

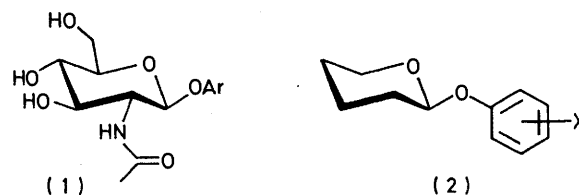
The Spontaneous Hydrolysis of Acetals: Sensitivity to the Leaving Group †

By **Gabrielle-Anne Craze** and **Anthony J. Kirby**,* University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW

The spontaneous hydrolysis of acetals shows very high sensitivity to the basicity of the leaving group, measured as $\rho^- 2.7$ for the hydrolysis of 2-aryloxytetrahydropyrans. A Brønsted (leaving group) plot for the spontaneous hydrolysis of acetals and acylals of formaldehyde shows similar high sensitivity, and correlates also the rate of the acid catalysed hydrolysis of formaldehyde dimethyl acetal.

ACCORDING to our proposed mechanism¹ for the hydrolysis of 2-methoxymethoxybenzoic acids, the reaction co-ordinate for the intramolecular general acid catalysis reaction diverges from that for spontaneous hydrolysis only at fairly high degrees of bond-breaking. The mechanism for hydrolysis is strikingly similar to that of the phosphate monoester group (dianion) in the same position.² In the phosphate case the spontaneous³ reaction has been studied in detail, and has been shown to be characterised by a very high sensitivity to the leaving group, $\rho^- 2.6$.³ The spontaneous hydrolysis of acetals has been observed in a number of instances. Like the phosphate reaction⁴ it is observed for simple acetals when the leaving group is the anion of *p*-nitrophenol,⁵ or of a stronger oxyacid. And there is some evidence for a substantial dependence on the basicity of the leaving group. The directly relevant work is that of Piszkievicz and Bruice on the hydrolysis of substituted-phenyl 2-acetamido-2-deoxy- β -D-glucopyranosides (1). The hydrolysis of these compounds is thought to be catalysed by the 2-acetamido-group, since the spontaneous hydrolysis reaction is not observed for the α -glucoside.⁶ A 'partial Hammett plot'⁶ for three substituted compounds (1; Ar = *p*-NO₂⁻, *o*-NO₂⁻,

and *o*-CO₂Me-C₆H₄) gave a rough value of $\rho^- 2.6$, more recently modified to 2.28 by Dunn and Bruice,⁷ quoting their own unpublished observations.



insofar as the hydrolysis of the glycosides (1) is assisted by the neighbouring acetamido-group, a higher sensitivity to the leaving group might be expected for acetals hydrolysing without assistance. Of the small number of examples of the unassisted process known,^{7,8} the most accessible appeared to be the 2-aryloxytetrahydropyran system studied by Fife and Brod.⁵ In this paper we describe a study of the spontaneous hydrolysis of a series of *meta* and *para*-substituted derivatives (2), designed to quantify the role of the leaving group in this reaction.

EXPERIMENTAL

Materials.—Phenols were observed commercially and recrystallised before use with the exception of 3,5-dinitro-

⁵ T. H. Fife and L. H. Brod, *J. Amer. Chem. Soc.*, 1970, **92**, 1681.

⁶ D. Piszkievicz and T. C. Bruice, *J. Amer. Chem. Soc.*, 1968, **90**, 2156.

⁷ B. M. Dunn and T. C. Bruice, *Adv. Enzymol.*, 1973, **37**, 1.

⁸ D. Cocker and M. L. Sinnott, *J.C.S. Perkin II*, 1975, 1391.

† No reprints available.

¹ G.-A. Craze and A. J. Kirby, *J.C.S. Perkin II*, 1974, 61.

² R. H. Bromilow and A. J. Kirby, *J.C.S. Perkin II*, 1972, 149.

³ A. J. Kirby and A. G. Varvoglis, *J. Amer. Chem. Soc.*, 1967, **89**, 415.

⁴ A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, 1965, **87**, 3209.

phenol, which was prepared by the demethylation of 3,5-dinitroanisole with AlCl_3 .⁹ AnalaR dioxan was refluxed over sodium until the metal remained bright (at least 18 h), then distilled from the sodium. The purified solvent was stored for short periods in brown bottles, but was periodically re-purified. Inorganic salts were of analytical grade. Distilled water was distilled twice more from all-glass apparatus. 2-Aryloxytetrahydropyrans were prepared by the method of Woods and Kramer,¹⁰ as modified by Fife and Jao¹¹ for 2-(*p*-nitrophenoxy)tetrahydropyran. This compound had m.p. 62–63° (lit.,¹¹ 59–60°).

2-(*m*-Nitrophenoxy)tetrahydropyran was obtained (54%) as a dark orange-brown oil which could not be distilled. Preparative t.l.c. (CHCl_3 on a silica plate prewashed with AnalaR MeOH) gave an oil (Found: C, 59.05; H, 5.8; N, 6.35. $\text{C}_9\text{H}_{13}\text{NO}_4$ requires C, 59.15; H, 5.85; N, 6.3%).

2-(*p*-Cyanophenoxy)tetrahydropyran. The general method was improved by using dry ether in place of benzene as the solvent and two equivalents of 2,3-dihydropyran. The

0.2, and 0.5M-TRIS buffer, 75% free base, pH 8.45 ± 0.02 , with the ionic strength maintained at 1M (KCl).

Increasing the concentration of TRIS buffer from 0.1 to 0.5M at constant pH causes a small (<10%) decrease in the rate of hydrolysis of each acetal. This is probably a specific salt effect. Extrapolation to zero buffer concentration gives rate constants identical, within experimental error, to those obtained in NaOH. The rate of hydrolysis of each substrate is thus independent of pH from at least pH 8 to 11.5. These results are summarised in the Table. The rate constants shown in the final column are correlated by the Hammett equation, using substituent constants σ (σ^- for *para*-substituents) taken from Jaffe,¹² and assuming that substituent effects are additive for the dinitro-compounds. (The additivity rule is generally obeyed,¹³ and in particular the $\text{p}K_a$ values for 3,5-¹⁴ and 3,4-dinitrophenol¹⁵ do not deviate significantly from a Hammett plot for the ionisation of monosubstituted phenols.^{15,16} Least squares analysis (standard two variable linear regression program

Data for the spontaneous hydrolysis of 2-aryloxytetrahydropyrans (2), at 39° and ionic strength 1.0 (KCl)

Aryl substituent	λ nm	$k_{\text{obs}}/\text{min}^{-1}$ at pH 8.45	$k_{\text{obs}}/\text{min}^{-1}$ in NaOH ^d	k^e
3-NO ₂	252.5 ^a		6.24×10^{-4}	$6.24 \pm 0.11 \times 10^{-4}$
4-CN	275.5 ^a	2.45×10^{-3}	2.52×10^{-3}	$2.50 \pm 0.003 \times 10^{-3}$
4-NO ₂	402 ^a	2.19×10^{-2}	2.20×10^{-2}	$2.20 \pm 0.01 \times 10^{-2}$
3,5-(NO ₂) ₂	247.2 ^b	4.07×10^{-2}	3.90×10^{-2}	$3.92 \pm 0.05 \times 10^{-2}$
3,4-(NO ₂) ₂	402 ^a	1.34	1.37	1.36 ± 0.01

^a Followed at λ_{max} for ArO^- . ^b Followed at λ_{min} for ArO^- . ^c Extrapolated to zero buffer concentration. See text. ^d Mean of three or more values in 0.001–0.01M-NaOH. ^e Calculated from the values in columns 3 and 4.

yield of crude *p*-cyano-compound was thus increased to 95%, and this method was used also for the other acetals. Two recrystallisations from light petroleum (b.p. 60–80°) gave crystals, m.p. 69–70° (Found: C, 71.0; H, 6.5; N, 6.8. $\text{C}_{12}\text{H}_{13}\text{NO}_2$ requires C, 70.9; H, 6.45; N, 6.9%).

2-(3,5-Dinitrophenoxy)tetrahydropyran was obtained by the improved method as an oil (78%) which solidified only after prolonged standing. This gave yellow prisms from ether-light petroleum (b.p. 30–40°), m.p. 64–65° (Found: C, 49.35; H, 4.45; N, 10.55. $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 49.25; H, 4.5; N, 10.45%).

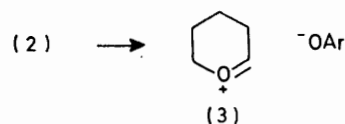
2-(3,4-Dinitrophenoxy)tetrahydropyran was obtained by the improved method as an oil (75%) which solidified on standing. The pale yellow crystals from ether-light petroleum (b.p. 30–40°) had m.p. 60–61° (Found: C, 49.05; H, 4.5; N, 10.3%).

Reactions were measured under pseudo-first-order conditions by following the release of the phenolate anion at $39.00 \pm 0.05^\circ$, at the absorbance maximum or minimum in the spectrum of the anion at which the greatest change in absorbance occurred (Table). The general technique has been described.¹ Reactions were started by injecting 10 μl of a stock solution of the substrate in dioxan into 2 ml of buffer, preincubated in the thermostatted cell holder of the spectrophotometer: the final proportion of dioxan was thus 0.5%. The rate of hydrolysis for each acetal was measured in 10^{-2} , 5×10^{-3} , and 10^{-3}M -NaOH, and in 0.1,

for a Hewlett-Packard 9100B programmable desk calculator) gives $\rho^- 2.7 \pm 0.1$ (r 0.998 for five data sets).

DISCUSSION

Five points are sufficient to define the sensitivity to leaving group of the spontaneous hydrolysis of the acetals (2). The value obtained, $\rho^- 2.7 \pm 0.1$, is consistent with the mechanism generally accepted for this reaction, unimolecular decomposition to aryloxide



anion and an oxocarbenium ion (3).⁵ As for the hydrolysis of phosphate monoester dianions,² ρ^- is greater for the hydrolysis reaction than for the ionisation of phenols (for which Bolton¹⁶ gives a value of 2.28 ± 0.09) implying that bond-breaking is far advanced, perhaps even complete, in the transition state. This can now be placed fairly precisely on the reaction co-ordinate, at one of the energy maxima flanking the minimum corresponding to the ion-pair (3) since the evidence that solvent is not involved in the transition state for hydrolysis of the *p*-nitro-compound^{5,7} rules out rate-determining attack of solvent on ion-pairs as well as on neutral

¹⁴ C. M. Judson and M. Kilpatrick, *J. Amer. Chem. Soc.*, 1943, **71**, 3110.

¹⁵ P. D. Bolton, F. M. Hall, and J. Kudrynski, *Austral. J. Chem.*, 1968, **21**, 1541.

¹⁶ P. D. Bolton, F. M. Hall, and I. H. Reece, *J. Chem. Soc. (B)*, 1967, 709.

⁹ N. V. Sidgwick and T. W. J. Taylor, *J. Chem. Soc.*, 1922, 1853.

¹⁰ D. N. Kramer and G. F. Woods, *J. Amer. Chem. Soc.*, 1947, **69**, 2246.

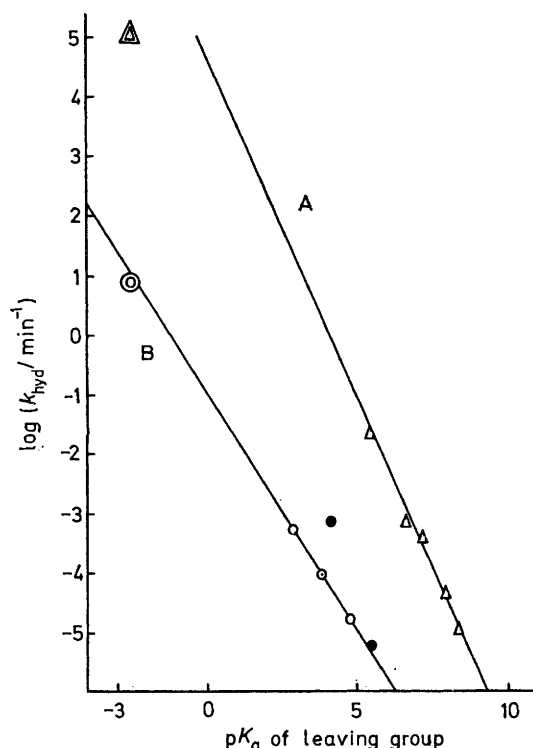
¹¹ T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, 1968, **90**, 4081.

¹² H. Jaffe, *Chem. Rev.*, 1953, **53**, 191.

¹³ O. Exner in 'Advances in Linear Free Energy Relationships', eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972.

substrate. Since ion-pair return is often not observed for reactions involving stable (tertiary) carbonium ions¹⁷ it seems marginally more likely that C-O bond cleavage, rather than diffusion apart of the ion-pair, is rate determining.

The only results in the literature which can be compared directly with those in this paper are for the spontaneous hydrolysis of a series of acylals, $\text{CH}_3\text{-OCH}_2\text{OCOR}$, derived from aliphatic carboxylic acids.¹⁸



Brønsted leaving group plots for the spontaneous hydrolysis reactions (open symbols) of 2-aryloxytetrahydropyrans (curve A, data from the Table) and of acylals $\text{CH}_3\text{OCH}_2\text{OCOR}$ [curve B (at 35°), from ref. 18]. The closed circles represent points for methoxymethoxy-3,4- and -2,4-dinitrobenzene,²⁴ and the double symbols are points calculated for the reactions of protonated dimethoxymethane (at 40°) and 2-ethoxytetrahydropyran (extrapolated from 30°) as described in the text. The positive deviation for methoxymethoxy-2,4-dinitrobenzene has precedent in plots of this sort,³ and probably results from a steric effect of the *o*-nitro-group

From these data (at 35° and zero ionic strength) Cordes¹⁹ has calculated a value of ρ^* of 1.4 ± 0.04 , equivalent to a value of β_{LG} of 0.82 (using Taft's value²⁰ of 1.72 for ρ^* for the ionisation of RCO_2H). This sensitivity is significantly lower than that found for the spontaneous hydrolysis of 2-aryloxytetrahydropyrans, for which $\rho^- 2.7$ corresponds to β_{LG} 1.18 (based on Bolton's $\rho^- 2.28$ for the ionisation of phenols¹⁶).

* Note added in proof: H. Lönnberg and V. Pohjola (*Acta Chem. Scand.*, 1976, **A30**, 669) have recently found $\rho^- 2.4 \pm 0.2$ for a different series of 2-aryloxytetrahydrofurans, at 85° and ionic strength 0.1.

¹⁷ J. M. Harris, *Progr. Phys. Org. Chem.*, 1974, **11**, 89.

¹⁸ P. Salomaa, *Acta Chem. Scand.*, 1965, **19**, 1263.

¹⁹ E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581.

The two sets of data are compared in the Brønsted leaving group plot shown in the Figure; which also includes points for the acid catalysed hydrolysis of dimethoxymethane²¹ and 2-ethoxytetrahydropyran.¹¹ Rate constants for the spontaneous hydrolysis of the protonated acetals are calculated using $\text{p}K_a$ values of -4.57 for the conjugate acid of formaldehyde dimethyl acetal,²² -4.43 for the protonated ethoxy-group of 2-ethoxytetrahydropyran,²² and -2.5 (Deno's value²³ for MeOH_2^+) for the conjugate acids of the leaving groups. The line (B) correlating Salomaa's data for acylal hydrolysis accurately predicts the rate of the specific acid catalysed hydrolysis of formaldehyde dimethyl acetal, and the points for the spontaneous hydrolysis of two methoxymethoxydinitrobenzenes²⁴ fall reasonably close. The line correlating the data of this paper for 2-aryloxytetrahydropyrans, on the other hand, overestimates the rate constant for hydrolysis of protonated 2-ethoxytetrahydropyran by several orders of magnitude. There is good evidence¹¹ for the A1 mechanism in this case, but the predicted rate constant approaches the diffusion control limit for leaving groups of $\text{p}K_a$ (conjugate acid) < -5 , consistent with the observation of Fife and Jao¹¹ that proton transfer and bond breaking become concerted for the acid-catalysed hydrolysis of 2-aryloxytetrahydropyrans with good leaving groups.

The spontaneous hydrolysis of formaldehyde acetals might have been expected to be more sensitive to the basicity of the leaving group than that of other acetals, rather than less so. Accepting that formaldehyde dimethyl acetal²¹ and 2-ethoxytetrahydropyran¹¹ are both hydrolysed by the A1 mechanism, this means (Figure) that the spontaneous hydrolysis of methoxymethyl derivatives with poor leaving groups is faster than expected.

A likely explanation for this is that solvent is involved in the transition state for spontaneous hydrolysis reactions involving the displacement of poor leaving groups from the primary centre: since the measured entropies of activation are *ca.* 15–20 units more negative than for the acid catalysed reactions.^{5,7,18,21,24} This point is discussed further in the following paper,²⁴ but it should be stressed that it appears to be relevant only to derivatives of formaldehyde. The spontaneous hydrolysis of acetals is generally a unimolecular process, characterised by a very high sensitivity to the basicity of the leaving group.

We thank the Enzyme Chemistry and Technology Committee of the S.R.C. for the award of a studentship to G.-A. C.

[7/1326 Received, 22nd July, 1977]

²⁰ R. W. Taft in 'Steric Effects in Organic Chemistry', ed. M. S. Newman, Wiley, New York, 1956, p. 607.

²¹ J. Koskikallio and E. Whalley, *Trans. Faraday Soc.*, 1959, **55**, 809.

²² A. Kankaanpera, *Acta Chem. Scand.*, 1969, **23**, 1723.

²³ N. C. Deno and J. O. Turner, *J. Org. Chem.*, 1966, **31**, 1969

²⁴ G.-A. Craze, A. J. Kirby, and R. Osbourne, following paper.