Nucleophilic Aromatic Substitution in Heterocycles: Alcoholysis and Hydrolysis of 2-Anilino-4,6-dichloro-1,3,5-triazines

A. Hunter M. Renfrew,[b] **John A. Taylor,**[b] **James M. J. Whitmore**[a] **and Andrew Williams** *[,a]
[a] *University Chemical Laboratories, Canterbury, Kent, UK CT2 7NH*
[b] *Zeneca Specialties, Hexagon House, Blackley, Manchester, UK M9 3DA*

Kinetics are reported for the alkaline hydrolysis of 2-anilino-4,6-dichloro-1,3,5-triazines to yield the corresponding mono-hydroxy species. The pseudo-first-order rate constants are independent of general-base concentration and obey the rate law eqn. (i), where $K_1 = K_w/K_a$, K_a is the ionisation

$$k_{obs} = (k_{H_2O} + k_{OH}K_1[OH])/([OH] + K_1) \qquad (i)$$

constant for the aniline proton and k_{OH} is the bimolecular rate constant for attack of hydroxide ion on the neutral triazine molecule. The parameters k_{OH} and K_a obey Hammett equations with σ° [eqns. (ii) and (iii)]. The kinetically determined pK_a of the 4-chloroanilino-4,6-dichloro-1,3,5-

$$\log k_{OH} = 1.06 \pm 0.15\sigma^\circ - 0.064 \pm 0.054 \quad (r = 0.9709) \qquad (ii)$$

$$pK_a = -2.13 \pm 0.16\,\sigma^\circ + 10.92 \pm 0.06 \quad (r = 0.9919) \qquad (iii)$$

triazine is close to that measured by pH-titration.

The kinetics for hydrolysis and alcoholysis of 2-(*N*-methyanilino)-4,6-dichloro-1,3,5-triazine are independent of general-base concentration and are first order in oxyanion and triazine concentration; the derived second-order rate constants (k_{RO^-}) (excepting the hydroxide term) obey the extended Brønsted equation (iv).

$$\log k_{RO^-} = 0.84 \pm 0.06\, pK_a^{ROH} - 10.89 \pm 0.87 \quad (r = 0.9886) \qquad (iv)$$

The hydroxide ion term is some three orders of magnitude less nucleophilic than an alkoxide of the same pK_a. The data exclude the conjugate base of the 2-anilino-4,6-dichloro-1,3,5-triazine as a major contributor to the reaction flux of the hydrolysis and are consistent with a mechanism involving addition of the hydroxide ion to the neutral triazine. The polar substituent effects on the hydroxide ion reactivity indicate that there is substantial charge accumulation in the triazine nucleus in the transition state of the addition step.

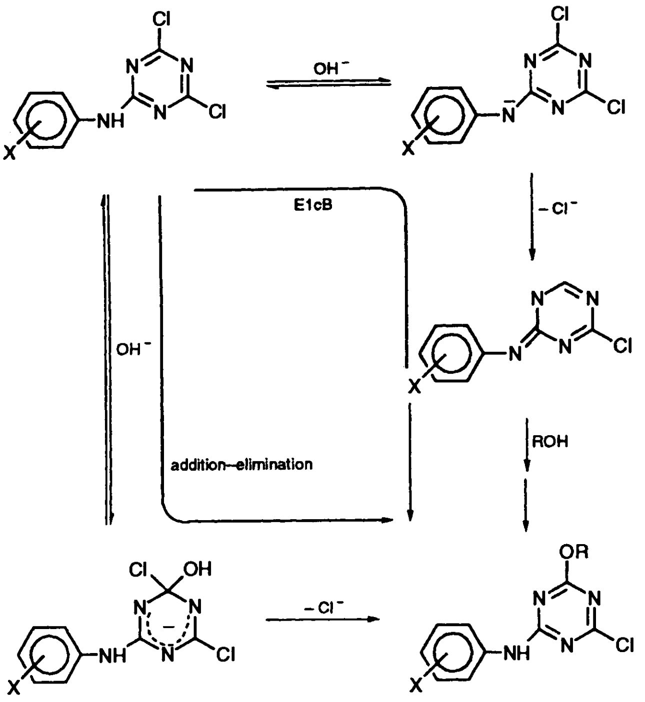
Recent work has indicated that the triazine nucleus can be very useful in studies of the general mechanism of nucleophilic aromatic substitution in aqueous solution because of the activating effect of the ring nitrogens.[1] The application of triazines in reactive dyeing and related chemical technologies involves linking functions to polymeric supports through triazinyl bridging groups. These techniques have been known since the late 1920s[2] but the detailed mechanism of the substitution process at triazines has not received substantial systematic study[3–9] compared with that at other aromatic nuclei especially the nitro benzenoids.[10] The nitro groups are very useful as they activate the aromatic nucleus and hence facilitate studies of aromatic substitution but they possess complicating features which make them otherwise unattractive as activators to study the fundamental mechanisms of nucleophilic aromatic substitution. Ring aza atoms activate the aromatic nucleus to a similar extent to the nitro groups but do not have their complications.

An E1cB[11] process involving a heteroaryne intermediate can reasonably be postulated as a mechanism for nucleophilic aromatic substitution in addition to the range of mechanisms already discussed.[10c] The heteroaryne species (Scheme 1), which can be thought of as a resonance hybrid between neutral and zwitterionic forms, has substantial precedent as an intermediate in other systems. The distinction between the E1cB[11] and the regular addition–elimination reactions[10c] (Scheme 1) is not clear cut[3,4] and the purpose of this work is to provide kinetic data under carefully controlled conditions. An additional aim is to chart the electronic nature of the transition state of the addition mechanism as revealed by the polar substituent effects on the reactivity of the triazines.

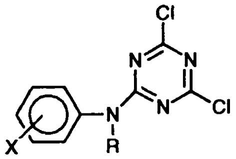
A range of triazines (**1**) was prepared with R = H or CH_3 with different substituents and the kinetics of alkaline hydrolysis and reaction with oxyanion nucleophiles determined.

Experimental

Materials.—2-Anilino-4,6-dichloro-1,3,5-triazines were prepared by the following general method which is a modification of that of Thurston and co-workers.[8] Cyanuric chloride (3.5 g, 20 mmol) was dissolved in acetone (30 cm^3) and heated to 50 °C and added, with stirring to a crushed ice–water mixture (20 cm^3) to produce a fine slurry. The appropriate aniline (2 equiv.) was then added slowly, with stirring, and the temperature was maintained below 5 °C. When the addition was complete the mixture was stirred for about 45 min. The product was isolated by filtration, washed with water and dried *in vacuo* over silica gel. The product was recrystallised from hot benzene or light



Scheme 1



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petroleum (b.p. 100–120 °C) after filtration to remove solid matter. The product was washed with light petroleum (b.p. 40–60 °C) and kept *in vacuo* over wax turnings. 2-(*N*-Methylanilino)-4,6-dichloro-1,3,5-triazine was obtained in a similar fashion. The melting points and analytical data are recorded in Table 1 and the structural identities of the compounds were confirmed by IR and NMR spectroscopy.

Water used throughout the investigation was doubly distilled from glass and degassed *in vacuo* prior to use. All the materials employed in the kinetics were of analytical reagent grade or were redistilled or recrystallised from bench grade materials. Dioxane (analytical reagent grade) was passed through a column of basic alumina and checked for the absence of peroxide contaminants with aqueous KI solution.

Methods.—Rates of hydrolysis were measured at 25 °C in the pH-region 9–14 using a dioxane–water medium maintained at $I = 0.25$ mol dm^{-3} with KCl. Solutions were prepared for the pH range 9–11.5 by adjusting the pH and ionic strength of a mixture of 0.25 mol dm^{-3} $KHCO_3$ (5 cm^3) and dioxane with KOH and KCl and then made up to 25 cm^3 with degassed water. Aliquots of KOH solution (1 mol dm^{-3}) were appropriately diluted with dioxane and KCl solution to give solutions of pH within the range 11.5–14. Stock solutions of the substrate were prepared with the triazine (**1**) (approximately 10 mg) in acetonitrile solution (5 cm^3).

Reactions were initiated by adding an aliquot (20 µl) of the substrate stock solution to sample buffer (2.5 cm^3) in a 1 cm path length silica cell in the thermostatted cell compartment of a UV-VIS spectrophotometer (Perkin-Elmer Lambda 5 or Unicam SP800 machine). The spectra were scanned repetitively in the first instance to determine the best single wavelength for monitoring the kinetics. Kinetics were measured by observing the absorbance change as a function of time at the single wavelength. Pseudo-first-order rate constants were obtained from the absorption–time data from linear plots of log ($A_t - A_{final}$) *versus* time or by the use of curve-fitting software with a desk top computer.

Table 1 Analytical results for 2-(substituted anilino)-4,6-dichloro-1,3,5-triazines

Compound	Formula	M.p./°C	%C[a]	%H[a]	%N[a]
Parent	$C_9H_6Cl_2N_4$	131–133[b]	44.84 (44.57)	2.51 (2.40)	23.24 (23.49)
4-Cl	$C_9H_5Cl_3N_4$	185–187[c]	39.20 (39.47)	1.83 (1.77)	20.42 (20.59)
4-MeO	$C_{10}H_8Cl_2N_4O$	171–172[d]	44.31 (44.43)	2.98 (2.90)	20.67 (20.64)
3-NO$_2$	$C_9H_5Cl_2N_5O_2$	197–199[e]	37.79 (37.44)	1.76 (1.60)	24.48 (24.83)
4-NMe$_2$	$C_{11}H_{11}Cl_2N_5$	296–297	46.50 (46.22)	3.90 (3.71)	24.65 (24.92)

[a] Figures in parentheses denote the percentage found. [b] Lit.,[12] m.p. 131–132 °C. [c] Lit.,[12] m.p. 185–186 °C. [d] Lit., m.p. 168–170 °C (F. H. S. Curd, J. K. Landquist and F. L. Rose, *J. Chem. Soc.*, 1947, 154). [e] Lit., m.p. 298–299 °C (W. W. Cuthbertson and J. S. Moffatt, *J. Chem. Soc.*, 1948, 561).

Values of pK_a for selected substrates were determined by spectrophotometric titration. The optimum wavelength for the studies was obtained by scanning the spectrum of the substrate at high and low pH corresponding to ionised and unionised forms. Aliquots (20 µl) of the substrate were added to a series of buffers (2.5 cm^3) in the spectrophotometric cell with a range of pH and the absorbance at the optimum wavelength extrapolated to zero time. The absorptions were fit to eqn. (1) where A_a

$$A_0 = (A_a + A_bK_a/[H^+])/(K_a/[H^+] + 1) \qquad (1)$$

and A_b are the absorptions of the acid and base forms of the substrate under the same conditions at the wavelength in question.

Results

The reaction of the dichlorotriazines in the aqueous buffers exhibited excellent pseudo-first-order kinetics in triazine concentration up to greater than 90% completion. Studies with varying buffer component (hydrogen carbonate ion) and constant pH and ionic strength indicated no change in rate constant for all the substrates employed here.

The pseudo-first-order rate constants for the triazines (**1**; R = H) obeyed a sigmoidal dependence on pH; they were fit to eqn. (2) and the parameters are collected in Table 2. The fit is

$$k_{obs} = (k_{H_2O} + k_{OH}K_1[OH^-])/([OH^-] + K_1) \qquad (2)$$

illustrated in Fig. 1 for the hydrolysis of 2-(4-dimethylaminoanilino)-4,6-dichloro-1,3,5-triazine and $K_1 = K_w/K_a$; K_a is the ionisation constant for the anilino proton.

The ionisation constants of the 4-chloro and 3-nitro species were measured titrimetrically and the data are recorded in Table 2. The pK_a values found titrimetrically agree with those found from the pH-dependence of the kinetics.

The data exhibited slight upward deviations from a regular ionisation equation at the low pH regions and this is probably due to the reaction of water with neutral triazine [k_{H_2O} in

Table 2 Hydrolysis of 2-(substituted anilino)-4,6-dichloro-1,3,5-triazines in the pH region 9.5–13.5[a]

H		4-Cl		4-MeO		4-Me_2N		3-NO_2	
pH	k_{obs}	pH	k_{obs}	pH	k_{obs}	pH	k_{obs}	pH	k_{obs}
13.75	2.09			13.35	3.31	13.61	4.47	13.48	0.347
13.30	2.29			12.75	3.16	13.25	4.57	12.75	0.345
12.95	2.09	12.60	1.35	12.00	2.88	12.87	4.47	12.48	0.460
12.40	2.29	12.05	1.32	11.75	2.00	12.55	4.47	11.75	0.406
12.01	1.86			11.50	1.59	12.35	3.80	10.97	0.390
11.58	1.66	11.25	1.12	11.25	1.29	12.16	3.54	10.49	0.368
10.95	1.38	11.01	1.00	11.00	1.24	11.58	2.04	10.01	0.341
10.50	0.81	10.50	0.98	10.73	0.83	11.15	1.45	9.56	0.286
10.23	0.44			10.51	0.49	10.93	1.05		
9.95	0.33	9.98	0.37			10.57	0.501		
9.83	0.15	9.78	0.30	10.00	0.23	10.24	0.309		
						9.95	0.155		
						9.50	0.059		
						9.25	0.050		
k_{OH}/dm^3 mol^{-1} s^{-1}	1.09 ± 0.21	2.01 ± 0.58		0.46 ± 0.074		0.476 ± 0.029		4.17 ± 0.55	
pK_a	10.79 ± 0.09	10.32 ± 0.15[d]		11.33 ± 0.09		11.47 ± 0.036		9.45 ± 0.03[b]	
r	0.9932	0.9835		0.9897		0.9985			
λ/nm[c]	[illegible]00	300		310		325		300	
k_{H_2O}/s^{-1}[e]	4.65 ± 6.98 × 10^{-6}	3.73 ± 7.43 × 10^{-6}		10.60 ± 4.69 × 10^{-6}		2.05 ± 0.46 × 10^{-6}		—	

[a] Conditions: 25 °C, I = 0.25 mol dm^{-3}, 20% dioxane–water (v/v) value in parentheses is the difference between the maximum and minimum values that can be fitted to the data; rate constants (k_{obs}) have the units 10^4 s^{-1}. [b] Value obtained by spectrophotometric pH-titration employing λ = 270 nm. [c] Wavelength for kinetic study. [d] The value obtained by spectrophotometric pH-titration at λ = 275 nm is 10.35 ± 0.11. [e] See the results section for the validity of this parameter.

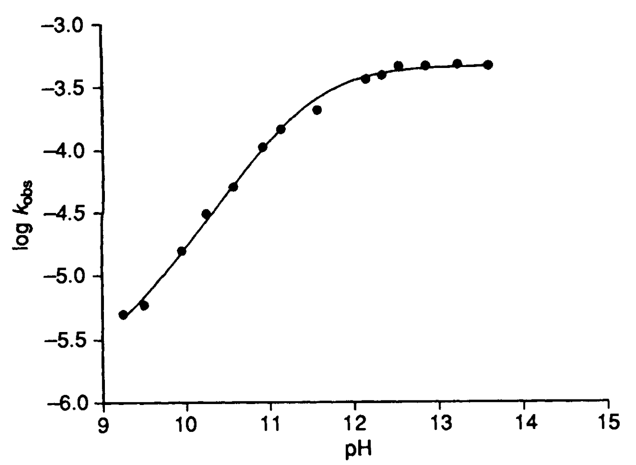


Fig. 1 Dependence of k_{obs} on pH for the hydrolysis of 2-(4-dimethylaminoanilino-4,6-dichloro-1,3,5-triazine; data and conditions from Table 2

eqn. (2)]. The incorporation of this extra parameter gave better fit of the data to k_{OH} and K_1 but in no case was the accuracy of the derived values of k_{H_2O} of a high order.

The reactivity of the alkoxide ions with the *N*-methylanilinotriazine (1; R = CH_3, X = H) was measured in alkaline buffers containing increasing amounts of the alcohol. The rate constants exhibited a linear dependence on the concentration of the alcohol. In the case of the 2-phenylsulfonylethanol the kinetics were measured at different pH corresponding to a range of values for the fraction of free alkoxide ion (0.00301 to 0.0447) and the slopes of the plots of rate constant against total alcohol concentration were shown to be linear in the fraction of base in agreement with the rate law [eqn. (3)].

$$k_{obs} = k_2[RO^-] \qquad (3)$$

It was assumed that eqn. (3) holds for the other alcohols in the series and the parameters are calculated from data at single pH values. The second-order rate constants are collected in Table 3.

The kinetic parameters for the hydrolysis of the substituted anilinotriazines obey Hammett relationships [eqns. (4) and (5)

$$\log k_{OH} = 1.06 \pm 0.15\sigma^0 - 0.064 \pm 0.054\ (r = 0.9709) \qquad (4)$$

$$pK_a = -2.13 \pm 0.16\sigma^0 + 10.92 \pm 0.06\ (r = 0.9919) \qquad (5)$$

and Fig. 2] against Exner's standard σ^0 parameters; regular Hammett σ and σ^- correlations give poorer fits.

The rate constants for attack of alkoxide ions on the *N*-methylanilinotriazine obey a Brønsted relationship [eqn. (6)] and this is illustrated in Fig. 3.

$$\log k_2 = 0.84 \pm 0.06\, pK_a^{ROH} - 10.89 \pm 0.87\ (r = 0.9886) \qquad (6)$$

Discussion

Reference to Tables 2 and 3 indicates that the second-order rate constants for the alkaline hydrolysis of (1; R = H and R = CH_3) are 1.09 and 0.245 $dm^3\ mol^{-1}\ s^{-1}$, respectively; alkaline hydrolysis therefore involves nucleophilic attack of the hydroxide ion on the neutral triazinyl dichloride substrate allowing for the small differences expected due to steric hindrance and inductive effects. This result together with the earlier data of Horrobin[3] and Ackermann and Dussy[4] unambiguously exclude the E1cB mechanism for the alkaline hydrolysis. An alternative formulation involving water attack on the anionic triazinyl species is additionally excluded as a major contributor compared with hydroxide ion attack on the neutral species because the water is a weaker nucleophile than hydroxide ion and the neutral species will be a stronger electrophile than the anion.

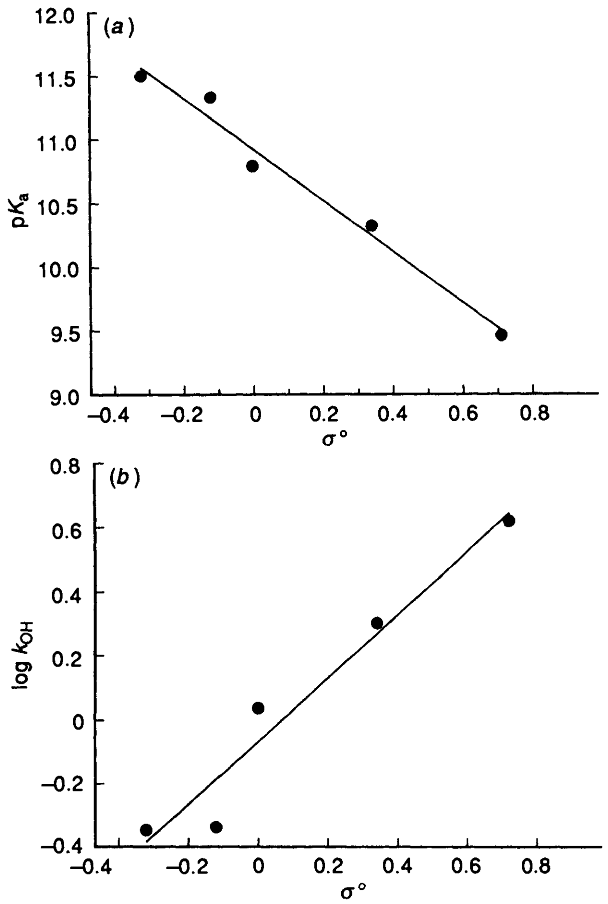


Fig. 2 Hammett dependence on σ^0 for k_{OH} and pK_a; data and conditions from Table 2

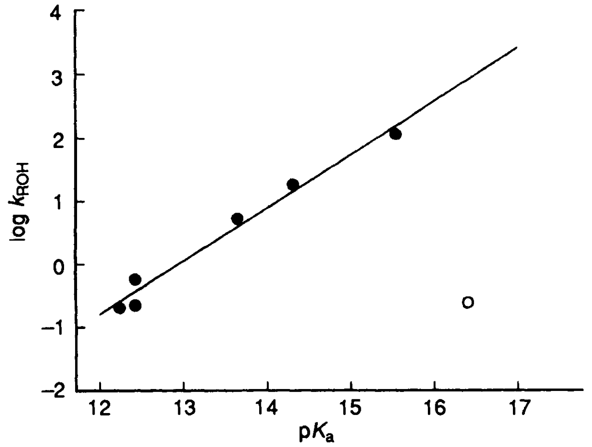


Fig. 3 Brønsted dependence of k_2 on the pK_a of the conjugate acid of the attacking alkoxide ion; data and conditions from Table 3; ○ refers to hydroxide ion

We are now in a good position to attribute the Hammett dependences of the system. The sensitivity of the pK_a to σ^0 is relatively large (−2.13) and is in the region that is expected for ionisation of an anilino proton.[13]

The sensitivity of k_{OH} to σ^0 (1.06) is relatively high and refers to charge development in the transition state for Meisenheimer

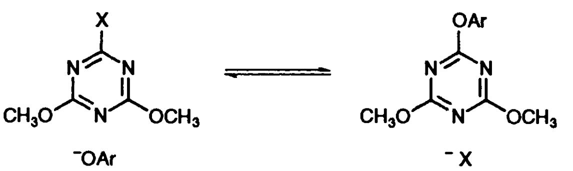
Table 3 Reaction of alkoxide ions with 2-(*N*-methylanilino)-4,6-dichloro-1,3,5-triazine[a]

Alcohol	pK_a^{ROH}	pH	N[b]	$k_{obs}/10^4\ s^{-1}$[c]	$k_2/dm^3\ mol^{-1}\ s^{-1}$	[Alcohol]/mol dm^{-3}[d]
$PhSO_2CH_2CH_2OH$	13.65	11.13–12.32	20	*e*	5.35	0.01–0.05
CCl_3CH_2OH	12.24	11.64	5	4.1–20.5	0.204	0.01–0.05
CF_3CH_2OH	12.43	12.20	5	2.2–21	0.582	0.01–0.1
Glucose	12.43	12.36	5	2.7–30	0.223	0.001–0.01
$ClCH_2CH_2OH$	14.31	10.82	5	5.9–30	18.2	0.1–0.5
Isosorbide	15.54	11.87	5	2.5–12.4	114	0.01–0.05
Water	16.4	10.2–12.99	11	0.519–268	0.245	—

[a] Wavelength for kinetic study 252 nm; conditions: 16% dioxane–water (v/v), 25 °C, ionic strength made up to 0.25 mol dm^{-3} with KCl. [b] Number of data points not including those from duplicate runs. [c] Range of rate constants obtained for the range of alcohol concentration employed. [d] Range of alcohol concentrations employed. [e] A range of base fractions were employed for this alcohol.

adduct formation. The observed magnitude of the ρ value can only arise from substantial development of charge adjacent to the anilino nitrogen and this is consistent with significant alteration of the homoaromatic nucleus. If charge were only developing at the carbon bearing the chlorine leaving atom, in the case for the example where bond formation is not far advanced, the system would insulate the charge from the anilino nitrogen by at least two atoms.

We have shown that the transfer of 4,6-dimethoxy-1,3,5-triazin-2-yl to substituted phenoxide ions has a Brønsted β_{eq} value of 1.55 [eqn. (7)].[1] It is reasonable that the β_{eq} value will be relatively insensitive to the 4,6-substituents on the triazinyl ring; moreover, results from the carbonyl acyl series of transfer reactions indicate that alkoxide ion and phenoxide ion fit similar Brønsted equations (except when solvation factors intervene for very basic alkoxides).[14] Given these assumptions it is possible to assign a Leffler parameter[15] α to the nucleophilic attack of alkoxide ion on the anilino dichlorotriazine using the value for β_{nuc} of 0.8 derived from the data in Table 3 and eqn. (5). The value of $\alpha = 0.8/1.55 = 0.52$ would indicate that the charge depletion on the attacking oxygen in the transition state for adduct formation is about 50% of the full charge change. Such an α value is consistent with substantial migration of charge into the aromatic ring as proposed from the effect on k_{OH} of change in polar substituent at the anilino function.



(7)

Perusal of Fig. 3 indicates that the hydroxide ion term is well below that expected from the linear corelation for the alkoxides. This could be due to the greater apparent steric bulk of the hydroxide ion caused by solvation. The possession of a relatively large ρ value (1.06) excludes the possibility that the desolvation of the nucleophile becomes rate limiting in this case. Carbohydrate oxyanions behave regularly and the reduced reactivity of the hydroxide ion means that for a given pH reaction with carbohydrate will predominate. Such a feature is most important technically in the reactive dyeing process.

Acknowledgements

J. M. J. W. thanks the SERC for a CASE award with Zeneca Specialties and the assistance of Mr. A. McKenzie is gratefully acknowledged in some of the kinetic measurements.

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Paper 4/04000G
Received 1*st July* 1994
Accepted 3*rd August* 1994