Bimolecular Nucleophilic Substitution on an Acetal †

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Bimolecular nucleophilic substitution at an acetal centre is identified for the first time, and the reaction characterised by a study of the second-order reactions of nucleophiles with methoxymethoxy-2,4-dinitrobenzene. The reaction is restricted to formaldehyde acetals with good (dinitrophenoxide) leaving groups, and shows a strikingly low sensitivity to the reactivity of the nucleophile: acetate is about half as reactive as hydroxide ion, and even the most effective nucleophiles (iodide, thiosulphate) are only a few times more reactive than solvent water. Reactions with nucleophilic anions are subject to positive specific salt effects, and an analysis based on the Setschenow equation has been developed. The results are interpreted in terms of the borderline S_N2 mechanism, with weak bonding of both nucleophile and leaving group in the transition state. The consequent build up of positive charge at the acetal centre explains the high secondary α-deuterium isotope effects observed for these reactions (5—16% per deuteron): this isotope effect cannot therefore safely be used to distinguish between concerted and carbonium ion mechanisms for enzyme catalysed glycosyl transfer reactions.

SUBSTITUTION reactions at acetal centres almost invariably involve dissociative processes. This is firmly established for specific acid catalysed hydrolysis, where there is strong evidence against the involvement of water or other nucleophiles in the transition state.[1-3] When the conjugate base of the acid is involved in the rate expression, the mechanism is considered to be classical general acid catalysis, with C–O bond breaking now concerted with protonation.[4,5] And in the rare cases where spontaneous hydrolysis is observed[4-6] a simple dissociative mechanism is preferred.[7]

Bimolecular nucleophilic substitution at the acetal centre is rarely, if ever, observed, for a number of reasons. The deactivating effect of the second heteroatom on the same carbon, well known for dihalogenomethanes,[8] presumably operates for acetals also, for the same mixture of steric and electronic reasons. Glycopyranosides will be particularly unreactive, because S_N2 reactions on six-membered rings are very slow.[8] And concerted displacements of alkoxide anions are not in any case to be expected because such leaving groups are not displaced from ethers even with very reactive centres. The alkaline hydrolysis of aryl glycosides is the only readily observed second-order reaction which leads to the cleavage of the glycosyl–oxygen bond. Here concerted displacements may be involved, but these are the result of neighbouring group participation occuring at the glycosidic centre when there is a hydroxy-group *trans* to the leaving group,[4] but leading, in at least some cases,[9,10] to aryl–oxygen fission when the relationship is cisoid. The 2-acetamido-group has a similar but larger effect on the spontaneous hydrolysis of the *p*-nitrophenyl glycoside of *N*-acetyl-β-D-glucosamine, and on the acid-catalysed hydrolysis of the methyl glycoside.[5,11]

These findings are of interest in connection with the possible role of aspartic acid-52 in the mechanism of action of lysozyme. There is general agreement[5,6] that glutamic acid-35 acts as a general acid, to assist the departure of the leaving group from a glycosidic centre of the polysaccharide substrate. But there is no agreement on a role for the aspartic acid also present (probably in the ionised form) in the active site. An early suggestion that the aspartate carboxylate group might act as a nucleophile has received little support. There is no evidence that a glycosyl enzyme is formed; Vernon[12] concluded, on the basis of an examination of molecular models of the enzyme substrate complex that such a reaction is unlikely; and the secondary deuterium isotope effect (k_H/k_D 1.11) observed[13] for the lysozyme-catalysed hydrolysis of a phenyl glucoside substrate is close to that expected for a dissociative mechanism.

This evidence is not conclusive. A glucosyl enzyme intermediate need not be long lived, and could escape detection, particularly if it were strained. And it is not possible to predict the secondary deuterium isotope effect for the nucleophilic reaction, because this reaction is not properly characterised.

In this paper we describe the reactions of nucleophiles with methoxymethoxy-2,4-dinitrobenzene, an acetal chosen to make the concerted nucleophilic displacement, of a good leaving group from a primary centre, as favourable a reaction as possible.

EXPERIMENTAL

Materials were mostly as described previously.[7,14] 2,4-Dinitroanisole was recrystallised from absolute ethanol. $H_2{}^{18}O$ (20.08 atom %) was obtained from Miles Laboratories. 1,2-Dimethoxyethane was refluxed with sodium until the metal remained bright (17 h), then distilled and stored over sodium wire. Liquid amines were distilled from KOH before use: solid compounds and hydrochlorides were recrystallised. *Ca.* 0.25M-H_2O_2 solution was made up by

† No reprints available.

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diluting commercial ' 100-volume ' material, and standardised by the iodine–thiosulphate method.

1-*Methoxymethoxy*-3,4-*dinitrobenzene* was prepared by the *general method* described previously for the synthesis of methyl 2-methoxymethoxybenzoates [14] with the following modification. Sodium hydride was freed from mineral oil by washing with n-pentane before use, and 1,2-dimethoxyethane used as solvent, allowing a much more concentrated phenol solution to be used. The yield of crude product was 91% after 21 h. The acetal was obtained as an oil by preparative t.l.c. ($CHCl_3$ on silica, pre-washed with AnalaR MeOH), δ 3.50 (3 H, s) and 5.28 (2 H, s) (OCH_2OCH_3) (Found: C, 41.9; H, 3.55; N, 12.05. $C_8H_8N_2O_6$ requires C, 42.1; H, 3.55; N, 12.3%).

1-*Methoxymethoxy*-2,4-*dinitrobenzene* was obtained by the same route (in dioxan under nitrogen) as a pale yellow solid (84% crude yield after 43 h). Recrystallised from $CHCl_3$–ether it had m.p. 92—93°, δ 3.54 (3 H, s), 5.40 (2 H, s), and 7.4—8.75 (3 H, m) (Found: C, 42.1; H, 3.6; N, 12.35%).

1-*Methoxy*[^{18}O]*methoxy*-2,4-*dinitrobenzene*.— 2,4-Dinitrophenol enriched with ^{18}O at the phenolic oxygen was prepared from $H_2{}^{18}O$ and 1-fluoro-2,4-dinitrobenzene,[15] and used to synthesise the labelled acetal, as described above.

Kinetic Methods.—The release of the dinitrophenolate anions was followed spectrophotometrically in the usual way,[7] at 39.00 ± 0.05° in water, generally maintained at ionic strength 1.0M. In no case was any build up of an intermediate apparent by u.v., and the final spectrum was always that of the dinitrophenolate anion. Some reactions of 1-methoxymethoxy-3,4-dinitrobenzene were followed by the initial rate method. Agreement was within 2% with rate constants obtained by following the reaction for >3 half-lives when both methods were used.

Position of Bond Cleavage.—A nucleophile can attack 1-methoxymethoxy-2,4-dinitrobenzene at either the acetal or the aromatic *ipso*-carbon atom. For an indication of the likely importance of nucleophilic aromatic substitution for a given nucleophile, we measured the rate of release of 2,4-dinitrophenolate (or other species absorbing at 362 nm) from 2,4-dinitroanisole, under the conditions used for the acetal. If no significant reaction was observed for the anisole (<1% after one acetal half-life), we concluded that aromatic substitution could be neglected. This was the case for all the nucleophiles used, apart from hydroxide, aniline, and methylamine. With aniline and methylamine the products of attack at the two positions are different, and the ratio of dinitroaniline to dinitrophenol produced is readily measured.[15] (The extinction coefficients of *N*-methyl-2,4-dinitroaniline and 2,4-dinitrophenolate at 400 nm are almost identical under the conditions of our experiments.)

Attack by hydroxide leads to 2,4-dinitrophenolate in either case, and the position of bond cleavage was determined by an isotopic method, based on one we have used before.[15] Some modification was necessary because of the low solubility of the acetal in water.

A solution of 1-methoxy[^{18}O]methoxy-2,4-dinitrobenzene (*ca.* 4 mg) in dioxan (2 ml) was added with magnetic stirring to a buffer solution (400 ml) of the same composition as used in the corresponding kinetic run, equilibrated at 39° for at least 1 h. After at least 10 half lives at 39° the solution was acidified with concentrated HCl and extracted with ether. The ether was evaporated and 2,4-dinitrophenol recrystallised from aqueous ethanol. The mass spectrum of the recovered phenol was recorded at least three and usually five times, and the $m + 2/m$ ratio of the strong molecular ion peak at *m/e* 184 used to calculate the percentage of phenol oxygen atoms remaining from the acetal. In stronger (1M) NaOH solutions a small correction was necessary to take into account a slow loss of label from 2,4-dinitro[^{18}O]phenolate.

RESULTS

The data given in Tables 1—3 show how the rates of hydrolysis of three related acetals are affected by the addition of substantial quantities (up to 1M) of various nucleophiles. The data in Table 1 are for the hydrolysis of 2-(3,4-dinitrophenoxy)tetrahydropyran,[7] which is expected to hydrolyse exclusively by the unimolecular decomposition mechanism discussed in the previous paper.[7] The main features of these results are: (a) the fastest run, with 1M-$Na_2S_2O_3$, is <35% faster than the slowest; (b) at constant ionic strength (1M) the effects of salts on the rate of hydrolysis are in the order $Cl^- \simeq S_2O_3{}^{2-} > N_3^- > I^- \simeq OH^- \simeq ClO_4^-$; (c) the rate constants increase with increasing ionic strength, as expected for this type of S_N1 reaction: but the effects are very small; (d) increasing the concentration of methylamine buffer from 0.1 to 0.5M (at constant pH and ionic strength) *decreases* the observed rate of hydrolysis by *ca.* 10%. (A similar effect is found with TRIS buffer.[7])

TABLE 1

Effects of added nucleophiles on the rate of hydrolysis of 2-(3,4-dinitrophenoxy)tetrahydropyran at 39°

Conditions	Ionic strength	k_{obs}/min^{-1}
1M-NaOH	1.0	1.19
0.01M-NaOH + $NaClO_4$ (0.99M)	1.0	1.20
0.01M-NaOH + NaI (0.99M)	1.0	1.21
0.01M-NaOH + NaN_3	1.0	1.32
0.01M-NaOH + KCl (0.99M)	1.0	1.37
0.01M-NaOH + $Na_2S_2O_3$ (0.33M)	1.0	1.39
0.01M-NaOH	0.01	1.04
0.01M-NaOH + $Na_2S_2O_3$ (0.21M)	0.64	1.28
0.01M-NaOH + $Na_2S_2O_3$ (0.16M)	0.50	1.11
0.1M-$MeNH_2$ buffer, pH 10.74	1.0 (KCl)	1.30
0.5M-$MeNH_2$ buffer, pH 10.74	1.0 (KCl)	1.25

TABLE 2

Effects of added nucleophiles on the rate of hydrolysis of 1-methoxymethoxy-3,4-dinitrobenzene, at 39° and ionic strength 1.0M

Conditions	10^4k_{obs}/min^{-1}
0.01M-NaOH + KCl (0.99M)	3.65
0.001M-NaOH + KCl	3.15
0.01M NaOH + KI (0.99M)	7.57
0.01M NaOH + NaN_3 (0.99M)	7.29
1M-NaOH	64.5
0.2M-$MeNH_2$ buffer, pH 10.74, + KCl (0.933M)	100

Table 2 shows the effects of several of the same nucleophiles on the much slower hydrolysis of 1-methoxymethoxy-3,4-dinitrobenzene. Here the effects are larger, and in the order $HO^- \gg I^- > N_3^- > Cl^-$. The order for the weakly basic nucleophiles is that of their conventional nucleophilicity towards saturated carbon. The much larger rate constants for hydroxide and methylamine suggest that these nucleophiles are reacting at aromatic carbon, and this was confirmed for the amine by acidification of the product solution.[15]

[15] A. J. Kirby and M. Younas, *J. Chem. Soc.* (*B*), 1970, 1165.

Table 3 records the much more extensive data for the reactions of nucleophiles with 1-methoxymethoxy-2,4-dinitrobenzene. The rate of hydrolysis [3.68×10^{-2} min^{-1} at ionic strength 1.0 ($NaClO_4$) and 39°] is independent of pH between 4 and 11, with only weak acid catalysis, and a significant alkaline hydrolysis reaction at high pH. Standard conditions were 0.01M-NaOH, made up to ionic strength 1.0M with the nucleophile and added $NaClO_4$ if necessary. Self-buffering solutions of nucleophiles with pK_a values in the region 4—11 were used in a number of cases, and the results obtained were not significantly different when both sets of conditions were used for the same nucleophile. We summarise the salient features of these data under the letter headings used in Table 3, before going on to describe our method of analysis of the results.

(a) Ionic strength effects are small. As the concentration of $NaClO_4$ in 0.01M-NaOH is increased from zero to 0.99M, the observed rate of hydrolysis decreases by *ca.* 15% at each of the three temperatures used. Using NaCl a larger, positive effect is observed.

(b),(c) The observed rate of release of 2,4-dinitrophenolate is increased by all anionic nucleophiles used, with the exception of perchlorate. Effects are larger for anions known to be better nucleophiles towards saturated carbon. The most effective anions are thiosulphate, which at the highest concentration used (0.33M) increases the rate of hydrolysis by a factor of five, and hydroperoxide. Plots of k_{obs} against anion concentration are generally curved (Figure 1) and were analysed as described below. The data for acetate at different buffer ratios show clearly that the

TABLE 3

Pseudo-first-order rate constants for the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene ($10^2 k_{obs}/min^{-1}$) in the presence of added nucleophiles

(a) Ionic strength effects, in 0.01M-NaOH

[Salt]/M	T/°C		
$NaClO_4$	30.0	39.0	50.2
0.32	1.52	4.30	13.9
0.66	1.44	4.11	13.2
0.99	1.28	3.68	11.8
NaCl			
0		4.30	
0.10		4.73	
0.40		5.85	
0.70		6.77	
0.99		7.57	

(b) Effects of added nucleophiles in 0.01M NaOH, at 39°, ionic strength 1.0M ($NaClO_4$)

[Salt]/M	NaCl	KCl	NaN_3	KF	NaOH [a]		NaOD [a]
0	3.68		3.68		3.68		3.12 [b]
0.10	3.96		4.47		4.41		3.81
0.40	4.94		6.89		6.95		
0.70	6.16		9.44		11.1		
0.99	7.57	7.46	12.1	6.56	16.5 [c]		
	NaOAc *		NaI (30°)		NaI *	KI	NaI (50.2°)
0	3.68		1.28		3.68		11.8
0.10			1.64		4.57		14.7
0.20	4.07		2.01		5.59		17.9
0.50	4.74		3.08		8.59		26.9
0.60	4.99						
0.99	6.10		5.14		13.7	14.0	40.9
	Na_2CO_3*		$Na_2S_2O_3$*				
0	3.68		3.68				
0.08	4.30		5.56				
0.16	5.00		7.82				
0.24	6.10		11.5				
0.33	8.07		17.3				

(c) Effects of anionic nucleophiles in buffers, at 39°

Buffer	% Free base (pH)	[Free base]/M	$10^2 k_{obs}/min^{-1}$
Acetate *	25 (4.22)	0.50	3.76
Acetate *	50 (4.70)	0.10	3.75
Acetate *	50 (4.70)	0.25	3.91
Acetate *	50 (4.70)	0.50	4.38
Phosphate *	33 (6.18)	0.04	4.01
Phosphate *	33 (6.18)	0.10	4.76
Phosphate *	33 (6.18)	0.20	6.90
Phosphate *	50 (6.53)	0.05	3.95
Phosphate *	50 (6.53)	0.15	4.95
Phosphate *	50 (6.53)	0.25	6.86
Phosphate *	75 (6.96)	0.075	4.12
Phosphate *	75 (6.96)	0.15	4.73
Phosphate *	75 (6.96)	0.30	6.89
Phosphate *	75 (6.96)	0.075	7.33 [d]
Phosphate *	75 (6.66)	0.15	7.31 [d]
Hydroperoxide *	10 (10.59)	0.012 5	8.05
Hydroperoxide *	10 (10.59)	0.025	12.8

TABLE 3 (*Continued*)

(d) Effects of neutral nucleophiles at 39°, ionic strength 1.0M

Nucleophile	% Free base (pH)	[Free base]/ M	Salt	10^2 k_{obs}/ min^{-1}
None	[b]		$NaClO_4$	3.64
Aniline	100 [b]	0.30	$NaClO_4$	3.89
Pyridine *	100 [b]	0.25	$NaClO_4$	3.63
Thiourea *	100 [b]	0.30	$NaClO_4$	5.33
Thiourea *	100 [b]	0.60	$NaClO_4$	7.03
Thiourea *	100 [b]	1.0	$NaClO_4$	9.32
None	[b]		KCl	7.46
4-Aminopyridine *	50(9.19)	0.30	KCl	7.54
Methylamine	60(10.61)	0.06	KCl	9.27 [a]
Methylamine	60(10.61)	0.12	KCl	11.2 [a]
Methylamine	60(10.61)	0.30	KCl	16.6 [a]
None	[b]		NaCl	7.57
Imidazole *	75(7.39)	0.75	NaCl	7.24
Triethylenediamine *	25(7.85)	0.062 5	NaCl	7.95
Triethylenediamine *	25(7.85)	0.125	NaCl	8.41
Triethylenediamine *	25(7.85)	0.187 5	NaCl	8.88
Triethylenediamine *	25(7.85)	0.25	NaCl	9.32
Triethylenediamine	50(8.33)	0.50	NaCl	11.2
Triethylenediamine	75(8.80)	0.187 5	NaCl	8.96
Triethylenediamine	75(8.80)	0.375	NaCl	10.3
Triethylenediamine	75(8.80)	0.562 5	NaCl	11.8
Triethylenediamine	75(8.80)	0.75	NaCl	13.3

* No significant reaction under these conditions with 2,4-dinitroanisole.

[a] Not corrected for attack on ring. [b] 0.01M-NaOH (NaOD): for $k_o^{NaClO_4}$ $k_H/k_D = 1.18 \pm 0.04$. [c] 1.0M-NaOH. [d] Ionic strength 1M (KCl).

hydrolysis reaction is not general acid catalysed. This is consistent with the observation that k_{obs} in 1M-HCl is 11×10^{-2} dm^3 mol^{-1} min^{-1}, little larger than the value in 1M-KCl (Table 3). Whether this represents weak acid catalysis or a specific salt effect of the hydroxonium ion cannot be determined without more extensive data, but cation effects are clearly small.

(d) Methylamine shows a simple first-order dependence on amine concentration, but the reaction is entirely accounted for by the amount of *N*-methyl-2,4-dinitroaniline produced. The small effect of 0.30M-aniline similarly represents aromatic nucleophilic substitution. Imidazole and pyridine have only small negative effects on the rate of release of 2,4-dinitrophenolate, and even the basic 4-aminopyridine is not significantly reactive. Triethylenediamine, on the other hand, shows a simple first-order dependence on amine concentration which cannot be due to aromatic substitution, since the initial product is known to be transparent at 362 nm, and stable under the conditions.[15,16] Only the free base reacts. A simple second-order reaction is also observed with thiourea.

Analysis of Data for Reactions with Anionic Nucleophiles.—The non-linear effects of changing the anion used to maintain ionic strength cannot reasonably be explained in terms of specific salt effects on the spontaneous hydrolysis reaction. The resulting increases in hydrolysis rate are larger than expected for electrolyte effects on an organic reaction in water. For example the specific salt effects observed for the hydrolysis of Bu^tCl [17] and 2-(3,4-dinitrophenoxy)tetrahydrofuran (Table 1) are much smaller. They are also qualitatively quite different. Typically for S_N1 reactions the effects of salts (which are almost entirely anion effects) are in the order [18] $ClO_4^- > Cl^- >$ no salt $>$ $F > OH^-$ (measured in mixed solvents containing *ca.* 50% of organic solvent). The very small effects on the hydrolysis of 2-(3,4-dinitrophenoxy)tetrahydrofuran in water

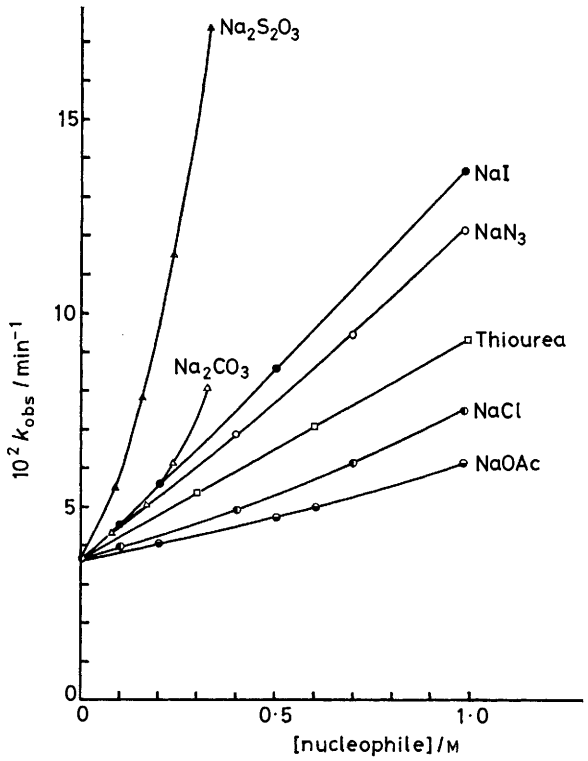


FIGURE 1 Plot of pseudo-first-order rate constants for the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene in the presence of various nucleophiles, against the concentration of the nucleophile. Data at 39° and ionic strength 1.0M ($NaClO_4$) from Table 3

(Table 1) are similar except that the positions of chloride and perchlorate are reversed. But both sequences are

[16] A. J. Kirby and A. G. Varvoglis, *J. Chem. Soc.* (*B*), 1968, 135.
[17] G. A. Clarke and R. W. Taft, *J. Amer. Chem. Soc.*, 1962, **84**, *2195*.
[18] C. A. Bunton, T. W. Del Pesco, A. M. Dunlop, and K-U. Yang, *J. Org. Chem.*, 1971, **36**, 887.

quite different from that found for the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene where the observed order is the order of nucleophilicity towards saturated carbon (see below). Finally, good neutral nucleophiles, present in concentrations too low to cause significant medium effects (50% dioxan *decreases* the rate in 0.01M-NaOH from 4.3×10^{-2} to 1.02×10^{-2} min^{-1}) increase the rate of appearance of 2,4-dinitrophenoxide to about the same extent as anions of similar nucleophilicity.

We conclude that added nucleophiles catalyse the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene. The rate constant observed for the appearance of 2,4-dinitrophenoxide must therefore be composed of contributions from catalysed and spontaneous reactions [equation (1)

$$k_{obs} = k_0^{NaClO_4} + k_N[N] \quad (1)$$

where $k_0^{NaClO_4}$ is the rate constant in 0.01M-NaOH in the absence of added nucleophile (ionic strength made up with $NaClO_4$), and k_N is the second-order rate constant for the reaction of the acetal with the nucleophile, N]. The observed curvature (Figure 1) must then be due to specific salt effects on either or both of these processes.

Since salt effects on both ground state and transition state are likely to be important [17,18] we expect at least quantitatively different behaviour for the spontaneous and uncatalysed reactions. A very detailed treatment is not warranted by the limited set of data available, but some quantitative treatment is essential, to allow a sensible comparison of the reactivities of different nucleophiles, and thus an opportunity to characterise the reaction more closely. We have therefore used two approximations, assuming that only the spontaneous hydrolysis or alternatively, that only the catalysed reaction, is sensitive to specific salt effects. The results of the alternative treatments diverge most where the second-order plots show most curvature, but not so far as to create difficulties of interpretation.

Specific salt effects on activity coefficients of uncharged solutes [19,20] and transition states [21] are described by the empirical Setschenow equation.[19] Applied to rates [17] this can be written as (2) where c_i is the concentration of any ion,

$$\log k/k^0 = \sum_i B_i c_i \quad (2)$$

B_i a constant (the sensitivity parameter), and k^0 the (hypothetical) rate in the absence of all ions.

(i) *Assuming that k_0 depends on Ionic Strength only, but that k_N is sensitive to Specific Salt Effects.*—Equation (2) describes k_N, and $k_0^{NaClO_4}$ is the rate constant for the spontaneous reaction under all conditions at ionic strength 1.0. Combining equations (1) and (2) gives (3), for sodium salts

$$\log (k_{obs} - k_0^{NaClO_4}) - \log [N] = \log k_N^{ClO_4} + (B_N - B_{ClO_4})[N] \quad (3)$$

of monoanions, where $k_N^{ClO_4}$ is the (hypothetical) second-order rate constant for the reaction with N in 0.01M-NaOH, ionic strength 1.0M ($NaClO_4$). Similar reasoning for sodium salts of dianions gives (4). When the left hand side of

$$\log (k_{obs} - k_0^{NaClO_4}) - \log [N] = \log k_N^{ClO_4} + (B_N - 3B_{ClO_4} - B_{Na})[N] \quad (4)$$

equation (3) or (4) is plotted against [N], acceptable straight lines ($r > 0.998$) are obtained. A typical example is the lowest curve of Figure 2. Least squares analysis [21] gives values of $k_N^{ClO_4}$, k_N^N (the second-order rate constant for the catalytic reaction in 0.01M-NaOH made up to ionic strength 1.0M with NaN or Na_2N only) and, for monoanions, $B_N - B_{ClO_4}$. These values appear in Table 4.

TABLE 4

Constants derived from the data of Table 3 (dm^3 mol^{-1} min^{-1})

Nucleophile	$10^2 k_N^{ClO_4}$	$10^2 k_N^N$	$(B_N - B_{ClO_4})$ [a]	$10^2 k_N^M$	$(K_N - K_{ClO_4})$ [a]
AcO^-	1.8	2.4	0.13	4.3	−0.30
F^-		2.9 [b]			
Cl^-	2.7	3.9	0.17	6.4	−0.47
N_3^-	7.7	8.5	0.041	10	−0.32
I^- (30.0°)	3.5 [c]	3.9 [d]	0.043		
I^- (38.0°)	9.4 [c]	10 [d]	0.033	12	−0.32
I^- (50.2°)	2.8 [c]	29 [d]	0.010		
$CO^{2}{}_3^-$	5.1	13			
$S_2O_3^{2-}$	17	42			
$H_2PO_4^-$		3.3			
HPO_4^{2-}		9.8			
HO_2^-	364 ± 9				
HO^-	3.8	6.1	0.21		−0.92
Triethylenediamine	7.7 ± 0.3				
Thiourea	5.46 ± 0.04				

[a] Units are dm^3 mol^{-1}. [b] Calculated from a single value in 0.01M-NaOH, 0.99M-KF: NaF and $KClO_4$ are too insoluble in water for mixtures of KF and $NaClO_4$ to be used. [c] These results give $\Delta H^‡$ 19.6 ± 0.1 kcal mol^{-1}, $\Delta S^‡ = -8.5 \pm 0.5$ cal K^{-1} mol^{-1}. [d] These results give $\Delta H^‡ = 18.9 \pm 0.2$ kcal mol^{-1}, $\Delta S^‡ = -11 \pm 2$ cal K^{-1} mol^{-1}.

(ii) *Assuming that k_N depends on Ionic Strength only, but k_0 is sensitive to Specific Salt Effects, according to Equation* (2).—Equation (1) becomes (5) where k_N^M is the constant

$$k_{obs} = k_0 + k_N^M[N] \quad (5a)$$

$$\log (k_{obs} - k_0) - \log [N] = \log k_N^M \quad (5b)$$

value of k_N at ionic strength 1M. If k_0 is given by equation (2), for sodium salts of monoanions equation (5) becomes (6)

$$\log k_0 = \log k_0^{NaClO_4} + (K_N - K_{ClO_4})[N] \quad (6)$$

using K_t for the (different) Setschenow constant for the spontaneous reaction. A range of values for $(K_N - K_{ClO_4})$ was used in equation (6) to generate values of k_0: these values were used to plot the left hand side of equation (5) against [N], which gave a set of straight lines (Figure 2). The line with zero slope defines the 'best' value of $(K_N - K_{ClO_4})$, and this was refined to the nearest 0.01 l mol^{-1} by least squares analysis.[21] The values of $(K_N - K_{ClO_4})$ and k_N^M which account for the curvature of the

[19] J. Setschenow, *Ann. Chim. Phys.*, 1891, **25**, 226.
[20] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **51**, 119.
[21] Hewlett–Packard Calculator Stat-Pac, Vol. 1, IV-10.

second-order plots of Figure 1 in terms of specific salt effects on k_0 are listed in Table 4.

This treatment fails for sodium salts of dianions, since the lines corresponding to those of Figure 2 become increasingly curved as the slope approaches zero. This is not

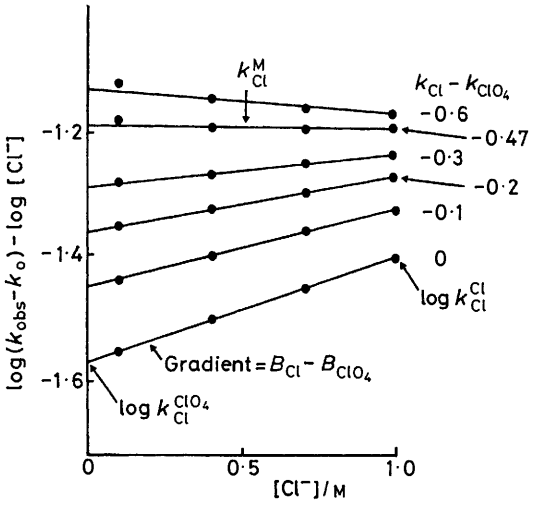


FIGURE 2 Typical plots used in the analysis of specific salt effects according to equations (3) and (6). See text

surprising, if, as seems likely, both k_0 and k_N are sensitive to specific salt effects.

No errors are quoted for the data (Table 4) derived from these treatments, because the approximations involved undoubtedly far outweigh the standard errors from the least squares calculations.

No special significance should be attached to the values of $(B_N - B_{ClO_4})$ and $(K_N - K_{ClO_4})$, except that they are a convenient measure of the magnitude of the specific salt effects of monoanions N relative to those of perchlorate. These are clearly least for iodide and greatest for chloride ion, as found also for anion effects on the k_0 reaction of 2-(3,4-dinitrophenoxy)tetrahydropyran (see above, and Table 1). The nature of the cation present (Na or K) has a negligible effect on the reaction [see data for KI, KCl in Table 3(b)].

Both treatments fail with phosphate buffers, where three different anions are present in most cases. But when the ionic strength is brought to 1.0M by using the maximum concentration of each buffer (no $NaClO_4$ present) the rate of release of 2,4-dinitrophenolate is a linear function (r 0.999) of the mole fraction of phosphate dianion. The rate constants quoted in Table 4 are the intercepts of this plot at 100% monoanion and 100% dianion, respectively.

The α-effect [22] nucleophile hydroperoxide anion causes a dramatic increase in the rate of hydrolysis of the acetal. The rate of release of 2,4-dinitrophenolate from 2,4-dinitroanisole under the same conditions [0.25M-H_2O_2, 10% free base; 39°; ionic strength 1.0M ($NaClO_4$)] is scarcely detectable after 10 acetal half lives (at least 5 000 times slower), so aromatic nucleophilic substitution is not likely. (Where the S_NAr reaction *is* observed, with methylamine and hydroxide, the rates are very similar for the acetal and the anisole.) At the low concentrations of hydroperoxide anion required for conveniently measureable rates, k_{obs} is linear in hydroperoxide concentration (r 0.999 for three data sets).

We looked for similar reactions with α-effect amines, but hydrazine and hydroxylamine showed side reactions; the observed absorbances at 362 nm first increasing rapidly, then decreasing. Product analysis showed that the predominant reaction was aromatic nucleophilic substitution, so no detailed analysis of these results was undertaken. Similar results were obtained with thioglycolate and thiolacetate anions.

Hydroxide Reaction.—The results of the isotopic analysis on 2,4-dinitrophenol produced on hydrolysis of 1-methoxy-[^{18}O]methoxy-2,4-dinitrobenzene in natural abundance water containing various concentrations of NaOH are shown in Table 5. When the labelled phenol was incubated

TABLE 5

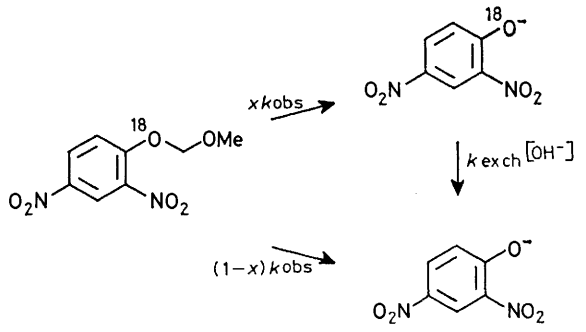
Isotopic analysis of 2,4-dinitrophenol formed on hydrolysis of 1-methoxy[^{18}O]methoxy-2,4-dinitrobenzene at 39° and ionic strength 1.0M ($NaClO_4$)

Conditions	Incubation time (min)	^{18}O (%) [a]	Acetal C–O cleavage (%) Uncorrected	Corrected [b]
0.01M-NaOH	210	20.0 ± 0.4	98 ± 4	98 ± 4
0.7M-NaOH	75	12.6 ± 0.4	60 ± 3	66 ± 5
1.0M-NaOH	60	11.2 ± 0.4	52 ± 3	59 ± 5
Enriched phenol,[c]	0	20.4 ± 0.3		
in 1.0M-NaOH	60	18.1 ± 0.2		

[a] By mass spectrometry (see text). 100 × intensity ratio ratio $(m + 2) : (m + 2) + m$ peaks. [b] Corrected for slow loss of label from enriched phenol. [c] Natural abundance phenol gives 1.09 ± 0.04 atom %.

in 1M-NaOH for 1 h at 39° the enrichment was found to have decreased by 11%. This presumably represents an oxygen-exchange reaction of 2,4-dinitrophenolate which can be assigned a rate constant k_{exch} of 2×10^{-3} dm^3 mol^{-1} min^{-1} under these conditions.

The results were therefore analysed according to the Scheme. Values of x, the true fraction of acetal C–O



SCHEME

cleavage, were obtained from the crude value (Table 5), measured k_{obs} [Table 3(b)], k_{exch}, and the time of incubation, using the usual formulae [23] for consecutive reactions.

As expected, the second-order rate constants obtained, $k_2 = (1 - x)k_{obs}/[OH^-]$ and $k_{OH} = (xk_{obs} - k_0^{NaClO_4})/[OH^-]$ are both subject to specific salt effects. To isolate the effects on the aromatic nucleophilic substitution reaction we examined the hydrolysis of 2,4-dinitroanisole under similar conditions.

[22] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, 1962, **84**, 16.

[23] G. W. Pratt, 'Gas Kinetics', Wiley, New York, 1969, pp. 33—39.

When the pseudo-first-order rate constants for the reaction of hydroxide ion with 2,4-dinitroanisole are plotted against the concentration of OH^- at ionic strength 1.0M, a (concave upwards) curve is obtained, which might suggest a greater than first-order dependence on hydroxide ion concentration. However, a different curve is obtained when a different salt is used to bring the ionic strength to 1M, and the derived second-order plots of $k_{obs}/[OH^-]$ against $[OH^-]$ are in most cases also curved. This suggests that the curvature is a result of specific salt effects, and indeed the data are correlated, for all those salts used ($NaClO_4$, NaCl, KCl) by equation (2). Plotting log $(k_{obs}/[OH^-])$ against $[OH^-]$ gives good straight lines (r 0.999 in each case) and the intercepts at $[OH^-]$ 0 and 1M give values of of k_{OH} in 1M-salt or -NaOH (Table 6). The order of anion

TABLE 6

Constants for the alkaline hydrolysis of 2,4-dinitroanisole at 39°, ionic strength 1.0M

Salt	$10^2 k_2$/dm^3 mol^{-1} min^{-1}	ΔB/dm^3 mol^{-1}	
$NaClO_4$	5.13 ± 0.05 [a]	$(B_{OH} - B_{ClO_4})$	0.37 ± 0.01
NaCl	8.3 ± 0.1 [a]	$(B_{OH} - B_{Cl})$	0.16 ± 0.01
KCl	9.85 ± 0.03 [a]	$(B_K - B_{Na})$	0.073 ± 0.005
NaOH	11.91 ± 0.03 [b]		

[a] Standard error from least squares analysis. [b] Error from the variation in log k_2^{NaOH} from three correlations.

effects is $OH > Cl > ClO_4$, and cation effects (K > Na) are also significant. Bunton [24] found the same order, for both cations and anions, in a detailed study of the influence of salts on the S_NAr reactions of hydroxide and thiophenoxide with 1-chloro-2,4-dinitrobenzene in water. The relationship between the second-order rate constants and the concentrations of added salts was approximately logarithmic, as found here.

The rate constants for acetal C–O cleavage were analysed by the two methods discussed above, used for the data for other anions, and the results appear in Table 4. The precision of the results for hydroxide is lower than for reactions with other anions, since more operations are involved in their derivation, and since the specific salt effects of hydroxide are larger than those of any other monoanion studied. Nevertheless it is reassuring that the values obtained fit the pattern observed for all the other nucleophiles listed in Table 4.

Secondary Deuterium Isotope Effects.—1-Methoxy[$^2H_2$]-methoxy-2,4-dinitrobenzene was prepared as described above for the protio-compound, using $MeOCD_2Cl$.[25] The product contained 33% of the [$^2H_5$]compound, CD_3OCD_2OAr (by mass spectrometry and n.m.r.), even though a large excess of CH_3OH was used in the preparation: possibly because CD_2O, supplied by Merck as a 30% solution in D_2O, with 11% [$^2H_4$]methanol added as stabiliser, is present to a substantial extent as CD_3OCD_2OD, which is converted to the chloride faster than it exchanges the methoxy-group. Since we expected a relatively small isotope effect for the CD_2 group, it was important to establish whether isotopic substitution at the methyl group affects the rates of reaction at the methylene centre. So we prepared also 1-[$^2H_4$]methoxymethoxy-2,4-dinitrobenzene, using [$^2H_4$]methanol and CH_2O. This contained 26% of the all-protio-compound: clearly the CH_3OH in the formalin solution affects this preparation exactly as before. The results of experiments with the isotopically substituted acetals are summarised in Table 7.

Isotopic substitution at the methyl group produces small, irregular effects (Table 7), slightly outside experimental error; but since the CD_2 compound is only 33% deuteriated at the methyl group we conclude that the consequent effects on reactivity can be neglected. On the

TABLE 7

Secondary deuterium isotope effects for the reactions of nucleophiles with 1-methoxymethoxy-2,4-dinitrobenzene, at 39° and ionic strength 1.0M [a]

	$10^2 k_2$/dm^3 mol^{-1} min^{-1} for reaction with				
	H_2O [b]	Thiourea [c]	Triethylenediamine [c]	NaI [c]	NaOAc [d]
CD_3OCH_2OAr [e]	3.80 ± 0.13 [f]	5.31 ± 0.05		10.37 ± 0.1	
CH_3OCH_2OAr	3.68 ± 0.02	5.54 ± 0.02	8.76 ± 0.07	10.45 ± 0.03	1.73 ± 0.01 [h] 2.43 ± 0.21 [i]
CH_3OCD_2OAr [g]	2.97 ± 0.02	4.35 ± 0.04	7.92 ± 0.015	8.00 ± 0.08	1.29 ± 0.02 [h] 1.87 ± 0.02 [i]
k_{CH_2}/k_{CD_2}	1.24 ± 0.02	1.27 ± 0.02	1.11 ± 0.03	1.31 ± 0.02	1.35 ± 0.02 [h] 1.30 ± 0.02 [i]
k_H/k_D [j]	1.11	1.13	1.05	1.14	1.16 [h] 1.14 [i]

[a] Conditions as for Table 3. [b] k_0/min^{-1}. [c] From linear second-order plot, with at least six points. [d] Curved second-order plots, treated as described in text. [e] 26% CH_3OCH_2OAr. See Experimental section. [f] Mean of two measurements. [g] 33% CD_3OCD_2OAr. See Experimental section. [h] $10^2 k_N^{ClO_4}$. [i] $10^2 k_N^N$. [j] Isotope effect per deuteron, $(k_{CH_2}/k_{CD_2})^{\frac{1}{2}}$.

When the corrected second-order rate constants for the S_NAr reaction of 1-methoxymethoxy-2,4-dinitrobenzene were treated in this way, we obtained values of $(1 - x)k_{obs} = k_2$ as follows: $k_2^{NaClO_4} = (3 \pm 2) \times 10^{-2}$; $k_2^{NaOH} = (6.8 \pm 0.8) \times 10^{-2}$ dm^3 mol^{-1} min^{-1}; and $(B_{OH} - B_{ClO_4}) = 0.3 \pm 0.3$ dm^3 mol^{-1}. The results are necessarily imprecise, being based on measurements at only two hydroxide ion concentrations, but suffice to show that the results are very similar to (rate constants *ca.* 60% of) those found for 2,4-dinitroanisole.

[24] C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5965.

other hand, substantial deuterium isotope effects are observed for substitution at the methylene group, ranging from 12—18% per deuteron $(k_{CH_2}/k_{CD_2})^{\frac{1}{2}}$, decreasing slightly over the series acetate > iodide > thiourea > water, down to only 5% for triethylenediamine. The data for iodide gave almost linear second order plots (r >0.997), and were treated accordingly. The more pronounced curvature of the corresponding plots for acetate necessitated the more complex treatment (i) above. The values for $k_N^{ClO_4}$ and k_N^N give similar isotope effects.

[25] T. C. Jones and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 4863.

Products of Nucleophilic Attack.—Although there is no doubt that the reaction we are measuring involves attack at the acetal centre, we need specific evidence that the nucleophiles used (Table 4) do actually act as nucleophiles, rather than as general bases, or simply *via* specific salt effects on the hydrolysis reaction. We therefore examined the products of reaction with one nucleophile by n.m.r.

In most cases the initial product of displacement of 2,4-dinitrophenoxide from 1-methoxymethoxy-2,4-dinitrobenzene is expected to be itself a reactive compound. We chose to look at the reaction with thiosulphate, on the grounds that the Bunte salt (1) produced should be relatively stable to hydrolysis. When 1-methoxymethoxy-

$$CH_3OCH_2OAr + SSO_3^{2-} \longrightarrow CH_3OCH_2SSO_3^- + ArO^- \quad (1)$$

2,4-dinitrobenzene (20 mg in 36 μl of CD_3CN) was added to carbonate buffer [1 ml of 0.136M-carbonate–DCO_3^-; 10% in free base, in D_2O containing 30% CD_3CN (final concentration)], the disappearance of the acetal signals was readily followed by n.m.r. (Varian HA 100 instrument, locked onto Bu^tOH). The singlets at δ 3.52 and 5.48 from the CH_3 and CH_2 protons of the methoxymethyl group gradually disappeared, and new singlets at δ 3.32 (MeOD) and 4.77 [$CH_2(OD)_2$] appeared at the same rate. Rate constants could not be measured under these conditions, which are a compromise dictated by the need to dissolve sufficient acetal to give good signals (more organic solvent) and the requirement that the results be relevant to the kinetic measurements, done in water. Under the conditions used, strong signals of reaction products were obtained, but some acetal precipitated at the start of the reaction, to dissolve as reaction proceeded. The *rates* in 30% acetonitrile were measured by the u.v. method, at much lower concentrations of acetal.

When the experiment described above was repeated (10% free base carbonate buffer in D_2O, exactly as described) with 0.2M-$Na_2S_2O_3$ added, the rate of disappearance of the acetal was almost exactly doubled (measured rates 2.04×10^{-2} and 4.24×10^{-2} s^{-1} at 39°). The acetal peaks disappeared and the CH_3OD and $CH_2(OD)_2$ peaks appeared as before, but two new singlets also appeared, at δ 3.43 and 5.18. These can only be due to the Bunte salt, which turns out not to be hydrolysed at a significant rate under these conditions. Relative peak heights show that the Bunte salt accounts for 62% of the total reaction products rather than the expected 52% (the rate is increased by 108% by the added thiosulphate). The discrepancy is probably accounted for by the increase in ionic strength on adding thiosulphate, which will depress the rate of the hydrolysis reaction in the n.m.r. experiment [Table 3(a)].

DISCUSSION

Hydrolysis Reaction.—The spontaneous hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene differs significantly in several respects from the corresponding reactions of 2-aryloxytetrahydropyrans described in the preceding paper.[7] The results are consistent with a transition state for the hydrolysis of the methoxymethoxy acetal with important involvement of the solvent.

The entropy of activation [-6.7 ± 1.0 cal K^{-1} mol^{-1} at 39°, ionic strength 1.0M ($NaClO_4$)] is nine units more negative than for 2-(*p*-nitrophenoxy)tetrahydropyran at 50°, ionic strength 0.1M (KCl).[26] Entropies of activation for solvolytic reactions exhibiting borderline behaviour are often *ca.* 10 units more negative than those for limiting solvolyses of substrates with similar leaving groups.[27] [Compare the values for the tetrahydropyran and methoxymethyl acetals with those for the hydrolysis in water of t-butyl [28] and isopropyl [29] chlorides (3.42 and −5.26 cal K^{-1} mol^{-1}, respectively).]

Secondly, the reaction is relatively insensitive to solvent effects. In 50% (v : v) dioxan–water the rate is reduced by a factor of only 4.2 ± 0.1, compared with a factor of 49 for the hydrolysis of 2-(*p*-nitrophenoxy)-tetrahydropyran.[26] Two point Grunwald–Winstein plots [30] give crude estimates of *m* 0.77 for the hydrolysis of the tetrahydropyran acetal, in the region ($m \geqslant 0.7$ [31]) expected for S_N1 mechanisms, and *m* 0.29 for the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene, in a region (0.25—0.35) generally associated with concerted S_N2 reactions.[32] Chloromethyl methyl ether, which is hydrolysed by an 'S_N1-like' mechanism [25] has *m* 1.01 ± 0.02 in dioxan–water mixtures (80—95% dioxan) at 24.87°.

Thirdly, ionic strength effects, though not large, are in the opposite direction for methoxymethyl and tetrahydropyranyl acetals. The ratio $k_0^{NaClO_4}/k_0^0$ is 0.86 for the hydrolysis of 1-methoxymethyl-2,4-dinitrobenzene (Table 3), compared with 1.16 for the reaction of 2-(3,4-dinitrophenoxy)tetrahydropyran (Table 1). Added salts, especially perchlorates, generally increase the rates of S_N1 reactions: [18] for example, the unimolecular hydrolysis of *p*-methoxybenzyl chloride in 50% aqueous acetone is accelerated by a factor of 1.062 by the addition of 0.05M-$NaClO_4$,[33] whereas for the bimolecular reaction of *p*-nitrobenzyl chloride the factor is 0.961.

Fourthly, the hydrolysis of methoxymethyl acetals is less sensitive to the basicity of the leaving group than the corresponding reaction of tetrahydropyranyl acetals,[7] whereas it would be expected to be more sensitive if the same mechanism applied for both reactions (less stable oxocarbonium ion).

All this evidence is consistent with a transition state for the pH-independent hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene with a considerably greater involvement of solvent than that for the hydrolysis of 2-aryloxytetrahydropyrans or chloromethyl methyl ether. [Isotope effects are not a useful criterion of

[26] T. H. Fife and L. H. Brod, *J. Amer. Chem. Soc.*, 1970, **92**, 1681.
[27] G. Kohnstam, *Adv. Phys. Org. Chem.*, 1967, **5**, 121.
[28] E. A. Moelwyn-Hughes, R. E. Robertson, and S. E. Sugamori, *J. Chem. Soc.*, 1965, 1965.
[29] R. L. Heppolette and R. E. Robertson, *Canad. J. Chem.*, 1966, **44**, 677.
[30] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.
[31] E. M. Kosower, 'An Introduction to Physical Organic Chemistry', Wiley, New York, 1967, p. 318
[32] H. D. Cowan, C. L. McCabe, and J. C. Warner, *J. Amer. Chem. Soc.*, 1950, **72**, 1194.
[33] B. J. Gregory, G. Kohnstam, A. Queen, and D. J. Reid, *Chem. Comm.*, 1971, 797.

mechanism in this situation: the solvent deuterium isotope effect (k_{H_2O}/k_{D_2O} 1.18 ± 0.04, Table 3) does not provide a basis for a clear distinction between different S_N mechanisms, as discussed by Robertson,[34,35] and the secondary α-deuterium isotope effect (12% per deuteron, Table 7) is similar to that observed for S_N2 reactions at this centre, as discussed below.]

Though unexpected, in view of a great deal of evidence pointing to the rate determining formation of the methoxymethyl cation in water,[25,36,37] this conclusion is readily rationalised. The oxocarbonium ion is much less stable than that formed from 2-substituted tetrahydropyrans (which are hydrolysed 10^3—10^4 times more rapidly), and the leaving group is relatively poor,* in a reaction which is highly sensitive to the nature of the leaving group.[7] On the other hand, steric factors (substitution is at a primary centre) are favourable for nucleophilic attack.

We conclude that the spontaneous hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene is another example of a borderline mechanism for nucleophilic substitution, of the sort commonly observed for the solvolysis of simple secondary substrates in reasonably nucleophilic solvents,[38] but not previously observed for acetal hydrolysis. The rate-determining step could be attack of water on either the neutral acetal or derived tight ion-pair. In either case the transition state is characterised by weak involvement of the nucleophile (low solvent deuterium isotope effect) and substantial oxocarbonium ion character (high sensitivity to the leaving group.

Nucleophilic Substitution.—If the transition state for the loss of 2,4-dinitrophenolate from 1-methoxymethoxy-2,4-dinitrobenzene is stabilised by water acting as a nucleophile, we would expect to observe nucleophilic attack on the acetal by other, stronger nucleophiles. The evidence is described in detail in the Results section. Strong neutral nucleophiles (triethylenediamine, thiourea) catalyse the release of 2,4-dinitrophenolate in simple second-order reactions. Anionic nucleophiles are also effective, but the second-order plots (Figure 1) generally show more or less curvature. This can be accounted for in terms of specific salt effects as the anion of the salt used to maintain the ionic strength (non-nucleophilic perchlorate) is progressively replaced by the nucleophile anion. We have used two approximate treatments to analyse the results. The more successful assumes that only the nucleophilic reaction is susceptible to specific salt effects, and leads to two series of values for the second-order rate constant for reaction with anions, $k_N^{ClO_4}$ (extrapolated to zero catalyst concentration, thus the value in 1M-$NaClO_4$), and k_N^N, the value when the ionic strength is made up to 1M with the sodium salt of nucleophile. (Cation effects are negligible, and ionic strength effects on the spontaneous hydrolysis are small.) If it is assumed, alternatively, that only the *hydrolysis* reaction is susceptible to specific salt effects, constants k_N^M (at ionic strength 1M) are obtained for monoanions: this latter treatment fails for dianions.

These second-order rate constants have been used to construct the Swain–Scott [39] plot shown as Figure 3.

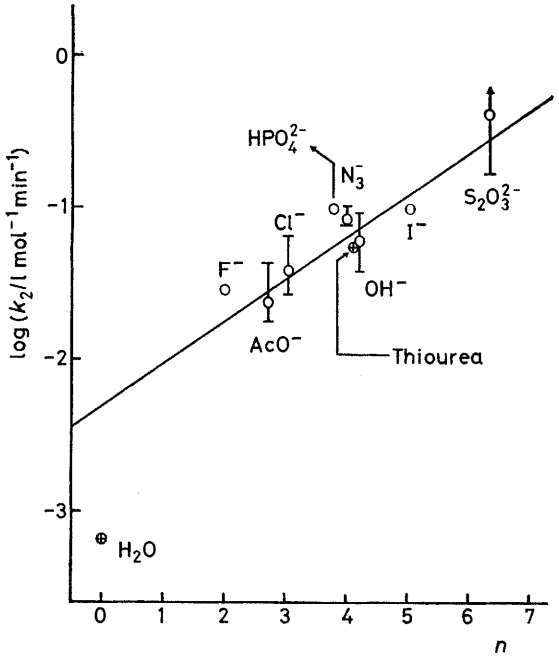


FIGURE 3 Swain–Scott plot for the reactions of nucleophiles with 1-methoxymethoxy-2,4-dinitrobenzene at 39° and ionic strength 1.0M. Data are from Table 4. For each monoanion the the central point (open circle) is k_N^N, the bottom of the error bar (cross) is $k_N^{ClO_4}$, and the top of the error bar is k_N^M

It is at once apparent that there is a strong correlation between the second-order rate constants for attack on the acetal and the Swain–Scott nucleophilicity parameter, n; *i.e.* with the second-order rate constants for the reactions of the same nucleophiles with methyl bromide, also in water.[39] Least squares analysis of $k_N^{ClO_4}$ and k_N^N values gives identical substrate constants: $s_N^{ClO_4}$ 0.26 ± 0.04; s_N^N 0.27 ± 0.04 (r 0.936 and 0.942) for seven and eight data sets, respectively). For the five points obtained by the alternative treatment, s_N^M 0.18 ± 0.04 (r 0.942). Thus without specifying precise conditions, or understanding salt effects in detail, we can set a value for s in the region 0.2—0.3. This is substantially lower than values of the Swain–Scott sensitivity parameter measured for other nucleophilic substitution reactions, for which s is generally in the

* 2,4-Dinitrophenolate, though a good leaving group in the context of acetal chemistry, is a very poor one for the S_N2 reaction. Even the strongest nucleophiles do not displace it from the methyl group of 2,4-dinitroanisole at a detectable rate under the conditions of our experiments.

[34] R. E. Robertson, *Progr. Phys. Org. Chem.*, 1967, **4**, 213.
[35] K. M. Koshy, R. E. Robertson, and W. M. J. Strachan, *Canad. J. Chem.*, 1973, **51**, 2958.
[36] P. Salomaa in ' The Chemistry of the Carbonyl Group ', ed. S. Patai, Interscience, New York, 1966, p. 184.
[37] A. Kankaanpera, *Acta Chem. Scand.*, 1969, **23**, 1728.
[38] J. M. Harris, *Progr. Phys. Org. Chem.*, 1974, **11**, 89.
[39] C. B. Scott and C. G. Swain, *J. Amer. Chem. Soc.*, 1953, 75, 141.

region of unity, and always greater than 0.66.[39,40] (Koskikallio [41] found a lower sensitivity, s 0.43 ± 0.07, for the reaction of three 'basic' nucleophiles with methyl benzenesulphonate, but a normal value, s 0.70 ± 0.15, for a larger series of less basic reagents. There is no evidence from our results for separate correlations for basic and non-basic [41,42] nucleophiles.)

This very low sensitivity to conventional nucleophilicity towards saturated carbon is not associated with an increased sensitivity to the basicity of the nucleophile. The data for oxyanions (Table 4) are correlated (roughly) by the Brønsted equation. The value of the Brønsted exponent, β 0.05 ± 0.01, again represents a sensitivity considerably smaller than the (already low) sensitivity to basicity normal for S_N2 reactions for which typically β *ca.* 0.20.[42-44]

Two features of these data require special comment. The negative deviations of the points for attack by water though not unusual, are not readily explained. They do, however, add weight to the arguments presented above that spontaneous hydrolysis is not a simple S_N1 process, which would then be expected to give a *positive* deviation. The large positive deviation of the point for hydroperoxide anion (about two orders of magnitude) is a measure of the α-effect [22] in this reaction. It has been noted before [44] that the correlation between the magnitude of the Bronsted coefficient β and the size of the α-effect, observed for nitrogen nucleophiles like hydrazine, is not apparent for hydroperoxide reactions. There does, however, appear to be a correlation between the magnitude of the α-effect, as measured by the ratio k_{HOO^-}/k_{HO^-}, and the amount of positive charge developed at the electrophilic centre (amount of 'S_N1-character') in the transition state. This ratio for the acetal is 96, substantially smaller than the value of 10^4 found for addition to the carbonium ion malachite green,[44] but larger than values found for normal S_N2 reactions, which range from 45 (methyl tosylate) [44] and 35 (benzyl bromide) [45] to 13 (bromoacetate).[46]

These results are consistent with a borderline S_N2 mechanism for nucleophilic substitution on 1-methoxymethoxy-2,4-dinitrobenzene,* with bond breaking well advanced in the transition state but with little bond formation to the nucleophile. The evidence does not allow a firm distinction between attack of the nucleophile on the neutral acetal, by way of a very loose transition state, as described, and nucleophilic attack on a tight ion-pair. We favour the former, just about concerted, process, since there is no evidence which specifically supports an ion-pair mechanism: adding an equal concentration of 2,4-dinitrophenoxide (in 0.01M-NaOH–0.99M-$NaClO_4$) had no effect on the hydrolysis rate; the specific salts effects are in the wrong direction; the second-order rate constants for nucleophilic attack show a correlation with Swain–Scott n values, and none with N^+ values; [47] and structural changes in the acetal, to give a more stable oxocarbonium ion, and hence presumably more prominent ion-pair behaviour, lead to the disappearance of the nucleophilic reaction. And the data do not fit the rate law derived by Sneen [48] for the ion-pair mechanism (taking into account the fact that ionic strength was maintained constant in our experiments). This failure is no surprise, because the apparent order in the nucleophile *increases* with nucleophile concentration (Figure 1) in our reactions and is never less than one. Sneen [49] originally assumed that the non-nucleophilic effects of, for example, NaN_3 on the solvolysis of 1-methylheptyl mesylate in aqueous dioxan, resemble the small *positive* salt effects observed for $LiClO_4$ and other non-nucleophilic salts; that is, that salt effects are non-specific. Schleyer pointed out soon afterwards [50] that the experimental results were equally consistent with a concerted S_N2 mechanism, if the salt effect of NaN_3 is small and negative. Although negative salt effects on solvolysis reactions of this type are not predicted by simple electrostatic theory,[51] they have been observed previously,[33,52] particularly in highly aqueous solvents; and the effect of varying $NaClO_4$ concentration on the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene [Table 3(a)] provides another example.

The entropy of activation for the nucleophilic reaction of iodide ion with the acetal is a few units more negative than that for the hydrolysis reaction (−8 or −11 ± 2 cal K^{-1} mol^{-1}, compared with −6.7 for hydrolysis). Though this parameter is not a very useful criterion of mechanism in this reaction, as discussed above, the values observed are at any rate consistent with a concerted displacement process. (Compare the reaction of methyl iodide with iodide ion and water, for which $\Delta S^{\ddagger} = -13.9$ [53] and −6.7 [54] cal K^{-1} mol^{-1}, respectively.)

Secondary Deuterium Isotope Effects.—The α-deuterium isotope effect is generally regarded as a good criterion of mechanism for nucleophilic substitution reactions at

* The results with the 3,4-dinitrophenyl acetal (Table 2) show that the reaction occurs with this compound also, and that the sensitivity to leaving group is comparable for hydrolysis and nucleophilic substitution.

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saturated carbon. S_N1 processes typically show an effect of 12—15% ($k_H > k_D$) per deuteron, while k_H/k_D for S_N2 reactions is close to unity.[54,55] The secondary α-deuterium isotope effects for the reactions of nucleophiles with 1-methoxymethoxy-2,4-dinitrobenzene (Table 7), range from 5—16% per deuteron ($k_{CH_3}/k_{CD_3})^{\frac{1}{3}}$, and mostly fall in the region usually associated with the S_N1 mechanism. Yet we have good evidence, discussed above, that these are concerted displacement reactions. If our conclusions about mechanism are correct, therefore, the secondary deuterium isotope effects associated with bimolecular nucleophilic substitution at this acetal centre, at least by the nucleophiles listed in Table 7, are substantially larger than those observed for less borderline S_N2 reactions.

Most α-deuterium isotope effects measured for nucleophilic substitution reactions actually involve solvolysis.[56] When reactions with good nucleophiles have been studied, k_H/k_D has often been found to be greater than unity. For thiosulphate reacting with methyl and ethyl bromides in 50% aqueous ethanol at 25°, for example, $k_H/k_D = 1.03$ and 1.07,[57] compared with values for hydrolysis (water at 80°) [58] of 0.90 and 0.98, respectively. Similarly k_{CH_3}/k_{CD_3} for the iodide exchange reaction of methyl iodide is 1.10 in water at 20°, compared with a value of 0.87 for hydrolysis (water at 70°).[58] These are small effects, up to *ca.* 4% per deuteron, but the results show clear trends, as discussed by Seltzer and Zavitsas.[56] The secondary α-deuterium isotope effect for the S_N2 process depends on the relative nucleophilicities of nucleophile and leaving group: the more important is bond-breaking and the less important bond-making in the transition state, the larger is the value of k_H/k_D. The isotope effect is also increased by electron-donating substituents on the α-carbon atom, as shown for example by the values for the reactions of thiosulphate with methyl and ethyl bromides, above,[57] and by increasing the ionising power of the solvent.

All these factors combine when good nucleophiles displace the 2,4-dinitrophenoxide ion from the methoxymethyl centre of the acetal. The poor leaving group means that bond-breaking is well advanced in the transition state; with a good nucleophile bond making will be at an early stage; and the resulting partial positive charge at the central carbon atom is stabilised, by the methoxy-group. We are aware of one other case in the literature where all these factors are present. Westaway [59] measured the rate of debenzylation of $PhCD_2N^+Me_2Ph$ by thiophenoxide ion (in DMF at 0°) and found a secondary deuterium isotope effect of 9% per deuteron, the highest value previously found for an S_N2 reaction. The effect was attributed to the size of the leaving group, but this is not likely to be an important factor in our reaction.

This picture of the transition state agrees well with the conclusions reached above on the basis of the other evidence. Formally we are suggesting an extreme case of variable transition state structure [60] to account specifically for second-order reactions with good nucleophiles (though the properties of the hydrolysis reaction are clearly very similar). Possibly the single most convincing piece of evidence specifically supporting this interpretation is the variation of the secondary deuterium isotope effect for different nucleophiles (Table 7). Thiourea and triethylenediamine, for example, both neutral nucleophiles, with no complications associated with specific salt effects, show very different α-deuterium isotope effects (13 and 5% per deuteron, respectively). The value for the amine is substantially lower than those for other nucleophiles. Leffek [61] also found low values (k_H/k_D *ca.* 0.9) for the reactions of tertiary amines with CD_3I in benzene, raising the possibility that this may be characteristic of reactions of nitrogen nucleophiles.

This variation in the α-deuterium isotope effect is direct evidence for an interaction between the nucleophile and the CD_2 group in the transition state, and most easily reconciled with the concerted displacement mechanism. The absolute values have to be seen in the light of the value of 24% per deuteron found by Jones and Thornton [25] for the 'S_N1-like' hydrolysis of CH_3OCD_2Cl. There is now a good deal of evidence that nucleophilic substitutions at centres with strongly electron-donating substituents are characterised by large α-deuterium isotope effects, for S_N2 as well as S_N1 mechanisms.

Conclusions.—The nucleophilic attack of acetate ion on 1-methoxymethoxy-2,4-dinitrobenzene is the first example of bimolecular attack by the carboxylate group at an acetal centre. Our results make clear why this mechanism is not normally observed. The reaction is restricted to acetals of formaldehyde (primary centres), because the introduction of an alkyl substituent not only greatly accelerates the alternative S_N1 process, but also substantially increases steric hindrance to nucleophilic attack, at a centre already notably sensitive to steric effects (no detectable reaction with pyridines or imidazole). It is also observed only with good (dinitrophenolate) leaving groups, because of the high sensitivity to the group displaced.

A more important class of good leaving group is fully or partially protonated alkoxide, as found in specific or general acid catalysed reactions of naturally occurring glycosides. Though bimolecular nucleophilic substitution at such acetal centres is not to be expected, the evidence that intramolecular nucleophilic displacement by carboxylate can occur,[5,6,62] shows that this reaction is

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entirely feasible as a step in an enzyme-catalysed glycosyl transfer mechanism. In the light of our results it is possible to describe the expected properties of this type of process in some detail.

The most striking property of the reaction is the exceedingly low sensitivity to the strength of the nucleophile, and particularly to its basicity. This has the result of levelling out the reactivity of different nucleophiles, so that acetate, for example, in our reaction, is not much less (about half as) reactive as hydroxide ion. The cause of this levelling effect is the weak bonding of the nucleophile to the acetal centre in the transition state. The leaving group is similarly weakly bound, so that the reaction is very sensitive to factors, such as general acid catalysis, which increase leaving group capability.

This weak bonding of both nucleophile and leaving group in the transition state leave the acetal centre with a substantial amount of positive charge, comparable with that developed in the transition states of some S_N1 reactions. Consequently criteria such as the secondary α-deuterium isotope effect cannot readily distinguish such borderline S_N2 mechanisms from S_N1 reactions.

In particular, the secondary deuterium isotope effect (k_H/k_D 1.11) for the lysozyme-catalysed hydrolysis of phenyl 4-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside [13] does not rule out the direct or double-displacement mechanisms for this enzyme.

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