Substituent Effects Leading to Ultra-slow Proton Removal from an Intramolecular Hydrogen Bond

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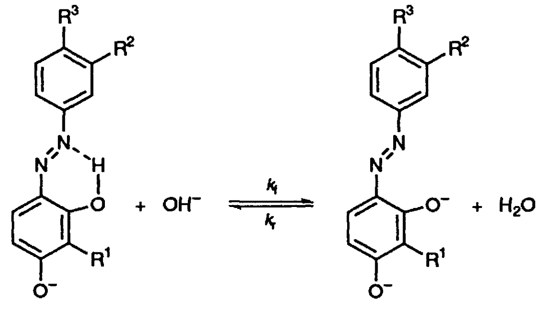
Electron-withdrawing substituents (R^2 and R^3) result in a remarkable reduction in the rate coefficient for removal of the hydrogen-bonded proton from 2-alkyl-4-(R^2,R^3-phenylazo)resorcinol monoanions by hydroxide ion such that the reaction can be followed by conventional spectrophotometry with $t_{1/2}$ in the range of minutes.

In previous work the rates of deprotonation of the intramolecularly hydrogen-bonded monoanions of substituted phenylazoresorcinols (Scheme 1) were studied by stopped-flow and temperature-jump methods and it was shown that reaction occurs through an open non-hydrogen-bonded form of the monoanion.[1] In the present work we have investigated the effects of changes in the substituents R^1, R^2 and R^3 on the rate coefficient (k_f) and equilibrium constant for deprotonation. Information about the rate coefficients and equilibrium constant for the interconversion between the intramolecularly hydrogen-bonded form and the open non-hydrogen-bonded form of the monoanion is obtained.



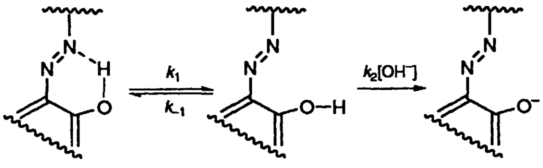
Scheme 1

Spectrophotometric measurements (300 to 700 nm) of the equilibrium in Scheme 1 were made for anions **1–10** (see Table 1) in 90% (v/v) $Me_2SO–H_2O$ at 15 °C and ionic strength 0.1 mol dm^{-3} over a range of hydroxide ion concentrations. Values of the equilibrium constant (K) for the reaction, $K =$ [dianion]/[monoanion][OH^-] are given in Table 1. The values of K increase with increasing electron-withdrawing ability of the substituent R^3 as expected for increasing stabilization of the dianion. The best correlation[2] between log K and σ is obtained by omitting the point for **5** and the relationship log $K = \sigma\rho + 2.29$ is then obtained with $\rho = 0.55$ and regression coefficient 0.97.

Kinetic results for the deprotonation of anions **1–10** (see Table 1) have been obtained in 90% (v/v) $Me_2SO–H_2O$. Kinetic measurements were previously made[1] for 2-ethyl- and 2-isopropyl-4-(4-nitrophenylazo)resorcinol (**7** and **8**, respectively) and similar procedures have been used for **1–6**. Measurements were made by use of the stopped-flow technique by observing the increase in absorbance at *ca.* 525 nm on mixing a solution of the phenylazoresorcinol (*ca.* 1×10^{-4} mol dm^{-3}) with a solution of tetramethylammonium hydroxide containing sufficient tetramethylammonium chloride to give an ionic strength of 0.1 mol dm^{-3} for the mixed solution. The solvent used was 90% (v/v) $Me_2SO–H_2O$ except in the case of **1** and **2** for which 95% (v/v) $Me_2SO–H_2O$ was a more suitable solvent because the reaction could be studied over a wider range of hydroxide ion concentrations owing to the higher value of K in this solvent. Rate coefficients for **1** and **2** in 90% (v/v) $Me_2SO–H_2O$ were estimated from data for **4** in both solvents by assuming the same solvent effect [*ca.* 1.4-fold lower value of the second-order rate coefficient in 90% (v/v) $Me_2SO–H_2O$]. Kinetic measurements of the reaction of **9** at low hydroxide ion concentrations were made by conventional spectrophotometry and at high concentrations by the stopped-flow technique. Deprotonation of **10** at all hydroxide ion concentrations was followed using a conventional spectrophotometer. For example on introduction of **10** (*ca.* 3×10^{-5} mol dm^{-3}) into a solution of hydroxide ion (0.001 mol dm^{-3}) in 90% (v/v) $Me_2SO–H_2O$ spectral scans over 400–700 nm gave excellent isosbestic points at 455, 515 and 534 nm as the hydrogen-bonded monoanion was converted into the deprotonated species in an exceptionally slow reaction with $t_{1/2} = 5.6$ min.

In all cases a first-order decrease in the concentration of the phenylazoresorcinol monoanion or increase in the concentration of the dianion was observed. For compounds **1–6**, the first-order rate coefficient (k_{obs}) varied linearly with hydroxide ion concentration, according to eqn. (1). The values of k_f and k_r are given in Table 1 and the ratios k_f/k_r were found to be consistent within experimental error with the separately measured value of the equilibrium constant (K) for the reaction. For **7–10**, a rectilinear dependence of k_{obs} *vs.* [OH^-] was observed with k_{obs} reaching a limiting value at high [OH^-] and with k_{obs} *ca.* 0 at low hydroxide ion concentrations. For **7–10** deprotonation occurs to completion at all hydroxide ion concentrations studied. The rectilinear dependence of k_{obs} *vs.* [OH^-] has previously been found for **7** and **8** and has been explained by the mechanism in Scheme 2 which leads to the rate expression in eqn. (2) on the assumption that the open form is present as a low concentration intermediate.

$$k_{obs} = k_f[OH^-] + k_r \qquad (1)$$



Scheme 2

$$k_{obs} = k_1k_2[OH^-]/(k_{-1} + k_2[OH^-]) = k_f[OH^-];\ \text{if}\ k_{-1} \gg k_{-2}[OH^-] \qquad (2)$$

At low hydroxide ion concentrations where the inequality $k_2[OH^-] \ll k_{-1}$ applies, eqn. (2) is reduced to $k_{obs} = (k_1k_2/k_{-1})[OH^-]$ and under these conditions

Table 1 Equilibrium constants and rate coefficients for deprotonation of phenylazoresorcinol monoanions[a]

Phenylazoresorcinol monoanion				σ[b]	K/dm^3 mol^{-1}	k_f/dm^3 mol^{-1} s^{-1}	k_r/s^{-1}	k_1/s^{-1}	k_{-1}/k_2 (mol dm^{-3})
1	R^1 = Et	R^2 = H	R^3 = NMe$_2$	−0.63	81 ± 13	2.2 ± 1 × 10^5 (est.)[c]	uncertain[d]	—	—
2			R^3 = OMe	−0.28	153 ± 14	1.4 ± 0.5 × 10^5 (est.)[c]	uncertain[d]	—	—
3			R^3 = Me	−0.14	173 ± 21	7.1 ± 0.9 × 10^4	476 ± 150	—	—
4			R^3 = H	0	191 ± 30	5.7 ± 0.5 × 10^4	253 ± 100	—	—
5			R^3 = Cl	+0.24	623 ± 80	4.0 ± 0.4 × 10^4	59 ± 30	—	—
6			R^3 = SO$_3^-$	+0.37	300 ± 52	2.5 ± 0.3 × 10^4	91 ± 50	—	—
7			R^3 = NO$_2$[e]	+1.25	>2000[f]	8.0 ± 1 × 10^2[g]	*ca.* 0	4.4 ± 0.7	0.5 ± 0.2 × 10^{-2}
8	R^1 = Pr^i	R^2 = H	R^3 = NO$_2$[e]		>2000[f]	1.1 ± 0.2 × 10^2[g]	*ca.* 0	1.4 ± 0.3	1.3 ± 0.3 × 10^{-2}
9	R^1 = Et	R^2 = CN	R^3 = NO$_2$[h]	+1.87	>2000[f]	1.8 ± 0.4 × 10[g]	*ca.* 0	0.11 ± 0.03	0.6 ± 0.2 × 10^{-2}
10	R^1 = Pr^i	R^2 = CN	R^3 = NO$_2$		>2000[f]	2.2 ± 0.5[g]	*ca.* 0	0.025 ± 0.005	1.1 ± 0.2 × 10^{-2}

[a] At 15.0 °C in 90% (v/v) Me$_2$SO–H$_2$O with ionic strength 0.1 mol dm^{-3}. [b] σ values taken from ref. 2. [c] See text. [d] The values of k_{obs} were measured over a limited range of hydroxide ion concentrations and the extrapolations to [OH$^-$] = 0 to give values of k_r were extremely uncertain. [e] Data for **7** and **8** taken from ref. 1. [f] Fully dissociated in the presence of 0.001 mol dm^{-3} hydroxide ion. [g] The value of k_f was calculated from data at low [OH$^-$] where the the reaction is first order in OH$^-$. [h] The sigma value for **9** was taken as the sum of σ_p for NO$_2$ and σ_m for CN.

it follows that $k_f = k_1k_2/k_{-1}$ and deprotonation of the open form is rate-limiting. At high hydroxide ion concentrations eqn. (2) is reduced to $k_{obs} = k_1$. Under these conditions opening of the intramolecular hydrogen bond is rate-limiting and the reaction is of zero order with respect to hydroxide ion. For compounds **1**–**6** it is assumed that the reaction occurs by the same mechanism but that the inequality $k_2[OH^-] \ll k_{-1}$ applies at all hydroxide ion concentrations. Hence for **1**–**6** the measured values of the rate coefficients in terms of the mechanism in Scheme 2 are given by $k_f = k_1k_2/k_{-1}$ and $k_r = k_{-2}$ where k_{-2} is the rate coefficient for protonation of the deprotonated species by water to give the open intermediate. The values of the rate coefficients k_f and k_r for phenylazoresorcinols **1**–**10** are shown in Table 1. Values of k_1 and k_{-1}/k_2 for **7**–**10** obtained by fitting eqn. (2) to the experimental results for these compounds are also given.

The values of k_f decrease with increasing electron-withdrawing ability of R^3 and with the introduction of R^2 = CN in place of R^2 = H. The data for compounds with R^1 = Et(**1**–**7**, **9**) are roughly fitted by the relationship $\log k_f = \sigma\rho + 4.70$ with $\rho = -1.71$ and regression coefficient 0.95. A slightly improved fit is obtained by omitting the data for **7** and **9** and the results are then correlated by the expression $\log k_f = \sigma\rho + 4.78$ with a very different value of $\rho = -0.94$ and a regression coefficient of 0.97.

The forward rate coefficient for the reaction in Scheme 1 for compounds **1**–**6** under all conditions and for **7**–**10** at low hydroxide ion concentrations is given by $k_f = k_1k_2/k_{-1}$. It is likely that deprotonation of the open intermediate will be diffusion-controlled and the rate coefficient (k_2) will have the same value for all the phenylazoresorcinols. Hence the observed variation of k_f with substituent results from a change in strength of the hydrogen bond as measured by the value of the equilibrium constant ($K_1 = k_1/k_{-1}$) between open and closed forms. The value of K_1 decreases and the strength of the intramolecular hydrogen bond increases with increasing electron-withdrawing ability of R^3. By assuming a value of $k_2 = 1 \times 10^{10}$ dm^3 mol^{-1} s^{-1} for the proton transfer step values of K_1 were calculated for **1**–**10**; the values show a gradual decrease along the series **1**–**10** from *ca.* 2 × 10^{-5} for **1** to *ca.* 2 × 10^{-10} for **10** with a very approximate value of ρ *ca.* −1 based on the data for **1**–**7** and **9**.

Since for **1**–**6** a linear dependence of k_{obs} *vs.* [OH$^-$] is observed, it is concluded that $k_{-1} \gg k_2[OH^-]$. For **7**–**10** at high hydroxide ion concentrations the reaction is of zero order in hydroxide ion and the condition $k_{-1} \ll k_2[OH^-]$ applies under these conditions. It probably follows that the value of k_{-1} is lower for **7**–**10** than for compounds **1**–**6**, although the differences may not be large because the more rapid rates observed for **1**–**6** meant that the reactions could only be studied at lower hydroxide ion concentrations. The change in rate-limiting step with hydroxide ion concentration observed for compounds **7**–**10** permits values to be obtained for k_1 and k_{-1}/k_2. Assuming a value of k_2 *ca.* 1 × 10^{10} dm^3 mol^{-1} s^{-1}, values of k_{-1} *ca.* 1 × 10^8 s^{-1} are calculated for the rate coefficient for closing of the intramolecular hydrogen bond. For these compounds with strongly electron-withdrawing constituents the hydrogen bonds are strong and the values of k_1 and K_1 are low showing that the kinetic and thermodynamic barriers for opening of the hydrogen bond are large. The CN substituent reduces the values of k_1 and K_1 but the value of k_{-1} is largely unaffected. An isopropyl group adjacent to the site of the hydrogen bond also reduces the rate coefficient (k_1) and the equilibrium constant (K_1) for opening of the hydrogen bond compared with an ethyl substituent. This effect probably arises from steric compression of the hydrogen bond.

The most remarkable feature of the present results is the rate at which deprotonation occurs from the hydrogen-bonded monoanions **9** and **10**. For **10** at hydroxide ion concentrations of 0.001 and 0.06 mol dm^{-3} the reaction occurs with $t_{1/2}$ 5.6 and 0.56 min, respectively. Very slow removal of protons attached to electronegative centres has been observed previously, *e.g.* in the reactions of bicyclic diamines[3] and proton sponges.[4] In these latter two cases, attack at the acidic proton is severely sterically hindered and this is thought to be a major factor in reducing the rate of reaction. For **9** and **10** at low hydroxide ion concentrations the reaction is slow because a low concentration intermediate is involved (the open non-hydrogen-bonded species) and at high hydroxide ion concentrations the reduced rate arises because thermodynamically unfavourable opening of the hydrogen bond becomes rate-limiting and this is a surprisingly slow process. The kinetic results and the increase in strength of the intramolecular hydrogen bond with electron-withdrawing substituents could arise because an ionic tautomer of the closed species, such as $-N^- \cdots H-O^+=$, is stabilized by electron-withdrawing groups.

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Paper 4/06403H
Received 19*th October* 1994
Accepted 1*st November* 1994