Intramolecular base catalysed hydrolysis of *ortho*-hydroxyaryl esters: the anomalous position of methyl 3,5-dinitrosalicylate on the Linear Free Energy Relationship plot

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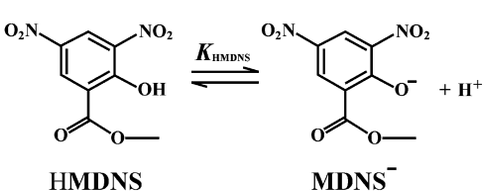
The pK_a of the *ortho*-hydroxy group in methyl 3,5-dinitrosalicylate, H**MDNS**, is 2.45. Rate constants for the reaction of its conjugate base, **MDNS**$^-$ with hydroxide anion and water are 5.3×10^{-2} mol dm^{-3} s^{-1} and 6.6×10^{-6} s^{-1}, respectively at 25 °C. The rate constant for the uncatalysed reaction of H**MDNS** and water is 6.5×10^{-6} s^{-1} and so there is no evidence for intramolecular general base catalysis of the water reaction with **MDNS**$^-$ by the weakly basic *ortho*-O$^-$. By means of Brønsted plots the water reaction of **MDNS**$^-$ is compared with that of a group of other salicylate esters ($\beta = 0$) and also a structurally different group of esters ($\beta = 0.4$), both of which undergo intramolecular base catalysed hydrolysis. Although the title ester structurally belongs to the first set of compounds, its anomalous position on the plot clearly corresponds to the trend of the second set. This is explained in terms of differences in resonance stabilisation and hydrogen bonding in the transition state.

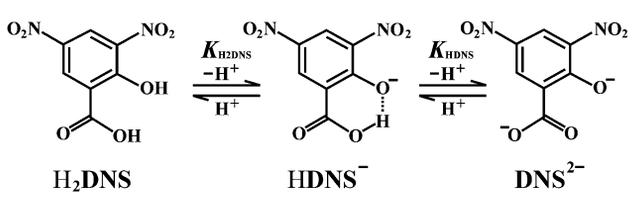
Introduction

It is generally accepted that the pH-independent hydrolysis of salicylate esters, **SE**$^-$, and catechol monobenzoate, **CMB**$^-$, involves the attack of a water molecule on the ester anion catalysed by the neighbouring O$^-$.[1–3] Bruice has shown that the rate constants calculated for the intramolecular base catalysed hydrolysis of a range of phenyl 4- and 6-substituted salicylate esters are independent of the pK_a of the *ortho*-hydroxy group and, moreover, are very similar to the rate constants for similar methyl salicylate esters.[4] Thus these rate constants are independent of the basicity of the catalytic group and of the nature of the leaving group. The similarity of rate constants extends to that of the attack of a water molecule on the triarylmethane dye, Green S, **D**$^{2-}$, which also has an O$^-$ *ortho* to the carbon under attack.[5] In contrast, literature results show that the rate constants for the intramolecular base catalysed attack of water on catechol esters, **CE**$^-$, and other esters, **EI**$^-$ and **AHN**$^-$, are dependent upon the basicity of the catalytic group.[2,6–9] This prompted the present study of the neighbouring group effect of the *ortho*-hydroxy substituent on the hydrolysis reactions of methyl 3,5-dinitrosalicylate, **MDNS**$^-$, and its conjugate acid, H**MDNS**, shown in Scheme 1. The acid dissociation



Scheme 1

constant of H**MDNS**, K_{HMDNS}, is the highest of any salicylic acid ester whose hydrolysis has been studied and **MDNS**$^-$ therefore has the least basic catalytic group. Moreover, in the hydrolysis product, dinitrosalicylate monoanion, H**DNS**$^-$, a very recent ^{1}H NMR study[10] suggests that the proton is biased toward the carboxylate residue, as shown in Scheme 2, whereas in less acidic salicylic acids, as expected, the proton is part of the phenolic group.



Scheme 2

Experimental

Methyl 3,5-dinitrosalicylate (MDNS) 99+% was purchased from Aldrich and used as received. Measurements were carried out at 25 ± 0.2 °C in aqueous solutions, generally ionic strength 0.1 mol dm^{-3}, using acetate, phosphate or carbonate buffers or potassium chloride–hydrochloric acid or sodium hydroxide, as described previously.[5] The two hydrochloric acid solutions of lowest pH, however, were above ionic strength 0.1 mol dm^{-3}. Solutions of MDNS in distilled water were prepared shortly before use to avoid a substantial loss of reagent due to hydrolysis. Measurements of pH and pH titrations were carried out on a 702 SM Titrino calibrated with Hydrion™ buffers. UV/vis spectra were obtained using a Pharmacia Biotech Ultraspec 2000 spectrophotometer with a thermostatic cell-holder. The hydrolysis was followed at the wavelength of maximum MDNS absorbance, A, 365 nm using a concentration of 6×10^{-5} mol dm^{-3} in most cases. First order rate constants, k_{obs}, were calculated from the slopes of plots of $\ln(A_\infty - A)$ or $\ln(A - A_\infty)$ against time using linear regression.

Results

Fig. 1 shows the spectra of MDNS at various pH values; differences in the UV region below 250 nm are due to the different buffer systems used. The drop in absorbance of the band at

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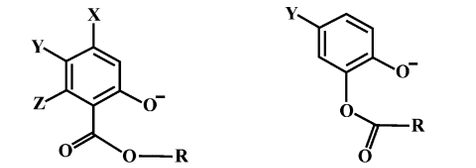
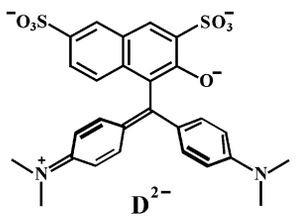
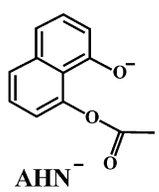


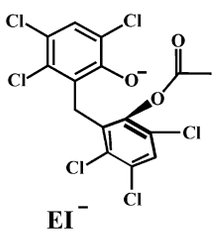
Salicylate esters, $\mathbf{SE}^-$ Catechol esters, $\mathbf{CE}^-$



$\mathbf{D}^{2-}$



$\mathbf{AHN}^-$



$\mathbf{EI}^-$

365 nm and the increase at lower wavelengths with an isosbestic point at 320 nm correspond to the formation of the colourless H**MDNS** species from the bright yellow $\mathbf{MDNS}^-$ as shown in Scheme 1. Fig. 2 shows the pH dependence of the absorbance of

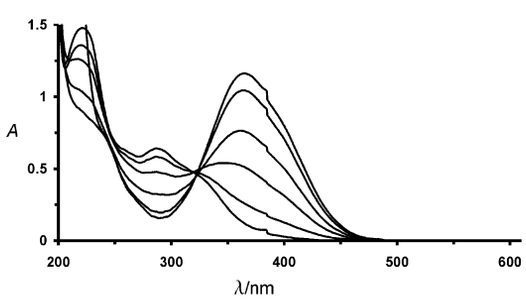


Fig. 1 Absorption spectra of 9.0×10^{-5} mol dm^{-3} MDNS at 25 °C at the following pH values, in order of decreasing absorbance of the band at 365 nm: 10.04, 3.87, 2.76, 2.31, 1.52, 0.81.

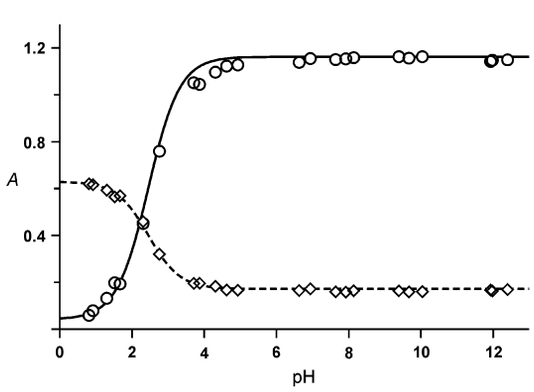


Fig. 2 Dependence upon pH of the absorbance of MDNS, conditions as for Fig. 1; circles, 365 nm; diamonds, 292 nm.

MDNS at two different wavelengths. These data were fitted using non-linear regression, as described previously,[5] to yield a value of the pK_a of the ester, p$K_{\mathbf{HMDNS}}$ 2.45 ± 0.03.

Changes in absorbance during the hydrolysis of MDNS were typically only 8% of the initial value and were negative below the pK_a of the ester and positive above it. Observed first order

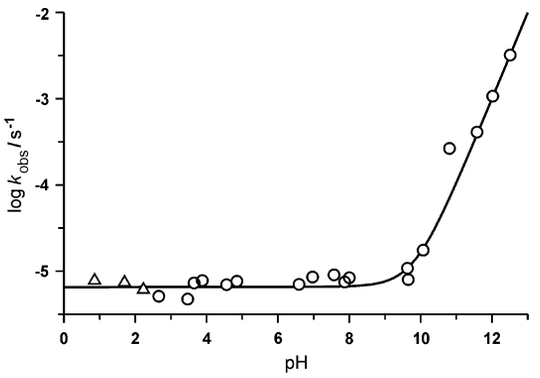


Fig. 3 Dependence upon pH of decimal logarithm of the observed first order rate constant for the hydrolysis of 6.0×10^{-5} mol dm^{-3} MDNS at 25 °C. The circles correspond to pH values where the first derivative dA/dt at λ = 365 nm was negative, the triangles to pH values where dA/dt was positive. The curve represents the best fit of eqn. (5) to the data.

rate constants are shown in Fig. 3 as a function of pH. Comparable rate constants were observed at 8×10^{-6} and 2.5×10^{-4} mol dm^{-3} MDNS (results not shown) and at 1.4×10^{-2} mol dm^{-3} using a pH-stat method at pH 11.5 recording the volume of 0.1 mol dm^{-3} NaOH consumed. The product of MDNS hydrolysis at pH 11.5 was shown by pH titration with 0.1 mol dm^{-3} HCl to be a dibasic acid with the higher pK_a, 6.8 at ionic strength 0.1 mol dm^3, and the lower pK_a below the limit measurable by this technique. This is consistent with the product being dinitrosalicylate whose pK_a values (p$K_{\mathbf{H2DNS}}$ and p$K_{\mathbf{HDNS}}$ respectively, Scheme 2) at minimal ionic strength using a spectrophotometric method are 7.36 and 0.13.[10]

The results shown in Fig. 3 are consistent with the reaction scheme shown in eqns. (1) to (4). Following a data treatment

$$\mathbf{MDNS}^- + HO^- \xrightarrow{k_{HO}^{MDNS}} \text{Products} \quad (1)$$

$$\mathbf{HMDNS} + HO^- \xrightarrow{k_{HO}^{HMDNS}} \text{Products} \quad (2)$$

$$\mathbf{MDNS}^- + H_2O \xrightarrow{k_{H_2O}^{MDNS}} \text{Products} \quad (3)$$

$$\mathbf{HMDNS} + H_2O \xrightarrow{k_{H_2O}^{HMDNS}} \text{Products} \quad (4)$$

described previously,[5] taking the overall rate equation corresponding to this reaction scheme, the equation for $K_{\mathbf{HMDNS}}$, corresponding to the acid dissociation shown in Scheme 1, the mass balance equation for MDNS, and the ionic product of water, K_W, leads to eqn. (5) for the observed rate constant for the hydrolysis of MDNS, where k_{0obs}, k_{1obs} and k_{2obs} are defined in eqns. (6) to (8). The value of $K_{\mathbf{HMDNS}}$ is substituted into eqn. (5) and the best fit values of the kinetic parameters and their standard deviations shown in Table 1 are obtained using non-linear least squares with proportional weighting to fit k_{obs}. Calculated values of the individual rate constants, taking K_w, 1.88×10^{-14} mol^2 dm^{-6}, are also shown in Table 1.

$$k_{obs} = \frac{k_{0obs} + k_{1obs}[H^+] + k_{2obs}[H^+]^2}{K_{HMDNS}[H^+] + [H^+]^2} \quad (5)$$

$$k_{0obs} = k_{HO}^{MDNS} K_{HMDNS} K_w \quad (6)$$

$$k_{1obs} = k_{HO}^{HMDNS} K_w + k_{H_2O}^{MDNS} K_{HMDNS} \quad (7)$$

$$k_{2obs} = k_{H_2O}^{HMDNS} \quad (8)$$

Table 1 Observed rate constants for the hydrolysis of MDNS for pathways involving *n* protons and the corresponding rate constants calculated according to eqns. (6) to (8)

n	$k_{n\ obs}$/(dm^3 mol^{-1})$^{n+1}$ s^{-1}	k^{MDNS}_{HO}/dm^3 mol^{-1} s^{-1}	$k^{MDNS}_{H_2O}$/s^{-1}	$k^{HMDNS}_{H_2O}$/s^{-1}
0	$(3.5 \pm 0.5) \times 10^{-18}$	5.3×10^{-2}		
1	$(2.3 \pm 0.2) \times 10^{-8}$		6.6×10^{-6} [a]	
2	$(6.5 \pm 1.2) \times 10^{-6}$			6.5×10^{-6}

[a] Alternatively, k^{HMDNS}_{HO}, 1.2×10^6 dm^3 mol^{-1} s^{-1}.

Table 2 Substrate structures and their pK_a values

Ref.	Substrate		X	Y	Z	R	pK_a
1	*p*-Nitrophenyl 5-nitrosalicylate		H	NO_2	H	*p*-$NO_2C_6H_4$	6.02
5	Green S (Lissamine Green B)	**D**$^{2-}$					7.66
4	Phenyl 6-methoxysalicylate		H	H	OCH_3	C_6H_5	8.46
4	Phenyl 6-methylsalicylate		H	H	CH_3	C_6H_5	8.63
11	Phenyl salicylate		H	H	H	C_6H_5	8.80
4	Phenyl 4-methoxysalicylate		OCH_3	H	H	C_6H_5	9.1
12	Methyl salicylate		H	H	H	CH_3	9.26
4	Phenyl 4-methylsalicylate		CH_3	H	H	C_6H_5	9.44
13	Ethyl salicylate		H	H	H	C_2H_5	10.1
4	Phenyl β-resorcylate		O^-	H	H	C_6H_5	10.76
6	Ethyl 2-hydroxy-5-nitrophenyl carbonate			NO_2		OC_2H_5	5.48
8	Hexachlorophene monoacetate	**EI**$^-$					7.9
2	Catechol monobenzoate	**CMB**$^-$		H		C_6H_5	8.7
14	Catechol monocinnamate			H		$CH{=}CHC_6H_5$	8.9
7	Catechol monoacetate			H		CH_3	9.01
9	1-Acetoxy-8-hydroxynaphthalene	**AHN**$^-$					9.69

Discussion

Table 1 shows the rate constants for the uncatalysed reaction of hydroxide and **MDNS**$^-$; for the reaction involving one additional proton, which, in line with the accepted mechanism,[1–3] is assumed to be the reaction of **MDNS**$^-$ and water; and for the uncatalysed reaction of H**MDNS** and water. It is clear that there is no intramolecular base catalysis in the case of the **MDNS**$^-$ water reaction because the rate constant is the same as that for the H**MDNS** water reaction. Clearly, the *ortho*-O^- is simply too weakly basic (pK_{HMDNS}, 2.45) to have any catalytic activity. Fig. 4 shows Brønsted plots for the water

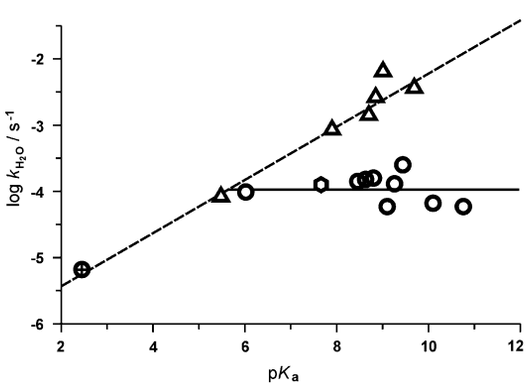
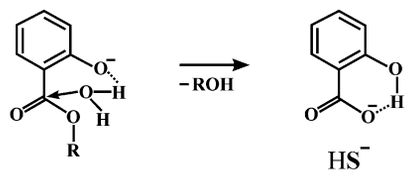


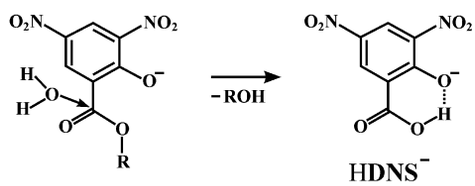
Fig. 4 Brønsted plots of the dependence of the rate constant for water reaction on pK_a neighbouring hydroxy group: circles, salicylate esters (**SE**$^-$); triangles, other esters; hexagon, Green S; crossed point, MDNS.

reaction of **MDNS**$^-$ and the range of *ortho*-hydroxyaryl esters shown in Table 2, together with Green S. The values of the individual rate constants are deduced from the data given in the literature for kinetics carried out in the range 25 to 35 °C and in aqueous-based solutions.[1,4,6–9,11–13] Rate constants for the hydrolysis of the 4-nitrophenyl esters of benzoate and *ortho*-methoxybenzoate are considerably less than that of 4-nitrophenyl salicylate,[1] which, notwithstanding the electron donating character of the O^- substituent, indicates the catalytic nature of the latter. Moreover, all of the cited literature data show that the rate constant corresponding to the water reaction involving the *ortho*-O^- species is considerably greater than the upper limit of that involving the unionised reactant, indicating significant intramolecular base catalysis. Table 2 also gives the literature values of pK_a for the *ortho*-OH groups, which range between 5 and 11, and we have extended this range down to about 2 with MNDS. The lack of effect of pK_a on the intramolecular base catalysed reaction of the salicylate esters and the similarity of the corresponding rate constant for Green S, which also has an O^- *ortho* to the electrophilic carbon under attack, is interesting. (The Brønsted slope is close to zero, ignoring **MDNS**$^-$.) This is particularly so, since the catechol esters, **CE**$^-$, that undergo intramolecular base hydrolysis in a similar way to the salicylates, show the expected increase of rate constant for the base catalysed reaction with increasing basicity of the adjacent O^- group,[2,6,7,14] where the Brønsted slope is *ca.* 0.4. (**EI**$^-$ and **AHN**$^-$ also appear to belong in this group, despite their somewhat disparate structures.[8,9]) The catechol esters and **EI**$^-$ and **AHN**$^-$ are not conjugated between the carbonyl site of attack of water and the adjacent O^-, unlike the salicylates and Green S. Hence, for salicylates there appears to be a high degree of correlation between opposing factors that increase the basicity of the catalytic O^- whilst decreasing the electrophilicity of the carbonyl site of attack. The importance of resonance effects in intramolecular general acid base catalysis has been discussed in general terms by Kirby.[15] The opposing factors in the case of salicylates, however, are not exactly balanced over the widest range of conditions as evidenced by the lower rate constant with **MDNS**$^-$, which actually falls into the group of non-conjugated esters in Fig. 4. There must therefore be an additional factor in the catalysis that does not come into effect in the case of **MDNS**$^-$. This factor is related to hydrogen-bonding. Kirby has given many examples where intramolecular hydrogen-bonding stabilisation of the product, manifest as an unusually low pK_a of the group in question, is reflected in the stabilisation of the transition state for intramolecular acid base catalysis.[15] The present work with **MDNS**$^-$ is the exception that proves that this is also the rule for the other

salicylate esters, $\mathbf{SE}^-$, where hydrogen bonding of the *ortho*-O^- and the attacking water in the transition state is followed by the formation of a salicylic acid $\mathbf{HS}^-$ with a protonated phenol group, Scheme 3. In $\mathbf{HDNS}^-$ very recent NMR work shows that the proton is biased to the carboxylate residue,[10] and this is reflected in the fact that the *ortho*-O^- confers no energetic advantage in terms of hydrogen bonding in the transition state, Scheme 4.



Scheme 3



Scheme 4

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