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Alkoxide-catalysed hydrolyses of a chlorotriazine in alcohol–water mixtures. A new indirect probe for hydroxide-catalysed hydrolysis

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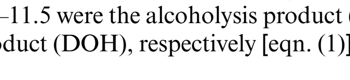
Pseudo-first order rate constants (k_{obs}) and product ratios are reported for competing hydrolyses and alcoholyses of the reactive dichlorotriazine dye (**2**) in water containing small amounts (usually <0.05 M) of added alcohols (methanol, propan-1-ol, and four polyols: α- or β-methylglucopyranoside, mannitol or sorbitol) at pH 11.2. Additional data are reported in the presence of ethane-1,2-diol, prop-2-yn-1-ol and 2,2,2-trifluoroethanol. Dissection of k_{obs} for solvolysis of the dye (DX) into the separate contributions from hydrolysis (k_{DOH}) and alcoholysis (k_{DOR}) shows that k_{DOH} increases in polyol–water mixtures for **2**, but not for the monofluorotriazine (**1**), and k_{DOH} also increases for **2** in aqueous trifluoroethanol. The results are consistent with alkoxide-catalysed hydrolysis for **2**, but with an uncatalysed or weakly-catalysed hydrolysis for **1**, and provide indirect support for the possibility of a third order process in which hydroxide could act as a base catalyst. Additional kinetic data for **2** in methanol–water mixtures, containing both sodium carbonate and tetraalkylammonium salts, show rate enhancements particularly when the amount of sodium carbonate is low.

Third order reactions involving nucleophilic attack by water may be assisted by general base catalysis by an additional neutral water molecule as shown by studies of kinetic isotope effects: *e.g.* third order hydrolyses at pH < 7 of esters,[1,2] anhydrides,[3] amides,[4] and acid chlorides.[5] Similar reactions in alcohols and in alcohol–water mixtures are also well established, especially for solvolyses of acid chlorides;[5,6] *e.g.* for solvolyses of *p*-nitrobenzoyl chloride in ethanol- and methanol–water mixtures, the rates and products can be explained by four competing third order reactions, without postulating an additional medium effect of the added alcohol.[6]

Corresponding third order reactions involving hydroxide or alkoxide as general bases towards nucleophilic attack by water are much less well established. Kinetic isotope effects do not provide clear supporting evidence,[7] and Brønsted plots are subject to various interpretations (see below). In basic aqueous media, catalysis by increasing concentrations of hydroxide ions is expected to dominate catalysis by typical general bases, so catalysis by alkoxide may not be observable.[8] Also, catalysis by hydroxide has to be distinguished from direct nucleophilic attack by hydroxide.

We now report an alternative method to approach the problem of establishing alkoxide-catalysed hydrolyses. If an alcohol is present in an aqueous solution of high pH (*e.g.* >9), substantial alcoholysis occurs, and much of the earlier work was concerned with alkoxide–hydroxide equilibria and with the solvent effects of the added alcohols on reaction rates.[9] By simultaneous determination of both rates and products, the effects of added alcohols on the rates of hydrolysis can be calculated separately from alcoholysis rates.

We showed previously that the presence of small amounts (0.13 M, <*ca.* 1% w/w) of various alcohols did not affect the rate of hydrolysis of the monofluorotriazine dye (**1**);[10a] *i.e.* the small amount of added alcohol exerted a negligible medium effect on rates. However, in preliminary studies, we obtained evidence that the dichlorotriazine (**2**) may be susceptible to alkoxide-catalysed hydrolysis,[10b] and others have shown that hydrolysis of the chlorotriazine (**3**) is susceptible to general base catalysis by phosphate buffer.[11] By comparing the reactions of **1** and **2** under very similar experimental conditions, we obtain evidence for alkoxide-catalysed hydrolyses, and indirect support for hydroxide-catalysed hydrolysis, a third order process which is difficult to verify by direct experimental methods.



Scheme 1 Catalysed hydrolysis by two base catalysts of a substrate R′X.

Results

The products of the reactions of each dye (DX) in alcohol–water at pH 9–11.5 were the alcoholysis product (DOR) and the hydrolysis product (DOH), respectively [eqn. (1)]. The reactions

$$DX + RO^-/HO^- \longrightarrow DOR/DOH + X^- \qquad (1)$$

were monitored after suitable time intervals by analysing quenched aliquots of reaction mixtures by reversed-phase ion-pair high performance liquid chromatography (HPLC). Pseudo-first order rate constants (k_{obs}) were calculated from the rate of decay of DX, and product ratios (P) were obtained from the slopes of the linear region of plots of [DOR] *vs.* [DOH]; this procedure corrects for the small amounts of hydrolysed dye present in the starting material and gives the product ratio for up to *ca.* 90% reaction, before the onset of the displacement of the second chlorine in the dichlorotriazine **2**. Dissected rate

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Table 1 Effect of added alcohols and cosolvent (0.044 M) on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for dichlorotriazine (**2**) in 0.094 M aqueous sodium carbonate at pH 11.2 and 25.0 °C[a]

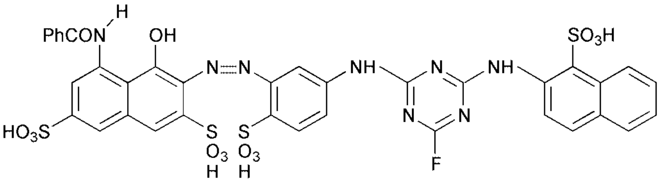
Alcohol	k_{obs}	P	k_{DOR}	k_{DOH}
(No added alcohol)[b]	8.37 ± 0.11			8.37 ± 0.11
(Diglyme)[c]	(9.3 ± 0.2)			(9.3 ± 0.2)
Methanol	11.0 ± 0.2	0.33 ± 0.01	2.7 ± 0.1	8.3 ± 0.3
(Methanol)[d]	(17.2 ± 0.9)	(1.06 ± 0.02)	(8.9 ± 0.5)	(8.4 ± 0.5)
Propanol	9.5 ± 0.2	0.062 ± 0.001	0.55 ± 0.02	8.9 ± 0.2
4	15.0 ± 0.8	0.62 ± 0.01	5.7 ± 0.3	9.3 ± 0.5
5	18.1 ± 1.4	0.88 ± 0.02	8.5 ± 0.7	9.6 ± 0.8
6	28.7 ± 1.7	1.62 ± 0.04	17.7 ± 1.2	11.0 ± 0.7
7	28.5 ± 0.7	1.87 ± 0.03	18.6 ± 0.6	9.9 ± 0.3

[a] Errors shown are based on regression analysis, except where stated otherwise. [b] Triplicate measurements; errors shown are average deviations; a value of (8.42 ± 0.08) × 10^{-4} s^{-1} was obtained in independent studies by Dr J. Ratcliff (PhD Thesis, University of Wales, Swansea, 1996). [c] The medium effects of this relatively hydrophobic cosolvent were not investigated in detail, and were not included in our earlier work (ref. 10). [d] In the presence of a 3-fold higher concentration of methanol (0.136 M); also there is a linear relationship between k_{obs} and [MeOH].

Table 2 Effect of added alcohols (0.044 M) on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for dichlorotriazine (**2**) in 1.58 mM aqueous sodium hydroxide controlled at pH 11.2 and 25.0 °C[a]

Alcohol	k_{obs}	P	k_{DOR}	k_{DOH}
(No added alcohol)[b]	2.65 ± 0.08[c]			2.65 ± 0.08
Methanol[b]	3.67 ± 0.11	0.36 ± 0.03	0.97 ± 0.10	2.69 ± 0.02
4	5.3 ± 0.1	0.74 ± 0.04	2.3 ± 0.2	3.0 ± 0.2
5[b]	5.3 ± 0.2	0.87 ± 0.07	2.45 ± 0.05	2.85 ± 0.25
6	10.2 ± 0.4	1.92 ± 0.07	6.7 ± 0.4	3.5 ± 0.2
7	11.9 ± 0.8	2.06 ± 0.04	8.0 ± 0.6	3.9 ± 0.3

[a] As for Table 1. [b] Duplicate measurements; errors shown are average deviations. [c] A slightly higher result (2.89 ± 0.07) × 10^{-4} s^{-1} was obtained when the solution was inadequately protected from atmospheric carbon dioxide.



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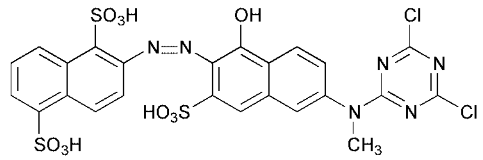

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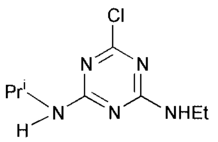

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constants for hydrolysis (k_{DOH}) and alcoholysis (k_{DOR}) were then calculated from eqns. (2) and (3).

$$k_{obs} = k_{DX} = k_{DOH} + k_{DOR} \quad (2)$$

$$P = [DOR]/[DOH] = k_{DOR}/k_{DOH} \quad (3)$$

The alcohols included in this study were methanol, ethane-1,2-diol, prop-2-yn-1-ol (propargyl alcohol), 2,2,2-trifluoroethanol, α-methylglucopyranoside (**4**), β-methylglucopyranoside (**5**), D-sorbitol (**6**) and D-mannitol (**7**). Data for reactions of the dichlorotriazine (**2**), buffered at pH 11.2 by 0.094 M sodium carbonate, are given in Table 1; alternatively, control of pH was achieved using a pH stat apparatus, with addition of sodium hydroxide (Table 2). The effect of changing the concentrations of the alcohols was also investigated; data for various concentrations of methanol–water, buffered at pH 11.35 by 0.025 M sodium hydrogen orthophosphate, are given in Table 3; data for prop-2-yn-1-ol or trifluoroethanol, buffered at pH 9.35 by 0.1 M sodium tetraborate, are given in Table 4; data for ethane-1,2-diol in 0.1 M sodium carbonate at pH 11.46 are given in Table 5.

For pH 11.46 and 25.0 °C as standard conditions, the effects of added salts (0.1 M sodium carbonate or sulfate) on the rates of hydrolyses of **2** are given in Fig. 1. We also investigated the effect of added tetraalkylammonium salts on reaction rates in the presence of sodium carbonate as buffer; the possible dependence of the product ratio on the presence of a quaternary salt was investigated simultaneously by carrying out these experiments in 0.044 M methanol–water. The effect of 1% w/v of quaternary salt (*i.e.* about the same amount as carbonate) was studied for several quaternary cations and for a wide range of anions (Table 6), and the effect of varying the amount of tetrabutylammonium bromide from 0–10% w/v is given in Table 7. Hydrolyses in D_2O are shown in Table 8.

Table 3 Effect of the concentration of methanol on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for dichlorotriazine (**2**) in 0.025 M aqueous sodium hydrogen orthophosphate at pH 11.35 and 25.0 °C[a,b]

[Alcohol]/M	k_{obs}	P	k_{DOR}	k_{DOH}
(No added alcohol)[c]	5.0 ± 0.1			5.0 ± 0.1
0.045	6.9 ± 0.1	0.41 ± 0.01	2.0 ± 0.1	4.9 ± 0.1
0.133	10.8 ± 0.2	1.17 ± 0.03	5.8 ± 0.2	5.0 ± 0.1
0.303	18.1 ± 0.1	2.63 ± 0.06	12.9 ± 0.2	5.2 ± 0.1

[a] As for Table 1. [b] The results in this Table show a linear relationship between k_{obs} and [MeOH]–slope 43.3 ± 0.4 × 10^{-4} s^{-1} M^{-1} (r = 0.999); see also Table 1, footnote *d*. [c] Duplicate measurements; error shown is the average deviation.

Table 4 Effect of the concentration of prop-2-yn-1-ol and trifluoroethanol on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for dichlorotriazine (**2**) in 0.1 M aqueous sodium tetraborate at pH 9.35 and 25.0 °C[a]

[Alcohol]/M	k_{obs}	P	k_{DOR}	k_{DOH}
(No added alcohol)[b,c]	0.134 ± 0.007			0.134 ± 0.007
Prop-2-yn-1-ol				
0.045	1.03 ± 0.04	6.2 ± 0.5	0.89 ± 0.11	0.143 ± 0.013
0.089	1.92 ± 0.12	13.5 ± 1.8	1.78 ± 0.36	0.132 ± 0.019
Trifluoroethanol[d]				
0.023	1.25 ± 0.05	7.6 ± 0.4	1.10 ± 0.09	0.145 ± 0.010
0.047	2.7 ± 0.1	15.7 ± 1.0	2.6 ± 0.2	0.163 ± 0.011
0.066	3.7 ± 0.1	18.9 ± 1.7	3.5 ± 0.4	0.184 ± 0.017

[a] As for Table 1. [b] Duplicate measurements; errors shown are average deviations. [c] A value for k_{3H} of 1.1 × 10^{-2} M^{-2} s^{-1} is obtained from $k_{DOH} = k_{3H}[HO^-][H_2O]$. [d] The data give a linear relationship [eqn. (4)] between k_{DOH} and [RO$^-$], slope = $k_{3R}[H_2O]$ = 0.084 ± 0.010 M^{-1} s^{-1} (r = 0.985), giving a third order rate constant (k_{3R}) of 1.5 × 10^{-3} M^{-2} s^{-1}.

Table 5 Effect of the concentration of ethane-1,2-diol cosolvent on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for dichlorotriazine (**2**) in 0.1 M aqueous sodium carbonate at pH 11.46 and 25.0 °C[a]

[Alcohol]/M	k_{obs}	P	k_{DOR}	k_{DOH}
(No added alcohol)[b]	9.35 ± 0.15			9.35 ± 0.15
0.048	13.7 ± 0.3	0.47 ± 0.01	4.4 ± 0.2	9.3 ± 0.3
0.10[c]	18.7 ± 0.5	1.04 ± 0.02	9.5 ± 0.4	9.2 ± 0.3

[a] As for Table 1. [b] Triplicate measurements; error shown is the average deviation; a value for k_{3H} of 5.8 × 10^{-3} M^{-2} s^{-1} is obtained from $k_{DOH} = k_{3H}[HO^-][H_2O]$. [c] Duplicate measurement; error shown is the average deviation.

Table 6 Effect of 1% w/v of tetraalkylammonium salts on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for hydrolysis of the dichlorotriazine (**2**) in 0.094 M aqueous sodium carbonate containing 0.044 M methanol at pH 11.2 and 25.0 °C[a]

Quaternary ammonium salt	k_{obs}	P	k_{DOR}	k_{DOH}
(None added)[b]	11.0 ± 0.2	0.33 ± 0.01	2.7 ± 0.1	8.3 ± 0.3
Me_4NBr[c]	15.3 ± 0.3	0.22 ± 0.02	2.8 ± 0.4	12.5 ± 1.3
Me_4NCl	12.2 ± 0.4	0.29 ± 0.01	2.7 ± 0.2	9.5 ± 0.4
Et_4NBr	9.9 ± 0.9	0.31 ± 0.01	2.3 ± 0.2	7.6 ± 0.7
(Et_4NBr)[d]	(19.0 ± 1.3)	(0.31 ± 0.02)	(4.5 ± 0.5)	(14.5 ± 1.4)
n-Pr_4NBr	12.5 ± 0.5	0.32 ± 0.01	3.0 ± 0.2	9.5 ± 0.5
n-Bu_4NBr	13.6 ± 0.8	0.30 ± 0.01	3.2 ± 0.2	10.4 ± 0.7
n-Bu_4NI	12.5 ± 0.6	0.30 ± 0.01	2.9 ± 0.2	9.6 ± 0.5
n-Bu_4NSCN	13.1 ± 0.6	0.29 ± 0.02	2.9 ± 0.3	10.2 ± 0.8
n-Bu_4NCl	13.1 ± 0.5	0.30 ± 0.01	3.0 ± 0.2	10.1 ± 0.5
n-Bu_4NF	14.0 ± 0.7	0.28 ± 0.01	3.1 ± 0.2	10.9 ± 0.7
n-Bu_4NHSO_4[e]	7.8 ± 0.4	0.27 ± 0.01	1.7 ± 0.1	6.1 ± 0.4

[a] As for Table 1. [b] Data from Table 1. [c] Duplicate measurements; errors shown are average deviations. [d] 10% w/v Et_4NBr added. [e] Adjustment of pH to 11.1 by the addition of 12.5 mL of 1 M sodium hydroxide; in the absence of added base the pH = 10.3.

Discussion

General base catalysis by alkoxide separated from medium effects

Interpretation of the kinetic results requires consideration of the possible medium effects of added alcohol cosolvents and electrolytes. The effect of added salts is large (Fig. 1), and the uncertainties in the salt effect are too large to ascertain the catalytic effects of anionic general bases. In contrast, k_{DOH} is independent of added alcohol at concentrations of <0.3 M methanol (Table 3), for 0.09 M prop-2-yn-1-ol (Table 4), and for 0.1 M ethane-1,2-diol (Table 5). Although the importance of medium effects on reactions in basic alcohol–water mixtures is well established,[9,13] the detailed studies of 1-fluoro-2,4-dinitrobenzene (**8**, X = F) by Murto[13] also show that up to 2.4 wt% (and possibly even up to 8%) of methanol does not significantly

Table 7 Effect of % w/v of tetrabutylammonium bromide on the rate constants (10^4 k/s^{-1}) and product ratios [P, eqn. (3)] for hydrolysis of the dichlorotriazine (**2**) in 0.094 M aqueous sodium carbonate containing 0.044 M methanol at pH 11.2 and 25.0 °C[a]

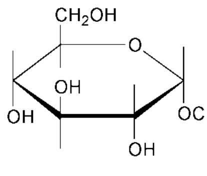
n-Bu_4NBr (% w/v)	k_{obs}	P	k_{DOR}	k_{DOH}
0[b]	11.0 ± 0.2	0.33 ± 0.01	2.7 ± 0.1	8.3 ± 0.3
1	13.6 ± 0.8	0.30 ± 0.01	3.2 ± 0.2	10.4 ± 0.7
2	13.7 ± 0.5	0.31 ± 0.01	3.2 ± 0.2	10.5 ± 0.5
5	16.4 ± 0.4	0.30 ± 0.01	3.8 ± 0.2	12.6 ± 0.6
10[c,d]	15.4 ± 0.9	0.32 ± 0.02	3.7 ± 0.3	11.7 ± 1.0
0[e,f]	(9.4 ± 0.9)	(3.1 ± 0.1)	(7.1 ± 0.8)	(2.3 ± 0.2)
10[e]	(26.2 ± 1.9)	(3.0 ± 0.3)	(19.7 ± 3.1)	(6.5 ± 0.8)

[a–c] As for Table 4. [d] Cloudy solution. [e] At pH = 11.0, with reduced amounts of carbonate (0.019 M) and 0.37 M methanol–water. [f] Data from ref. 10a.

Table 8 Kinetic solvent isotope effects on the rate constants (10^4 k/s^{-1}) for hydrolysis of the monofluorotriazine (**1**) and the dichlorotriazine (**2**) in 0.094 M aqueous sodium carbonate at pH 11.2 (pD 12.1[a]) and 25.0 °C

Dye	$k_{obs}(H_2O)$	$k_{obs}(D_2O)$	$k(H_2O)/k(D_2O)$
1	0.56 ± 0.04	0.61 ± 0.03	0.92 ± 0.08
2	8.37 ± 0.11[b]	7.7 ± 0.3	1.09 ± 0.04

[a] The measured pH in D_2O was 11.66, and the pD value was calculated by adding 0.44—see ref. 12. [b] Data from Table 1.



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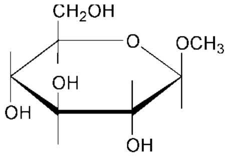

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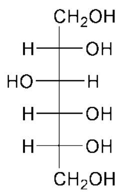

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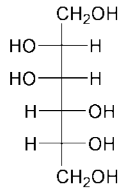

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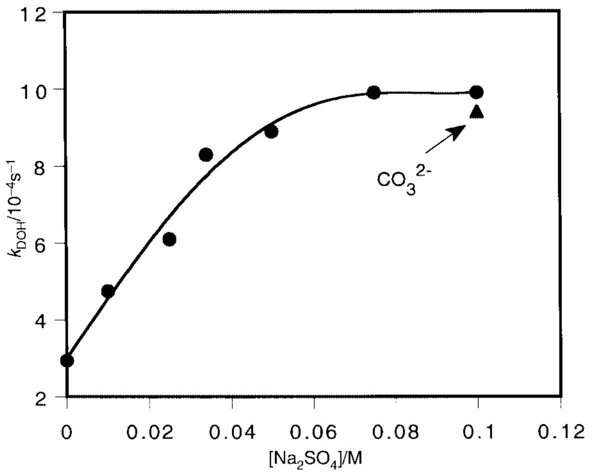


Fig. 1 Plot of observed first order rate constant for hydrolysis of the dichlorotriazine (**2**) $vs.$ concentration of sodium sulfate (plotted as circles); additional results are: $k = 9.4 \pm 0.1 \times 10^{-4}$ s^{-1} (duplicate) in the presence of 0.1 M sodium carbonate (plotted as a triangle); $k = 9.8 \times 10^{-4}$ s^{-1} in the presence of 0.05 M sodium carbonate and 0.05 M sodium sulfate (compare with $k = 9.9 \pm 0.1 \times 10^{-4}$ s^{-1} (duplicate) in the presence of 0.1 M sodium sulfate).

affect the second order hydrolysis rates (denoted $k_h°$, but closely approximated by the tabulated values[13a] of k_h). These results support the assumption that medium effects of added alcohols can be ignored at very low alcohol concentrations (<0.1 M)—most of our data are at a concentration of only 0.044 M added alcohol (in contrast to 0.132 M in our earlier work[10]), to obtain detectable kinetic effects at very low alcohol concentrations.

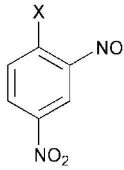
A key aspect of this work is the increase in the dissected first order rate constants (k_{DOH}) in the presence of the polyols (**4**–**7**) for reactions of the dichlorotriazine (**2**), both in the presence of sodium carbonate (Table 1) and in its absence (Table 2), and also in the presence of trifluoroethanol (Table 4). These results contrast with the behaviour of the fluorotriazine (**1**), which gives constant values of k_{DOH}, except possibly for the glucopyranosides (**4** and **5**) for which the experimental evidence is less clear.[10a]

Hence, as the 10–30% increase in the dissected first order rate constants (k_{DOH}, Tables 1 and 2 for the polyols (**4**–**7**) and Table 4 for trifluoroethanol) does not appear to be due to medium effects, an additional term in the rate law is required. We propose that hydrolysis of **2** by hydroxide may be supplemented by a general base-catalysed process involving alkoxide ($i.e.$ a third order reaction in which alkoxide deprotonates a water molecule which attacks **2** (see k_{3R}, Scheme 1)). Observed first order rate constants (k_{DOH}) in alcohol–water would then have two components [eqn. (4)].

$$k_{DOH} = k_{DOH} \text{ (in the absence of added alcohol)} + k_{3R}[RO^-][H_2O] \quad (4)$$

The proposal is consistent with the Brønsted base catalysis law,[14] as the change in first order rate constants (k_{DOH}) can be used to calculate values for the third order rate constants (k_{3R}) in 0.1 M buffer of $ca.$ 2×10^{-2} M^{-2} s^{-1} for the polyols (**4**–**7**) having pK_a > 13.5,[10a,15] whereas the less basic trifluoroethoxide (pK_a = 12.4[16]) gives a smaller third order rate constant (k_{3R}) of 1.5×10^{-3} M^{-2} s^{-1} (Table 4, footnote d).

Knowing the pK_a values of the added alcohols, second order rate constants (k_{RO^-}) for alcoholyses can be calculated from the pseudo-first order values of k_{DOR} in Tables 1, 4 and 5.[10a] The k_{RO^-} results give satisfactory Brønsted plots, with $\beta = 0.38$ for **2** and 0.56 for **1**, but there are major deviations of $ca.$ 10^2 for hydroxide (R = H) from the best lines through the other relevant data points (see Fig. 2). Similar deviations were observed for the alcoholyses of **8** (X = F[13b]) in water ($\beta = 0.22$, deviation = 10^2), and of the dichlorotriazine (**9**) in 16% dioxane–water ($\beta = 0.84 \pm 0.06$, deviation = $10^{3.5}$).[18]



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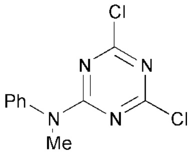

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The reduced reactivity of hydroxide when solvated by water is established from gas phase studies[19] and from studies in aqueous dimethyl sulfoxide,[20] and may be due to electrostatic effects[14] and/or to a greater apparent steric bulk of solvated hydroxide.[18] As discussed further below, the deviations of hydroxide from Brønsted plots (typically greater than 10-fold in rate[7d,13b,14,18]) may be crucial to an understanding of why alkoxide-assisted hydrolysis could occur.

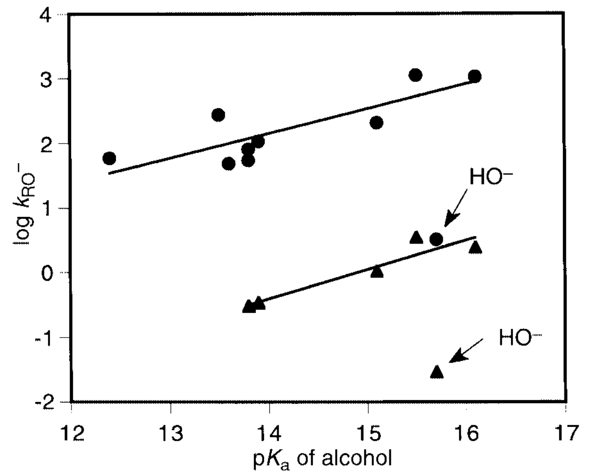

Fig. 2 Brønsted plots for second order alcoholysis rate constants (k_{RO^-}) at 25 °C; data for **2** (points plotted as circles and as log k_{RO^-} + 1) at pH 9.35–11.5 (0.1 M buffer) calculated from values for k_{DOR} (Tables 1, 4 and 5) as described in ref. 10*a*; data for **1** (triangles) from ref. 10*a* refers to 0.132 M alcohol; pK_a values for alcohols from refs. 10*a* and 16, and for glucopyranosides as follows: (**4**, pK_a = 13.8[15]) and (**5**, pK_a = 13.6[15]); pK_a values for ethane-1,2-diol, mannitol, and sorbitol were statistically corrected by adding 0.3 to the observed pK_a value;[17] correlations excluding hydroxide: for **2**, $\beta = 0.38 \pm 0.10$, $r = 0.82$; for **1**, $\beta = 0.56 \pm 0.10$, $r = 0.97$.

Indirect evidence for catalysis by hydroxide

If hydroxide were to act as the catalyst as in k_{3H} (Scheme 1), the process would be more favourable thermodynamically than catalysis by alkoxides (pK_a 12.4–14) as in k_{3R} (Scheme 1). Hence, it could be argued that an implication of the observation of any alkoxide-catalysed hydrolysis is that the dominant hydrolysis reaction at pH 11.2 is hydroxide as base catalyst, attacking water as nucleophile, which attacks the substrate (Scheme 1). Furthermore, the thermodynamic advantage of hydroxide appears to be so great[8] that, unless β is very small or hydroxide deviates from the Brønsted plot (*e.g.* Fig. 2), it is somewhat surprising that catalysis by the alkoxides can be detected at a pH as high as 11.2.

If a third order mechanism is assumed for hydrolysis by hydroxide, a value for k_{3H} (Scheme 1) of 5.8×10^{-3} M^{-2} s^{-1} can be obtained from the first order rate constant for hydrolysis in the absence of added alcohol (Table 5, footnote *b*); this value is consistent with the value for k_{3R} (Scheme 1) of 1.5×10^{-3} M^{-2} s^{-1} (Table 4, footnote *d*) for the less basic trifluoroethoxide catalyst, so it is plausible that two third order mechanisms could be operating (as shown in Scheme 1). In other nucleophilic aromatic substitutions, quite good Brønsted plots including carbonate and hydroxide have been obtained,[7b,c] but inevitably there is a leverage effect of the data point for hydroxide (the strongest base) and it could be argued that hydroxide falls below the best line through all of the other data points. In contrast, direct second order nucleophilic attack by hydroxide could lead to higher than expected rates.[1]

Whilst third order hydrolyses catalysed by water usually show kinetic solvent isotope effects (KSIE) of >2,[1–5,7a,b,e] hydroxide-catalysed hydrolyses give smaller[7a] or even inverse[7b–e] KSIEs. Our results (Table 8) show very similar KSIEs for hydrolyses of both **1** and **2**, with no significant KSIE. These data alone do not permit us to distinguish between second or third order hydrolyses by hydroxide.

In addition to work on hydroxide-catalysed hydrolyses in S_N(Ar) reactions,[7a–c] the possibility of hydroxide as base, attacking water as nucleophile, prior to attack on the substrate has been considered previously for reactions of carbonyl compounds.[1a,21,22] Experimental support is scarce, but recent work on general base-catalysed hydrolysis of aryl trifluoroacetates shows good Brønsted plots including hydroxide for *m*- and *p*-chlorophenyl trifluoroacetates.[1a] Also, Guthrie has calculated a uniquely high intrinsic barrier for the attack of hydroxide on a carbonyl group,[23a] and also a very small intrinsic barrier to proton transfer along a preformed hydrogen bond.[23b] Consequently, third order reactions may occur through a hydrogen-bonded complex.[7b,c,21]

Salt effects

The results for sodium sulfate (Fig. 1) and for quaternary ammonum salts (Tables 6 and 7) show relatively large rate increases for the chlorotriazine (**2**), whereas sodium chloride shows a rate decrease.[10a] The same qualitative trends (but smaller kinetic effects) were found for the reaction of hydroxide ion with 1-chloro-2,4-dinitrobenzene (**8**, X = Cl).[24] Detailed kinetic data for a wide range of mostly inorganic salts are available;[24] cations of low charge density (*e.g.* tetramethylammonium) stabilise the transition state, whereas alkali metal cations have the opposite effect. The results for anions did not fit a simple pattern, but all monovalent sodium salts lowered reaction rates, and the effect for nitrate was not as rate retarding as the more delocalised perchlorate.

We also examined the kinetic salt effects of quaternary ammonium salts relevant to phase transfer catalysis (PTC). In liquid–liquid PTC, a reactive anion is usually transferred from an aqueous phase to an organic phase, but inverse PTC[25] may involve transfer of an organic substrate to the aqueous phase. Quaternary ammonium salts would help to solubilise an organic substrate in the aqueous phase, and may influence rates and/or product selectivities. Under our reaction conditions, none of the cations investigated (Table 6) form micelles,[26] and others have investigated micellar effects of other quaternary ammonium salts on the rates and selectivities in S_N(Ar) reactions.[27] As the dye (**2**) is readily soluble in the aqueous phase, it is a suitable molecular probe to study the kinetic effects of quaternary salts.

In the presence of 1% (<0.1 M) quaternary ammonium salts, rates usually increase and product ratios are relatively constant (Table 6), except for an increase in the hydrolysis product (k_{DOH} increases) for tetramethylammonium bromide. For tetra-*n*-butylammonium salts, the effect of the counteranion is relatively small, except for the acidic hydrogen sulfate which cannot be compared directly with the other salts (Table 6).

At higher concentrations (0.3 M), it is proposed[26] that tetra-*n*-butylammonium bromide (TBAB) reaches a critical hydrophobic interaction concentration ("chic") at which there is overlap of hydration shells (10% w/v TBAB is *ca.* 0.3 M). Studies of the effect of 10% quaternary ammonium salts (Table 7) again show rate increases and relatively constant product ratios. Investigations were curtailed because TBAB forms a cloudy solution in the presence of 0.094 M sodium carbonate at 25 °C, and the 40% rate increase for 10% TBAB is not significantly greater than the rate increase for 1% TBAB (Table 7), probably due to precipitation of TBAB in alkaline solution.[26] In contrast, at pH 11 in the presence of only 0.019 M sodium carbonate, 10% TBAB gives a nearly 3-fold rate increase (Table 7). At pH 11.2, addition of 10% of the more soluble tetraethylammonium bromide (entry 5 of Table 6) gives a larger rate increase than 10% TBAB, whereas reaction in 1% TBAB is faster than in 1% tetraethylammonium bromide (Table 6). These results indicate that the rate enhancements of quaternary salts occur in the aqueous solution phase.

Conclusions

By investigating solutions containing very low concentrations of added alcohols (0.044 M) in water, and then dissecting observed first order rate constants into the separate contributions from hydrolysis and alcoholysis, we have uncovered evidence for an alkoxide-assisted process for hydrolysis by water of the dichlorotriazine (**2**). Although the kinetic effects are not large, an indirect implication of the presence of alkoxide-assisted hydrolysis is that there should be a competing process involving hydrolysis by water with hydroxide acting as a base. The same experimental procedure could be applied more generally: (i) to explore the scope of general base-catalysed reactions at high pH; (ii) to obtain data complementary to Brønsted coefficients and solvent kinetic isotope effects. Despite the thermodynamic advantage of hydroxide over alkoxides as catalysts, the relatively low reactivity of hydroxide (shown by deviations of 100-fold in rate from Brønsted plots, Fig. 2) provides an opportunity for competing catalysis.

Experimental

Materials

Dyes (**1** and **2**), polyols (**4**–**7**) and some of the alcohols were available from earlier work.[10] Ethane-1,2-diol (Fisons SLR grade) was pre-dried over magnesium sulfate and was distilled at reduced pressure (bp 86–88 °C at 20 mmHg). Trifluoroethanol (99%, Avocado Research Chemicals Ltd) and prop-2-yn-1-ol (97%, Lancaster Synthesis Ltd) were used as supplied. Sodium carbonate (Fisons) was shown by acid–base titration to be 94% pure (presumably with 6% water) and sodium sulfate was BDH GPR grade. Sodium tetraborate decahydrate and sodium hydrogen phosphate were AR grade. Quaternary ammonium salts were from the following sources and were used as supplied: tetramethylammonium bromide (Aldrich, 98%); tetramethylammonium chloride (Aldrich, 97%); tetraethylammonium bromide (Aldrich, 98%); tetra-*n*-propylammonium bromide (Aldrich, 98%); tetra-*n*-butylammonium bromide (Avocado, 98%); tetra-*n*-butylammonium iodide (Aldrich, 98%); tetra-*n*-butylammonium thiocyanate (Aldrich, 98%); tetra-*n*-butylammonium chloride hydrate (Aldrich, 98%); tetra-*n*-butylammonium fluoride hydrate (Aldrich, 98%); tetra-*n*-butylammonium hydrogen sulfate (Lancaster). Deuterium oxide (Aldrich) was 99.9% D and 'Carbosorb' Soda Lime was BDH GPR grade.

Analytical methods

Ion-pair reversed-phase HPLC was carried out at 40 °C, as described earlier,[10a] except that a greater concentration (0.02 M instead of 0.01 M) of the ion pair reagent (tetra-*n*-butylammonium bromide) was added to the eluent for the analyses of the reactions containing the polyols (**4**–**7**). The HPLC equipment was as before,[10a] except that a Thermo Separation Products ConstaMetric 3200 pump was used.

Kinetic methods

Aliquot sampling procedures, and calculations of rate constants for reactions buffered with sodium carbonate were as described earlier;[10] as our procedure does not involve the use of an internal standard, it is important to ensure that the volumes of aliquots, quenching solutions and chromatographic injections are controlled within a narrow range. The pH was checked at the end of each reaction and it was usually not more than 0.04 pH units lower than at the start of the reaction.

pH stat measurements were obtained using the pH stat option on a Radiometer RTS 822 automatic titrator; the glass titration vessel was thermostatted by circulating water through an outer jacket, the 1.58 mM aqueous sodium hydroxide solution (Table 2) was diluted from a relatively fresh stock solution (from an ampoule) protected from carbon dioxide contamination *via* a drying tube containing Carbosorb and purged with nitrogen before use, and 0.1 M sodium hydroxide was added automatically as required to maintain the pH at 11.2 (higher rate constants (by 10–20%) were obtained if this procedure was not followed). Aliquots were removed quickly at predetermined times, and for hydrolyses were not quenched, but were chromatographed immediately using a relatively fast analysis time; aliquots of alcohol–water mixtures were quenched using 0.1 M HCl followed by pH 7 buffer, and were then chromatographed as usual.

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