Some Aspects of Glycoside and Acetal Hydrolysis

by

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DEDICATION

To my parents

ACKNOWLEDGEMENT

I should like to sincerely thank Dr.B.Capon for his helpful guidance and constant encouragement throughout the course of this work. Thanks are also due to Miss C.McLellan who typed this thesis, and to S.R.C.for their financial support.

The work described in this thesis was carried out by the author in the departments of chemistry of the University of Leicester and the University of Glasgow, under the supervision of Dr.B.Capon. No part of it is concurrently being submitted for any other degree.

Oct.1966-Oct.1969.

Signed,

J.M.Williams.

ABSTRACT

The evidence leading to the various mechanisms for acetal and glycoside hydrolysis is reviewed.

A series of fourteen aryl di-O-acetyl-β-D-glucofuranosiduronolactones was prepared. The β-naphthyl, phenyl, p-cresyl and p-methoxyphenyl compounds yielded the corresponding β-D-glucofuranoside on reduction with lithium aluminium hydride. The attempted preparation of m- and p-chlorophenyl β-D-glucofuranoside by this method afforded the unsubstituted phenyl glucoside *via* removal of the halogen atom. p-Nitrophenyl tetra-O-acetyl-β-D-glucofuranoside, prepared from a mixture of the penta-O-acetyl-D-glucofuranoses, decomposed during deacetylation attempts. p-Nitrophenyl di-O-acetyl-β-D-glucofuranosiduronolactone also failed to yield p-nitrophenyl β-D-glucofuranoside on reduction with lithium aluminium hydride and sodium borohydride. Phenyl β-D-galactofuranoside was prepared from phenyl tetra-O-acetyl-β-D-galactofuranoside.

The hydrolyses of the aryl β-D-glucofuranosides and phenyl β-D-galactofuranoside were studied in aqueous perchloric acid solutions. The positive entropies of activation measured in 1.00M acid are consistent with a unimolecular process. The variation of rate constant with acid concentration is interpretable in terms of the Hammett-Zucker hypothesis for an A-1 process.

The hydrolysis of phenyl β-D-glucofuranoside and of phenyl 2-deoxy-α-D-glucopyranoside were studied in a series of monochloroacetate and phosphate buffers. The results are consistent with a specific-acid catalysed mechanism, as are the solvent isotope effects for five glycosides studied.

Series of 2-aryloxytetrahydropyrans and tetrahydrofurans were prepared and their hydrolysis studied in aqueous acid and in aqueous buffered solutions of acetic, formic and monochloroacetic acids. A general-acid term was observed in the rate-law for the hydrolysis of 2-phenoxytetrahydrofuran in acetate buffers, 2-(p-nitrophenoxy)-tetrahydropyran and 2-(p-nitrophenoxy)-tetrahydrofuran in all three buffers but not for 2-phenoxytetrahydropyran in acetate buffers. Possible A-S $_E$2 mechanisms are discussed and a concerted mechanism favoured. The catalytic coefficients are greater for the tetrahydrofurans than for the corresponding tetrahydropyrans, and an explanation of this is advanced.

The hydronium-ion catalysed reactions for both series yielded small negative ρ values and the deuterium solvent isotope effect decreased with basicity of the acetal oxygen.

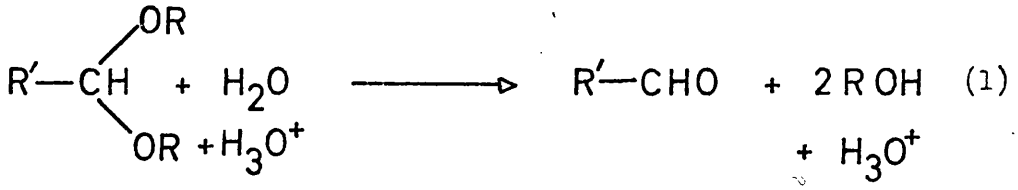
The 2-p-nitrophenoxy- compounds but not the 2-phenoxy- undergo a spontaneous hydrolysis.

CONTENTS

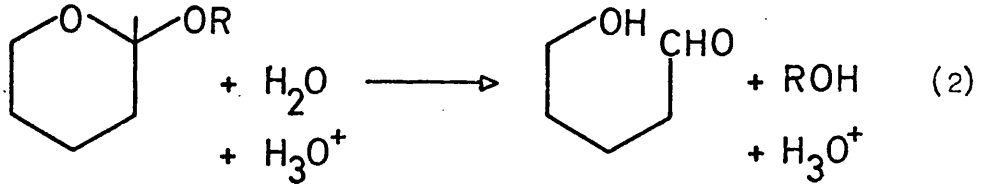
INTRODUCTION

The acid catalysed hydrolysis of acetals and of glycosides has been the subject of much work. Several reviews have appeared dealing with various aspects of their hydrolytic decomposition.[1-5]

Equations (1) - (3) show the overall scheme for the hydrolysis of an acyclic acetal, a cyclic acyclic acetal and a glycoside (a β - D - glucopyranoside) respectively.



(1)



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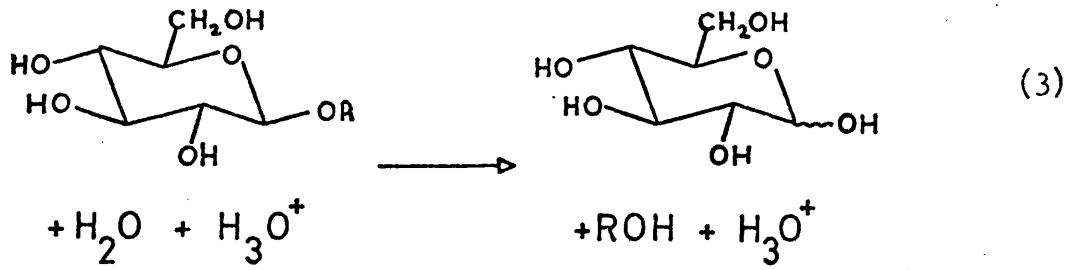
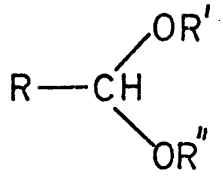


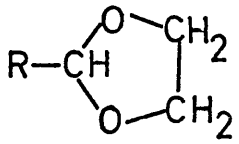
(3)

Acyclic acetals are derived from a straight chain aldehyde and two mono-functional alcohol molecules.



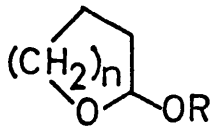
acyclic

Cyclic acetals are derived from diols.



cyclic

Cyclic acyclic acetals, although they are normally prepared from cyclic vinylic ethers by an acid catalysed reaction with an alcohol or phenol, are derived from a compound possessing an alcohol and a carbonyl function in one molecule and a separate molecule of alcohol or phenol.



cyclic acyclic

In the present work, a study has been made of some phenyl furanosides and of a series of 2 - (substituted phenoxy) - tetrahydrofurans and pyrans, i.e. cyclic acyclic acetals:

R = aryl, n = 1,2.

Alkoxy - and aryloxy - tetrahydrofurans and pyrans have been considered by some workers[6,7] as model systems for furanosides and pyranosides. Although the skeletal structure is comparible, the

parallels between these compounds are in several respects limited as will be explained later.

Much of the earlier work has already been reviewed.[1-5] Hence discussion of the earlier studies will be kept to a minimum except where it is felt that expansion of a particular theme is of importance in the light of more recent work.

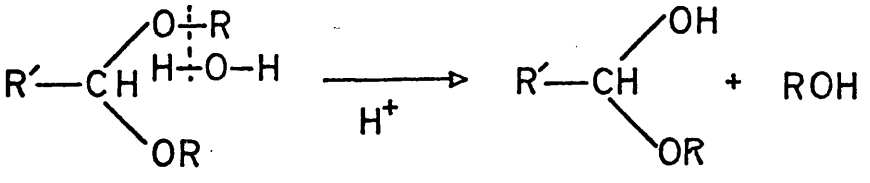
I. The mechanism of hydrolysis of cyclic and acyclic acetals

The hydrolysis of these compounds is almost exclusively acid-catalysed[8] although Bender and Silver[9] observed some spontaneous hydrolysis in their study of some 2 - (hydroxysubstituted phenyl) - 1,3 - dioxanes,[9] and some dioxolones[10] also show an uncatalysed reaction.

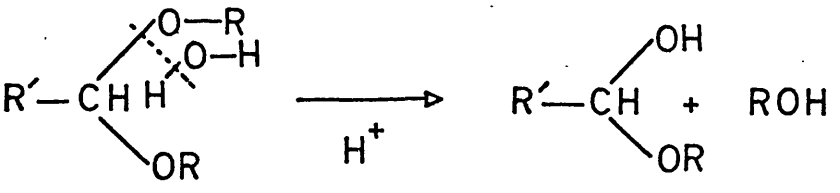
a. The position of bond cleavage

Whatever mechanism is operating, a carbon - oxygen bond must be broken at some stage. Various lines of evidence suggest that acetal hydrolyses occur with carbonyl - oxygen fission, Scheme 2, as opposed to alkyl - oxygen fission, Scheme 1.

Scheme 1



Scheme 2



For acyclic acetals the evidence includes studies of optical activity in the alcohol moiety[11] and hydrolyses of aliphatic and aromatic carbonyl derived acetals in ^{18}O enriched water[12] which produced alcohols of normal ^{18}O content.

Even studies with acetals prepared from alcohols capable of forming stable carbonium ions, e.g. (-) α - phenyl ethyl alcohol, methyl vinyl carbinol and phenyl vinyl carbinol[13], pointed to carbonyl - oxygen cleavage.

Fewer hydrolyses of ketals or of cyclic acetals have been studied, but Boerseken and Derx[14] found that the acetone ketal of cis - tetrahydronaphthalene 1,2 - diol gave the original cis - diol in high yield on hydrolysis and Hermans[15] found the same to be true of cis - hydrindane 1,2 - diol and of cis - tetrahydronaphthalene 2,3 - diol.

More recently Garner and Lucas[16] showed that D (-) - 2,3 - butanediol was recovered optically unchanged from the hydrolysis of cyclic acetals derived from this diol.

b. The nature of the acid catalysis

The hydrolysis of cyclic and acyclic acetals is almost invariably dependent on acid - catalysis, i.e. in dilute aqueous solution the rate law has the form:

$$k_{obs} = k_{H^+}(\overset{+}{H}) + \sum k_{HA_i} \cdot (HA_i) \qquad (4)$$

General - acid catalysis is well established for orthoester hydrolysis[17] but until recently in cyclic and acyclic acetal hydrolysis all attempts to observe general - acid catalysis had failed, i.e. the summation on the right hand side of equation (4) was negligible.

Bronsted and Wynne-Jones[18] reported only specific - acid

catalysis for the hydrolysis of acetaldehyde diethyl acetal in formate buffers, in contrast to the strong general - acid catalysis observed in the ethyl orthoesters of acetic, propionic and butyric acids in p - nitrophenolate and cacodylate buffers. No measurable catalysis was observed for the hydrolysis of acetone diethyl ketal.[18] Kreevoy and Taft[19] studied the hydrolysis of acetal in 50% dioxane and reported a very slight catalysis by molecular formic acid, which could be accounted for by the variations of ionic strength in the buffers used.

It is of interest that DeWolfe and Roberts[20] could find only specific - acid catalysis in aqueous solution for ethyl orthoformate, whereas general - acid catalysis was observed in 70% dioxane buffers.

In their study of the hydrolysis of some 2 - phenyl - 1,3 - dioxanes having ortho or para phenolic substituents, Bender and Silver[9] observed a pH independent reaction as well as the acid - catalysed reaction. These workers suggest that this is the hydronium ion - catalysed hydrolysis of the ionised form of the substrate, using solvent isotope effects in their evidence. This use of isotope effects, but not the conclusion reached in this case[9] has been criticised,[21] on the grounds that isotope effects do not allow the position of the proton to be determined.

A recent review[22] on general - acid catalysed ($\underline{A}$-$\underline{S}_E$ 2) reactions outlines the criteria normally used for assigning a general - acid mechanism. These will be expanded later in this and other relevant sections.

General - acid studies are normally carried out in buffered solutions containing HA and H^+, the latter also being a proton source.

Hence we have our rate law

$$-\frac{1}{(S)} \cdot \frac{d(S)}{dt} = k_{H^+}(\overset{+}{H}) + \sum k_{HA_i}(HA_i) \qquad (4)$$

If the proton is transferred after the rate determining step (R.D.S.) the reaction is not acid - catalysed. If the proton is transferred in a fast step prior to the R.D.S. the rate law takes the simple form shown in equation (5), providing the anion A—

$$-\frac{1}{(S)} \cdot \frac{d(S)}{dt} = k_{H^+}(\overset{+}{H}) \qquad (5)$$

does not become attached to the substrate in some way prior to or during the R.D.S. If it does become so attached the rate law is again given by equation (4).[22]

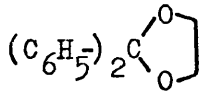
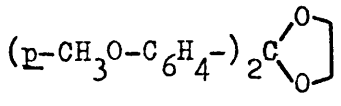
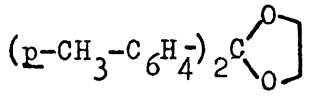
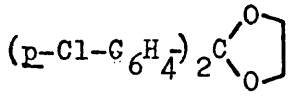
Hence one should in principle be able to distinguish between the $\underline{A}\text{-}S_{\underline{\underline{E}}}2$ and the $\underline{A}$-1 mechanism, but not the $\underline{A}$-2, by studying the rate law in buffers. DeWolfe, Ivanetich and Perry[23] have observed general - acid catalysis in a study of benzophenone ketals and discuss what they consider to be the two extreme mechanistic possibilities for acetal hydrolysis, $\underline{A}\text{-}S_{\underline{\underline{E}}}2$ and $\underline{A}$-1, discounting an $\underline{A}$-2 mechanism.

Koehler and Cordes[24] state that they could observe no catalysis by carboxylic acids in the hydrolysis of acetone diethyl ketal and acetophenone diethyl ketal, but do not specify the solvent system used.

Capon and Smith[25] observed only specific - acid catalysis in the hydrolysis of benzaldehyde diethyl acetal and of benzophenone diethyl ketal. They determined rates at different buffer concentrations holding the buffer ratio, ionic strength and pH constant.

DeWolfe et al[23] in their preliminary experiments using formate buffers in 20% dioxane failed to detect any general - acid reaction. However in monochloroacetate and dichloroacetate buffers, catalysis was observed in 20% and 50% aqueous dioxane (v/v). Their results are summarised in Table 1.

Table 1

Ketal	k_{HA} l mole^{-1}	k_{H^+} sec^{-1}
	9×10^{-4}	3.6×10^{-2}
	1.7×10^{-2}	8.5×10^{-1}
	7×10^{-3}	1.7×10^{-1}
	0	3.3×10^{-3}

Catalytic coefficients for benzophenone ketal hydrolysis at 30° . Cl_2CH COOH, 20% dioxane, $\mu = 0.131$
Date of DeWolfe, Ivanetich and Perry[23]

The possibility that the observed catalysis was produced by salt effects was considered but rejected, as no catalysis could be observed with 2,2 - di - (p-chlorophenyl) - 1,3 - dioxolane in dichloroacetate buffers, nor for 2,2 - di - (p - methoxyphenyl) - 1,3 - dioxolane in formate buffers.[23] The reactions were studied

in buffers of different concentration but constant buffer ratio, ionic strength and pH, similarly to Capon and Smith.[25] For the latter reaction the rate was observed to increase as the concentration of acetic acid decreased so that the specific salt effect appears to be in the opposite direction to that necessary to give a spurious catalysis. This is similar to the observation of Koehler and Cordes.[24]

Fife[7] has observed a weak catalysis by increased concentrations of formic acid at 40° in aqueous solution, for 2 - (p - methoxyphenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolane. Based on this and other criteria such as solvent isotope effect, Fife says of the 2 - (substituted phenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolanes. "It has indeed been found that the hydrolysis reaction of these acetals proceeds by an A-2 mechanism with general - acid catalysis being detectable".[7] As stated earlier, A-2 and A-S_E 2 mechanisms cannot be distinguished by buffer studies. DeWolfe et al[23] have criticised the reasoning of Fife stating that in their opinion acetal hydrolysis must proceed by a mechanism somewhere in the spectrum A-1 and A-S_E 2.

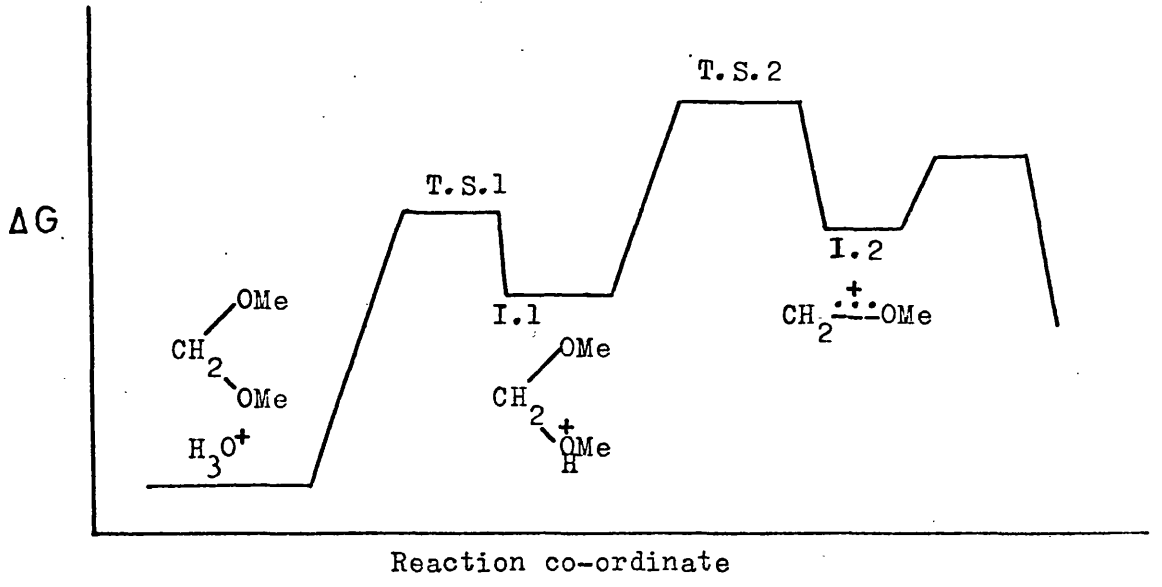
In the author's opinion the classification of the hydrolysis of the 2 - aryl - 4,4,5,5 - tetramethyl - 1,3 - dioxolanes as A-2 seems to be quite reasonable. The hydrolysis of the p - methoxyphenyl derivative need not necessarily be mechanistic general - acid catalysis, but might proceed by specific - acid catalysis and nucleophilic catalysis by formate. The arguments involved here will be discussed in more detail in a later section in terms of molecularity.

In contrast to the small catalysis observed for 2 - (p - methoxyphenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolane Capon and Anderson[26]

have detected general - acid catalysis for benzaldehyde methyl phenyl acetal in aqueous acetate buffers. It was considered that true mechanistic general - acid catalysis was being observed, since no catalysis could be detected for formaldehyde methyl phenyl acetal for which a mechanism involving nucleophilic and specific - acid catalysis should be more important. For the hydrolysis of the benzaldehyde acetal $k_{H^+}/k_{D^+} = 1.01$, and the Bronsted α - coefficient for catalysis by acetic, formic and chloroacetic acids is 0.58 compared with $k_{H^+}/k_{D^+} = 0.5$ and $\alpha = 0.8$ for the $\underline{A}\text{-}S_{\underline{E}}2$ hydrolysis of orthoesters.

In the full paper on benzaldehyde methyl phenyl acetals Capon and Anderson[27] discuss the structural features in an acetal, which would favour general - acid catalysis in its hydrolysis. Commencing with the free energy / reaction co-ordinate diagram, Fig. 1. To change from specific - to general -

Fig. 1



acid catalysis the free energy of T.S.1 will need to become greater than that for T.S.2. This can be achieved by increasing the free energy of T.S.1, decreasing that of T.S.2, or both. Assuming that the free energies of these transition states will follow those of the intermediates, I.1 and I.2, then general - acid catalysis will result from decreasing the basicity of the acetal oxygen and/or stabilising the carbonium ion. By Hammond's postulate T.S.2 will move to the left and T.S.1 to the right. Depending on the extent of stabilisation etc., they may or may not merge; these are shown in Figs. 2 and 3.

Fig. 2

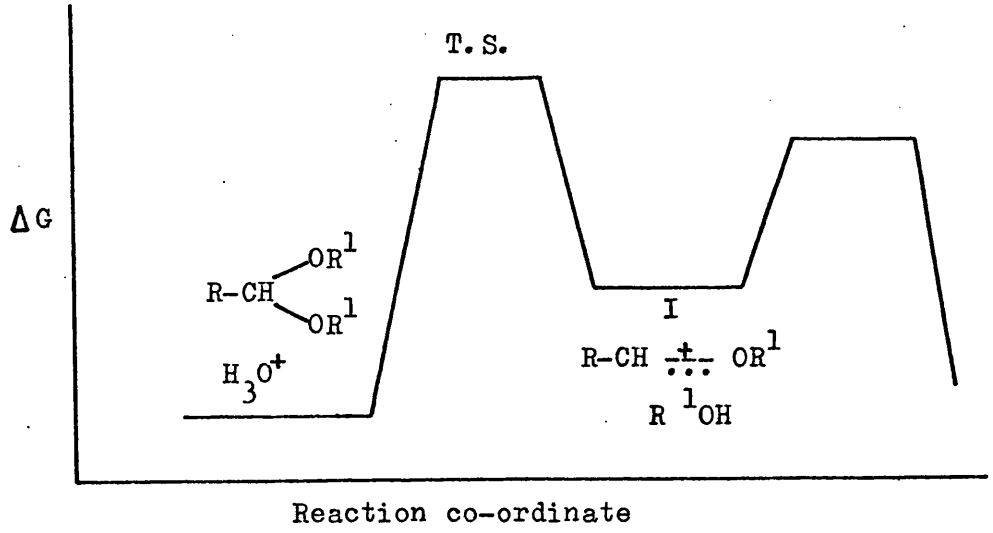
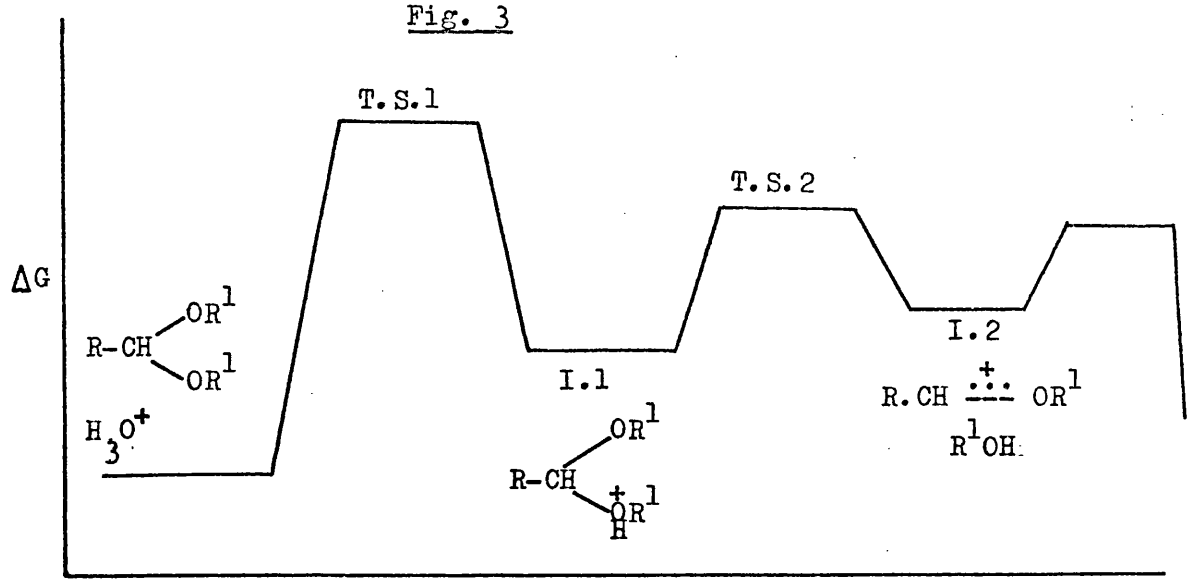


Fig. 3



Reaction co-ordinate

In the event of a merger, the slow step becomes a proton transfer between two oxygens, Fig. 2.

Fig. 3 depicts a concerted A-S$_E$ 2 displacement on oxygen.

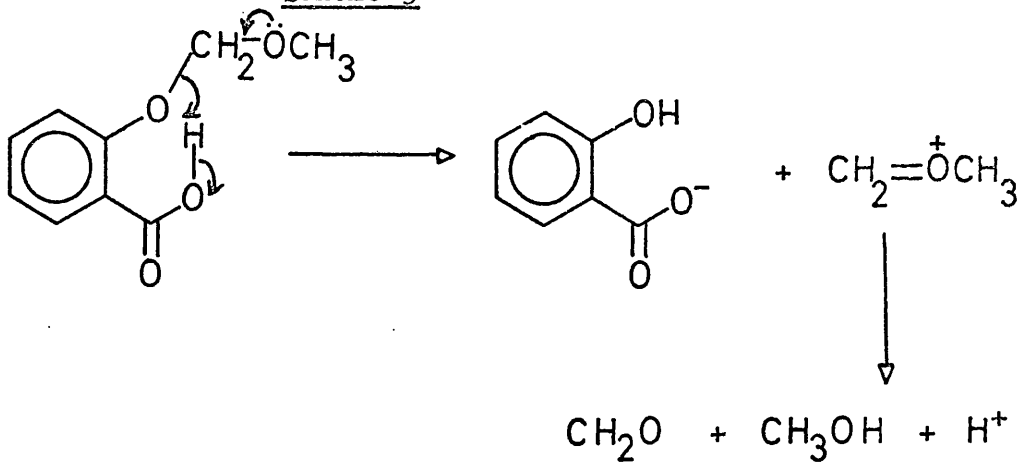
Thus the necessary structural changes are to use an aldehyde capable of forming a stable carbonium ion, and decreasing the basicity of the acetal oxygens; hence the use of benzaldehyde methyl phenyl acetal[27] as substrate.

It has been shown[28] that the formal o - methoxymethoxybenzoic acid at 45° in aqueous solution obeys the rate law,

$$k_{obs} = k \text{ (formal)}$$

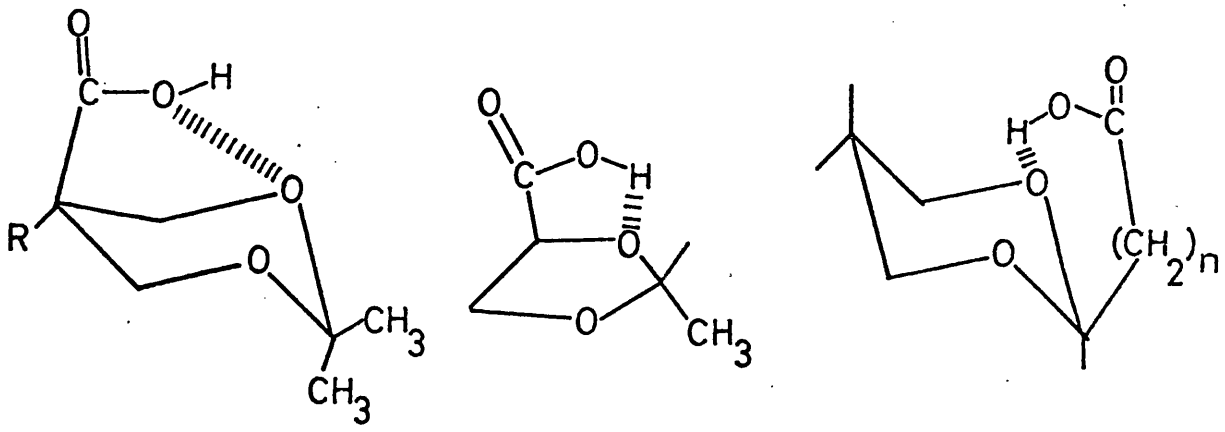
in the pH range 2 - 5 with an enhancement over the para - isomer of 400 - 650. Of the mechanisms considered the one shown in Scheme 3, was preferred.

Scheme 3



The deuterium isotope effect and later work[29] on substituent effects have confirmed these conclusions.

In the light of their hydrolysis studies Bruice and Piskiewicz[21] criticised this interpretation, but later accepted[30] Capon's reasoning. Among the substrates studied in a search for intra - molecular general - acid catalysis[21] were :



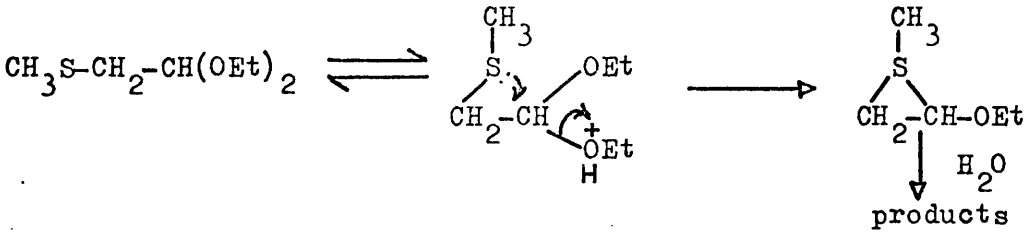
R = CH_3 , CH_2OH .

(1) (2) (3)

This unfortunate choice of substrates, each necessitating an unstable conformation for proton transfer to occur between the carbonyl oxygen and ketal oxygen, has been pointed out by Capon, Perkins and Rees.[31] "With compound (3) the distance between the carbonyl and ketal oxygens would increase on going to the transition state, a circumstance hardly likely to favour proton transfer between them." [31]

Speck et al[32] have suggested that the methyl - thio group of methyl - thio acetaldehyde diethyl acetal participates in its hydrolysis, as shown in Scheme 4.

Scheme 4



This is an example of nucleophilic catalysis. The acetal hydrolyses 10 times more slowly than acetaldehyde diethyl acetal, but about 100 times faster than the corresponding methoxy compound. These workers[32] argue that since the σ^* values of methyl - thio and methoxy are approximately the same, the rate enhancement must be due to nucleophilic participation.

c. The effect of ring size

Newman and Harper[33] have studied a series of dioxolanes and

dioxanes derived from cyclopentanone and cyclohexanone. Their results consistently show that the rate of hydrolysis of five membered rings is faster than for six membered. A typical result is shown in Table 2.

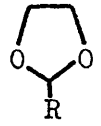
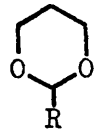
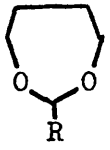
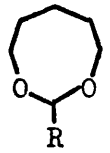
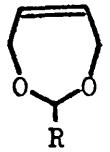
Table 2

1,3-dioxolanes of	$\underline{k}$ sec^{-1}	$\underline{k}$ relative
Cyclopentanone	25.1×10^{-5}	13
Cyclohexanone	1.93×10^{-5}	1

Spectrophotometrically determined rate data[33]

More recently, two series of workers have studied a series of hydrolyses on variation of diol ring size. Watts[34] has studied cyclic ketals of ring size 5 - 8 and Jary et al [35] have studied cyclic benzaldehyde acetals of ring size 5 -7. These results are summarised in Table 3.

Table 3

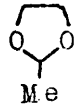
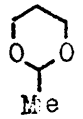
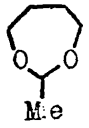
Substrate	Rate and (relative rate) a.	b.
	4.59 (3)	238 (6.1)
	1.67 (1)	39.2 (1)
	70.1 (42)	1000 (25.2)
	610 (365)	
		87.2 (2.2)

a. R = CH_3, Watts[34], spectrophotometrically determined data $\underline{k}_2 \times 10^2$, 1 $mole^{-1}$ sec^{-1}, at 36.0° in aqueous solution.

b. R = Ph, Jary et al[35], polarographic determined data $\underline{k}_1 \times 10^5$, sec^{-1}, at 25° in aqueous ethanol.

Watts[34] discusses his variations in rate in terms of inductive effects from the polymethylene chain and from the interactions between the two oxygens. He concludes that these inductive effects are of apparently little importance in determining the relative rates since both would be expected to lead to an increase in rate with ring size. The activation data given in Table 4, can be explained as arising from restriction of rotation in the molecule.[34]

Table 4

Substrate	$\Delta H^{\ddagger}$ k cal mole^{-1}	$\Delta S^{\ddagger}$ cal mole^{-1} deg^{-1}
	21.7	+4.84
	13.7	-23.17
	18.4	-0.41

Activation parameters calculated at 25° from spectrophotometrically determined rate data in dilute aqueous solution.[34]

d. Solvent isotope effects

Table 5 includes a selection of typical k_D/k_H values for various hydrolyses.

Table 5

Substrate	Temperature °C	Solvent	k_D/k_H	reference
acetaldehyde diethyl acetal	25	water	2.66	37
acetaldehyde diethyl acetal	25	50% dioxane	3.7	8
meta and para substituted benzaldehyde diethyl acetals	30	50% dioxane	2.8-3	38
2-methyl-1,3-dioxolane	25	water	3.7	39
2-(substituted phenyl) -1,3-dioxolanes	30	50% dioxane	2.9-3.3	38
2-(substituted phenyl) -1,3-oxathiolanes	30	water	2	40,41
ethyl orthoformate	15,25,35	water	>2	37,44
benzaldehyde methyl phenyl acetal	20	water	0.9	26,27
2-aryl-2-alkyl -1,3-dioxolanes		water	>2.75	42
2-aryl-4,4,5,5 -tetramethyl -1,3-dioxolane	30	water	2.4	43
2,2-diphenyl -1,3-dioxolane	30	1.3% dioxane	2.63	23
o-methoxy methoxy benzoic acid	45	water	0.7	28,29

Included is ethyl orthoformate, which has an isotope effect typical of these general - acid catalysed substrates. Ranges of values generally accepted for A-1 and A-2 mechanisms are 2.3 - 3.0[45] and 1.3 - 1.7[46] respectively although a value outside these ranges does not necessarily discount that particular mechanism, if only for the reason that as an empirical formulation they are based on assignments of mechanism from other criteria.

In a recent review on A-S_E 2 mechanisms[22] Kreevoy and Williams give the range of values 0.2 - 0.4 for k_D/k_H, and discuss the importance of primary and secondary isotope effects. Although it is fair to say that these data (Table 6) are taken from hydrolyses where proton transfer is onto carbon, it is interesting that DeWolfe et al[23] in assigning an A-S_E 2 mechanism to benzophenone ketals in dichloroacetate buffers quote a range of k_D/k_H of the order 2.0 - 2.7, with a value of 2.63 for 2,2 - diphenyl - 1,3 - dioxolane at 30° in 1.3% dioxane in 0.0197 N hydrochloric acid.

Table 6

Reaction	$(k_D/k_H)_I$	$(k_D/k_H)_{II}$	k_{D^+}/k_{H^+}
Isotope exchange in azulene	0.156	1.48	0.23
Isotope exchange in 1,3,5 - trimethoxybenzene	0.161	1.725	0.28
Ethyl vinyl ether hydrolysis	0.204	1.51	0.31
Allylmercuric iodide cleavage	0.2	1.54	0.31
Isobutenylmercuric bromide cleavage	0.212	1.85	0.395
2-Dichloromethylene - 1,3 - dioxolane hydrolysis	0.278	1.39	0.386

I primary solvent isotope effect

II secondary solvent isotope effect defined by $k_{D^+}/k_{H^+} = (k_D/k_H)_I \times (k_D/k_H)_{II}$

See Cordes [1]

Certainly, as can be seen from the results of Capon et al[27,29] for general - acid catalysed reactions where the rate determining protonation is on oxygen, the range of isotope effects might be better stated as 0.7 - 1.0. The buffer catalysis observed by DeWolfe et al[23] was in 20% and 50% dioxane, and dichloroacetate

buffer, but no catalysis was observable in formate solutions. Hence if we take up their postulate ".... the A-1 and S_E 2 mechanisms are extremes of a mechanistic continuum"[23] one could add from their solvent isotope findings, that the hydrolysis of benzophenone ketals and dioxolanes is more A-1 than A-S_E 2.

e. Entropy of activation

Entropy of activation, reviewed by Schaleger and Long[47], has been used extensively in the study of acid-catalysed hydrolysis. Experience from these studies shows that unimolecular reactions usually produce a value of approximately zero or slightly positive, whereas those proceeding by A-2 mechanisms have large negative entropies of activation ($\Delta S^{\ddagger}$).

The common standard state for entropy determinations is 1.00M acid at 25°. This is however not universal, as it may be impossible to measure the rate in 1M acid. In this respect it is of interest to consider results from sources using different methods or in differing solvents, Table 7.

Table 7

Substrate	medium	acid	temp	method	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	ref.
1,3 - dioxolane	water	H Cl	25	dilat.	24.9	-0.6	48
	water	H Cl	20-30	sulphite	26.5	+3.9	49
2,2 - dimethyl - 1,3 - dioxolane	water	H Cl	25	dilat.	18.2	-3.3	48
	50% dioxane	H Cl	30	spectral	18.5	-5.9	42
2 - phenyl - 1,3 - dioxolane	water	H Cl	20-30	spectral	14.8	-9.4	49
	50% dioxane	H Cl	30	spectral	15.5	-8.9	38
2 - phenyl - 2 - methyl - 1,3 - dioxolane	water	H Cl	20-30	spectral	17.5	-3.3	49
	50% dioxane	H Cl	30	spectral	16.6	-8.6	42

Firstly consider the various methods used. These include titrimetric determination of the aldehyde produced, dilatometric methods, which assume that changes in volume during a reaction are directly proportional to the rate of product formation, which has been shown not always to be true,[50] and spectrophotometric methods. The first two necessitate a high concentration of substrate and although they may give quite reproducible results, the observed rates may be far removed from the values observed in more dilute solutions, due to the substrate affecting the medium. Spectrophotometric methods, when used to monitor production of a chromophone with a high extinction coefficient are by far the best methods.

Consider the first entries in Table 7. Although Kankaanpera et al[48] quote a reproducibility of ± 1% in the rates (which would lead to an uncertainty of ± 1 entropy unit) their value of -0.6 and Ceders[49] value of +3.9 are well outside probable experimental error. Also in poor agreement are the values for 2,2 - dimethyl 1,3 - dioxolane measured in different media by different methods and the values for 2 - phenyl 2 - methyl - 1,3 - dioxolane determined by the same method in different solvents. In some compounds the possibility of two isomers exists and differing compositions might cause a discrepancy between different workers. However in the 2 - phenyl 2 - methyl - 1,3 - dioxolane both workers quote the same physical constants.

These data show that solvent changes and different methods of monitoring product formation do seem to affect entropy determinations. In Tables 8, 9 and 10, are listed some activation data typical of di-ethyl ketals and 1,3 - dioxolanes.

A further point that warrants discussion is the method used

to correct data to standard state. One method frequently used is to divide by the acid concentration[43] thus quoting a second order rate constant and using this for activation calculations. This is unreasonable whether reducing from 2M acid to 1M, or correcting 0.1M to a standard 1M state, and totally unacceptable for reducing rates determined in buffers (aqueous or dioxane) at varying pH's by dividing by a_H as determined from the apparent pH, especially when these values are then compared with values determined by other methods. These criticisms apply to a great deal of work.[23, 38, 42]

Table 8

Substrate	$\Delta H^{\ddagger}$ Kcal mole^{-1}	$\Delta S^{\ddagger}$ e.u.	reference
Acetophenone diethyl ketal	14.0	-0.4	42
Propiophenone diethyl ketal	15.4	+1.7	42
acetone diethyl ketal	15.2	+6.0	42
p-methoxy benzaldehyde - diethyl acetal	14.2	+0.7	38
p-methyl benzaldehyde - diethyl acetal	15.8	+2.0	38
benzaldehyde diethyl acetal	16.5	+1.0	38
p-chlorobenzaldehyde diethyl acetal	17.3	+1.0	38
p-nitrobenzaldehyde diethyl acetal	20.2	+1.3	38
2-phenyl-2-methyl-1,3-dioxolane	16.6	-8.6	42
2-phenyl-2-ethyl-1,3-dioxolane	17.4	-8.9	42
2-2-dimethyl-1,3-dioxolane	18.2	-3.3	42
2-(p-methoxyphenyl)-1,3-dioxolane	13.2	-9.6	38
2-p-cresyl-1,3-dioxolane	15.2	-6.9	38
2-phenyl-1,3-dioxolane	15.5	-8.9	38
2-(p-chlorophenyl)-1,3-dioxolane	16.9	-7.1	38
2-(p-nitrophenyl)-1,3-dioxolane	19.7	-7.3	38

Table 9

Substrate	acid	$\Delta H^{\ddagger}$ kcal mole^{-1}	$\Delta S^{\ddagger}$ e.u.	ref.
2-phenyl-4,4,5,5-tetramethyl -1,3-dioxolane	0.1M HCl	16.1	-14.2	43,51
2-(p-nitrophenyl) -4,4,5,5 - tetra-methyl - 1,3-dioxolane	0.1M HCl	17.5	-15.8	51
2-phenyl-2-methyl-4,4,5,5-tetra methyl -1,3 -dioxolane	0.1M HCl	21.6	-8.6	51
2-phenyl-1,3-oxathiolanes	0.1M HCl	14.9	-17.8	40
	1.0M HCl	16.8	-13.2	41
2-phenyl-2-methyl-1,3-oxathiolanes	0.1M HCl	12.6	-24.7	40

Table 10

Substrate	$\Delta S^{\ddagger}$ e.u.
Benzophenone diethyl ketal	+1.4
2-2-diphenyl-1,3-dioxolane	-8.3
2-2-di-(p-methoxyphenyl)-1,3-dioxolane	-6.0

Data of DeWolfe et al[23]
30% dioxan at 25°

However, one point that does stand out in the entropy data is the consistently more positive value of diethyl acetals and ketals, relative to the equivalent 1,3-dioxolane. This can be partly explained in terms of the molecularity of the process, and will be discussed later.

f. Volume of activation

This has been considered as a more reliable method than entropy, for determining the molecularity of a reaction.[52] Whalley[52] has used this method, which consists essentially of measuring the effect of pressure on reaction rate. Stated briefly, values of $\Delta V^{\ddagger}$ in the range -2 - + 6 cm^3 $mole^{-1}$ are typical of uni-molecular reactions and -6 - - 10 of bi-molecular. On this criterion acetal hydrolysis can be classified as A-1. Dimethyl acetal $\Delta V^{\ddagger} = + 1.5 \pm 0.5$.

A problem in both entropy and volume of activation determinations, and assignments based on them, is that the calculated value is a compound of the activation parameters for two steps, the equilibrium protonation and the rate determining heterolysis. It has been claimed that the volume of activation for the protonation step is negligible,[52] but this is based on very few actual measurements on some amine protonations. Thus the values of $\Delta S^{\ddagger}$ and $\Delta V^{\ddagger}$ for this step are indeterminant and not necessarily negligible, although they are normally given small positive values.

g. Acidity dependence

Most acetal hydrolyses studied in strong acid solutions have produced linear plots of log k_{obs} against $-H_o$ with slopes of approximately unity.[53] This, according to the Hammett - Zucker hypothesis[54] classifies them as A-1. Bimolecular reactions should give linear plots of log k_{obs} versus log $C_{H_3O^+}$. Assignments

based on this hypothesis are open to attack[55] at least on the question of the assumptions used.

The proportionality of log $\underline{k}_{obs}$ to $-H_o$ for an $\underline{A}$-1 mechanism is based on two assumptions:

1. That the ratio (SH^+) / (S) i.e. conjugate acid: substrate should change with medium in proportion to the quantity (BH^+) / (B), where B is the Hammett indicator base.

2. That the activity coefficient ratio, $\underline{f}_{SH^+}/\underline{f}_{TS^+}$ (where SH^+ is the conjugate acid and TS^+ is the transition state), is independent of the medium.

The conclusion that an $\underline{A}$-2 process should give a linear plot of log $\underline{k}_{obs}$ against log $C_{H_3O^+}$ is also based on two assumptions:

1. That the ratio (SH^+) / (S) should change with medium in proportion to the quantity (BH^+) / (B).

2. That the activity coefficient ratio, $\underline{f}_S \cdot \underline{f}_{H_3O^+}/\underline{f}_{TS^+}$, (where $\underline{f}_S$, $\underline{f}_{H_3O^+}$, $\underline{f}_{TS^+}$ are the activity coefficients of the substrate, H_3O^+, and the transition state respectively), is independent of the medium.

In each case neither assumption is necessarily valid. For the first assumption it has been shown, that the protonated to unprotonated ratio for substrate varies disproportionately to the ratio for base, and that the behaviour of the ratio is dependent on the specific structure of S and SH^+. Similarly for the second assumption, the activity coefficient ratio can depend on the structure of the conjugate acid and transition state.[56]

Bunnett[57] has suggested various other plots to make allowances for changes in medium effects, between ground state and transition state. These plots include log $\underline{k}_{obs}$ + H_o *versus* log $\underline{a}_{H_2O}$, with

the slope, w, determining the assignment.

Both the Hammett - Zucker and the Bunnett approaches have received their share of criticism[58,47] as have all empirical and semi-empirical formulations; however both are still applied and the approach seems to be, to use them if they produce a result consistent with other evidence.

In contrast to the normal unimolecular behaviour of acetals, Fife[43] has found that plots of log k_{obs} versus $-H_o$ are non-linear for the hydrolysis of 2 - (p-nitrophenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolane in concentrated solutions of hydrochloric acid, and that in this case log k_{obs} is proportional to log $C_{H_3O^+}$ over the range 1.0M to 5.51M acid. The slope of this latter plot is 2.0 rather than unity as predicted by the Hammett - Zucker hypothesis. A Bunnett plot gives a w - value of +1.9 suggesting that water is acting as a nucleophile. Certainly the data for the hydrolysis of this series of tetramethyl - 1,3 - dioxolanes (w - value, highly negative entropy of activation) seems to suggest that the mechanism has some bimolecular character, although this conclusion has been challenged by DeWolfe.[23]

h. Structure reactivity correlations

Table 11 records some of the correlations obeyed, with the values of parameters, for some acetals.

In a unimolecular hydrolysis of benzaldehyde diethyl acetals, involving rapid reversible protonation, and rate determining heterolysis to a carbonium ion, electron withdrawal in the aromatic ring should decrease the equilibrium concentration of protonated intermediate, and the rate of heterolysis. These two effects will reinforce one another and hence the relatively small ρ value obtained may reflect less conjugative interaction with the ring

than in the unimolecular solvolyses of benzhydryl derivatives.

In their study of substituted benzaldehyde diethyl acetals and 2 - (substituted phenyl) - 1,3 - dioxolanes, Fife and Jao[38] using σ values, obtained a curved plot, the point for the p - methoxy compound falling above the line obtained for the meta - substituted substrates. This was taken to indicate that the substituents were interacting with the carbonium ion through a resonance effect.[38]

Using σ^+ values for the diethyl acetal series produced a curve with downward curvature, the point for the p - methoxy substituted compound fell well below the best line. "Thus the σ^+ constants are overcompensating for the interaction of the substituents with the carbonium ion.[38]" Capon, Perkins and Rees[59] state that in their view the measured rate constant is a composite of the equilibrium constant for protonation (correlated by σ) and the rate constant (correlated by σ^+). Cordes[1] has treated the data of Fife and Jao, according to the considerations of Yukawa and Tsuno[60] using a linear free energy correlation of the form:

$$\log (k / k_o) = \rho \left[\sigma + r(\sigma^+ + \sigma)\right]$$

Applying this correlation produced good linear plots for $\rho = -3.35$ and $r = 0.5$ in the case of the diethyl acetals, and $\rho = -3.25$ and $r = 0.5$ for the benzaldehyde - 1,3 - dioxolanes.

In contrast to these data, measured in 50% dioxane, the hydrolysis of 2 - (p - substituted phenyl) - 4,4,5,5 - tetra methyl - 1,3 - dioxolanes in 0.1M hydrochloric acid correlates with $\sigma\rho$[43] with a ρ value of - 2.0. In this series which probably possesses some bimolecular character, electron withdrawal should facilitate

Table 11

Substrate	Solvent	Temperature °	$\log(k/k_o)$ Correlation obeyed	ρ	Reference
Substituted benzaldehyde diethyl acetals	50% aqueous dioxane	30	$\rho\left[\sigma + r(\sigma^+ + \sigma)\right]$	-3.35 r=0.5	38
2-(p-substituted phenyl) -1,3-dioxolane	50% aqueous dioxane	30	$\rho\left[\sigma + r(\sigma^+ + \sigma)\right]$	-3.25 r=0.5	38
2-(p-substituted phenyl) -4,4,5,5-tetramethyl -1,3-dioxolane	water	30	$\rho\sigma$	-2.0	43
2-2-di-(p-substituted phenyl) -1,3-dioxolane	20% dioxane	30	$\rho\sigma$	-4.6	23
2-alkyl-4,4,5,5 -tetramethyl-1,3-dioxolane	50% aqueous dioxane	30	$\rho^*\sigma^*$	ρ^*=-2.2	51

the reaction. Certainly the value of - 2.0 is suggestive of less carbonium ion character in the transition state than the - 3.35 for the diethyl acetals.

The value of - 4.6 found in the study of 2,2 - di - (p - substituted phenyl) - 1,3 - dioxolanes would seem to be in keeping with a mechanism involving more carbonium ion character, although DeWolfe et al[23] think to the contrary, on the grounds that log k_{H^+} does not correlate well with the Brown and Okamoto values of σ^+ [61].

In correlations involving alkyl substituents the ρ^* value of - 2.2 for 2 - alkyl - 4,4,5,5, - tetra methyl - 1,3 - dioxolanes[51] is rather less negative than the value of - 3.60 for the hydrolysis of diethyl acetals as correlated by the relation[62]

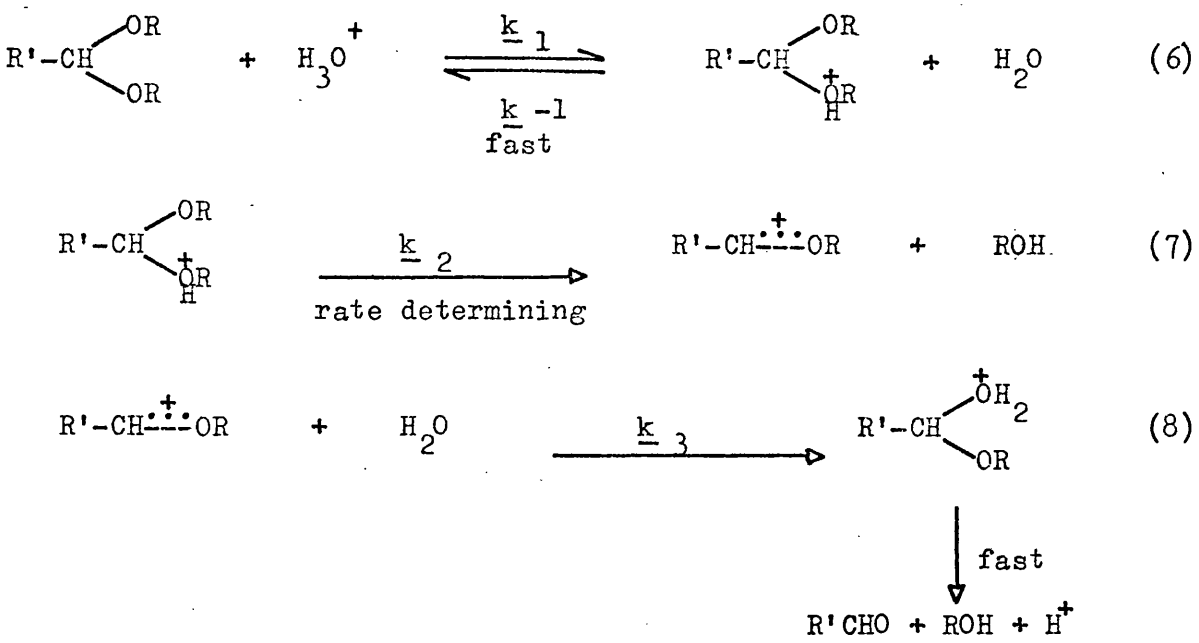
$$\log (k / k_0) = (\sum \sigma^*) \rho^* + (\Delta n)\, h \text{ for } h = 0.54$$

The value - 2.2 is again indicative of a mechanism involving some solvent participation in the transition state.

One final point concerning medium effects, Fife and Brod[51] have noted that the rate differences for benzaldehyde acetals are less pronounced in 50% aqueous dioxan than in water. This is a complicatory factor to be considered in comparing ρ values between various series.

i. Molecularity

The generally accepted mechanism of hydrolysis of acyclic acetals is shown in equations (6) - (8). It is a unimolecular process, consisting of a rapid reversible proton transfer, followed by a rate determining breakdown of this conjugate acid to a resonance stabilised carbonium ion, which is captured by water or other nucleophiles present in a further fast step.

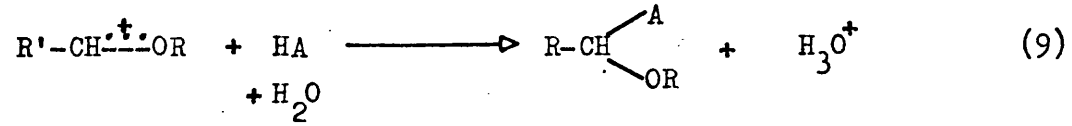


The regularity with which evidence added weight to this relatively straightforward picture, coupled with the observability of an A - S_E 2 mechanism for ortho - esters, in some respects a similar system, prompted several groups of workers to look for an acetal that would show non - general behaviour.

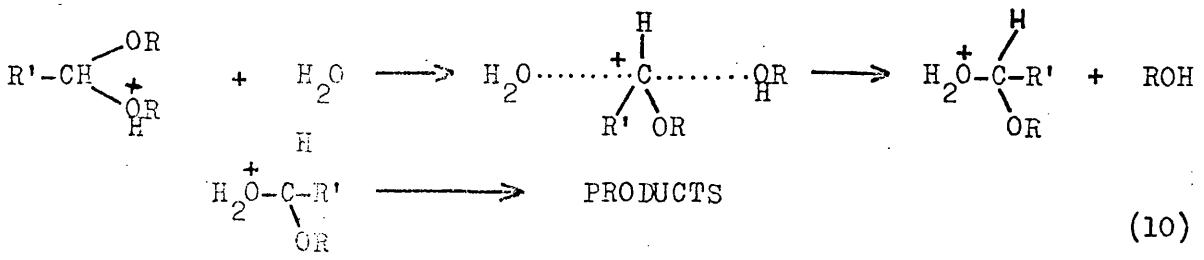
The deviations from the norm that have been considered are:

a Inducing step (6) to be rate determining, producing an A - S_E 2 reaction.

b Appearance of some bimolecular and possibly general - acid character, as shown in equation (9).



c Induction of a bimolecular attack, as shown in equation (10).



(10)

We can see from equations (6), (7), (8) and (9) that if step (7) was made reversible, as has been postulated in the case of 1,3 - dioxolanes,[64] this could lead to step (9) becoming rate limiting (b above).

Similarly if the reversibility or rapidity could be removed from step (6) this would produce a rate determining proton transfer (a).

Either of these, although they could not be distinguished from each other could be postulated on the detection of a dependence of rate on increasing concentrations of molecular acid.

Thus if buffer catalysis is observed, one could either evoke true general - acid catalysis or as arising from step (9) by a mechanism involving nucleophilic and specific - acid catalysis.

In their study of some benzaldehyde methyl phenyl acetals, Capon and Anderson[26] ruled out the possibility of nucleophilic and specific catalysis for this system, since they could observe no general - acid catalysis in the hydrolysis of formaldehyde methyl phenyl acetals, for which the nucleophilic pathway would be expected to be more important. Thus true general - acid catalysis is taking place and they assigned an A - S_E 2 mechanism.

Fife[43] has observed general - acid catalysis by formic acid in the hydrolysis of 2 - p - methoxyphenyl - 4,4,5,5 - tetramethyl - 1,3 - dioxolane, which he attributes to the operation of an A - 2 mechanism. This evidence includes solvent isotope effects and

entropy of activation for the phenyl and p - nitrophenyl - 4,4,5,5 - tetramethyl - 1,3 - dioxolanes. (See Table 12). Thus in this case step (6) is rapid and a mechanism such as equation (10) would seem to be partly rate limiting.

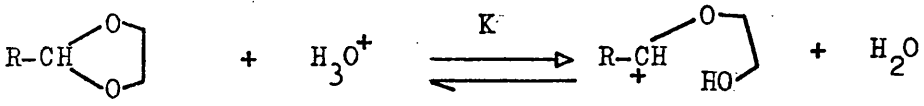
In the equivalent compounds lacking the alkyl substituents in the dioxolane ring, an entropy of activation of the order - 8 e.u. was found, compared with an average of + 1e.u. for the analogous diethyl acetals[38, 43] (see table 8). This was attributed to a normal A - 1 mechanism for both the 2 - (p - substituted - phenyl) - 1,3 - dioxolane and 2 - (p - substituted - phenyl) - diethyl acetals. The consistently more negative entropy of activation for dioxolanes was explained in terms of high solvation of the conjugate acids or transition states, or of restriction of rotation about the bond breaking in the transition state.

Capon and Thacker[64] suggested that the second step of the mechanism is reversible (equation (7)) i.e. the heterolysis of the carbon - oxygen bond. This is reasonable since the hydroxyl group produced on bond breaking is still part of the same molecule, and ring closure in five membered rings is favourable kinetically, certainly more so than in six membered rings.

The rate would then be given by

$$k_{obs} = k_2 \cdot K$$

where K is the equilibrium constant for the equilibrium



and k_2 is the rate constant for the reaction of this ion with water.

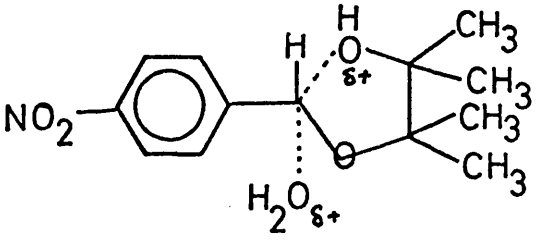
The observed entropy would be $\Delta S^{\ddagger} = \Delta S^{o} + \Delta S_2^{\ddagger}$

where ΔS^{o} is the standard entropy change for the above equilibrium, and would presumably be positive, while $\Delta S_2^{\ddagger}$ would be large and negative.

Thus the net entropy would be negative, but not so highly negative as for a normal A - 2 mechanism. Capon and Thacker applied this argument to their study of the hydrolysis of methyl D - glycofuranosides.[64]

This then would explain the negative entropies of activation of the phenyl - 1,3 - dioxolanes and would give their hydrolyses some degree of A - 2-character.

Fife and Brod[51] have recognised this suggestion and have applied it to explain the entropies of activation in the hydrolysis of 2 - (p - substituted-phenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolanes. The value of - 15.8 for the p - nitro derivative being particularly indicative of a bimolecular displacement such as that shown in (O).



(O)

This assignment gains weight when one considers the relative rates and activation data for the tetramethyl and pentamethyl - 1,3 - dioxolanes shown in Table 12.

Table 12

Substrate	Relative Rates Aqueous solution	50% Aqueous dioxane	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
2-p-nitrophenyl -4,4,5,5-tetra-methyl -1,3-dioxolane	0.044	-	17.5	-15.8
-4,4,5,5-phenyl -tetramethyl -1,3-dioxolane	1	1	16.1	-14.2
2-phenyl-2,4,4, 5,5-pentamethyl -1,3-dioxolane	0.00185	0.003	21.6	-8.6
2-phenyl-1,3-dioxolane	342	-		

From the relative rates of 2 - phenyl - 1,3 - dioxolane and 2 - phenyl - 4,4,5,5 - tetramethyl - 1,3 - dioxolane it is evident that in the alkylsubstituted compound the unimolecular rate determining heterolysis has been suppressed to a great extent, allowing the normally extremely slow bimolecular mechanism to become observable.

Also in contrast to the activation data for the tetramethyl compounds, which is typically A - 2, the pentamethyl 1,3 - dioxolane has an entropy more positive by 6.4 e.u. Both this and its overall slower rate could be reasonably explained in terms of steric inhibition of the bimolecular attack on C2, with no release of suppression of the unimolecular reaction.

Two recent studies of a series of meta - and para - substituted

- 1,3 - oxathiolanes, which contain certain inconsistencies, have recently appeared.[40, 41] Fife and Jao[41] have assigned a unimolecular mechanism to the hydrolysis of phenyl - 1,3 - oxathiolanes, based on linearity of log k_{obs} versus $-H_o$ (for the p - nitro substituted compound), ρ value of - 2.8, k_D / k_H = 1.93 and $\Delta S^{\ddagger}$ = - 13.2 and have criticised Fedor and De[40] who proposed some degree of A - 2 character from their data (ρ = - 1.66, k_D / k_H = 2.15, $\Delta S^{\ddagger}$ = - 17.8) for phenyl - 1,3 - oxathiolane.

Fedor[63] has corrected his rate constant for the p - nitrophenyl - 1,3 - oxathiolane hydrolysis and has amended his value of ρ to agree reasonably with Fife.[41]

The entropy of activation quoted by Fedor[40] for 2 - phenyl - 2 - methyl - 1,3 - oxathiolane is certainly consistent with a bimolecular process (see Table 9). It is interesting that Fedor and De[40] could find only a small decrease in rate in going from 2 - phenyl - 1,3 - oxathiolane to 2 - phenyl - 2 - methyl - 1,3 - oxathiolane (0.665: 0.565) compared with 2 - phenyl - 1,3 - dioxolane relative to 2 - phenyl - 2 - methyl - 1,3 - dioxolane (5: 1 relative rates). It is of greater interest that Fife and Jao[41] quote a rate increase by a factor of 2 for these oxathiolane compounds, using this in their argument against a bimolecular attack.

No catalysis by chloroacetic or acetic acids was detected in the hydrolysis of 1,3 - oxathiolanes.[40]

Another interesting problem in these compounds is the position of protonation. Here again Fife and Fedor disagree. Fedor favours protonation on oxygen, since the rate of hydrolysis of 2 - phenyl - 1,3 - dithiolane is extremely slow in 1 M acid.[40] The value of the solvent deuterium isotope effect (1.93) for 2 - (p -

methoxyphenyl) - 1,3 - oxathiolane which is quite low for an acetal, prompts Fife to suggest that protonation might be on sulphur, with the lower isotope effect bound up with the different energetics of - OH and - SH bonds. As further evidence Fife states that oxygen would stabilise the intermediate ion better than sulphur and that "ring opening reactions of this type generally proceed to give the most stable carbonium ion when two different heterocyclic atoms are in the ring."[41,42]

II. The mechansim of hydrolysis of cyclicacyclic acetals

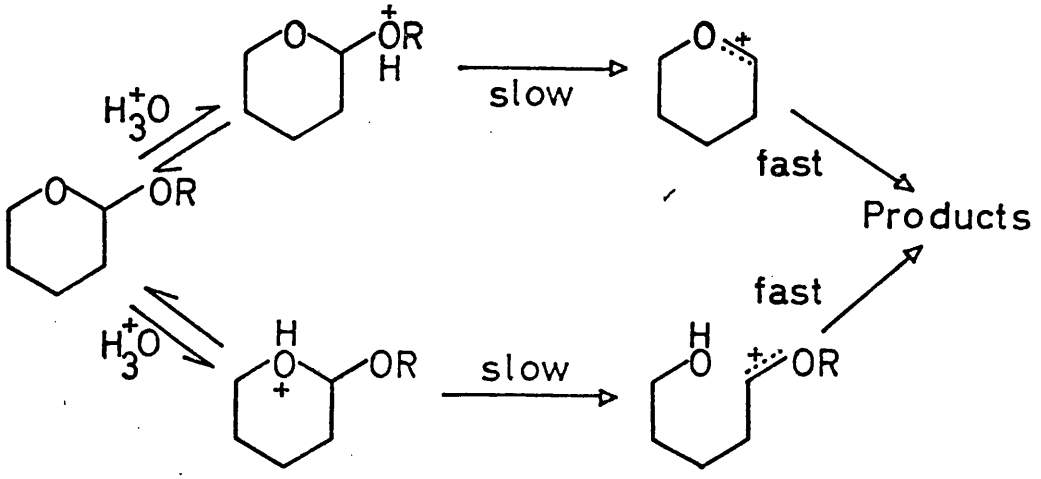
Recently work has appeared[6,7,43] on various cyclic acyclic acetals which since they act as a bridge between acyclic and cyclic acetals, and the glycosides, will be discussed on their own merit. The work of Kankaanpera and Mikki[6] has focussed on a series of 2 - alkoxytetrahydropyrans and 2 - alkoxytetrahydrofurans and was initiated[6] partly to investigate the mechanistic anomaly arising from the negative entropies of activation found for alkyl D - glycofuranosides[64] and cyclic acetals and ketals[38,42,51,65] relative to the positive entropies of the pyranosides[66] and acyclic acetals.[38,42]

Some of the work of Fife et al[7,43] overlaps that of Kankaanpera[6] and hence allows some interesting comparisons. It also includes a mechanistic study of some 2 - (substituted phenoxy)-tetrahydropyrans. Fife[7] states "..... a systematic study of the effect of the leaving group on the mechanism of acetal or glycoside hydrolysis has not been made ..... the hydrolysis reactions of a series of 2 - alkoxy and 2 - aryloxy tetrahydropyrans have been studied. These tetrahydropyran derivatives offer several advantages for study over the corresponding glycoside, including ease of synthesis and much faster rates of hydrolysis." This work[7] was conducted spectrophotometrically in 50% dioxane, although in the phenoxy tetrahydrofurans and pyrans studied in the present work, the author found that by optimising

concentration of stock solution and buffer strength, the hydrolyses could be followed with acceptable absorbance changes in aqueous solution. Certainly the ease of synthesis is a good point and the faster rate of hydrolysis is quite reasonable in view of the slower rates observed in dioxane solutions. But in aqueous solution the hydrolysis rates of the 2 - phenoxy tetrahydropyrans are too fast, certainly to measure activation parameters in an acceptable acid concentration, and the tetrahydrofurans are hydrolysed faster in aqueous perchloric acid solution by a factor of 2 over the tetrahydropyrans. It is perhaps pertinent that Fife has conducted his studies on 2 - phenyl - 4,4,5,5 - tetramethyl - 1,3 - dioxolanes and 2 - phenyl - 2,4,4,5,5 - pentamethyl - 1,3 - dioxolanes in aqueous solution.

In addition to the problems introduced in the assignment of mechanism to acyclic acetals, there is in the case of cyclic acyclic acetals the additional problem of position of protonation. This is the same problem as is encountered in glycoside hydrolysis, and the two productive protonation sites and possible subsequent stages of the unimolecular mechanism are shown in Schemes 5 and 6 for a tetrahydropyran derivative.

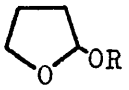
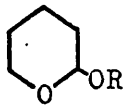
Scheme 5



Scheme 6

Table 12 shows some of the findings of Kankaanpera and Mikki.[6] It can be seen that the entropies of activation are indicative of a unimolecular reaction. The deuterium solvent isotope effect for the 2 - methoxy tetrahydrofuran and pyran are equal, $\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+}$ being 2.94,[6] which adds weight to a specific-acid catalysed unimolecular reaction.

Table 12

Structure	Substrate R	Rate $mole.^{-1}\ sec.^{-1}$ 25°	E $\underline{k}$ cal.$mole^{-1}$	$\Delta S^{\ddagger}$ e.u.
	CH_3	0.432	22.4	+13.0
	$CH_3.CH_2$	0.0658	21.5	+10.8
	$(CH_3)_2\ CH$	1.48	20.8	+9.9
	$CH_3O.CH_2.CH_2$	0.613	21.8	+11.6
	$Cl.CH_2.CH_2$	0.936	21.2	+10.4
	CH_3	0.0971	24.4	+16.7
	$CH_3.CH_2$	0.117	24.1	+16.0
	$(CH_3)_2\ CH$	0.201	23.8	+16.2
	$CH_3O.CH_2.CH_2$	0.136	24.1	+16.3
	$Cl.\ CH_2.CH_2$	0.189	23.1	+13.5

On these bases the unimolecular hydrolysis outlined in Schemes 5 and 6 would seem a reasonable starting point. Kankaanpera and Mikki[6] have attempted to correlate their data in terms of the partial

hydrolyses of a series of similarly substituted acyclic formaldehyde acetals.[67] The relative rates of hydrolysis derived from Table 12 are given in Table 13.

Table 13

R =	Cl.	$CH_2.CH_2$-	$CH_3O.CH_2.CH_2$-	CH_3-	$CH_3.CH_2$-	$(CH_3)_2$:CH-
k_{rel} Furan		2.11	1.41	1	1.51	3.40
k_{rel} Pyran		1.98	1.45	1	1.29	2.11

Considering Schemes 5 and 6, the rate of reaction is equal to the product of two factors viz, the equilibrium constant for the protonation step and the rate of the slow step. In the ring opening mechanism (Scheme 6) the polar influence of the group R on the basicity of the endocyclic oxygen atom will be slight, hence the effect of R on the equilibrium protonation step will also be slight. But the effect of R on the rate determining ring opening will be greater. The polar effects of R will be large and as R becomes more electron releasing the rate will be increased considerably by stabilisation of the oxonium - carbonium ion.

Consider the effect of these two factors on the partial hydrolysis reactions of formaldehyde acetals as determined by Salomaa,[67] shown in equations 11 and 12.

$$RO\text{-}CH_2\text{-}OR' \overset{H_3O^+}{\rightleftharpoons} RO\text{-}CH_2\text{-}\overset{+}{O}HR' \xrightarrow{\text{slow}} RO{=}\overset{+}{C}H_2 \qquad (11)$$

$$RO\text{-}CH_2\text{-}OR' \overset{H_3O^+}{\rightleftharpoons} RO\text{-}\overset{+}{C}H_2\text{-}OR' \xrightarrow{\text{slow}} \overset{+}{C}H_2{=}OR' \qquad (12)$$

The partial reaction for the formals, equivalent to scheme 6 for the alkoxytetrahydropyrans and furans is equation 11. Salomaa has found that for the partial hydrolysis, 11, using rate constants from following production of R'OH, the relative rates are as shown in Table 14.

Table 14

R =	$Cl.CH_2.CH_2$-	$CH_3O.CH_2.CH_2$-	CH_3-	$CH_3.CH_2$-	$(CH_3)_2$:CH-
k_{rel}	0.0480	0.201	1	4.48	22.1

Data from Salomaa[67], partial hydrolysis, relative rates for equation (11).

Comparison of these relative rates with those in Table 13 shows a big difference in the effect of R. In reaction 11, the rate increases along the series as the electron withdrawing power of R decreases. The effect is large, a factor of 460 being observed between the 2 - chloroethoxy and the isopropoxy derivatives, in contrast to the tetrahydropyran and furan data.

The partial reaction for the formaldehyde acetals equivalent to Scheme 5, is equation (12). The relative rates as determined by Salomaa for this reaction, the production of ROH are shown in Table 15.

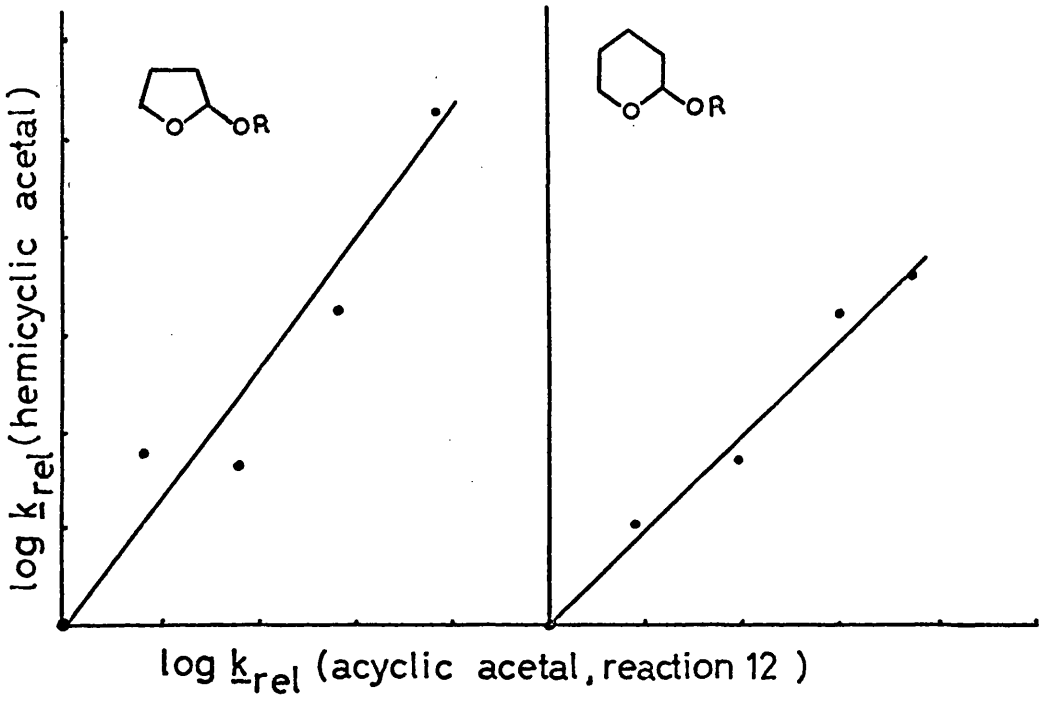
Table 15

R	$Cl.CH_2.CH_2$-	$CH_3O.CH_2.CH_2$-	CH_3-	$CH_3.CH_2$-	$(CH_3)_2$:CH-
k_{rel}	1.96	1.53	1	1.21	2.27

Data from Salomaa[67], partial hydrolysis, relative rates for equation (12).

Kankaanpera and Mikki[6] plotted the logarithm of the relative rates of hydrolysis of 2 - alkoxytetrahydrofurans and 2 - alkoxytetrahydropyrans, against the logarithms of the relative rates of equation (12). These plots are depicted in Fig.4.

Fig. 4

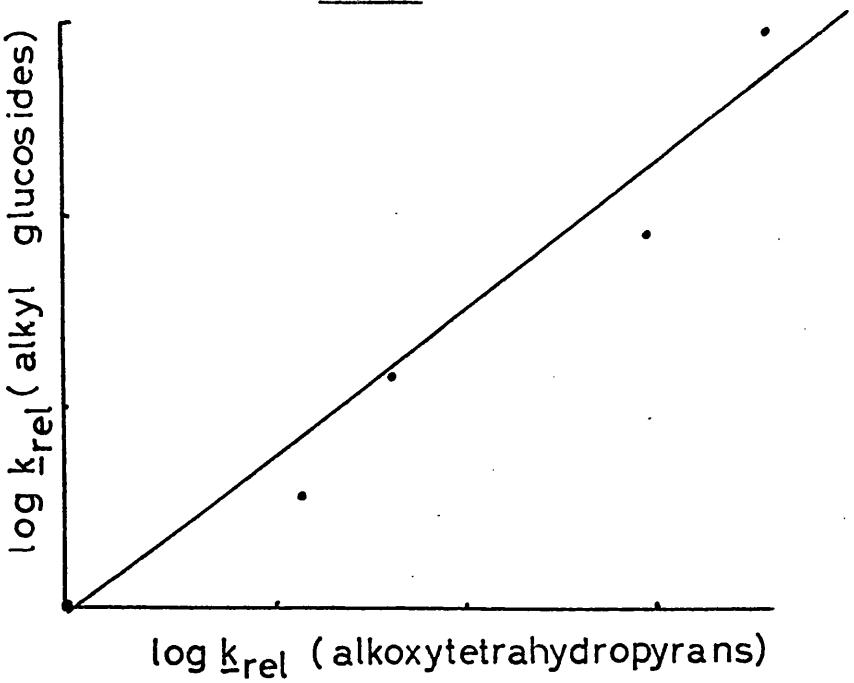


These plots ".... indicate a good linear free energy relationship ..... in accord with the assumption that 2 - alkoxytetrahydrofurans and pyrans hydrolyse via a cyclic carbonium ion (Scheme 5)"[6] The slopes 1.0 ± 0.1 and 1.3 ± 0.2 respectively show that the susceptibility to inductive effects is about the same in the hydrolysis of the acyclic and the cyclicacyclic acetals.[6]

Carrying these arguments a stage further a logarithm plot for

the relative rates of 2 - alkoxytetrahydropyran[6] versus alkyl β-D-glucopyranosides[68] is shown in Fig. 5.

Fig. 5



This plot shows that the structural effects in the hydrolysis of these pyranosides are consistent with Kankaanpera's data, which serves as additional proof of the hydrolysis of cyclicacyclic acetals proceeding through a cyclic carbonium ion. This would seem to be better evidence than that based on the Salomaa partial formal hydrolyses, since the mechanism of hydrolysis of alkyl glycopyranosides, and certainly the position of protonation has been established with a high degree of certainty.

The kinetic procedure of Kankaanpera and Mikki[6] involved gas chromatographic determination of alcohol. The standard error in rate determination is quoted as less than 2% and although the results,

and the parameters derived from them are probably quite consistent within the series, they do not compare very favourably with the data of Fife[7]; although this might be attributed to the aqueous dioxane medium used in the latter work. Table 16 allows a comparison of the activation parameters for 2 - ethoxytetrahydropyran and 2 - ethoxytetrahydrofuran as determined by these two groups.

Table 16

	Data of Fife & Jao[7,43] 30°		Data of Kankaanpera and Mikki[6] 25°		
	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	k_{rel}
2 - Ethoxytetrahydrofuran	-	+3.3	21.5	+10.8	5.6
2 - Ethoxytetrahydropyran	22.2	+7.9	24.1	+16.0	1

Fife[43] also quotes that for 2 - ethoxytetrahydrofuran a deuterium solvent isotope effect characteristic of an A - 1 mechanism was found, but leaves the reader to guess the acid strength and medium used. The isotope effects quoted by Fife and Jao[7] in their study of 2 - substituted tetrahydropyrans are given in Table 17.

Table 17

Substrate	k_D/k_H	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
2 - Ethoxytetrahydropyran	2.82	22.2	+7.9
2 - (p - methoxyphenoxy) - tetrahydropyran	2.48	-	-
2 - (p - methylphenoxy) - tetrahydropyran	2.39	-	-
2 - phenoxytetrahydropyran	2.29	17.9	-3.0
2 - (p - chlorophenoxy) - tetrahydropyran	2.01	-	-
2 - (p - nitrophenoxy) - tetrahydropyran	1.33	17.7	-7.6

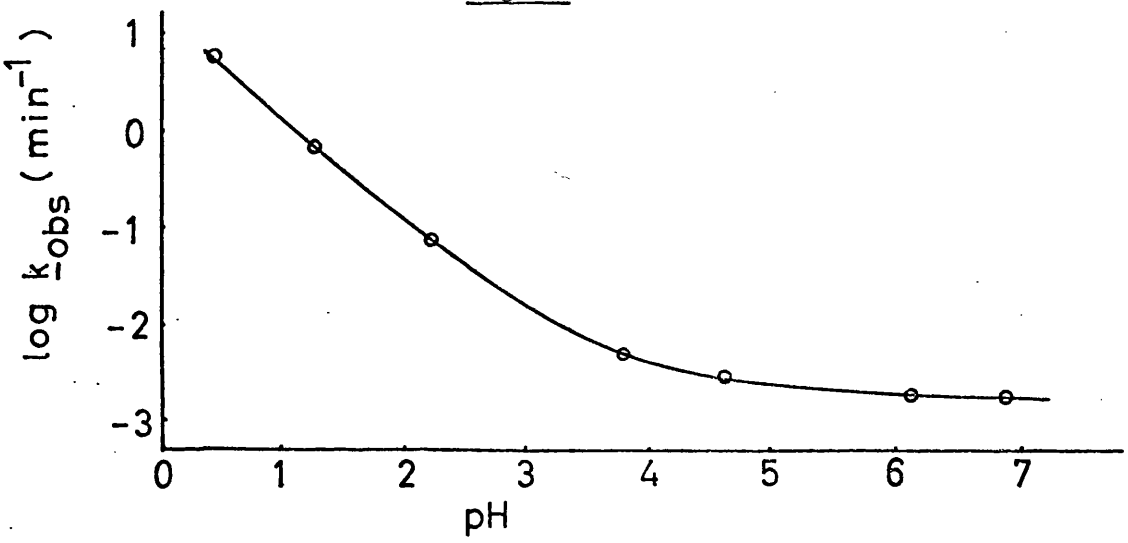
Data of Fife and Jao,[7] determined at 30° in 50% dioxane at pH 1.30.

From the data available in Table 17, we can see that there is a progression in $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and k_D / k_H in the compounds studied. The value k_D / k_H observed in the hydrolysis of 2 - ethoxytetrahydropyran is typical of an A - 1 mechanism,[45] whereas the value of 1.33 quoted for the p - nitro substituted compound is uncharacteristic of a unimolecular process and suggests a change in mechanism. That no abrupt change in mechanism is occuring in the substituted phenoxy series is shown by the linear plot of log k versus σ, the Hammett substitution constant, a value of -0.92 being quoted for the rho - value.[7] Other mechanisms considered were a bimolecular displacement and a general - acid catalysed mechanism. The data in table 17 are consistent with both of these. The observation of slight catalysis by molecular formic acid in the p - nitro - and

p - chloro - substituted compounds, which was undetectable in the 2 - (p - methoxyphenoxy) - tetrahydropyran, does not serve to distinguish between mechanisms involving nucleophilic and general - acid catalyses, but indicates the same gradation as the data of Table 17. Fife and Jao on the basis of solvent attack on acetals normally being an unfavourable process, favour the $\underline{A}\text{-}\underline{S}_E$ 2 mechanism, with the decreasing isotope effects explained in terms of the extent of proton transfer, ranging from complete in the ethoxy compound, to a concerted protonation and C - O bond breaking in the p - nitrophenoxy derivative.[6]

The pH - rate profile of 2 - (p-nitrophenoxy) - tetrahydropyran is shown in Fig. 6.

Fig. 6



From Fife and Jao[6], 50% aqueous dioxan at 50°.

The slope at lower pH is -1.0, but as the pH increases above 3 the profile flattens out to a plateau. The plot (Fig.6) was calculated[6] using the relation:

$$k_{obs} = k_o + k_H a_H$$

with the constants $k_o = 0.0014$ min^{-1} and $k_H = 10.7$ l. mole^{-1} min^{-1} at 50°.

In 0.05M sodium hydroxide the observed rate 0.0013 min^{-1} is approximately the same as for the spontaneous reaction.

III. The mechanism of acid-catalysed hydrolysis of glycosides

Both glycopyranosides and glycofuranosides generally exhibit both acid - and base - catalysed hydrolyses. The latter are frequently facile reactions. Although the base catalysed decomposition has received much attention,[69,70,71] the following discussion will be limited to hydrolyses in acid solution.

a. The position of bond cleavage

In a study of both anomers of methyl and phenyl D - glucopyranosides, Bunton et al[72] showed that the hydrolyses conducted in ^{18}O enriched water, produced methanol and phenol of normal isotopic abundance for oxygen. Further work[73] on o - hydroxymethylphenyl β - D - glucopyranoside, lactose, maltose and methyl 2 - deoxy - α - and β - D - glucopyranoside yielded similar results. Thus the hydrolysis proceeds by hexose - oxygen bond fission, Scheme 7.

Scheme 7

$$(C_6H_{11}O_5) - O - R + H_2{}^{18}O \longrightarrow (C_6H_{11}O_5) - {}^{18}OH + R - OH$$

However the acid - catalysed hydrolysis of t - butyl β - D - glucopyranoside was found to involve alkyl - oxygen fission[73] Scheme 8, which explains the anomalous rate of hydrolysis of this compound.[68]

Scheme 8

$$(C_6H_{11}O_5) - O - R + H_2{}^{18}O \longrightarrow (C_6H_{11}O_5) - OH + R - {}^{18}OH$$

This is understandable, if the reaction involves a unimolecular process, in terms of the greater stability of the t - butyl carbonium ion over the glycosyl carbonium ion.

In alkyl furanoside hydrolysis Capon and Thacker[64] have shown that the hydrolysis of ethyl β - D - galactofuranoside proceeds by hexose - oxygen fission, Scheme 7.

b. Nature of the acid - catalysis

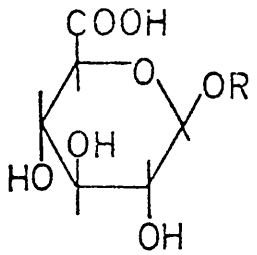
The slow rate of hydrolysis generally observed for glycosides relative to the equivalent acetals, has rendered their study in any medium other than strong acid solutions impossible. Only those glycosides exhibiting facile reactions have been studied in buffers. Capon and Smith[25] have studied the hydrolysis of methyl 2,5 - anhydro - α - L - arabinofuranoside in aqueous buffers, but could find only specific - acid catalysis. It is however possible that the mechanism of hydrolysis of this arabinofuranoside may be different to that of methyl α- D - glucopyranoside, since the former shows a strong tendency to undergo ring opening,[25] but whatever the mechanisms, buffer catalysis was not observed.

Bruice and Piszkiewicz[21] in a review of searches for intramolecular catalysis, include the o - carboxyphenyl β - D - glucopyranoside and 2 - naphthyl β- D - glucuronide studies of Capon et al.[74,75] In the former case a rate enhancement of 10^4 was found at pH 3.5, by extrapolation from results obtained at higher acidities. The mechanisms considered were intramolecular general - acid catalysis, intramolecular displacement by carboxylate ion on the O - 1 protonated glucoside and intramolecular nucleophilic electrophilic catalysis.[74] In the series of substituted-phenyl β - D - glucopyranosides studied by Nath and Rydon[70] the fastest reacting compound,

o - methoxy phenyl β - D - glucopyranoside, was hydrolysed only 27 times more rapidly than the slowest, p - nitro phenyl β - D - glucopyranoside. Ortho substituted phenyl - glycosides usually react faster than the corresponding para compounds, by a small factor, always less than ten. Thus an enhancement of ten is the maximum to be expected from inductive, mesomeric and steric effects of an ortho - carboxylate group. A mechanism involving general - acid catalysis was favoured,[74,29] evidence for this assignment stemming from the similarity between the hydrolysis of 2 - carboxyphenyl β - D - glucoside and 2 - methoxymethoxybenzoic acid. The solvent isotope effects are $k_{D_2O} / k_{H_2O} \simeq 0.64$ at 60.2° for the glucoside and 0.7 at 45° for the acetal. The effect of a 4 - nitro substituent for the glucoside is $k_{4\text{-}NO_2} / k_H = 4.8$ at 60.2° compared with 3.37 at 45° for the acetal.

2 - Carboxy α - D - glucopyranoside has been shown to behave similarly to the β - glucoside.[29]

Capon and Ghosh[75] observed a pH - rate profile characteristic of apparent intramolecular carboxyl group catalysis, for 2 - naphthyl β - D - glucuronide ((1), R = 2 - naphthyl).



(1)

However assuming a specific - acid mechanism they deduced that "..the relative rates of specific hydrogen ion - catalysed hydrolysis of the ionised glucuronide, glucoside, and deionised glucuronide are 1580 : 78 : 1 which correlate well with the inductive substituent constants".[75] Thus they concluded that this and many other glucuronides

hydrolyse only by a specific - acid catalysed mechanism.[75]

Saunders and Timell[76] in a study of the effects of substitution at C-5 observed a similar ratio, viz 2820 : 74 : 1, for methyl α - D - ionised uronic acid, glucoside, and unionised acid ((1), R= methyl), although the basis of this estimation is not clear.[77]

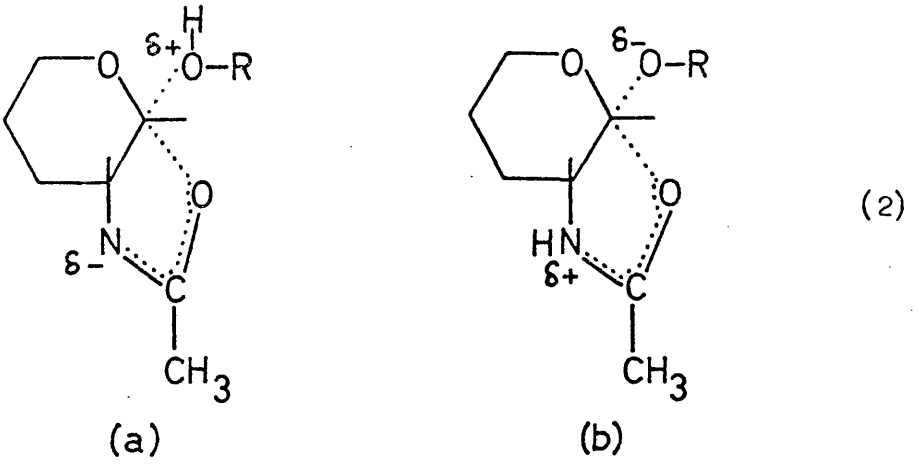
The rates of hydrolysis of methyl α- and β - D - glucopyranosid-uronic acids are slightly lower than the equivalent glucopyranosides.[78] An enhancement in rate of approximately 100, has been claimed for the carboxymethyl β - D - glucopyranosiduronic acid ((1), R = carboxymethyl), over carboxymethyl β - D - glucopyranoside.[78] In discussing these results Saunders and Timell have used similar arguments to those of Capon[74] in the case of o - carboxyphenyl β - D - glucoside, again preferring an interaction involving general - acid catalysis, although they admit their compound is less favourably set up for intra molecular catalysis.

It is perhaps of interest to note here that the rate of hydrolysis of carboxymethyl β - D - glucopyranoside in 0.5 M sulphuric acid is only about three times faster than that of methyl β - D - glucopyranoside,[68] in contrast to the enhancement observed between the 2 - carboxyphenyl and the phenyl glucosides.[74]

In a study of the hydrolyses of o - and p - nitro phenyl 2 - acetamido - 2 - deoxy - D - glucopyranosides and o - and p - nitrophenyl D - glucopyranosides at 78.2° between pH 0.75 and 11.72, spontaneous hydrolysis has been observed in the β - anomers, with specific - acid and specific - base catalysis operating in the α- anomers.[30] The spontaneous hydrolysis of the β - anomers was attributed to stereospecific anchimeric assistance by the acetamido and hydroxy groups. The acetamido group being 10^3 times more effective in this participation than the hydroxyl group.

Mechanisms considered were (a) intramolecular nucleophilic attack

by neutral acetamido group, and (b) intramolecular nucleophilic attack of the ionised acetamido group on the protonated glucosides. The transition states are shown in (2).



(2)

R = o - nitrophenyl, p - nitrophenyl

The leaving - group, as can be seen from (2)a, is a nitrophenol in the acid - catalysed hydrolyses and from (2)b, is a nitrophenolate anion in their neutral hydrolyses. The solvent isotope effects (see Table 19) suggest that the proton is not transferred in the rate determining step, and that water itself is not involved. The former point is confirmed by the lack of any observable buffer catalysis.

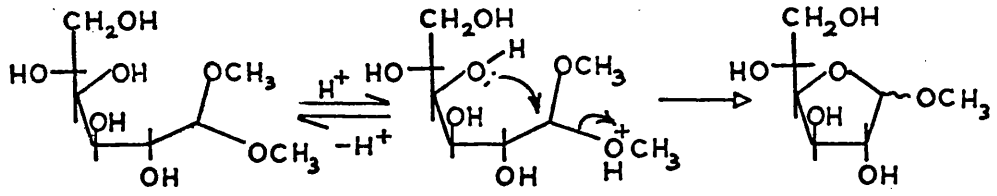
Further work from Bruice and Piszkiewicz[79] has shown that at 78.2° the spontaneous hydrolysis of o - carboxyphenyl - 2 - acetamido - 2 - deoxy - β - D glucopyranoside (3, not shown) is 7.1 times greater than that for o - carboxyphenyl β - D - glucopyranoside (4, not shown), although the σ^* constants for acetamido and hydroxyl groups are very similar. The conclusion drawn from this is that in the acid region (4) hydrolyses via neighbouring carboxyl group catalysis, and (3) with

concerted intramolecular acetamido and carboxyl group catalysis.[79]

Similarly, the specific - acid catalysis of methyl 2 - acetamido - 2 - deoxy - β - D-glucopyranoside proceeds with amido group participation. Hydrolysis in this case proceeds about 20 times faster than that of methyl β - D - glucopyranoside, and about 50 times faster than estimated for an unassisted hydrolysis.[80]

Examples of nucleophilic assistance in glycofuranose chemistry have been reported,[81,82] but these are not strictly hydrolyses. The rates of ring closure of the dimethyl acetals of D - glucose, D - galactose and L - arabinose in dilute aqueous acid are substantially greater than the rates of ionisation of hexanol dimethyl acetals, as calculated using Taft's $\rho^*\sigma^*$ relationship. They are also greater than the rate of hydrolysis of D - glyceraldehyde dimethyl acetal. Thus a synchronous process, as shown in Scheme 9, was postulated.

Scheme 9



c. The effect of ring size

Rate comparisons between analagous pyranosides and furanosides, of the same anomeric configuration and the same chirality, are complicated by the probable operation of more than one mechanism.

Table 18 gives a comparison between some alkyl glycosides of varying ring fusion, in 0.01 N hydrochloric acid at 95°.[4]

Table 18

Glycoside			$10^5 . k$ (sec^{-1})
Methyl	α -	D - mannopyranoside	0.38
Methyl	α -	D - galactopyranoside	0.88
Methyl	α -	D - glucopyranoside	0.96
Methyl	β -	D - glucopyranoside	1.15
Methyl	α -	D - mannofuranoside	57.5
Methyl	α -	D - galactoseptanoside	77
Ethyl	β -	D - glucofuranoside	220

d. Solvent isotope effects

Some deuterium solvent isotope effects observed in glycoside hydrolysis are summarised in Table 19.

The first four entries of Table 19, have values of k_D / k_H characteristic of specific - acid catalysed reactions, and hence of normal glycoside hydrolyses. The other entries are the low values normally associated with rate determining proton transfer or of reactions involving intramolecular catalysis, as discussed in section b.

Table 19

Glycoside	k_D / k_H	Temperature	Acid/Medium for Study	Ref.
	2.5	45	$HClO_4/D_2O$	73
Methyl 2-deoxy-α-D-glucopyranoside	2.5			
Methyl α-D-glucopyranoside	1.9	60	HCl/D_2O	66
Methyl α-D-xylofuranoside	2.5	25	DCl/D_2O	64
Some 3-indolyl β-D-glucopyranosides	2 - 2.6	50-60	D_2O	83
o-nitrophenyl 2-acetamido-2-deoxy- β -D-glucopyranoside	0.94	78	buffer/D_2O	30
o-nitrophenyl β -D-glucopyranoside	1.2	78	buffer/D_2O	30
N-p-tolyl-D-glucosamine	1.05	25	buffer/D_2O	84
	0.45	25	DCl/D_2O	
2-carboxyphenyl β -D-glucopyranoside	0.64	60.2	DCl/D_2O	29

e. Activation parameters

Some typical activation data for glycoside hydrolysis are reproduced in Table 20. Overend, Rees and Sequira[66] studied 24 pyranosides, their mean value for entropy of activation being 13.7, which is similar to the average value of Timell[68] in his study of 20 pyranosides. A recent comprehensive study of alkyl and aryl β-D-xylopyranosides in

0.5 M hydrochloric acid has produced results comparible with the analogous glucopyranosides.[85,86] In general comparison between different workers in differing solutions is good.

Table 20

Glycoside	Temperature °C	Acid	$\Delta S^{\ddagger}$ cal deg^{-1} mole^{-1}	E kcal mole^{-1}	Reference
Methyl α-D-glucopyranoside	60	2.0N HCl	+14.8	34.1	66
Methyl α-D-glucopyranoside	60	0.5M H_2SO_4	+16.9	35.1	68
Methyl α-D-glucofuranoside	25	1.0M $HClO_4$	-11.0	19.2	64
Ethyl β-D-galactofuranoside	60	2.0N HCl	-7.0	12.4	66
Ethyl β-D-galactopyranoside	60	2.0N HCl	+11.2	31.6	66
Phenyl β-D-glucopyranoside	60	2.0N HCl	+10.8	31.0	66
Phenyl β-D-glucopyranoside	60	-	+10	29.9	88
Methyl 2-chloro-2-deoxy β-D-glucopyranoside	60	2.0M HCl	+ 7.6	33.6	87
Methyl β-D-xylopyranoside	60	0.5M HCl	+16.1	33.2	85

Timell[89] has studied the effect of substitution at C - 3 and C - 5, in a series of pyranosides. The average value of $\Delta S^{\ddagger}$ for 5 - alkyl pyranosides was +15.7 e.u. The presence of a carboxyl group at C - 5

reduces this to +0.8 e.u. This type of reduction was found to be general for a series of methyl gluco -, galacto and mannosides and their uronic acids, and also for a series of alkyl β - $\underline{\underline{D}}$ - glucosides and glucuronides.[90] This sharp decrease was not observed in the phenyl analogues, and it was concluded that the phenyl glucuronide and the phenyl glucoside are hydrolysed by similar mechanisms.[88] Timell et al[90] attribute their differences to the fact that both polar and conformational factors are contributing to differing extents in different conditions, but also considered the possibility of a bimolecular mechanism. Capon and Ghosh[91] have found that $\underline{k}_{obs}$, for 2 - naphthyl β - $\underline{\underline{D}}$ - glucuronide, varies with acidity according to the equation:

$$\text{rate} = \underline{k}_{obs}.(\text{total glucuronide}) = \underline{k}_1.(\text{unionised glucuronide}) + \underline{k}_2.(\text{unionised glucuronide}) \times h_o$$

Thus the relative rate and activation data for glucuronides are complicated, since it seems likely that $\underline{k}_{obs}$ contains contributions from the rate constants for the hydrolysis of the ionised and unionised forms. There is no reason why the contributions of the two terms will be in the same proportion for any two glycuronides. Hence any discussion of relative reactivity in terms of $\underline{k}_{obs}$ is meaningless.[91] The same criticisms apply to entropy calculations for these compounds.

Tomita, Hirota and Nitta[92] have studied a similar set of glucuronides to Timell,[90] producing rather more negative entropies of activation. Since however some of the physical constants of their substrates appear to be inconsistent with values quoted in the literature, they will not be discussed further.

From the negative entropies observed for alkyl furanosides[64,66]

it would appear that there is a considerable degree of bimolecular character in their hydrolyses. *c.f.* section h.

Volume of activation calculations have returned values of + 6 $cm.^3$ $mole^{-1}$ for the inversion of sucrose,[93] and +5 $cm.^3$ $mole^{-1}$ for the acid - catalysed hydrolysis of methyl α - D - glucopyranoside,[58] which are consistent with the generally accepted unimolecular mechanism of hydrolysis of pyranosides.

f. Acidity dependence

Glycosides are hydrolysed far more slowly than skeletally equivalent acetals; a fact which can partly be attributed to the inductive effect of the hydroxyl groups, particularly the 2 - hydroxy group. As a result glycosides have been extensively studied in strongly acidic media.

For pyranoside hydrolysis the Hammett - Zucker hypothesis[54] for unimolecularity is normally satisfied. Plots of log k_{obs} versus $-H_o$ are linear with the unit slope condition approximately satisfied, deviations being apparent in either sense.[68,72,73,87,88,94] The variation of slope, for a given substrate, with change in acid has been studied[68] in an attempt to explain a variation in rate constants quoted for a given H_o value in different acids. The slopes were in the order $HCl > HClO_4 > H_2SO_4 > H_3PO_4$, the last acid giving a slope far removed from unity. The non-coincidence of these plots may be because H_o values, frequently measured at 25°, are applied to reactions in acids at 60 - 80°, when it has been noted that H_o is not independent of temperature.[95]

In their work on alkyl β - D - xylopyranoside hydrolysis, De Bruyne and Wijnendaele[85] calculate Bunnetts w and w* parameters, observing curves for these Bunnett plots and thus ranges for w and w*. w Was found to be zero or slightly negative, indicative of a unimolecular process while w* ranged from - 5 to - 13 which in Bunnetts terms

suggests a bimolecular reaction. In the phenyl β- D - xylopyranoside hydrolysis, w values were consistently small and positive, but the $\overset{*}{w}$'s were again in the range - 5 to - 13.[86] These results could either be interpreted in terms of a more complicated mechanism, or could show that not too much emphasis should be placed on a single piece of empirical evidence.

In alkyl furanoside hydrolysis,[64] plots of log k_{obs} versus $-H_o$ were linear with slopes considerably less than unity, and plots of log k_{obs} versus log C_{H^+} were curves. The value of w is in the range +1.05 - + 2.43 and in Bunnetts terms is within the limits of an A - 2 mechanism, in contrast to the w parameters calculated for pyranosides. In the alkyl furanosides this interpretation is quite consistent with the negative entropy of activation, although some other considerations will be discussed in section h.

g. Structure reactivity correlations

Rates of hydrolysis of aryl glycosides are affected only slightly by substitution in the aromatic ring, i.e. they have small rho values, due to cancellation of the opposing electron withdrawal effects on the protonation and heterolysis steps. Nath and Rydon[70] quote a ρ value of - 0.66 for the hydrolysis of phenyl β - D - glucopyranosides and of approximately zero for the α- D - glucosides. Semke and Williams[88] calculate ρ = - 0.48 for the former reaction and - 0.09 for a series of phenyl β - D - glucuronides.

The ρ value for a series of phenyl β - D - xylopyranosides is - 0.146[86] but many of the points were significantly removed from the best straight line, which was calculated by regression analysis. Indeed this plot could equally well have produced a maximum at the phenyl compound.

Frequently correlations based on alkyl substituents are less

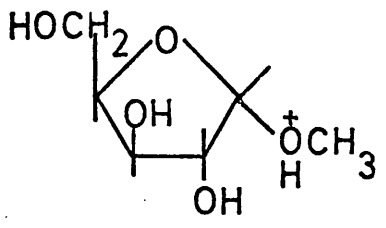
definite than for aryl compounds due to smaller rate differences within a series. This may be the reason that both Timell[78] and Tomita[92] both produced linear $\rho^* \sigma^*$ correlations for alkyl β - D - glucuronides but in the equivalent glucosides Timell gives a ρ^* value of approximately zero, whereas Tomita's results are correlated by two ρ^* values, one for electron releasing and another for electron attracting aglycones. On this basis he suggests a change in mechanism for these conditions.

h. Molecularity

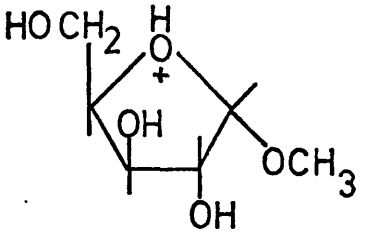
The bulk of the foregoing evidence suggests that glycopyranosides in general, hydrolyse by a specific - acid catalysed unimolecular process, as shown in Scheme 10.[96]

Partial A - 2 character has been suggested in the hydrolysis of methyl 2 - chloro - 2 - deoxy - β - D - glucopyranoside, mainly on the basis of an entropy of activation, more negative than the 2 - hydroxy glucoside (see Table 20), although all the other available data are characteristic of a unimolecular reaction.[87]

In contrast to the wealth of work on pyranosides the mechanisms of hydrolysis of furanosides have very infrequently been the subject of a major study. Capon and Thacker[64] reported negative entropies of activation for 7 methyl furanosides, which are consistent with the value of - 7.0 for ethyl β - D - galactofuranoside.[66] The deuterium solvent isotope effect (Table 19) for methyl α - D - xylofuranoside, suggests a specific - acid catalysed reaction producing a conjugate acid which could be either (5) or (6).

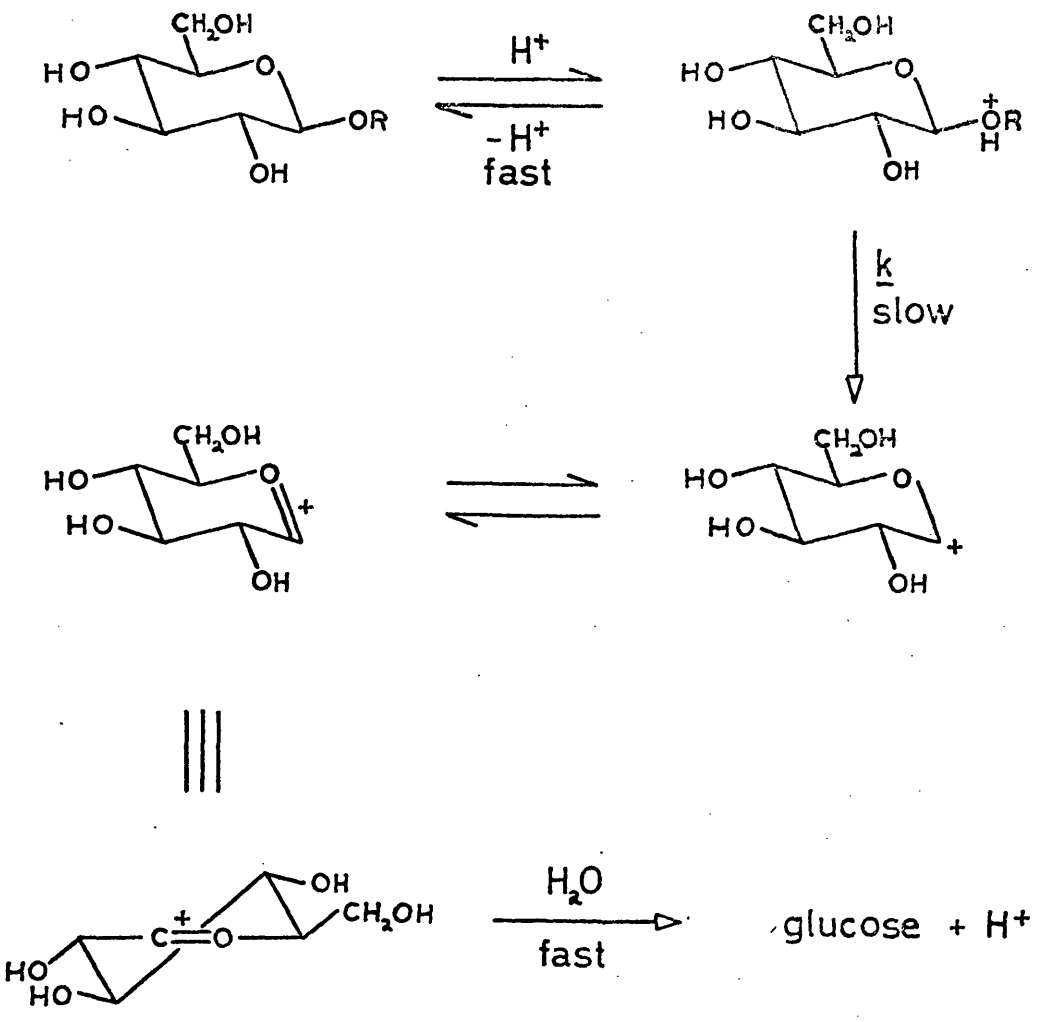


(5)



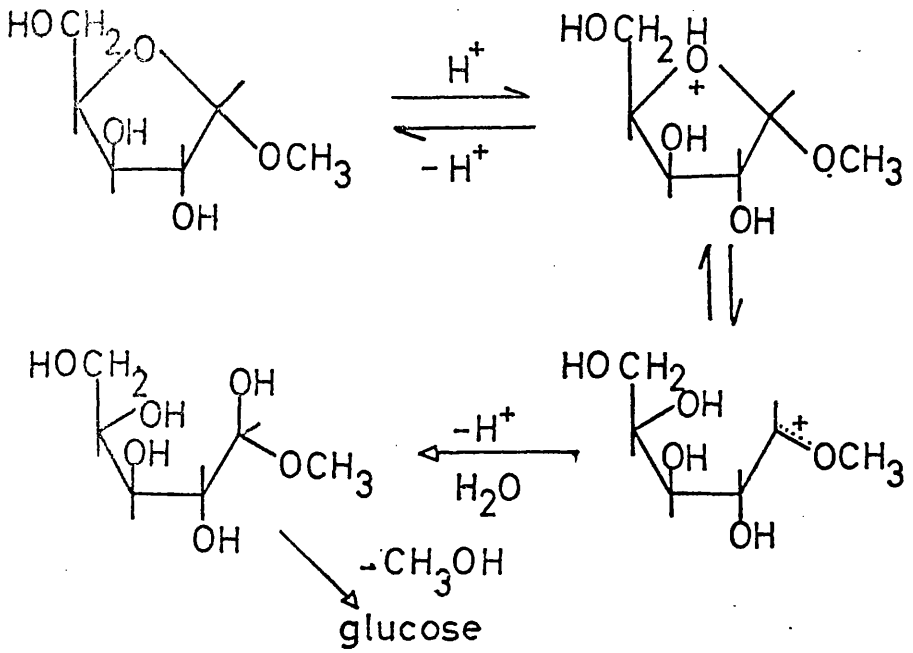
(6)

Scheme 10



One explanation considered was to assign a bimolecular mechanism to these furanosides, a process involving (5). An alternative explanation was that the mechanism proceeded via (6) with the subsequent ring opening being reversible (Scheme 11). This mechanism (see page 33-34) was also suggested for the hydrolysis of 1,3 - dioxolanes,[64] which also have negative entropies and which must proceed by ring opening.

Scheme 11



The entropy observed for such a mechanism would be less negative than for a normal A - 2 process. Either mechanism invokes some bimolecular character. Watts[34] attempted to observe the reversibility of the ring opening step by measuring the rates of hydrolysis and of racemisation of D - 1,2 - O - isopropylidene glycerol. Unfortunately the rate of racemisation could not be measured with sufficient accuracy to yield a conclusive result.

EXPERIMENTAL

1. Preparative experimental

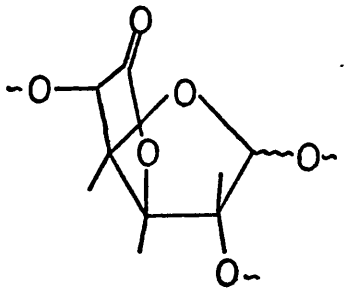
Melting points were measured on a Kofler - Reichert hot stage melting - point apparatus, and are uncorrected.

Rotations were measured on a Perkin-Elmer model 141 polarimeter.

Unless otherwise stated N.M.R. spectra were run on 60MHz. machines. The machines used were Varian T-60 and A-60, and a Perkin-Elmer R-10. 100MHz spectra were run on a Varian HA-100. Peak positions are measured downfield from internal T.M.S.

An L.K.B. Ultrorac, type 7000 fraction collector was used in glucoside purifications.

In the literature, names such as glucuronolactone and glucofuranosiduronolactone are used for the 3.6 - γ - lactone derived from glucofuranosiduronic acid. In this section the trivial names glucurone or glucuronide will be used exclusively and refer to the system:



1,2,5 - Tri - O - acetyl - β - D - glucurone

Tri - O - acetyl - β - D - glucurone was prepared from D - glucorone by the method of Goebel and Babers.[1]

M.p. 196 - 196.5° from ethyl acetate

$[\alpha]_D^{20}$ + 91.2° (c 1.5 in chloroform)

(lit.[1] 193 - 194° $[\alpha]_D^{20}$ + 89.6° (c 2 in chloroform)).

N.M.R. ($CD Cl_3$)

Multiplet 124 Hz. (9), acetyl methyls;
multiplet 300 - 318 Hz. (4), (H-2, H-3, H-4, H-5);
singlet 370 Hz. (1), anomeric proton.

I.R. (nujol mull) ν $cm.^{-1}$

1810 m., (lactone C=O str.); 1760 s., (acetyl C=O str.); 1240 b.s., (acetyl C-O str.); 1097, 1082 m., 1013 s., 980 w., 970, 960, 940, 920, 903, 840, (probably mostly associated with C-O-C, C-O-C-O-C and other vibrational modes available in the furanoside and lactone rings); 882 w., 808, 735, (various ring breathing).

2 - Naphthyl di - O - acetyl - β - D - glucuronoside

Following the method of Tsou and Seligman,[2] a finely ground mixture of tri - O - acetyl - β - D - glucurone (2g.), 2 - naphthol (3.5g.) and p - toluenesulphonic acid (0.1g.) was fused in vacuum for 30 minutes at 100.° The melt was crystallised by addition of ethanol. Recrystallisation from ethyl acetate gave 2g.(80%) of product in fine clusters, m.p. 227 - 230.° Two further recrystallisations gave pure compound, m.p. 231 - 232° (lit.[2] 231 - 232°).

I.R. (nujol mull) ν cm.$^{-1}$

1808 s., (lactone C=O str.); 1745 s., (acetyl C=O str.); 1627 w., 1600, (aromatic C=C str.); 1254 m., 1240, 1225 s., 1210 m., 1180, (various C-O str.); 1120 m., 1086, 1065, 1048, 1018 w., 985 m., 951, 898, (associated with C-O-C and C-O-C-O-C str.); 878 w., 827 v.w., (ring breathing); 855 m., 811, 752, (one, two and four adjacent aromatic C-H out of plane deformations).

Substituted phenyl 2,5 - di - O - acetyl - β - D - glucuronosides

A series of phenyl di - O - acetyl - β - D - glucuronosides was prepared by fusing tri - O - acetyl - β - D - glucurone with a phenol using p - toluene sulphonic acid as catalyst. Unless stated otherwise the technique was identical to that described for the 2 - naphthyl compound. Yields are of crude material.

Phenyl di - O - acetyl - β - D - glucuronoside

63%, m.p. 188 - 189°, $[\alpha]_D^{22}$ + 74.8° (c 1 in chloroform)

(lit.[3] m.p. 188 - 189°, $[\alpha]_D^{22}$ + 74.5° (c 1.85 in chloroform)).

N.M.R. (DMSO - d_6)

Two singlets 94, 127 Hz. (6), acetyl methyls;
multiplet 309 - 331 Hz. (4), (H-2, H-3, H-4, H-5);
singlet 363 Hz. (1), anomeric proton;
multiplet 410 - 450 Hz. (5), aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1805 m., (lactone C=O str.); 1755, 1747 m., (acetyl C=O str.); 1220 s., (acetyl C-O str.); 1050 m., 982, 948, 896, 885, 843 w., 840, (C-O-C and C-O-C-O-C str.); 875 w., (possibly ring breathing); 750 m., 685, (five adjacent aromatic C-H out of plane deformations).

p - Cresyl di - O - acetyl - β - D - glucuronoside

70%, m.p. 169 - 169.25° from methanol, chloroform and ethyl acetate.

$[\alpha]_D^{22}$ + 75.5° (c 1 in chloroform)

(Found: C, 58.44; H, 5.18. $C_{17}H_{18}O_8$ requires: C, 58.29; H, 5.18%).

N.M.R. ($CD Cl_3$)

Two singlets 103, 129 Hz. (6), acetyl methyls;
singlet 137 Hz. (3), 'cresyl' methyl;
multiplet 305 - 320 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 351 Hz. (1), (H-1, anomeric proton);
AA' BB' system 410, 418, 424, 433 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

1795 m., (lactone C=O str.); 1750 m., (acetyl C=O str.); 1590 w., (aromatic C=C str.); 1220 m., (acetyl C-O str.); 1120 w., 1050 m., 982, 944, 896, 850, (C-O-C and C-O-C-O-C str.); 885 w., 808, (ring breathing); 750 m., (p - subst. aromatics).

m - Cresyl di - O - acetyl - β - D - glucuronoside

The fused syrup which was miscible with ethanol, was triturated with petrol yielding a white crystalline mass.

60%, m.p. 175 - 175.5° from ethyl acetate
m.p. 176.5 - 176.8° from methanol.

$[\alpha]_D^{22}$ + 78.1° (c 1 in chloroform)

(lit.[4] - no physical properties quoted.)

(Found: C, 58.39; H, 5.22. $C_{17}H_{18}O_8$ requires: C, 58.29; H, 5.18%).

N.M.R. ($CDCl_3$)

Two singlets 101, 129 Hz. (6), acetyl methyls;
singlet 139 Hz. (3), 'cresyl' methyl;
multiplet 303 - 317 Hz. (3), (H-3, H-4, H-5);
singlet 330 Hz. (1), (H-2);
singlet 353 Hz. (1), (H-1, anomeric proton);
multiplet 408 - 440 Hz. (5), aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

1805 m., (lactone C=O str.); 1740 s., (acetyl C=O str.); 1600 w., (aromatic C=C str.); 1224 s., (acetyl C-O str.); 1122 w., 1080 m., 1060, 1046, 980, 948, 852, (various C-O-C and C-O-C-O-C str.); 872 m., 820 w., (possibly ring breathing); 895 m., 776, (m - subst. aromatics).

p - Methoxyphenyl di - O - acetyl - β - D - glucuronoside

The syrupy product was triturated with petrol.
70%. m.p. 128 - 130° from ethyl acetate.

$[\alpha]_D^{22}$ + 64.8° (c 1 in chloroform)

(Found: C, 55.96; H, 5.08. $C_{17}H_{18}O_9$ requires: C, 55.74; H, 4.95%).

N.M.R. ($CDCl_3$)

Two singlets 106, 128 Hz. (6), acetyl methyls;
singlet 225 Hz. (3), methoxyl;
multiplet 308 - 317 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 348 Hz. (1), (H-1, anomeric proton);

apparent doublet 415 Hz., J_{ab} 1.5 Hz.(4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1802 s., (lactone C=O str.); 1750 s., (acetyl C=O str.); 1128 m., 1113, 1095, 1082, 1055, 1030, 992, 948, 905, 856 w., (probably mostly associated with various C-O-C and C-O-C-O-C str.); 887 w., 829 m., (ring breathing); 738 m., (p - subst. aromatics).

p - Chlorophenyl di - O - acetyl - β - D - glucuronoside

67%, m.p. 157.5 - 158° from methanol.

$[\alpha]_D^{22}$ + 65° (c 0.5 in chloroform)

(Found: C, 50.27; H, 3.97. $C_{16}H_{15}O_8Cl$ requires: C, 51.83; H, 4.08%).

N.M.R. ($CD Cl_3$)

Two singlets 105, 130 Hz. (6), acetyl methyls;
multiplet 304 - 320 Hz. (3), (H-3, H-4, H-5);
singlet 330 Hz. (1), (H-2);
singlet 350 Hz. (1), (H-1);
AA' BB' system 413, 422, 434, 443 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1792 m., (lactone C=O str.); 1730 m., (acetyl C=O str.); 1582 v.w., 1570 w., (aromatic C=C str.); 1218 s., (acetyl C-O str.); 1118 w., 1078 m., 1045, 978, 937, 860, (C-O-C and C-O-C-O-C str.); 882 m., 820 w., (ring breathing); 812 s., (p - subst. aromatics); 732 w., (possibly C-Cl str.).

m - Ethoxycarbonylphenyl di - O - acetyl - β - D - glucuronoside

79% m.p. 166.5 - 167° from ethyl acetate and methanol.

$[\alpha]_D^{22}$ + 54.2° (c 0.75 in chloroform)

(Found: C, 55.75; H, 4.88. $C_{19}H_{20}O_{10}$ requires: C, 55.88; H, 4.94%).

N.M.R. ($CDCl_3$)

Triplet 82 Hz., J_{ab} 7 Hz. (3), CH_3 of ethyl group;
two singlets 100, 129 Hz. (6), acetyl methyls;
quartet 263 Hz., J_{ab} 7 Hz. (2), CH_2 of ethyl group;
multiplet 309 - 320 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 355 Hz. (1), (H-1);
multiplet 430 - 470 Hz. (4), aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

1800 m., (lactone C=O str.); 1755 s., (acetyl C=O str.); 1730 m., (ethyl ester C=O str.); 1245 m., 1220, 1197, (various C-O str.); 1119, 1082, 1073, 1058 s., 1015 w., 982 m., 946, 882, 850, (associated with various multiple - C-O-C- str.); 892 m., 744 s., (m - subst. aromatics); 876 m., 832 w., (possibly ring breathing).

m - Chlorophenyl di - O - acetyl - β - D - glucuronoside

71%. m.p. 196.5 - 197° from methanol.

$[\alpha]_D^{22}$ + 53.0° (c 0.5 in chloroform)

(Found: C, 51.75; H, 4.07. $C_{16}H_{15}O_8Cl$ requires: C, 51.83; H, 4.08%).

N.M.R. ($CD Cl_3$)

Two singlets 105, 129 Hz. (6), acetyl methyls;
multiplet 302 - 320 Hz. (3), (H-3, H-4, H-5);
singlet 328 Hz. (1), (H-2);
singlet 349 Hz. (1), (H-1);
multiplet 406 - 449 Hz. (4), aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

1817 m., (lactone C=O str.); 1750 s., (acetyl C=O str.); 1600 w., 1585 v.w., (aromatic C=C str.); 1228 s., (acetyl C-O str.); 1128 w., 1100, 1088, 1070, 1050, 985, 954, (various C-O-C and C-O-C-O-C str.); 884 w., (ring breathing); 857 m., (m - subst. aromatics); 780 m., (C-Cl str.).

p - Bromophenyl di - O - acetyl - β - D - glucuronoside

Fusion at 100° for 15 minutes at a pressure of 1 torr gave a red syrup which on trituration with petrol gave a semi - solid product 40%.

M.p. 151 - 151.5° from chloroform

$[\alpha]_D^{22}$ + 82.1° (c 0.75 in chloroform).

N.M.R. ($CD Cl_3$)

Two singlets 104, 129 Hz. (6), acetyl methyls;
multiplet 307 - 317 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 350 Hz. (1), (H-1);
AA' BB' system 409, 419, 442, 452 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1798 s., (lactone C=O str.); 1750 s., (acetyl C=O str.); 1590 v.w. 1580 w., (aromatic C=C str.); 1250 s., 1230, 1220, 1170, (acetyl and other C-O str.); 1080 m., 1050 s., 1027 m., 988, 955, 902, 852 w., (mostly C-O-C and C-O-C-O-C str.); 883 w., 840, (ring breathing); 830 m., (p - subst. aromatics).

m - Bromophenyl di - O - acetyl - β - D - glucuronoside

77%, m.p. 197 - 197.5° sublimed.

$[\alpha]_D^{22}$ + 81.66° (c 0.7 in chloroform).

(Found: C, 47.44; H, 4.27. $C_{16}H_{15}O_8Br$ requires: C, 46.43; H, 4.17%).

N.M.R. ($CD Cl_3$)

Two singlets 103, 126 Hz. (6), acetyl methyls;
multiplet 300 - 318 Hz. (3), (H-3, H-4, H-5);
singlet 325 Hz. (1), (H-2);
singlet 346 Hz. (1), (H-1);
multiplet 408 - 438 Hz. (4), aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1810 m., (lactone C=O str.); 1745 s., (acetyl C=O str.); 1595 v.w. 1585 w., (aromatic C=C str.); 1227 s., (acetyl C-O str.); 1126 m., 1069, 1045, 983, 953, (various C-O-C and C-O-C-O-C str.); 880 v.w., (ring breathing); 857 m., (m - subst. aromatics).

p - Nitrophenyl di - O - acetyl - β - D - glucuronoside

The dark brown immobile syrup left after 30 min. fusion at 100° was dissolved in chloroform. The chloroform solution was washed repeatedly with 1M sodium bicarbonate to remove p - nitrophenol. The solution was dried with sodium sulphate and evaporated, the product (1 spot T.L.C. - ethyl acetate - benzene) was a syrup, (90%). Sublimation gave a seed crystal. Recrystallisation from ethyl acetate gave 82%, m.p. 164 - 170°. Two further recrystallisations gave pure product, m.p. 178 - 179°.

(lit.[5] 179 - 180°) $[\alpha]_D^{22}$ + 55.0° (c 0.5 in chloroform)

(lit.[5] $[\alpha]_D^{22}$ + 54.5° (c 1 in chloroform)).

N.M.R. ($CD Cl_3$)

Two singlets 101, 131 Hz. (6), acetyl methyls;
multiplet 314 - 322 Hz. (3), (H-3, H-4, H-5);
singlet 331 Hz. (1), (H-2);
singlet 360 Hz. (1), (H-1);
AA' BB' system 424, 433, 491, 500 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

1796 s., (lactone C=O str.); 1750 s., (acetyl C=O str.); 1610 w., 1588 m., (aromatic C=C str.); 1512 m., 1370, (asymmetric and symmetric NO_2 str.); 1220 - 1210 s., (acetyl C-O str.); 1118 m., 1103, 1082, 1070, 1036 s., 1016 m., 975, 948, 840, (various C-O-C and C-O-C-O-C str.); 896 m., 830 w., (ring breathing); 740 m., (p - subst. aromatics)

m - Fluorophenyl di - O - acetyl - β - D - glucuronoside

76%, m.p. 201.5 - 202.5° from chloroform.

$[\alpha]_D^{22}$ + 68.4° (c 0.5 in chloroform)

(Found: C, 55.00; H, 4.02; F, 5.6. $C_{16}H_{15}O_8F$ requires: C, 54.24; H, 4.26; F, 5.4%).

N.M.R. ($CDCl_3$)

Two singlets 105, 129 Hz. (6), acetyl methyls;
multiplet 305 - 318 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 351 Hz. (1), (H-1);
multiplet 400 - 416 Hz. (4), aromatics

I.R. (KBr disc) ν $cm.^{-1}$

3120 w., 3080, 3060, (aromatic =C-H str.); 1815 s., (lactone C=O str.); 1755 s., (acetyl C=O str.); 1380 m., (C-F str.?); 1230 s., (acetyl C-O str.); 1137 m., 1092, 1060 s., 1038 m., 990, 953, 902, 860, (probably mostly associated with C-O-C and C-O-C-O-C str.); 880 w., 823, (ring breathing); 837 s., (m - subst. aromatics).

p - Fluorophenyl di - O - acetyl - β - D - glucuronoside

66%, m.p. 181 - 181.5° from ethyl acetate,
m.p. 181.5 - 182° sublimed.

$[\alpha]_D^{22}$ + 70.8° (c 0.4 in chloroform).

N.M.R. ($CD Cl_3$)

Two singlets 105, 128 Hz. (6), acetyl methyls;
multiplet 303 - 320 Hz. (3), (H-3, H-4, H-5);
singlet 329 Hz. (1), (H-2);
singlet 349 Hz. (1), (H-1);
apparent doublet 420 Hz., J_{ab} 6 Hz. (4), p - subst. aromatics.

I.R. (KRr disc) ν $cm.^{-1}$

1812 s., (lactone C=O str.); 1755 s., 1745, (acetyl C=O str.); 1618 w., 1598, (aromatic C=C str.); 1375 m., (C-F str.?); 1230 s., (acetyl C-O st.); 1142 m., 1128, 1090, 1075, 1052, 988, 900 w., 857 w., (various C-O-C and C-O-C-O-C str.); 880 w., 830 v.w., (ring breathing); 852 m., (p - subst. aromatics).

m - Nitrophenyl di - O - acetyl - β - D - glucuronoside

70%, m.p. 145 - 150° from ethyl acetate.

$[\alpha]_D^{22}$ + 55° (c 5.0 in chloroform).

N.M.R. ($CD Cl_3$)

Two singlets 102, 130 Hz. (3), acetyl methyls;
multiplet 310 - 322 Hz. (3), (H-3, H-4, H-5);
singlet 331 Hz. (1), (H-2);
singlet 356 Hz. (1), (H-1);
multiplet 440 - 480 Hz. (4), aromatics.

I.R. (KBr disc) ν $cm.^{-1}$

1795 s., (lactone C=O st.); 1740 s., (acetyl C=O str.); 1616 w., 1580 m., (aromatic C=C str.); 1520 s., 1350, (asymmetric and symmetric

NO_2 str.); 1230 - 1210 s., (acetyl C-O str.); 1120 s., 1075, 1020, 980, 952, 840, (various C-O-C and C-O-C-O-C str.); 897 m., 830, (ring breathing); 880 m., 796, (m - subst. aromatics).

Attempted preparation of m - methoxyphenyl di - O - acetyl - β - D - glucuronoside

The fused syrup was miscible with ethanol and failed to crystallise on trituration with ether or petrol. 1g. of the syrup was dissolved in chloroform and adsorbed on silica gel (10g.) and added to a dry packed column of silica gel. Elution with 50% ether - petrol gave a positively rotating fraction (30 ml.). Elution with ethyl acetate gave no further rotating fractions. The 30 ml. fraction gave a syrup on evaporation that crystallised on addition of methanol. Recrystallisation from ethyl acetate gave 500 mg. needles m.p. 195 - 196°. N.M.R. showed this to be tri - O - acetyl - β - D - glucurone. Admixture with an authentic sample gave no depression of melting point.

Attempted condensation of p - hydroxybenzoic acid with tri - O - acetyl - β - D - glucurone

A mixture of p - hydroxybenzoic acid (2.5 g.) m.p. 216°, tri - O - acetyl - β - D - glucurone (2 g.) and p - toluene sulphonic acid failed to fuse when heated at 100° under water pump pressure or at 150° under 1 m.m. pressure.

Attempted condensation of methyl p - hydroxybenzoate with tri - O - acetyl - β - D - glucurone

A mixture of methyl p - hydroxybenzoate (2.5 g.) m.p. 131°, tri - O - acetyl - β - D - glucurone (2 g.) and p - toluene sulphonic acid (100 m.g.) failed to fuse when heated at temperatures up to 120° under 1 m.m. pressure.

Attempted condensation of methyl salicylate with tri - O - acetyl - β - D-glucurone

Following the general procedure, with a reaction time of 35 minutes, gave a melt that crystallised on addition of ethanol. Three re-crystallisations from ethyl acetate gave fine needles, m.p. 196 - 196.5°. The N.M.R. was identical with that of tri - O - acetyl - β - D - glucurone. No depression of melting point was observed on admixture with authentic tri - O - acetyl - β - D - glucurone. None of the desired product could be detected by T.L.C. on the mother liquors.

Attempted preparation of phenyl 2,5 - di - O - acetyl - α - D - glucuronoside

Using a fusion technique similar to Montgomery[6] utilising zinc chloride as catalyst in a mixture of acetic acid and acetic anhydride, with a reaction time of 15 minutes at 100°, produced a crystalline mass. Recrystallisation from ethyl acetate gave 60% of a phenyl di - O - acetyl - D - glucuronoside m.p. 189 - 190°.

$[\alpha]_D^{22}$ + 71.2°. (lit.[3] m.p. for phenyl di - O acetyl - β - D - glucuronoside 188 - 189°, $[\alpha]_D^{22}$ + 74.8°, chloroform).

Attempted isomerisation of phenyl di - O - acetyl - β - D - glucuronoside

Phenyl di - O - acetyl - β - D - glucuronoside (2 g.) was dissolved in analar chloroform (20 ml.). Boron trifluoride mono - diethyl etherate (5 ml.) was added dropwise over 5 minutes. The mixture was allowed to stand at room temperature for 1 hour. The solution was washed with water, dried and evaporated to a positively rotating syrup, from which only phenyl di - O - acetyl - β - D - glucuronoside could be obtained.

M.p. 188 - 189° undepressed on admixture with authentic material. N.M.R. of crude syrup, crystalline material and mother liquors showed a singlet anomeric proton.

Preparation of penta - O - acetyl - glycofuranoses

1. Penta - O - acetyl - D - glucofuranoses

a. 1,2 - O - isopropylidene - 3,5,6 - tri - O - acetyl - α - D - glucofuranose

1,2 - isopropylidene tri - O - acetyl - α - D - glucofuranose was prepared from 1,2 - O - isopropylidene - α - D - glucofuranose by the method of Ohle and Spencker.[7]

M.p. 73 - 74.5°

$[\alpha]_D^{22}$ + 23.2° (c 1.0 in chloroform)

(lit.[7] m.p. 75°, $[\alpha]_D^{22}$ + 24.6 (c 3.5 in chloroform)).

N.M.R. 100MHz. ($CDCl_3$)

Two singlets 135, 155 Hz. (6), isopropylidene methyls;
two apparent singlets 205 Hz. (9), overlapping acetyl methyls;
quartet 413 Hz. J_{ab} 5.5 Hz. (1), (H-6);
quartet 443 Hz. J_{ab} 3 Hz. (1), (H-4);
doublet 450 Hz., J_{ab} 3 Hz. (1), (H-2);
quartet 458 Hz., J_{ab} 2 Hz. (1), (H-6);
octet 524 Hz., J_{ab} 2.5 Hz. (1), (H-5);
doublet 537 Hz., J_{ab} 3 Hz. (1), (H-3);
doublet 595 Hz., J_{ab} 3.5 Hz. (1), (H-1);

I.R. (nujol mull) ν cm.$^{-1}$

1745 s., (acetyl C=O str.); 1240 s., (acetyl C-O str.); 1080 m., 1070, 1050, 1030, 965, 850, (C-O-C-O-C str.); 896 w., 878, (ring breathing).

b. Penta - O - acetyl - D - glucofuranoses

The syrupy mixture of penta - O - acetyl - D - glucofuranoses was prepared essentially by the method of Jerkeman and Lindberg.[8]

1,2 - O - isopropylidene - 3,5,6 - tri - O - acetyl - α - D - glucose (0.06 mole) was dissolved in a mixture of acetic acid (250 ml.) and acetic anhydride (25 ml.). The solution was cooled in ice, and concentrated sulphuric acid (13.5 ml.) was slowly added with stirring. After standing at room temperature for 24 hours, the mixture was poured onto 1 l. of iced water. The aqueous slurry was extracted with chloroform (3 X 100 ml.), and the extract washed with water, saturated sodium bicarbonate, and again with water. After drying with anhydrous sodium sulphate, the solution was concentrated to a colourless syrup (23 g.).

T.L.C. (ethyl acetate / benzene[9]) showed the presence of a major product, with a small amount of starting material.

N.M.R. (CD Cl_3) showed the syrup to be a 3:1 mixture of β:α.

Assignments of particular peaks from this anomeric mixture proved impossible, although a pattern similar to that of 1,2 - O - isopropylidene tri - O - acetyl - D - glucose precursor could be seen.

N.M.R. 100MHz. (CD Cl_3)

Singlet 596 Hz., (β - anomeric proton H-1);

doublet 630 Hz., J_{ab} 4 Hz., (α - anomeric proton H-1).

I.R. (neat) ν cm.$^{-1}$

1730 s., (acetyl C=O str.); 1220 s., (acetyl C-O str.); 1040 s., (C-O-C-O-C str.); 880 m., (ring breathing).

2. Penta - O - acetyl - β - D - galactofuranose

Following the method of Fletcher et al,[10] D - galactose was converted into a syrup containing penta - O - acetyl - β - D - galactoses. Seeding a solution of this syrup in ethanol gave penta - O - acetyl - β - D - galactopyranose in 30% yield. The remaining syrup was shown, by T.L.C.[9] and N.M.R., to contain the β - D - furanose contaminated with about 5% of the pyranose - acetate. All attempts to purify this syrup failed.

Penta - O - acetyl - β - D - galactopyranose
N.M.R. ($CDCl_3$)

Complex series of overlapping singlets 120 Hz. (15) acetyl methyls;
Complex of peaks 300 - 360 Hz. (7), ring protons.

Penta - O - acetyl - β - D - galactofuranose
N.M.R. ($CDCl_3$)

Complex series of overlapping singlets 120 Hz. (15), acetyl methyls;
complex of peaks 250 - 384 Hz. ring protons.

Preparation of phenyl tetra - O - acetyl - β - D - glycofuranoside syrups

1. Phenyl tetra - O - acetyl - β - D - glucofuranoside

The mixture of penta - O - acetyl - D - glucofuranoses (23 g.),

phenol (40 g.) and p - toluene sulphonic acid (200 mg.) were fused together at 100° under water pump pressure for 30 minutes. Benzene (250 ml.) was added to the hot melt. The benzene solution was washed with water, 1M sodium hydroxide (3 X 250 ml.) and water until the washings were neutral, dried over sodium sulphate and concentrated to a straw coloured syrup (22 g.).[8] T.L.C. (benzene / ethyl acetate) showed the presence of a major product, together with some unreacted pentacetates.

2. p - Nitrophenyl tetra - O - acetyl - β - D - glucofuranoside

Penta - O - acetyl - α - and β - D - glucofuranose (5 g.), p - nitrophenol (10 g.) and p - toluene sulphonic acid were fused together at 100°, under water pump pressure for 40 minutes. Benzene (250 ml.) was added and the solution washed with water, 2N sodium bicarbonate (12 X 250 ml.) and water. The solution was dried and evaporated to a light brown syrup. T.L.C. (ethyl acetate / petrol) showed the absence of p - nitrophenol and the presence of a major product and some starting penta - O - acetates.

N.M.R. ($CD Cl_3$)

Multiplet 120 Hz., acetyl methyls;
complex multiplets 240 - 350 Hz., ring protons;
singlet 342 Hz., anomeric proton;
AA' BB' system 420, 430, 484, 494 Hz., p subst. aromatics.

3. Attempted preparation of p - cresyl tetra - O - acetyl - β - D - glucofuranoside

Following the procedure, as described for the phenyl compound, with a reaction time of 30 minutes or 60 minutes produced a syrup containing 90% starting material (T.L.C. and N.M.R.).

4. Phenyl tetra - O - acetyl - β - D - galactofuranoside

Phenyl tetra - O - acetyl - β - D - galactofuranoside was prepared by the method of Jerkemann and Lindberg from penta - O - acetyl - β - D - galactofuranose.[8] T.L.C. (ethyl acetate / benzene) showed approximately 75% conversion of penta - O - acetate to phenyl tetra - O - acetate.

N.M.R. ($CD Cl_3$)

Multiplet 124 Hz. (12), acetyl methyls;
complex multiplets 248 - 270, 300 - 380 Hz. (6), ring protons;
singlet 242 Hz. (1), anomeric proton;
multiplet 410 - 440 Hz. (5), aromatics.

Preparation of aryl D - glycosides

Aryl β - D - glycofuranosides

The two methods of approach to these compounds were the sodium methoxide deacetylation of the corresponding tetra - O - acetyl-β - D - glycofuranoside[8] and the lithium aluminium hydride reduction / deacetylation of 2,5 - di - O - acetyl-β - D - glucuronosides.[4,11]

a. 2 - Naphthyl β - D - glucofuranoside

2 - Naphthyl β - D - glucofuranoside was prepared by the method of Kato et al,[11] by the action of an excess of lithium aluminium hydride on 2 - naphthyl 2,5 - di - O - acetyl - β - D - glucuronoside in tetrahydrofuran.

M.p. 140 - 142°

$[\alpha]_D^{22}$ - 186° (c 1, in water)

(lit.[11] 140 - 141° $[\alpha]_D^{22}$ - 184° (c 0.25, in water)).

N.M.R. (DMSO - d_6)

Complex series of peaks 200 - 260 Hz. (6), ring protons;
singlet 338 Hz. (1), anomeric proton;
multiplet 430 - 480 Hz. (7), aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

3530 s., 3460, 3420, (O-H str.); 1633 w., 1604, (aromatic C=C str.); 1340 m., 1258, 1221, (C-OH bend); 1067 s., 1040, (primary and secondary O-H bend); 1003 m., 972, 962, (C-O-C-O-C str.); 890 w., (ring breathing); 851 m., 820, 752, (one, two and four respectively, adjacent aromatic C-H deformations).

b. Phenyl β - D - glucofuranoside

Samples of this compound prepared by either of the above methods proved difficult to crystallise. In order to free the compound of phenol and free glucose, which were shown to be present (T.L.C), and also in the hope of separating any phenyl α - D - glucofuranoside present, the syrupy mixture was purified on an ion - exchange column.[12] The column (De Acidite F.F. (S.R.A. 64), 2 - 3% cross - linkage, >200 mesh (stored in the acetate form)) was of diameter 2 cm., length 30 cm., and was packed by the method of Thacker.[13] The syrup (2 g.) dissolved in water (2 g.) was added to the column and the flow rate adjusted to about 30 ml. / hour. 100 drop fractions were collected.

Fractions 20 - 32 had a negative rotation, no positively rotating fractions being observed. Freeze drying or concentration to a syrup, followed by three recrystallisations from ethyl acetate gave pure product. The column could be used for three purifications of up to 10 g. of syrup prepared by one of the above methods.

M.p. 78.5 - 79.5°

$[\alpha]_D^{22}$ - 141° (c 0.5 in water)

(lit.[8] m.p. 79 - 80°, $[\alpha]_D^{22}$ - 142° (c 2 in water))

(Found: C, 56.3; H, 6.28. $C_{12}H_{16}O_6$ requires: C, 56.25; H, 6.29%).

100MHz. N.M.R. (pyridine - d_5)

Apparent septet 430 Hz. (2), (probably arising from two overlapping quartets, H-6 and H-6',
H-6: 420 Hz., J_{ab} 5.2 Hz. (1);
H-6': 438 Hz., J_{ab} 3.5 Hz. (1));

broad multiplet 480 Hz. (1), (H-5);

hyperfinely split singlet 502 Hz. (3), (H-2, H-3, H-4);

singlet 609 Hz. (1), anomeric proton;

series of broad peaks 620 - 710 Hz., hydroxy groups - removed on shaking with D_2O;

apparent doublet 728 Hz. (5), aromatics.

I.R. (KBr disc) ν $cm.^{-1}$

3420 s., 3340 - 3200, (O-H str.); 1602 m., 1592, (aromatic C=C str.); 1337 m., 1299, (C-OH bend); 1237 s., (C-O str.); 1096 s., 1082, 1070, 1045, 1037, 1022, (various O-H bends and C-O-C str.); 995 s., 964 m., 876, (C-O-C-O-C str.); 896 m., 800 w., (ring breathing); 762 s., 700 m., (monosubst. aromatic C-H deformation).

c. p - Methoxyphenyl β - D - glucofuranoside

p - Methoxyphenyl di - O - acetyl - β - D - glucuronoside was reduced by the method of Kato et al[11] to yield 30% crude glucoside,

m.p. 112 - 115°. Recrystallisation from ethyl acetate and from methanol gave pure p - methoxyphenyl β - D - glucofuranoside.

M.p. 120 - 120.5°

$[\alpha]_D^{22}$ - 138.1° (c 0.5 in ethanol)

$[\alpha]_D^{22}$ - 148° (c 0.5 in water)

recrystallisation from dry acetone m.p. 128 - 129.5°.

(Found: C, 54.01; H, 6.19. $C_{13}H_{18}O_7$ requires: C, 54.54; H, 6.34%).

100MHz. N.M.R. (pyridine - d_5)

Singlet 350 Hz. (3), methoxyl group;
apparent septet 440 Hz. (2), (H-6: quartet 430 Hz., J_{ab} 5.3 Hz; H-6': quartet 448 Hz., J_{ab} 3.2 Hz.);
broad multiplet 490 Hz. (1), (H-5);
hyperfinely split doublet 508 Hz., J_{ab} 3 Hz. (3), (H-2, H-3, H-4);
singlet 609 Hz. (1), anomeric proton;
no apparent hydroxyl groups;
AA' BB' system 690, 699, 728, 737 Hz. (4), p - subst. aromatics.

I.R. (KBr disc) ν $cm.^{-1}$

3440 - 3300 s., (O-H str.); 1590 v.w., (aromatic C=C str.); 1365 w., 1295, (C-OH bend); 1220 m., (C-O str.); 1080 s., 1050, 1030, 980 m., (O-H bend and C-O-C str.); 790 w., (ring breathing); 834 m., (p - subst. aromatics).

d. p - Cresyl β - D - glucofuranoside

p - Cresyl di - O - acetyl - β - D - glucuronoside (13 g.) was

reduced by the method of Kato et al[11] to yield 42% crude glucoside as a syrup. Trituration with ether gave a crystalline product m.p. 50 - 60°. Recrystallisation twice from acetone gave 3 g. 32%, m.p. 69 - 72.°

M.p. 72 - 73° from ethyl acetate.

$[\alpha]_D^{22}$ - 139° (c 1.0 in water)

(Found: C, 57.60; H, 6.62. $C_{13}H_{18}O_6$ requires: C, 57.77; H, 6.71%).

100MHz. N.M.R. (pyridine - d_5)

Singlet 218 Hz. (3), 'cresyl' methyl;
apparent unsymmetric septet 428 Hz. (2), (H-6: quartet 420 Hz., J_{ab} 5.3 Hz.; H-6': quartet 436 Hz., J_{ab} 3.4 Hz.);
broad multiplet 479 Hz. (1), (H-5);
hyperfinely split doublet 500 Hz., J_{ab} 3 Hz. (3), (H-2, H-3, H-4);
singlet 605 Hz. (1), anomeric proton;
no apparent hydroxyl groups;
AA' BB' system 698, 707, 715, 724 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

3410 s., 3320 m., 3260, (O-H str.); 1619 w., 1590 v.w., (aromatic C=C str.); 1243 m., 1230, (C-O str.); 1080 m., 1070, 1022, (O-H bend); 998 m., 965 w., 877, (C-O-C-O-C str.); 897 w., (ring breathing); 822 m., (p - subst. aromatics).

T.L.C. of glucofuranosides

The purity (not anomeric purity) of these glucosides was checked by T.L.C., in ether / 5% methanol. Each gave a single spot at R_f 0.7 - p - methoxyphenyl, 0.6 - p - cresyl, 0.5 - phenyl.

e. Attempted preparation of p - chlorophenyl β - D - glucofuranoside

p - Chlorophenyl 2,5 - di - O - acetyl β - D - glucuronoside was reduced in tetrahydrofuran using lithium aluminium hydride, with a reaction time of 30 min. at 50°, to yield a syrup, which was purified on an ion - exchange column. Fractions 13 - 30 had negative rotations, which produced a sharp smooth plot of rotation versus fraction number. These fractions were freeze dried. Trituration with ether gave a crystalline mass, m.p. 73 - 75°. N.M.R. (DMSO - d_6) showed a singlet at 328 Hz., but lacked the characteristic A_2B_2 aromatics.

M.p. 77.0 - 77.5° from ethyl acetate

$[\alpha]_D^{22}$ - 140° (c 0.4 in water).

(Found: C, 55.67; H, 6.14. $C_{12}H_{15}O_6Cl$ requires: C, 49.1; H, 5.67%).

T.L.C., N.M.R., and I.R. showed this compound to be identical to phenyl β - D - glucofuranoside, the chlorine presumably having been removed by the reducing agent.

Mixed m.p. with phenyl β - D - glucofuranoside 77.5 - 78°.

($C_{12}H_{16}O_6$ requires: C, 56.25; H, 6.29%).

f. Attempted preparation of m - chlorophenyl β - D - glucofuranoside

m - Chlorophenyl 2,5 - di - O - acetyl - β - D - glucuronoside was reduced [11] at 50° with a reaction time of 60 min. The standard work-up gave a syrup which was purified on an ion - exchange column. Fractions 15 - 40 were concentrated to give a syrup which crystallised on trituration with ether containing ethyl acetate. Recrystallisation from ethyl acetate gave m.p. 69 - 72°. Two further recrystallisations gave a pure product m.p. 78 - 79°.

$[\alpha]_D^{22}$ -139° (c 0.2 in water)

(Found: C, 55.60; H, 6.14. $C_{12}H_{15}O_6Cl$ requires: C, 49.1; H, 5.64%).

This compound was shown to be identical to phenyl β - D - glucofuranoside (mixed m.p., T.L.C., N.M.R., I.R.). No trace of the desired compound could be found in the mother - liquors from the re-crystallisations, which on concentration failed to give a positive test for chlorine.

($C_{12}H_{16}O_6$ requires: C, 56.25; H, 6.29%).

A repeat of the reduction with a reaction time of 10 min. gave a similar result.

g. Attempted preparations of p - nitrophenyl β - D - glucofuranoside

i). p - Nitrophenyl 2,5 - di - O - acetyl - β - D - glucuronoside was reduced by the lithium aluminium hydride method using reaction times ranging from 90 minutes to 10 minutes. In all cases on addition of the solution of glucuronoside to the hydride suspension, a dark brown colouration was produced. The aqueous solution obtained after deionisation was concentrated and extracted with ethyl acetate. This solution was dried and concentrated to a mobile syrup which failed to crystallise. The syrup was dissolved in a small amount of water and committed to an ion - exchange column. Monitoring fractions by polarimetry and by their U.V. spectrum failed to detect any product in 120 fractions.

ii). p - Nitrophenyl 2,5 - di - O - acetyl - β - D-glucuronoside (0.1 g.) was dissolved in 50% ethanol (10 ml.). Sodium borohydride (0.05 g.) in 50% ethanol (5 ml.) was added. An instant intense yellow colour was produced, the rotation of the solution changing in about 30 seconds to a large negative value. Work-up of this solution in a

similar manner to i) yielded no product.

iii). Deacetylation of p - nitrophenyl 2,3,5,6 - tetra - O - acetyl - β - D - glucofuranoside syrup by the sodium methoxide method used for the equivalent phenyl compound was unproductive. An immediate intense yellow colour due to p - nitrophenol, released on fission of the glucoside, was observed.

iv). Deacetylation of p - nitro phenyl tetra - O - acetyl - β - D - glucofuranoside (2g.) in dry methanol (100 ml.) saturated with ammonia at 0° with reaction times of 24 hours, 12 hours and 1 hour also produced p - nitro phenol as the only detectable product.

v). p - Nitrophenyl tetra - O - acetyl - β - D - glucofuranoside (2.4 g.) was dissolved in dry methanol (100 ml.) and a 2% (w / v) solution of magnesium methoxide[14] (10 ml.) added. The results were identical with those observed using sodium methoxide (iii).

h. Phenyl β - D - galactofuranoside

Phenyl 2,3,5,6 - tetra - O - acetyl - β - D - galactoside was deacetylated with sodium methoxide by the method of Jerkemann and Lindberg.[8]

Due to the presence of galactosides other than the desired β - furanoside, the syrupy product was purified on an ion - exchange column. Fractions 9 - 11 had positive rotations, 12 negative, 13 - 21 positive and 22 - 50 contained the major product having a negative rotation. Concentration gave a syrup which crystallised on trituration with ether. Four recrystallisations from ethyl acetate gave pure phenyl β - D - galactofuranoside.

M.p. 81 - 82°

$[\alpha]_D^{22}$ - 146° (c 0.75 in water)

(lit.[8] m.p. 82 - 83°, $[\alpha]_D^{22}$ - 148° (c 2.0 in water))

(Found: C, 56.41; H, 6.34. $C_{12}H_{16}O_6$ requires: C, 56.25; H, 6.29%).

100MHz. N.M.R. (pyridine - d_5)

Series of complex multiplets 430 - 520 Hz., (ring proton - possibly singlet at 439 Hz. from H-3);
doublet 612 Hz., J_{ab} 2.7 Hz., anomeric proton;
apparent doublet 730 Hz., aromatics.

N.M.R. (DMSO - d_6)

Doublet 325 Hz., J_{ab} ~ 3 Hz. (1), anomeric proton;
apparent unsymmetrical pentet 410 - 444 Hz. (5), aromatics.

I.R. (KBr disc) ν cm.$^{-1}$

3400 s., 3340, 3260 m., (O-H str.); 1605 m., 1596, (aromatic C=C str.); 1370 w., 1320, (C-OH bend); 1231 s., (C-O str.); 1090 s., 1050, 1038, (O-H bend); 983 s., 870 w., (C-O-C-O-C str.); 898 v.w., 826, (ring breathing); 762 m., 700, (monosubst. aromatic C-H deformation

Aryl D - glucopyranosides

Phenyl 2 - deoxy α - D-glucopyranoside

This was prepared by Dr. J.S. Sequeira[15] of Birkbeck College, London University.

m.p. 162 - 163°

$[\alpha]_D^{21}$ + 159° (c 0.55 in water).

1,2 : 3,5 - di - O - benzylidene - D - glucofuranose

This was prepared by the method of Fletcher et al[16]
m.p. 160.5 - 161° from ethyl acetate

$[\alpha]_D^{22}$ + 41.2° (c 0.5 in chloroform)

(lit.[16] m.p. 160 - 161°, $[\alpha]_D^{20}$ + 40° (c 1.0 in chloroform)

I.R. (nujol mull) ν $cm.^{-1}$

3510 m., (O-H str.); 1320 w., (C-OH bend); 1225 m., (C-O str.); 1147 m., (ArC -O-C str.); 1098 m., (C-O-C str.); 1072 m., 1054, (O-H str.); 1018 w., 1004 m., 996, 988, 980, 958, 924 w., (probably associated with various C-O-C-O-C str.); 910 w., 896, 878, 863, 836, 812, (ring breathing or some possibly multiple -C-O-C- str.); 752 m., 698, (mono - subst. aromatic C-H deformation).

Attempted hydrogenolysis of 1,2 : 3,5 - di - O - benzylidene - D - glucofuranoside

Hydrogenolysis in a low pressure hydrogenation apparatus or at atmospheric pressure, with reaction times of up to 3 days, always returned 90% of the starting material, with vague T.L.C. spots of glucose and of a product, possibly 1,2 - O - benzylidene - D - glucofuranose. Solvents used were dry ethyl acetate, tetrahydrofuran and dioxane, with palladium black and palladium (10%) on charcoal as catalyst.

Preparation of benzyl D - glucosides

a. Benzyl α - D - glucopyranoside

Benzyl alcohol (150 ml.) containing p - toluene sulphonic acid (200 mg.) was heated to 200°. Finely powdered anhydrous α - D -

glucose (15 g.) was added slowly with stirring and the mixture refluxed for 2 hours. After cooling, benzene (50 ml.) was added and the mixture extracted with water (3 X 100 ml.). The combined aqueous extracts were saturated with salt, and extracted with ethyl acetate, until the rotation of the dried organic layer was low. After decolorising with animal charcoal the ethyl acetate solution was concentrate to a mobile oil, which was purified on an ion - exchange column. The oil (2 g.) was dissolved in ethanol (2 ml.), added to the column and eluted with boiled - out distilled water. The initial fractions contained some benzyl alcohol, benzaldehyde and benzoic acid; fractions 7 - 12 had a positive rotation. Concentration of these gave a syrup which crystallised spontaneously. Recrystallisation from ethyl acetate gave 1 g. of crystalline material m.p. 114 - 117°.

Three further recrystallisations gave pure benzyl α - D - glucopyranoside.

M.p. 122 - 122.25° from ethyl acetate

$[\alpha]_D^{22}$ + 132° (c 1.5 in water)

(lit.[17] m.p. 122° $[\alpha]_D^{13}$ + 131° (in water)).

(Found: C, 57.91; H, 6.76. $C_{13}H_{18}O_6$ requires: C, 57.71; H, 6.71%).

Variation in reaction time and temperature merely changed the yield of α - pyranoside. No benzyl β - D - glucopyranoside nor benzyl D - glucofuranosides could be isolated.

100 Hz. N.M.R. (pyridine - d_5)

Series of well resolved complex peaks 406 - 509 Hz. (8), ring protons and benzyl protons;

doublet 539 Hz., J_{ab} 3.5 Hz. (1), anomeric proton;

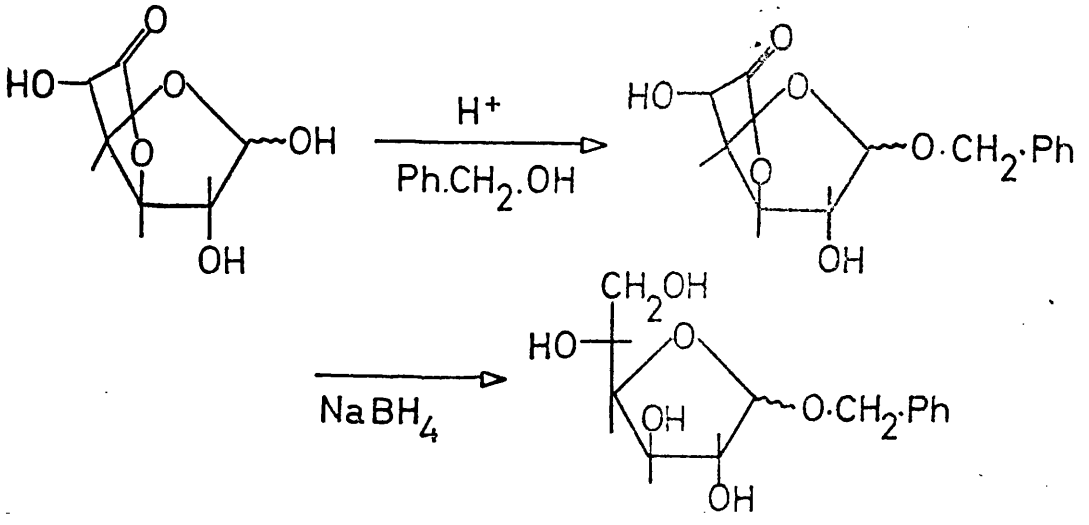
apparently four closely spaced singlets 725 Hz. (5), aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

3480 s., 3380, 3260, (O-H str.); 1650 w., (aromatic C=C str.); 1244 m., (C-O str.); 1227 m., (C-OH bend); 1040 s., 1020, 1010, 995, (O-H bend and C-O-C-O-C str.); 741 m., 703 (monosubst. aromatic C-H deformations).

b. Benzyl D - glucofuranosides

A mixture of these compounds was prepared by the method of Phillips.[1]



D - Glucurone (5 g.) was shaken with a 2% solution of dry hydrogen chloride in benzyl alcohol (50 ml.) until the mixture was homogenous. Benzene (50 ml.) was added and the mixture extracted with water (6 X 50 ml.). The aqueous solution was saturated with salt and extracted (8 X 100 ml.) with ethyl acetate. The organic solutions were combined, dried and evaporated to a mobile syrup, which was shown by N.M.R. to be mainly benzyl β - D - glucuronoside.

N.M.R. (DMSO - d_6)

Series of complex peaks 240 - 294 Hz., benzylic and ring protons;
singlet 300 Hz. anomeric proton;
doublets 342, 356 Hz., J_{ab} ~ 6 Hz., J_{ab} ~ 7 Hz., two hydroxyl groups;
apparent singlet 438 Hz., aromatics.

The reduction procedure of Phillips[18] was followed producing a colourless syrup which was purified on an ion - exchange column. Collecting 100 drop fractions, fraction 12 had a positive rotation, fractions 13 - 60 had negative rotations.

The latter fractions were concentrated to a syrup which was recrystallised from ethyl acetate/ether

m.p. 55 - 60° (520 mg.).

Three further recrystallisations gave pure benzyl β - D - glucofuranoside

m.p. 71 - 72°

$[\alpha]_D^{22}$ - 99° (c 0.5 in water).

(Found: C, 56.40; H, 6.64. $C_{13}H_{18}O_6$ requires: C, 57.74; H, 6.71%).

Benzyl β - D - glucofuranoside

100 Hz. N.M.R. (pyridine - d_5)

Apparent octet 433 Hz. (2), (comprised of: H-6 quartet 423 Hz., J_{ab} 5.5 Hz.; H-6 quartet 442 Hz., J_{ab} 3.5 Hz.);
complex of peaks 458 - 502 Hz. (4), (possible doublet of H-2 at 492 Hz., J_{ab} 3.5 Hz., together with H-3, H-4, H-5);

singlet 552 Hz., (1), anomeric proton;
singlet 555 Hz., (2), benzyl protons;
multiplet 730 Hz., (5), aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

3490 m., 3405 s., 3340, (O-H str.); 3090 w., 3060, 3040, (aromatic =C-H str.); 1610 v.w., 1589, (aromatic C=C str.); 1340 m., 1295, 1278, (C-OH bend); 1240, 1210, (C-O str.); 1113 s., (C-O-C str.); 1072 s., 1060, (O-H str.); 1025 s., 1011, 980 m., 947, 930 873, (probably mostly associated with C-O-C-O-C str.); 886 m., 798, (ring breathing); 735 s., 700 m., (mono-subst. aromatic C-H deformation).

Benzyl α - D - glucofuranoside

The positive fraction 12 was concentrated to a syrup which crystallised yielding 3 mg. of crystalline material, m.p. 125 - 126.5°, which was shown to be different to benzyl α - D - glucopyranoside (mixed m.p. 100 - 106°). A satisfactory analysis was not obtained on the α - D - furanoside.

I.R. (KBr disc) ν cm.$^{-1}$

3480 s., 3380, 3200 m., (O-H str.); 1256 m., (C-OH bend); 1250 m., 1210 (C-O str.); 1160 m., (ArC -O-C str.); 1080 s., 1050 m., (O-H str.); 1018 s., 1010, 950 m., 930, 860, (C-O-C-O-C str.); 880 m., 823, (ring breathing); 735 s., 695, (mono-subst. aromatic C-H deformation).

T.L.C. of benzyl D - glucosides

T.L.C. (6% methanolic ether) showed that the benzyl α - pyranoside (R_f 0.3) prepared from glucose was different from the benzyl α - furanoside (R_f 0.5) prepared from D - glucurone. The β - furanoside also had R_f 0.5.

Hydrogenolysis of benzyl β - D - glucofuranoside

Benzyl β - D - glucofuranoside (50 mg.) was dissolved in dry ethyl acetate in a 25 ml. pear-shaped flask. The system was flushed out with dry nitrogen and palladium black (5 mg.) added. Dry hydrogen was bubbled through the stirred solution. The reaction was followed by T.L.C. until no starting material remained (12 hours). The product which had precipitated out was removed with the catalyst. I.R. was identical with that of D - glucose.

N.M.R. (DMSO - d_6)

Two doublets 374 Hz., J_{ab} 4.5 Hz., 396 Hz., J_{ab} 7 Hz., D - glucose C-1 hydroxyl groups.

Addition of D_2O removed these, confirming then to be hydroxyl groups, and revealing:

an apparent doublet 297 Hz., $J_{ab} < 4$ Hz.

(lit.[19] N.M.R. (DMSO - d_6)

α - D - glucose 369 Hz., J_{ab} 4.5 Hz.;

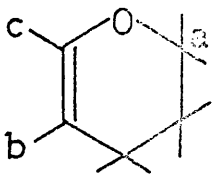
β - D - glucose 391 Hz., J_{ab} 7.0 Hz.).

Preparation of 2 - (substituted phenoxy) - tetrahydropyrans

The phenoxy - tetrahydropyran derivatives were made, by the general method of Woods and Kramer,[20,21] from 2,3 - dihydropyran and a phenol, with p - toluene sulphonic acid as catalyst.

Commercial 2,3 - dihydropyran was shaken up with anhydrous sodium sulphate, filtered and dried with sodium wire. Before use it was re-distilled from sodium, b_{760} 86°.

N.M.R. (neat)



Multiplet 113 Hz. (4);
hyperfinely split triplet 233 Hz., J_{ab} 5 Hz. (2), a;
multiplet 274 Hz. (1), b;
hyperfinely split doublet 376 Hz., J_{ab} 7 Hz. (1), c.

I.R. (neat) ν cm.$^{-1}$

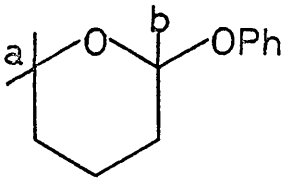
3060 w., (aliphatic =C-H str.); 1650 s., (alkene C=C str.); 1240 s., (ether C-O str.); 1070 s., (=C-O-C str.); 730 w., (=C-H out of plane deformation).

a. 2 - Phenoxytetrahydropyran

Phenol (9.4 g.) was slowly added to 2,3 - dihydropyran (17 g.) containing p - toluene sulphonic acid (100 mg.), with cooling to prevent charring. After 2 hours ether (200 ml.) was added. The ethereal solution was washed with 2 N sodium hydroxide (3 X 200 ml.), dried and evaporated to remove ether and dihydropyran. The residue was distilled giving a major fraction b_{15} 140 - 142° 80% yield. Three further distillations gave pure product b_{15} 142° (lit.[22] b_4 103°).

(Found: C, 73.76; H, 7.85. $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92%).

N.M.R. ($CDCl_3$)



Multiplet 90 Hz. (6);
multiplet 210 Hz. (2), a;
singlet with signs of splitting 315 Hz. (1), b;
multiplet 420 Hz. (5), aromatics.

I.R. (neat) ν $cm.^{-1}$

3060 - 3020 triplet v.w., (aromatic C-H str.); 1602, 1595 m., (aromatic C=C str.); 1230 s., (C-O-C str.); 1120, 1110, 1080, 1040, 1020, 970, 930 m., (acetal C-O-C-O-C str.); 815 w., (ring breathing); 760, 695 m., (mono-subst. aromatics).

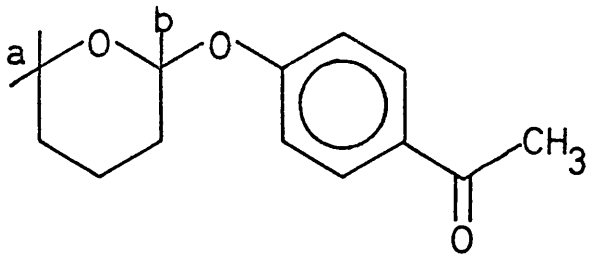
b. 2 -(p - Acetylphenoxy) - tetrahydropyran

This was prepared from 2,3 - dihydropyran and p - hydroxyacetophenone by the general method. Evaporation of the ethereal solution gave a crystalline residue (88%), m.p. 84 - 85°. Three recrystallisation from ethanol gave pure product.

M.p. 89 - 89.25°

(Found: C, 70.96; H, 7.37. $C_{13}H_{16}O_3$ requires: C, 70.89; H, 7.32%).

N.M.R. ($CD Cl_3$)



Broad multiplet 90 - 117 Hz. (6);
singlet 150 Hz. (3), acetyl CH_3;
multiplet 222 Hz. (2), a;
singlet with signs of splitting 330 Hz. (1), b;
AA' BB' system 420, 429, 471, 480 Hz. (4), p - subst. aromatics.

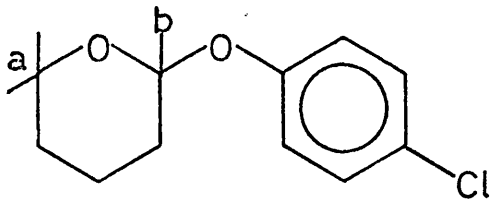
I.R. (nujol mull) ν $cm.^{-1}$

1670 s., (acetyl C=O str.); 1605 s., 1575 m., (aromatic C=C str.); 1248 m., (acetyl C-O str.); 1200 s., (C-O-C str.); 1170?, 1118, 1114 s. 1052, 1040, 1020 m., 950, 920 s., (associated with cylic acylic acetal vibrations); 840, 830, 810 w., (aromatic out of plane deformations); 816 w., (ring breathing).

c. 2 - (p - Chlorophenoxy) - tetrahydropyran

Prepared in 70% yield.
M.p. 48 - 49°, from methanol,
$b_{0.1}$ 74 - 78°.
(lit.[23] m.p. 48.5 - 49°, b_3 125 - 127°).

N.M.R. ($CD Cl_3$)



Broad multiplet 85 - 115 Hz. (6);
multiplet 220 Hz. (2), a;
singlet with signs of splitting 318 Hz. (1), b;
AA' BB' system 410, 420, 427, 437, Hz. (4), p - subst. aromatics.

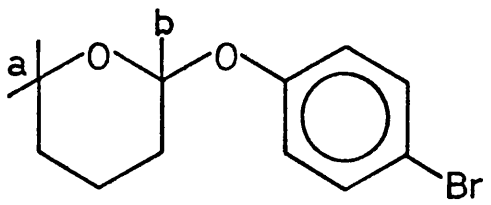
I.R. (nujol mull) ν $cm.^{-1}$

1600 s., 1583 m., (aromatic C=C str.); 1240, (C-O str.); 1200 s., (C-O-C str.); 1125, 1112, 1094, 1050, 1040, 1020, 1010, 968, 920 s., (probably mostly associated with C-O-C-O-C acetal vibrations); 890, 806 w., (ring breathing); 875, 825 s., (aromatics); 710 m., (C-Cl str.)

d. 2 - (p - Bromophenoxy) - tetrahydropyran

Prepared in 65% yield.
M.p. 58 - 59° from methanol,
(lit.[24] m.p. 58 - 59°).
(Found: C, 51.30; H, 4.93. $C_{11}H_{13}O_2Br$ requires: C, 51.38; H, 5.09%).

N.M.R. ($CD Cl_3$)



Broad multiplet 85 - 115 Hz. (6);

multiplet 200 - 240 Hz. (2) a;

broad singlet 319 Hz. (1), b;

AA' BB' system 409, 418, 435, 444 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

1592 m., 1580 w., (aromatic C=C str.); 1238 s., (C-O str.); 1202 m., (C-O-C str.); 1122, 1115, 1072, 1050, 1040, 1020, 1010 m., 968, 921 s., (associated with C-O-C-O-C str.); 890, 808, 803 w., (ring breathing); 875 m., 822 s., (aromatic C-H's); 660 m., (C-Br str.).

e. 2 - (p - Nitrophenoxy) - tetrahydropyran

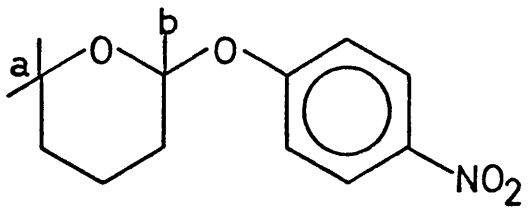
Reaction between 2,3 - dihydropyran and p - nitrophenol produced a violent reaction. The 2,3 - dihydropyran was diluted with an equal volume of benzene, the reaction still proceeding highly exothermically to give 50% yield.

M.p. 60 - 60.5° from methanol

(lit.[25] m.p. 59 - 60°).

(Found: C, 59.10; H, 5.86; N, 6.08. $C_{11}H_{13}O_4N$ requires: C, 59.19; H, 5.87; N, 6.27%).

N.M.R. ($CD Cl_3$)



Multiplet 84 - 117 Hz. (6) showing signs of separating into two separate multiplets (99 Hz. (2); 110 Hz. (4));

multiplet 219 Hz. (2), a;

singlet with shoulders 330 Hz. (1), b;

AA' BB' system 421, 430.5, 485, 494.5 Hz. (4), p - subst. aromatics

I.R. (nujol mull) ν cm.$^{-1}$

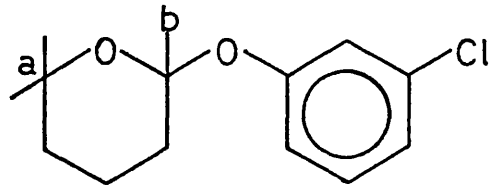
1611 w., 1593 m., (aromatic C=C str.); 1510 m., (asymmetric NO_2 str.); 1342 s., (symmetric NO_2 str.); 1250 s., (C-O or C-O-C str.); 1120, 1110 s., 1050, 1035, 1025 m., 954, 920 s., (C-O-C-O-C str.); 890, 814, 798 w., (ring breathing); 845 m., (aromatic C-H);

f. 2 - (m - Chlorophenoxy) - tetrahydropyran

This compound was prepared in 80% yield, b_8 148 - 152°. Pure, b_8 152°.

(Found: C, 62.31; H, 6.23. $C_{11}H_{13}O_2Cl$ requires: C, 62.13; H, 6.16%).

N.M.R. ($CD Cl_3$)



Multiplet 90 - 110 Hz. (6);

triplet 234 Hz., J_{ab} 5 Hz. (2), a;

broad singlet 320 Hz. (1);

complex multiplet 400 - 420 Hz., aromatics.

I.R. (neat) ν cm.$^{-1}$

3070 v.w., (aromatic C-H str.); 1600 s., 1585 m., (aromatic C=C str.); 1245, 1232 m., (C-O str.); 1209 m., (C-O-C str.); 1125, 1077 m.

1045 s., 1030, 1004 m., 970, 935 s., (C-O-C-O-C str.); 900, 825 w., (ring breathing); 880, 780 m., (aromatic C-H deformation); 690 m., (C-Cl str.).

g. 2 - (p - Methoxyphenoxy) - tetrahydropyran

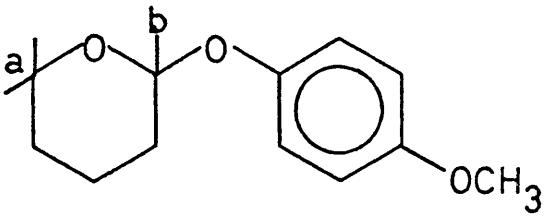
Prepared in 68% yield by the general method

m.p. 29°, $b_{0.1}$ 80 - 82°

(lit.[25] $b_{1.5}$ 120°).

(Found: C, 69.15; H, 7.67. $C_{12}H_{16}O_3$ requires: C, 69.21; H, 7.72%).

N.M.R. ($CD Cl_3$)



Multiplet 80 - 110 Hz. (6);

singlet 219 Hz. (3), methoxyl group;

multiplet 200 - 240 Hz. (2), a;

singlet with signs of splitting 313 Hz. (1), b;

AA' BB' system 400, 408, 414, 423 Hz. (4), p - subst. aromatics.

I.R. (neat) ν $cm.^{-1}$

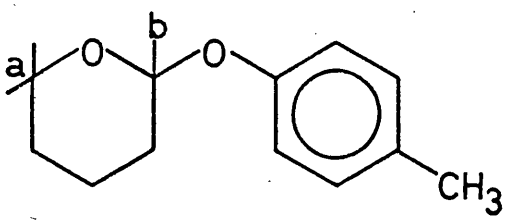
2830 w., (methoxyl C-H str.); 1592 v.w., (aromatic C=C str.); 1230 s., (C-O str.); 1202 s., (C-O-C str.); 1110, 1078 m., 1038 s., 1022 m., 970 s., 921 m., (C-O-C-O-C str.); 830 m., (aromatic C-H deformation).

h. 2 - (p - Methylphenoxy) - tetrahydropyran

Prepared in 60% yield b_7 138 - 142°. Repeated distillation gave b_7 142° (lit.[25] b_3 98 - 99°). A satisfactory analysis could not be obtained. T.L.C. (10% ether / petrol) showed the presence of an impurity which distillation from metallic sodium failed to remove.

(Found: C, 75.54; H, 7.31. $C_{12}H_{16}O_2$ requires: C, 74.97; H, 8.39%).

N.M.R. (neat)



Multiplet 80 - 105 Hz. (6);
singlet 130 Hz. (3), CH_3;
multiplet 190 - 230 Hz. (2), a;
broad singlet 312 Hz. (1), b;
singlet 414 Hz. (4), accidentally degenerate p - subst. aromatics.

I.R. (neat) ν $cm.^{-1}$

1608 w., 1580 v.w., (aromatic C=C str.); 1220 s., (C-O str.); 1195 s., (C-O-C str.); 1120, 1100, 1040 m., 970 s., 922 m., (C-O-C-O-C str.); 880 w., 820 m., (aromatic C-H two adjacent protons).

i. Attempted preparation of 2 - (o - carboxyphenoxy)-tetrahydropyran

To a stirred suspension of salicylic acid (4 g.) in 2,3 - hydropyran (5.2 g.) was added p - toluene sulphonic acid (100 mg.). The salicylic acid dissolved during 5 minutes. The reaction was followed

by T.L.C. (ether / petrol) for 12 hours, after which most of the salicylic acid had reacted and five additional spots had appeared. The thick syrupy mass was extracted with 4 N sodium hydroxide (2 X 100 ml.). T.L.C. on the residue showed the removal of the majority of major product (R_f 0.8). Careful neutralisation of the basic solution with continuous ether extraction, followed by drying and evaporation of the ether, gave an oil. T.L.C. showed this to be different from the major product, which had decomposed in the extraction and neutralisation procedure.

j. Attempted preparation of 2 - (p - carboxyphenoxy) - tetrahydropyran

Following the above procedure for the o - hydroxy benzoic acid produced a vigorous, highly exothermic reaction. Reaction in benzene solution gave the same series of spots on thin layer as the ortho isomer. Work up in a similar manner gave an identical result.

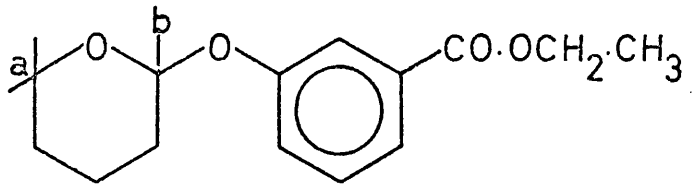
k. Attempted preparation of 2 - (o - methoxycarbonylphenoxy) - tetrahydropyran

Dry redistilled methyl salicylate (4.5 g.) was added dropwise to a solution of p - toluene sulphonic acid in 2,3 - dihydropyran (5 g.). T.L.C. after 1 hour and 12 hours revealed eight additional spots, major product R_f 0.8. Ether (50 ml.) was added. Washing with 1 N sodium hydroxide (3 X 100 ml.) precipitated the methyl salicylate as its sodium salt. This was filtered and washed well with ether. Concentration of the dried ethereal solutions gave a colourless oil. T.L.C. confirmed the removal of methyl salicylate and the presence of five products. Distillation gave a major fraction $b_{0.5}$ 80 - 82°. N.M.R. showed the absence of any aromatic protons.

l. 2 - (m - Ethoxycarbonylphenoxy) - tetrahydropyran

Prepared in 60% yield, by the general method b_7 151 - 152°.

N.M.R. ($CD Cl_3$)



Triplet 76 Hz., J_{ab} 7 Hz. (3), CH_3 of ethyl group;
multiplet 76 - 114 Hz. (6);
multiplet 198 - 234 Hz. (2), a;
quartet 256 Hz., J_{ab} 7 Hz. (2), CH_2 of ethyl group;
singlet 323 Hz. (1), b;
multiplet 432 - 468 Hz. (5), aromatics.

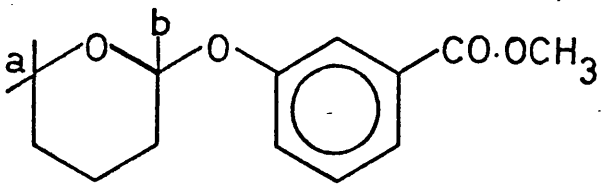
I.R. (neat) ν $cm.^{-1}$

3070 w., (aromatic C-H str.); 1720 s., (ester C=O str.); 1600 w., 1584 m.,(aromatic C=C str.); 1270, 1115 m., (benzoate C-O str.); 1214, 1200 m., (acetal C-O-C str.); 1098, 1074, 1033, 1020, 1000, 964 m., (acetal C-O-C-O-C str.); 900 m., 816 w., (ring breathing); 870 m., 758 s., (m - subst. aromatic C-H out of plane deformation).

m. 2 - (m - Methoxycarbonylphenoxy) - tetrahydropyran

Prepared in 55% yield, by the general method b_8 152 - 153°.

N.M.R. ($CD Cl_3$)



Multiplet 84 - 114 Hz. (6), ring methylene protons other than a;
multiplet 201 - 240 Hz. (2), a;
singlet 231 Hz. (3), ester methyl group;
broad singlet 326 Hz. (1), b;
multiplet 432 - 468 Hz. (5), aromatics.

I.R. (neat) ν $cm.^{-1}$

3075 w., (aromatic C-H str.); 1725 s., (benzoate ester C=O str.); 1596, 1590 m., (aromatic C=C str.); 1285 s., 1120 m., (benzoate C-O str.); 1220, 1206 s., (acetal C-O-C str.); 1120, 1100, 1080, 1040, 1025, 1007, 964, 930 m., (acetal C-O-C-O-C str.); 900 m., 797 w., (ring breathing); 876 m., 760 s., (m - subst. aromatics).

Attempted hydrolysis of these esters to produce 2 - (m - carboxyphenoxy) - tetrahydropyran, using sodium hydroxide in various media resulted in the decomposition of the tetrahydropyran ring system.

Preparation of 2- (substituted phenoxy) - tetrahydrofurans

These compounds were made by reaction of 2,3 - dihydrofuran with a phenol using p - toluene sulphonic acid as catalyst.

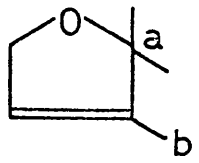
2,3 - Dihydrofuran was prepared by the isomerisation of 2,5 - dihydrofuran.[26]

2,5 - Dihydrofuran

2,5 - Dihydrofuran was supplied by Koch-Light and was dried and redistilled before use.

b_{760} 67° (lit.[26] 67°).

N.M.R. (neat)



Singlet 273 Hz. (2), a;
singlet 353 Hz. (1), b.

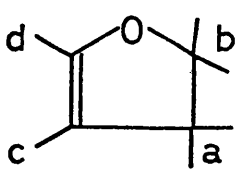
I.R. (neat) ν cm.$^{-1}$

Very complicated spectrum. 3082 w., (aliphatic =C-H str.); 1350 s., (ether C-O str.); 1075 v.s., (C-O-C str.); 890 s., 800 m., 738 s., (ring breathing); 665 v.s., (cis - alkene).

2,3 - Dihydrofuran

A 6% solution of potassium in t - butanol (45 g.) and 2,5 - dihydrofuran (34.6 g.) were heated in a sealed tube at 180° for 12 hours.[26] The remaining liquid was fractionated. Combination of similar fractions from repeat isomerisations refractionation gave a major fraction b_{760} 55 - 56° (lit.[26] b_{757} 55°). N.M.R. showed the presence of a small amount of 2,5 - dihydrofuran and the absence of t - butanol.

N.M.R. ($CD Cl_3$)



Triplet of triplets 152 Hz., J_{ab} 10 Hz., J'_{ab} 2.5 Hz. (2), a;
triplet 254 Hz., J_{ab} 10 Hz. (2), b;
quartet 294 Hz., J_{ab} 2.5 Hz. (1), c;
quartet 376 Hz., J_{ab} 2.5 Hz. (1), d.

I.R. (neat) ν $cm.^{-1}$

3090 w., (aliphatic =C-H str.); 1620 v.s., (C=C str.); 1135 s., (=C-O-C str.); 1080 - 1050 s., (C-O-C str.); 915, 710 s., (ring breathing); 663 s., (cis - alkene disubstituted, C-H out of plane deformation).

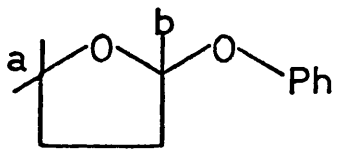
a. 2 - Phenoxytetrahydrofuran

Phenol (4 g.) was slowly added to a cooled solution of p - toluene sulphonic acid (25 mg.) in 2,3 - dihydrofuran (4 g.). After 2 hours the dark mixture was taken up in ether, washed with 2 N sodium hydroxide, dried and evaporated. The residue was distilled under reduced pressure to yield 5 g. (43%) of crude 2 - phenoxytetrahydrofuran. b_8 106 - 108°. Three further distillations gave pure sample,

b_8 107 - 108° (lit.[27] b_{13} 117 - 118°).

(Found: C, 72.98; H, 7.43. $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37%).

N.M.R. ($CD Cl_3$)



Multiplet 122 Hz. (4);
multiplet 232 Hz. (2), a;

triplet 343 Hz., J_{ab} 2 Hz. (1), b;
complex multiplet 410 - 440 Hz., aromatics.

I.R. (neat) ν cm.$^{-1}$

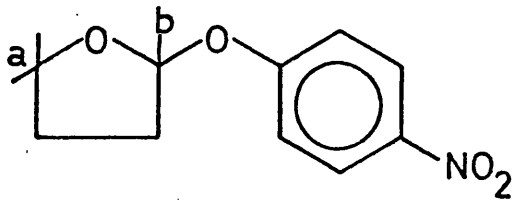
3030 - 3060 v.w., (aromatic C-H str.); 1601, 1590 m., (aromatic C=C str.); 1230 s., (C-O-C str.); 1070, 1040, 1030 s., 1000 m., 970 s., 922 m., (acetal C-O-C-O-C str.); 755, 692 s., (mono - subst. aromatics).

b. 2 - (p - Nitrophenoxy) - tetrahydrofuran

p - Nitrophenol (6 g.) was slowly added to 2,3 - dihydrofuran (2.5 g.) and p - toluene sulphonic acid (20 mg.) in anhydrous benzene (50 ml.). After 3 hours at room temperature the benzene solution was washed with 2 N sodium bicarbonate, dried and evaporated to a yellow solid (2.2 g. 30%). Recrystallisation from methanol gave 2 g. of light yellow crystals, m.p. 78 - 80°. Three further recrystallisations gave pure product, m.p. 80.5 - 81°.

(Found: C, 57.41; H, 5.30; N, 6.70. $C_{10}H_{11}O_4N$ requires: C, 57.23; H, 5.29; N, 6.52%).

N.M.R. ($CD Cl_3$)



Multiplet 110 - 136 Hz. (4);
triplet 241 Hz., J_{ab} 6 Hz. (2), a;
broad singlet 353 Hz. (1), b;
AA' BB' system 419, 428, 483, 492 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν cm.$^{-1}$

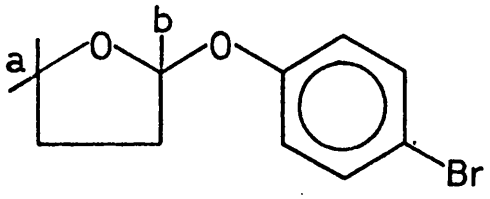
1605 v.w., 1590 w., (aromatic C=C str.); 1510 w., 1340 m., (asymmetric and symmetric NO_2 str.); 1250 m., (C-O or C-O-C str.); 1105, 1070, 1030, 960, 940 m., (C-O-C-O-C str.); 845 m., (aromatic C-H deformation, two adjacent protons).

c. 2 - (p - Bromophenoxy) - tetrahydrofuran

Prepared in 95% yield by reaction of p - bromophenol with undiluted 2,3 - dihydrofuran. Redistilled from sodium hydroxide, b_8 145°.

(Found: C, 49.49; H, 4.45. $C_{10}H_{11}O_2Br$ requires: C, 49.40; H, 4.57%).

N.M.R. ($CD Cl_3$)



Multiplet 125 Hz. (4);
triplet 239 Hz., J_{ab} 5.5 Hz. (2), a;
triplet 344 Hz., J_{ab} 2 Hz. (1), b;
AA' BB' system 408, 418, 436, 445 Hz. (4), p - subst. aromatics.

I.R. (neat) ν cm.$^{-1}$

1594 m., 1581 w., (aromatic C=C str.); 1240 s., (C-O-C or C-O str.); series of peaks s. and m. 1230 - 940, (C-O-C-O-C str.); 830 s., (aromatic C-H deformation, two adjacent protons).

d. 2 - (p - Acetylphenoxy) - tetrahydrofuran

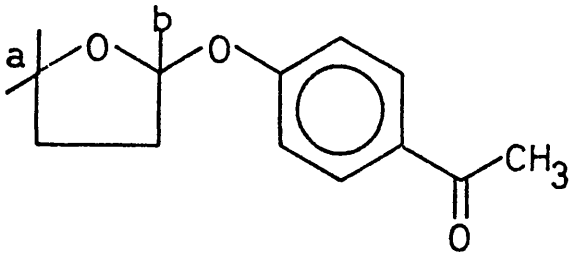
Prepared in 70% yield, m.p. 63.5 - 64.5°, by the procedure described for the p - nitrophenoxy compound.

M.p. 64.5 - 65° from methanol,

b_8 170°.

(Found: C, 69.82; H, 6.85. $C_{12}H_{14}O_3$ requires: C, 69.89; H, 6.84%).

N.M.R. ($CDCl_3$)



Multiplet 110 - 136 Hz. (4);

singlet 154 Hz. (3), acetyl CH_3;

triplet 240 Hz., J_{ab} 5 Hz. (2) a;

singlet 353 Hz. (1), b;

AA' BB' system 418, 427, 469, 478 Hz. (4), p - subst. aromatics.

I.R. (nujol mull) ν $cm.^{-1}$

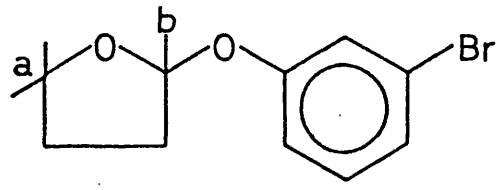
1680 s., (acetyl C=O str.); 1602 s., 1580 m., (aromatic C=C str.); 1247 s., (C-O-C str.); 1110 m., 1075, 1040 s., 970, 922 m., (acetyl C-O-C-O-C str.); 840 m., (aromatic out of plane deformations).

e. 2 - (m - Bromophenoxy) - tetrahydrofuran

Prepared in 66% yield by direct reaction between m - bromophenol and 2,3 - dihydrofuran. Redistilled from sodium hydroxide, b_8 142°.

(Found: C, 49.22; H, 4.50. $C_{10}H_{11}O_2Br$ requires: C, 49.40; H, 4.57%).

N.M.R. (neat)



Multiplet 100 - 120 Hz. (4);
triplet 228 Hz., J_{ab} 5.5 Hz. (2), a;
triplet 336 Hz., J_{ab} 2 Hz. (1), b;
multiplet 410 - 436 Hz. (4), aromatics.

N.M.R. ($CD Cl_3$)

Shifted the peak of proton 'b' to 340 Hz.;
all other peaks remaining stationary.

N.M.R. (DMSO - d_6)

Shifted the peak of proton 'b' to 345 Hz.;
all other peaks remaining stationary.

I.R. (neat) ν cm.$^{-1}$

3060 w., (aromatic C-H str.); 1590 s., 1574 s., (aromatic C=C str.); 1235, 1225 m., (C-O or C-O-C str.); 1110 m., 1075, 1035, 970 s., 920 m., (C-O-C-O-C str.); 890 m., 770 s, (aromatic C-H deformation, three and one adjacent proton).

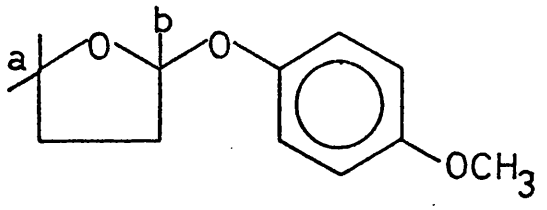
f. 2 - (p - Methoxyphenoxy) - tetrahydrofuran

Prepared in 70% yield by the procedure described for the p - nitro phenoxy compound.

b_8 146 - 148°, $b_{0.6}$ 95°.

(Found: C, 67.99; H, 7.37. $C_{10}H_{14}O_3$ requires: C, 68.02; H, 7.27%).

N.M.R. ($CDCl_3$)



Apparent doublet 121 Hz., J_{ab} 3 Hz. (4);
singlet 219 Hz. (3), methoxyl CH_3;
multiplet 235 - 240 Hz. (2), a;
triplet 327 Hz., J_{ab} 2 Hz. (1) b;
AA' BB' system 398, 408, 411, 421 Hz. (4), p - subst. aromatics.

I.R. (neat) ν cm.$^{-1}$

2830 w., (methoxyl C-H str.); 1590 v.w., (aromatic C=C str.);

1220 s., (C-O or C-O-C str.); 1110 w., 1070 m., 1035 s., 970 m., 920 w., (C-O-C-O-C str.); 824 m., (p - subst. aromatic C-H deformation).

2. Kinetics experimental

Solutions

Perchloric acid solutions used in the hydrolysis of the glycosides were prepared by dilution of AnalaR 72% perchloric acid. These solutions were then diluted and standardised against 0.1N 'carbonate-free' sodium hydroxide. The strength of the acid used for the determination of activation parameters was adjusted to 1.00M, and re-standardised to confirm the adjustment.

Chemicals used for the preparation of all solutions related to kinetics were of the highest grade available. Buffers were prepared by dilution of a solution of AnalaR grade acid with 1N or 0.1N 'carbonate-free' sodium hydroxide, to give the required buffer ratio, and with water if necessary to hold the ionic strength constant. For general - acid catalysis studies, buffers were diluted with 0.1M sodium chloride. Buffers were 10^{-4}M in EDTA and, unless otherwise stated, had an ionic strength of 0.1. The pH's of solutions were measured at the temperature of the kinetic measurement using a Radiometer Model 26 pH Meter, with external temperature compensator, standardised against standard buffer preparations to BS 1647, 1961.

Solvent isotope effects were determined in solutions of commercial 20% D Cl in D_2O (isotopic purity 99.5%) diluted with commercial D_2O (99.8%). For glycoside hydrolyses an approximately 1 M solution of D Cl in D_2O was prepared. This was diluted and standardised against 0.1N sodium hydroxide, and an H Cl solution of the same molarity prepared. The 0.01M acid solutions for the tetrahydropyrans and furans, were prepared from these 1 M solutions by dilution using the same

pipette and standard flask in each case.

D Cl / D_2O solutions were stored for minimum possible periods in tightly sealed vessels in a dessicator. Periodic tests were conducted on these solutions before and after a kinetic run. Dioxane (30 μl.) was injected into 2.5 ml. acid in cell. N.M.R. of this solution showed the presence of $< 1\%$ protonated species.

Kinetic procedure and rate determinations

1 cm. Spectrosil quartz U.V. cells were used in all kinetic work.

Approximate rate constants were determined using a Unicam SP 800 spectrophotometer, by a method of repeat scans. From these a wavelength at or near the maximum absorbance was chosen to follow the reaction.

All accurately determined rates were made on a Cary model 14 spectrophotometer, fitted with a 5 cell compartment. Thermostatting was achieved using a Lauda electronic thermostatting bath with water circulating through the central spindle of the cell-holder, then passing through channels in the cell compartment. Temperature losses to the surroundings were maintained relatively constant by working in a temperature controlled, air conditioned room. Temperatures were measured in the cell with an N.P.L. calibrated thermometer, a correction being applied for the lack of 100 cm. immersion. Temperature control was better than $\pm 0.05^{\circ}$.

Five cells were thermostatted for about 30 minutes. In glycoside hydrolysis 3 μl of a 1 M aqueous or DMSO stock solution was injected, using a Hamilton syringe, into 2.5 ml. of acid. For the tetrahydropyran and furan compounds a more dilute dioxane stock was used, but in no case did the final dioxane concentration exceed 0.5%. Using

stronger stock solutions caused some of these compounds to precipitate.

After injection, the cell was shaken, or in the case of fast reactions stirred. A period of time depending on the rate of reaction was allowed to pass before following absorbance changes. This was to allow any air bubbles to clear and to give the cell temperature a chance to recover from being out of the cell block.

The pen drive - wire on the spectrometer drove a highly linear potentiometer across which was applied a potential from a Mallory 1.35 volt standard cell. The output from this potential - divider was fed to a Solartron Compact Data Logger which digitised the absorbance reading and output it on 5 - channel paper tape *via* a Creed punch. The chart speed and time interval were determined by the rate of reaction, with a minimum of about 25 and a maximum of 250 punches per half-life. Reactions were followed for at least 3 half-lives; infinity readings were taken after 9 half-lives.

Rate constants were determined on a KDF 9 computer. The generalised - least - squares programme (written in Kidsgrove Algol by Dr. B. Capon[28]) would accept up to 750 values. In the form used it was found that after following a reaction for 3 or 4 half-lives the rate constant calculated on the basis of an estimated infinity value was identical to the value calculated using the observed infinity value. After this point had been confirmed for a given compound, data from some of the longer reactions of that compound were treated in this manner.

The infinity spectrum was taken at the conclusion and was in all cases equivalent to the spectrum of the appropriate phenol in the acid / buffer used.

RESULTS

In the following tables all rates were determined spectrophotometrically. When a single value is quoted it is an average of three or more determinations. With each rate is quoted the associated standard error, or average standard error. These are quoted as $\underline{k}_{err}$ (%) and are the internal errors produced by the generalised - least squares computer program used to process data. (See reference 28 in the experimental section). Reproducibility between parallel rate determinations was generally good and better than 4% spread.

Index to results

Table 21

The hydrolysis of 2 - phenoxytetrahydropyran - See Graph 1.
Temperature 49.95° Ionic strength 0.1

Buffer	pH	10^6 k (sec^{-1})	k_{err} (%)
Chloroacetate	2.26	73130	0.64
Chloroacetate	2.89	15000	0.27
Formate	3.68	2662 2800	0.25 0.26
Acetate	4.05	1020 1012	0.30 0.39
Acetate	4.67	245.8 253.8	0.36
Phosphate [a]	6.56	4.152 4.026	2.11 2.16

a These reactions were only followed for about 1.5 half-lives. Thus some uncertainty may exist in the rate constants.

Table 22

The hydrolysis of 2 - phenoxytetrahydrofuran - See Graph 2.
Temperature 49.95° Ionic strength 0.1

Buffer	pH	10^5 k (sec^{-1})	k_{err} (%)
Chloroacetate	2.89	6110 6160	0.50 0.63
Formate [a]	3.68	1100	0.56
Acetate [a]	4.05	437.5	0.29
Acetate [a]	4.67	105	0.30
Phosphate	6.56	2.179 2.329	0.33 0.31

a. Rates determined by extrapolation to zero buffer concentration.

Table 23

The hydrolysis of 2 - (p - nitrophenoxy) - tetrahydropyran - See Graph 1.

Temperature 49.95° Ionic strength 0.1

Buffer	pH	10^3 k (sec^{-1})	k_{err} (%)
Chloroacetate [a]	2.89	3.86	0.53
		4.03	0.49
Chloroacetate [a]	3.515	1.69	0.80
Formate [a]	3.68	1.504	0.49
Acetate [a]	4.05	1.31	0.92
Acetate	4.67	1.2	0.69
Phosphate [b]	6.56	1.17	0.47
		1.15	0.35
		1.18	0.34
		1.17	0.39
Phosphate [c]	6.57	1.13	0.49
Sodium hydroxide	10.78	1.139	0.84
		1.094	0.29

a. Rates determined by extrapolation to zero buffer concentration.

c. Na_2HPO_4 / NaH_2PO_4 buffer 1 : 1 dilution of phosphate buffer (b) with 0.1M sodium chloride.

Table 24

The hydrolysis of 2 - (p - nitrophenoxy) - tetrahydrofuran - See Graph 2.

Temperature 49.95° Ionic strength 0.1.

Buffer	pH	10^3 k (sec^{-1})	k_{err} (%)
Chloroacetate [a]	2.89	0.1290 0.1295	0.83 0.64
Chloroacetate [a]	3.515	4.75	0.51
Formate [a]	3.68	3.65	0.55
Acetate [a]	4.05	2.74	1.48
Acetate	4.67	2.283 2.199	1.05 1.01
Phosphate [b]	6.56	2.063 2.003 2.053	0.37 0.38 0.13
Phosphate [c]	6.57	2.056	0.42
Sodium hydroxide	10.78	2.011	0.33

a. Rates determined by extrapolation to zero buffer concentration.

c. Na_2HPO_4 / NaH_2PO_4 buffer 1 : 1 dilution of phosphate buffer (b) with 0.1M sodium chloride.

Table 25

Hydrolysis of 2 - phenoxytetrahydropyran derivatives in 0.01M hydrochloric acid (pH = 2.04) at 30.01°

2 - tetrahydropyran	$10^3 k$ (sec^{-1})	k_{err} (%)
p - Methoxyphenoxy-	18.56	0.65
	18.51	0.68
	18.62	0.45
p - Phenoxy-	11.8	0.52
	12.7	0.54
p - Chlorophenoxy-	6.15	0.46
	5.97	0.77
m - Chlorophenoxy-	5.0	0.39
p - Acetylphenoxy-	3.90	0.33
p - Nitrophenoxy-	2.15	0.96
	2.29	0.87

Using the σ values reproduced in Hine[111] gives a good linear correlation, see Graph 4 with a ρ value of -0.875.

Table 26

Hydrolysis of 2 - phenoxytetrahydropyran derivatives in 0.01M hydrochloric acid (pH 2.04) at 20.30° (See Graph 4)

2 - tetrahydropyran	$10^4 k$ (sec^{-1})	k_{err} (%)
p - Methoxyphenoxy-	65.74	0.39
Phenoxy-	46.6	0.77
	44.8	0.44
p - Acetylphenoxy-	13.13	0.33
	13.33	0.53
p - Nitrophenoxy-	7.303	0.46
	7.374	0.56
	7.508	0.41

Table 27

Hydrolysis of 2 - phenoxytetrahydrofuran derivatives in 0.01M hydrochloric acid (pH 2.04) at 20.00°

2 - tetrahydrofuran	10^3 k (sec^{-1})	k_{err} (%)
p - Methoxyphenoxy-	44.6	0.38
	43.96	0.35
	45.13	0.63
Phenoxy-	29.26	0.84
	28.02	0.36
	28.06	0.35
p - Bromophenoxy-	12.50	0.29
	12.95	0.25
	12.22	0.25
p - Acetylphenoxy-	7.292	1.01
	7.384	0.64
p - Nitrophenoxy-	3.862	1.14
	3.823	1.79

This data gives a good linear correlation with a ρ value of -0.97 ± 0.05 (See Graph 3).

Solvent deuterium isotope effects

2 - (p - Substitutedphenoxy) - tetrahydropyrans and furans

0.01M H Cl , pH = 2.04.

0.01M D Cl , pD = 1.65.

Table 28

2 - (p - Methoxyphenoxy) - tetrahydropyran

At 20.88° H Cl $\underline{k} = 6.57 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.24\%$

D Cl $\underline{k} = 1.27 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 0.39\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.94.$

2 - Phenoxytetrahydropyran

At 20.88° H Cl $\underline{k} = 5.04 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.26\%$

D Cl $\underline{k} = 8.20 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.30\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.63.$

2 - (p - Acetylphenoxy) - tetrahydropyran

At 20.88° H Cl $\underline{k} = 1.28 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.50\%$

D Cl $\underline{k} = 2.05 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.55\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.59.$

2 - (p - Nitrophenoxy) - tetrahydropyran

At 20.88° H Cl $\underline{k} = 7.32 \times 10^{-4}$ sec^{-1}, $\underline{k}_{err} = 0.49\%$

D Cl $\underline{k} = 10.27 \times 10^{-4}$ sec^{-1}, $\underline{k}_{err} = 0.61\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.40.$

Table 29

2 - (p - Methoxyphenoxy) - tetrahydrofuran

At 20.88° H Cl $\underline{k} = 3.98 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 0.6\%$

D Cl $\underline{k} = 8.21 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 0.57\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 2.06.$

2 - Phenoxytetrahydrofuran

At 20.88° H Cl $\underline{k} = 2.86 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 0.59\%$

D Cl $\underline{k} = 5.47 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 0.47\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.91.$

2 - (p - Acetylphenoxy) - tetrahydrofuran

At 20.88° H Cl $\underline{k} = 7.519 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 1.69\%$

D Cl $\underline{k} = 1.228 \times 10^{-2}$ sec^{-1}, $\underline{k}_{err} = 1.78\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.68.$

2 - (p - Nitrophenoxy) - tetrahydrofuran

At 20.88° H Cl $\underline{k} = 4.40 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.54\%$

D Cl $\underline{k} = 5.63 \times 10^{-3}$ sec^{-1}, $\underline{k}_{err} = 0.89\%$

$\underline{k}_{D_3O^+} / \underline{k}_{H_3O^+} = 1.28.$

Table 30

Solvent deuterium isotope effects in 2 - (p - substituted phenoxy) - tetrahydrofurans and pyrans at 20.88°.

p - Substituent	Solvent isotope effect	
	phenoxy-tetrahydrofuran	phenoxy-tetrahydropyran
Methoxy-	2.06	1.94
Hydrogen-	1.91	1.63
Acetyl-	1.68	1.59
Nitro-	1.28	1.40

General - acid catalysis studies

Rate data recorded in general - acid searches are recorded in Tables 31 to 38. In these experiments all kinetic measurements were made at 49.95°, and at an ionic strength of 0.1.

Any slopes quoted are the second order rate constants for general - acid catalysed reactions, and intercepts are the rates extrapolated to zero buffer concentration.

Table 31

2 - Phenoxytetrahydropyran

Acetate buffer (CH_3COOH) = 4 (CH_3COO^-).

$\underline{M}$ CH_3COOH	pH	10^4 $\underline{k}$ (sec^{-1})	$\underline{k}_{err}$ (%)
0.0072	4.05	9.645 9.587	0.35 0.33
0.0144	4.04	10.18 10.14	0.35 0.38
0.0216	4.05	10.44 10.13	0.49 0.35
0.0288	4.05	10.12 10.64	0.39 0.31
0.036	4.08	9.953 10.20	0.40 0.27

These results show that any general - acid catalysis term is smaller than the experimental error.

Table 32

2 - Phenoxytetrahydrofuran - See Graph 5

Acetate buffer $(CH_3COOH) = 4\ (CH_3COO^-)$

$\underline{M}$ CH_3COOH	pH	$10^3\ \underline{k}\ (sec^{-1})$	$\underline{k}_{err}$ (%)
0.0072	4.05	4.391	0.29
0.0144	4.04	4.521	0.26
		4.510	0.33
0.0216	4.05	4.482	0.32
		4.592	0.26
0.0288	4.05	4.634	0.33
		4.632	0.25
0.036	4.08	4.699	0.33
		4.683	0.24

Slope: $10^3.\ \underline{k}\ (1\ mole^{-1}\ sec^{-1}) = 1.8 \pm 0.16$

Intercept: $10^3.\ \underline{k}\ (sec^{-1}) = 4.375 \pm .025$

Table 33

2 - (p - Nitrophenoxy) - tetrahydropyran - See Graph 6.
Acetate buffer $(CH_3COOH) = 4.(CH_3COO^-)$

$\underline{M}$ CH_3COOH	pH	$10^3 . \underline{k}$ (sec^{-1})	$\underline{k}_{err}$ (%)
0.0072	4.05	1.323	0.93
		1.324	0.92
0.0144	4.04	1.338	0.96
		1.351	0.91
0.0216	4.05	1.314	0.89
		1.324	0.97
0.0288	4.05	1.335	0.90
		1.325	0.96
0.036	4.08	1.346	0.94
		1.341	0.89
		1.354	1.46
		1.363	0.95
0.072	4.085	1.467	1.55
		1.487	1.10
0.108	4.095	1.459	0.91
		1.465	0.97
		1.470	0.87
0.144	4.115	1.523	1.01
		1.533	1.03
		1.540	0.82
0.180	4.120	1.554	0.98
		1.566	1.15
		1.570	0.92

Slope: $10^3 . \underline{k}$ ($l\ mole^{-1} sec^{-1}$) = 1.46
Intercept: $10^3 . \underline{k}$ (sec^{-1}) = 1.31

Table 34

2 - (p - Nitrophenoxy) - tetrahydropyran - See Graph 7.
Formate buffer (HCOOH) = ($HCOO^-$)

M HCOOH	pH	$10^3 . k$ (sec^{-1})	k_{err} (%)
0.01	3.70	1.566	0.35
		1.570	0.56
0.02	3.68	1.625	0.60
		1.634	0.56
0.03	3.68	1.696	0.32
		1.702	0.49
0.04	3.68	1.736	0.44
		1.784	0.51
0.05	3.68	1.828	0.49

Slope: $10^3 . k$ ($l\ mole^{-1}\ sec^{-1}$) = 6.55 ± 0.14

Intercept: $10^3 . k$ (sec^{-1}) = 1.504 ± 0.005

Table 35

2 - (p - Nitrophenoxy) tetrahydropyran - See Graph 8.
Chloroacetate buffer $(Cl.CH_2.COOH) = (Cl.CH_2.COO^-) / 4.27$

$\underline{M}$ Cl CH_2 COOH	pH	10^3. $\underline{k}$ (sec^{-1})	$\underline{k}_{err}$ (%)
0.00466	3.51	1.769	0.73
0.00932	3.51	1.949	0.76
0.01398	3.515	2.025	0.88
0.01864	3.515	2.091	1.06
0.0233	3.525	2.213	0.82

Slope: $10^3 \underline{k}$ ($l\ mole^{-1}\ sec^{-1}$) = 23.0 ± 0.55
Intercept: $10^3 \underline{k}$ (sec^{-1}) = 1.69 ± 0.005

Table 36

2 - (p - Nitrophenoxy) - tetrahydrofuran - See Graph 9.
Acetate buffer $(CH_3COOH) = 4\ (CH_3COO^-)$

M CH_3COOH	pH	10 k (sec^{-1})	k_{err} (%)
0.0072	4.05	2.608	1.48
		2.663	1.50
0.0144	4.04	2.699	1.45
		2.657	1.15
0.0216	4.05	2.727	1.47
		2.776	1.13
0.0288	4.05	2.793	1.48
		2.880	1.04
0.036	4.08	2.987	1.34
		2.960	0.54
		2.932	0.52
0.072	4.085	3.278	0.33
		3.307	0.53
		3.218	0.51
0.108	4.095	3.455	0.56
		3.452	0.53
		3.371	0.47
0.144	4.115	3.733	0.39
		3.59	0.65
		3.653	0.53
0.180	4.120	3.805	0.42
		3.832	0.39

Slope: $10^3\ k\ (1\ mole^{-1}\ sec^{-1}) = 6.0 \pm 0.08$

Intercept: $10^3\ k\ (sec^{-1}) = 2.74 \pm 0.02$

Table 37

2 - (p - Nitrophenoxy) - tetrahydrofuran - See Graph 10.
Formate buffer (HCOOH) = ($HCOO^-$)

M HCOOH	pH	10^3 k (sec^{-1})	k_{err} (%)
0.01	3.70	3.751	0.42
		3.719	0.61
0.02	3.68	3.918	0.69
0.03	3.68	3.992	0.48
		4.034	0.96
0.04	3.68	4.110	0.63
0.05	3.68	4.200	0.51
		4.213	1.28

Slope: 10^3 k (1 $mole^{-1}$ sec^{-1}) = 10.8 ± 0.5

Intercept: 10^3 k (sec^{-1}) = 3.65 ± 0.025

Table 38

2 - (p - Nitrophenoxy) - tetrahydrofuran - See Graph 11.
Chloroacetate buffer $(ClCH_2COOH) = (ClCH_2COO^-) / 4.27$

M $ClCH_2COOH$	pH	10^3 k (sec^{-1})	k_{err} (%)
0.00466	3.51	4.991 4.961	0.70 0.67
0.00932	3.51	5.109	0.51
0.01398	3.515	5.504 5.610	0.50 0.55
0.01864	3.515	5.614 5.834	0.52 0.59
0.0233	3.525	5.963 6.041	0.42 0.51

Slope: 10^3 k (1 $mole^{-1}$ sec^{-1}) = 53.3

Intercept: 10^3 k (sec^{-1}) = 4.75

Table 39

Phenyl 2 - deoxy α - $\underline{\underline{D}}$ - glucopyranoside, Temperature 64.75°
0.1$\underline{\underline{M}}$ $HClO_4$, ionic strength 0.1, pH = 1.10.

$10^2\ \underline{k}\ (sec^{-1})$	$\underline{k}_{err}$ (%)
1.686	0.56
1.698	0.73
1.721	0.44
1.684	0.68

Average $10^2\ \underline{k}$ = 1.697

$\underline{k}_{H^+} = \underline{k} / (H^+) = 0.216$ 1 $mole^{-1}$ sec^{-1}.

0.01$\underline{\underline{M}}$ $HClO_4$, ionic strength = 0.1 , pH = 2.08.

$10^3\ \underline{k}\ (sec^{-1})$	$\underline{k}_{err}$ (%)
1.796	0.46
1.774	0.42
1.761	0.88
1.761	0.78

Average $10^3\ \underline{k}$ = 1.773

$\underline{k}_{H^+} = \underline{k} / (H^+) = 0.213$ 1 $mole^{-1}$ sec^{-1}

For phenyl 2 - deoxy α - $\underline{\underline{D}}$ - glucopyranoside in 0.1$\underline{\underline{M}}$ and 0.01$\underline{\underline{M}}$ $HClO_4$ at 64.75°, $\underline{k}_{H^+}$ = 0.2145 1 $mole^{-1}$ sec^{-1}.

General - acid catalysis studies in phenyl 2 - deoxy α - D - glucopyranoside hydrolysis.

Table 40

Temperature 65.10°

Phosphate buffer
Ionic strength 0.1

M H_3PO_4	pH	10^3 k	k_{err} (%)
0.1	1.748	3.680	0.41
		3.617	0.34
		3.553	0.32
0.2	1.595	5.406	0.31
		5.062	0.30
		4.967	0.29
		5.310	0.41
		5.191	0.33
0.3	1.503	6.622	0.84
		6.180	0.38
		6.148	0.32
		6.409	0.30
		6.363	0.30
0.4	1.44	7.245	0.90
		7.326	0.37
		7.756	0.28
		7.632	0.34
		7.796	0.37
0.5	1.39	8.486	0.63
		8.305	0.73
		8.507	0.78
		8.622	0.65
		8.239	0.70

In Table 41 these results are corrected to a single pH.

Table 41

Correction of phosphate buffer rate data from Table 40 for phenyl 2 - deoxy α - D - glucopyranoside, for variation of pH, using the identity $k = k_{H^+}(H^+) + k_{HA}(HA)$.

pH	$10^3 (H^+)$	$\Delta(10^3 (H^+))$	$k_{H^+} \times \Delta(10^3 (H^+))$	$10^3 k_{obs}$ (sec^{-1})	$10^3 k_{corr}$ [a] (sec^{-1})
1.748	17.86	22.88	4.907	3.616	8.523
1.595	25.41	15.33	3.288	5.187	8.475
1.503	31.44	9.33	2.001	6.344	8.345
1.44	36.31	4.43	0.9501	7.539	8.489
1.39	40.74	0	0	8.432	8.432

a. Data corrected to pH 1.39.

Table 42

Phenyl β - D - glucofuranoside. Temperature 65.00°
0.1M $HClO_4$, ionic strength 0.1, pH = 1.10.

10^4 k (sec^{-1})	k_{err} (%)
1.612	0.27
1.604	0.28
1.597	0.38
1.588	0.29
1.595	0.28

Average 10^4 k = 1.599

$k_{H^+} = k / (H^+) = .00201$ l $mole^{-1}$ sec^{-1}.

For phenyl β - D - glucofuranoside in 0.1M $HClO_4$ at 65.00°, 10^3 k_{H^+} = 2.01 l $mole^{-1}$ sec^{-1}.

General - acid catalysis studies in phenyl β - D - glucofuranoside hydrolysis.

Table 43

Temperature 65.08°

Phosphate buffer

Ionic strength 0.1

M	H_3PO_4	pH	10^5 k	k_{err} (%)
	0.1	1.748	3.416	0.81
			3.486	0.64
			3.380	0.65
	0.2	1.595	4.869	0.81
			4.929	1.22
			4.929	0.57
			5.115	0.52
	0.3	1.503	6.359	0.89
			6.110	0.50
			6.320	0.43
			6.367	0.54
			6.282	0.35
	0.4	1.44	7.178	0.51
			7.355	0.43
			7.321	0.37
			7.371	0.37
	0.5	1.39	8.151	0.78
			8.148	0.72
			8.060	0.47
			8.253	0.34

In Table 44 these results are corrected to a single pH.

Table 44

Correction of phosphate buffer rate data from Table 43 for phenyl β - D - glucofuranoside, for variation of pH, using the identity $k = k_{H^+}(H^+) + k_{HA}(HA)$.

pH	$10^3 (H^+)$	$\Delta(10^3 (H^+))$	$k_{H^+} \times \Delta(10^5 (H^+))$	$10^5 k_{obs}$ (sec^{-1})	$10^5 k_{corr}$ [a] (sec^{-1})
1.748	17.86	22.88	4.599	3.427	8.026
1.595	25.41	15.33	3.07	4.961	8.031
1.503	31.41	9.33	1.875	6.288	8.161
1.44	36.31	4.33	0.89	7.306	8.196
1.39	40.74	0	0	8.153	8.153

a. Data corrected to pH 1.39.

General - acid catalysis studies in phenyl 2 - deoxy α - D - glucopyranoside hydrolysis.

Table 45

Temperature 65.10°

Monochloroacetate buffers

Ionic strength 0.1

M $ClCH_2COOH$	pH	$10^3 k$ (sec^{-1})	k_{err} (%)	$10^3 k_{corr}$ [a]
0.1	2.28	1.021	0.61	1.253
		1.020	0.42	
		1.034	0.36	
0.2	2.25	1.136	0.43	1.282
		1.168	2.27	
		1.184	0.34	
0.3	2.22	1.275	0.39	1.304
		1.229	0.42	
		1.225	0.34	
0.4	2.213	1.245	0.36	1.334
		1.272	0.36	
		1.307	0.35	
0.5	2.20	1.262	0.41	1.268
		1.249	0.50	
		1.292	0.33	

a Rate constants corrected to pH 2.20 by the method used in Table 44.

General - acid catalysis studies in phenyl β - D - glucofuranoside hydrolysis.

Table 46

Temperature 65.08°

Ionic strength 0.1
Monochloroacetate buffer

M $ClCH_2COOH$	pH	$10^5 k$ (sec^{-1})	k_{err} (%)
0.1	2.28	0.935	0.57
0.2	2.24	1.018	0.42
0.3	2.22	1.057	0.40
0.4	2.213	1.056	0.38
0.5	2.20	0.938	0.53

Table 47

Data for aqueous perchloric solutions at 25°.

Molarity	H_0 [56] Paul-Long	Yates-Wai[109]	$\log_{10} a_{H_2O}$ [110]	$\log_{10} c_{H^+}$
1.00	-0.20	-0.152	-0.0164	0.0
2.00	-0.78	-0.626	-0.043	0.3030
2.995	-1.225	-1.075	-0.0805	0.4783
3.947	-1.675	-1.488	-0.1315	0.5982
5.021	-2.25	-1.987	-0.217	0.7027

Table 48

Hydrolysis of phenyl β - D - glucofuranoside at 44.96°.

M $HClO_4$	10^4 k (sec^{-1})	k_{err} (%)
1.00	1.760	0.44
2.00	6.367	0.48
2.995	19.51	0.26
3.947	48.43	0.47
5.021	140.4	0.56

Table 49

Hydrolysis of p - cresyl β - D - glucofuranoside at 44.95°.

M $HClO_4$	10^4 k (sec^{-1})	k_{err} (%)
1.00	1.490	0.58
2.00	5.287	0.27
2.995	15.47	0.59
3.947	39.93	0.37
5.021	109.3	0.56

Table 50

Hydrolysis of p - methoxyphenyl β - D - glucofuranoside at 45.65°.

M $HClO_4$	10^4 k (sec^{-1})	k_{err} (%)
1.00	1.367	3.8
2.00	4.798	0.54
2.995	13.67	1.11
3.947	35.75	0.44
5.021	107.2	0.65

Table 51

Hydrolysis of phenyl β - D - galactofuranoside at 35.16°.

M $HClO_4$	10^4 k (sec^{-1})	k_{err} (%)
1.00	1.599	0.27
2.00	5.169	0.59
2.995	14.23	0.33
3.947	34.87	0.35
5.021	94.66	0.58

Table 52

a. Hammett - Zucker plots

$-H_o$ plotted against $\log_{10} k$

Rates determined at 45°.

Glycoside	Slope From Paul-Long[56] Values	Slope From Yates-Wai[109] Values
Phenyl β- D - glucofuranoside	0.96 ± 0.02	1.00 ± 0.02
p - Cresyl β- D - glucofuranoside	-	1.006 ± 0.016
p - Methoxyphenyl β- D - glucofuranoside	0.962 ± 0.032	1.001 ± 0.014 x
Phenyl β- D - galactofuranoside	-	1.015 ± 0.075

x. See Graph 12.

b. Bunnett plots

$\log_{10} k + H_o$ plotted against $\log_{10} a_{H_2O}$

Bunnett plots for the phenyl β- D - glycofuranosides studied were curvilinear with slope of zero for the best line through the experimental points.

c. $\log_{10} k$ plotted against $\log_{10} c_{H^+}$

All these plots were curves - See Graph 13.

Table 53

Activation parameters for the hydrolysis of phenyl β- D - hexofuranosides in 1.00M perchloric acid, determined at the lowest temperature quoted for the substrate.

furanoside	Temperature	10^4 k (sec^{-1})	k_{err} (%)	$\bar{E}$ kcal $mole^{-1}$	log A	$\Delta S^{\ddagger}$ e.u.
Phenyl β- D - gluco-	44.96	1.76	0.44	29.43	37.92	14.71
	55.06	7.144	0.35			
	64.40	25.78	0.56			
p-Cresyl β- D - gluco-	44.95	1.49	0.57	28.67	36.56	11.97
	55.14	6.18	0.40			
	65.14	22.34	0.51			
p-Methoxyphenyl β- D - gluco-	45.65	1.359	3.0	29.85	38.23	15.28
	54.99	5.252	0.47			
	64.40	18.36	1.05			
Phenyl β- D - galacto-[a]	35.16	1.592	0.47	26.10	33.88	6.71
	44.99	5.945	0.27			
	54.81	20.58	0.48			
	65.06	68.83	0.45			

a. See Graph 14 for a plot of 1 / T versus log k.

Glycoside solvent deuterium isotope effects

Table 54

Phenyl β - D - glucofuranoside

At 55° in 1.03M HCl, 10^4 k = 6.571 sec^{-1} k_{err} = 0.27%

1.03M DCl, 10^4 k = 1.385 sec^{-1} k_{err} = 0.44%

$k_{D_3O^+} / k_{H_3O^+}$ = 2.11

p - Cresyl β - D - glucofuranoside

At 55° in 1.03M HCl, 10^4 k = 5.718 sec^{-1} k_{err} = 0.22%

1.03M DCl, 10^4 k = 13.22 sec^{-1} k_{err} = 0.44%

$k_{D_3O^+} / k_{H_3O^+}$ = 2.31

p - Methoxyphenyl β - D - glucofuranoside

At 55° in 1.03M HCl, 10^4 k = 5.020 sec^{-1} k_{err} = 0.55%

1.03M DCl, 10^4 k = 11.73 sec^{-1} k_{err} = 0.26%

$k_{D_3O^+} / k_{H_3O^+}$ = 2.34

Phenyl β - D - galactofuranoside

At 55.35° in 1.04M HCl, $10^3 k = 2.116 \text{ sec}^{-1}$ $k_{err} = 0.45\%$

1.04M DCl, $10^3 k = 4.345 \text{ sec}^{-1}$ $k_{err} = 0.41\%$

$k_{D_3O^+} / k_{H_3O^+} = 2.05$

Phenyl 2 - deoxy - α - D - glucopyranoside

At 20.29° in 1.04M HCl, $10^4 k = 9.677 \text{ sec}^{-1}$ $k_{err} = 0.58\%$

1.04M DCl, $10^4 k = 21.11 \text{ sec}^{-1}$ $k_{err} = 0.44\%$

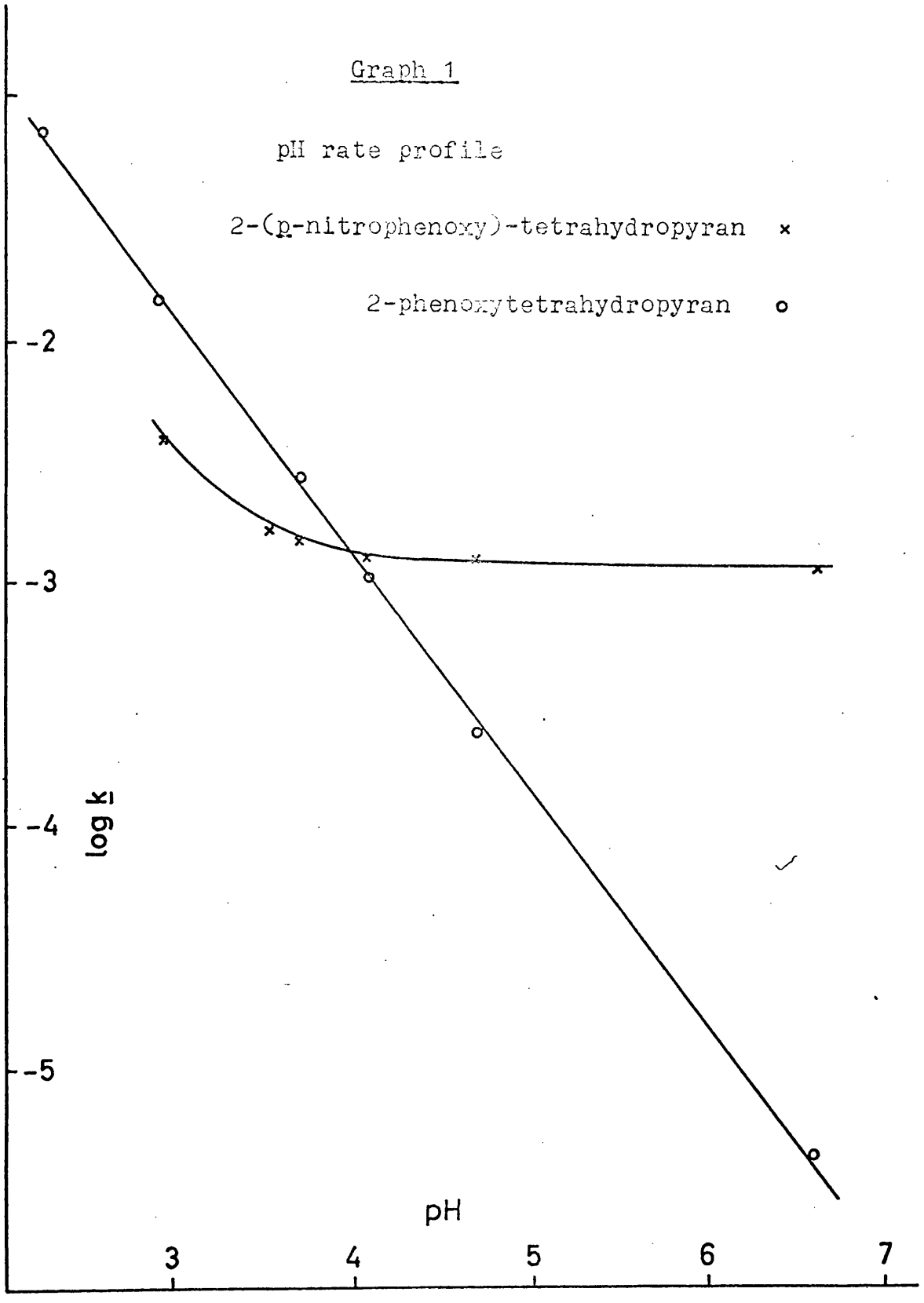
$k_{D_3O^+} / k_{H_3O^+} = 2.18$

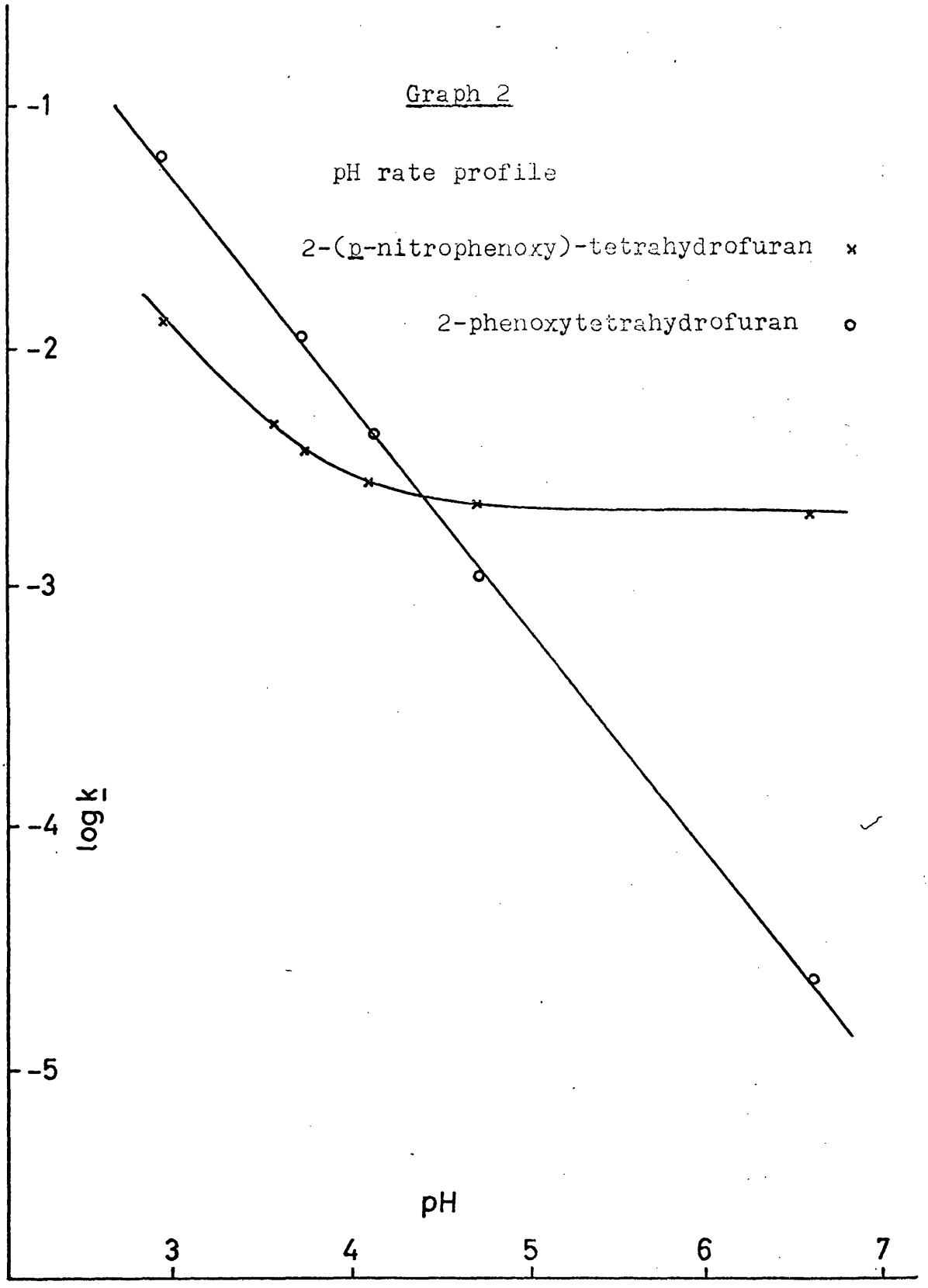
Graph 1

pH rate profile

2-(p-nitrophenoxy)-tetrahydropyran ×

2-phenoxytetrahydropyran o



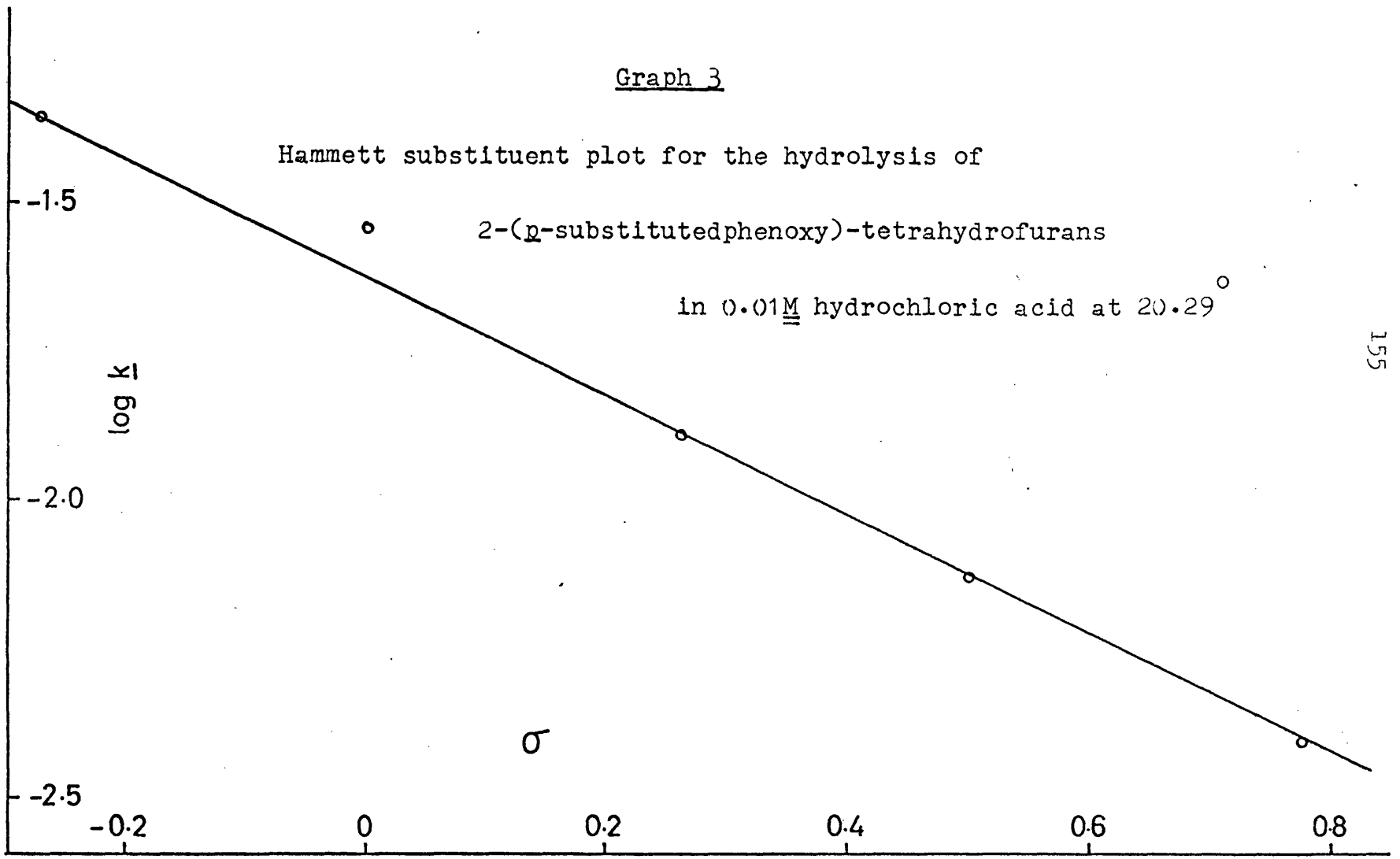

Graph 2
pH rate profile
2-(p-nitrophenoxy)-tetrahydrofuran ×
2-phenoxytetrahydrofuran o
-1
-2
-3
-4
-5
log k
pH
3
4
5
6
7

Graph 3

Hammett substituent plot for the hydrolysis of

o 2-(p-substitutedphenoxy)-tetrahydrofurans

in 0.01M hydrochloric acid at 20.29°



Graph 4

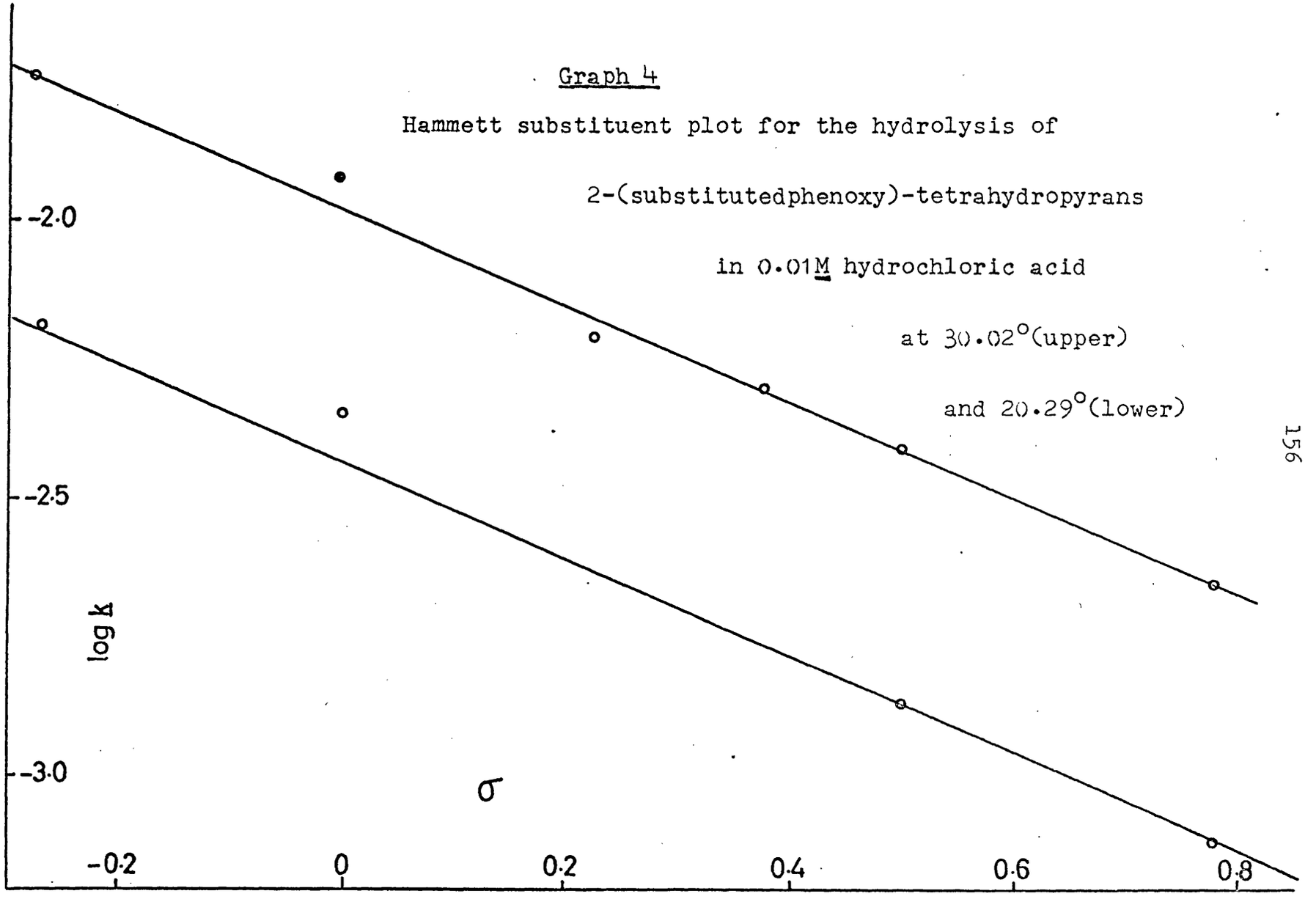
Hammett substituent plot for the hydrolysis of

2-(substitutedphenoxy)-tetrahydropyrans

in 0.01M hydrochloric acid

at 30.02°(upper)

and 20.29°(lower)

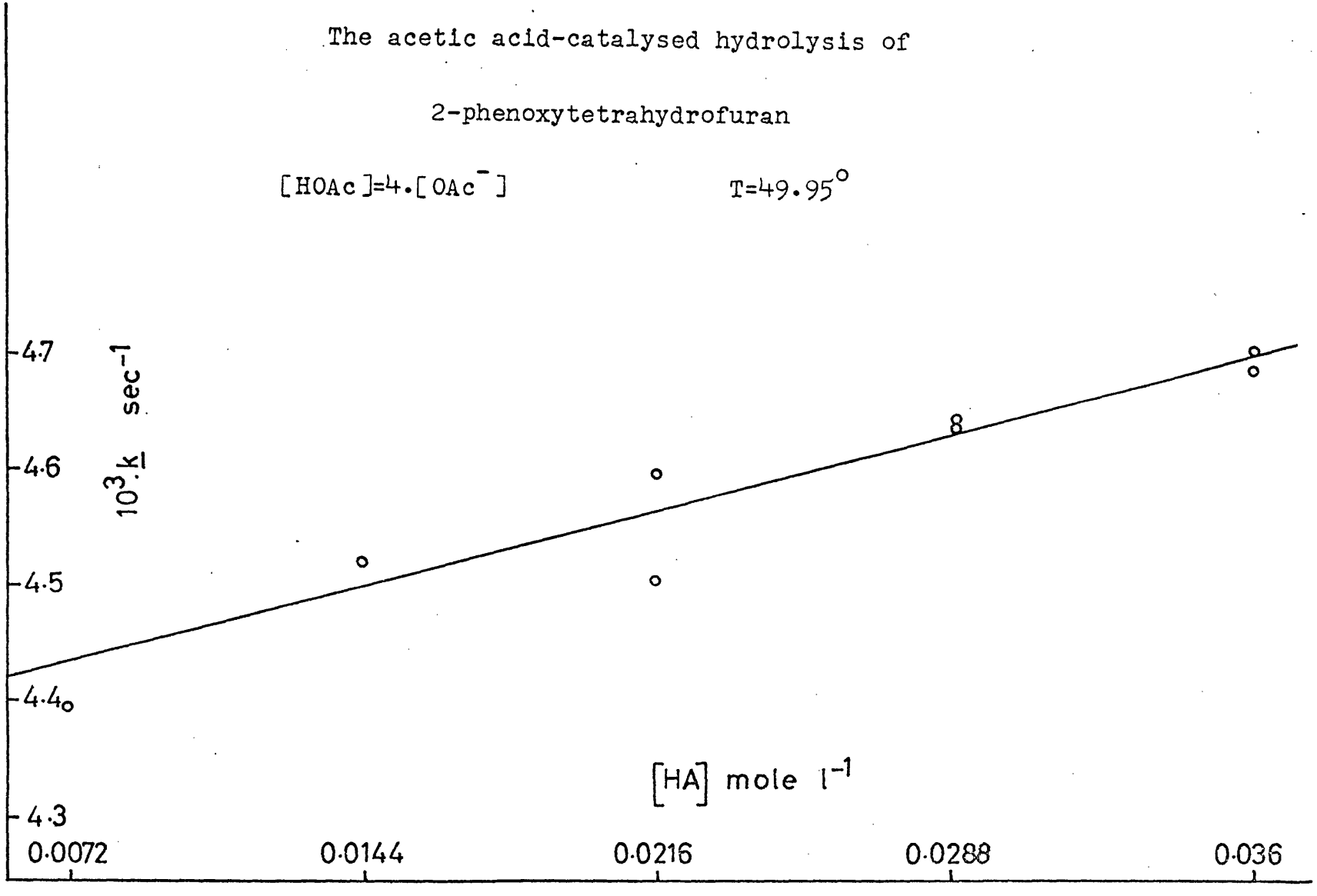


Graph 5

The acetic acid-catalysed hydrolysis of

2-phenoxytetrahydrofuran

$[HOAc]=4.[OAc^-]$ $T=49.95^{\circ}$

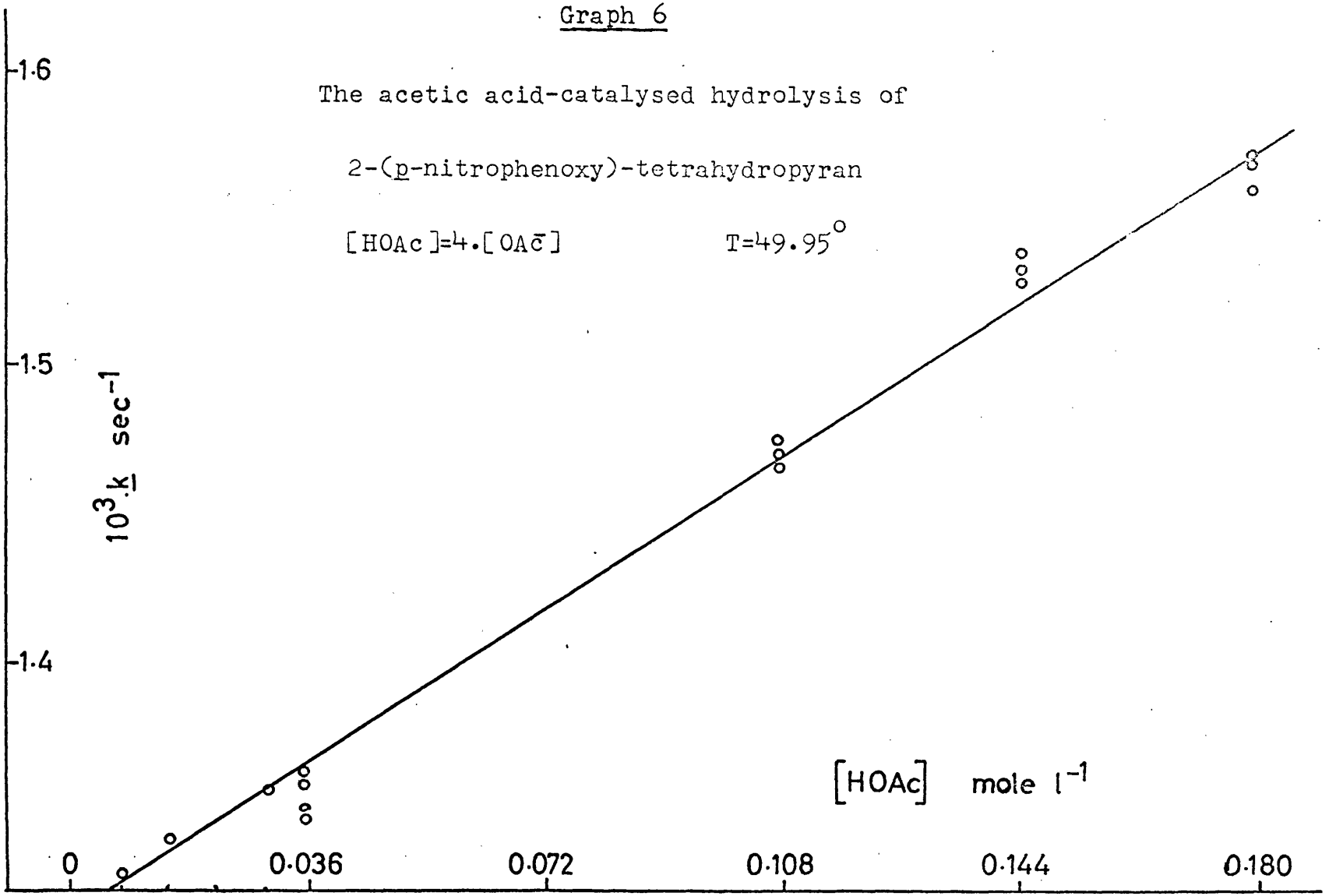


Graph 6

The acetic acid-catalysed hydrolysis of

2-(p-nitrophenoxy)-tetrahydropyran

[HOAc]=4.[OAc$^-$] T=49.95°

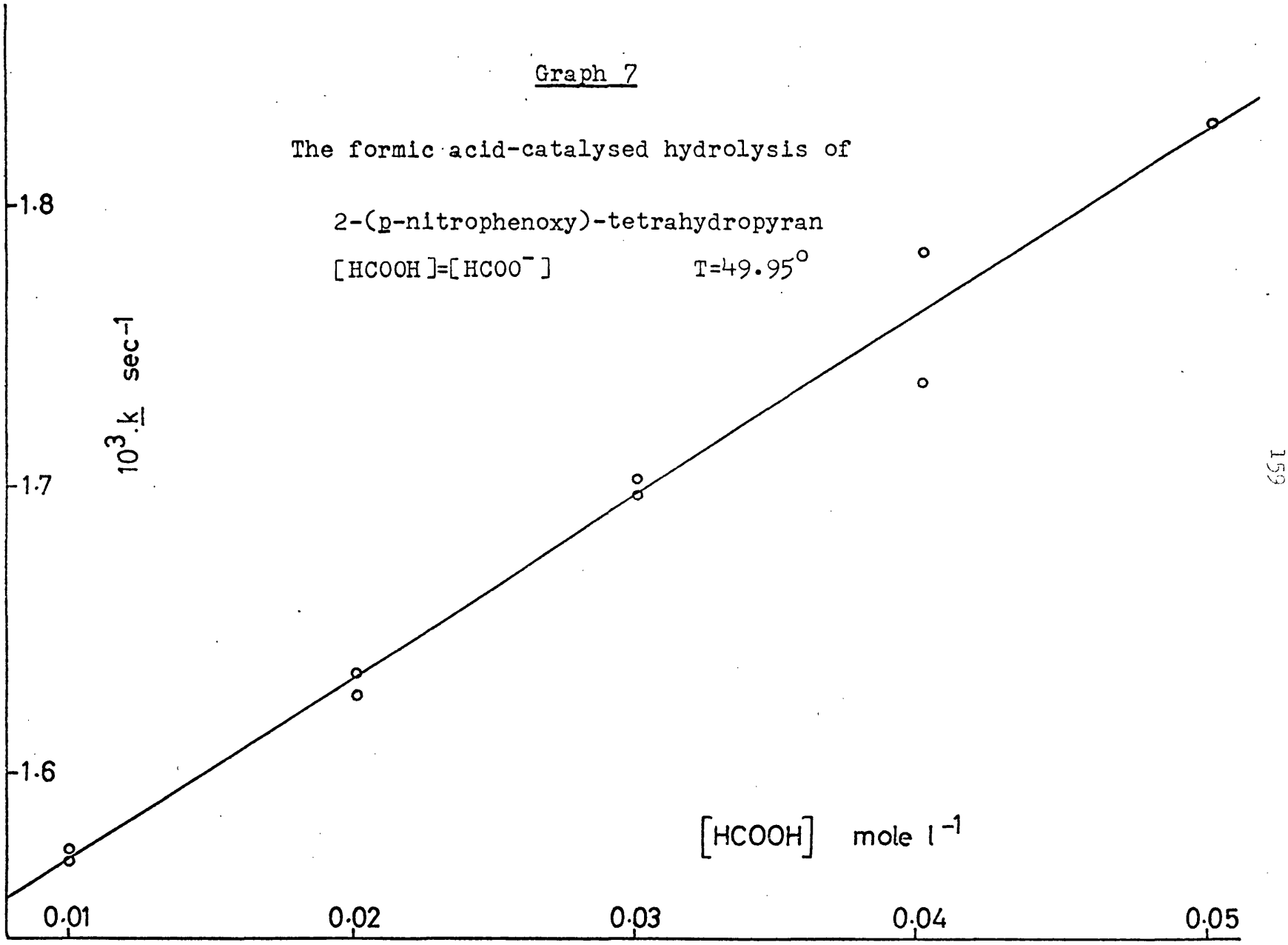


Graph 7

The formic acid-catalysed hydrolysis of

2-(p-nitrophenoxy)-tetrahydropyran

[HCOOH]=[HCOO$^-$] T=49.95°



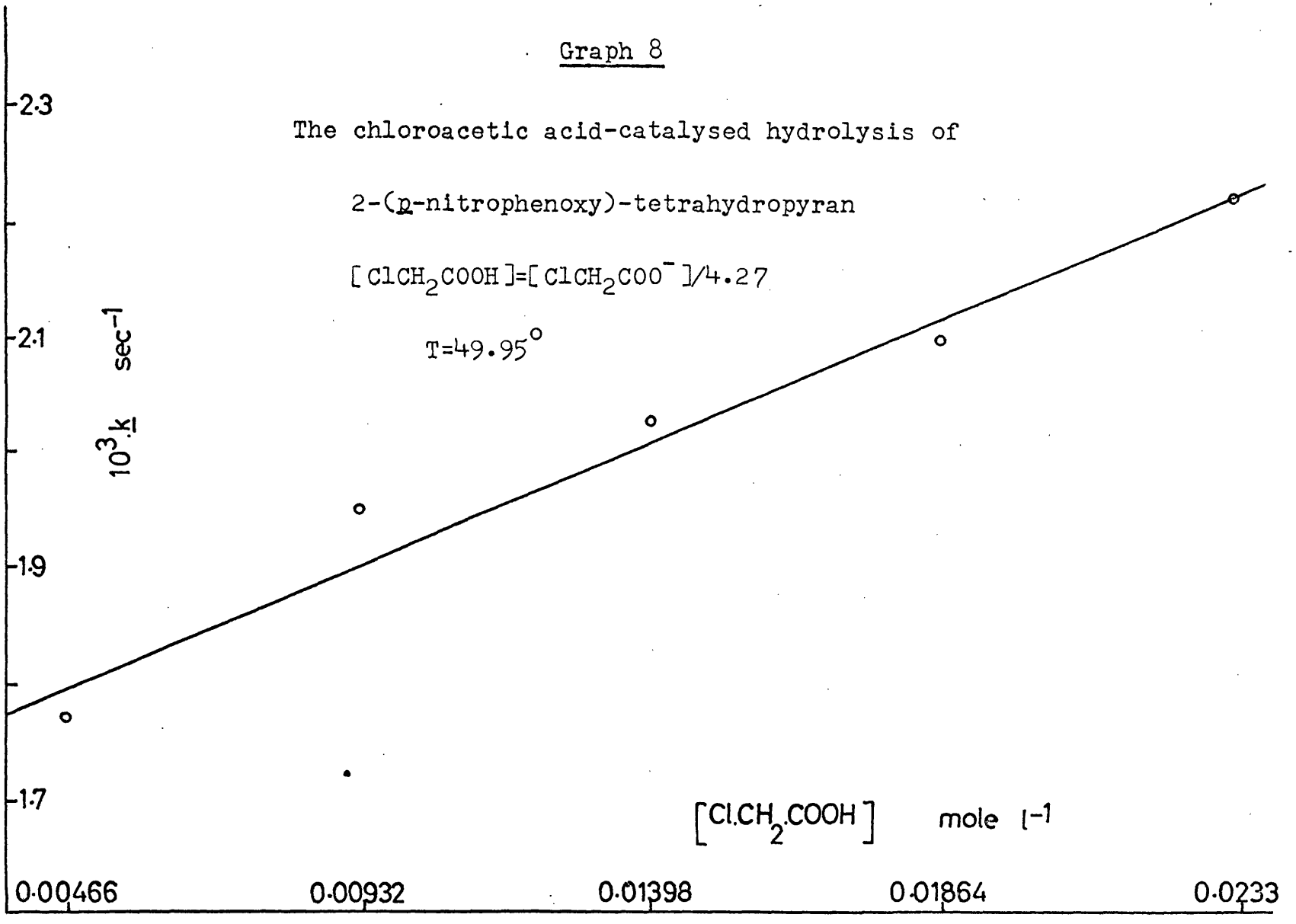
Graph 8

The chloroacetic acid-catalysed hydrolysis of

2-(p-nitrophenoxy)-tetrahydropyran

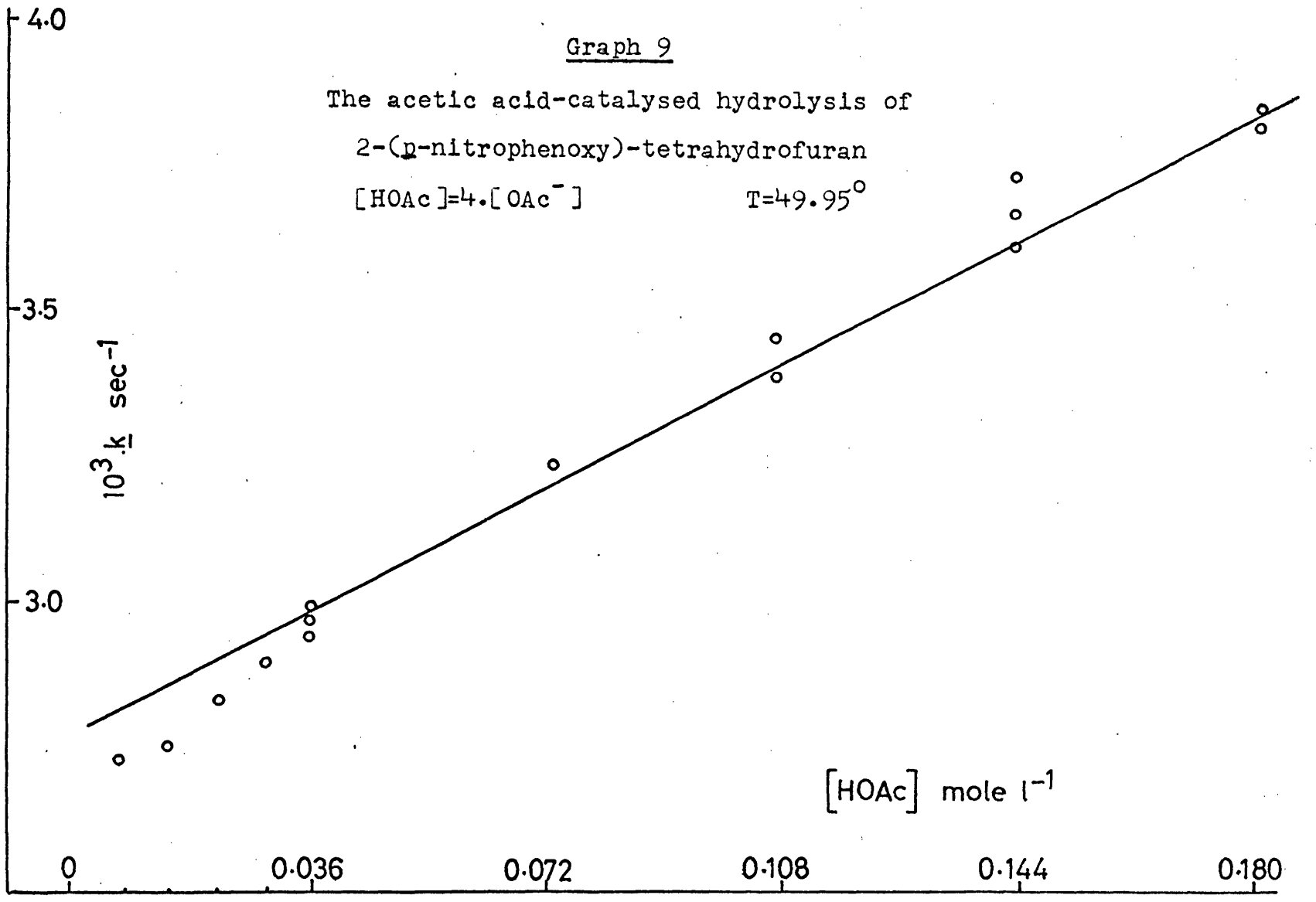
$[ClCH_2COOH]=[ClCH_2COO^-]/4.27$

$T=49.95^{\circ}$



Graph 9

The acetic acid-catalysed hydrolysis of
2-(p-nitrophenoxy)-tetrahydrofuran
[HOAc]=4.[OAc$^-$] T=49.95°

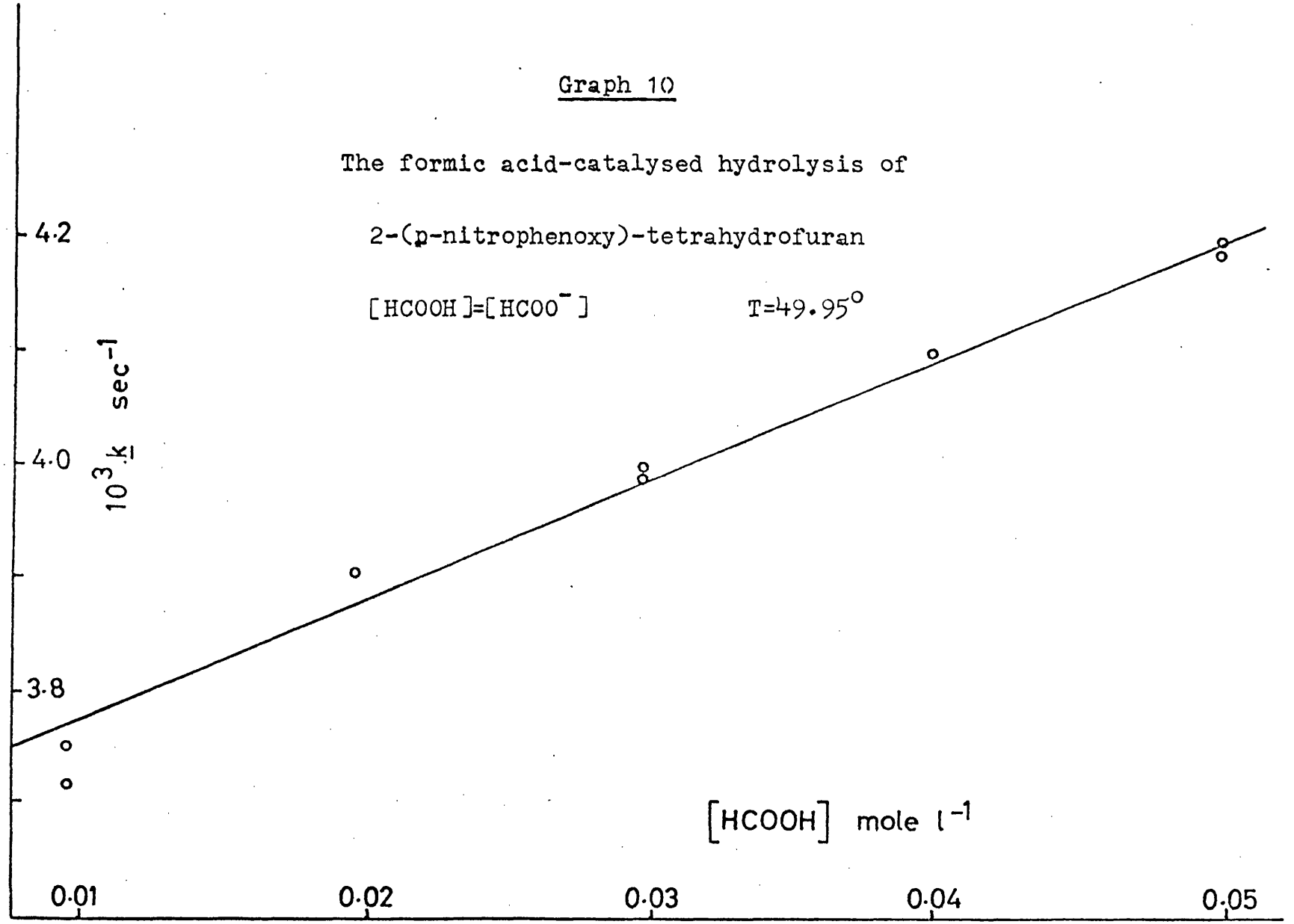


Graph 10

The formic acid-catalysed hydrolysis of

2-(p-nitrophenoxy)-tetrahydrofuran

[HCOOH]=[HCOO$^-$] T=49.95°



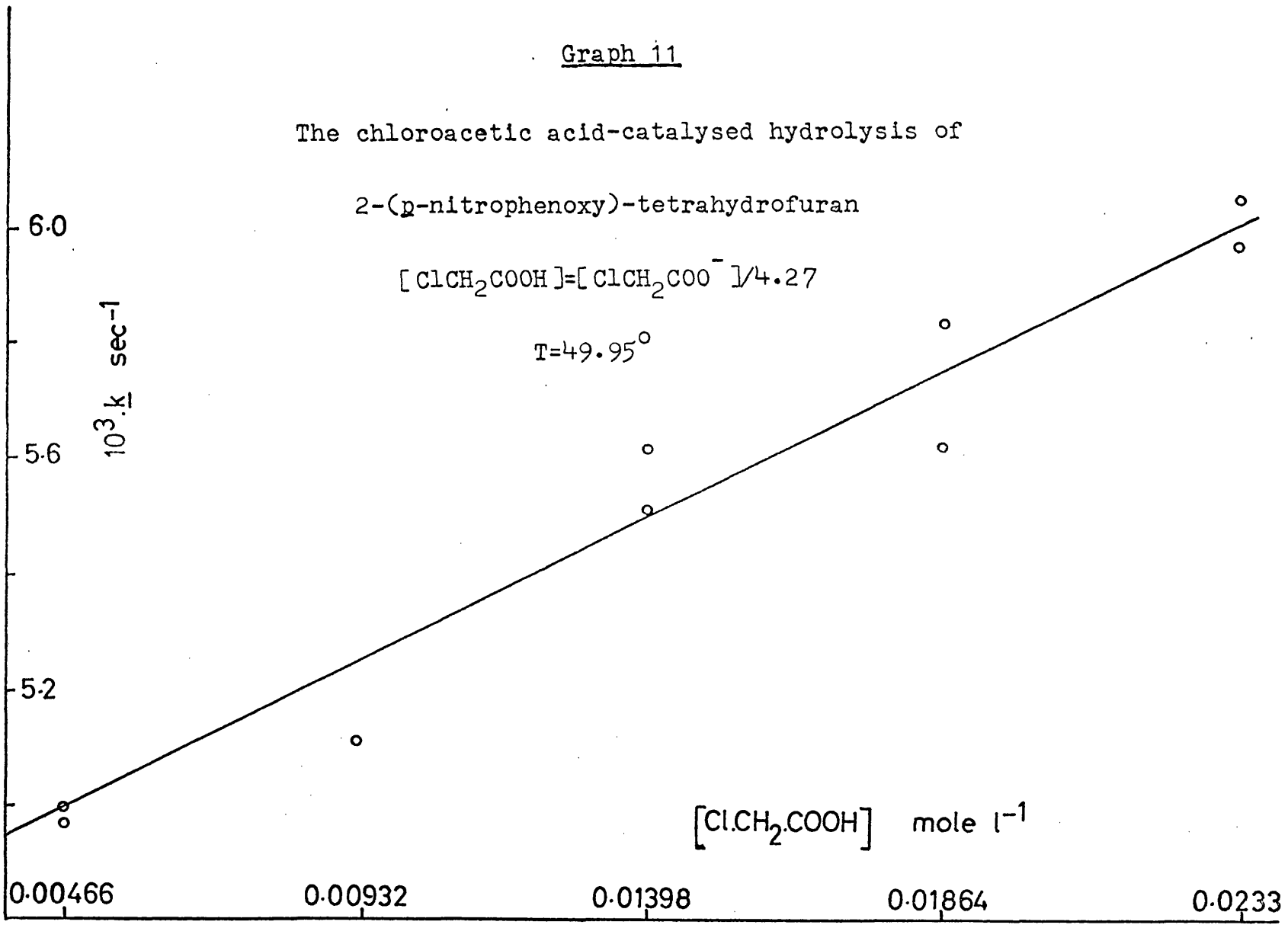
Graph 11

The chloroacetic acid-catalysed hydrolysis of

2-(p-nitrophenoxy)-tetrahydrofuran

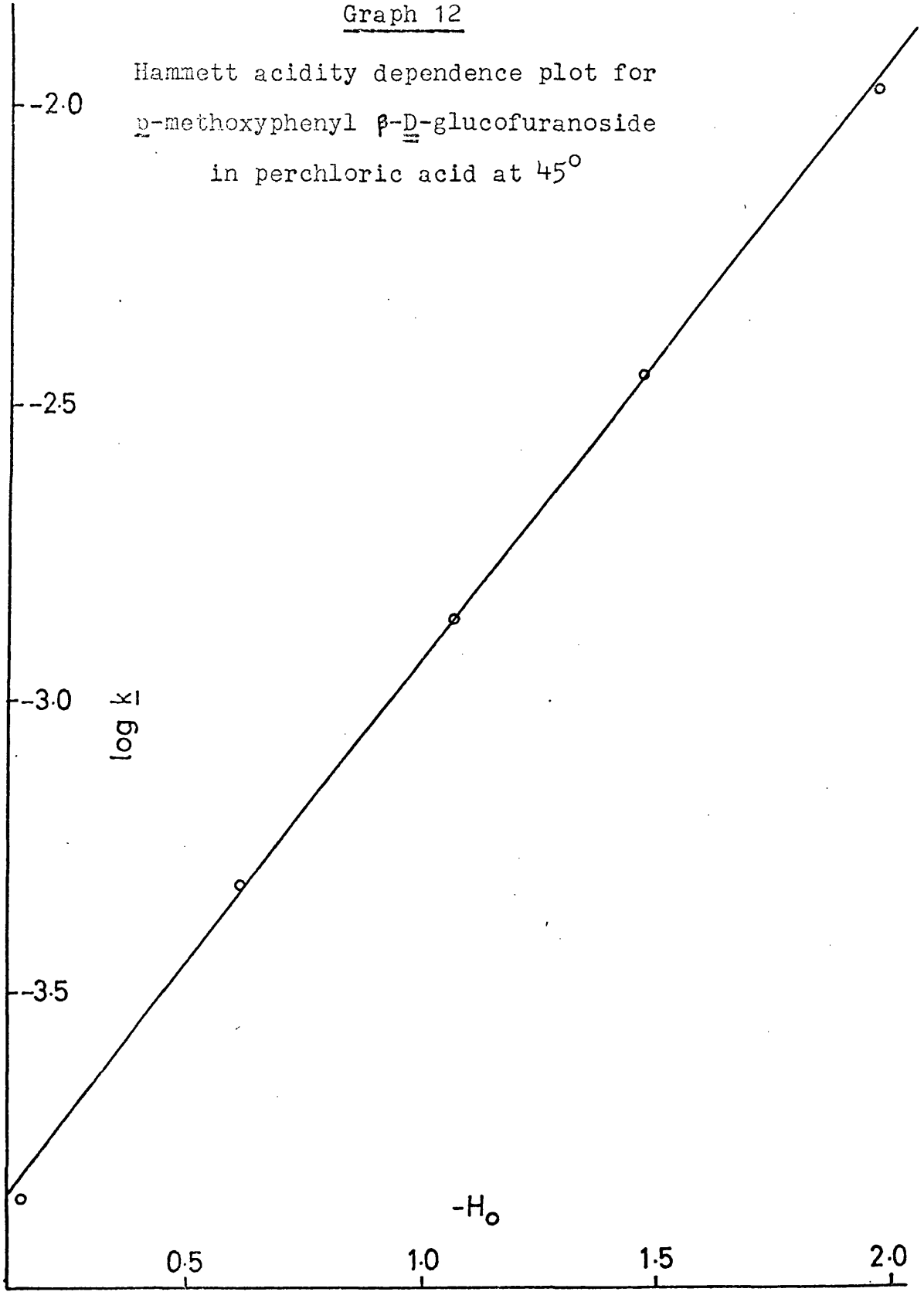
$[ClCH_2COOH]=[ClCH_2COO^-]/4.27$

$T=49.95^{\circ}$



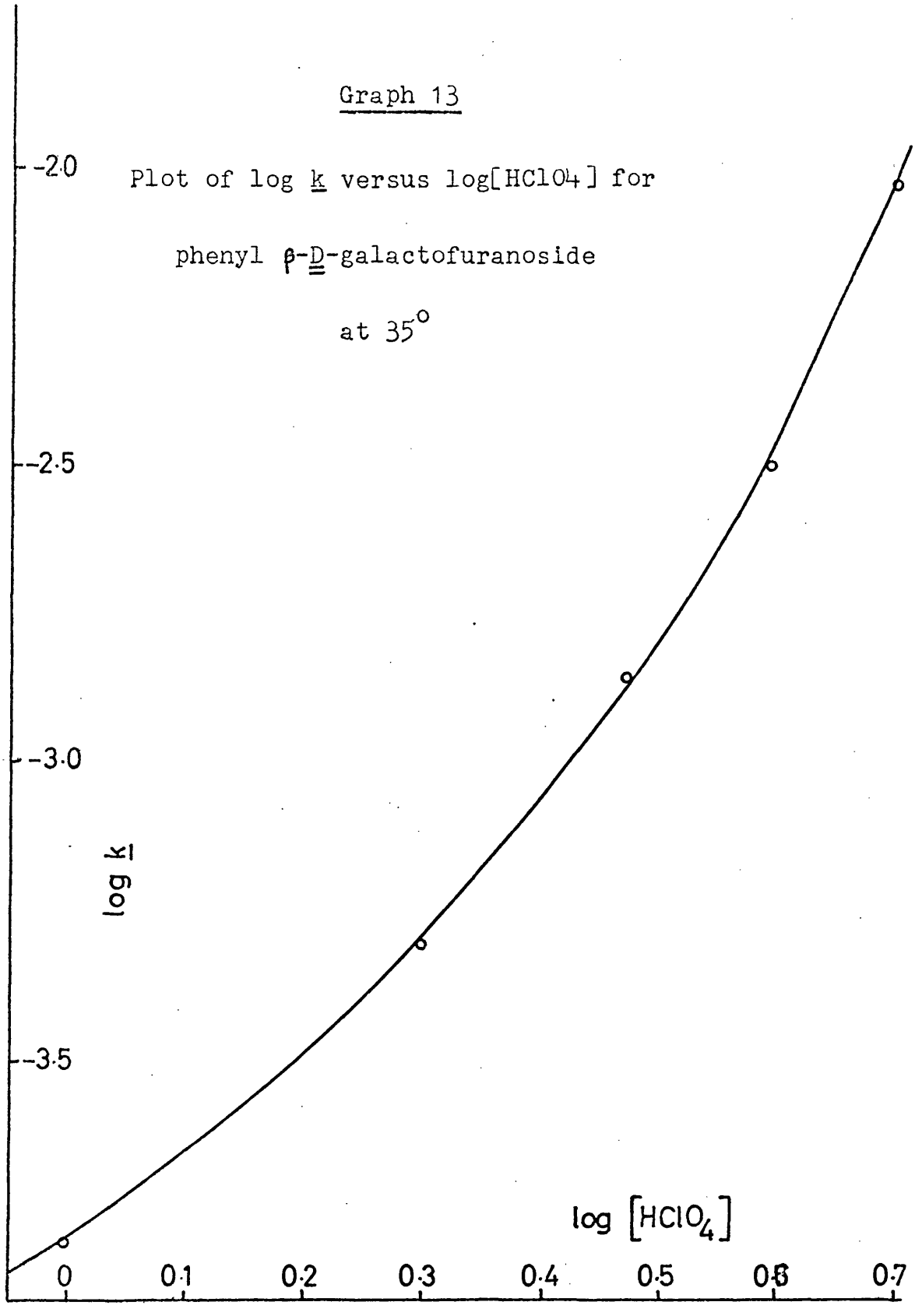
Graph 12

Hammett acidity dependence plot for p-methoxyphenyl β-D-glucofuranoside in perchloric acid at 45°



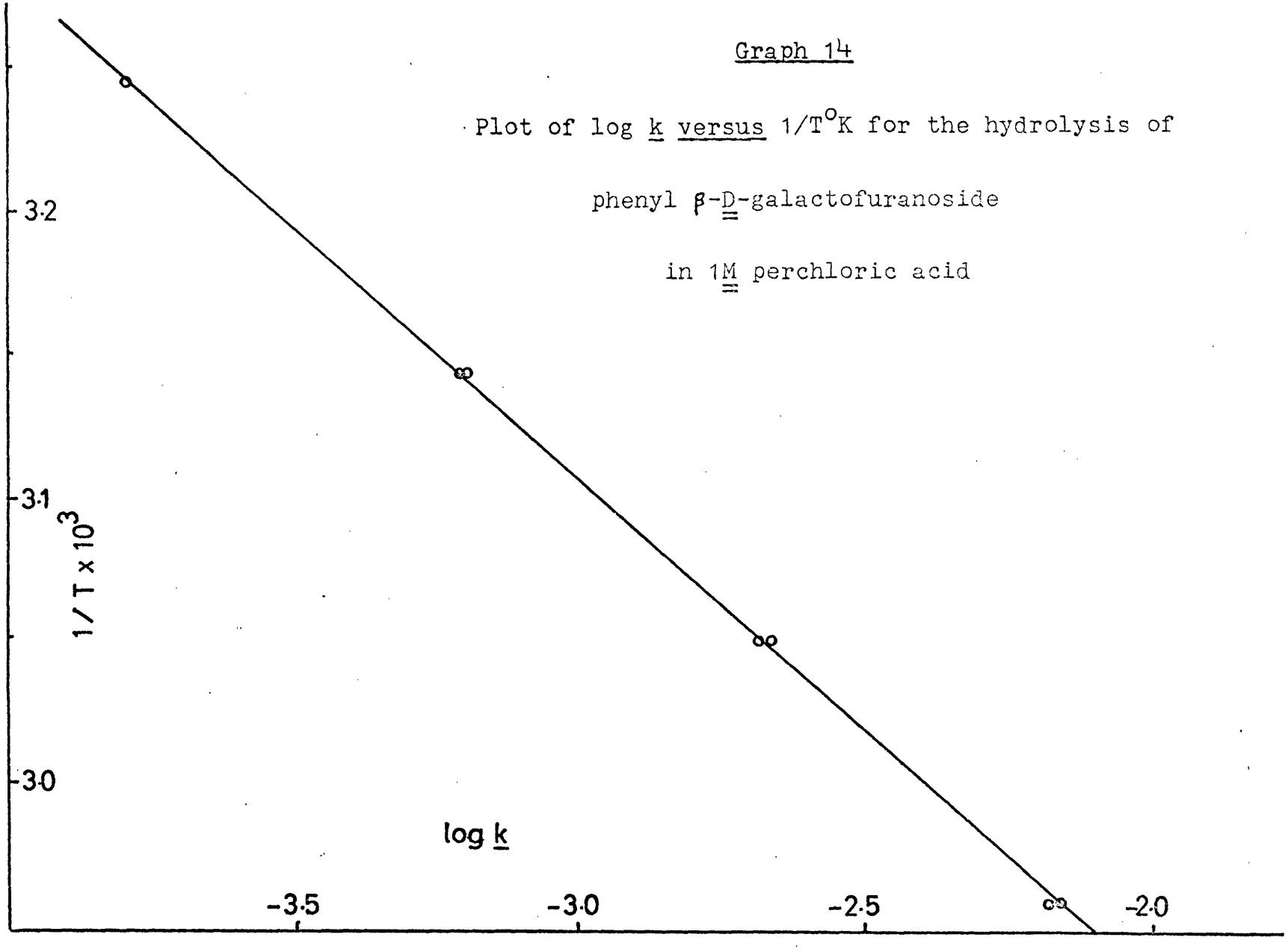
Graph 13

Plot of log k versus log[HClO4] for phenyl β-D-galactofuranoside at 35°



Graph 14

Plot of log $\underline{k}$ versus $1/T^{\circ}K$ for the hydrolysis of phenyl β-$\underline{D}$-galactofuranoside in 1$\underline{M}$ perchloric acid



DISCUSSION

1. Aryl cyclic acyclic acetals

a. Carboxylic acid-catalysis

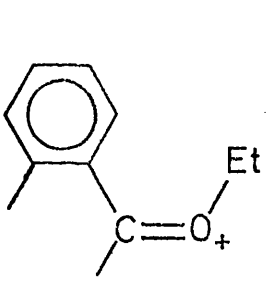
The recent analyses of structural features favouring a general - acid catalysed hydrolysis of acetals have already been introduced (see Figs. 1 - 3 and associated text). The reported observations of $\underline{A} - \underline{S_E} 2$ mechanisms in acetal hydrolysis will now be resolved in terms of these recent advances. But before discussing these let us consider some points to be borne in mind when determining the effect of buffered solutions on reaction rates.

Firstly it must be remembered that the hydrolytic medium can play a large part in such studies. In the hydrolysis of ethyl orthoformate with aqueous dioxane as the solvent, buffer catalysis is observable,[97] although the rate-law in water does not contain any terms dependent on buffer concentration.[18] Thus to avoid distortion of quoted catalytic coefficients, it is necessary to make an allowance for such medium effects and permit the quoted catalyses to be viewed in perspective. Ionic strength and pH must be maintained constant in general-acid studies for the results to have any significance. Quite frequently the pH's of buffered solutions vary due to secondary salt effects, these variations being more prevalent in acids with lower pK_a's. Rate data must be adjusted to allow for such variations. In the event of observing a buffer catalysis, there is the possibility that this may arise from specific salt effects. Even discounting this does not remove all the problems. One still has to distinguish between kinetically equivalent mechanisms, which might evolve from either mechanistic general-acid catalysis or from nucleophilic catalysis associated with specific - acid catalysis.

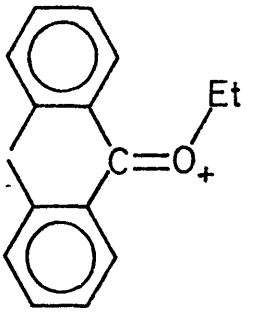
The first claim of buffer participation in acetal hydrolysis was by Fife for 2 - (p - methoxyphenyl) - 4,4,5,5 - tetramethyl - 1,3 - dioxolane. The rate constant for the general - acid catalysed reaction is 4.3×10^{-5} l mole^{-1} sec^{-1} measured in formate buffers (ionic strength 0.5). This causes a 15% to 20% increase in rate over that of the hydronium-ion catalysed reaction. To check that this catalysis was not due to medium effects caused by increasing buffer concentrations Fife studied the hydrolysis of diethyl acetal in these buffers and found no rate enhancement. He also found that the slope of a plot of observed rate versus total formate concentration increased with decreasing pH, quoting a single catalytic coefficient for the two pH studies. Thus the rate is proportional to the concentration of formic acid and not of formate and kinetic general - acid catalysis is being observed. This could arise from an $S_E 2$ mechanism or from one involving nucleophilic and specific hydronium-ion catalysis. Fife favours an A - 2 mechanism for the H_3O^+ - catalysed reaction, with a molecule of water featuring in the transition state, and argues that if water can participate then so also might the anion of a general - acid.

The system chosen as being most suitable for observing general - acid catalysis, by DeWolfe et al,[23] was benzophenone diethyl ketal and the series of benzophenone ketals shown in Table 1. Support for this choice was gathered from the relative hydrolytic rates of benzophenone diethyl ketal and benzaldehyde diethyl acetal. The fact that the latter is twenty times more reactive than the former towards hydronium-ion catalysed hydrolysis in 50% dioxane at 25°, could be interpreted in terms of no change in mechanism and that the monoaryl ion was more stable than the diaryl ion. Alternatively we could accept

DeWolfe's reasoning that this is an anomaly, that factors other than carbonium ion stability are involved and that an S_E 2 mechanism could be operating. An examination of the ions (7b) derived from di - p - substituted benzophenone diethyl ketals reveals a factor that might affect their stability relative to the ion from benzaldehyde diethyl acetal (7a).



(a)



(b)

(7)

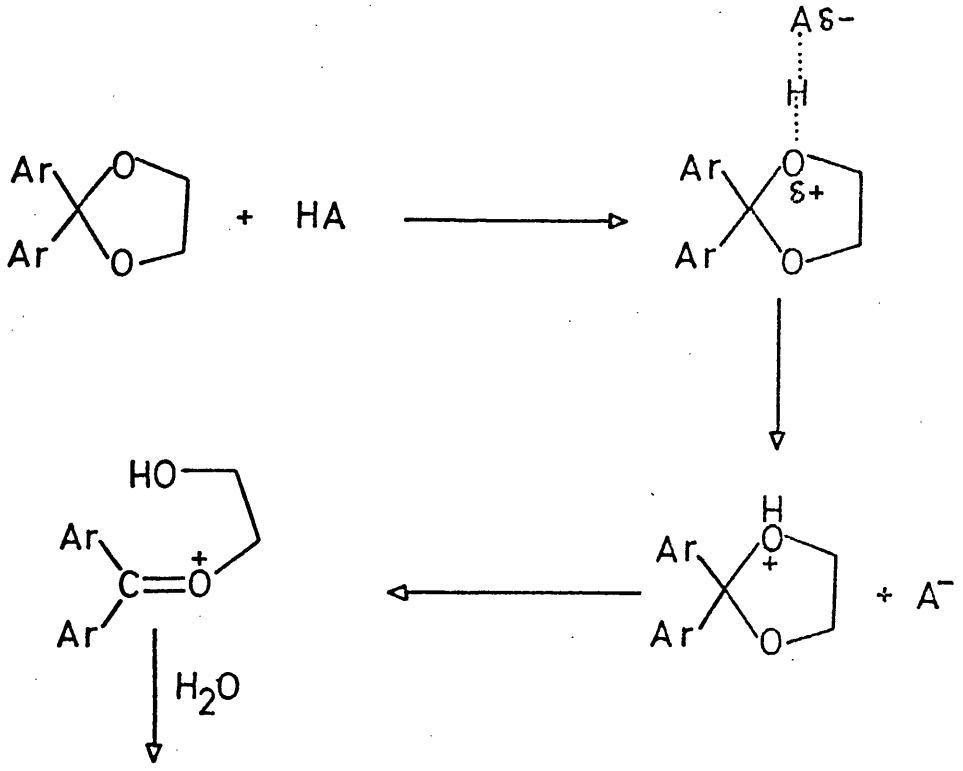
It can be clearly seen from a model of (7b) that both aryl groups cannot be in the same plane as the rest of the ion. Thus one would lose the stabilising mesomeric delocalisation of positive charge and be left with the inductive electron withdrawing effect of the out of plane aryl group. Hence the stabilities of (7a) and (7b) might not be very far apart, which does little to help DeWolfe's justification of choice of substrates. It is perhaps of interest that acetophenone diethyl acetal is hydrolysed thirty-four times more rapidly than benzaldehyde diethyl ketal under identical conditions.[42]

The fact that catalysis is observed does not necessarily justify all DeWolfe's original premises, neither does it invalidate the above comments on the intermediate ions. In DeWolfe's study,[23] specific

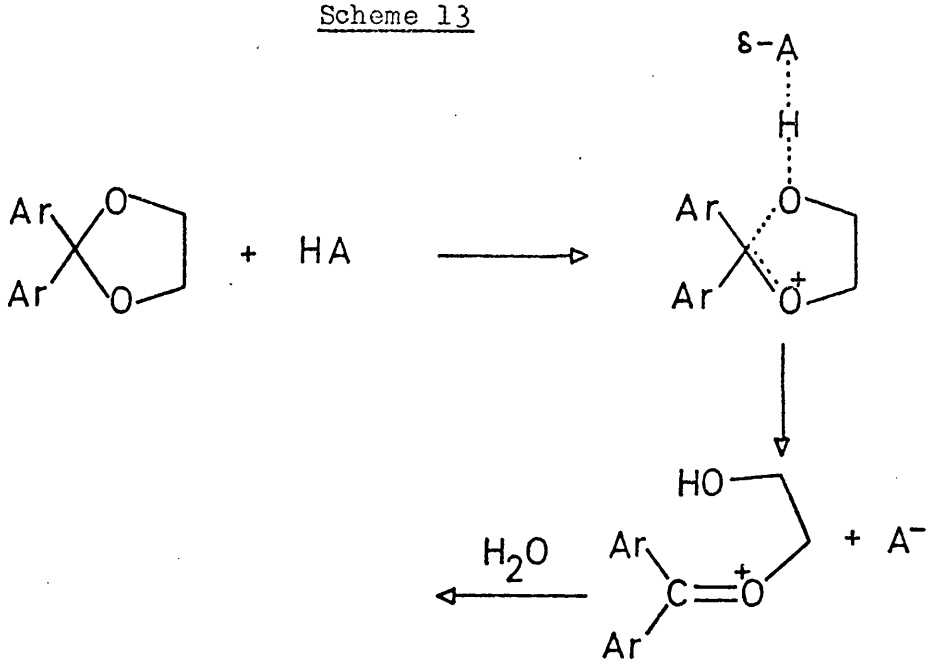
salt effects on dissociation constants were allowed for in data analysis. The observed catalyses are therefore quite real - if small (up to 25% increase over the hydronium-ion catalysed reaction) even though the rates were determined in 20% and 50% dioxane. No catalysis was observed in formate buffers and the only catalytic coefficient quoted for monochloroacetate buffers was 7×10^{-5} l mole^{-1} sec^{-1} (5% increase) for benzophenone diethyl ketal in 50% dioxane (ionic strength 0.125).

The discussion of DeWolfe et al[23] contains only minimal examination of the possible $\underline{A}$ - $\underline{S_E}$ 2 mechanisms, with reference to the system under study. At one point, referring to orthoester hydrolysis he adds "... a concerted mechanism seems more likely" than a reaction involving "... a conjugate acid ... that is a discrete intermediate." These two mechanisms are shown below for the 2,2 - diaryl - 1,3 - dioxolanes, where HA is the general - acid.

Scheme 12



Scheme 13

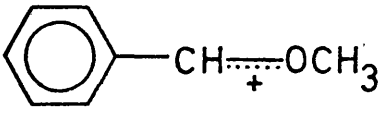


The slow step of Scheme 12 is the formation of the conjugate acid, the rate of which will be increased by electron releasing substituents in the aryl ring. The observation that these compounds appear to be more sensitive to general acid - catalysis with electron release in the ring appears to be consistent with this mechanism.

DeWolfe claims that the observed deuterium solvent isotope effect ($k_D / k_H = 2.63$) is consistent with a slow proton transfer. This is in fact a value close to the upper limit expected of a unimolecular reaction proceeding with a rapid proton transfer. In view of the isotope effect of approximately unity observed by Capon and Anderson[27] for a system exhibiting a high degree of $S_E 2$ character, the value 2.63 may be of the order to be expected from a non-concerted slow proton transfer. DeWolfe et al argue that the transition state for Scheme 12 and the emergence of the same discrete conjugate acid, are

features paralleled by an A - 1 mechanism, and thus one might expect a similar isotope effect.

After their rationale of the structural changes necessary to induce mechanistic general - acid catalysis in acetal hydrolysis, Capon and Anderson[27] chose systems based on benzaldehyde methyl phenyl acetal. The basis of this choice was that the oxygen of an aryl acetal would be less basic than that of an alkyl acetal, and that a mixed aryl alkyl acetal would produce a more stable carbonium ion, if the rate determining step involved loss of the aryloxy group producing the ion:



A diaryl acetal would similarly give less basic oxygens but the ion produced would be far less stable.

These studies were conducted in wholly aqueous solutions so that the observed catalyses by acetic acid, summarised in Table 55, indicate a large general - acid term in the rate law..

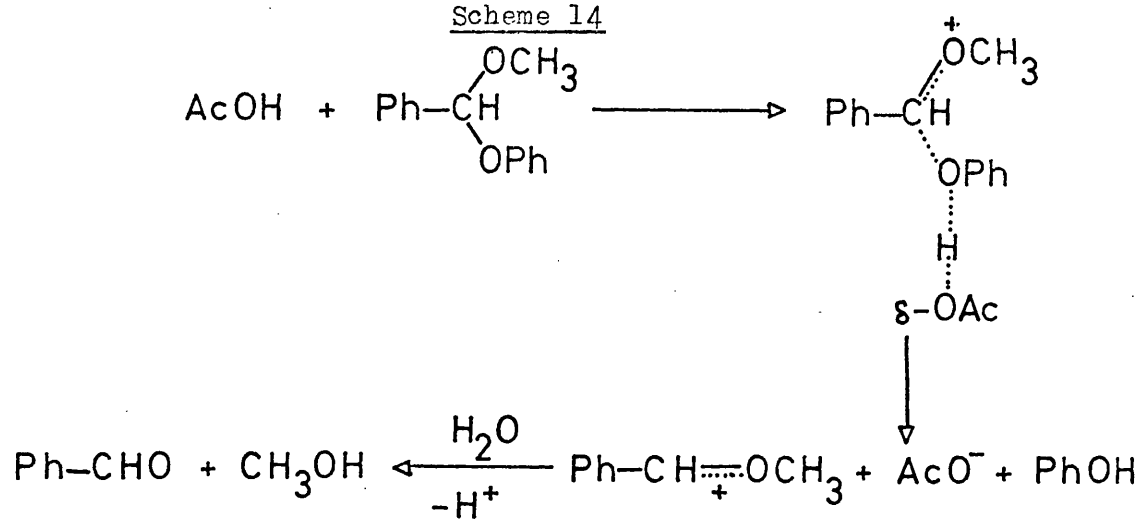
Table 55

Substrate	$10^3.k_{HA}$ (l mole^{-1} sec^{-1}
Benzaldehyde m - nitrophenyl methyl acetal	30.3
Benzaldehyde m - fluorophenyl methyl acetal	8.91
Benzaldehyde phenyl methyl acetal	5.89
Benzaldehyde m - tolyl methyl acetal	4.1

Determined in acetate buffer, ionic strength 1.0 at 20°.

Of the mechanisms considered the concerted mechanisms shown in Scheme 14 was preferred.

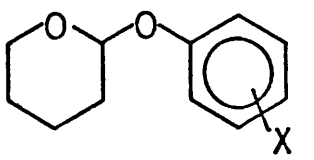
Scheme 14



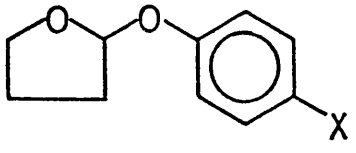
If the mechanism involved slow proton transfer to oxygen, electron releasing groups should cause an increase in the S_E2 reaction. The increase in general - acid catalysis observed by electron withdrawal is only explicable in terms of a concerted mechanism.

These results would seem to confirm the original arguments and speculations that lower acetal basicity and increased stability of the transition state or intermediate ion might result in the revelation of a general - acid catalysed reaction.

Consider now the hemicyclic acetal systems (8a) and (8b) under study in the present work.



(a)



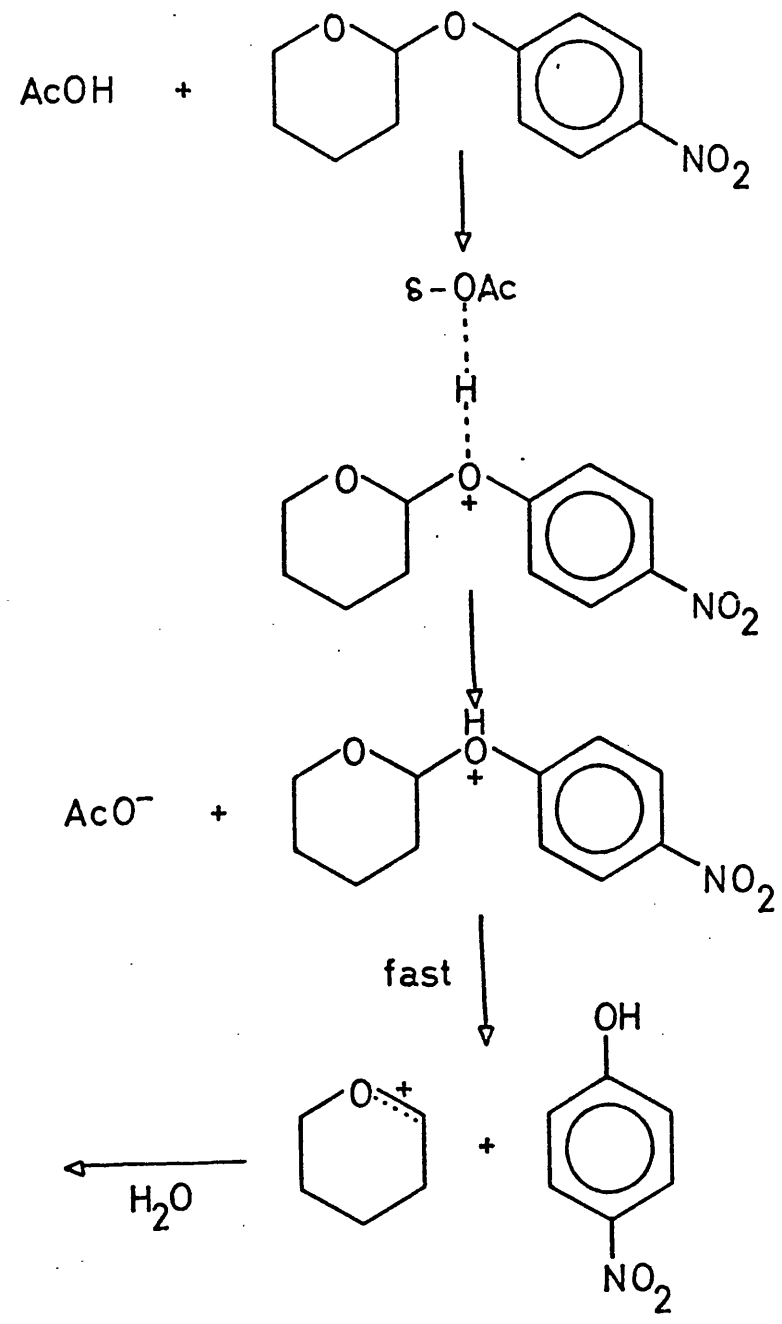
(b)

(8)

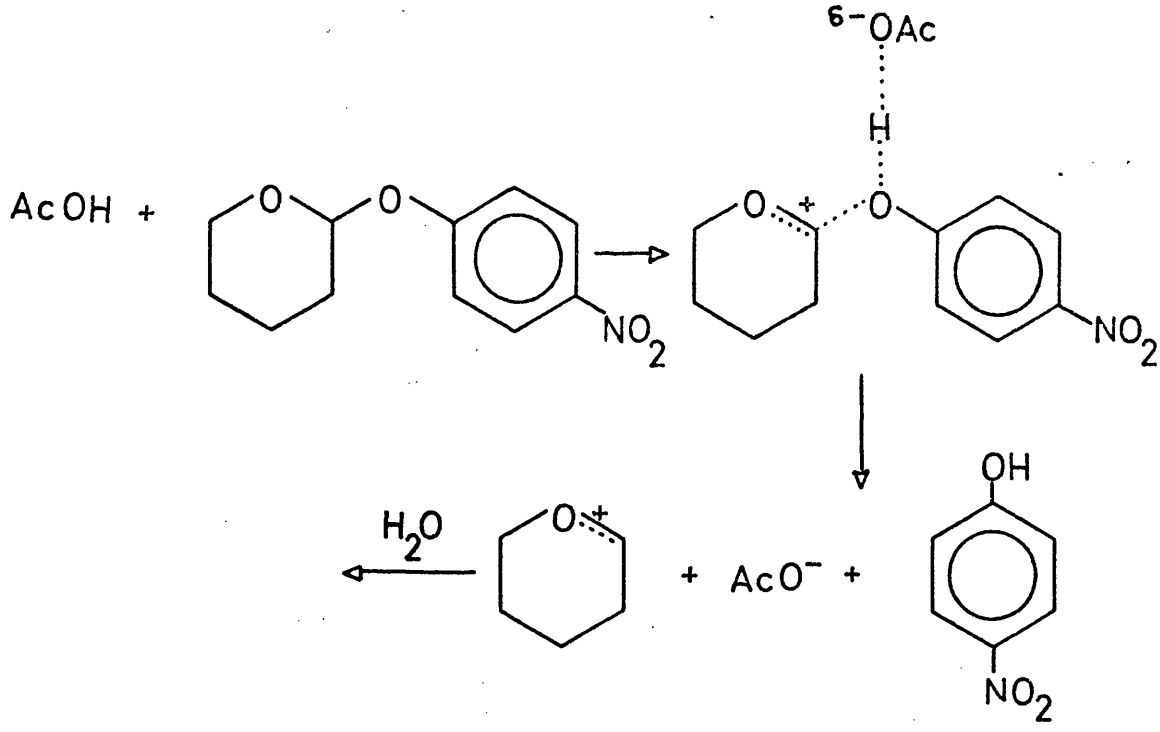
The general - acid studies were made in wholly aqueous acetate, formate and chloroacetate buffers.

As discussed below these reactions probably proceed *via* protonation on the exocyclic oxygen. The possible general - acid catalysed mechanisms are shown in Schemes 15 and 16.

Scheme 15



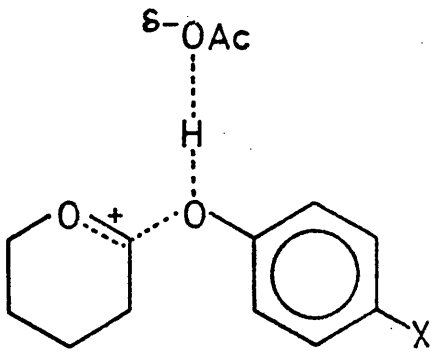
Scheme 16



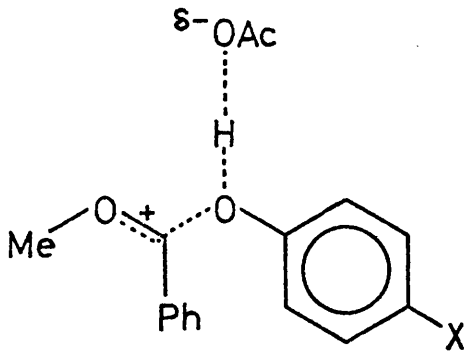
If Scheme 15 was being followed, with slow proton transfer to the phenolic oxygen, the rate should decrease with decreasing basicity of the oxygen. The ρ value calculated for the acetic acid - catalysed reaction, from buffer studies on 2 - phenoxytetrahydrofuran and 2 - (p - nitrophenoxy) - tetrahydrofuran at 50° is +0.68. The value for the pyran series is also positive, the actual value being indeterminant to any degree of accuracy due to the approximately zero catalysis observed for 2 - phenoxytetrahydropyran. The ρ value of 0.89 observed by Capon and Anderson[27] in the acetic acid - catalysed hydrolysis of four benzaldehyde phenyl methyl acetals (substituents in the phenoxy - group) at 20°, led them to conclude that a concerted mechanism (Scheme 14) was operating. The present ρ value of 0.68

would seem to be similarly consistent with a concerted mechanism (Scheme 16).

The effects due to the tenfold difference in ionic strength apart, the catalytic coefficients quoted for the benzaldehyde phenyl methyl acetals at 20° are greater than those calculated in the present study at 50°. This is in part a consequence of the greater stability of the carbonium ion in the mixed benzaldehyde acetals. Assuming a degree of concerted catalysis in each of these mechanisms, consider the transition states



(a)



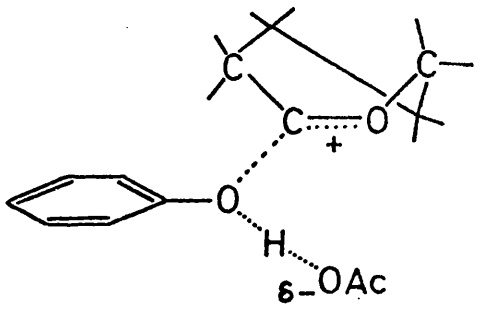
(b)

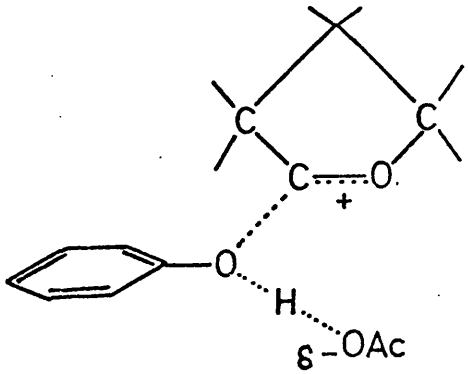
(9)

The mesomeric interaction of the phenyl group will stabilise (9b) compared with transition state (9a) which will produce an ion of wholly alkyl character. An additional destabilising factor in the hemicyclic acetals is the internally restricted motions of the ring, associated with the approach to the approximately planar conformation necessary to promote the inductive effect of the ring oxygen. This will destabilise the transition state (9a) and simultaneously decrease the availability of the S_E2 pathway.

At this stage we might raise the question of why the catalyses observed in the tetrahydrofuran series are in all cases under study, greater than those of the phenoxytetrahydropyrans. This can also be explained in terms of transition state stability with respect to the conformational changes necessary to place the various ring atoms in approximate planarity. A conformation with C-5, O-6, C-1 and C-2 of a 2 - (p substitutedphenoxy) - tetrahydropyran in one plane is shown in (10). The equivalent transition state for a tetrahydrofuran is shown in (11).

(10)





(11)

It should be energetically more demanding for the original tetrahydropyran (8a) to assume the half-chair form (10) than for the substrate (8b) to reach one of its slightly strained envelope conformations (11). On this basis one would expect a tetrahydrofuran derivative to display more general - acid catalysis than an equivalently substituted tetrahydropyran, as observed.

Table 56 is a summary of the catalytic coefficients observed at 50° and ionic strength 0.1, in the present study.

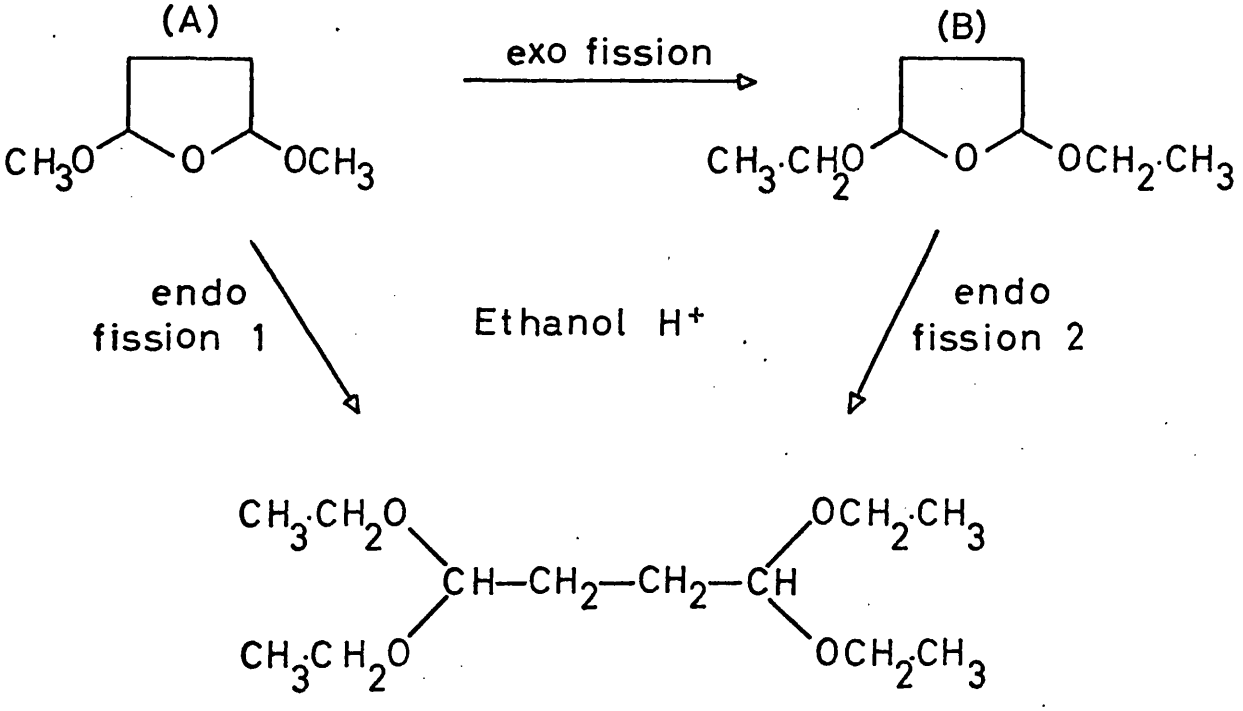
Table 56

Substrate	Buffer acid	pKa	pH	$10^3.k_{HA}$ $l\ mole^{-1}\ sec^{-1}$	$10^3.k_{H^+}$ (sec^{-1})
2-Phenoxytetra-hydropyran	CH_3COOH	4.756	4.05	~0	1.1
2-(p-Nitrophenoxy) -tetrahydropyran	CH_3COOH	4.756	4.05	1.46	1.31
2-(p-Nitrophenoxy) -tetrahydropyran	HCOOH	3.752	3.68	6.55	1.504
2-(p-Nitrophenoxy) -tetrahydropyran	$Cl\ CH_2COOH$	2.86	3.52	23.0	1.69
2-Phenoxytetra-hydrofuran	CH_3COOH	4.576	4.05	1.8	4.375
2-(p-Nitrophenoxy) -tetrahydrofuran	CH_3COOH	4.576	4.05	6.0	2.74
2-(p-Nitrophenoxy) -tetrahydrofuran	HCOOH	3.752	3.68	10.8	3.65
2-(p-Nitrophenoxy) -tetrahydrofuran	$Cl\ CH_2COOH$	2.86	3.52	53.3	4.75

b. Hydronium - ion catalysis

The position of protonation for alkyl hemicyclic acetals has been determined with a reasonable degree of certainty.[6] Further evidence has recently appeared from Kankaanpera,[107] following some studies of 2,5 - dialkoxytetrahydrofurans and 2,6 - dialkoxytetrahydropyrans. The rate constants for the aqueous hydrochloric acid - catalysis of these substrates are of the order 1×10^{0} to 5×10^{-2} 1 $mole^{-1}$ sec^{-1}. Kankaanpera argues that the comparible rates for 1,3 - dioxolanes of acetaldehyde are 1×10^{-2} to 2×10^{-3} 1 $mole^{-1}$ sec^{-1}, whereas one would expect the dialkoxy compounds to hydrolyse slower if the mechanism involved endo carbon - oxygen bond fission. To confirm the conclusions drawn from the rate comparisons, the ethanolysis of 2,5 - dimethoxy - tetrahydrofuran and the methanolysis of 2,6 - diethoxytetrahydropyran were studied. The pathways for the first of these reactions are shown in Scheme 17.

Scheme 17

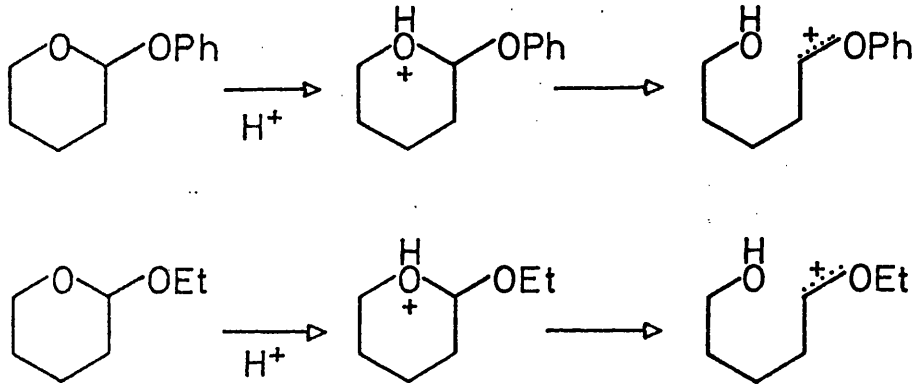


It is found that the substrate (A) is almost completely transformed into (B) in the early stages of the reaction. The concentration of the latter is observed to be high throughout the ethanolysis. These results show that the rate of exo fission is much greater than the rate of endo fission (2). The same was found to occur in the 2,6 - diethoxytetrahydropyran. It is reasonable therefore that the aqueous acid - catalysed hydrolysis of these dialkoxy substrates and thus of the monoalkoxy compounds proceeds by exocyclic protonation and fission.

This does not of course automatically apply to the aryl hemicyclic acetals, and an attempt to rationalise the relative rates observed for these alkyl and aryl acetals in terms of position of protonation will now be made.

At this stage we will assume that the 2 - ethoxy - tetrahydropyran and 2 - phenoxytetrahydropyran hydrolyse by a mechanism involving a high degree of unimolecular character.

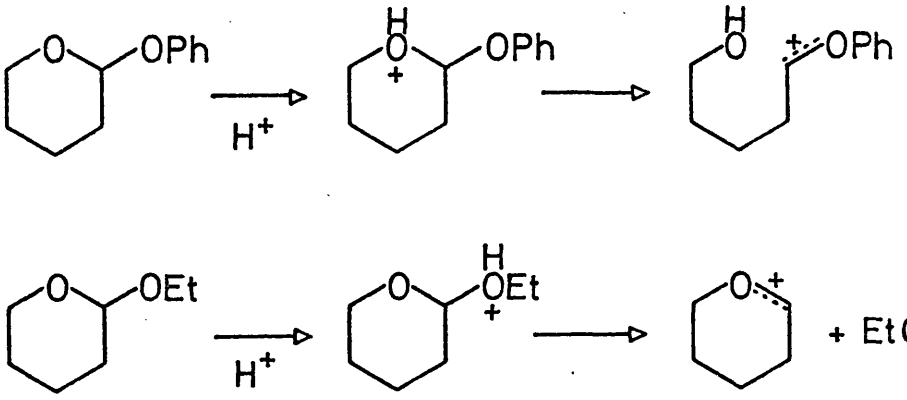
If the mechanism involved protonation on the endocyclic oxygen the first two stages would be as shown:



In view of the distance from the 2 - substituent, it is unlikely

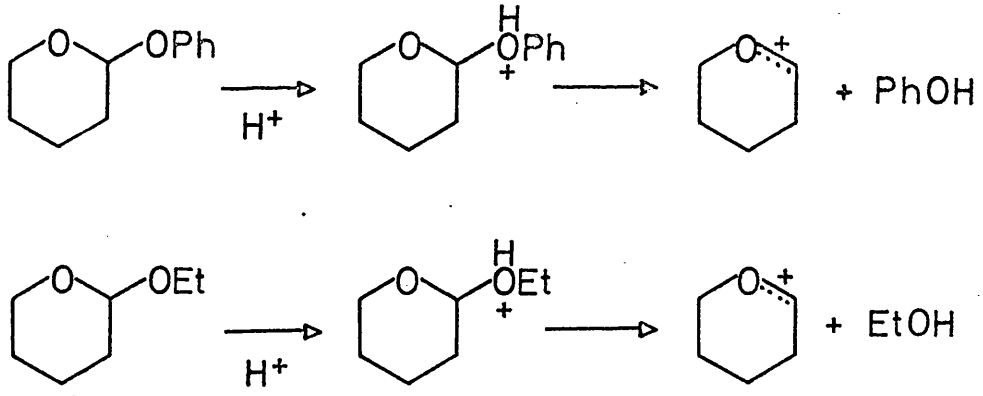
that the basicity of the endocyclic oxygen and with it the ~~rate~~ extent of protonation, will be affected much by the substitution of ethoxy - for phenoxy -. Thus the rate of reaction will be dependent on the stability of the carbonium ions and thus should be greater for the ethoxy compound. That the relative rate of phenoxy : ethoxy is about 6 : 1 tends to suggest that both compounds do not hydrolyse <u>via</u> an acyclic ion, which is consistent with Kankaanpera and Mikki's interpretation of alkyl hemicyclic acetal hydrolysis.[6]

Also consistent with their interpretation is that the first two stages are



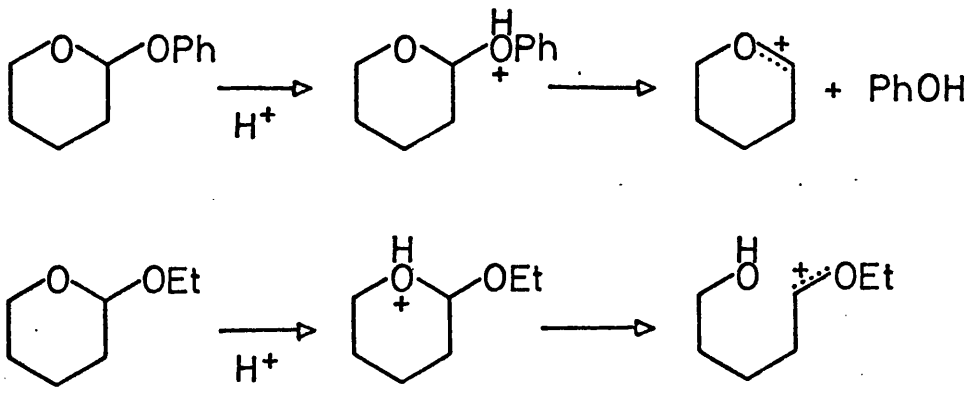
In this case each step is under the control of different factors. The exocyclic oxygen in the 2 - ethoxy compound might be marginally more basic than the endocyclic oxygen of the 2 - phenoxy compound. The ionic stability should also be in favour of the 2 - ethoxy compound with the acyclic phenoxy ion having greater intrinsic energy. So here both stages would favour the 2 - ethoxytetrahydropyran hydrolysing faster than the 2 - phenoxy compound. Again this is in opposition to the observed results.

Another possibility is that both compounds hydrolyse via a cyclic ion:



The ionic stability would be approximately the same, with rate differences caused by oxygen basicity or by relative goodness of leaving group. Here these two factors are in opposition with the better leaving properties of the protonated phenol favouring heterolysis and the greater basicity of the ethoxy oxygen facilitating protonation. The second stage would be expected to control the overall rate, and the greater rate of the 2 - phenoxy compound could be explained in terms of exocyclic oxygen protonation.

The final case involving exocyclic phenoxy protonation and endocyclic ethoxy protonation is, like the first mechanism involving endocyclic ethoxy protonation, inconsistent with the findings of Kankaanpera et al.[6]

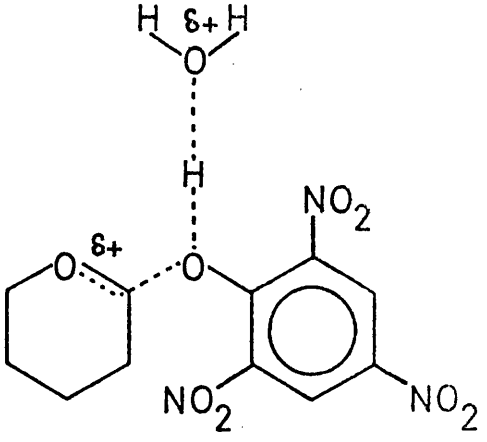


It is difficult to say how the change of substituent would affect the rate in this case. Possibly one would expect easier protonation in the ethoxy case. The ions also would be of comparible stability.

To return to the third case considered above, where it was deemed possible to explain the relative rates on the basis of exocyclic oxygen protonation. The ρ values for the hydrolysis of 2 - (p - substituted-phenoxy) - tetrahydrofurans and 2 - (substitutedphenoxy) - tetrahydro-pyrans in 0.01M hydrochloric acid at 20° are - 0.97 and - 0.875 respectively. These low values show that the hydronium - ion catalysed hydrolysis is under the control of both the protonation and the heterolysis step, and is thus consistent with our assumption of a unimolecular process for the hydronium - ion catalysis of these substrate The slightly negative values suggest that the protonation step is the more important of these two stages in determining the overall rate. Since a p - nitrophenoxy substituent would affect the balance of the two steps, it is unfair to make a direct comparison of rates between the 2 - ethoxy and the 2 - (p - nitrophenoxy) - tetrahydropyrans. The slightly more negative ρ values for the deuterium - ion catalysed hydrolysis show that the inductive electron withdrawing substituents are reducing the acetal basicity and making protonation (deuteration) more difficult. This is not invalidating our unimolecular assumption, but it does point to a lessening in degree of A - 1 character. To carry electron - withdrawal to its limit with, say, the 2,4 - dinitro or 2,4,6 - trinitrosubstituted compounds would suppress the protonation equilibrium step to the extent that a slow, rate determining proton transfer takes place. This argument neglects any steric effects due to the substituents ortho to the acetal linkage. An intermediate of

a mechanism involving a concerted mechanism is shown below for the trinitro case.

To sum up, we have postulated an S_Ei 2 mechanism (kinetic general - acid catalysis) in the carboxylic - acid catalysed hydrolysis and an A - 1 process (kinetic specific - acid catalysis) in the hydronium - ion catalysed reaction.



c. Spontaneous hydrolysis

Another effect caused by the reduced basicity of the acetal oxygen is the incursion of a spontaneous hydrolysis, i.e. a water - catalysed or uncatalysed reaction. The pH rate profiles for the phenoxy - and p - nitrophenoxy - in each series are plotted in Graphs 1 and 2 from the data of Tables 21 - 24. The logarithms of the observed rates for the unsubstituted phenoxy compounds show an inverse linear dependence on pH. In the equivalent plots for the p - nitro-substituted phenoxy compounds below pH 3.5, the plots show pH and log k_{obs} to be inversely proportional, but on increasing pH a plateau is observed with the limiting values as shown in Table 57.

Table 57

Substrate	Spontaneous rate [a] $10^3 . k_o$	$10^3 . k_{OH}$ [b]
2-(p-Nitrophenoxy)-tetrahydrofuran	1.995	2.011
2-(p-Nitrophenoxy)-tetrahydropyran	1.122	1.139 1.094

a 50°, Ionic strength 0.1 extrapolated to pH 7 from data of Tables 22 and 24.

b 50°, Ionic strength 0.1, pH = 10.78, 0.01M sodium hydroxide.

Also included are the rates measured in 0.01M sodium hydroxide, which are nearly identical to the rates observed for the spontaneous reaction.

The line for 2 - (p - nitrophenoxy) - tetrahydropyran in Graph 1 was calculated from equation (13).

$$k_{obs} = k_o + k_H \cdot a_H \qquad (13)$$

The constants $k_o = 1.22 \times 10^{-3}$ sec^{-1} and $k_H = 2.0$ l mole^{-1} sec^{-1} at 50° were calculated from the rate data of Table 22. Table 58 shows the values of k_{obs} and the recalculated rates k_{calc} using these values of k_o and k_H.

Table 58

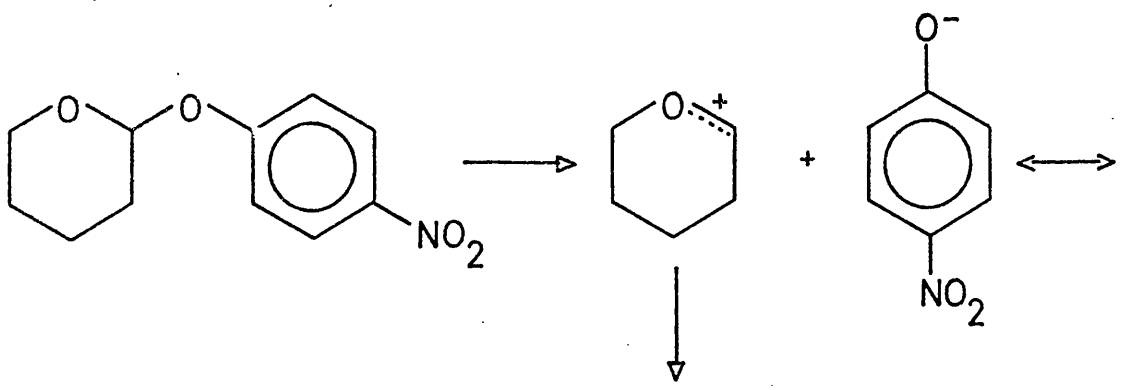
pH	$10^3.k_{obs}$	$10^3.k_{calc}$
2.89	3.95	3.70
3.515	1.69	1.73
3.68	1.504	1.504
4.05	1.31	1.30
4.67	1.17	1.165

Similarly the line for 2 - (p - nitrophenoxy) - tetrahydrofuran in Graph 2 was calculated from equation (13) using the constants $k_o = 1.995 \times 10^{-3}$ sec^{-1} and $k_H = 8.5$ l mole^{-1} sec^{-1} at 50° which were calculated from the rate data of Table 24. Table 59 gives the values of k_{obs} and k_{calc}.

Table 59

pH	$10^3.k_{obs}$	$10^3.k_{calc}$
2.89	12.9	12.94
3.515	4.75	4.59
3.68	3.65	3.77
4.05	2.74	2.75
4.67	2.241	2.177

Since the p - nitrophenolate anion is a far better leaving group than the phenolate anion, this spontaneous reaction could be formulated as occurring by the ionisation:



That the 2 - (p - nitrophenoxy) - tetrahydrofuran shows a slightly faster spontaneous hydrolysis (almost a factor of two) is consistent with this fission mechanism, since the carbonium ion would be that much more stable.

If this is a true reflection of the relative stabilities of the carbonium ions, it is surprisingly small. In view of the conformational strain associated with a half-chair form of the pyran ring on the one hand and the almost ground state envelope conformation of the furan ring on the other, one might expect a greater basic rate difference.

II Glycosides

a. Glycofuranoside preparation

Preparation of anomeric mixtures of alkyl glycofuranosides and the precursors of aryl glycofuranosides is in many cases a quite facile, if multi - stage process.

The general method of approach to alkyl furanosides - the Fischer glycoside synthesis - commences with a free suger, forming a glycosidic link in a solution of the appropriate alcohol with an acid catalyst. Some degree of control must be maintained on the reaction due to the possibility of producing the four isomeric glycosides. Much research has gone into these reactions in recent years.[112] With methanol, using various catalysts, it has been found that D - xylose, D - ribose, D - glucose and D - galactose generally form furanosides first and pyranosides later. The factors determining which furanoside is formed first are not well understood, with the thermodynamically less stable isomer frequently being formed more rapidly.

A general method for use with alkyl D - glucofuranoside synthesis is the method of Phillips.[113] By commencing with D glucurone, a system fused in the five membered ring form, the complicatory ring expansion to pyranosides encountered with Fischers' method is eliminated.

In the present study some exploratory experiments were made with the D - glucurone - methanol and D - glucurone - 2 - chloroethanol systems. D - Glucurone dissolves in acidic methanol to give a clear negatively rotating solution, which slowly converts to one of positive rotation. The time of original dissolution and of mutarotation are dependent upon the percentage of catalyst and the dryness of the methanol. In view of the specific rotation of methyl D - glucuronosides in water, - 59° and + 148° for the β and α respectively,[113]

it appears the β- anomer is the kinetically controlled product. The negatively rotating solution gives a syrup displaying a singlet at 312 Hz., in it's N.M.R. spectrum, whereas the mutarotated solution gives a syrup showing a doublet at 319 Hz., J_{ab} 4 Hz. Each has a singlet at approximately 212 Hz. due to the CH_3O - group at C-1. These values are consistent with those reported for the equivalent methyl D - glucofuranosides.[114] It is interesting that in both the alcohol - glucurone systems studied using hydrogen chloride as catalyst, the β- anomer (presumably the thermodynamically more stable isomer) is formed first. This is in contrast to the D - glucose - methanol system in which the thermodynamically less stable α- anomer is formed initially.[115]

In the D - glucurone - hydrogen chloride - benzyl alcohol system the solution formed on initial dissolution of the sugar has a large negative rotation, which changes over a long period to a slightly positive value. The yield of benzyl α- D - glucofuranoside increases with the reaction time, although this is at all times the minor product (see ref. 103).

Although many aryl and substituted - aryl glycopyranosides have been prepared,[70,86] few aryl glycofuranosides are known. The general method of preparation of these is the condensation of the fully - O - acetylated glycofuranose with a phenol using a sulphonic acid, normally p - toluene sulphonic acid, as a catalyst. This method has yielded phenyl β- D - xylo,- phenyl α- L - arabino -, phenyl β- D - galacto -, phenyl β- D - gluco[71]-, m - tolyl β- D - galacto - and o - methoxy- phenyl β- D - galactofuranosides,[116] via deacetylation by the Zemplen

method. Aryl β- D - glucofuranosides may be prepared from the aryl di - O - acetyl β- D - glucuronoside by lithium aluminium hydride reduction in tetrahydrofuran.[108] Phenyl, m - cresyl and 2 - naphthyl β - D - glucofuranosides have been prepared in this manner.

In the present work phenyl β- D - gluco - and galactofuranosides were prepared by the procedure of Jerkeman and Lindberg.[71] Attempts to condense p - cresol with penta - O - acetyl - D - glucofuranose and to deacetylate p - nitrophenyl tetra - O - acetyl - β - D - glucofuranoside failed. Phenyl β- D - glucofuranoside was also prepared by the method of Kato et al[108] as were p - cresyl and p - methoxyphenyl β- D - glucofuranosides. Several attempts to prepare m or p - chlorophenyl β - D - glucofuranoside from the equivalent chlorophenyl di - O - acetyl β - D - glucuronoside by lithium aluminium hydride reduction were unsuccessful, the reducing agent also removing the halogen atom. (Two interesting syntheses of phenyl β- D - glucofuranoside!)

The glycosidic link of p - nitrophenyl di - O - acetyl β- D - glucuronoside and p - nitrophenyl tetra - O - acetyl β- D - glucofuranoside proved to be very susceptable to cleavage, both by reducing agents and alkoxide ions. It has been shown that phenyl[101] and 2 - naphthyl di - O - acetyl β- D - glucuronoside[102] are similarly degraded by sodium methoxide. The lithium aluminium hydride reduction of these compounds also proceeds with production of reasonable amounts of phenol and 2 - naphthol respectively.

The preparation of p - nitrophenyl α- L - arabinofuranoside by a Zemplen deacetylation has been reported,[104] so all such furanosides are not so labile. It may be relevant that methyl β- D - glucofuranoside is more easily split by alkali than other methyl aldofuranosides.[105]

So perhaps there is some factor inherent in β- D - glucofuranosides which when coupled with the normally greater lability of aryl glycosides towards alkali, renders them particularly reactive. One could speculate that p - nitrophenyl β- D - galactofuranoside might contain a more stable glycosidic link, although it still contains a cis arrangement of glycosidic link and hydroxyl at C-2, one factor that might be responsible for the lability. (See for example ref. 105).

A possible route to the chlorophenyl and nitrophenyl β- D - glucofuranosides might be the direct chlorination or nitration of phenyl β- D - glucofuranoside. That these would yield a mixture of isomers would be just one of the problems to be considered.

Having thus synthesised some aryl D - glycofuranosides we can reveal the antithetic nature of this type of chemistry and discuss their hydrolyses.

b. Glycoside hydrolysis

The majority of the evidence advanced on aldopyranoside hydrolysis is consistent with a mechanism involving a large degree of unimolecular character (Scheme 10). In contrast much of the data available for alkyl furanoside hydrolysis suggests that they react by a different mechanism to the pyranosides.[64,66] These mechanisms are discussed elsewhere.[105] Results derived from the present work on aryl aldofuranosides contrast sharply with most of the mechanistically meaningful data reported for the alkyl aldofuranosides.

The slow rate of hydrolysis of the average glycopyranoside has made it impossible to conduct buffer studies to determine whether their hydrolysis is specific - or general - acid catalysed. It has only been possible to note effects, such as deuterium solvent isotope effects,

and suggest that they are in the range normally associated with reactions involving initial rapid reversible proton transfer, as they frequently are.

The buffer studies that exist for glycosides were conducted on systems such as furanosides or on compounds exhibiting anomalously fast reactions. Capon and Thacker[64,105] studied the hydrolysis of both anomers of methyl D - xylofuranoside in acetate buffer (pH 3.8) at 80° to explore a possible mechanism involving intramolecular acid - catalysis. Capon and Smith[25] studied the hydrolysis of methyl 2,5 - anhydro - α - L - arabinofuranoside in a series of acetate and imidazolinium buffers, but observed no general - acid catalysis in this anhydro - glycoside. Bruice and Piszkiewicz[30] could find no catalysis in p - nitrophenyl 2 - acetamido - β - D - glucopyranoside.

In the present work, buffer studies at 65° were conducted in monochloroacetate and orthophosphate buffers. The results are shown in Tables 39 and 46. The pH's of the buffers, especially of the phosphate solutions, varied within the series. The data were corrected to a common acidity by the method of Gold et al[106] and these data are shown in Tables 41 and 44. They show quite positively that there is no general - acid catalysis in the hydrolysis of either phenyl β - D - glucofuranoside or phenyl 2 - deoxy - α - D - glucopyranoside in the pH range used with the specified buffers.

The solvent isotope effects for the aryl D - glycosides studied ranged from 2.05 to 2.34 (Table 54) and are thus in line with a specific - acid catalysis.

It is difficult to evaluate the uncertainty of these figures, although the rates from which they were determined agreed to ± 1%.

Hence it may be significant that the k_D / k_H value increases with electron - releasing power of the para - substituent. This is reminiscent of the gradation observed in the 2 - (p - substituted-phenoxy) - tetrahydropyrans and furans. Obviously some experiments with an electron withdrawing group are necessary before any definite conclusions can be reached.

One might expect secondary isotope effects to be observable in a glycoside relative to the 2 - deoxy glycoside. The isotope effect has not been measured for the phenyl D - glucopyranosides, but the values reported for methyl α- D - glucopyranoside and methyl 2 - deoxy α- D - glucopyranoside are 2 and 2.5 respectively. Relevant comment on these must surely await the figure for phenyl α- D - glucopyranoside.

Having established the nature of the acid catalysis we are led to experiments designed to decide the molecularity of the slow step. Of these empirical approaches, entropy of activation and dependence of rate on acidity have been applied in the furanoside study.

The entropy of activation data are summarised in Table 60, where a comparison is drawn between the furanosides and the equivalent pyranosides. Other activation data are collected in Table 53.

Table 60

	$\Delta S^{\ddagger}$ (e.u.)	
	Furanoside [a]	Pyranoside
Phenyl β- D - galacto-	+ 6.7	+ 4.1 [b]
Phenyl β- D - gluco-	+14.7	+10.8 [b]
p - Cresyl β- D - gluco	+12.0	+11.0 [c]
p - Methoxyphenyl β- D - gluco	+15.3	-

a 1M $HClO_4$ at 45° for glucosides and 35° for galactoside.

b 2N HCl at 60°.[66]

c 0.855 N H_2SO_4 at 59.95°.[88]

These figures will be used later, but suffice it to say at present that the furanoside values are as consistent with a unimolecular process as are the pyranoside values, and contrast strongly with the alkyl furanoside values. The average value is - 8.3 e.u. for seven methyl aldofuranosides[64] calculated at 25° and in 1 M perchloric acid, and - 7.1 e.u. for ethyl β - D - galactofuranoside calculated at 60° in 2 N hydrochloric acid.

The data for the aqueous perchloric acid solutions used in the acidity dependence studies are presented in Table 47. The rate data appear in Tables 48 - 51 and the slopes calculated for various associated plots are summarised in Table 52.

As pointed out in the introduction, these empirical correlations as mechanistic criteria have received their criticisms. As can be seen from Table 52, the Hammett - Zucker plots using the older Paul and Long[56] values of H_o give slightly low slopes. However using the more recent Yates and Wai[109] values gives a better correlation, with slopes very close to unity. Thus the results are interpretable in terms of the Hammett - Zucker hypothesis and are good evidence for a unimolecular hydrolysis. The values of w from a Bunnett plot are approximately zero and are consistent with an A - 1 process. The fact that plots of log k versus log c_{H^+} are curves strongly rules out a bimolecular mechanism.

Some of the relative rate data for various glycosides taken from the present work and from the literature would appear to contain inconsistencies. For example the methyl to phenyl ratio for β - D - glucofuranosides is about eleven, whereas the methyl to phenyl ratio for the β - D - galactofuranosides is one fourteenth. This inversion

and other aspects of the relative rate data are contained in Tables 62 and 63. Table 62 allows a comparison of rate data as determined by Overend, Rees and Sequeira[66] for β- D - pyranosides in 2 M hydrochloric acid at 60°. Table 63 contains similar data for β- D - furanosides, as determined by Capon and Thacker[64] for the methyl furanosides at 35° and in the present work for phenyl furanosides at 35°, 45°, 55° and 65°, both conducted using 1 M perchloric acid.

The entropies of activation for the substrates appearing in Tables 62 and 63 are given in Table 61 (see footnotes to Tables 62 and 63 for the conditions of hydrolysis).

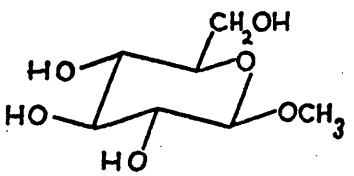
Table 61

	$\Delta S^{\ddagger}$ (e.u.)	
	β- D - Pyranoside	β- D - Furanoside
Methyl gluco-	+16.5	-9.0
Methyl galacto-	+13.3	-8.7
Phenyl gluco-	+10.8	+14.7
Phenyl galacto-	+ 4.1	+ 6.7

The vast majority of data available for the glycopyranosides suggests that they hydrolyse via a specific - acid catalysed mechanism involving a cyclic carbonium ion. There is nothing about the rate and relative rate data of Table 62 that is inconsistent with this picture. The transition state is destabilised by greater non-bonded interactions due to the axial hydroxyl at C-4 in galacto-relative to glucopyranosides. The greater rate observed for the phenyl relative to these methyl glycopyranosides could be explained in similar terms to the arguments used in the tetrahydropyran series to explain the

Table 62

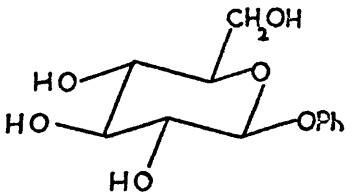
β-D-pyranosides



Methyl gluco-

k=1.26

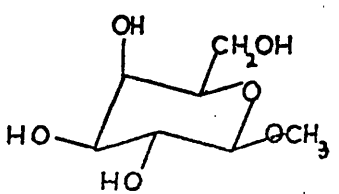
7.4



Phenyl gluco-

k=9.33

4

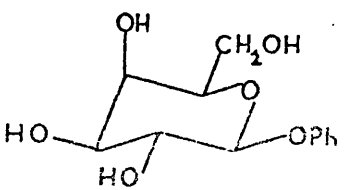


Methyl galacto-

k=5.13

4.8

2.6



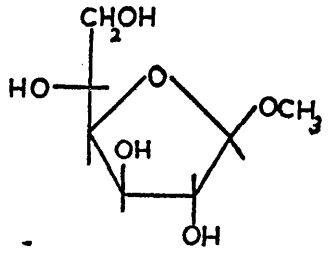
Phenyl galacto-

k=24.5

Rates quoted below compounds are absolute rates $\times 10^5$, determined in 2M hydrochloric acid at 60°.[66] Relative rates are quoted between relevant compounds.

Table 63

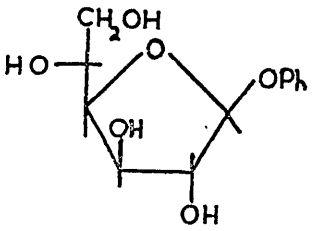
β-D-furanosides



Methyl gluco-

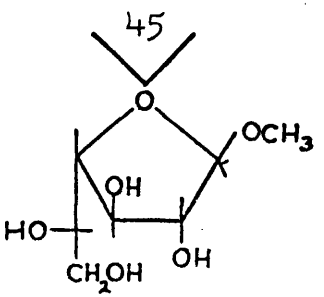
k=64.3

10.7



Phenyl gluco-

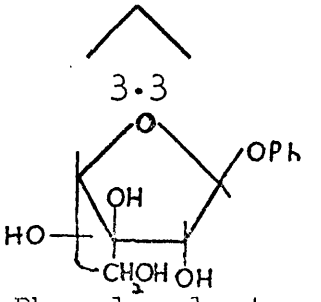
k=6



Methyl galacto-

k=1.43

14



Phenyl galacto-

k=16.0

Rates quoted below compounds are absolute rates $\times 10^5$, determined in 1M perchloric acid at, or extrapolated to, 35°. Relative rates are quoted between relevant compounds

relative rates of the 2 - phenoxy and 2 - ethoxy substituted compounds, the protonated phenol being a better leaving group. It is interesting to note here that for a mechanism involving ring oxygen protonation and an acyclic ion, the phenoxy ion would be less stable than the methoxy ion,[105] which would lead to the methyl hydrolysing faster than the phenyl glycopyranosides. Since most of the space around the hexose ring is claimed by non-bonded electrons of the hydroxyl groups, one might speculate that the bulky phenyl group is helped on its way by repulsive electronic and steric effects. This type of interaction is of course more important in the phenyl α- D - glycopyranosides and could account for the faster rate of hydrolysis observed for phenyl α- D - glucopyranoside relative to the β - anomer.

The rate data in Tables 62 and 63 were determined in different acids and at different temperatures. Similar rate ratios can be obtained from work conducted in 1 M perchloric acid which acts as a bridge between pyranosides and furanosides. These figures are given in Table 64.

Table 64

Substrate	$10^5.k$ (sec^{-1})
Methyl β - D - glucopyranoside [a]	2.12
Phenyl β - D - glucopyranoside [a]	11.63
Methyl β - D - glucofuranoside [b]	6000
Phenyl β - D - glucofuranoside [c]	676

a Data of Bunton et al[72] 1 M $HClO_4$ at 72.9°

b Data of Capon and Thacker[64] 1 M $HClO_4$ at 25° and 34° extrapolated to 72.9°

c Data from present work 1 M $HClO_4$ at 45°, 55° and 65° extrapolated to 72.9°

The ratios obtained from Table 64 are

Phenyl β - D - glucopyranoside : Methyl β-D - glucopyranoside = 5.6 : 1

Phenyl β - D - glucofuranoside : Methyl β - D - glucofuranoside = 1 : 8.9 (which in view of the rather extreme extrapolation for the methyl furanoside are quite comparible with the values in Tables 62 and 63), and

Phenyl β - D - glucofuranoside : Phenyl β - D - glucopyranoside = 58 : 1

Methyl β - D - glucofuranoside : Methyl β - D - glucopyranoside = 2800 : 1

These differences are reflected in the figures quoted in Tables 62 and 63 for the same substrates, hydrolysed under different conditions.

On the basis of the deuterium isotope effects known for these compounds and the fact that no general - acid catalysis was found in the present study of phenyl β - D - glucofuranoside and phenyl 2 - deoxy - α - D - glucopyranoside, we will assume that the methyl and phenyl glycosides hydrolyse by a specific - acid pathway.

Limiting our comparisons for the moment to compounds possessing the same sugar residue and ring fusion, we are faced with the anomaly mentioned above of the inversion in rate between methyl and phenyl gluco- and galactofuranosides.

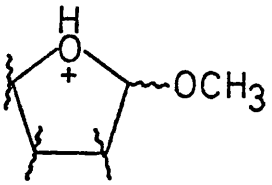
There are two main approaches to the rationalisation of these facts. Either we can postulate that the compound out of line is methyl β - D - glucofuranoside whose hydrolytic rate is enhanced, or that the rate of both phenyl furanosides has been reduced and that the anomaly arises from a further suppression of the methyl β - D - galacto- furanoside rate. In view of the large relative rate observed between methyl β - D - glucofuranoside and methyl β - D - glucopyranoside and the similar phenyl galacto- to phenyl gluco- ratio for pyranosides and

furanosides, the former postulate seems the more likely.

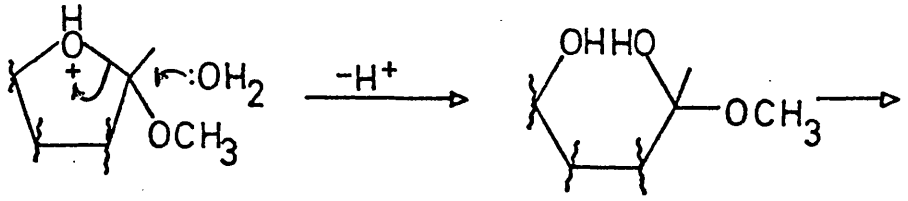
On the basis of the negative entropies of activation observed for the methyl furanosides, we assume that these compounds hydrolyse largely via a ring opening process.

$$\text{i.e.} \qquad \underline{k}_{\text{methyl acyclic}} >> \underline{k}_{\text{methyl cyclic}} \qquad (14)$$

This mechanism involves the conjugate acid:



which may undergo reversible opening (see Scheme 11), or a concerted opening:



The rate limiting step for hydrolysis of a phenyl β- D - furanoside, which we assume to proceed largely by a cyclic ion, is

This gives the relation

$$\underline{k}_{\text{acyclic}}^{\text{phenyl}} \ll \underline{k}_{\text{cyclic}}^{\text{phenyl}} \qquad (15)$$

~~(14) and (15) lead to the inequalities~~ It is also assumed that

$$\underline{k}_{\text{acyclic}}^{\text{methyl}} \gg \underline{k}_{\text{acyclic}}^{\text{phenyl}} \qquad (16)$$

$$\underline{k}_{\text{cyclic}}^{\text{phenyl}} \gg \underline{k}_{\text{cyclic}}^{\text{methyl}} \qquad (17)$$

We must further assume that the total rate only receives contributions from cyclic and acyclic processes as defined in the above rate limiting steps,

$$\underline{k}_{\text{total}}^{\text{phenyl}} = \underline{k}_{\text{cyclic}}^{\text{phenyl}} + \underline{k}_{\text{acyclic}}^{\text{phenyl}} \qquad (18)$$

$$\underline{k}_{\text{total}}^{\text{methyl}} = \underline{k}_{\text{cyclic}}^{\text{methyl}} + \underline{k}_{\text{acyclic}}^{\text{methyl}} \qquad (19)$$

Dividing (19) by (18) leads to

$$\frac{\underline{k}_{\text{total}}^{\text{methyl}}}{\underline{k}_{\text{total}}^{\text{phenyl}}} = \frac{\underline{k}_{\text{cyclic}}^{\text{methyl}} + \underline{k}_{\text{acyclic}}^{\text{methyl}}}{\underline{k}_{\text{cyclic}}^{\text{phenyl}} + \underline{k}_{\text{acyclic}}^{\text{phenyl}}} \qquad (20)$$

From Table 63

For glucose $\underline{k}_{\text{total}}^{\text{methyl}} / \underline{k}_{\text{total}}^{\text{phenyl}} \simeq 10$

and for galactose $\underline{k}_{\text{total}}^{\text{methyl}} / \underline{k}_{\text{total}}^{\text{phenyl}} \simeq 1/14$

Placing the entries on the right hand side of equation (20) in terms of the inequalities required we have

$$\begin{array}{ccc} \underline{k}_{\text{cyclic}}^{\text{methyl}} & < & \underline{k}_{\text{acyclic}}^{\text{methyl}} \\ \wedge & & \vee \\ \underline{k}_{\text{cyclic}}^{\text{phenyl}} & > & \underline{k}_{\text{acyclic}}^{\text{phenyl}} \end{array}$$

It is possible, by choosing values of the respective terms to give a range of rate ratio observed for phenyl : methyl in gluco - and galactofuranosides,

$$\text{i.e. gluco} \quad \frac{\text{methyl}}{\text{phenyl}} \quad \frac{\sim 0.1 + 10}{1 + \sim 0.01} \simeq 10$$

$$\text{galacto} \quad \frac{\text{methyl}}{\text{phenyl}} \quad \frac{\sim 0.036 + 3.6}{50 + \sim 0.5} \simeq \frac{1}{14}$$

We assume here that the contribution of the minor pathway is a constant proportion ($1 / 100^{\text{th}}$) of the major pathway in both galacto - and glucofuranosides.

These substituted rates give us the correct methyl : phenyl ratio, but incorrect methyl gluco - to methyl galacto - and phenyl gluco - to phenyl galacto - ratios. If we scale up the gluco - results by a factor of fifteen we get

$$\begin{array}{lll} \text{gluco} & \dfrac{\text{methyl}}{\text{phenyl}} & \dfrac{\sim 1.5 \;+\; 150}{15 \;+\; \sim 0.15} \simeq 10 \\ \text{galacto} & \dfrac{\text{methyl}}{\text{phenyl}} & \dfrac{\sim 0.036 \;+\; 3.6}{50 \;+\; \sim 0.5} \simeq 1/14 \end{array} \qquad (21)$$

The ratios derived from these, for the furanosides, are

$$\frac{\text{phenyl } \beta\text{-}\underline{\underline{D}}\text{-galacto-}}{\text{phenyl } \beta\text{-}\underline{\underline{D}}\text{-gluco-}} = 3.3 \qquad (22)$$

$$\frac{\text{methyl } \beta\text{-}\underline{\underline{D}}\text{-gluco}}{\text{methyl } \beta\text{-}\underline{\underline{D}}\text{-galacto}} = 42$$

These are in good agreement with the observed ratios, given in Table 63.

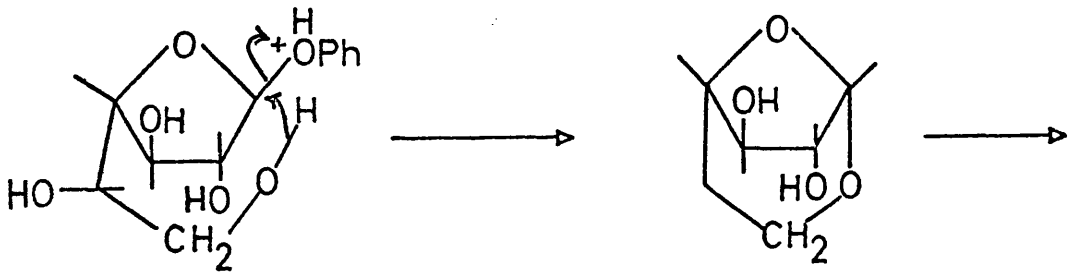
Thus it appears that based on the above assumptions, the analysis used can explain the facts. The explanation is therefore that the apparently anomalous rates arise from a change in mechanism. It could be argued that we have not removed the anomaly, but have merely shifted it, and that we must now explain why the term $\underline{k}_{\text{cyclic}}^{\text{phenyl}} / \underline{k}_{\text{cyclic}}^{\text{methyl}}$ is so large in the galactofuranosides.

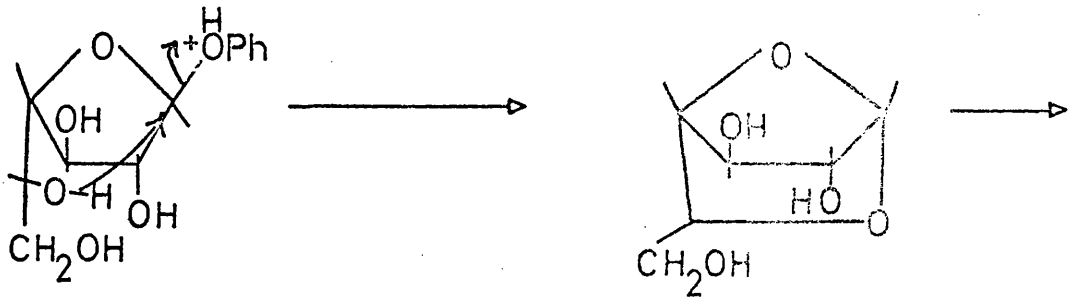
While substituting the above trial figures into (20) we assumed that the cyclic pathway contribution to the overall rate was the same in methyl glucofuranoside as in methyl galactofuranoside, which is not necessarily true. If the cyclic pathway contributed a little more to the rate in the galactofuranoside it would, without grossly affecting the ratios (21) and (22) decrease the phenyl : methyl ratio. This

would however still leave the ratio well in excess of 50, whereas the equivalent ratio for the galactopyranosides is about 5 (see Table 62).

It may well be that the changes in the various glycoside rate ratios used to explain some of the facts in the foregoing discussion, are merely reflecting energy changes in the ground state conformations and / or in the transition state. Clearly until the various conformations are better understood much of the discussion in terms of rate differences must be based on assumption and speculation. It may be possible to see changes in the ground state conformations in the high resolution N.M.R. spectra.

If we break our assumption that no other mechanism is contributing to the overall rate, we can suggest a mechanism that might intervene to increase the hydrolysis rate of phenyl β- D - galactofuranoside over that of the methyl compound. We will not change our positions of protonation so we are not introducing a large perturbation to our arguments. It is possible that a mechanism involving an anhydro sugar as intermediate might occur, from participation by the hydroxyl group on either C-5 or C-6.





These are both known compounds, although no quantitative hydrolytic data is available. Since they are derived from bicyclic dioxanes and dioxolanes, their rate of hydrolysis could well be quite fast. So some degree of contribution from a mechanism of this sort could increase the rate.

Capon and Thacker[64] dismissed such a mechanism for the hydrolysis of methyl β- D - galactofuranoside in view of the comparible rates of the α- and β- anomers. A study of the two anhydro sugars and phenyl α- D - gluco - and galactofuranoside would answer many of the questions. So also would various p - nitrophenyl glycofuranosides, and a series of alkyl β- D - glucofuranosides in order to investigate the effect of substitution on methyl β- D - glucofuranoside. This would make an interesting comparison with the alkoxytetrahydropyran and furan series.[6]

Obviously further work is necessary on glycofuranoside hydrolysis.

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