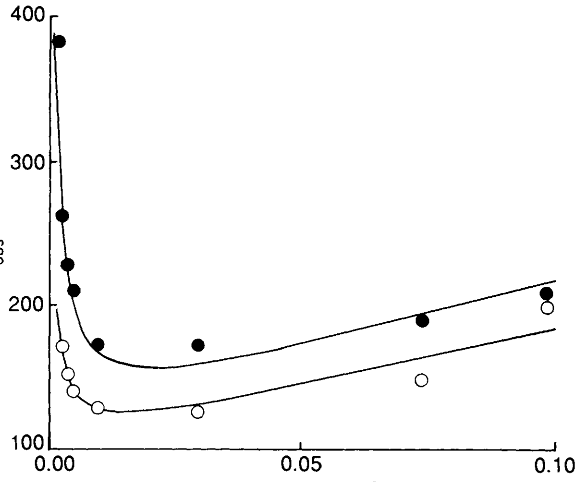


Fig. 1 Observed first-order rate coefficients (k_{obs}) for the approach to equilibrium in the ionisation of 2-isopropyl-4-(4-nitrophenylazo)-resorcinol monoanion in the presence of hydroxide ion in aqueous solution (○) and in 30% (v/v) Me_2SO–H_2O (●)

dried for at least 24 h under vacuum at room temperature before use.

Equilibrium Measurements.—Ionisation of the hydrogen-bonded proton from the monoanions of the 2-alkyl-4-(4-nitrophenylazo)resorcinols to give the dianions was studied spectrophotometrically. Values of the equilibrium constants for the reactions in eqn. (1) were obtained from measurements over a range of hydroxide-ion concentrations in Me_2SO–H_2O mixtures at 15 °C and ionic strength 0.1 mol dm^{-3}. Concentrations of the 2-alkyl-4-(4-nitrophenylazo)resorcinols were typically 2×10^{-5} mol dm^{-3}. The dianions (λ_{max} = *ca.* 600 nm) absorbed at longer wavelengths than the monoanions (λ_{max} = *ca.* 450 nm) and good isosbestic points were obtained in the presence of varying hydroxide-ion concentrations. The absorbance maxima shifted to longer wavelength in solvents richer in Me_2SO. Absorbance measurements were usually taken from the spectra at λ_{max} for the monoanion or dianion. The spectrum of the monoanion was obtained in the presence of low concentrations of hydroxide ion or in phenol/phenolate buffers and the dianion spectrum was obtained in the presence of high concentrations of hydroxide ion. The equilibrium constant (K) for the reaction in eqn. (1) was calculated using eqn. (2) in which A is the measured

$$K = (A_m - A)/(A - A_d)[OH^-] \qquad (2)$$

absorbance at a suitable wavelength for a solution containing a particular hydroxide-ion concentration and A_m and A_d are the absorbance values at the same wavelength for solutions in which **1**, **2** or **3** is present entirely as the monoanion and dianion, respectively. In some cases it was not possible to obtain an absorbance value corresponding to complete dissociation into the dianion and the value of the equilibrium constant was then obtained as the gradient of a plot of $(A_m - A)/[OH^-]$ against A, as in eqn. (3).

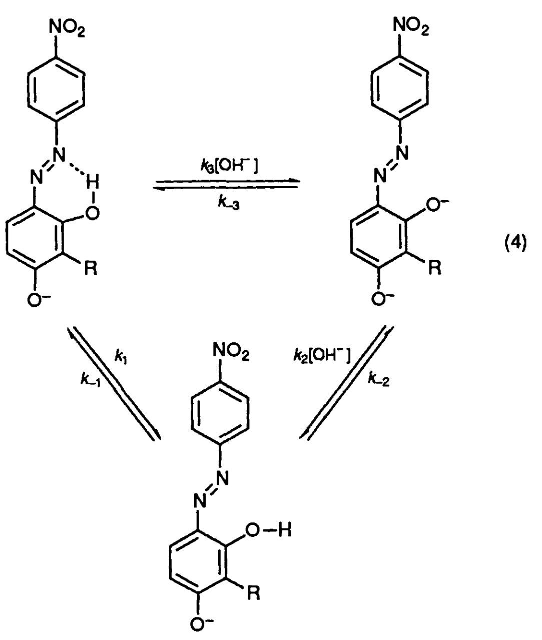
$$(A_m - A)/[OH^-] = KA - KA_d \qquad (3)$$

Kinetic Measurements.—The ionisations of **1**, **2** and **3** were followed spectrophotometrically at *ca.* 600 nm using the stopped-flow technique (Hi-Tech SF-51). Reactions were begun by mixing equal volumes of solutions of **1**, **2** or **3** with a solution containing hydroxide ions. Under these conditions the second dissociation of **1**, **2** or **3** is observed since the first dissociation occurs extremely rapidly. In some cases the reactions were initiated by mixing a solution of the monoanion of **1**, **2** or **3** with a solution of hydroxide ion and identical results were obtained. The signal generated at the measuring photomultiplier by the change in absorbance was passed *via* an analogue-to-digital converter (Daisi Electronics Inc. A1-13) to an Apple II microcomputer for analysis. The reactions were accurately first order and rate coefficients were reproducible to within ±2%.

Results and Discussion

The first and second dissociations of the 2-alkyl-4-(4-nitrophenylazo)resorcinols are well separated. The present data refer to the second dissociation and values for the equilibrium constant (K) between the hydrogen-bonded monoanions and hydroxide ion to give the dianions, eqn. (1), are given in Table 1. The results show that the acidity of the hydrogen-bonded proton decreases along the series R = Me > Et > Pr^i. The magnitude of the decrease is larger than expected for an inductive effect. It may be the result of a strengthening of the hydrogen bond in the monoanion due to steric compression or the result of steric inhibition of solvation of the dianion. The increase in K values as the solvent is made less aqueous is explained by the increased basicity of hydroxide ion.[5]

The dependence of the first-order rate coefficient (k_{obs}) for the approach to equilibrium on mixing aqueous solutions of 2-isopropyl-4-(4-nitrophenylazo)resorcinol and hydroxide ion is given in Fig. 1. The observed reaction corresponds to the equilibrium in eqn. (1). A similar dependence of k_{obs} on $[OH^-]$ is found in 30% (v/v) Me_2SO–H_2O and can be explained by the mechanism in eqn. (4) on the assumption that the non-hydrogen-bonded form of the monoanion is present as a low concentration intermediate and that the value of the rate of proton transfer from this species is greater than the rate at which it reverts to the closed form, $k_2[OH^-] > k_{-1}$. Under these conditions the dependence of k_{obs} on $[OH^-]$ is given by eqn. (5). The decrease in k_{obs} observed at low hydroxide-ion concentrations arises because the rate of the reverse reaction from the dianion through the open form to the monoanion is inversely dependent on hydroxide ion concentration. The best fit of eqn. (5) to the experimental results was obtained from a linear regression analysis of a plot of $k_{obs}/(1 + 1/K[OH^-])$ against $[OH^-]$, as in eqn. (6). The values of K from equilibrium measurements were used. The best fits were obtained with the values k_3 = 8000 dm^3 mol^{-1} s^{-1} and k_1 = 15 s^{-1} in aqueous



(4)

$$k_{obs} = (k_1 + k_3[OH^-])(1 + 1/K[OH^-]) \qquad (5)$$

$$k_{obs}/(1 + 1/K[OH^-]) = k_1 + k_3[OH^-] \qquad (6)$$

solution and $k_3 = 970\ dm^3\ mol^{-1}\ s^{-1}$ and $k_1 = 3.5\ s^{-1}$ in 30% (v/v) Me_2SO-H_2O. The lines in Fig. 1 are plots of eqn. (5) using these values.

In 90% (v/v) Me_2SO-H_2O the values of k_{obs} increase with hydroxide-ion concentration approaching a limiting value as shown in Fig. 2. This dependence is also explained by the mechanism in eqn. (4), but in this case it is assumed that reaction occurs entirely from the hydrogen-bonded monoanion to the dianion through the non-hydrogen-bonded species which is present in low concentration. In 90% Me_2SO-H_2O the value of the equilibrium constant for the deprotonation of the monoanion of **3** is large ($K > 2000$) and the equilibrium is almost entirely in favour of the dianion so that the reverse reaction makes a negligibly small contribution to the approach to equilibrium. Under these conditions the expression in eqn. (7)

$$k_{obs} = k_1[OH^-]/(k_{-1}/k_2 + [OH^-]) \qquad (7)$$

applies. The solid line in Fig. 2 through the experimental points for the reaction of **3** in 90% (v/v) Me_2SO-H_2O is a plot of eqn. (7) using the best-fit values of k_1 and k_{-1}/k_2 shown in Table 2. The best-fit values were obtained from a linear-regression analysis of a plot of $1/k_{obs}$ against $1/[OH^-]$ as in eqn. (8). The

$$1/k_{obs} = (k_{-1}/k_1k_2) \times 1/[OH^-] + 1/k_1 \qquad (8)$$

dependence of k_{obs} on $[OH^-]$ shown in Fig. 2 arises because at low hydroxide-ion concentrations proton transfer from the open intermediate is rate-limiting, $k_2[OH^-] < k_{-1}$, and at high hydroxide-ion concentrations opening of the hydrogen bond becomes rate-limiting, $k_2[OH^-] > k_{-1}$.

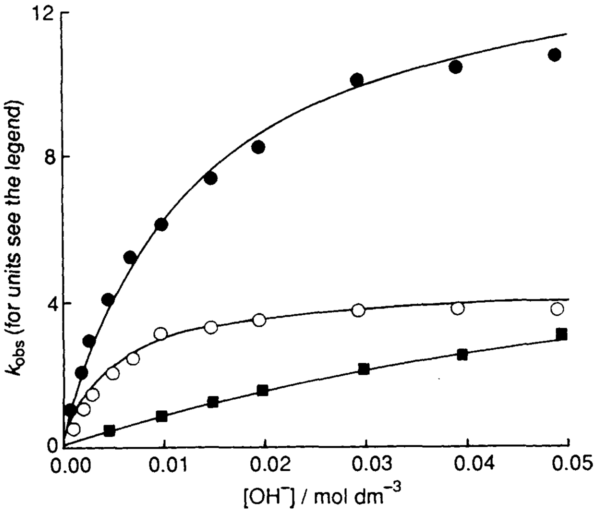


Fig. 2 Observed first-order rate coefficients (k_{obs}) for the approach to equilibrium in the ionisation of 2-isopropyl-4-(4-nitrophenylazo)-resorcinol (**3**) and 2-ethyl-4-(4-nitrophenylazo)resorcinol (**2**) monoanions in the presence of hydroxide ion in 80 and 90% (v/v) Me_2SO-H_2O. ●, 10 k_{obs}/s^{-1} for **3** in 90% Me_2SO-H_2O; ○, k_{obs}/s^{-1} for **2** in 90% Me_2SO-H_2O; ■, $k_{obs}/10\ s^{-1}$ for **2** in 80% Me_2SO-H_2O

Table 2 Fits of eqn. (7) to kinetic data in 80 and 90% (v/v) Me_2SO-H_2O

Solvent	Alkyl substituent	k_1/s^{-1}	$(k_{-1}/k_2)/10^{-3}\ mol\ dm^{-3}$
80% (v/v) Me_2SO-H_2O	R = Me	180	55
	R = Et	69	69
90% (v/v) Me_2SO-H_2O	R = Me	10	2.8
	R = Et	4.4	5.0
	R = Pr^i	1.4	13

For the ionisation of **3** in 60 and 80% (v/v) Me_2SO-H_2O a linear dependence of k_{obs} on $[OH^-]$ was observed, to within experimental error. This can be fitted by eqn. (5) with $k_3[OH^-] > k_1$ or by eqn. (7) with $k_{-1} > k_2[OH^-]$ or by a combination of both. A similar explanation will account for the linear dependence observed for the second ionisation of 2-methyl-4-(4-nitrophenylazo)resorcinol (**1**) and 2-ethyl-4-(4-nitrophenylazo)resorcinol (**2**) in aqueous solution and in solvent mixtures up to 60% (v/v) Me_2SO-H_2O. For **1** and **2** curvature in the plots of k_{obs} against $[OH^-]$ was observed in 80 and 90% (v/v) Me_2SO-H_2O as shown for **2** in Fig. 2. The solid lines in Fig. 2 through the experimental data are plots of eqn. (7). The values of k_1 and k_{-1}/k_2 that provide the best fit to the experimental results for **1**, **2** and **3** are given in Table 2.

The data in Table 2 permit conclusions to be drawn about the effect of a change in solvent from 80 to 90% (v/v) Me_2SO-H_2O and about the effect of a change in substituent on the intramolecular hydrogen bonds. In 80 and 90% (v/v) Me_2SO-H_2O reaction (1) occurs by opening of the hydrogen bond followed by proton transfer from the open intermediate. The proton-transfer step is thermodynamically favourable and usually such a reaction between a phenol and hydroxide ion would occur at a diffusion-limited rate. However, the site of proton removal in the open forms of **1**, **2** and **3** is hindered and the value of k_2 is likely to be lower than $1 \times 10^{10}\ dm^3\ mol^{-1}\ s^{-1}$.

The value of the rate coefficient for opening of the intramolecular hydrogen bond (k_1) is reduced along the series Me > Et > Pr^i in the ratio 1:0.44:0.14 in 90% (v/v) Me_2SO-H_2O. It is probable that the transition state for opening the hydrogen bond is increasingly hindered, relative to the closed form, by the larger alkyl substituents. This hindrance could lead to internal strain between the hydroxy group and the alkyl substituent or could inhibit solvation of the hydroxy group in the transition state. The increase in k_{-1}/k_2 with an increase in the size of the alkyl substituent could result from an increase in the value of k_{-1} or more likely from a decrease in the value of k_2 due to increased crowding at the site of proton removal in the open intermediate.

The values of k_1 and k_{-1}/k_2 for **1** and **2** are lower in 90% than in 80% (v/v) Me_2SO–H_2O. The effect on k_{-1}/k_2 could arise from changes in k_{-1} or k_2 or both. However, if the proton-transfer step is diffusion-controlled it is likely that the value of k_2 will not be greatly affected by the solvent. If it is assumed that the change in k_{-1}/k_2 arises entirely from a difference of k_{-1} in 80 and 90% (v/v) Me_2SO–H_2O, it follows from the similar difference in k_1 that the value of the equilibrium constant (k_1/k_{-1}) for opening the intramolecular hydrogen bond is largely unaffected by the change in solvent. The decrease in k_1 and k_{-1} with the solvent change means that the transition state for opening of the hydrogen bond is destabilised, relative to the hydrogen-bonded species, in going from 80 to 90% (v/v) Me_2SO–H_2O.

The change in kinetic behaviour from aqueous solution to 90% (v/v) Me_2SO–H_2O is due to a change in the relative values of the rate coefficients for the individual steps in eqn. (4). In the less aqueous solvent mixtures, reaction of the hydrogen-bonded species with hydroxide ion becomes less important than reaction through the open species. The rate coefficient (k_3) for the reaction of hydroxide ion with the hydrogen-bonded species **3** changes from a value of 8000 $dm^3\ mol^{-1}\ s^{-1}$ in aqueous solution to 970 $dm^3\ mol^{-1}\ s^{-1}$ in 30% (v/v) Me_2SO–H_2O. The value of k_1 deduced for the reaction of **3** from the hook-shaped dependence of k_{obs} against $[OH^-]$ in aqueous solution and in 30% (v/v) Me_2SO–H_2O (Fig. 1) has values of 15 s^{-1} and 3.5 s^{-1}, respectively and the result deduced from the rectilinear dependence in 90% (v/v) Me_2SO–H_2O (Fig. 2) is 1.4 s^{-1}. The relative values of k_{-1} and $k_2[OH^-]$ are also dependent on the solvent. In aqueous solution and 30% (v/v) Me_2SO–H_2O the inequality $k_2[OH^-] > k_{-1}$ is satisfied at all accessible hydroxide-ion concentrations for the reaction of **3** but in 80 and 90% (v/v) Me_2SO–H_2O, $k_2[OH^-] > k_{-1}$ applies at low hydroxide-ion concentrations and $k_2[OH^-] > k_{-1}$ is found at high hydroxide-ion concentrations.

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