Mechanism and Catalysis in the Hydrolysis of Some Acetals and Esters

by

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A Thesis submitted for the Degree of Doctor of Philosphy of the University of Glasgow.

April 1970

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to Caroline

ACKNOWLEDGEMENTS

I would like to record my sincere gratitude to Dr. B. Capon, my supervisor, for his helpful advice and for many stimulating discussions throughout the course of this work.

I am greatly indebted to the technical staff of this department for the services they have provided. I would also like to thank Miss J. Pollock for typing this thesis. Finally, I would like to acknowledge the Science Research Council for financial support.

April 1970

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SUMMARY

Recent advances in the study of acetal hydrolysis and the effect of neighbouring hydroxyl groups on ester hydrolysis are reviewed. Some of the criteria used to elucidate the mechanism of such reactions are discussed.

The enhanced rates of intra-molecular reactions over their inter-molecular counterparts are suggested to be due to factors other than just a 'concentration' effect, product stability reflected in the transition state may be important.

Intra-molecular and inter-molecular general-acid catalysis have been detected in the hydrolysis of benzylidene 2,3-dioxy benzoic acid and benzylidene catechol, respectively. Several kinetic parameters of these reactions have been determined and are discussed.

An example of nucleophilic catalysis by a carboxyl group has been found in the hydrolysis of o-carboxy benzylidene catechol. o-carboxy benzylidene 2,3-dioxy benzoic acid, a system which apparently contains suitably disposed carboxyl groups to act as general-acid and nucleophilic catalysts, was synthesised. However, the hydrolysis of this acetal showed no evidence of bifunctional catalysis.

Ring opening during the acid catalysed hydrolysis of benzaldehyde acetals of 2,3-exo-norbornanediol is shown to be reversible. An A-2 mechanism is suggested to be the pathway of hydrolysis of these 1,3-dioxolanes.

The facilitated rate of hydrolysis of β-hydroxy esters, in particular β-hydroxy butyrates and 2-hydroxy cyclopentane carboxylates, has been shown not to be due to any direct interaction between the two functional groups. 'Solvent sorting' is tentatively suggested to account for the observed phenomenon.

CONTENTS

INTRODUCTION

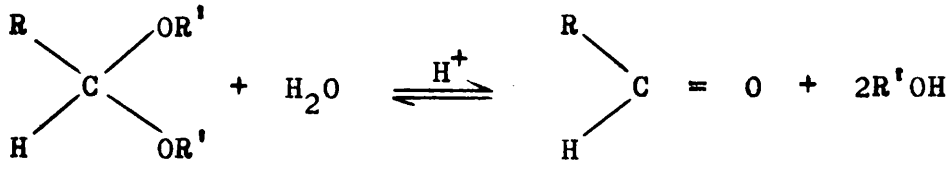
It is in vogue to justify many organic reaction mechanism studies by relating the findings to the mechanism of catalysis of an enzymatic reaction. The analogy has been expressed thus by Jencks[1] "At the present time we are in the position of the drunk on his hands and knees under the corner street light who, when approached by a citizen asking his intentions, replies that he is looking for his keys here, rather than in the poorly illuminated centre of the block where they were lost, because the light is better at the corner".

The Hydrolysis of Acetals and Related Compounds

Due to the fact that it is commonly accepted that acetals hydrolyse by the A-1 mechanism, they, and related compounds, have been the basis of many mechanistic studies. However, because of their structural relationship to glucosides, and the interest stimulated by the elucidation of the structure of glycosidases, such as lysozyme,[2] acetals have been used as substrates to find "non-classical" behaviour in attempts to relate them to the enzyme mechanism.

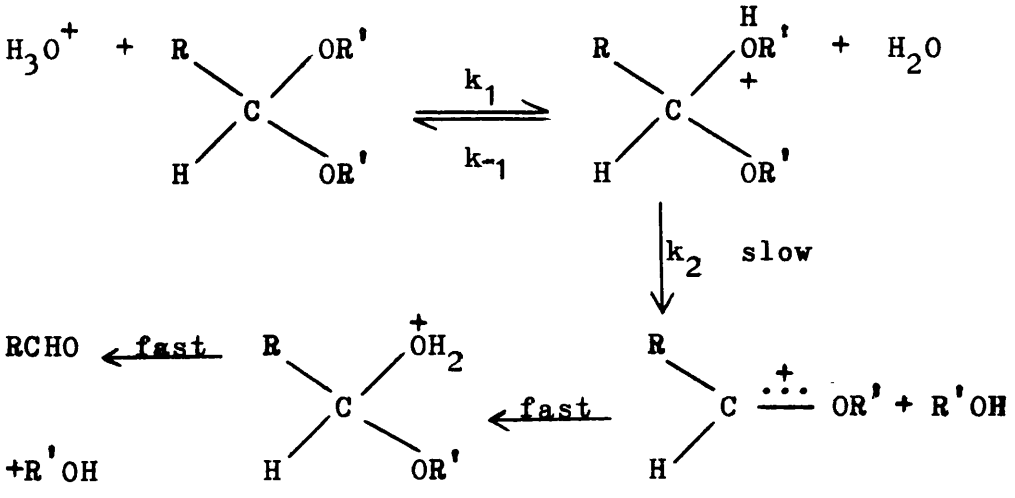
Since the subject and mode of hydrolysis of acetals[3,4,5,6,49] and glucosides[7,8] have been thoroughly reviewed, only a brief discussion will be given here, and the main emphasis will be on the more unusual mechanistic pathways followed by some of these compounds.

In acidic aqueous solutions, acyclic acetals hydrolyse according to the equation



This general reaction has been studied by a number of workers, and all of the evidence indicates that the A-1 mechanistic pathway is followed.[58] A pre-equilibrium

protonation of the substrate is followed by a rate-determining, unimolecular decomposition



to an alcohol or phenol and a resonance stabilised oxy-carbonium ion.[3]

The evidence supporting the A-1 mechanism is summarised below; the word acetal used here, implies acyclic acetal.

1) The reaction is specific acid catalysed,[9] bases do not generally catalyse the reaction, although some glucosides are hydrolysed under these conditions.[7]

2) Although general acid catalysis is well established for ortho ester hydrolysis,[13] no substantiated example of inter-molecular such catalysis in acetal, ketal, or glucoside hydrolysis was reported prior to 1966.

3) Reported correlation of rates of hydrolysis with acidity functions support the unimolecular reaction

path.[16,17]

4) Hydrolysis proceeds with cleavage of the carbonyl carbon-oxygen bond since:

a) The hydrolysis of acetals derived from optically active alcohols yields the alcohol of the same optical purity as the starting material.[10]

b) Hydrolysis of benzaldehyde di-n-butyl acetal and n-butyraldehyde di-n-butyl acetal in O^{18} enriched water gives alcohols of normal isotopic O^{18} content.[11]

c) Even acetals prepared from alcohols capable of forming stable carbonium ions, which could then undergo re-arrangement or racemisation, produced no evidence of alcohol carbon-oxygen fission.[12]

5) Second order rate constants for acetal, ketal and glycoside hydrolysis are sensitive to alterations in the aldehyde and alcohol moieties.

a) The hydrolysis of a series of m-substituted diethyl acetals of benzaldehyde in 50% aqueous dioxan, are correlated by the Hammett sigma values and yield a rho value of -3·35.[14]

b) The acid catalysed hydrolysis of a series of substituted aryl β-D-glucopyranosides fit a Hammett plot with a rho value of -0·66,[15] reflecting the opposing electronic requirements of the two step process.

6) The deuterium solvent isotope effects on the rates of hydrolysis of acetals, ketals and glucosides are invariably in the range 2-3, indicative of a specific acid catalysed reaction.[18]

7) Values of the volumes of activation fall into the range typical of reactions involving unimolecular decomposition of a protonated species.[19]

8) Remembering the two step nature of the mechanism proposed, entropies of activation also support the A-1 mechanism.[20]

Each of the criteria cited provides support for the rapid pre-equilibrium formation of the conjugate acid of the substrate; and a transition state containing the acetal and a proton only, a large amount of positive charge on the aldehydic carbon, aldehydic carbon-oxygen bond fission, and no nucleophilic assistance. This is consistent with the rate limiting unimolecular decomposition path stated earlier.

LYSOZYME

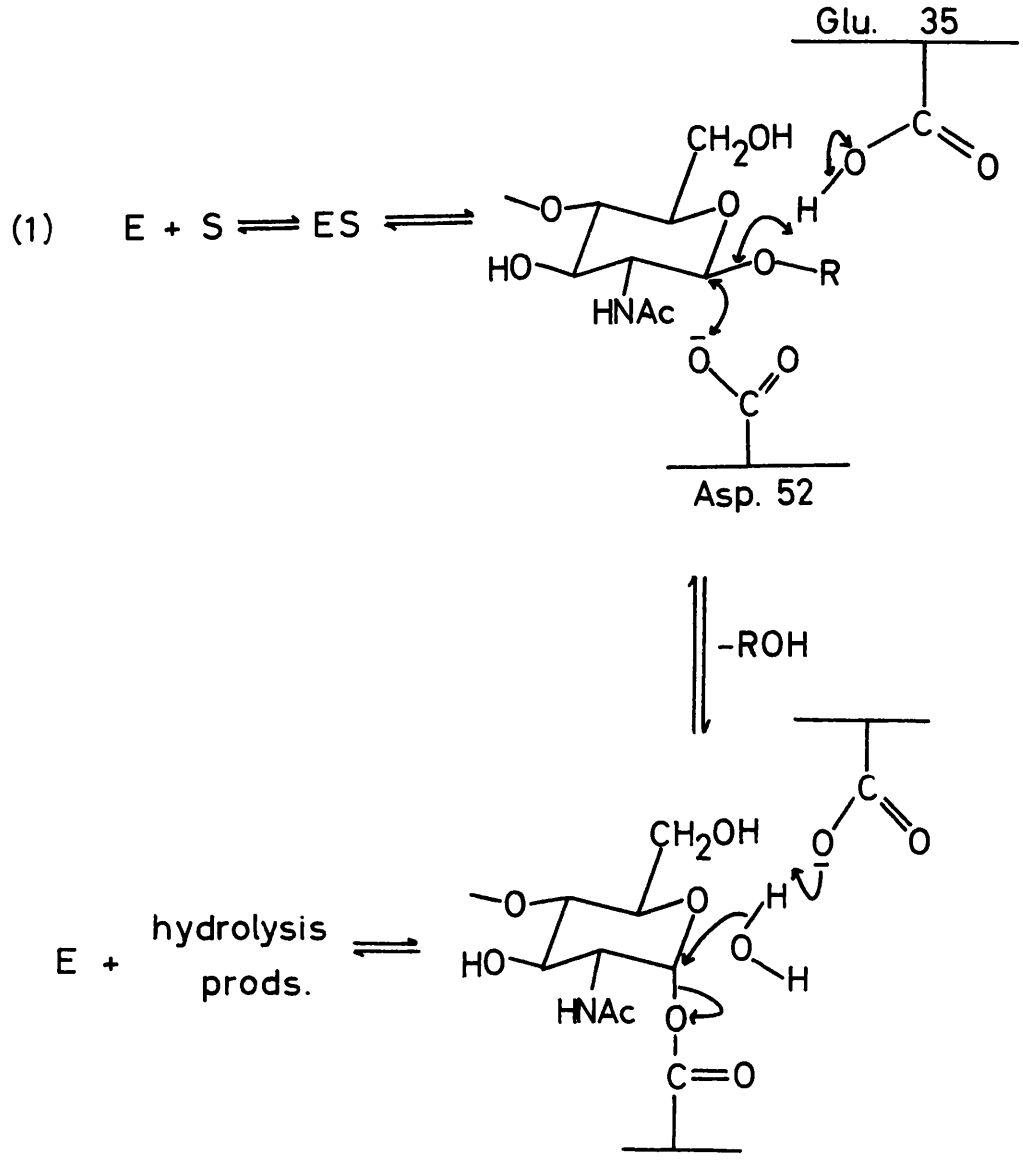
Lysozyme is a glucosidase[174] whose physiological role and physico-chemical properties have been thoroughly reviewed.[94,175,176,189] Its conformation in the crystalline state was determined by Philips and co-workers.[2] Lysozyme destroys the cell walls of certain

bacteria by catalysing the hydrolysis of the carbohydrate component, a β-1,4 linked polysaccharide with alternate N-acetylglucosamine and N-acetylmuramic acid residues. Bond cleavage occurs between the glycosyl C1 and oxygen,[177] similar to simple glycosides.

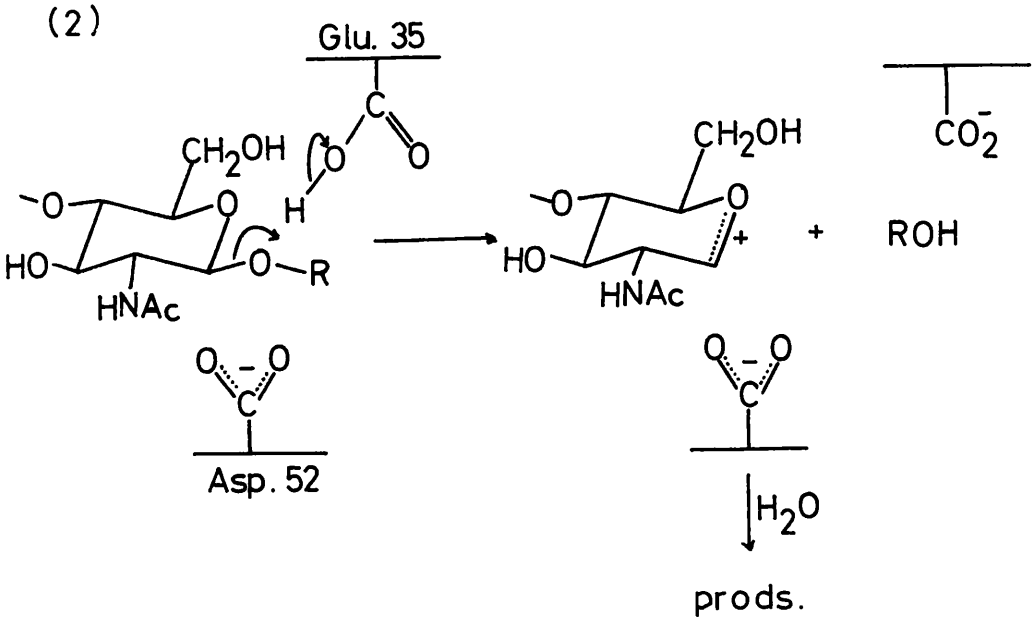
From X-ray diffraction studies of the enzyme-inhibitor complex, the active site has been located and it was found that the only functional groups available for catalytic action were the carboxylic acid residues of glutamic acid 35 and aspartic acid 52, which were disposed either side of the 1,4 linkage.[178] These groups are in rather different environments, the glutamic acid side chain lies in a predominantly non-polar region and is suggested to unionised, while the aspartic acid is in an essentially polar region and is dissociated.[179] Carboxyl group modification procedures have also suggested the presence of these two groups at the catalytic site.[180]

All mechanisms suggested[162,181,94] for the catalytic behaviour of lysozyme have involved the undissociated glutamic acid 35 acting as a general acid. Three functions have been suggested for the dissociated aspartate group: (1) nucleophilic, and so form a glycosyl-enzyme intermediate (eq. 1).[181,184,185] (2) electrostatic stabilisation of the glycosyl carbonium ion (eq. 2).[182,183,186]

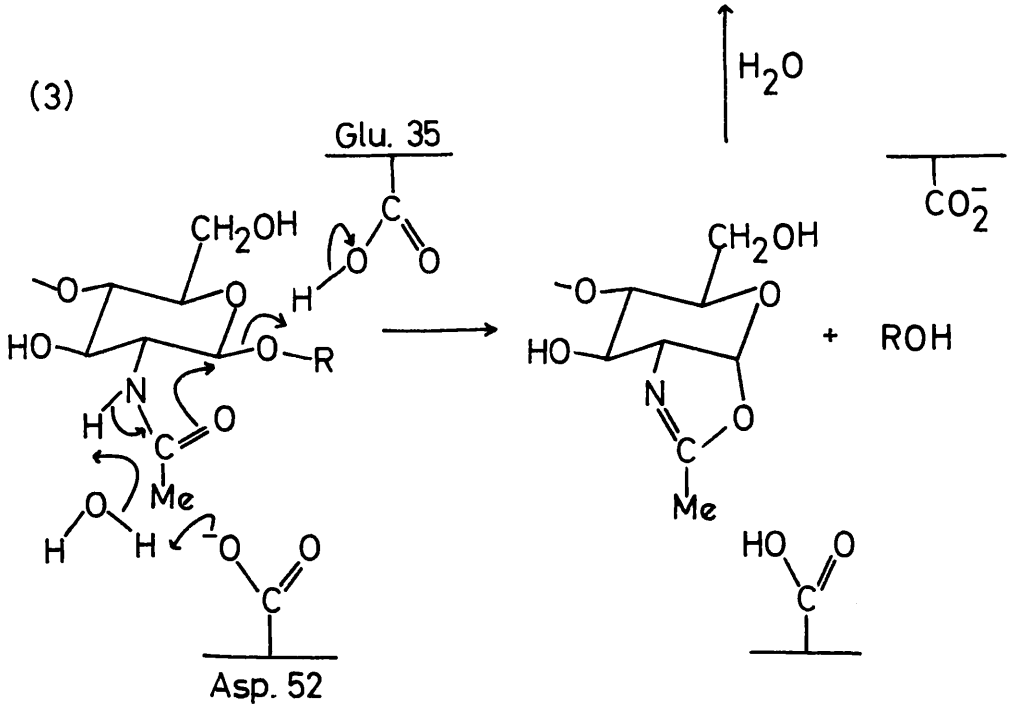
(3) general base catalysis for substrate acetamido group nucleophilic participation (eq. 3).[181,184]



(2)


Glu. 35
CH2OH
HO
HNAc
R
Asp. 52
CO2-
ROH
H2O
prods.

(3)


H2O
Glu. 35
CH2OH
HO
R
N
H
Me
Asp. 52
CO2-
ROH

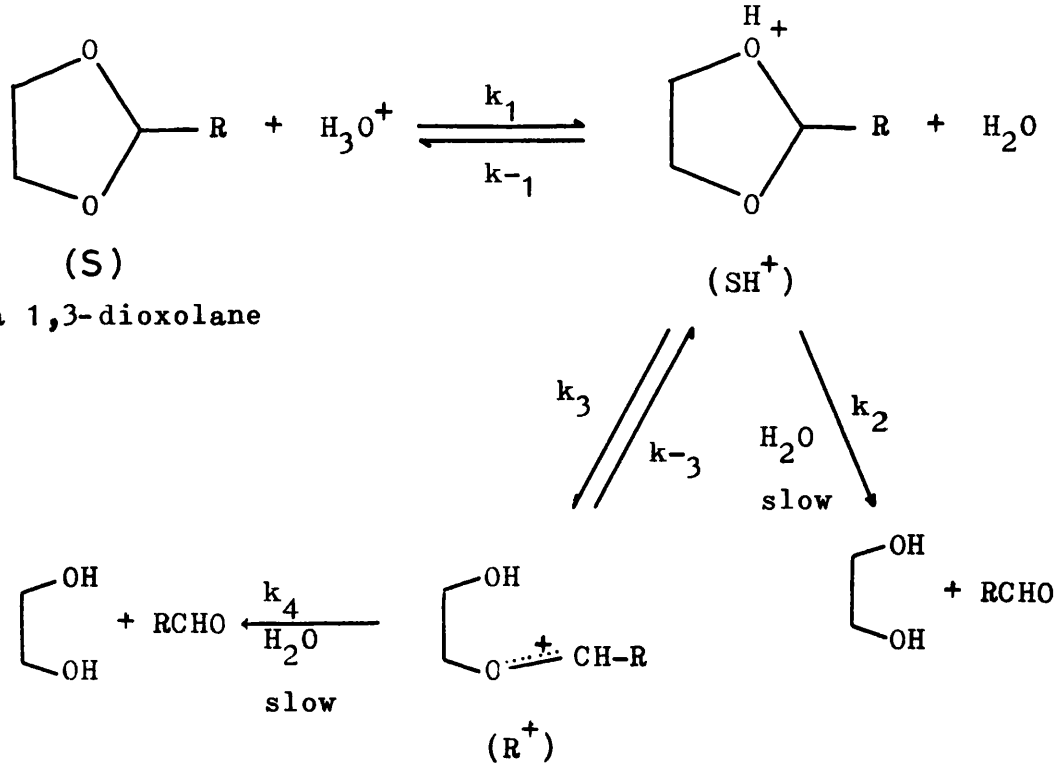
Two more alternative mechanisms could involve just general acid catalysis by glutamic acid 35, or the latter plus nucleophilic assistance of the acetamido group without general base catalysis.

General acid catalysis in the hydrolysis of acetals and glucosides has been established,[163-166] as has the nucleophilic participation of the acetamido group.[159] To date, there has been no substantiated reported example of type suggested by eq. 3 (see ref. 166 however). There is no reported example of nucleophilic participation by carboxyl groups in acetal or glucoside hydrolysis, or the bifunctional type of eq. 1 and 2. The latter was one of the objects of the investigation reported here.

I Cyclic Acetals and the A-2 Mechanism

Cyclic acetals are derived from diols, and although there have been several studies of these compounds reported,[14,21-28,46,49,50,148] the mechanism of their hydrolysis is not as unanimously accepted as is that of their acyclic counterparts.

These compounds are of interest because of the possibility that ring opening, that is to say cleavage of the carbon-oxygen bond, may not be the slow step in the hydrolysis of cyclic acetals. This is because neutral molecule-ion pair return may take place. The leaving hydroxyl group is still part of the same molecule and it is conceivable that intra-molecular recapture of the carbonium ion by this species will be faster than capture by solvent water. Hence another step for hydrolysis would become rate controlling, this would either be attack of water on the conjugate acid of the acetal, k_2, a classical A-2 mechanism, or solvation of the carbonium ion, step k_4. The experimental proof of water being involved in the transition state of a reaction carried out in aqueous solution is an extremely difficult problem.

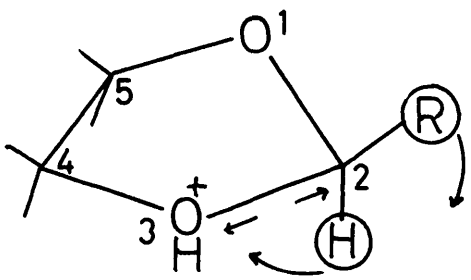


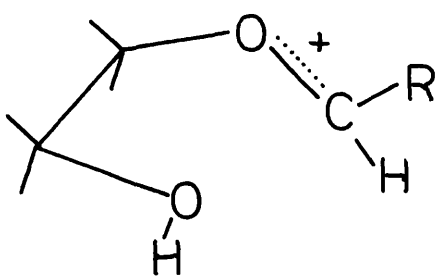
Of course, there is the possibility that both mechanisms represent accessible reaction paths, or that steps 3 and 4 are both rate controlling i.e. the rate of the forward reaction stage 4 is of similar magnitude to the rate of the reverse step of specific rate constant k_{-3}. For the latter situation, application of the steady state assumption to the intermediate carbonium ion, gives the following rate equation:

$$\text{Rate} = \frac{k_1 . k_3 . k_4 . (S)(H_3\overset{+}{O})}{k_{-1}(k_{-3} + k_4(H_2O))}$$

When $k_4 >> k_{-3}$, the equation reduces to an A-1 mechanistic classification, whereas under the conditions $k_4 << k_{-3}$, the equation represents the kinetic expression for an A-2 reaction.

The A-1 pathway could also become unfavourable, compared with other possible mechanisms, in cyclic acetal hydrolysis, due to hindrance by the ring of a conformational requirement of the transition state of the reaction or a less favourable dissociation constant of the conjugate acid of the acetal, say, due to steric hindrance of solvation.[33] The intermediate alkoxy carbonium ion, if formed, probably has a planar structure and if any of this planarity is reflected in the transition state, then the reaction has certain stereo-electronic requirements. This is because the C-2 substituents must move 'out', and the C-2 hydrogen 'in' to the ring, to avoid steric interaction with the C_4 and C_5 substituents. For steric interactions during ring opening, either themselves, or they being the cause of inhibition of resonance, to be effective, the transition state must have a significant amount of oxo-carbonium character, (see later).





However, with few exceptions, the general consensus of opinion appears to favour the A-1 mechanism for the hydrolysis of cyclic acetals. Some of the evidence used to assign this mechanism will now be briefly discussed.

1. Entropies of Activation

Of the reported activation parameters for cyclic acetal hydrolysis, four kinetic methods have been used to follow the reaction, spectral, gas chromatographic, dilatometric and chemical analysis. In view of the large acetal concentration required for the latter two methods, and their invalidity for following this particular reaction,[29] since the product does not have constant composition and the acidity of the medium changes as hydrolysis proceeds,[29] the results obtained thus must be viewed with some scepticism. Difficulties also arise from the choice of standard states, these are usually referred to 1M in acid concentration, although the actual kinetics may have been followed at higher or lower concentration than this. Sometimes, first order rate constants measured in say 0·01M acid, have been converted to second order rate constants by multiplying by 100,[27] and yet on other occasions by the reciprocal of the hydrogen-ion activity, as determined by the pH [28] measured by the glass electrode. Also a variety of solvent

Compound	Medium	Kinetic Method	Temp. °C	$\Delta H^{\ddagger}$ Kcal.mole^{-1}	$\Delta S^{\ddagger}$ e.u.	Mechanistic Classification	Ref.
2Aryl-1,3-dioxolanes	water	spectral	30	14 to 18	-9to-12	A1	46
ditto	50% dioxan water(v/v)	spectral	30	13 to 20	-7to-10	A1	14,21
2Phenyl-4,4,5,5-tetramethyl 1,3-dioxolane	water	spectral	30	16·1	-14·2	A2	27
1,3-dioxolane	water	titrimetric	25	24·9	-0·6	A1	22
ditto	water	sulphite	30	26·5	+3·9	A1	46
2Methyl 1,3-dioxolane	water	dilat.	25	21·7	+5·6	A1	22
ditto	water	spectral*	25	21·7	+4·8	A1	39
2Methyl 1,3-dioxan	water	ditto*	25	13·7	-23·2	A1	39
Pentamethyl-2,4,4,5,5-dioxolane	water	dilat.	25	20·0	-3·8	A1	24

* but 1M in acetal and at 2 temps. only 10° apart.

systems have been used.

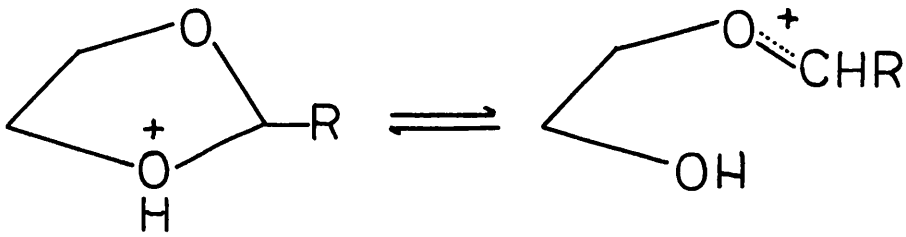
A selection of some of the published activation parameters is given on page 14.

The observed entropies of activation probably qualifies these reactions for A-1 or borderline A-2, according to the classification of Schaleger and Long.[20] It is noteworthy, that on comparison of the differences in $\Delta S^{\ddagger}$ for the cyclic and acyclic acetals of the same aldehyde or ketone, the 1,3-dioxolanes have consistently a more negative value by about 8 to 12 e.u., and appears to be independent of the substituent at position 2. This is probably, therefore, just a function of the five membered ring.

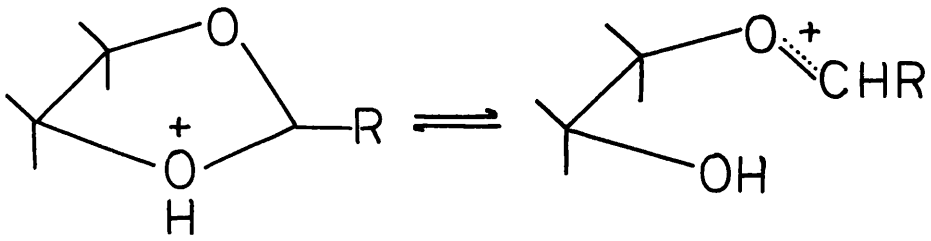
The negative entropies of activation have been rationalised to 'fit' an A-1 mechanism by such factors as high solvation of the conjugate acid or transition state or restriction of rotation in the latter as determined by the amount of mesomeric interaction.[14,39]

Of all the reported studies of acetals and ketals by Fife,[14,21,27,28] only one class of compounds have been suggested to hydrolyse by the bi-molecular path, the tetramethyl ethylene glycol acetals, which have entropies of activation of -14 to -16 e.u.[28] Fife considers that this value is more compatible with an A-2 mechanism. In

view of the 'justification' of the negative entropies of activation for other cyclic acetals, it would be of interest to know the entropy changes accompanying the following reactions, especially in view of



and



the 'geminal effect' favouring rates of ring closure.[98] It has been suggested that much more subtle factors than simple order-disorder effects are involved in determining the magnitude of the entropy of activation.[152]

Partial A-2 character has been suggested in the hydrolysis of methyl-2-chloro-deoxy-β-D-glucopyranoside which has a $\Delta S^{\ddagger}$ of +7·5 e.u. compared to the $\Delta S^{\ddagger}$ for methyl-β-D-glucopyranoside of +16·5 e.u., although all other available data are characteristic of a unimolecular path.[30] Capon and Thacker[31] postulated, on the basis of entropies of activation of -8 to -11 e.u., that the

hydrolysis of alkyl furanosides followed a bi-molecular reaction path, although aryl furanosides appear to hydrolyse by the A-1 mechanism.[32]

2. Acidity Dependence

The acidity dependence of the rate constants of some 1,3-dioxolanes in aqueous sulphuric acid, up to 4M, has been reported.[34] Plots of log k_{obs} against the Hammett acidity function $-H_o$, were linear with approximately unit slopes, which was considered by the authors to be indicative of an A-1 mechanism. Kaeding and Andrews[148] studied the rates of hydrolysis of p-nitrobenzophenone diethyl ketal in aqueous ethanolic solutions of hydrochloric acid, and since the authors did not observe the usual acidity dependence they suggested that this compound hydrolyses by the A-2 mechanism. By application of their empirical solvent composition -acidity function criterion,[149] Kwart and co-workers[150] postulated nucleophilic solvent participation for the hydrolysis of this compound and also methyl ortho p-nitrobenzoate. The interpretation of these results has been criticised.[3]

For the hydrolysis of 2-p-nitrophenyl - 4,4,5,5 tetramethyl - 1,3 - dioxolane, Fife[27] has observed rates proportional to the stoichiometric acid concentration, the log-log plot having a slope of 2·0. A Bunnett plot[17] of

$\log(k_{obs} + H_o)$ against $\log a_{H_2O}$ is curved.

According to the Zucker-Hammett hypothesis,[35] a plot of $\log k_{obs}$ against $-H_o$ should be linear and of unit slope for an A-1 process, but for an A-2 mechanism $\log k_{obs}$ against the logarithm of the concentration of acid should be linear. Only above 2·5M perchloric acid do the quantities $-H_o$ and $\log [HClO_4]$ diverge significantly.

However, in view of criticisms and failures,[36-38,187] the variance of reaction rate constant in media of high acid concentration, is not a very reliable criterion of mechanism.

Bunnett plots for the hydrolyses of glucopyranosides in aqueous perchloric acid yield positive slopes of w value 1·7 - 3·0, which suggests nucleophilic attack by water,[47] but the plots of the hydrolyses of methyl α-D glucopyranoside and a large series of alkyl xylopyranosides in hydrochloric acid are curves with negative slopes.[48]

3. Effect of Ring Size

The rate of hydrolysis of the 1,3-dioxolane derived from cyclopentanone is 13 times greater than that from cyclohexanone,[25] which Newman and Harper[25] interpreted as indicative of an A-1 mechanism. However, rate determining attack of water on the free carbonium ion, or

a classical bi-molecular nucleophilic displacement with a large amount of bond breaking and little bond making in the transition state, would similarly be expected to show this rate enhancement for the compound forming the more favourable trigonal centre.

Watts[39] has studied the rates of hydrolysis of cyclic ketals of ring size 5-8, and Jary and co-workers[40] cyclic benzaldehyde acetals of ring size 5-7. The eight membered ring hydrolyses about 120 times faster than the corresponding five membered system.[39]

4. Solvent Isotope Effects[18]

Orvik[26] has calculated that the magnitude of the solvent isotope effect cannot be used to distinguish between the A-1 and A-2 mechanism, for cyclic acetal hydrolysis. The isotope effects were calculated by the method of Bunton and Shiner.[41] This treatment assumes that the isotope effect arises only out of the difference between the zero point vibrational energies of the corresponding hydrogen and deuterium bonds. It further assumes that the differences in stretching frequencies of the bonds is a function of the type of hydrogen bridging situation in which the bond is involved. Account is taken of the change in number and kind of hydrogen bonds upon reaction, in the calculation of the isotope effect.

Using an estimated pKa of -3·5 for the acetal, Orvik[26] calculated that the solvent isotope effect k_{D^+}/k_{H^+} at 25°C equals 2·1 - 2·6 for the A-1 mechanism, 1·6 - 2·6 for attack of water on the open carbonium ion, and 1·4 - 3·0 for the classical S_N2 mechanism.

The values usually quoted[27] for the solvent isotope effects are 1·9 - 2·6 for the A-1 pathway, and 1·3 - 1·7 for the A-2 mechanism. These are the values of Long and Pritchard,[42] the former relate to the acid hydrolysis of several epoxides, and the latter to acid catalysed hydrolysis of esters in which water acts as a nucleophile. Fife[27] has suggested that solvent isotope effects may be used to distinguish between the A-1 and A-2 mechanisms, using these values. Reported effects for cyclic acetals vary from k_{D^+}/k_{H^+} of 2·4 to 3·7 at 25 - 30°C, ranging from pure aqueous solution to 50% dioxan-water.[14,21,27,43,44] A solvent isotope effect of k_{D^+}/k_{H^+} = 2·4 for the hydrolysis of 2-phenyl 4,4,5,5-tetramethyl-1,3-dioxolane is said to be considerably less than the normal values for acetal hydrolysis 2·7 - 3·0, and it was considered that this is indicative of an A-2 mechanism.[27]

5. Effect of Substituents

This is possibly one of the most fruitful mechanistic tools to distinguish between the possible mechanisms.

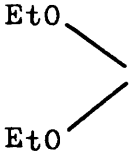
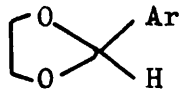
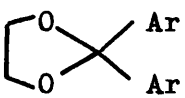
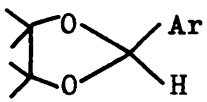
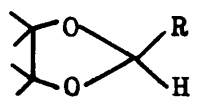
Since an alkoxy carbonium ion is the potential intermediate in acetal hydrolysis, it would seem at first sight that no nucleophilic assistance would be required. However, as mentioned earlier, this is not necessarily the case for cyclic acetal hydrolysis. The resemblance of the transition state to the protonated acetal or the intermediate alkoxy carbonium ion, and hence the amount of carbon-oxygen bond fission, will depend on the relative stabilities of these two species.[78,151] A substrate whose conjugate acid is unstable and forms a relatively stable carbonium ion will probably have a transition state resembling the former and hence little carbon-oxygen bond fission will have taken place.

Electron withdrawal in the aldehydic portion of the acetal should hinder protonation and destabilise the incipient carbonium ion in an A-1 reaction. Depending on the relative development of bond making and bond breaking in the transition state, nucleophilic attack should generally be facilitated by electron withdrawal. Solvent participation should therefore result in a less negative rho value, if bond formation is at all important in the transition state. However, a mechanism involving rate-controlling attack of water on the open carbonium ion may

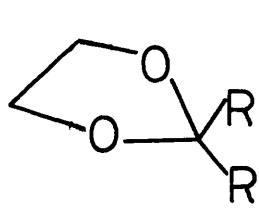
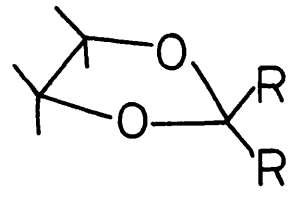
well have similar substituent effects on rate constants as a mechanism in which unimolecular cleavage of the protonated acetal is the rate-limiting step (A-1). Complications may also arise because the latter step may be correlated by σ^+ whereas the equilibrium constant for protonation may be correlated by σ. The resulting correlation may therefore be a composite quantity because of the two step nature of the mechanism. A correlation with σ^+ does not necessarily imply a carbonium-like transition state.[67] Some cases of reported structure-reactivity relationships are given in the table on the following page.

Bearing in mind the different solvent systems used, the reduced rho value for the tetramethyl ethylene glycol acetals suggests that there is less charge development in the transition state than in the other cases cited. This lead the authors[27,28] to postulate an A-2 mechanism for the hydrolysis of these compounds.

Kankaanpera[24] has published a detailed study of the hydrolysis of all possible methyl substituted 1,3-dioxolanes. Substituent effects do not always parallel those in acyclic acetals, presumably because of the different steric and conformational effects in the initial and transition states. The relative rates of hydrolysis of

Compound and position of substitution		Solvent	Temp. °C	Correlation	rho	Ref.
	m	50% dioxan water	30	$\log k/k_o = \rho\sigma$	-3·35	14
ditto	p	water	25	$\log k/k_o = \rho\sigma$	-3·3	188
ditto	m and p	50% dioxan water	30	$\log k/k_o = \rho[\sigma + r(\sigma^+-\sigma)]$	ρ = -3·35 r = 0·5	14
	p	ditto	30	ditto	ρ = -3·25 r = 0·5	14
	p	20% dioxan water	30	$\log k/k_o = \rho\sigma$	-4·7	44
	p	water	30	$\log k/k_o = \rho\sigma$	-2·0	27
		50% dioxan water	30	$\log k/k_o = \rho^*\sigma^*$	-2·2	28
$(EtO)_2CR_1R_2$		50% dioxan water	25°	$\log k/k_o = (\Sigma\sigma^*)\rho + 0{\cdot}54(\Delta n)$	-3·60	45

some of the acetals studied in water at 25°C are given below.[24]

R		
H, H	5	1
H, Me	28,000 (7)	4,000 (1)
Me, Me	310,000 (800)	400 (1)

2,2-dimethyl 1,3-dioxolane hydrolyses only 10 times faster than the 2 monosubstituted derivative, much less than the normal 10^3 fold increase found going from alkyl acetals to ketals.[45] Utilising the arguments presented earlier, regarding the interaction between the alcohol substituents and those attached to the carbonyl carbon during ring opening, the relatively small rate differences observed on placing methyl substituents in the glycol residue may be rationalised, assuming the A-1 mechanism. Particularly noticeable, however, is the effect of 4,4,5,5-tetramethyl groups, the 2,2,4,4,5,5-hexamethyl derivative hydrolyses 10 times slower than the 2 monosubstituted compound, and nearly 10^3 times slower than the corres-

ponding dioxolane unsubstituted in the glycol residue. Is this simply steric hindrance to ring opening, inhibition of the normal resonance interaction or due to a change from the A-1 mechanism?

Aftalion[34] has reported similar studies in 1,3-dioxolanes and 1,3-dioxanes, a single alkyl substituent at position 2 in the former series obey a Taft relationship, but 2,2-disubstituted 1,3-dioxolanes do not follow a linear correlation. The author concluded that this was a steric effect, and that the mechanism of hydrolysis was similar to acyclic acetals. Fife and Hagopian,[21] however found that the logarithm of the rate constants for five 2,2-dialkyl 1,3-dioxolanes, less a hyperconjugation term, gave a linear correlation with Taft's σ^* constants with one exception, 2,2-di-isopropyl.

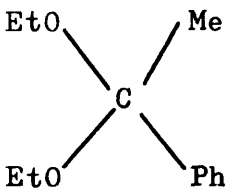
It has also been found that 2,2-diphenyl 1,3-dioxolane hydrolyses 120 times more slowly than 2-phenyl - 1,3 - dioxolane, which is to be compared with the 20 fold slower rate of benzophenone diethyl ketal than of benzaldehyde diethyl acetal.[50] Three mechanisms have been proposed for the hydrolysis of this dioxolane, A-1,[50] possibly A-2[150] and $A_{SE}2$.[44] The latter will be discussed under general-acid catalysis in the hydrolysis of acetals.

The slower rates of hydrolyses, of these compounds,

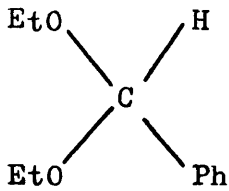
than 'expected' for an A-1 mechanism, could either be due to a different mechanism followed, a more favourable initial state energy or severe restrictions of the normal A-1 transition state. The latter could arise from steric inhibition of resonance[50] between the aryl or alkyl group and the incipient carbonium ion or prevention of the required co-planarity of the oxonium ion. Steric inhibition of solvation of the conjugate acid, thereby decreasing the basicity of the acetal, would have two effects because of the two step nature of the process. One must consider mechanistic parameters for both of these steps, in this particular case, decreased basicity would result in a lower concentration of the conjugate acid in a given solution, and could result in a transition state resembling the protonated acetal so that conjugation with substituents is relatively unimportant.

Fife and co-workers[27,28] have published extensive studies of the glycol acetals of benzaldehyde derivatives. Diethyl acetals of benzaldehyde hydrolyse 40 - 60 times faster than the corresponding 1,3-dioxolane derivative,[14,21] due to more favourable entropies of activation. But, again, as the following table shows, the largest effects are obtained with the tetramethyl ethylene glycol derivatives,

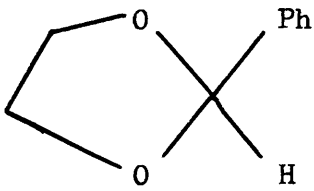
Relative Rates of hydrolysis in water at 30°C[14,21,27,28]



3×10^{8}[a]

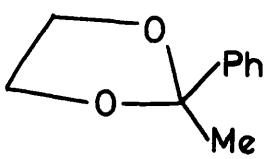


9×10^{6}

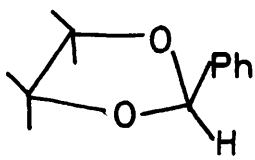


18×10^{4}

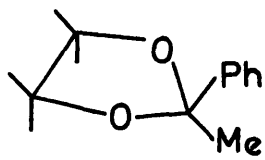
$\Delta H^{\ddagger}$ Kcal.mole^{-1}	14·0[a]	16·5[a]	14·8[b]	and	15·5[a]
$\Delta S^{\ddagger}$ e.u.	-0·4	+1·0	-9·4	and	-8·9



4×10^{4}



540



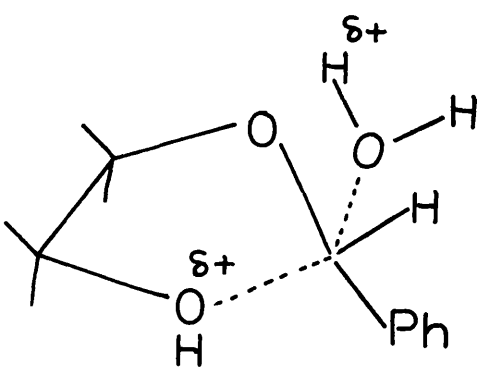
1

$\Delta H^{\ddagger}$ Kcal.mole^{-1}	17·5[b],	16·6[a]	16·1	21·6
$\Delta S^{\ddagger}$ e.u.	-3·3,	-8·6	-14·2	-8·6

a) 50% dioxan-water v/v used as solvent

b) from ref. 46.

The relative rates are substituent and solvent dependent, the p-methoxy benzaldehyde compounds accentuate the rate differences, but the latter are less pronounced in 50% dioxan-water than water. Perhaps of relevance, Fife and Brod[28] found rate differences when the 2-substituent was alkyl rather than aryl, but the effects are less marked. The large rate decrease (540x) produced by replacing the acetal hydrogen by a methyl group in 2-phenyl 4,4,5,5-tetramethyl - 1,3 - dioxolane is much greater than Kankaanpera[24] observed for a similar substitution of a methyl group in 2-methyl 4,4,5,5-tetramethyl - 1,3 - dioxolane, the former hydrolysing 10 times slower than the latter. This is unexpected, considering the greater electron releasing ability of an alkyl group compared to hydrogen.[45] Fife has stated[27,28] that this data is indicative of an A-2 mechanism for the 4,4,5,5-tetramethyl - 1,3 - dioxolanes. The reaction path involving nucleophilic attack of water on the conjugate of the acetal.



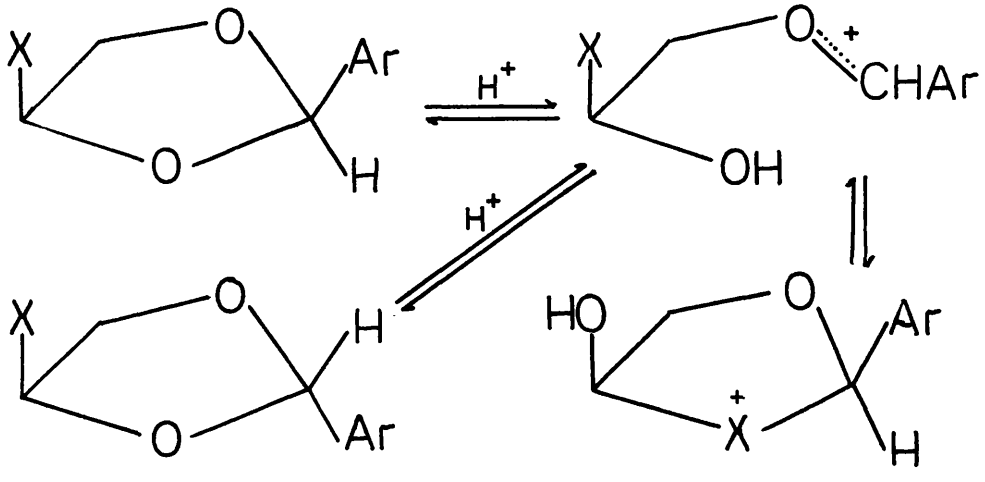
The same author[21] considers that the rate retardation in other 1,3-dioxolanes is due to steric inhibition of resonance with the incipient carbonium ion in the A-1 transition state. Steric interactions between the carbonyl substituents and those on the glycol residue, as proposed by Kankaanpera,[24] are thought to be unimportant. However, it would be difficult to separate 'cause and effect' in this case.

Recalling that a difference in the value of the entropy of activation of 5 e.u. is equivalent to a rate difference of about 12 at room temperature, the activation parameters show that 2,2-phenyl methyl - substituted and unsubstituted - 1,3-dioxolanes hydrolyse slower than the 2-phenyl derivatives due to an unfavourable enthalpy of activation, despite a more favourable entropy term.

Reversibility of the Ring Opening Step

If it could be shown that the reversal of the ring opening step occurred during hydrolysis, or better, at a rate faster than hydrolysis, then this would be the least ambiguous evidence for a path other than unimolecular fission of the carbon-oxygen bond (A-1) being the mechanism of hydrolysis. This may be detectable in a reaction in which ring closure of the alkoxy carbonium ion intermediate resulted in a different compound or an isomer

of the starting material.

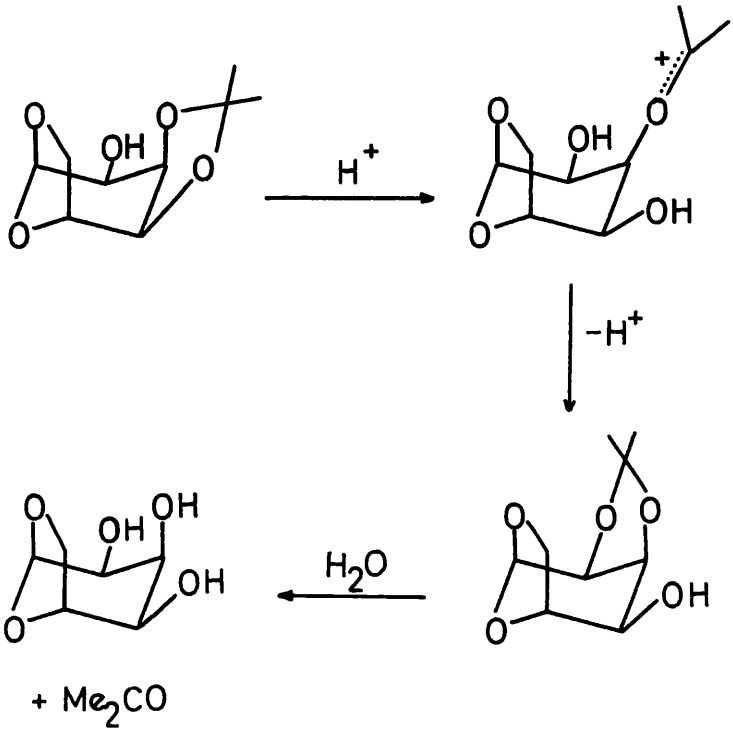


Ceder[46] studied the rates of hydrolysis of the 1,3-dioxolane of cinnamaldehyde and found the rate of disappearance of the acetal to be different from the rate of appearance of aldehyde, but the difference was too small to allow kinetic analysis.

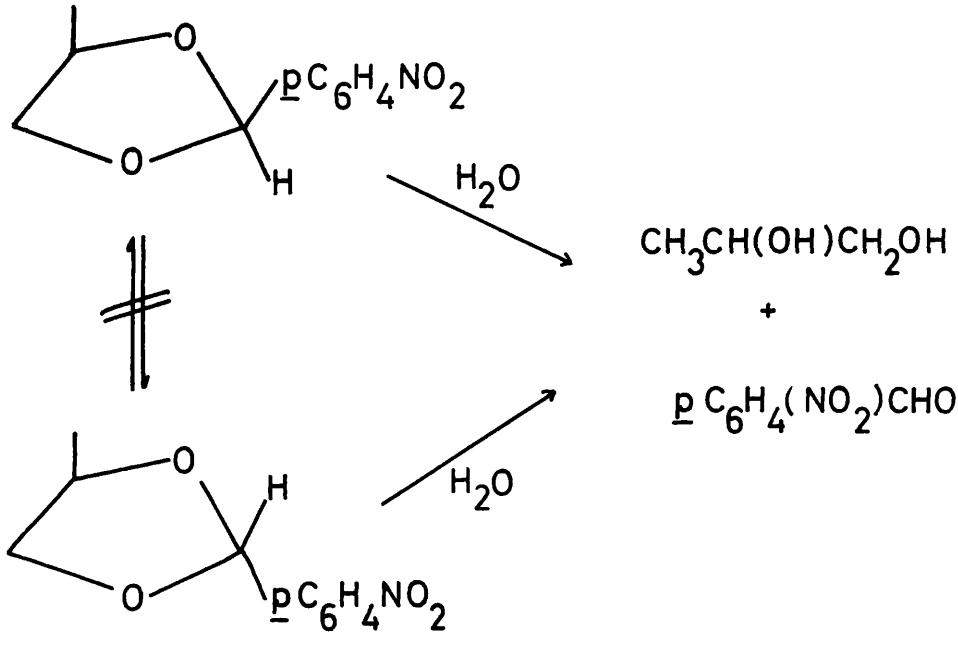
Watts[39] attempted to observe the reversibility of the ring opening step by measuring the rates of hydrolysis and racemisation of D-1,2-O-isopropylidene glycerol. Unfortunately, the rate of racemisation could not be measured with sufficient accuracy to yield a conclusive result. The author concluded from the similar magnitudes of the two rates that the reverse reaction was unimportant.

Hughes[154] has shown that, at least in part, the

hydrolysis of 1,6 - anhydro - 2,3 - O - isopropylidene - β-D talopyranose proceeds via the 3,4-isopropylidene derivative.



In 66% dioxan-water, using n.m.r. to follow isomerisation and u.v. spectroscopy to monitor the rates of hydrolysis, Orvik[26] found no evidence of interconversion between the two isomeric dioxolanes, shown overleaf, during hydrolysis. However, in dioxan solutions where the molarity of water was below 1M isomerisation occurred during hydrolysis; and with 0·05M water only in the system, isomerisation was faster than hydrolysis.



Orvik[26] interpreted this to mean that in such solutions the hydrolysis mechanism involved attack of water on the intermediate carbonium ion. Unfortunately, as will be discussed later, this was not a very suitable aldehyde to choose to witness isomerisation.

There have been several reports of the acid catalysed isomerisation of acetals occurring in non-aqueous solvents.[49,155]

Summary regarding the A-2 mechanism

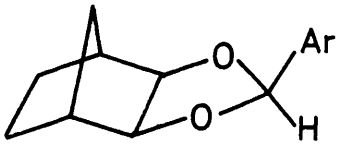
The general consensus of opinion appears to favour the A-1 mechanism for cyclic acetal hydrolysis. Noteable

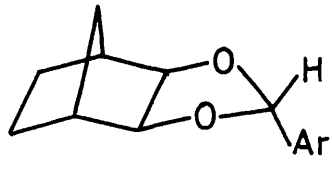
exceptions being Orvik[26] and Fife[27,28] for the hydrolysis of tetramethyl ethylene glycol acetals. De Wolfe[44] has stated he considers the experimental evidence of the latter for assigning the A-2 mechanism to this class of compounds is too ambiguous to justify this conclusion, and the author thinks it is more compatible with an S_E2 mechanism. This ambiguity certainly exists, since on some of the criteria used by Fife, one could argue that most dioxolanes hydrolyse by the A-2 mechanism. However, De Wolfe has even gone so far as to state[44] "It seems reasonable to conclude that acid-catalysed hydrolysis reactions of acetals, ketals and ortho esters rarely <u>if ever</u> occur by the A-2 mechanism". In fairness, this statement was written before the publication of Fife's work on the effect of 2-methyl substitution in 4,4,5,5 tetramethyl - 1,3 - dioxolanes.[28]

Accepting, for the moment, that some 1,3-dioxolanes hydrolyse by the A-2 mechanism, what are the causes of this change from the normal reaction path? Fife and Brod[28] have stated " ··· the differences in behaviour between tetramethyl ethylene glycol acetals and ethylene glycol or diethyl acetals are produced by steric inhibition of the normal A-1 reaction by the presence of methyl groups at the 4 and 5 positions of the 1,3-

dioxolane ring, thus allowing other mechanisms to become observable". At what stage is this inhibition effective; does steric hindrance prevent the unimolecular opening of the ring and hence formation of the oxycarbonium ion, or is the latter reasonably facile but the newly formed internal hydroxyl group competes more effectively for the ion than does water, thus making ring opening a reversible equilibrium?[31] If the latter is true, what is the mechanism of hydrolysis, bimolecular attack of water on the carbonium ion or on the conjugate acid of the acetal?

In this thesis some of these problems are resolved for the cyclic acetals studied. It has been found that in a series of substituted benzaldehyde acetals of 2,3-exo-norbornane diol isomerisation can occur much faster



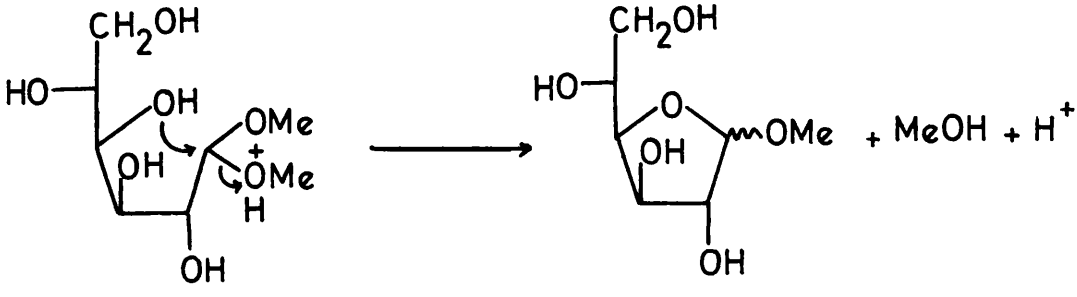


than hydrolysis. A classical A-2 mechanism involving nucleophilic attack of water on the conjugate acid of the acetal is suggested as the mode of hydrolysis. There is now definite evidence for nucleophilic participation

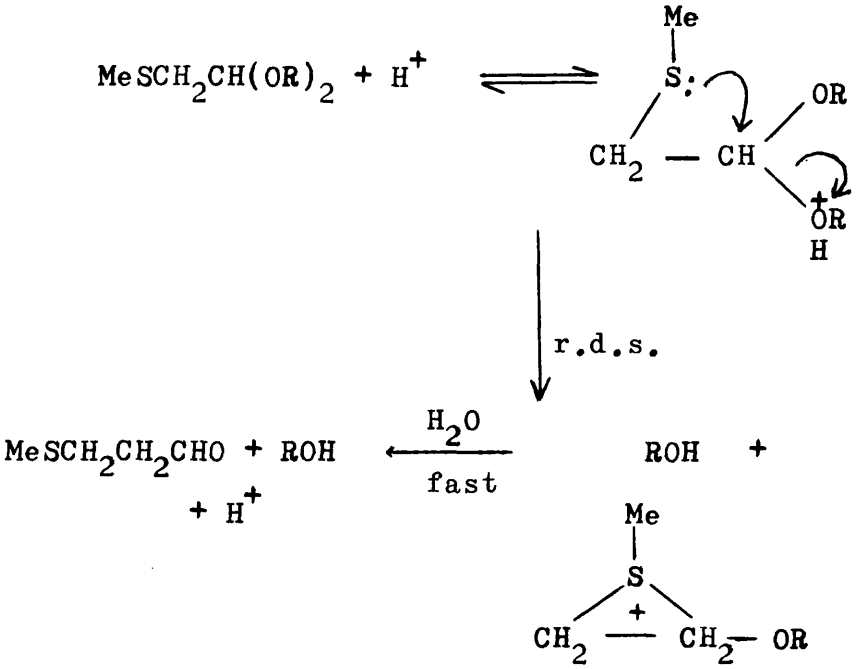
in acetal hydrolysis.

II Nucleophilic Catalysis

Capon and Thacker[156] have shown that acid catalysed ring closure, not hydrolysis, of dimethyl acetals of glucose and galactose to the methyl furanosides involves nucleophilic participation. Since the rate depended on the configuration at C-4 and the rate enhancement was 30 - 300 times that predicted from related substrates, the authors proposed nucleophilic attack of the hydroxyl group synchronous with fission of the acetal bond.



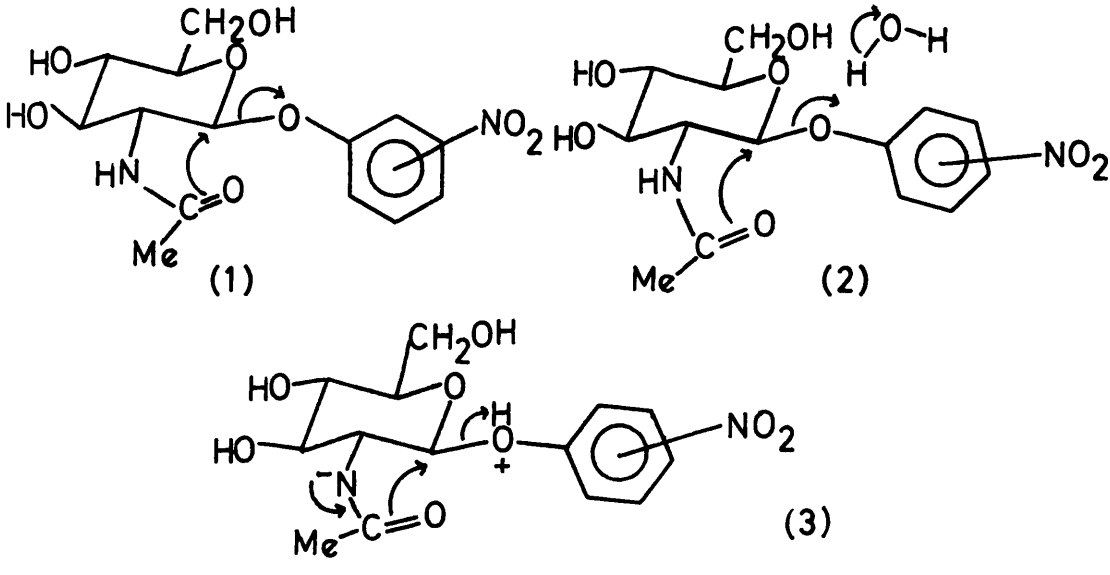
Speck and co-workers[157] have suggested that the acid catalysed hydrolysis of methylthio-acetaldehyde diethyl acetal involves nucleophilic assistance of the methylthio group.



The rate of hydrolysis was found to be 100 times that of the corresponding methoxy compound, which has a similar polar substituent constant, but is 10 times slower than the parent compound, diethyl acetal.

The solvolysis, in methanol and aqueous dioxan, of 2-N-benzoyl and 2-N-acetyl - 1,3,4,6 - tetra-O-acetyl β-D glucopyranoside and β-D galactopyranoside proceed faster than the corresponding α anomers, although no detailed kinetics were reported.[158] Anchimeric assistance by the amide group was considered to facilitate the departure of C-1 acyloxy group. The intermediate oxazolinium ion was then stereospecifically captured by the solvent at C-1.

In a more extensive study, Bruice and Piszkiewicz,[159] observed a spontaneous hydrolysis at 78°C between pH 0·7 and 11·7 for o-and p-nitrophenyl 2- acetamido-2-deoxy-β-D glucopyranosides and o-and p-nitrophenyl β-D gluco-pyranosides. The former hydrolyse 10^5 and the latter 10^2 times faster than the corresponding α-anomers, which undergo specific acid and specific base catalysed hydro-lysis only. No rate enhancement for the β-anomers was observed for the specific acid catalysed reaction. The possible kinetically equivalent mechanisms, for the spontaneous hydrolysis, are shown below.



The authors preferred (1) the intra-molecular nucleophilic displacement of the nitrophenoxide ion by the neutral acetamido group. Using reasonable estimates of the constants for the pre-equilibrium steps, mechanism 3 would

have to have a specific rate constant, for the step shown, of the order of 10^{16} sec^{-1}. Rate determining proton transfer (from the amide NH or to the aglycone oxygen ?) was considered unlikely since no buffer catalysis was observed and in view of a solvent isotope effect of k_D/k_H 0·83 - 1·36. The latter also suggested to the authors that water was not involved in the transition state. This range is considerably less than the normal values found in glycoside hydrolysis of k_D/k_H 1·9 - 2·7, and appears to the reviewer to be compatible with the known effects for rate limiting proton transfer to glucosides and acetals k_D/k_H 0·6 - 1·5. Of course, it is also in the region expected for just a transfer effect. Mechanism 2 definitely requires consideration in view of the similar mechanism proposed by Fife and Jao[160] for the spontaneous hydrolysis of 2-p-nitrophenoxy - tetrahydropyran, for which the acid catalysed reaction has a k_D/k_H of 1·33 (see later discussion). Methyl α-and β-2-acetamido - 2-deoxy-β-D-glucopyranosides both appear to be specific acid catalysed, and the evidence of whether there is any intra-molecular nucleophilic catalysis is ambiguous.[161]

Bruice interpreted his results in relation to the mechanism of action of lysozyme. Recent evidence has

demonstrated that the neighbouring 2-acetamido group is not essential for enzymatic activity.[162]

Inter-molecular nucleophilic assistance has been reported by Fife,[27] who suggested that the observed buffer catalysis of 2-p-methoxyphenyl - 4,4,5,5-tetramethyl-1,3-dioxolane involves nucleophilic attack by carboxylate ion on the protonated acetal.

Orvik[26] considers that the aniline buffer catalysis found for the hydrolysis of the ethylene acetal of anisaldehyde arises from nucleophilic capture by the amine of the reversibly formed carbonium ion.

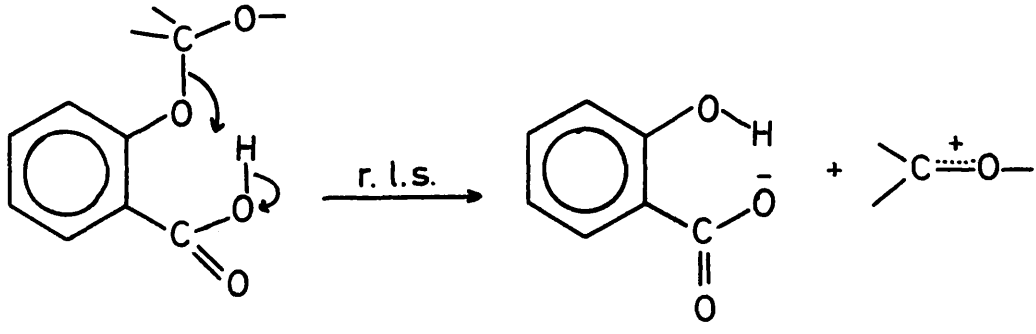
III General Acid Catalysis

Intra-molecular general acid catalysis has been demonstrated to occur in the hydrolysis of o-carboxyphenyl glucosides and acetals,[163-166] but until recently inter-molecular catalysis has never been demonstrated in these systems, although it is well established for the hydrolysis of the structurally related ortho-esters.[3]

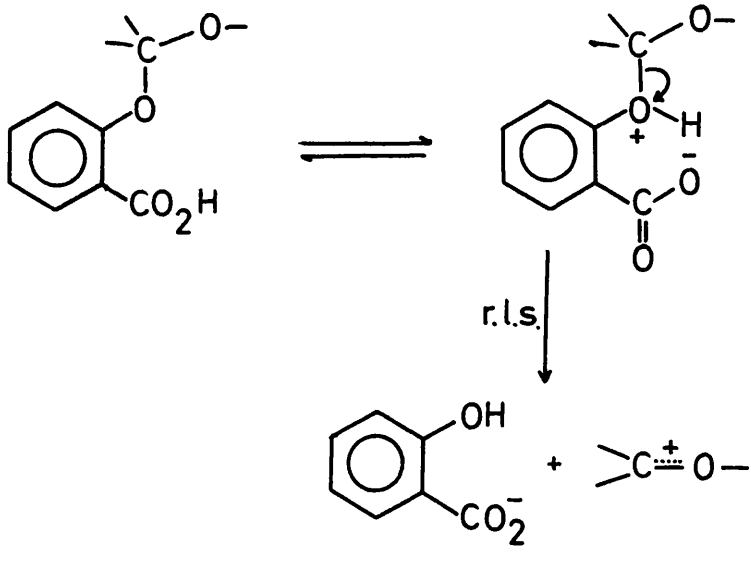
Such intra-molecular catalysis is shown by the enhanced rates of hydrolysis over suitable model compounds ($\sim 10^2 - 10^4$), and sigmoid pH-rate profiles, showing a term in the rate law dependent only on the undissociated acid or its kinetic equivalent, a proton and the dissociated carboxyl group. The possibility that for 2-methoxy-

methoxy benzoic acid the rate enhancement was due to the carboxy group providing intra-molecular nucleophilic catalysis was excluded by showing that the expected intermediates from such action were not formed.[164] The alternative mechanisms, in general for 2-carboxy-phenyl derivatives, are:

1) intra-molecular general acid catalysis by the unionised carboxyl group:



2) a field or electrostatic effect by the ionised carboxyl group.



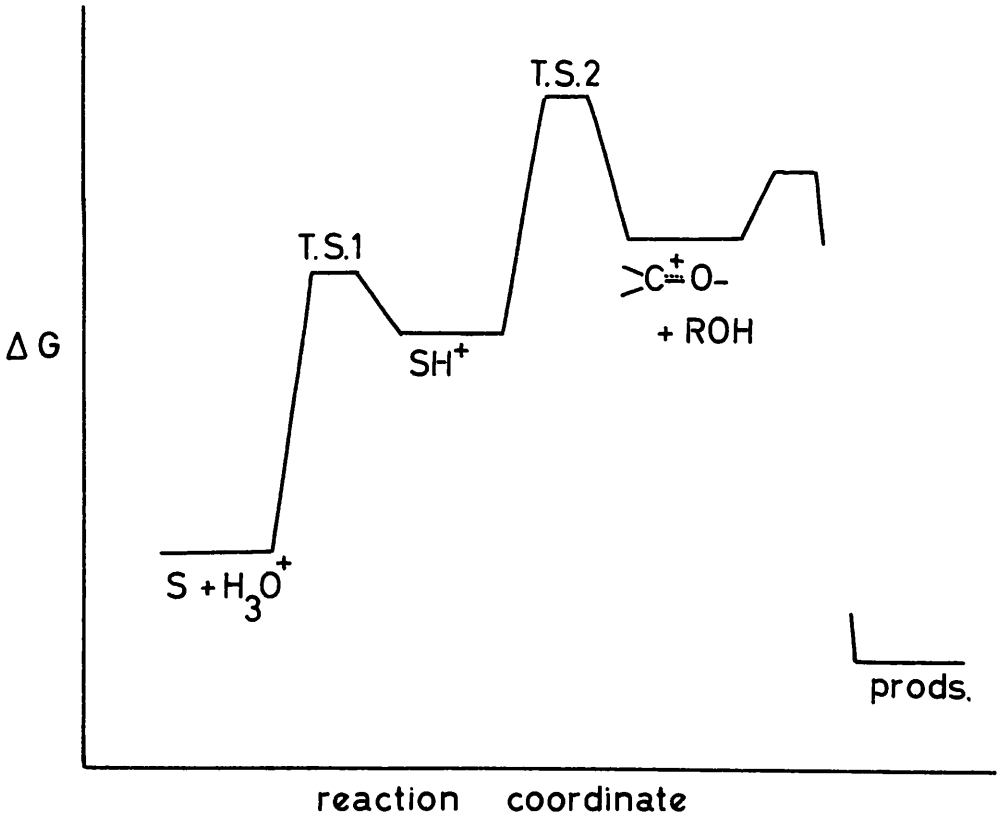
At the present time this problem is not resolved, although the results of system exhibiting both inter- and intra-molecular general acid catalysis, which may clarify the situation, are reported here.

Intra-molecular carboxyl group catalysis in acetal[167,165] and glucoside[165] hydrolysis has been reviewed, and the obvious geometrical disposition of the catalytic groups and reactive centre emphasised.[165] The effect of substituents, interpretable in terms of electronic and steric effects, in such reactions has also been reported.[165,168,169]

The history of the search for inter-molecular general acid catalysis in acetal hydrolysis has been summarised.[170]

Mechanistic specific acid catalysis implies reversible proton transfer, whereas for general acid catalysis the transfer of the proton is rate limiting, concerted with other molecular motions. For the latter mechanism proton transfer may well not be reversible. As can be seen from the following free-energy versus reaction co-ordinate diagram for the specific acid catalysed hydrolysis of acetals, in order to make proton transfer rate limiting it is necessary to make transition-state (T.S.) T.S.1 of greater free energy than T.S.2. If initial state energies are constant, this may be done by lowering T.S.2[171]

or raising T.S.1 or both.



Assuming that the free energy is a better measure of potential energy effects than the enthalpy,[67] the reaction co-ordinate can be used as a guide to the amount of bond fission, and that the T.S. free-energy is related to the intermediates,[78] several deductions may be made. The diagram is 2-dimensional and the overlap of the potential energy surface of SH^+ with that of S and H_3O^+ relates to

vibration of the OH bond, whereas with that of the carbonium it relates to the C-O bond. T.S.2 may be lowered by having a more stable carbonium ion or a better leaving group, this will presumably result in there being less carbon-oxygen bond fission in the T.S., which occurs earlier along the reaction co-ordinate. T.S.1 will be raised if the acetal oxygen is made less basic, which will result in a T.S. occurring later along the reaction co-ordinate, and a concomitant greater degree of proton transfer to the acetal oxygen. If the transition states then merge, the mechanism becomes a concerted $A_{SE}2$ displacement on oxygen.

A quantitative estimate of whether the reaction may be general acid catalysed has been formulated by Bunton and De Wolfe[172] for the hydrolysis of ortho-esters.

$$S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ + H_2O$$

$$SH^+ \xrightarrow{k_2} \text{products}$$

Steady-state treatment of the conjugate acid gives a second order rate constant.

$$k_H = \frac{k_1 k_2}{k_{-1}(H_2O) + k_2}$$

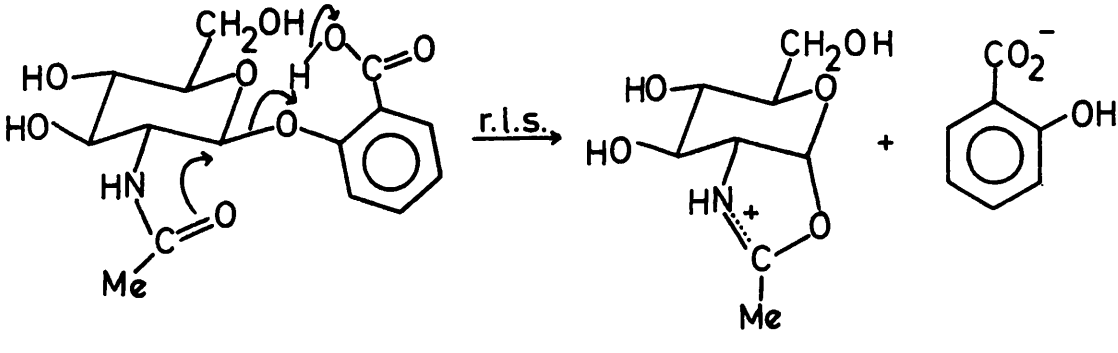
Making estimates of the pKa of the conjugate acid of the substrate and knowing the second order rate constant it is possible to evaluate whether $k_2 \ll k_{-1}(H_2O)$ - the rate of proton transfer from a very strong acid to water - i.e. the mechanism is A-1, or of comparable magnitude and hence the mechanism is possibly concerted $A_{SE}2$. Replacing the acetal hydrogen by an alkoxy group decreases the basicity and increases the stability of the intermediate carbonium ion, resulting in general acid catalysis in ortho-ester hydrolysis.

Capon and Anderson found buffer catalysis for the hydrolysis of benzaldehyde methyl phenyl acetal in water,[173] these authors emphasise the importance of having a stable carbonium ion intermediate. Fife and Jao[160] have reported that the hydrolysis of 2-p-nitrophenoxy and 2-p-chlorophenoxy (but not 2-p-methoxyphenoxy) tetrahydropyran show weak general acid catalysis in formate buffers in 50% aqueous dioxan, great emphasis is placed on the basicity of the acetal oxygen and protonation being made more difficult. Of course a phenol with a lower pKa is also a better leaving group, and, as seen earlier, this also favours an $A_{SE}2$ mechanism. General acid catalysis has also been reported in benzophenone ketal hydrolysis,[44] but the experimental evidence is ambiguous.

Several mechanistic parameters for an intermolecular general acid catalysed hydrolysis of an acetal are reported in this thesis.

IV Bifunctional Catalysis

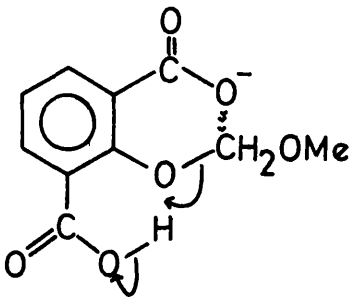
The rate constant for the spontaneous hydrolysis of o-carboxyphenyl-2-acetamido-2-deoxy-β-D-glucopyranoside is 7 times greater at 78°, and 16 times greater at 30°, than that for o-carboxyphenyl-β-D-glucopyranoside.[166] The σ^* constants for the acetamido and hydroxyl groups are similar, and Bruice and Piszkiewicz suggested the following cencerted nucleophilic general-acid mechanism represented the reaction path.[166] However, the specific acid catalysed reactions of the acetamido glucosides are generally 2-3 times faster than the corresponding glucoside at 78°, which if this were also true for the general acid catalysed reaction gives a rate difference of only 2-3 for the di-substituted compound.



The authors 'explain' why the catalytic effects are not additive in terms of the orientation requirements of the two catalytic groups which cause a less favourable entropy of activation (a difference of about 6 e.u.).

A rationale for this and a similar phenomenon found in this work is given in the discussion section.

Bruice and Dunn[168] have attempted unsuccessfully to find bifunctional catalysis in the hydrolysis of 2-methoxy-methoxy 3-carboxy benzoic acid, of the type shown below.



The small enhancement found was attributed to steric and electronic effects. The authors conclude that since participation is absent in this model compound 'it is unlikely for the carboxyl anion to electrostatically participate in the hydrolytic mechanism of lysozyme'.

In a better model compound, nucleophilic participation by a neighbouring carboxyl group is reported here for the hydrolysis of an acetal.

The Neighbouring Aliphatic Hydroxyl Group in Ester Hydrolysis.

There have been numerous reports of the rate accelerating effects of neighbouring hydroxyl groups, both phenolic and alcoholic, in ester hydrolysis.[98] The hydroxyl function is a potential nucleophile, general acid and general base. Their nucleophilic reactivity has been well demonstrated in ester hydrolysis; δ-hydroxy valero, γ-hydroxy butyro[126] and o-hydroxy phenyl acetic acid esters[133] show extremely large rate enhancements over suitable model compounds. This type of activity will not be discussed further.

Esters containing suitably disposed neighbouring phenolic groups often shown enhanced rates of hydrolysis, even when nucleophilic participation is unlikely. The large rate of the water reaction of mono-anionic phenyl salicylates has been interpreted as being due to an intramolecular general base reaction.[134,135] Bender and Killian[136] have suggested that bifunctional catalysis is operative in the hydrolysis of 2,6-dihydroxy methyl benzoate, since the latter shows a bell-shaped pH-rate profile and a rate enhancement of 10^5 - 10^6 relative to the 2,6-dimethyl derivative. The authors suggested two mechanisms, either concerted general-acid general base

catalysis or a hydroxide in catalysed reaction aided by bifunctional general acid catalysis. Since the rate of hydrolysis is slower than the corresponding derivative with only one catalytic species present a better model compound is required.

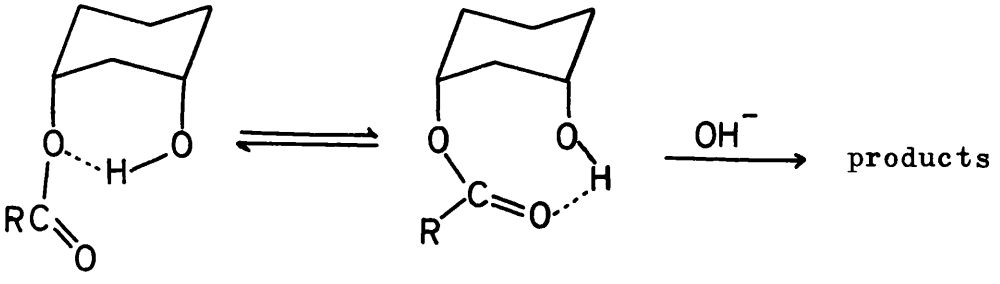
Menger and Smith[148] have suggested that the phenolic hydroxyl group acts as a general acid in the aminolysis of phenyl salicylate in acetonitrile.

Henbest and Lovell[137] found that in a series of cholestane and coprostane 3-acetoxy 5-hydroxy steroids, the axial esters solvolyse faster than the equatorial esters, if the ester bond were cis to the hydroxyl group (aqueous methanol - K_2CO_3 65 hr. 20°C). The percentage of hydrolysis given by these authors corresponds to rate enhancements of 6-10. Similar acceleration of the base catalysed methanolysis of other cyclohexane type 1,3-diol monoacetates has been reported by Kupchan and co-workers. The same author has reported rate enhancements of up to 4000, over suitable standards, for the methanolysis of some 1,3-diaxial hydroxy acetates in triethylamine buffers in 10% chloroform-methanol. Also in the cyclohexane series, neighbouring group participation has been observed in the hydrolysis of a 1,4-equatorial axial disposition of the hydroxyl group, this isomer hydrolyses 10^4 times faster than its epimer.[140] Bruice and Fife

have reported a rate enhancement of 37 for cis-ethyl 2-hydroxy cyclopentane carboxylate over the unsubstituted compound,[141] but in the solvent systems and conditions used by the author these results were not reproducible.

With regard to the mechanism of the above facilitation, Henbest and Lovell showed from I.R. studies that the hydroxyl group was intra-molecularly hydrogen bonded to the alcoholic ester oxygen in cyclohexane 1,3-diol monoacetates, and suggested that this was the reason for the favourable rates of hydrolysis. Johnson and co-workers[142] have interpreted this as meaning electrophilic catalysis of the breakdown of the tetrahedral intermediate, which is probably not the rate determining step in water, so therefore could not affect the rate of hydrolysis. Rate enhancements must be ascribed to the lowering of the free energy of activation of the rate determining steps, and not the consequent stages along the reaction co-ordinate. However, there is no evidence demanding the presence of a tetrahedral intermediate in aprotic solvents, and the mechanism under such conditions could be a direct displacement.[143] Similarly, Jencks and Gilchrist,[146] in a definitive paper, have shown the conditions under which breakdown of the tetrahedral intermediate, if formed, is rate determining; generally this is for attacking nucleo-

philes of much lower pKa than the leaving group. Johnson[142] also pointed out that the kinetically important species may be that with hydrogen bonding to the carbonyl group, which could lead to stabilisation of the tetrahedral intermediate and presumably the transition state to it.

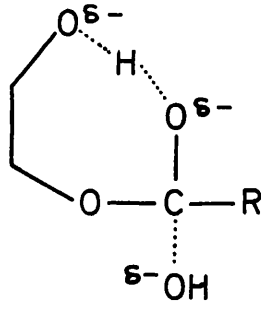


Of course, hydrogen bonding studies carried out in organic solvents bear no relevance to the initial state in aqueous solution. All they show is that certain overlap of potential energy curves is possible without very large changes in geometry.

Kupchan also favours the hydroxyl group acting as a general acid or electrophilic catalyst either to the more basic carbonyl oxygen or to the alcoholic oxygen atom.[139,138]

In an attempt to clarify the situation, Bruice and Fife[144] examined the infra-red spectra and the rates of

alkaline hydrolysis of a number of cyclopentane and norbornane acetates and diol monoacetates. Hydrogen bonding to the carbonyl oxygen in 1,2-diol monoesters leads to a 7 membered ring, and in the 1,3-disposition an 8 membered ring. With bonding to the alcoholic oxygen the former class produce a 5, and the latter a 6 membered ring. Intra-molecular hydrogen bonding, measured in carbon tetrachloride, to either of the oxygen atoms was found to be associated with enhanced rates of hydrolysis, which were greater than could be explained on the basis of inductive effects. In a related paper,[145] the authors concluded that facilitation is greatest for the more difficulty hydrolysable groups and is not at all important in the general base catalysed hydrolysis of esters. Although Bruice and Fife[144] consider that the hydroxyl group may change the microscopic medium surrounding the ester bond, they favour "internal solvation" as the reason for the enhanced rates of hydrolysis. The hydroxyl hydrogen is considered to solvate the incipient tetrahedral intermediate, and in so doing release solvent molecules from fulfilling this task.



The authors consider that this is a qualitative explanation of their observed compensation in the enthalpy and entropy of activation associated with hydroxyl group facilitation. It is of interest to note that their evidence for this compensation is a linear plot of $T\Delta\Delta S^{\ddagger}$ versus $\Delta\Delta H^{\ddagger}$. If one plots $\Delta H^{\ddagger}$ versus $\Delta S^{\ddagger}$ a straight line plot is not obtained, but, more important, in the same paper is a given plot of log k versus $^{1}/_{T}$, for all the compounds studied, which does not have a common point of intersection. The relationship is therefore a false one.[68] In my opinion this mechanism is no different in kind from that suggested by Johnston,[142] except that the 'release of water molecules' is considered to be the cause of the lower free energy of activation. Presumably, only when the proton is completely transferred from the alcoholic hydroxyl group to another site is the mechanism true

general acid catalysis.

It is of interest to note that the rates of hydrolysis of the model compounds studied by Bruice and Fife[144] do not give as large rate enhancements as the methanolysis reactions reported by Kupchan.[138,139] This is in spite of the fact that the systems studied by the latter involve 8 membered rings when hydrogen bonding to the carbonyl oxygen is considered to contribute to the reaction mechanism.

In the work reported here a study was made of the rates of hydrolysis of some β-hydroxy esters, in which it was possible for a 6 membered ring to be formed between the hydroxyl group and the carbonyl ester oxygen. However, this, presumably, more stable arrangement, leads to no large rate enhancements; and, indeed, isomers in which this type of interaction was geometrically impossible hydrolysed, under certain conditions, slightly faster than the former type. The results tend to indicate that 'solvent sorting' (see later discussion) in binary solvent systems is responsible for some of the modest rate increases observed, compared with the unsubstituted compound. Similar "negative" results were obtained in the methanolysis reactions studied, and it would seem improbable that the large rate enhancements observed by Kupchan[138,139] is due to some type of electrophilic catalysis in the formation of the tetrahedral intermediate.

Aqueous Medium Effects

A complete understanding of a reaction mechanism in aqueous solution would necessarily involve knowledge of the interaction forces between the reactants, in their initial state and along the reaction co-ordinate towards the transition state, and the solvent molecules; and how in turn these forces contribute to the free-energy barrier of activation. The first step in gaining such knowledge would be an understanding of the pure liquid phase, or more specifically the structure of water. Theoretical treatments of liquids have generally been approached from the stand-point of dense gases or imperfect solids, and so far have not been very successful.[51] The emphasis has therefore been on empirical treatments, whilst at the same time appreciating that macroscopically determined properties are not necessarily related to the microscopic level.

Normally, the interactions between the solvent molecules near the solute will be different from those in the bulk solvent and this will lead to a structural arrangement of the solvent molecules near the solute which is different from the main pure phase. The whole volume of solvent molecules whose structure is so affected in known as the cybotactic region. For many chemical

reactions, it may be this local environment created by the solvent molecules around the initial state and transition state which determines the course of the reaction. The more different the cybotactic region is from the bulk solvent, the less reliable will be the predictions made on the basis of the properties of the bulk solvent.

Most of the models proposed for the structure of liquid water may be discussed in terms of the extremum models - continuum and mixture. The subject has recently been reviewed by Wicke.[52] The continuum models regard liquid water as a homogeneous, irregular, and extensively hydrogen bonded system.[53] The mixture models agree that there are discrete molecular varieties ranging from free non-hydrogen bonded entities to complexes of many molecules organised into "clusters" or "icebergs". Because of the single di-electric relaxation time of water and other physical properties, Frank and Wen[54] proposed their "flickering clusters" hypothesis, in which the polymeric entities were extremely short lived. Némethy and Scheraga [55] used this model to calculate the thermodynamic properties of liquid water to within reasonable agreement.

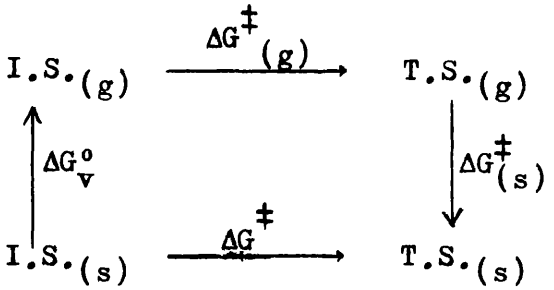
It should be emphasised that these are <u>models</u>, and

the best one can do at the present time is to see if the models specified properties can account for the phenomenon under discussion. Sometimes they are not even internally consistent, and, as always, it is extremely difficult to demonstrate a clear "cause and effect" relationship between the observed phenomenon and, for example, changes in water structure.

The theorectical analysis of solvation must allow for solute-solvent, solvent-solvent and, possibly, solute-solute interactions, and modifications of one by the other. Because of their reasonable success with liquid water, Scheraga and co-workers have extended their method to aqueous solutions of non-polar and ionic solutes[56] (see discussion section on intra-molecular reactions). Various workers emphasise the different interactions. Some consider that water-water interaction is the predominant factor, the water molecules arranging themselves in clathrate - like segments of the solvation shell so as to optimize their mutual hydrogen-bonding, the solute then "rattles" around inside.[54] Grunwald[57a] favours the dominance of solute-solvent interaction, with the water molecules packing efficiently round the solute with a concomitant deformation of their normal hydrogen-bonded structure, London

dispersion forces compensating for the loss of structure.[57b] Qualitatively, these interactions are usually referred to as "structure-making" and "structure-breaking" effects, depending on whether a solute creates more or less order in the solvent structure. Perhaps one could be content with the qualitative rationalisation, that restriction of motion, causing decreases in entropy, must arise from favourable interaction energies, and therefore decreased enthalpies, as occurs with structure making. Although reasonable on the surface it does not justify a linear relationship between the enthalpy and entropy, nor does it give any indication of the relative magnitude of the changes in the two quantities. Nevertheless, it is possible for the increased order through extra hydrogen-bonding in water under structure making conditions to produce no net free-energy change.

Solute-solvent interactions are important in determining the correlations found in linear free-energy relationships (see discussion on the latter), and mechanistic interpretations, as may be illustrated by the following Born-Haber type thermodynamic cycle



where I.S. and T.S. represent the initial and the transition states respectively, and s and g are solvated and gaseous species respectively. $\Delta G^{\ddagger}$ the free-energy of activation in solution differs from that in the gas-phase $\Delta G^{\ddagger}_{(g)}$, by the sum of $\Delta G^{\ddagger}_{(s)}$, the free-energy of solution of the transition state, and ΔG^{o}_{v}, the free-energy of vapourisation of the initial state from the solvent. If one was studying the changes in rate in a series of reactions, these changes in the free-energy of activation would be given by:

$$d\Delta G^{\ddagger} = d\Delta G^{\ddagger}_{(g)} + d\Delta G^{\ddagger}_{(s)} + d\Delta G^{o}_{v}$$

It is conceivable that these free-energy changes will not vary monotonically in a series. Classically observed solvent effects on reaction rates were interpreted in terms of the electrostatic interactions between the solute and solvent molecules in the initial and transition states.[58] Although the predictions using this concept are often qualitatively correct, their quantitative

inaccuracy was shown by Winstein and Fainberg,[59] who demonstrated that the change in rate of solvolysis of t-butyl chloride with a solvent change from methanol or ethanol to water was due substantially to the change in the free-energy of solution of the initial state.

It has been suggested[60] that the break-down of the initial state solvation shell is responsible for the negative values of the heat capacity changes of activation in the solvolysis of t-butyl chloride. Arnett[61] has made several extensive studies of solvent effects in organic chemistry, and on the basis of measurements on the partial molal heats of solution of salts in mixtures of solvents concluded that the importance of the initial state is due to the effect of the solute on the local structure of the solvent.[62]

Since the rates of proton transfer to carbon bases in D.M.S.O. were found to be greater than those, with the same equilibrium constant, in methanol,[63] solvent re-organisation was considered to contribute to the free-energy of activation.

The difference in strength between acetic acid and polyhaloacetic acids is due primarily to a more positive entropy of ionisation for the latter.[120] It appears that either the undissociated acid must be a

powerful structure maker, or the conjugate base is a strong structure breaker. Rochester and Rossall[153] have emphasised the effect of solute-solvent interactions in determining the acidity of phenols.

It is as well not to forget the solvent when interpreting reaction mechanism parameters.

Linear Free Energy Relationships

In modern kinetic studies attempts to give an insight into the problem are often made by a systematic variation of the reactant structure or reaction conditions, while keeping other variables constant. The data are then expressed by one of the numerous empirical equations, for example, the Brönsted relationship[64] relates ~~equates~~ the rate constant of an acid catalysed reaction to the dissociation constant of the acid:

$$k_a = G K_a^{\alpha} \qquad \log k_a = \log G_A + \alpha \log K_a$$

neglecting statistical factors, G is a constant for the reaction and α is the proportionality factor. An analogous equation may be written for base catalysed reactions. A correlation between equilibria and rate data is at first sight not expected since the former are independent and the latter completely dependent upon the reaction path between reactants and products.

Similarly the Hammett relationship[65] equates the logarithm of the rate or equilibrium constant of aromatic side-chain reactions to structural parameters

$$\log k/k_o = \rho \sigma$$

where k and ko arethe rate constants for substituted and

parent compound respectively, σ is a constant depending on the substituent and ρ is the proportionality factor. "The meaning attached to the magnitude and sign of rho depends upon the interpretation given to the sigma values."[66] The correlation merely yields the reaction parameter as a proportionality factor, whose value depends upon the response of a particular reaction series to substituent changes relative to that of the standard reaction. Qualitative concepts of reacting systems usually depend on ones intuitive ideas of a group's electronic and electrostatic effects, which in turn permits rho to be thought of as the susceptibility of a reaction to these effects.

All linear free-energy relationships (L.F.E.R.) are based on the criterion that the free-energy changes produced by a systematic variation of the reactant structure or conditions of a particular reaction are linearly related to the free-energy change that those variations bring about in another reaction. It is only recently that the underlying concepts of L.F.E.R. and the implications that arose therefrom have been critically analysed.[66,67,68]

The overall success of these relationships for comparing structural changes with reactivity is

unquestionable. Such correlations provide invaluable means for the storage and prediction of rate and equilibrium data. However, it has long been recognised that our ideas on structure-reactivity are concerned with the potential-energies of reacting systems[69] whether this be the amount of charge delocalised in the transition state or the position of a proton in the latter state. Real systems, however, are governed by both potential and kinetic energies, and hence it may seem surprising that even qualitative predictions may be made on chemical reactivity. With few exceptions,[70] it is generally accepted that free-energy changes are the most practical criterion of chemical reactivity. Common mechanistic interpretations in organic chemistry really refer to relative potential energy changes at 0°K in the gas phase, the implications are that free-energy changes measured in solution near room temperature are a good guide to these changes. This extraordinary conclusion has some justification for large changes in free-energy.[67]

It is important to remember that relative rates of reaction are governed by the <u>changes</u> in the free-energy differences between the ground state and the transition state, those factors which change the free-energies of

these states by the same amount make no contribution to the change in rate.

The problem of why should L.F.E.R. exist may be approached from two directions. Firstly, consider the structural effects on heat capacity changes[71] in a series of chemical reactions. The heat capacity change for a process affects the free-energy change at temperatures above absolute zero through the following equation:

$$\Delta G^{\circ} = \Delta H^{\circ} + \int_{0}^{T} \Delta C_p dT - T\int_{0}^{T} \Delta C_p d\ln T$$

where ΔH° = enthalpy change at 0°K and the two integral terms represent the excess enthalpy and excess entropy at the temperature T. The change in the free-energy change brought about by some variable, say a substituent, is then a function of the heat capacity changes as follows:

$$d\Delta G^{\circ} = d\Delta H^{\circ} + \int_{0}^{T} d\Delta C_p dT - T\int_{0}^{T} d\Delta C_p d\ln T$$

A L.F.E.R. would therefore require the heat capacity changes in a series of reactions to be either constant, negligible or vary systematically. Therefore, small but erratic changes in the heat capacities of solution

within a series of similar compounds in aqueous solution could produce an erroneous estimate of their relative potential energies referred back to 0°K. It is often considered[72] that heat capacity changes in chemical reactions are negligible or constant. There is a lack of experimental evidence to support this claim, which has often been criticized.[67] Lately, however, measurements of the heat capacity of organic compounds in solution have been reported,[73] and the simplifying assumption that the heat capacity differences within a series of similar compounds in solution are constant or negligible disproved.[73] The authors concluded that "Although it is not uncommon to find even small rate or equilibrium constant differences interpreted in quite considerable detail in terms of potential energy differences, the large heat capacities found in this paper serve as a warning that in water or highly aqueous media, there may be incursion of heat capacity effects from several sources not commonly recognised."

The second approach to L.F.E.R. is to realise that the relative standard free-energy change is a composite quantity, and factored thermodynamically into relative enthalpy and entropy changes. The thermodynamic implications of L.F.E.R. has been summarised in the

excellent review by Wells.[66] Briefly, his logic is set out below:

The variations of the standard free-energy change with a variable x may be expressed by

$$d\Delta G = RT\ d \log k = \left(\frac{\partial \Delta G}{\partial x}\right)_T dx$$

with all other variables held constant. For a finite change in x from some arbitary standard value x_o to x_i, the free-energy change will be given by

$$\Delta G_i - \Delta G_o = \left(\frac{\partial \Delta G}{\partial x}\right)_T (x_i - x_o)$$

which is a linear relationship between log k and x provided that $(\partial \Delta G/\partial x)_T = g_x^o$ remains constant within the range of variation of x. g_x^o is a measure of the susceptibility of a particular reaction to changes in x, another reaction would have a susceptibility constant, say g_x^A. To obtain a correlation between these two susceptibilities the following equality must hold

$$\gamma = \frac{g_x^o\ T_A}{g^A_x\ T_o}$$

γ will be constant provided the <u>ratio</u> of g_x^o/g_x^A is constant, they may vary individually providing there is

parallel variation in these terms.

γ is equivalent to, say, the Hammett rho value or the Brönsted exponent α or β.

Since $\Delta G = \Delta H - T\Delta S$

$$\left(\frac{\partial \Delta G}{\partial x}\right)_T = \left(\frac{\partial \Delta H}{\partial x}\right)_T - T\left(\frac{\partial \Delta S}{\partial x}\right)_T$$

This type of equation was probably first appreciated by Winstein and Fainberg in 1957.[59] It would be expected that the two derivatives in the right hand side of the equation would be completely different functions of the variable x in a reaction series. Therefore, for a L.F.E.R. to hold, three broad categories arise:

1) <u>isoentropic series</u> $(\partial \Delta S/\partial x)_T = 0$

An example of an approximately constant entropy of activation is the hydrolysis of <u>m</u>-and <u>p</u>-substituted benzoates. Yet there is a linear relationship between log k/k_o for the latter reaction and log k/k_o for the ionisation of substituted benzoic acids (i.e. sigma values), in which entropy changes are variable.

2) <u>isoenthalpic series</u> $(\partial \Delta H/\partial x)_T = 0$

For this series of reactions, the susceptibility constant would be temperature invariant.

3) isokinetic series

The enthalpy and entropy changes are linearly related.

The experimental proof of this latter category is particularly susceptible to error and false correlations are ubiquitous.[68,95]

Ritchie and Sager[67] have found no reactions simultaneously obeying the Hammett equation and the iso-kinetic relationship, which effectively removes any worry about variations in the magnitude and sign of rho with temperature earlier suggested by Leffler.[74]

A popular explanation of iso-kinetic relationships or the compensation law[68] is in terms of solute-solvent interactions, a decrease in enthalpy due to solvent bonding is accompanied by a restriction of solvent molecules and a concomitant decrease in entropy.[75] Similar arguments, in terms of the energetics of cavity formation, were presented earlier.[76] But since several reactions which are correlated by L.F.E.R. show real variations in their entropies of activation, and furthermore do not simultaneously obey the isokinetic relationship, one is left with the problem of how potential-energy models are able to correlate these cases where the kinetic energies evidently must be considered.

Hepler[77] has taken the view that the energies may be separated into internal and external contributions, and, furthermore, the external energies (solvation effects etc.) contribute in such a way as to cancel in the ($\Delta H - T\Delta S$) terms, leaving the free-energy entirely determined by internal energies, which are probably isoentropic. But as mentioned earlier, it is difficult to justify a linear relationship between the enthalpy and entropy, even in the case of just considering the external energies.

The problem has been treated statistical mechanically by Ritchie and Sager,[67] and all of the treatments devised by these authors lead to a temperature dependent relationship between the changes in the enthalpy and entropy, thus the isokinetic temperature is not constant for a reaction series. They concluded: "Contributions of the kinetic energies of the systems to the enthalpy and to the entropy, show a temperature dependent relationship, and lead to at least an appreciable cancellation in $\Delta H - T\Delta S$ at all temperatures". The free-energy change of a system was also found to be a better measure of potential energy changes than the enthalpy change.

The solvent could conceivably modify the suscepti-

bility constant either directly, or through the modification of the substituent. Tightly bound or oriented solvent molecules could even be considered as part of the reactant or substituent group, and hence completely modify its properties. Even loosely bound solvent molecules could exert an influence on the thermodynamic functions, because of the restriction in their vibrational motions. Such specific forces as hydrogen-bonding could act in a selective manner so as to convert the particular group involved into an entirely new entity, and such specific forces would be expected to destroy linear relationships. Especially in a binary mixture of solvents such specific interactions between solute and solvent could conceivably cause particular solutes in a series of reactions to have completely different local environments. Such interactions have been found in some of the work reported here.

The Brönsted Relationship

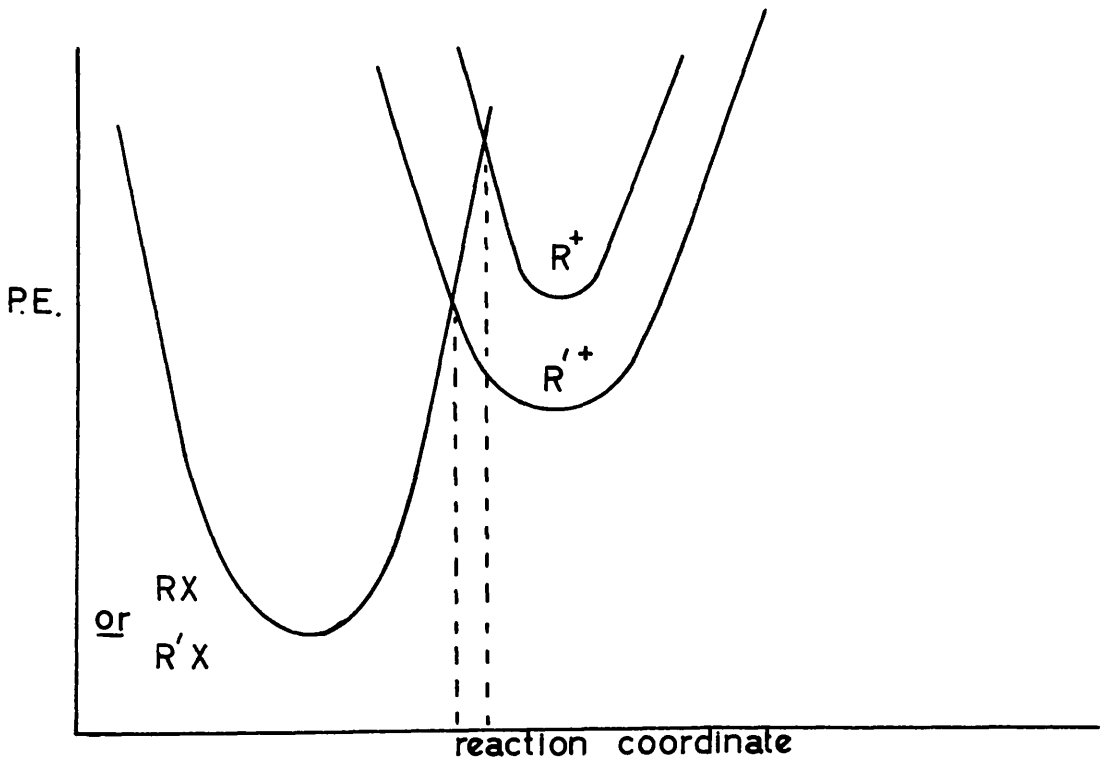
It is worth considering, in the light of the previous discussion, the meaning attached to the Brönsted exponent α, and a related topic the Hammond postulate.

Hammond[78] originally stated his hypothesis as follows

"If two states, as for example, a transition state and an unstable intermediate, occur consecutively during a reaction process and have nearly the same energy content, their interconversion will involve a small re-organisation of the molecular structure".

This postulate gave rise to the vogue[79] of interpreting reaction mechanisms as having more or less bond breaking in the transition state either on the absolute scale or relative to some standard. Similarly, along the reaction co-ordinate of the transfer of a proton from one basic site to another, the most unfavourable energetic configuration, the transition state, is regarded as that corresponding to the proton being nearest the weakest base. Both of these interpretations are, of course, really potential energy effects, and the problem again arises of how free-energy changes are a guide to these terms. Hammond himself[78] pointed this out, and mentions the expected loss of translational entropy and electro-restriction of solvent molecules on bringing two ions together in the transition state. When the structure of a reactant is changed and the transition state, which describes <u>both</u> the energy and geometrical configuration, is then assumed to occur earlier along the reaction co-ordinate for the faster

and thermodynamically more favoured reaction, this implies that the shape of the potential energy curves does not alter greatly with variation of the structure of the reactant. For example, in the unimolecular decomposition of R-X to form the R^+ carbonium ion, if R^+ was to be made more stable the transition state would occur with less R-X bond fission. This may be shown simply by the following potential energy curves, assuming that RX and R'X (the latter producing the more stable carbonium-ion) have the same initial state energies, and, furthermore, the same force restricting constant (the same slopes of their Morse curves).



By lowering the energy of R^+, the point of intersection of the P.E. curves is lowered and moved to the left i.e. the T.S. occurs with less stretching of the R-X bond. These arguments assume that such factors as repulsion, solvation effects and diffusion contribute to the free-energy of activation the same amount in a reaction series. Presumably, the amount of solute-solvent interaction varies according to the position of the T.S. along the reaction co-ordinate. For example, a T.S. having more "carbonium-ion-like" character would be expected to require more solvation. If such interactions as these cancel in the $\Delta H - T\Delta S$ term, then the Hammond postulate may be meaningful for a series of closely related reactions at the same temperature.

Probably, a L.F.E.R. could be set up for the Hammond postulate; by measuring the rates of reactions and relating these to some arbitary standard reaction, one could presumably extract some "constant", which would no doubt be interpreted by some workers as a number representing an exact amount of bond fission. In actual fact, if such a relationship could be set up the "constant" would only be a proportionality factor and would measure the susceptibility of the reaction under investigation compared to the standard reaction. Its

meaning could only be elucidated if it was known exactly the factors which caused the changes of rate in the standard reaction.

Similarly, the Brönsted co-efficient α has been interpreted as the measure of proton transfer in a reaction,[72] or the bond order of the bond being formed.[118] It is sometimes quoted, for example, that an α value of 0·58 means that the proton is 58% transferred in the transition-state.[80] Gold has stated that it is improbable that the value of α is a quantitative measure of the degree of proton transfer,[81] other authors have similar views, especially in relation to isotope effects and transition-state geometry.[82,87] α is a measure of the susceptibility of the reaction to the strength of the catalysing acid and is equivalent to $\alpha = \left(\frac{\partial \Delta G^{\ddagger}}{\partial pKa}\right)_T$

A low value of α implies that the reaction has a low sensitivity to the strength of the catalysing acid, the opposite is true for a high value of α. In aqueous solution, for $\alpha = 0$, the reaction is hardly dependent on the acidity of the proton donor, therefore this value probably originates from water or spontaneous hydrolysis, since the solvent is in such large excess of the other acidic species present in solution. For a reaction of this type, the proton is probably still very much on the

proton donor in the transition state. An α value of 1·0 implies kinetic specific acid catalysis, since the reaction has a large dependence on the acidity of the proton donor, the observed rate will be proportional only to the hydroxonium ion, catalysis by other acids is almost impossible to detect. Proton transfer is probably almost complete in reactions of this type, and so, in general, it is expected that the value of α will increase as this state is approached i.e. as the transition state goes from 'reactant-like' to 'product-like'.

The Brönsted co-efficients α and β are independent of the acid dissociation constant according to the integrated form of the equation. But this is only an approximation, and, indeed, a constant value of α, if it were just a measure of the position of the proton in the transition state, would contradict Hammond's postulate. The latter would predict the position of the proton to change as the pK difference between the donor and acceptor varied.

In aqueous solution, the rates of reactions with the solvated proton and the hydroxide ion have been studied for a great variety of compounds, including a large number of organic acids and bases. Comprehensive

tables[83,84] show that in most cases of the recombination of H_3O^+ and a base, or OH^- and an acid, the rates approach the limit of diffusion controlled reactions (10^{10} - 10^{11} M^{-1} sec^{-1}). They show certain influences of charge and steric requirements, solvent and hydrogen bonding effects which have been discussed thoroughly.[83,84] Proton transfer reactions which are diffusion controlled are necessarily independent of the pKa of the acids involved i.e. $\alpha = 0$, since the proton transfer step is not the rate limiting one. Since in aqueous solution H_3O^+ and OH^- are very strong acids and bases respectively, most of these cases of proton transfer are associated with an appreciable gain in free-energy i.e. $pK_{H_3O^+} \ll pK_{HX}$ or $pK_{H_2O} \gg pK_{HX}$.

However, if this condition is not fulfilled, when, for example, the pKa of the acid formed in the reaction is a lot lower than that of H_3O^+ (e.g. in the protonation of an acetal) the reaction can no longer be diffusion controlled (although the reverse reaction may be) and usually gives rise to unit α values. Whereas, the rates of of proton transfer reactions in those acid-base systems which show small pK differences, between the donor and acceptor, will be dependent on this difference and will show intermediate values of α. The transition from

α = 0 to 1 has been calculated by Eigen[85] for idealised cases. Bell[86] and Eigen[85] have suggested that the value of α depends on the slopes of the two overlapping potential energy functions, provided there is no deviation from linearity within the area of intersection. However, the finite curvature of the potential energy functions will cause continuous variation of α with ΔpK (the pK difference between donor and acceptor), especially in the neighbourhood of the "bottom of the valley". L.F.E.R. are expected to exist in the middle of the transition region α = 0 to 1, where linearity is closely approximated. Deviations from the theoretical expected behaviour has been suggested by these authors to be due to a lack of parallelism in the P.E. curves.

Experimentally, several types of Brönsted plot, extending over wide ranges of pK differences between donor and acceptor, have been reported. Rose and Stuehr[88] have reported what they believe to be the closest experimental representation of the idealised curves proposed by Eigen, finding a very narrow region of curvature as α changes from 1 to 0. Ritchie and Uschold[63] have found that the Brönsted slopes undergo a change from 0 to 1 in a narrower range of strength of donor to acceptor in dimethyl sulphoxide than they do

in methanol. Proton transfers between A and B may be written as a series of equilibria:

$$B + HA \overset{k_1}{\rightleftharpoons} [AH \cdots\cdots B] \rightleftharpoons [A \cdots\cdots HB] \rightleftharpoons A + HB$$

The bracketed species represent hydrogen bonded complexes. If HA is a poor hydrogen bond donor and B is strongly solvated with the solvent, then this will cause k_1 to be small and hence there will be a levelling off below the diffusion limit even when there is a large difference in the pKa's. The authors considered that such solvent re-organisation contributed to the free energy of activation of proton transfer.

The non-linear behaviour of such relationships is not however general, there have been several reported cases where the data are correlated by a single linear Brönsted plot over an unusually wide range of pKa values.[89,90,91] For the muta-rotation of glucose,[94] and the hydration and dehydration reactions of several carbonyl compounds, Eigen[85,93] has suggested that the linearity is due to proton transfer being coupled with the making and breaking of other bonds in the molecule. The rates for the forward and reverse reaction do not reach the diffusion controlled limit even with very strong acids and bases. The step-wise nature of the transfer of protons rather than synchronous motion in

the cyclic transition-state has been emphasised.[92]

Pedersen suggested that for acids of the same pKa the strongest catalyst is the least positively charged species for $\alpha \geq 0{\cdot}5$, and the opposite held for $\alpha < 0{\cdot}5$, and this was substantiated by Brönsted plots for the decomposition of nitramide. However, there are several examples where, for a series of general acids, water, the hydronium ion, as well as neutral, negatively and positively charged species the data are correlated by a single linear Brönsted plot.[89,90] Thomas and Long[97] found that the plot for the general-acid catalysed detritiation of azulene -1-t and guaiazulene -3-t could not be correlated by a single linear relationship, although reasonably linear plots were obtained by grouping the acids according to charge type their relative effectiveness was not that predicted by pedersen. It is of interest that the α value of 0·54 for guaiazulene obtained by these authors is similar to that obtained by Kresge[89] (0·52) for trimethoxy benzene, although the substrate differ in basicity by about 5 pKa units. Factors other than basicity must therefore be involved if α is considered to be a measure of the extent of proton transfer.

Brönsted co-efficients greater than one and less

than zero have been reported for proton transfer from nitroalkanes,[119] the rates for the latter being more sensitive than equilibria to structural change. The view that the position of the transition state on the reaction co-ordinate may be deduced from the magnitude of the Brönsted co-efficient requires modification, at least for carbon acids.

Inter and Intra-Molecular Reactions

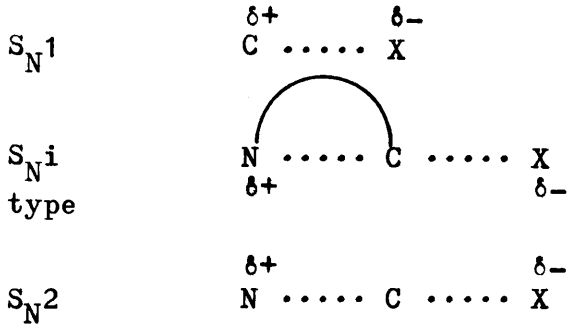
The bringing together of groups in an intra-molecular reaction may influence the reaction by simply lowering the free-energy of activation, and yet maintain the gross mechanistic features of the inter-molecular reaction. It may also favour a reaction mechanism which may not be observable in the bi-molecular case, and so change the mechanism of the reaction. Thirdly, the intra-molecular reaction may have a rate-limiting step which is not so in the inter-molecular system.

It is often stated[98,99,108] that the intra-molecular reaction is favoured over the bi-molecular process since the latter involves a considerable loss of translational entropy on bringing the reactants together in the transition state. Also, in some cases the catalytic groups of the intra-molecular reaction may be held in a more favourable orientation, and it is often anticipated[98,99] that this type of reaction will have a more favourable activation entropy. Koshland[121] and Jencks[1] have expressed reservations about rate facilitations of intramolecular reactions being due solely to favourable concentration and orientation effects, the latter author has, particularly, emphasised

the other factors which must be involved.[1]

A problem of comparing intra and inter-molecular reactions is that this often involves extrapolating rate data from one temperature to another in order to make free-energy comparisons under comparable conditions. The free-energy of activation is related to the heat capacity changes as seen in the previous discussion. If the extrapolation is a long one and the heat capacity of activation is large, appreciable errors can result. For example, a heat capacity term of 70 cal. $mole^{-1}$ $deg.^{-1}$ would give a rate difference of 10 for every 20° extrapolation. Similarly a $\Delta Cp^{\ddagger}$ value of -30 cal. $mole^{-1}$ $deg.^{-1}$ implies that the entropy of activation at 0°C and 50°C differ by 5 cal. $deg.^{-1}$ $mole^{-1}$. There is some evidence that the entropy of activation for solvolysis depends not only on the mechanism, but also on the structure of the substrate in the immediate vicinity of the reaction centre.[60,100]

It is of interest to compare the S_N1, S_N2 and the intra-molecular nucleophilic displacement mechanism of a solvolysis mechanism

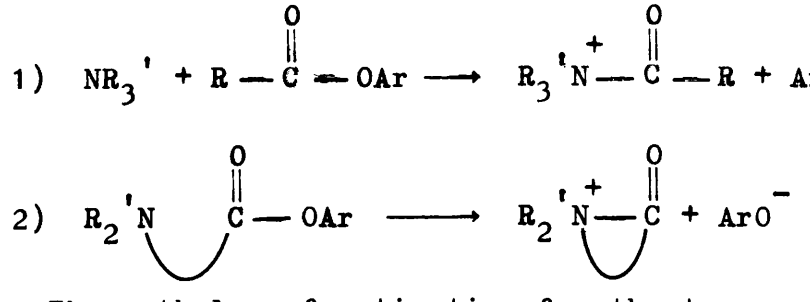


All of the mechanisms involve the partial fission of the C - X bond,[101] but the S_N2 and S_Ni pathways require some sort of interaction between the nucleophile and the substrate. As mentioned earlier, ideally, one should also consider the changes in solvent-solvent and solute-solvent interactions caused by the activation process which are usually supposed to be independent of the reaction mechanism. This assumption is probably not justified,[60,71,73] but their quantitative contribution to the overall activation process is still uncertain. For example, does extracting a water molecule from the structured initial state solvent <u>always</u> outweigh the degrees of freedom lost by an internal nucleophile on going to the transition state?

As an example of the traps, one may compare the solvolysis reactions of chlorohydrins,[102] for which the entropies of activation are temperature dependent.[60,61] At 100° $\Delta S^{\ddagger}$ for the S_Ni reaction is greater than that for

the S_N2 reaction, yet at 40° the converse is true. This is because $\Delta C_p^{\ddagger}$ in water is about 50 cal. deg.$^{-1}$ mole^{-1} greater for the S_Ni process than for the S_N2 solvolysis.[103]

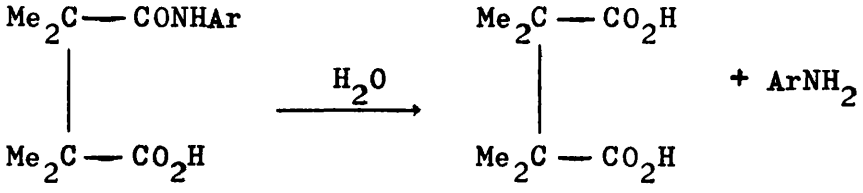
Even assuming that entropies of activation are a measure of the order in a system,[109] the arguments suggested at the beginning of this chapter are not borne out by the little experimental data available. Also, the comparison of uni and bi-molecular reactions has unit problems. Bruice and Benkovic[105] have studied the catalysis of aryl ester hydrolysis by the amino group, both intra and intermolecularly.

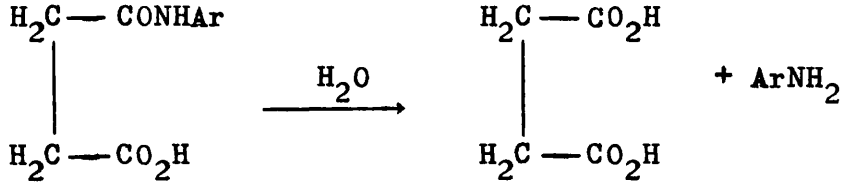


The enthalpy of activation for the two processes were almost identical, and the authors concluded that the difference in reaction rates was due to a favourable $\Delta S^{\ddagger}$ for the intra-molecular reaction (~15 e.u. at 25° for the formation of a five membered ring and ~13 e.u. for a six membered ring).

However, other examples have been reported in which

the enhanced rate of the intra-molecular reaction is due to a more favourable enthalpy of activation. Succinanilic acid is hydrolysed about 10^3 times slower than the tetra-methylated derivative.[106]





The 'geminal effect' showed up in a favourable enthalpy of activation difference of 6·6 Kcal. $mole^{-1}$, despite an <u>unfavourable</u> entropy activation difference of 7 e.u. This is opposite to that predicted,[99] using simple models of degrees of rotational freedom lost.

Also of relevance to this discussion is the finding of Rony[107] that the enhanced rate of muta-rotation of tetra-methyl glucose by 2-pyridone over that of phenol/pyridine is due to the differences in activation enthalpies. However, the result was obtained by assuming phenol/pyridine acts via an ion-pair, and since the mechanism of the reaction is cloudy, this may not be a true comparison.

The increased rate of lactonisation of 3, 6 - dimethyl 2-hydroxymethyl benzoic acid is accompanied by a decreased enthalpy and entropy of activation.[117] On a simple basis restriction of initial state freedom of rotation should tend to increase, not decrease, $\Delta S^{\ddagger}$. Differential solvation of the initial and transition states may cause this discrepancy. Steric acceleration of other 3, 6-substituents was considered to arise from exclusion of certain low energy initial state conformations, expressed by a diminished enthalpy of activation.

According to the transition-state theory, the free energy of activation measures the free-energy difference between the initial and transition states; the activation changes on the solvent as well as the solute must, of course, be considered. There are several examples, especially in equilibria systems, where the former appears to be a major factor, since in some cases the bringing together of species is accompanied by an overall positive entropy change.

According to Némethy and Scheraga[109] the contribution from the van der Waals interaction between two hydrocarbons molecules is only about 45% of the total free energy of formation of a hydrophobic bond in water at 25°C. The rest is provided by the change in solvent

structure, and despite the bringing together of two entities, the partial reversal of the solution process releases solvent molecules, and the dominance of this term makes an overall positive entropy of hydrophobic bond formation. Several solution processes are endothermic, but spontaneous, the free energy change is negative because of the positive entropy of transfer. Tobaco mosaic virus exists as sub-units in aqueous buffer at the ice-point, but as rods at 25°, the release of solvent molecules was considered to be responsible for the overall positive entropy change.[110] The aggregation of molecules into micelles is accompanied by a positive enthalpy and entropy change.[111] Even moderately polar solutes may associate spontaneously, this process is accompanied by a favourable enthalpy of activation.[1]

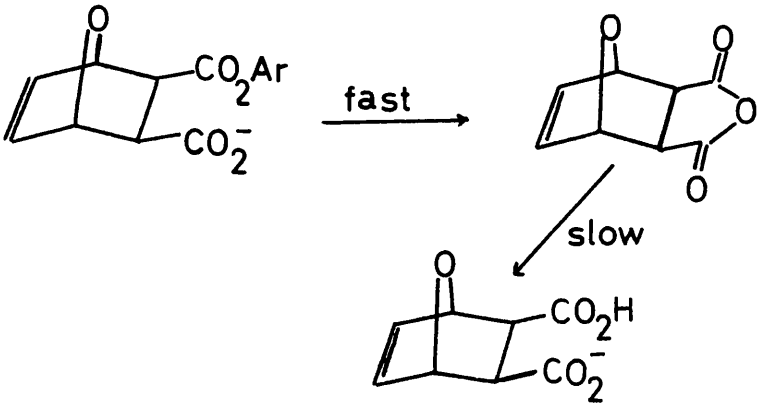
For an intra-molecular reaction, therefore, the reduction of the number of species present in the transition state is not necessarily expected to be reflected uniquely in the entropy of activation. Furthermore, even when the intra-molecular reaction has the same gross mechanistic features as its intermolecular counterpart, the former may not involve such a high enthalpic intermediate.

Consider an intra-molecular reaction as having an enhanced rate over the equivalent intermolecular reaction, simply because the reacting species are held together, and therefore do not have to encounter one another, and for no other reason. That is to say, that the free energy of activation is not different in any way for the two reactions apart from this collision frequency factor. By treating the diffusive motions of molecules like that of macroscopically spherical particles in a viscous fluid, and ignoring steric factors, the number of encounters between two solutes may be calculated,[112] and taking the viscosity as 0·01 poise, is 7×10^9 M^{-1} sec^{-1}. The theory was extended by Debye[113] for ionic solutes, and according to the latter's formula, the rate of reaction between two particles is a function of their diffusion coefficients and the reaction radius. The calculated value of the rate constant is rather insensitive to the choice of the reactive-reaction distance, and for reactions of oppositely charged univalent ions it is $10^{10} - 10^{11}$ M^{-1} sec^{-1}. For a standard state of 1 mole $litre^{-1}$ this corresponds to a free-energy of activation of 2·4-3·8 Kcal. $mole^{-1}$, and 4·0 Kcal. $mole^{-1}$ for the neutral species. This latter figure would correspond to a

maximum rate enhancement of 800. However, according to Noyes,[114] the rate of diffusion will contribute less than 1% to the overall reaction rate for rates slower than 10^7 M^{-1} sec^{-1} i.e. of reactions having free-energies of activation greater than 6 Kcal. $mole^{-1}$.

Undoubtedly this picture is extremely naive and further considerations are necessary, such as the free energy contributions of desolvation, dispersion forces, cavity formation and solvent interactions. Almost certainly, cases exist in which the functional group in an intramolecular system, just as in the intermolecular case, has to undergo a desolvation process before it is free to catalyse the reaction. An example may be provided in the work reported here. Calculations of the thermodynamic properties of aqueous solutions of non-polar solutes[109] and alkali-halide ions[115] show that the nearest neighbour solvent molecules in the first shell around the solute molecule contribute very much more than all other solvent molecules to the free energy of solvation of these substances, the same is therefore probably true of polar non-ionic solutes. Hence, unless two atoms approach each other to within a distance equal to the sum of their van der Waals radii plus the diameter of a water molecule, the solvent that is displaced is

assumed not to contribute to the free-energy.[116] It would appear therefore, that the removal of water molecules in a bi-molecular reaction cannot give much of an advantage to the intra-molecular reaction in those cases where the reacting atoms are solvated by at least one layer of solvent molecules. Jencks[1] has suggested that the rate of ring closure of the ester shown below

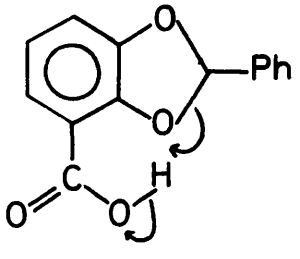


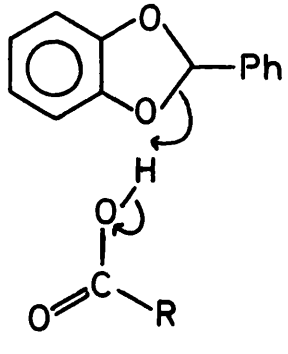
is facilitated since the carboxylate group is not solvated by water on the side which attacks the ester, and hence does not have to undergo a desolvation process.

The free-energy of cavity formation may be considerable in water, since it requires the separation of strongly interacting solvent molecules, but providing the water molecules have time to equilibrate, they may

form compensatory structure making effects, or hydrogen-bonds to the solute. There is the possibility of the uni and bi-molecular reactions having different solvent structures in the transition-state, especially when they form 'different' products.

Considering those cases of intra and inter-molecular reactions which utilize the same mechanism, what are the differences in the initial and transition state structures? A major factor may be that slightly different products are formed in the two cases. For example, in this work, inter and intra-molecular general acid catalysis have been detected in the hydrolysis of benzaldehyde catechol acetals.

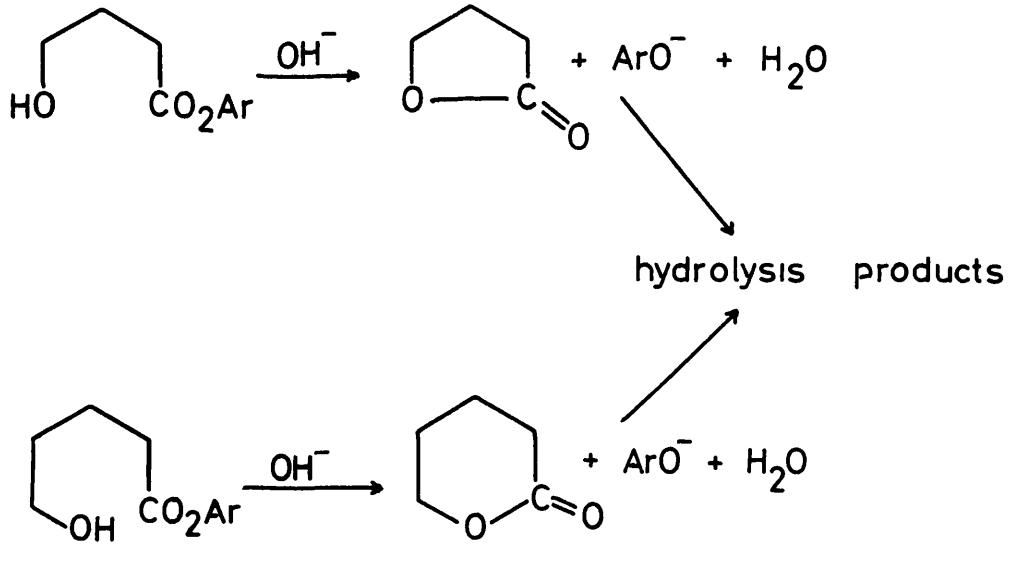




The first intermediate formed in the intra-molecular case, which hydrolyses faster, is a salicylic

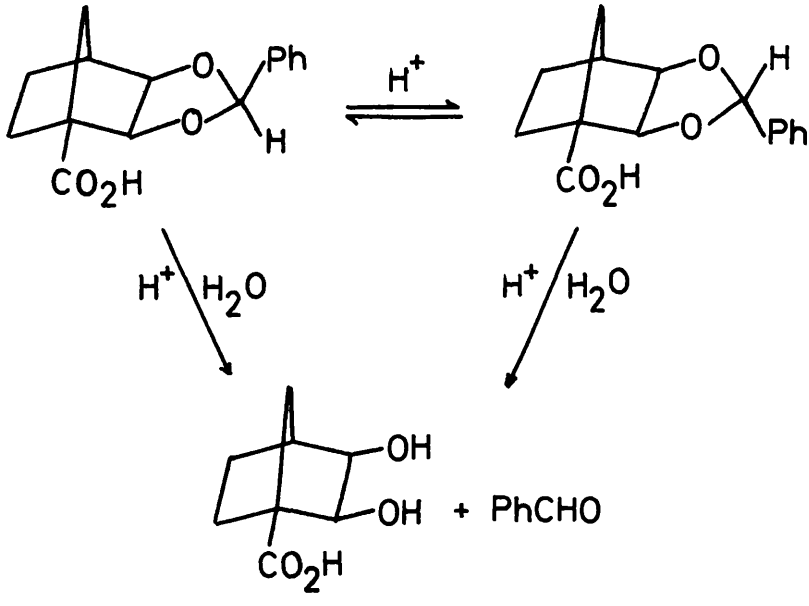
acid anion derivative. The factors which stabilise this entity, with respect to its conjugate acid, could well contribute to lowering the free-energy of activation of the hydrolysis reaction. For the large number of intra-molecular reactions reported involving neighbouring carboxylate groups, in which an anhydride is formed as an intermediate,[1,98,102] a large part of the lower free-energy of activation may arise from the thermodynamically more favourable cyclic intermediate compared to the equivalent acyclic one formed in the intermolecular system. For example, succinic anhydride is 7·4 Kcal. $mole^{-1}$ more stable than acetic anhydride relative to their respective acids.[123] If this free-energy difference were totally reflected in the transition state, of a reaction forming the anhydrides, this could give a maximum rate difference of 5×10^5. One is tempted to think there may be correlation between the rates of these intramolecular reactions and the corresponding equilibrium of acid and anhydride. It is well known that geminal substitution favours the cyclic form over the acyclic system.[122] If some of this energy is reflected in the transition state, this could be responsible for the increased rate of hydrolysis of these compounds, as well

as, or rather than, the more favourable initial state conformations.[98] The acid catalysed equilibrium constants for the formation of 5 and 6 membered lactones from γ-hydroxybutyric acid and δ-hydroxyvaleric acid are 2·67[124] and 0·34[125] respectively, at 25°C. The former was measured in water, but the latter in 50% v/v water-acetone. The free-energies of these equilibria differ by 1·25 Kcal. mole^{-1}, and if this were wholly reflected in the transition state of lactone formation, it would represent a rate difference of 8. However, the rate difference between the hydrolysis of some aryl esters of γ-hydroxybutyric acid and δ-hydroxyvaleric acid, which probably proceed via the lactones, is 18 at pH 9 and 30°C, but decreases to 0·5 in 1·0 $\underline{M}HClO_4$ at 30°C.[126]



Other considerations of such reactions should also include conformational electrostatic and steric effects in the transition state.[127]

If these views are correct, the implication is that it is necessary to have more than just a potential catalytic group held in close proximity to the reaction centre. This speculation is of relevance to the common practice of utilizing intra-molecular systems as models for enzyme action mechanisms, in the former the entity used has little resemblance to the enzyme system. For example, the enhanced rate of hydrolysis of o-carboxy phenyl glucopyranoside[128] is thought to be of relevance to the mechanism of action of lysozyme (see earlier discussion), and yet the enzyme is capable of hydrolysing glycosides in which the aglycone, or leaving group and the acid catalyst do not form such stable entities as the anion of salicylic acid. In support of this view, the benzaldehyde acetal of 1-carboxy-exo-2, 3-norbornane diol has been, found in the



work reported here, not to enhance the rate of isomerisation or hydrolysis over the unsubstituted compound. The carboxylic acid hydrogen is hydrogen bonded to the acetal oxygen in carbon tetrachloride, which shows that at least the pre-requisite for proton transfer could take place without unfavourable geometrical changes occurring in the rest of the molecule (see discussion section).

Efforts to explain the rather large catalytic activity of enzymes have often involved the hypothesis of the simultaneous and concerted involvement of two or more catalytic groups.[127] Although the concept of bi-functional catalysis was established by the strong

catalytic action of 2-pyridone on the muta-rotation of tetramethyl glucose,[129] surprisingly few examples of a similar nature are known, particularly of reactions in aqueous solution. According to a recent investigation[130] several reports of this type of action are incorrect. Rony[131] has suggested that in order for a concerted reaction to occur the reactants must be electronically coupled,[132] and that most examples of bifunctional catalysis reported in the literature are examples of tautomeric catalysis.

Catalysis by enzymes undoubtedly involves rate accelerating effects other than those which lower the energy of the bond forming and bond breaking steps.[1]

DISCUSSION

Figures and Tables, relating to experimental evidence, referred to in this section will be found in the Experimental section, p.220

The Hydrolysis of Acetals

The hydrolysis of several benzaldehyde acetals of catechol have been studied (Fig. 1.), with suitable substituents, this 1,3-dioxolane system shows intra- and inter-molecular general acid catalysis, and intra-molecular nucleophilic catalysis. Ring opening is believed to be the slow step in the hydrolysis of these compounds.

Intra-molecular general acid catalysis

The rate of hydrolysis of 2,3-benzylidene dioxy benzoic acid, II, was studied in water, and its pH-rate profile at 55·0°C is given in Fig. 2. The data, Table 1, may be fitted to a rate law of the following form

$$\text{Rate} = k_H(H^+)(RCO_2H) + k_o(RCO_2H) \qquad (1)$$

The curve in the graph is the theoretical one generated from the equation:

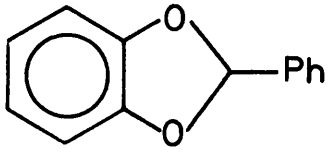
$$k_{obs} = \frac{k_H(H^+)^2 + k_o(H^+)}{K_a + (H^+)}$$

using the values $k_H = 1{\cdot}12 \times 10^{-2}\ M^{-1}sec^{-1}$, $k_o = 4{\cdot}94 \times 10^{-3}\ sec^{-1}$, and the kinetically apparent dissociation constant of the carboxyl group, $K_a = 9{\cdot}99 \times 10^{-5}$ M. The measured K_a, under identical conditions is $1{\cdot}05 \times 10^{-4}$.

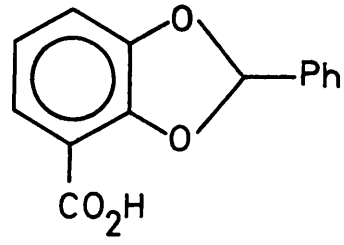
There is no detectable buffer catalysis in acetic acid buffers (Table 2). The first term on the right hand side

of equation (1) is first order in hydrogen ion, and k_H undoubtedly pertains to the normal specific acid catalysed hydrolysis of the unionised acid acetal. The k_H value for the 3,4-derivative, III, is $2{\cdot}02 \times 10^{-3}$ $M^{-1}sec^{-1}$, and that for the unsubstituted compound, I, is $6{\cdot}56 \times 10^{-3}$ $M^{-1}sec^{-1}$ at 55°C. The second term either

Fig. 1



I



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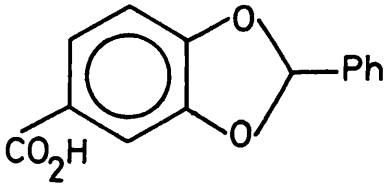
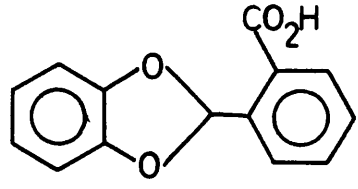


III



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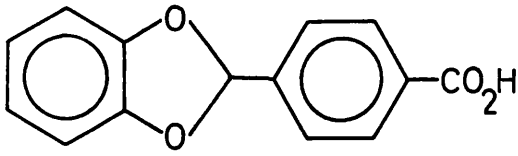
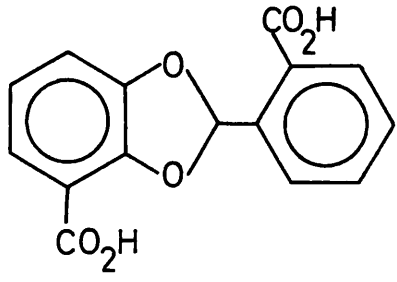
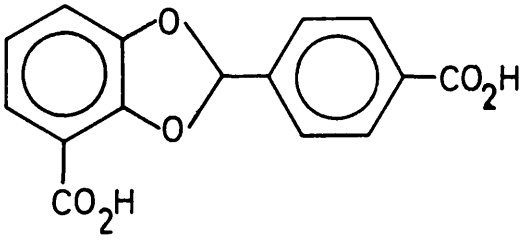


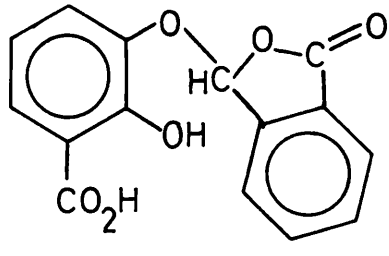
V



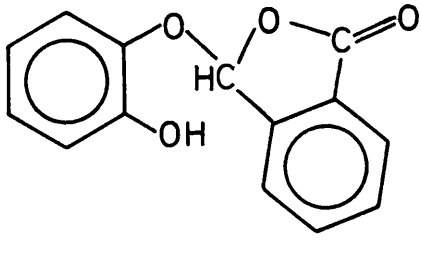
VI



VII



VIII



IX

corresponds to specific acid catalysed hydrolysis of the acetal with a dissociated carboxyl group (k') or to the kinetically equivalent spontaneous hydrolysis of the unionised acetal (k_o). The relationship between these specific rate constants is

$$k_o = k'K_a$$

therefore $k' = 49{\cdot}6\ M^{-1}sec^{-1}$, which is about 5,000 times greater than k_H for the same compound, and 25,000 times greater than k_H for the 3,4-derivative, III .

From the α value of the inter-molecular general acid catalysed hydrolysis of benzylidene catechol acetal, I, at 65°C, k_{HA}, for an acid of pK_a 4·0, for this reaction would be $1{\cdot}1 \times 10^{-4}\ M^{-1}sec^{-1}$; k_o for II at this temperature is $1{\cdot}24 \times 10^{-2}\ sec^{-1}$. Therefore the intramolecular carboxyl group is as efficient as 110 M intermolecular carboxylic acid HA.

The pH-rate profile for the hydrolysis of 3,4-benzylidene dioxy benzoic acid, III, is shown in Fig. 3. This reaction showed buffer catalysis, and for those rates measured in buffer solutions, the rate constants were obtained by extrapolation to zero buffer concentration. At low pH the slope is -1·0, but at higher pH a levelling off is observed indicative of a water catalysed or uncatalysed reaction.

At pH 3·0, 2,3-benzylidene dioxy benzoic acid has a k_{obs} nearly 300 times greater than the k_{obs}, combining both the specific acid catalysed and the spontaneous hydrolysis, for the 3,4-derivative.

Similar behaviour has been found in other salicylic acid derivatives, o-carboxyphenyl β-D glucoside[165,166] and 2-methoxymethoxybenzoic acid.[165,168] In these systems it has been found that the rate enhancement cannot be explained by a normal substituent effect of the o-carboxy group. Capon[165] has estimated that the latter could be expected to produce a maximum rate enhancement of 10, considering inductive, mesomeric and steric effects.

The solvent isotope effect for the spontaneous hydrolysis of II is $k_o(H_2O)/k_o(D_2O) = 1{\cdot}28$ at 55°C (see experimental section for details). However since the observed rate constant could be a composite quantity, considering the kinetically equivalent mechanism of specific acid catalysed hydrolysis, the following relationship holds

$$\frac{k_{obs}(H_2O)}{k_{obs}(D_2O)} = \frac{k_o(H_2O)}{k_o(D_2O)} = \frac{k'(H_2O)\ K_a(H_2O)}{k'(D_2O)\ K_a(D_2O)}$$

$K_a(H_2O)/K_a(D_2O)$ is generally about 2·5-4 for carboxylic acids,[190] therefore $k'(H_2O)/k'(D_2O)$ would be about 0·33-0·51, which is in the region expected for specific

acid catalysed hydrolysis of acetals. The solvent isotope effect cannot, therefore, be used to distinguish between these mechanisms.

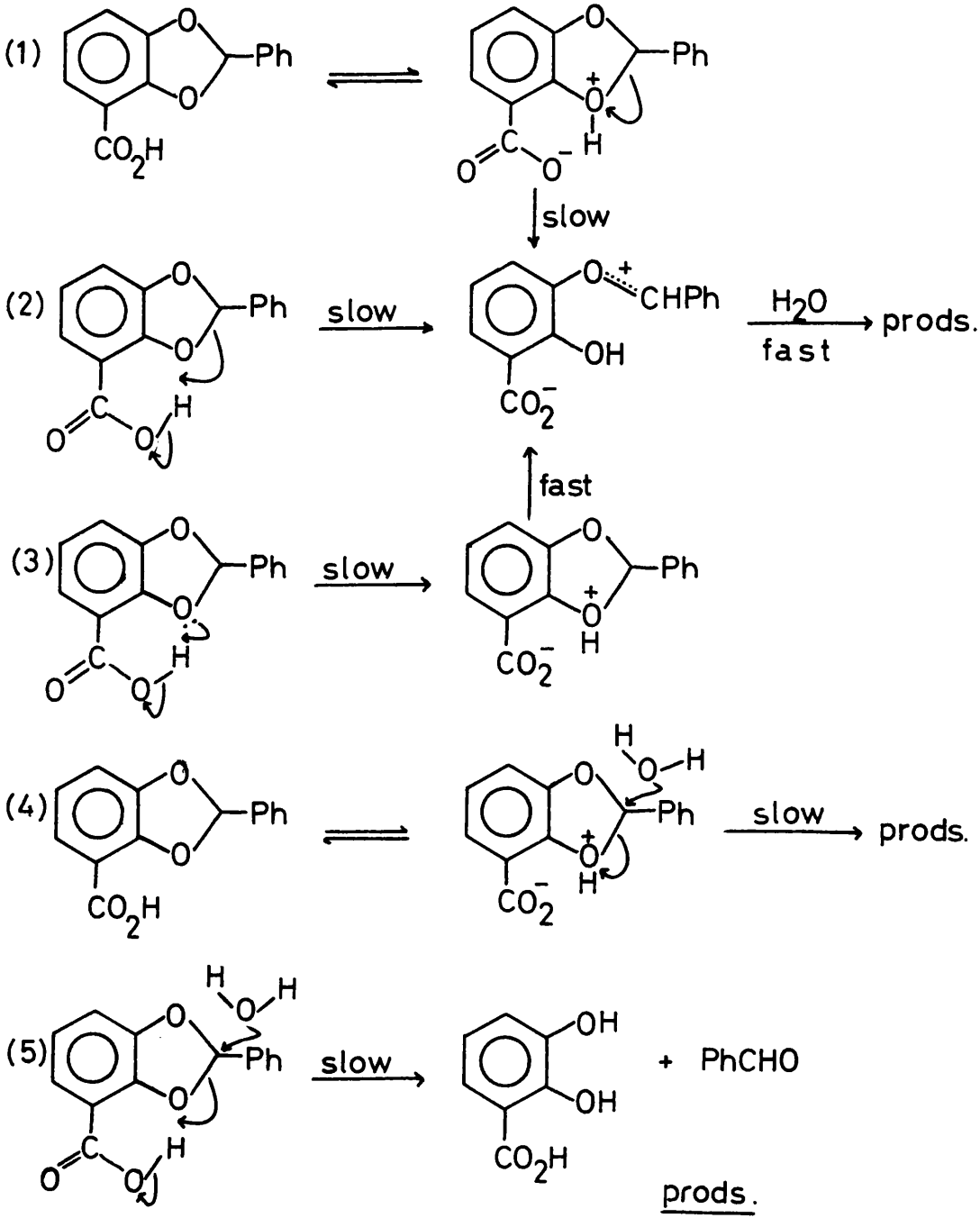
The entropy of activation for the spontaneous hydrolysis of II is -13·6 e.u. at 55°C, and the enthalpy of activation is 18·2 Kcal.mole^{-1}, calculated from the variation of the first order rate constant at 5 temperatures between 25 and 65°C (Table 5).

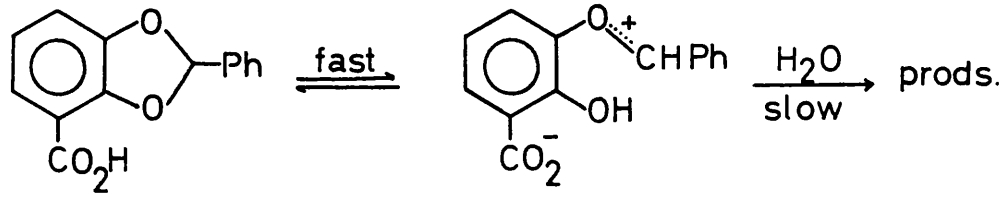
As mentioned in the introduction, for 1,3-dioxolanes one must consider the possibility of ring opening not being the rate limiting step. The kinetically equivalent mechanisms which could explain the increased rate of hydrolysis of the o-carboxy compound, II, are given in Fig. 4.

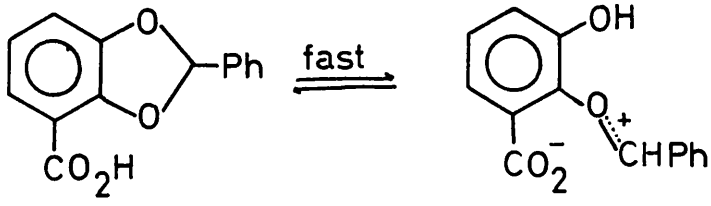
Mechanisms 1,2,4,5,8 and 10 involve rate limiting carbon-oxygen bond fission, mechanism 3 rate limiting proton transfer and the rest reversible ring opening. For the latter, the carboxy group, to affect the rate, must either favour the right hand side of this equilibrium or facilitate the subsequent step. Several of these mechanisms may be logically excluded.

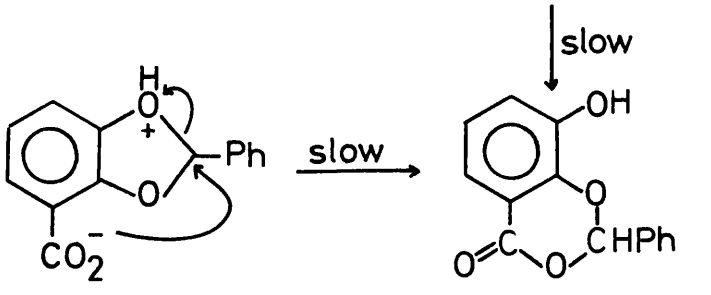
Mechanism (3) is considered since it has recently been suggested[44,197] that rate limiting proton transfer to acetal oxygens is possible. The reverse of this

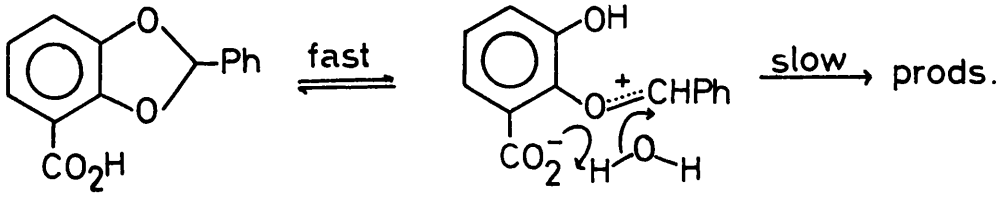
Fig. 4

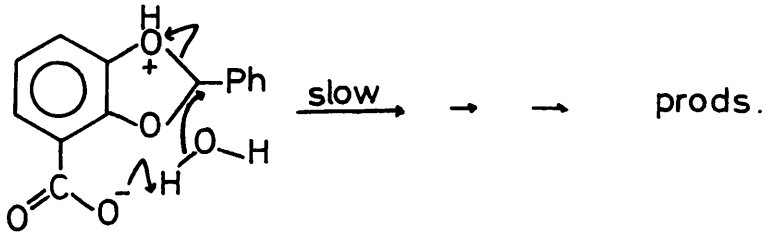

(1)
Ph
CO_2H
slow
(2)
slow
CHPh
OH
CO_2^-
H_2O
fast
prods.
fast
(3)
slow
(4)
slow
prods.
(5)
slow
OH
OH
CO_2H
+ PhCHO
prods.

(6) 
fast
CHPh
OH
CO_2^-
H_2O
slow
prods.
Ph
CO_2H

(7) 
fast
OH
CHPh
CO_2^-
Ph
CO_2H


slow
(8)
H
Ph
slow
OH
fast
H_2O
prods.
CHPh
CO_2^-

(9) 
fast
OH
CHPh
slow
prods.
Ph
CO_2H
CO_2^-

(10) 
H
Ph
slow
prods.
O—H
H

reaction, intra-molecular proton transfer from a strong acid to a basic site, is extremely fast, $\sim 10^{12}$ sec^{-1}, and may even occur by tunnelling.[85,201,202] For proton transfer to be rate limiting, therefore, the barrier in the forward direction would have to be less than about 1 $Kcal.mole^{-1}$ and greater than kT/h ($\sim 6 \times 10^{12}$ sec^{-1}). Such a short lived species could not be considered as an intermediate and the mechanism is therefore excluded.

Mechanism (8) is geometrically impossible. Mechanism (6) postulates that the enhanced rate is due to formation of a more favourable equilibrium constant for ring opening. This extra stability would arise from either the formation of a more stable carbonium ion or stabilisation due to intra-molecular hydrogen bonding. A carboxyl group substituted in other positions of the molecule, noteably III and V, allowing possible carbonium ion stabilisation produces no rate enhancement. The rate enhancement produced due to intra-molecular hydrogen bonding probably cannot be greater than the enhanced acidity of salicylic acid, which is equivalent to 1·5 pKa units, 2·1 $Kcal.mole^{-1}$, which could only give a maximum rate difference of 70. However, hydrogen bonding may be favoured by the carbonium ion enhancing the acidity of the hydroxyl group, but at the same time it would presumably

reduce the basicity of the carboxylate group. H-bonding in such systems is hindered by adjacent substituents.[191,192] For this mechanism, and the others involving pre-equilibrium ring opening, one would not expect the apparent kinetic pK_a to be the same as the experimentally determined value.[18] Mechanism (6) is therefore excluded.

Mechanisms (7) and (9) may also be excluded on the grounds that the di-acid VI, in which a carboxy group in the aldehydic protion ring closes to form a stable acylal VIII, (Fig. 1) as the sole product, undergoes autolysis at a similar rate to the hydrolysis of II and VII . The simplest explanation of this would be the carboxyl group trapping the open carbonium ion in a fast product determining step. The monocarboxy derivative IV is converted to the acylal, much more slowly than the rate of disappearance of II or VI. This seems to exclude any mechanism involving rate determining attack on the carbonium ion. If mechanisms (7) and (9) and (10) held for the dicarboxy acetal VI, the fast product determining step would then have to be a nucleophilic displacement, which was faster than the normal hydrolysis path. The solvent isotope effect for the general base type of reaction proposed in mechanism (10) is generally $k(H_2O)/k(D_2O) > 2$,[98,18] the observed effect therefore excludes

this mechanism.

All the mechanisms involving pre-equilibrium ring opening formation of a carbonium ion have therefore been eliminated. It was hoped to study the rate of racemisation and hydrolysis of optically active II[I], but attempts to prepare the latter by fractional recrystallisation techniques were not successful.

The remaining 'contenders' for the mechanism of hydrolysis are (1) (2) (4) and (5). 2,3-benzylidene dioxy benzoic acid II shows no detectable intra-molecular hydrogen bonding in carbon tetrachloride, it is therefore certainly not internally hydrogen bonded in aqueous solution. The only type of stabilisation possible for the conjugate acid of the acetal, by the neighbouring carboxy group, is electrostatic, which is presumably fairly small. Rate enhancements cannot therefore be ascribed to a higher standing cencentration of protonated acetal. However, as carbon oxygen bond fission proceeds it is conceivable that stabilisation of the leaving hydroxyl group by electrostatic, field effects or hydrogen bonding of the neighbouring carboxyl group may lower the free energy of the transition state.

Mechanisms (4) and (5) are analogous to (1) and (2) respectively, except that in the former the pathways are

bimolecular with water acting as a nucleophile. It may be possible to exclude the latter, since if the carboxylate group replaces water as the nucleophile in the autolysis of compound VI, one would have expected this intramolecular reaction to go faster. If this is not the case, the carboxy group would have to nucleophilically displace a hydroxide ion from the hemi-acetal faster than the latter hydrolyses, to give the experimentally found product, VIII. As discussed previously, this seems unlikely, and mechanisms (4) and (5) are therefore considered improbable.

The close similarity between the hydrolysis of 2,3-benzylidene dioxy benzoic acid II, 2-methoxymethoxy-benzoic acid[165,168] and 2-carboxyphenyl β-D glucoside,[165,166] suggests that their mechanisms are similar. The solvent isotope effect for the glucoside is $k_o(H_2O)/k_o(D_2O)$ = 1·57 at 60·2°,[165] that for the formal 1·43 at 45°C, and the acetal studied here 1·28 at 55°C. The mechanisms considered likely for the hydrolysis of these other salicylic acid derivatives[165] are equivalent to mechanisms (1) and (2) here.

Similar solvent isotope effects (S.I.E.) have been reported in related systems, for the hydrolysis of salicyl phosphate, Bender[242] quotes a $k(H_2O)/k(D_2O)$ of 0·96

at 25°C, for salicyl sulphate $k(H_2O)/k(D_2O)$ = 1·2 at 35°C.[243] Bender considers the value found is indicative of a pre-equilibrium proton transfer, since for rate-limiting protonation, the author anticipated a large S.I.E. (see discussion on latter).

Is it possible to distinguish between mechanisms (1) and (2)? The former involves a pre-equilibrium formation of the conjugate acid of the acetal, proton transfer is reversible and not rate determining. The faster rate of hydrolysis arises from a good leaving group, which lowers the free-energy of the transition state. Mechanism (2) postulates rate limiting non-reversible, proton transfer concerted with fission of the carbon-oxygen bond. The conjugate acid of the acetal does not lie on the reaction path. In mechanism (1) the proton remains in a potential minima, is excluded from the reaction co-ordinate and the O-H "unsymmetrical" stretching vibration remains real in the transition state. Asymmetric stretching of the C-O bond alone leads to fission and formation of the carbonium ion. Whereas in (2) the proton is at the top of a potential barrier in the transition state, at the latter stage vibration along the reaction co-ordinate does not have a positive force restoring constant for O-H "unsymmetrical" stretching. Is direct proton transfer between the carboxyl group and the acetal oxygen possible?

For this to occur, since the compound is not intra-molecularly hydrogen bonded in carbon tetrachloride, both species must be partially desolvated and undergo some unfavourable geometrical changes in order for their potential energy surfaces to overlap. The rate of proton transfer is decisively determined by the distance between the donor and acceptor group at the moment of transfer.[85,93] Since it determines how well the potential energy curves overlap along the reaction co-ordinate, it has a great influence on the activation energy. If a tunnelling mechanism is operative this distance is even more important. Therefore the formation of a hydrogen bond, providing an optimal overlap of potentials, is an important pre-requisite for facile proton transfer.[85,93] If direct proton transfer was the mechanism, in the case under consideration, this would be an example of an intra-molecular reaction being more facile than its inter-molecular counterpart, and yet having to undergo many of the activation processes generallly thought to be confined to inter-molecular reactions.

However, solvent participation in the proton transfer step is conceivable,[41b,193,194] and indeed Bell[90] and Eigen,[93] have suggested that proton transfer through a chain of water molecules may be important in some general acid catalysed reactions. The problem under consideration

could therefore be circumvented by postulating proton transfer to occur via a water molecule(s).

Capon[165] favours the general acid catalysed mechanism for the following reasons:

(1) 2-nitromethoxymethoxy benzene hydrolyses only 2 times faster than 4-nitromethoxymethoxy benzene. The nitro group has a strong dipole and could be expected to stabilise an incipient phenolic group by an electrostatic or field effect. However, with a 2-carboxy group, the stable salicyl anion is the leaving entity. Assuming similar conjugate base stabilities, there is no 'special' stability of o-nitrophenol compared to p-nitrophenol, as measured by their similar pK_a's.

(2) Inter-molecular general acid catalysis in aryl acetals is established.[173] If this were a valid argument, it would be even more substantial for the acetals reported in this thesis, where intra- and inter-molecular general acid catalysis are found in similar systems. This will be discussed in the next section.

(3) There is no rate enhancement from neighbouring acidic groups other than carboxyl.[165]

However, the same author,[165] does emphasise that the equivalent of mechanism (1) has not been rigorously excluded.

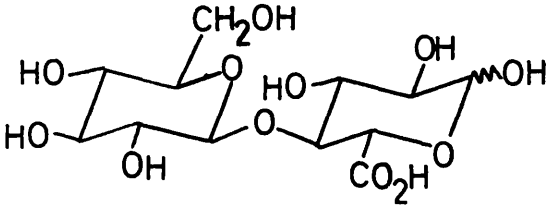
Salicylic acid is probably not intra-molecularly

hydrogen bonded in methanol or water,[195] but the salicylate monoanion probably is, even in water.[84,85] It has often been suggested that a 'pseudo-aromatic' character is responsible for the stability of some six-membered hydrogen bonded species.[191] In the 2-carboxy phenoxy systems, if this stability and hence better leaving group ability is reflected in the transition state, this could explain the enhanced rates of hydrolysis as in mechanism (1). Whether this mechanism could lower the free energy of activation sufficiently to explain the enhanced rates of hydrolysis is difficult to estimate. The pK_a of salicylic acid is a measure of the free-energy difference between conjugate acid and the combined solvated proton and salicylate anion. What one would like to known is the free energy difference between phenol and the salicylate anion.

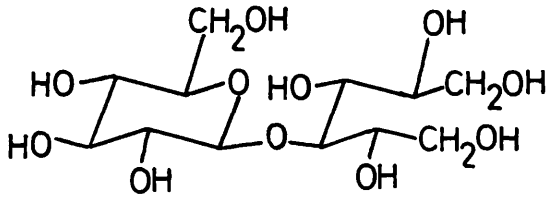
It is of interest to note that 8-methoxymethoxy naphthoic acid has a k' which is only 33 times greater than its k_H value.[165] The pK_a of 8-hydroxynaphthoic acid is 1·3 pK_a units more acidic than naphthoic acid,[196] but steric requirements and the formation of a 7-membered ring may be responsible for the smaller rate enhancement of this compound.

To date, there has only been one substantiated report of an enhanced rate of hydrolysis of a glucoside, invoking general acid catalysis, that is not a salicylic

acid derivative. Smidsrød and co-workers[198] found that the hydrolysis of X had a sigmoid pH-rate profile and proceeded nearly 10^3 times faster, at pH 4, than XI. That rates of hydrolysis were determined using viscosity



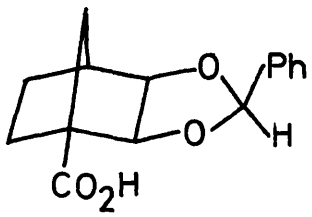
X



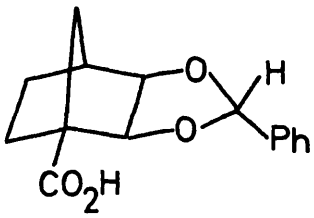
XI

measurements or the reducing power of the solution. If glycosyl C_1-oxygen fission is occuring then this could result from intra-molecular general acid catalysis.

It was hoped to prepare several rigid aliphatic β-hydroxy acid systems and thence glucosides or acetals of these. However, the synthetic steps towards these derivatives were plagued with dehydration products (see experimental section) and the project was 'shelved'. The isomers of the benzaldehyde acetals of 1-carboxy 2,3-exo-nonbornane diol, XII and XIII, were prepared. In this system, the carboxyl group is hydrogen bonded to the acetal



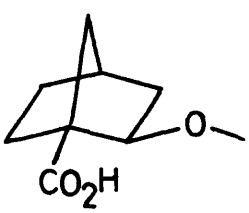
XII



XIII

oxygen in carbon tetrachloride, and yet the carboxyl group has little effect on either the rate of hydrolysis or isomerisation. These compounds hydrolyse by the A-2 mechanism, and will be discussed under this heading.

It would be interesting to study the rate of hydrolysis of a derivative of 1-carboxy 2-exo-norborneol XIV, since it would hydrolyse by the A-1 mechanism, and dehydration is



XIV

not possible in this tertiary carboxyl system.

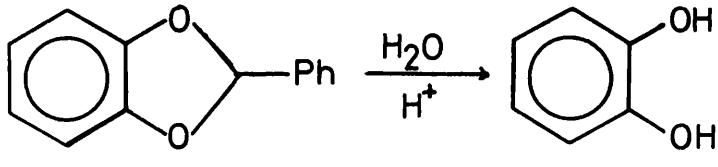
The problem of distinguishing between mechanisms (1)

and (2) remains basically unsolved, but will be taken up again in the next section considering inter-molecular general-acid catalysis.

Intermolecular General Acid Catalysis

Until recently, there were no reports of intermolecular general acid catalysis in the hydrolysis of acetals, ketals or glucosides. In the last year, however, several studies have been published, and these will be referred to in the discussion.

We have applied several of the usual mechanistic criteria for acid hydrolysis of the benzaldehyde acetal of catechol I.



(1)

I

I Buffer Catalysis

The technique of Bell[199] was used, and the pseudo first order rate constant for the hydrolysis reaction (1) was determined at different buffer concentrations, but with the buffer ratio, ionic strength and pH held constant. For phosphoric acid and chloroacetic acid the pH changed significantly on dilution, and these were corrected

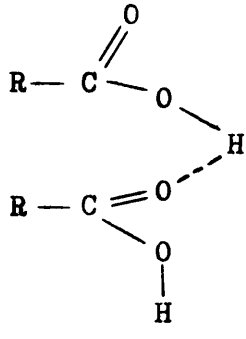
according to the method of Gold and Waterman.[200] For the other solutions the concentration of the undissociated acid was taken as the stoicheiometric concentration. The results of the variation of the rate constants with buffer concentration at 65°C and at ionic strength 0·5 M are given in Table 7-15. The rate constant increases with increasing concentration of the buffer at constant pH. The catalytic coefficients of the carboxylic acids were obtained from a least-squares plot of k_{obs} against the concentration of the undissociated acid. These plots, Figs. 5 - 7 are all linear except for acetic acid buffers and formic acid, but only in the latter case with a buffer ratio of $[HCO_2H] : [H_2CO_2^-]$ of 9:1. For these solutions an increasing amount of curvature is noticeable at higher concentrations, the experimental values of k_{obs} fall below the slope defined by the data for low concentrations. A similar phenomenon has been observed by Gold and Waterman,[200] who interpreted the results in terms of catalytically inactive dimers, resulting from the following equilibria:

$$2HA \rightleftharpoons (HA)_2$$

$$HA + A^- \rightleftharpoons HA_2^-$$

Using reasonable values of the dissociation constants,

the experimental curves could be satisfactorily computed. The interpretation has been applied to similar results obtained in methanol.[235] Rosotti[236] considers association leads to a catalytically active species, which seems reasonable in view of the suggestion that carboxylic acid dimers exist as the mono hydrogen-bonded species in water.[237] It has also been suggested that the observations may be due to a salt or activity coefficient effect.[1]



The curvature could be the result of a mechanistic complication rather than the property of the buffer. For the following reaction path, if k_2 and k_{-1} are of similar

$$S + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ + A^-$$

$$SH^+ \xrightarrow{k_2} \text{products}$$

magnitude, then the rate will fall off with increasing concentration of HA.[199] This proposal will be taken up again in the discussion of the mechanism of the reaction.

To ensure that the measured catalytic coefficients were on the linear part of the curve, the rates of hydrolysis of I were determined at low buffer concentration, $< 0{\cdot}03$ M, at I = $0{\cdot}05$ M. The results are given in Tables 17-19, and except for acetic acid, the results are in good agreement with those determined at higher buffer concentration, and higher ionic strength.

The catalytic coefficients are independent of pH, Tables 8-16, therefore the rate is proportional to the concentration of the undissociated acid and not its conjugate base. The catalytic coefficients are related to the dissociation constants of the acids, according to the Brönsted catalysis law, there being a straight line relationship between log k_{HA} and pK_{HA}. The Brönsted exponent calculated from a least-squares evaluation of such a graph is $0{\cdot}46$, and the data are approximately represented by the equation:

$$\log_{10} \frac{k_{HA}}{p} = 0{\cdot}46 \log_{10} \left(\frac{qK_{HA}}{p}\right) - 2{\cdot}08 \qquad (2)$$

with catalytic coefficients at I = $0{\cdot}5$ and dissociation constants at I = 0. The statistical factors p and q for carboxylic acids were taken as 1 and 2 respectively. The same α value was obtained from the catalytic coefficients at I = $0{\cdot}05$. Since the slope of this 3 point graph is

determined mainly be the first and last points, formic acid appears to exhibit a slight negative deviation (Fig. 8).

In this reaction the catalytic effect of the hydronium ion is smaller than expected, according to the catalysis law (Fig. 8). On the assumption that $K_{H_3O^+} = 55{\cdot}5$ M, p = 3 and q = 2, equation 2 would predict a catalytic coefficient of H_3O^+ to be $1{\cdot}19 \times 10^{-1}$ $M^{-1}sec^{-1}$, whereas the observed value is $1{\cdot}24 \times 10^{-2}$ $M^{-1}sec^{-1}$. Alternatively, $K_{H_3O^+}$, would have to be 1·85 to bring it on the line generated by the carboxylic acids. The water catalysed reaction has a large positive deviation from the Brönsted plot, and corresponds to an acid with a pK_a of 11, with p = 2 and q = 3. Similarly phosphoric acid is a more effective catalyst than is predicted from equation 2. According to Kreevoy and Williams,[205] this is indicative of an $A_{SE}2$ mechanism. But since the nature of ions present in phosphoric acid solutions is extremely complicated,[238] the behaviour remains basically empirical. No enhanced catalytic effect was observed with sulphuric acid as the protonating acid.

The Brönsted catalysis law, by itself, does not provide evidence of the reaction mechanism, since certain

acid and base catalysed reactions obey the law, without acting catalytically in the Brönsted sense.[239]

The hydrolysis of I was also studied in aniline buffers but the reaction is accompanied by a purple colouration, precipitation and a decrease in pH. This was not studied further. k_{HCO_2H}, at pH 3·1 for the hydrolysis of 3,4-benzylidene dioxy benzoic acid, III, is 4×10^{-5} $M^{-1}sec^{-1}$ at 55°C, which compares with $7{\cdot}4 \times 10^{-5}$ $M^{-1}sec^{-1}$ for the unsubstituted compound, I. The k_{H^+} values for III and I are $2{\cdot}0 \times 10^{-3}$ $M^{-1}sec^{-1}$ and $6{\cdot}6 \times 10^{-3}$ $M^{-1}sec^{-1}$ respectively. Both reactions are therefore retarded by electron withdrawal in the phenolic moiety, but since the leaving group remains attached to the molecule and so may affect the stability of the incipient carbonium ion no conclusions are drawn.

II pH-Rate Profile

Rate constants for the hydrolysis of benzylidene catechol, I, at various pH values at 65°C are reported in Table 20. Rates were measured in hydrochloric acid solutions and in buffer solutions, for the latter the constants were obtained by extrapolation to zero buffer concentration to give k_{int}. In Fig. 9 is shown a plot of log k_{obs} or log k_{int} against pH. At low pH values the slope is -1·0, but at higher pH a plateau is observed

indicative of a water catalysed or uncatalysed reaction. The line in Fig. 9 was calculated employing the equation $k_{obs} = k_o + k_H(H^+)$ with $k_o = 4{\cdot}9 \times 10^{-6}$ sec^{-1} and $k_H = 1{\cdot}25 \times 10^{-2}$ $\underline{M}^{-1}$sec^{-1}. In 0·1 N NaOH the observed rate constant is $5{\cdot}17 \times 10^{-6}$ sec^{-1}. Similarly, a linear least squares calculation of $(k_{int} - k_o)$ against the hydronium ion concentration gave a second order rate constant for k_H of $1{\cdot}34 \times 10^{-2}$ $\underline{M}^{-1}$sec^{-1}, which is in good agreement with that obtained in hydrochloric acid solutions, $1{\cdot}25 \times 10^{-2}$ $\underline{M}^{-1}$sec^{-1}. The intercept was $0{\cdot}95 \times 10^{-6}$ sec^{-1}.

The observed rate constant for the hydrolysis of I is therefore given by:

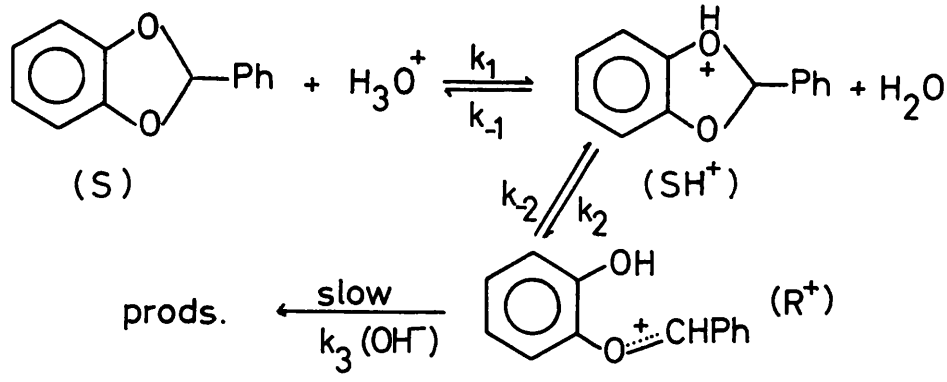
$$k_{obs} = k_o(H_2O) + k_H(H^+) + k_{HA}(HA)$$

The p-methoxy benzaldehyde acetal of catechol was prepared, but was impossible to study, since it hydrolysed on brief exposure to the atmosphere. This extremely facile spontaneous hydrolysis at least shows that the reaction has a very strong dependence on the stability of the intermediate carbonium ion.

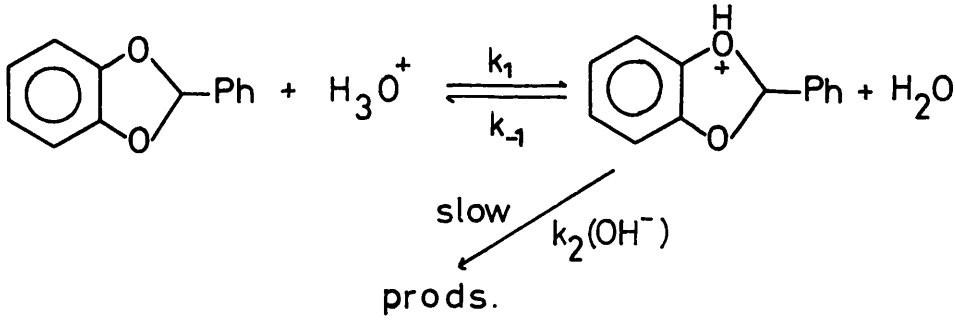
The mechanism for the water catalysed reaction is probably a bimolecular rate determining attack of water on the substrate, since the kinetically equivalent mechanisms shown below may be discarded.

It is difficult to estimate the pK_a of SH^+, that for

(1)



(2)



anisole is -6·5.[226] The inductive effects of the aldehydic phenyl group and the oxygen will presumably reduce the basicity of the acetal oxygen, whilst the oxygen which is not protonated could conceivably stabilise the conjugate acid. In the calculations below the pK_a is taken conseratively as -5, to significantly affect the conclusions the pK_a would have to be about 0 or greater.

For mechanism (1) steady-state treatment of the intermediate carbonium ion gives the following expression for k_{obs}.

$$k_{obs} = \frac{k_3 k_2 k_1 (H_3O^+)(OH^-)}{k_{-1}(k_{-2} + k_3(OH^-))}$$

$k_{-2} \gg k_3(OH^-)$ and $k_1/k_{-1} = 10^{-5}\ M^{-1}$

therefore

$$k_{obs} = \frac{k_3 k_2\ 10^{-14}\ 10^{-5}}{k_{-2}} = 4 \times 10^{-6}\ sec^{-1}$$

therefore

$$k_3 = 4 \times 10^{13} \times \frac{k_{-2}}{k_2}$$

For k_{-2}/k_2 equal to unity, k_3 would equal about $4 \times 10^{13}\ M^{-1} sec^{-1}$, which is faster than the rate constant of $1{\cdot}4 \times 10^{11}\ M^{-1} sec^{-1}$ for the fastest known diffusion controlled reaction in water, the reaction of the solvated proton with hydroxide ion.[227]

Similar treatment for mechanism (2) yields the expression

$$k_{obs} = \frac{k_2 k_1 (H^+)(OH^-)}{k_{-1} + k_2(OH^-)}$$

Again $k_{-1} \gg k_2(OH^-)$, and $k_1/k_{-1} = 10^{-5}\ M^{-1}$

therefore $k_2 = 4 \times 10^{13}\ M^{-1} sec^{-1}$

Therefore both mechanisms may be excluded from the reaction path. The alternative mechanisms for the spontaneous hydrolysis of I are:

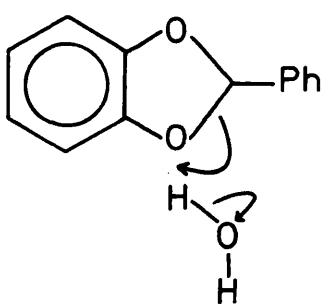
(1) unassisted ring opening to form the carbonium ion,

(2) nucleophilic attack of water on the free acetal,

(3) general acid catalysed ring opening by water,

(4) a termolecular reaction combining (2) and (3) above.

Mechanisms (2) and (4) may be excluded since if these were operative then one would expect a nucleophilically catalysed hydroxide ion reaction. The hydrolysis of a series of halides and benzene sulphonates have solvent isotope effects in the region k_{H_2O}/k_{D_2O} = 1·1 - 1·4.[60a] The value observed for the spontaneous hydrolysis of I is k_{H_2O}/k_{D_2O} = 1·61 at 75°. The entropy of activation for this process is -21 e.u. using the pseudo first order rate constant (Table 29). Path (1) is therefore almost certainly excluded, and the mechanism for the water catalysed hydrolysis is therefore represented by:



which is a concerted electrophilic displacement on oxygen, $A_{SE}2$. If this is the mechanism for the water catalysed reaction it seems conceptually satisfying that this is also the mechanism for the carboxylic acid and the hydronium ion catalysed hydrolysis.

Since ring opening is the slow step in the hydrolysis of 2,3-benzylidene dioxy benzoic acid, II, there is no reason why it should not be so in catechol benzaldehyde acetal, I. The low solvent isotope effect, k_{H3O^+}/k_{D3O^+} = 0·92 at 65°C, is certainly incompatible with those normally associated with pre-equilibrium proton transfer reactions, the A-1 mechanism, or the A-2 mechanism, specific acid-nucleophilic catalysis.

III Solvent Isotope Effects

One may, at first sight, expect that general acid catalysed reactions should be subject to large deuterium solvent isotope effects, since a proton is being transferred in the rate limiting step. The value found for the acid catalysed hydrolysis of benzylidene catechol, I, of k_{H3O^+}/k_{D3O^+} = 0·92 at 65°C, is similar to that for other reactions in which proton transfer between oxygen atoms is believed to be important in the transition state, but in which the deuterium isotope effect is small[3,172,173,197,203,204] (see Table 21). The acetic acid catalysed hydro-

lysis of I has a k_{AcOH}/k_{AcOD} of 1·33 at 65°C, and the solvent isotope effect (S.I.E.) for the spontaneous hydrolysis is k_{H_2O}/k_{D_2O} = 1·61 at 75°C (Table 22).

Similarly, for other $A_{SE}2$ proton additions, particularly to olefinic double bonds, the kinetic isotope effects are generally smaller than those expected from complete loss of the zero-point energy of the stretching vibration of the hydronium ion $k_{H_3O^+}/k_{D_3O^+}$ varying from 1·4 to 4·5.[205]

It is sometimes assumed that only pre-equilibrium proton transfer reactions (A1 and A2 mechanisms) will have faster rates in D_2O than in H_2O, and that rate determining proton transfer reactions will show a S.I.E. in the normal direction. As can be seen from Tables 21 and 22 this is not always the case.

However these S.I.E. are less diagnostic than they would first appear to be. Kinetic general acid catalysis leads to kinetically equivalent mechanisms, a concerted reaction involving slow proton transfer (1) or specific acid-nucleophilic catalysis (2)

$$S + HA \xrightarrow[\text{slow}]{k_o} \text{products} \qquad (1)$$

$$\left.\begin{array}{l} S + H_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ + H_2O \\ SH^+ + A^- \xrightarrow[\text{slow}]{k_2} \text{products} \end{array}\right\} \quad (2)$$

k_{obs} for mechanism (1) is given by:

$$k_{obs} = k_o(HA)$$

whereas that for (2) is:

$$k_{obs} = \frac{K_{HA}.k_2(HA)}{K_{SH^+}}$$

therefore $$k_o = \frac{K_{HA}.k_2}{K_{SH^+}}$$

Since the ratio of the ratios of equilibrium constants on transfer from H_2O to D_2O will be approximately unity, and for $k_2(H_2O)/k_2(D_2O)$ there will be a small medium effect, S.I.E. cannot be used to distinguish between these kinetically equivalent mechanisms.

For spontaneous hydrolysis the S.I.E. would be given by:

$$\frac{k_o(H_2O)}{k_o(D_2O)} = \frac{K_w(H_2O)}{K_w(D_2O)} \times \frac{K_{SD^+}}{K_{SH^+}} \times \frac{k_2(OH^-)}{k_2(OD^-)}$$

Although in this case, for the specific acid-nucleophilic mechanism, one may expect a slightly higher S.I.E., since

$K_w(H_2O)/K_w(D_2O)$ is 7, this will presumably be reduced by the higher nucleophilicity of OD^-, i.e. $k_2(OH^-)/K_2(OD^-) < 1$.

For the hydronium ion catalysed reaction

$$\frac{k_o(H_2O)}{k_o(D_2O)} = \frac{K_{H_3O^+}}{K_{D_3O^+}} \times \frac{K_{SD^+}}{K_{SH^+}} \times \frac{k_2(H_2O)}{k_2(D_2O)}$$

The relative magnitudes of the acidities of H_3O^+ and D_3O^+, and the nucleophilicities of H_2O and D_2O may well cancel or be near unity. Therefore the A-2 mechanism in this case would be similar to that for normal A-1 acetal hydrolysis i.e. $k_{H_3O^+}/k_{D_3O^+} = 0{\cdot}3 - 0{\cdot}4$.

Comparitive rate studies in light and heavy water are neeessarily accompanied by a medium effect. These transfer effects are likely to be relatively small.[60a] For example, S_N1 solvolysis of alkyl halides usually suffer about a 25% reduction in rate on being transferred from H_2O to D_2O.[206] These and other 'secondary' effects, arising from hydrogen atoms being close to the reaction site, must be considered together with the 'primary' isotope effect on hydrogen ion transfer. Therefore to know what to 'expect' for the value of the S.I.E. for rate limiting proton transfer reactions, it is necessary to be able to evaluate these quantities.

The hydronium ion is a special case of a proton donor since there are two types of protons or deuterons in the transition state. There is the unique transferred proton

and the remaining equivalent pair, which, if they become water-like, are more tightly bound in the T.S. than they were in the reactants. This secondary isotope effect of the 'non-reacting' bonds may be quite large and probably gives an inverse effect[41b,207,208] ($k_H/k_D < 1$), which will therefore oppose the primary effect. Assuming the applicability of the rule of the geometric mean, Kresge[209a] was able to measure the secondary isotope effect for proton transfer from the hydronium ion to aromatic carbon bases directly. An inverse effect of $k_H/k_D = 0{\cdot}59$ at 25°C was found, which was <u>insensitive</u> to the transition state structure, and in good agreement with the simplified calculation of Bunton and Shiner,[41b] which predicts a value of 0·61.

Whether there will be a similar secondary S.I.E. for proton transfer to oxygen is difficult to estimate. For such systems it is almost impossible to know what changes in hydrogen bonding, between reactants and solvent, occur on going to the transition state, and also to distinguish between primary and secondary effects for such transfers.[41b]

Estimation of the maximum primary isotope effect expected for loss of a vibrational stretch of one of the protons of the hydronium ion depends on the frequency assigned to this mode. This stretch has variously been quoted as 2900 cm^{-1} [209]

to 2060 cm^{-1}.[210] Taking the former value the maximum primary I.E. will be $k_H/k_D \sim 6$,[41b] this together with the secondary I.E. gives a maximum net effect of $k_{H_3O^+}/k_{D_3O^+}$ of 3·6.[41b] Consistent with this, Kresge and co-workers obtained a maximum value of $k_{H_3O^+}/k_{D_3O^+}$ of 3·5 for the hydrolysis of vinyl ethers in aqueous solution.[211] However, taking the value of 2060 cm^{-1} for the stretching frequency of the hydronium ion, the maximum primary I.E. would be $k_H/k_D = 4·2$,[205] and the secondary I.E. $k_H/k_D = 0·22$, and hence the net effect would be a k_H/k_D of 0·92, of course, the main contribution to this large inverse secondary I.E. should be absent when the proton donor is a carboxylic acid.

What is the maximum S.I.E. expected for rate limiting proton transfer between oxygen atoms? At present, this appears unpredictable, but there have been numerous rationalisations of the effects being lower than 'expected.'[3,44,41b,172,212,218]

Several factors may contribute to the observed value of the S.I.E. The possibility of the existence of a maximum in the I.E. for proton transfer reactions and that the ratio k_H/k_D should be a function of the position of the hydrogen atom in the transition state, has been proposed by many authors,[202,213] and has experimental support.[211,214,215,219] The maximum isotope effect occurs when ΔpK is near zero and

theory predicts a maximum for a symmetrical transition state.[202] Therefore the I.E. may be lower in a series of reactions for those transition states which are unsymmetrical i.e. the hydrogen atom is closer to one of the reactants, if there are mass dependent vibrational modes present which are a source of zero-point energy.[216] This is particularly important in multi-centre reactions, like the concerted type being considered here where the motions of at least four atoms are involved. Low I.E. are also expected when a 'bending' rather than a 'stretching' mode is converted to transitional motion.[217] Possibly tunnelling, which would increase k_H/k_D, is important in some proton transfers.[202,213]

For the hydrolysis of benzylidene catechol, I, changing the acid strength of the proton donor by 17·5 pK_a units (H_3O^+ to H_2O) has little effect upon the absolute magnitude of k_H/k_D (Table 22), although it increases with increasing pKa of the acid. On a simple basis, one would anticipate a large inverse secondary isotope effect for H_3O^+, but not for acetic acid. This effect may be independent of transition state structure.[209] If the maximum primary I.E. increases with increasing pKa of the donor, the maximum net S.I.E. would be larger for the weaker acid. The asymmetry of the transition state will be discussed in

the next section.

If the α value of 0·47 means that, for carboxylic acids, the proton is symmetrical in the transition state, then one would have anticipated the maximum S.I.E. to occur for these proton donors, unless secondary effects are dominant. Perhaps the stage of zero free-energy difference between donor and acceptor atoms has not been reached in this series, or simply that the proton is not at an energy maximum in the transition state.

The similarity of the S.I.E. for the inter- and intramolecularly catalysed reactions is of interest (Table 22), since it has recently been suggested that they may be quite different.[220]

IV Rates in Moderately Concentrated Acid

Zucker and Hammett[35] first proposed that if a T.S. contains the elements of water in addition to a proton and the substrate, then the log of the reaction rate should be linear with the log of the concentration of the hydronium ion rather than H_o.

Early attempts were made to identify $A_{SE}2$ reactions by such a criterion, but for reactions involving rate limiting proton transfer to carbon, linear correlations of log k_{obs} with H_o and the logarithm of the hydronium ion concentration have been reported.[205,221,222] The

relation between log k and H_0 may not be particularly informative, since the H_0 may not be the appropriate acidity scale for protonation of the substrate under consideration.[37] With a substrate based philosophy, Gold and Adsetts[38] have used the acidity function dependence for aromatic exchange to investigate the amount of proton transfer, which governs how loosely bound is the water molecule of $H^+ \cdots\cdots OH_2$, in the transition state.

For the acetal I, a plot of log k_{obs} against H_0 is a straight line of slope -1·08 (Fig. 10, Table 24) and the plot against log (H^+) is curved, for values determined at 25°C in perchloric acid solutions. No correlation was found with plots yielding w, w^*[17] and φ[223] values, all the plots yielding approximate curves of negative slopes.

V Salt Effects

It has been suggested that the catalytic order of strong acids may be used as a diagnostic tool in ester hydrolysis. For the A1 mechanism, perchloric acid is more effective than hydrochloric acid, but for the A-2 mechanism the order is reversed. It was concluded that acid hydrolyses which involve T.S. which are strongly hydrogen-bonded to water will be favoured by anions of high charge density.[224]

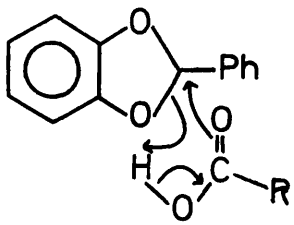
For acetal hydrolysis HCl is usually a more effective

catalyst than $HClO_4$, which has been interpreted as an initial state activity coefficient effect.[16] The hydrolysis of I at 65°C proceeds 30% faster in 1·00 M $HClO_4$ than in 1·00 M HCl, i.e. the reverse of the normal behaviour (Table 25).

The rates of the hydronium catalysed hydrolysis of I increases with increasing ionic strength, but the buffer catalysed and water catalysed reactions appear to be independent of added salts.(c.f. Tables8-15 with Tables 17-19).

To test the possibility of the kinetically equivalent specific acid-nucleophilic mechanism for the general acid catalysed hydrolysis, the ionic strength of a formate buffer was maintained constant with sodium chloride and potassium bromide. Since the nucleophilicity of these anions are different, and yet the added salts have no effect on the rate, Table 25, inter-molecular nucleophilic catalysis is therefore probably absent.[225] However, this does not eliminate a concerted specific acid-nucleophilic attack by the carboxylic acid.

This is a similar mechanism to that suggested by Kwart and Price[150] for ortho ester hydrolysis, based on the fact that H_3O^+ was a more effective catalyst than that predicted from a Brönsted plot of carboxylic acids. The



same proposal has been used to explain a negative deviation of H_3O^+ from a Brönsted plot.[240] But there is no reason why the hydronium ion cannot undergo such a reaction. It has been suggested that proton transfer, for example to amides, might be concerted with attack of water, because the proton could be moving very rapidly back and forth between substrate and solvent, and therefore could remain on the substrate for only 10^{-3} to 10^{-11} sec.[241] Bunton[242] has extended this idea to postulate that, in the acid catalysed hydrolysis of weakly basic phosphates, the attacking water molecule comes from the immediate hydration sphere of the proton.

It has been suggested that such concerted mechanisms, depending simultaneously upon the acidity and nucleophilicity of the proton donor, will have α values near zero.[244] But presumably this would depend upon the relative importance of bond making and breaking in the transition state.

VII Activation Parameters

There is a problem of how does one compare the activation parameters of a unimolecular reaction with those of a bimolecular process. The reasons for a facile intra-molecular reaction compared to its inter-molecular counterpart may be factored into a 'local concentration effect' and all other effects. As seen in the introduction the former may account for very little of the overall activation energy. However, Jencks[1] has suggested that this local concentration effect may be corrected for, by adding 8 e.u. to the observed entropy of activation for the bimolecular reaction. The factor is evaluated by using the unitary or mole fraction standard state, which is 55 M for aqueous solutions, instead of the normal standard state of 1 M. The second order rate constant would then correspond to the pseudo first order constant for a reaction of a small amount of A which is surrounded by B.

If one adopts this arbitrary scheme, the present author finds it conceptually more satisfying simply to imagine the first order rate constant for the intra-molecular process is a pseudo one, and hence its second order rate constant would be k_{obs} divided by 55. This effectively uses a standard state of 1 M in water, and amounts to subtracting 8 e.u. from the intra-molecular

case. This is purely arbitrary and has no physical significance, it simply enables one to compare contributions to the intra-molecular case other than 'local concentration effects'.

The rate constants for the hydrolysis of benzylidene catechol, I, were determined in aqueous 1·00 M perchloric acid, containing 1·0% dioxan, as a function of temperature, and are reported in Table 26. A plot of log k_{obs} against 1/T is given in Fig. 11. The entropy of activation is -8·78 ± 0·18 e.u. at 25°C, and the enthalpy of activation is +19·6 Kcal.mole^{-1}.

The activation parameters were also determined for the spontaneous hydrolysis, and the relevant data is given in Table 27. The entropy of activation, $\Delta S^{\ddagger}$, for this process is -21·1 e.u. using the pseudo first order rate constant and the enthalpy of activation, $\Delta H^{\ddagger}$, is 21·2 Kcal.mole^{-1}. Referring the reaction to a standard state of 1 M in water, by dividing the first order rate constants by 55·5 gives a $\Delta S^{\ddagger}$ of -29·1 e.u.

$\Delta S^{\ddagger}$ for the formic acid catalysed hydrolysis is -33 e.u. and $\Delta H^{\ddagger}$ is 14·70 Kcal.mole^{-1} (Tables 28, 29). These values are subject to quite a large error since the values of k_{HA} are probably known only to an accuracy of about ±5% (Fig. 14).

$\Delta S^{\ddagger}$ for a wide variety of $A_{SE}2$ reactions appear to be negative,[205] and those in which the rate limiting step is proton transfer to carbon carbon multiple bonds, values varying from 0 to -30 e.u. have been reported without recourse to a different protonation mechanism.[228] Although a more reliable range for such reactions in aqueous solution seems to be -5 to -20 e.u.,[205] for the hydronium ion as catalyst.

There have been two reports of activation parameters for $A_{SE}2$ reactions believed to involve rate limiting proton transfer to oxygen. The hydrolysis of 2-(p-nitrophenoxy) tetrahydropyran in 50% dioxan-water has a $\Delta S^{\ddagger}$ of -7·6 e.u. at 30°.[160] This was determined at pH 1·3, but it is not stated whether the second order rate constant was obtained by dividing the rates by the activity or the concentration of the hydronium ion. $\Delta S^{\ddagger}$ for the hydrolysis of 2-(2,2,2-trichloroethoxy) tetrahydropyran and 2-(2,2,2-trifluoroethoxy) tetrahydropyran are -13·0 e.u. and -3·8 e.u. respectively,[197] from rates determined in 0·01 to 0·001 M HCl and measured gas chromatographically. It is of interest to compare data obtained in this manner to that from spectrophotometric techniques. For example the latter method gave a $\Delta S^{\ddagger}$ of +7·9 e.u. for the hydrolysis of 2-ethoxy-tetrahydropyran in 50% dioxan-water.[160] Gas

chromatographic analysis for the same reaction in water gave a $\Delta S^{\ddagger}$ of +16·0 e.u.[229]

The entropy of activation for the H_3O^+ catalysed hydrolysis of I is not very diagnostic in this instance, since A-1 reactions of cyclic acetals appear to have $\Delta S^{\ddagger}$ varying from about +5 to -10 e.u. (see introduction).

A comparitive list of the activation parameters for the catalysed hydrolysis of I is given in Table 29. It would be useful to compare these quantities with the enthalpies and entropies of ionisation of the protonating acids. Unfortunately the hydronium ion is unique. The dissociation constant of H_3O^+ is usually taken as 55·5 M,[86] but since the density of water changes with temperature its molar concentration and hence the acidity constant is temperature dependent. The desired quantities near 25° are[232]

$$\Delta Hi_{H_3O^+} = -0{\cdot}05 \text{ Kcal.mole}^{-1}$$

$$\Delta Si_{H_3O^+} = +8{\cdot}1 \text{ e.u.}$$

However, it has been suggested that if water consists of large clusters of molecules then one should only use the concentration of unassociated water and not the stoicheiometric concentration to calculate the acidity constant.[233] there is little agreement upon the nature or

fraction of unassociated molecules present in liquid water.[53b] Kresge[232] has used the fraction 0·314 and the following parameters, with K_w = 17·4 M,

$$\Delta Hi_{H_3O^+} = 1{\cdot}10 \text{ Kcal.mole}^{-1}$$

$$\Delta Si_{H_3O^+} = +6{\cdot}0 \text{ e.u.}$$

The data for the dissociation of formic acid and water are[234]

$$\Delta Hi_{H_2O} = +10{\cdot}99 \text{ Kcal.mole}^{-1} \text{ at } 75°$$

$$\Delta Si_{H_2O} = -26{\cdot}51 \text{ e.u.} \text{ at } 75°$$

$$\Delta Hi_{HCO_2H} = -1{\cdot}56 \text{ Kcal.mole}^{-1} \text{ at } 60°$$

$$\Delta Si_{HCO_2H} = -22{\cdot}13 \text{ e.u.} \text{ at } 60°$$

Ignoring the effects of the degrees of freedom lost in the transition state, T.S., due to mesomeric stabilisation and other factors,[152] which will be small,[20] the observed parameters may be rationalised considering only the catalysing acid and relative solvation differences between the initial and transition states.

If one initially ignores the position of the T.S. on the reaction co-ordinate, then with a neutral catalyst, water or formic acid, proton transfer is accompanied by restriction of solvent molecules since the negatively

charged conjugate bases of these acids require solvation. This makes a negative contribution to the entropy of activation, just as it does in the ionisation equilibria of these acids. For the hydronium ion as the catalyst, proton transfer to the substrate may even be accompanied by a liberation of solvent molecules, depending on the relative solvation requirements of the transition state and the hydronium ion. If the latter is more strongly solvated then this will make a positive contribution to the entropy of activation.

The enthalpies of activation vary remarkably with the nature of the protonating acid (Table 29). Kresge[232] found for the acid catalysed hydrogen exchange in methoxy benzenes that $\Delta H^{\ddagger}$ were independent of the acid strength. But these results were obtained from acids having similar enthalpies of ionisation, and the reaction is a simple protonation as opposed to the complex concerted protonation and bond fission process being considered here. The formic acid catalysed hydrolysis has a remarkably low $\Delta H^{\ddagger}$ and is 6·5 Kcal.mole^{-1} more favourable than the water catalysed reaction. This is comparable to the carboxylic acids large favourable ΔHi compared with water.

Presumably, as the pKa of the proton donor decreases the T.S. will occur earlier on the reaction co-ordinate, with a concomitant lesser degree of solvation and desolv-

ation of the reactants. The grossly oversimplified approach, given above, ignores the relative free energy changes contributed by the varying amounts of C-O fission. It also completely ignores any contribution from non-adiabatic proton transfer effects.

Comparison with the intra-molecular reaction

The relative data are given in Tables 5 and 29. The pKa of formic acid is similar to that of 2,3-benzylidene dioxy benzoic acid II, and therefore the comparison will be made between these reactions. The leaving group in the intra-molecular reaction is the salicyl anion, and the ionisation parameters for its conjugate acid at 50°C are [257]

$$\Delta Hi = -0{\cdot}04 \text{ Kcal.mole}^{-1}$$

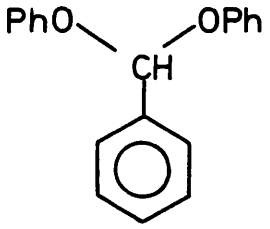
$$\Delta Si = -13{\cdot}8 \text{ e.u.}$$

Referring the intra-molecular reaction to a standard state of 1 M in water (Table 5), and the inter-molecular hydrolysis to a standard state of 1 M in formic acid (Table 29), the intra-molecular process is favoured over that of the inter-molecular one due to a more favourable ΔS^{*}, despite an adverse enthalpy change. In the opinion of the author this is not due to a 'proximity effect', but arises from the salicyl anion being the leaving group. The stability of this entity is reflected in the entropy,

just as it is in the ionisation of salicylic acid.

VII Benzaldehyde Diphenyl Acetal

In an attempt to see whether the observed general acid catalysis was a function of the ring or simply due to the formation of a stable carbonium ion and/or a good leaving group, benzaldehyde diphenyl acetal XV was prepared. Attempts to prepare the o-methoxy benzaldehyde diphenyl



XV

acetal yielded only the cyclic benzylidene catechol, I, presumably by electrophilic displacement on oxygen.

Unfortunately, XV was insoluble in aqueous solution and the kinetic studies were performed in 20% w/w dioxan-water. Making no allowance for the different solvent systems used, benzaldehyde diphenyl acetal has a k_H approximately 6 x 10^3 times greater than benzylidene catechol at 15°C and about 30 times smaller than that for benzaldehyde methyl phenyl acetal. As may be seen from Tables 30-32, XV also shows buffer catalysis. Because of the large slit-widths required to follow the reaction in

chloroacetic acid buffers, the results were not reproducible. Again, the plots of k_{obs} against the concentration of the undissociated acid were curves at high concentrations of acetic acid. The quoted values of k_{HA} were taken from rates measured in less than 0·3 M buffer. The α value using just the data for formic and acetic acids is 0·93 at 65°C. Using a calculated pKa of chloropropionic acid in 20% dioxan at 65°C of 4·65, the catalytic coefficient for this acid has a positive deviation from the Brönsted plot. The α value using just formic and chloropropionic acid is 0·7.

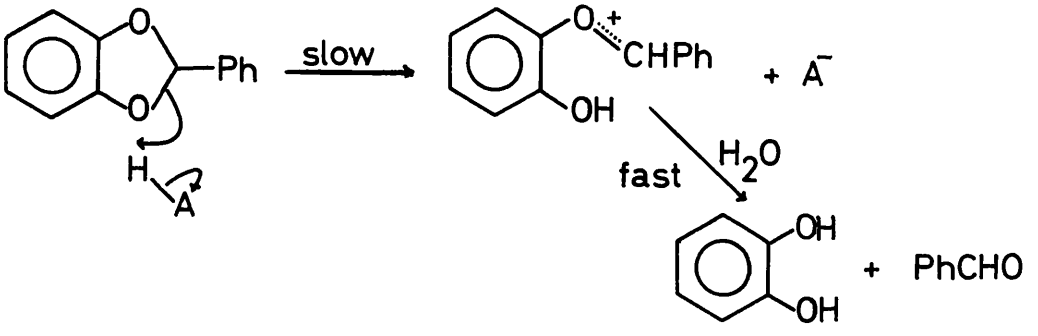
The solvent isotope effect at 15°C in 0·0519 mole fraction dioxan-water for this compound is $k_{H_3O^+}/k_{D_3O^+}$ = 0·67, Table 27, which is larger than the values normally found for A-1 hydrolysis of acetals.

As evidenced by the higher α value and lower solvent isotope effect, general acid catalysed hydrolysis of benzaldehyde diphenyl acetal occurs with a transition state more 'product-like' than the corresponding reaction of benzylidene catechol.

VIII Mechanism

The hydrolysis of benzylidene catechol has been interpreted in terms of an $A_{SE}2$ mechanism. Proton transfer occurs simultaneously with fission of the carbon oxygen bond,

producing an oxo-carbonium ion which is rapidly attacked by water to form the hydrolysis products. The reasons for the



departure from the normal A-1 mechanism of acetal hydrolysis were discussed in the introduction. A stable carbonium ion, in this case an o-hydroxy phenoxy carbonium ion, results in a more facile fission of the C-O bond. Formation of the unstable conjugate acid of the acetal is therefore not necessary for the reaction to occur. Similarly, the diphenyl acetal of benzaldehyde involves rate determining proton transfer, although here the transition state is more product-like. It is possible that the cyclic acetal is also abnormally weakly basic, and this may contribute to the observed phenomenon. It has recently been suggested that lone pair repulsions of the phenolic oxygen atoms in catechol sulphate cause severe distortions of the ring.[245] Such interactions in the present system could also enhance cleavage of the C-O bond.

The reverse of the slow step requires general base catalysed attack of a phenol on the oxo-carbonium ion, which is analogous to carbonyl addition reactions,[90,246] except that Ar replaces H.

The role of solvent molecules in proton transfer reactions has been emphasised by several authors,[90,93,194] and Grunwald has provided experimental evidence to support this claim.[247,193] For rate determining proton transfer to olefins, Gold[247] has found that the evidence is compatible with the simpler model of direct proton transfer i.e. protonation occurs from H_3O^+ rather than from its solvation shell, say, $H_9O_4^+$. The simpler model should therefore be adopted in this case, except perhaps, for the intra-molecularly general acid catalysed reaction.

It has been suggested that the slow step in these reactions could be rate limiting proton transfer to form the conjugate acid of the acetal, which then decomposes in a fast step.[44,229]

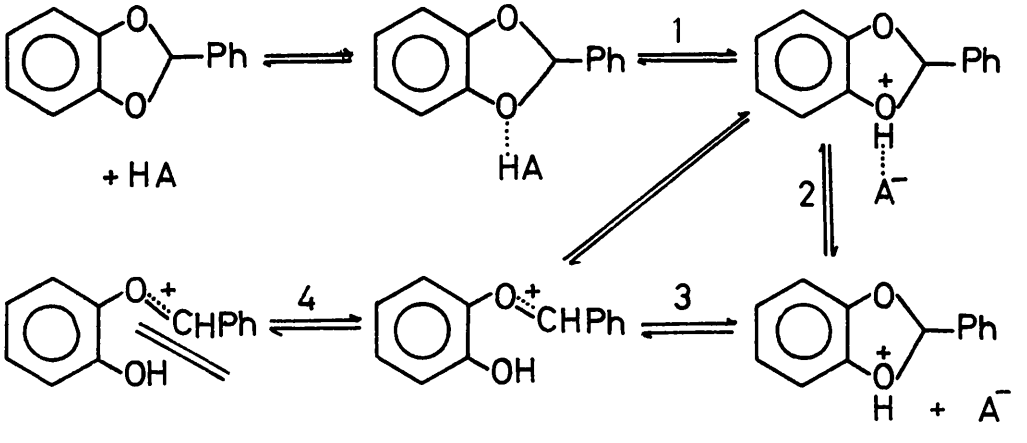
$$S + HA \underset{k_{-1}}{\overset{k_1 \text{ slow}}{\rightleftharpoons}} SH^+ \xrightarrow[k_2]{\text{fast}} \text{products}$$

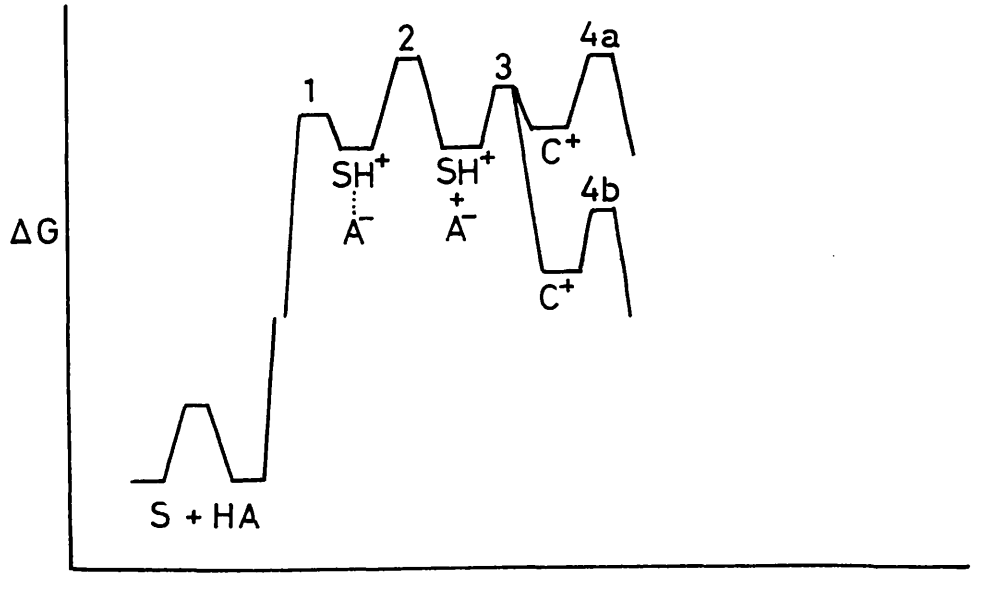
$$SH^+ \xrightarrow{k_{-3}(H_2O)} S + H_3O^+$$

This seems unlikely, since it requires k_2 to be greater than $\Sigma(k_{-1}(A^-) + k_{-3}(H_2O))$, proton transfer to water is

almost certainly diffusion controlled. The free energy barrier in the forward direction, to be compared with this diffusion step is either fission of the C-O bond or diffusion apart of the products of such a cleavage. If it is the latter, step 4a below, then it is probably of comparable free energy to diffusion of A^- and SH^+ (2). If fission of the C-O bond is extremely

Fig. 13





facile to form a carbonium-ion more stable than the conjugate acid of the acetal, then step 3 is to be compared with 2. The life-time of SH^+ would thus be less than 10^{-12} sec.

If A^- is in the transition state, which it is from the kinetic rate law, then steps 3 and 4 cannot be of greater free-energy than the diffusion away of A^- from SH^+, stage 2.

If rate limiting proton transfer with H_3O^+ as the catalyst is also suggested, then the argument is unique since the conjugate base of the acid is the solvent. If the conjugate acid of the acetal were in solvation equilibrium, which it may not be, then the slow step in the reverse reaction may only be proton transfer, stage 1, to solvent, since diffusion of reactants does not have to occur. Subsequent steps in the forward direction would have to be faster than this stage, such a mechanism is surely to be regarded as concerted.

Furthermore, the reverse step would have a β value of 0, therefore, if the relationship $1-\beta = \alpha$ is true, then α for the forward reaction would be 1, which is not the case.

It is conceivable that k_{-3} and k_2 are of similar magnitude, the problem is then how does one define con-

certedness. Eigen[93] has suggested there must be a correspondence between the motions of the atoms involved within times < 10^{-10} sec. The life-time of SH^+ will be less than 10^{-11} sec., therefore on this definition the reaction would be concerted.

Because of the small mass of the proton it has been proposed that a system undergoing proton transfer may not be in continuous equilibrium with the solvent and that the transfer may therefore be a non-adiabatic process.[202,205,232,248] This sort of 'Franck-Condon' state arises because the dielectric relaxation time of water, 10^{-10} to 10^{-11} sec.,[249] is probably greater than the time involved in a proton transfer between two properly oriented molecules, estimated at 10^{-12} to 10^{-13} sec.[250] The measured dielectric relaxation time is affected by solutes,[250] and these times are averages, and a 'few' molecules will have longer and shorter times than these. Similarly there will be a Maxwellian distribution of energies for the substrates. If most of the product is formed from the 'few' high energetic molecules, say with the proton donor already hydrogen bonded to the substrate, then, if they are sufficiently 'long-lived', these may be in a similar environment to the transition state. However, if most of the product is formed from 'many' low energy

molecules, undergoing high energetic collisions, then the transition state may have a non-equilibrated environment (see ref. 251).

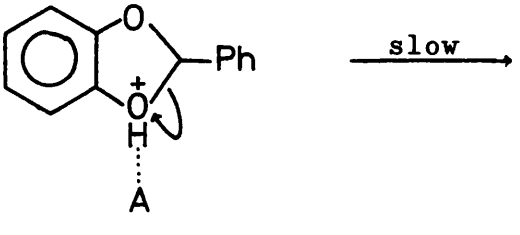
For acetals showing general acid catalysis one could say a more stable carbonium ion or a good leaving group causes there to be less C-O fission in the transition-state (T.S.), which implies that the oxygen will be less basic. Therefore the proton will be nearer to the oxygen atom in the T.S., which implies that latter is similar to the specific acid catalysed reaction. This is the opposite to that found experimentally. According to Swain's 'solvation rule',[252] the proton is nearer to the most basic oxygen in the T.S., which would unjustly circumvent the problem. The fallacy and naivety of these and similar arguments[253,254] based on postulating a T.S. and then placing the catalyst molecule in a position in which it will provide maximum stabilisation, has been amply criticised by Jencks.[255] One cannot just isolate 'part' of the reacting system and think that it will not be perturbed by the addition of the catalyst. Motion along the reaction co-ordinate is a dynamic and synergistic process.

Swain based his 'solvation rule' on the 'absence' of primary isotope effect in the general base catalysed ring

closure of chloro-alcohols,[252] but as seen earlier it is difficult to know what I.E. to expect for proton transfer between oxygen atoms. The authors concluded that proton transfer was not concerted with the reorganisation of the heavy atoms in the activated complex, but takes place rapidly either before or after the T.S. The role of the base in accelerating such reactions was suggested to be one of specific 'solvation', by hydrogen bonding. The proton is considered to be in a P.E. well in the T.S., it therefore retains its zero point energy since "translation of the proton does not contribute to motion along the reaction co-ordinate".[253]

The transition states to be considered for general acid catalysed acetal hydrolysis are therefore:

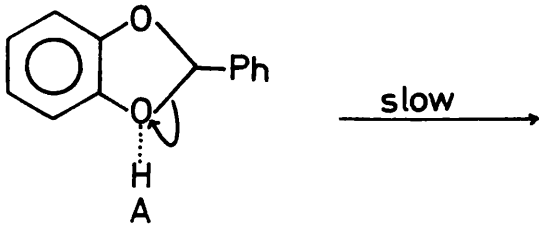
(a)



The proton remains in a stable P.E. well in the T.S. For this process to be the mechanism, fission of the C-O bond and diffusion apart of the products must be of lower free-

energy than diffusion away of A, otherwise the reaction will become specific-acid catalysed. This is the difference between the inter-molecular general acid catalysed reaction and the intra-molecular case, where for the equivalent mechanism ((1) p.104) fission of the C-O bond is rate limiting, with stage 3 of greater free energy than 1 or 2 (Fig. 13 p. 149); i.e. a normal A-1 mechanism. Although the life-time of the proton on the acetal is extremely short, when C-O fission occurs the basicity of the oxygen changes and proton transfer to another base becomes unfavourable. So although this mechanism (a) is unlikely for intermolecular general acid catalysis, it cannot be used as an argument to exclude the equivalent mechanism (1) for intra-molecular catalysis.

(b)



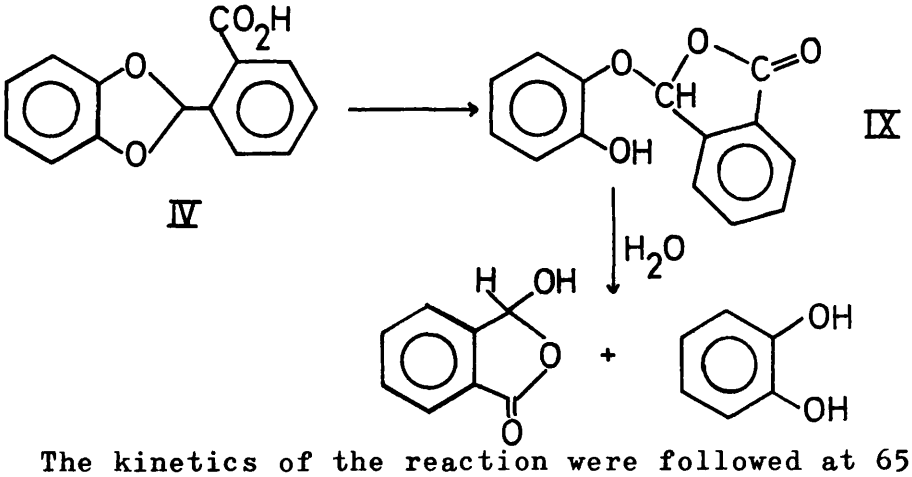
Again the proton is in a P.E. minimum. In this mechanism as C-O stretch along the reaction co-ordinate proceeds the phenolic oxygen would become more basic, the P.E. surface for the proton must change with a concomitant

reduction in the barrier to proton transfer. Whether in the T.S. this oxygen is of similar or greater basicity than the conjugate base of the proton donor is a semantic point, but proton transfer must occur extremely quickly after the transition state in this scheme. How fast is this process relative to the life-time of the T.S.?

(c) The alternative simpler approach is to say the reaction is truly concerted, and in the transition state the proton is transferred from one centre to another. The proton may or may not be in a potential well during this process. Since the difference in basicity between the donor and acceptor oxygen atoms changes during the reaction, it is conceivable that the proton never has to cross a significant energy barrier, and so remains in a potential minima.[256] Either way, it seems that the most sensible description of the reaction is to say that translation of the proton takes place in the transition state.

Intra-molecular Nucleophilic Catalysis

Catechol benzaldehyde acetals with carboxyl groups in the aldehydic residue of the molecule, IV and V (p. 99) were synthesised and their hydrolytic behaviour studied. If nucleophilic participation occurs or the o-carboxy group traps the intermediate carbonium ion, then the acylal IX would be formed. This compound was also prepared and its rate of hydrolysis measured.



The kinetics of the reaction were followed at 65°C in buffers of ionic strength 0·5 M. Hydrolysis of IV at pH 2·9, 3·4, and 4·0 proceeds via the acylal IX, the hydrolysis of the latter is slower than the ring closure reaction under these conditions. This was shown by a continuous scanning of the U.V. spectrum of the reaction mixture. Also at pH 3·55 the reaction mixture was extracted before hydrolysis was complete, the presence of acylal was shown by characteristic bands in the i.r.

spectrum (see experimental section). At pH 4·9 the U.V. spectrum again shows the intermediacy of the acylal but the rate of disappearance of the acetal is similar to the rate of hydrolysis of the acylal. The final spectra of the acylal and the acetal hydrolysis correspond exactly to that of the expected products, catechol and phthalaldehydic acid, under all these conditions. At pH 5·7 and 7·3 and in 0·1 N sodium hydroxide the acylal is hydrolysed rapidly, and there is no evidence of an intermediate in the hydrolysis of the acetal IV. Under these conditions the hydrolysis products are unstable, but the final spectra of the acylal and acetal correspond to this changed spectrum of the products. In 0·1 N and 1·0 N hydrochloric acid the spectra of the acylal and hydrolysis products are very similar, and there is no evidence of an intermediate in the hydrolysis of the acetal. Because of the small absorbance change , the rate of hydrolysis of the acylal is not known very accurately in 1·0 N HCl, but under the latter conditions it hydrolyses slower than the acetal. It cannot, therefore, be an intermediate in the hydrolysis of the acetal.

The pH-rate profile for the hydrolysis of the acylal, IX, at 65°C is given in Fig. 15, and the relevant data in Table 33. The rate constants in 1N HCl and at pH 2·7 are

not very reliable since the absorption spectrum of the acylal and hydrolysis products are very similar below pH 3, and the results were obtained from a small absorbance difference with a high background absorption. There is no evidence of buffer catalysis or spectral evidence of the acylal being converted to the acid acetal. Fig. 15 shows there is a specific acid and base catalysed hydrolysis, and possibly a small spontaneous hydrolysis.

Phthalaldehydic acid exists in the cyclic pseudo acid form in the solid state and in organic solvents as shown by its i.r. spectrum, and in DMSO as evidenced by its n.m.r. spectrum. It probably therefore does in aqueous acid solutions. The specific base catalysed hydrolysis could proceed via hydroxide ion attack on the aldehydic or the carbonyl carbon. General base catalysed nucleophilic attack of water by the ionised phenolic group is also a possibility. Similarly, several pathways may be written for the acid catalysed hydrolysis of acylals and the indications are that the mechanism is a delicate function of substrate structure, both uni-and bimolecular processes being observed.[258,259,260]

The pH-rate profile for the hydrolysis of the o-carboxybenzaldehyde acetal of catechol, IV, at 65°C is given in Fig. 16 and the relevant data in Table 34. The

reaction shows buffer catalysis and the values plotted in the graph were obtained by extrapolation to zero buffer concentration. Unfortunately, the generalised least squares program written for consecutive reactions failed to produce consistent results. The only wavelength available at which the extinction coefficients of the acetal, acylal and products were significantly different was with $E_{prods.} > E_{acylal} > E_{acetal}$, the absorption increased continually with time. The program always produced one rate constant, for this data, much larger than the other i.e. as if the data were for a simple first order reaction. The data given in Table 34 between pH 1 and 3·5 are the pseudo first order rate constants for conversion of acetal to acylal at 290 nm. At this wavelength the extinction coefficient of the acylal and hydrolysis products are identical, the absorption of the former does not change with time. Above pH 6·5 the spectrum of the hydrolysis products is unstable and changes with time, but appears to be reasonably stable at 255 nm. these questionable rate 'constants' which were obtained at this wavelength following the reaction only to 1·5 half lives are also given in Table 34. Between pH 3·4 and 4·4 the spectrum of the products change as the phthaladehydic acid dissociates, the acylal and the products no longer have

similar absorption spectra. The extinction coefficients of the acylal and acetal are now similar but significantly different ($\sim 20\%$) at 288 nm., but the rate of hydrolysis of the acylal is slow compared with ring closure of the acetal in this pH-range. Therefore the rate of the latter process was also followed at this wavelength. Above pH 5 the hydrolysis of the intermediate is faster than the disappearance of the acetal, the rate constants at pH 5·2 and 5·7 were also obtained at 288 nm. These were good first order constants, giving the same value using 1·5 to 4·5 half-lives.

If there is a specific acid and a water catalysed hydrolysis of both the undissociated and dissociated species, as well as a term representing participation by the neighbouring carboxyl group, then the overall rate will be given by:

$$\text{Rate} = k'_H(RCO_2H)(H^+) + k_o'(RCO_2H)(H_2O) + k_H^2(RCO_2^-)(H^+)$$

$$k_o^2(RCO_2^-)(H_2O) + k_N(RCO_2^-)$$

k_H are the acid catalysed reactions

k_o are the water catalysed reactions.

and k_N participation by the carboxylate group. The observed rate constant would then be given by:

$$k_{obs} = \frac{k_H'(H^+) + k_o(H_2O)}{1 + K_a/H^+} + \frac{k_H^2(H^+) + k_o^2(H_2O) + k_N}{1 + H^+/K_a}$$

The solid line in Fig. 16 is calculated from this equation - using the values given. There is no reason for including the purely water catalysed hydrolysis and the acid catalysed hydrolyses of the dissociated species other than the inclusion of these terms gives a better 'fit' to the observed pH-rate profile. The values used for these terms are purely arbitrary and intuitive. But even with these extra terms the 'fit' is not good, and the rate 'constants' obviously want a closer inspection.

The pH-rate profile for the hydrolysis of the p-carboxy derivative, V, at 65°C is given in Fig. 17 and the data in Table 35. Again, the hydrolysis is subject to buffer catalysis, and the constants plotted in the graph were obtained by extrapolation to zero buffer concentration. There is a specific acid catalysed reaction and a spontaneous hydrolysis. The increase in rate around pH 3·5 is undoubtedly due to the different substituent effects of the undissociated and dissociated carboxyl groups, the latter facilitating hydrolysis. The overall rate may probably be expressed by:

$$\text{Rate} = k_H'(RCO_2H)(H^+) + k_H^2(RCO_2^-)(H^+) + k_o'(RCO_2H)(H_2O) + k_o^2(RCO_2^-)(H_2O)$$

i.e. acid catalysed solvolysis of the undissociated acid, its conjugate base and the spontaneous hydrolysis of these two species. The observed rate constant is a complex quantity,

$$k_{obs} = \frac{k_H'(H^+)^2 + k_H^2K_a(H^+) + k_o'(H_2O)(H^+) + k_o^2(H_2O)K_a}{H^+ + K_a}$$

and the scanty data do not warrant extraction of these parameters.

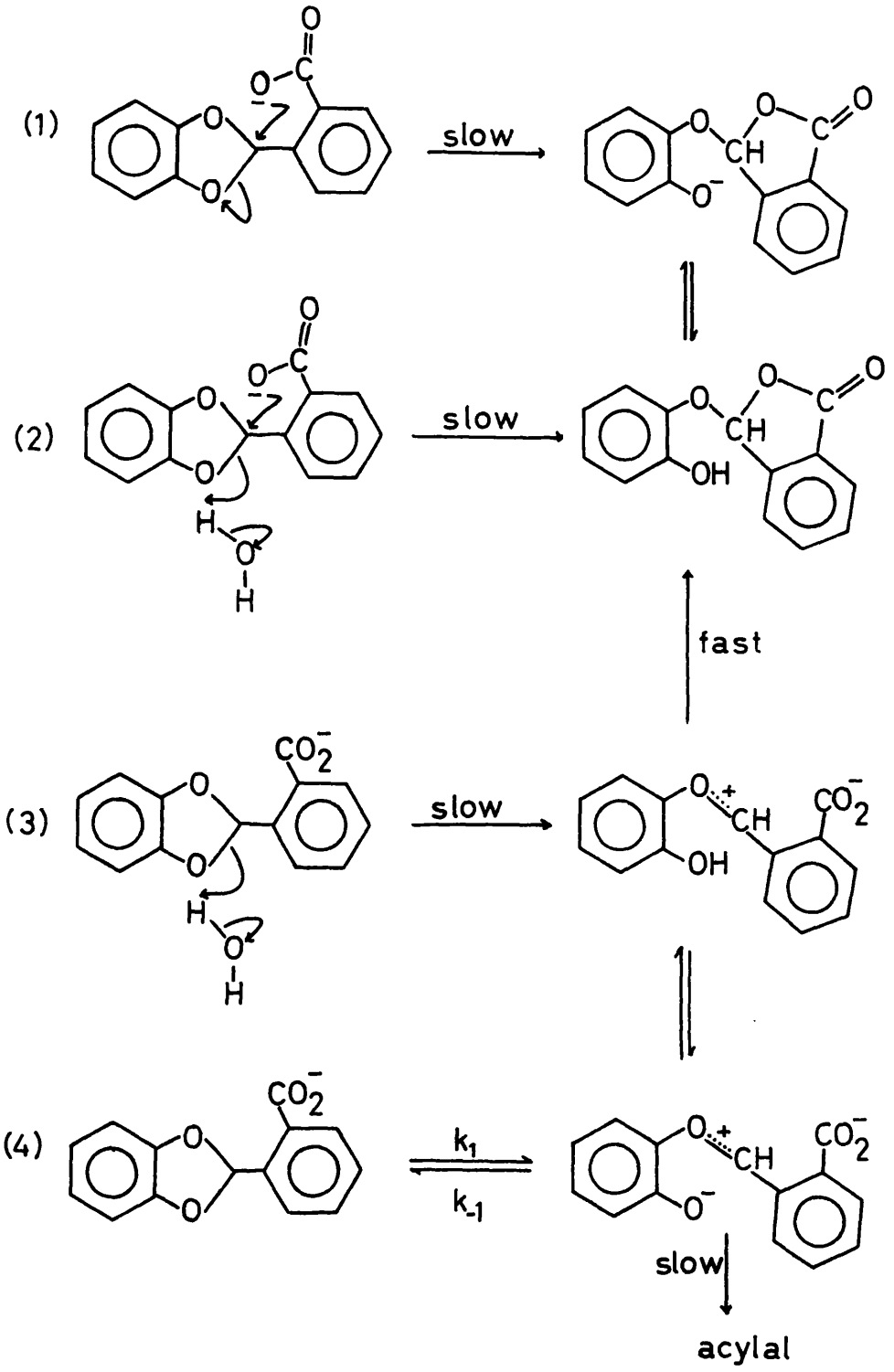
The k_H' value for the specific acid catalysed reaction of V is $7{\cdot}9 \times 10^{-4}$ $M^{-1}sec^{-1}$, that for the o-carboxy compound, IV, is $1{\cdot}25 \times 10^{-3}$ $M^{-1}sec^{-1}$, which may be compared with $1{\cdot}25 \times 10^{-2}$ $M^{-1}sec^{-1}$ for the unsubstituted derivative, I, at the same temperature. This 10 fold rate difference between IV and I is probably electronic in origin and shows that there is no large steric acceleration of the o-carboxyl group. The formic acid catalytic coefficients for the o-and p-compound are similar, $\sim 1 \times 10^{-5}$ $M^{-1}sec^{-1}$, and again about 10 times smaller than that for the unsubstituted compound, $1{\cdot}4 \times 10^{-4}$ $M^{-1}sec^{-1}$. At pH 2·7 k_{HCO_2H} is 9×10^{-6} $M^{-1}sec^{-1}$ and increases with

increasing pH, k_{AcOH} at pH 4·6 is also 9×10^{-6} $M^{-1}sec^{-1}$, showing the increased stability of the carbonium ion, due to an ionised carboxyl group, increases k_{HA}.

The spontaneous hydrolysis for the o-carboxy compound has a k_o of approximately $1{\cdot}0 \times 10^{-4}$ whilst that of the p-compound is $2{\cdot}3 \times 10^{-6}$ sec^{-1}, and that of the unsubstituted derivative I is $3{\cdot}8 \times 10^{-6}$ sec^{-1}. This rate enhancement of 40 is not due to some steric factor since the rate of the acid catalysed hydrolyses are similar. Is this enhancement due to nucleophilic participation by the ionised carboxyl group? Since up to pH 5 it is known that the acetal hydrolyses via the acylal it is fair to assume that this is so at higher pH. Plausible mechanisms for the reaction are given in Fig. 18. Below pH 5 the hydrolysis of the acylal is slower than its formation but this does not affect the general scheme.

Since the reaction exhibits buffer catalysis, which by analogy to the unsubstituted compound is general acid catalysis, it seems probable that the spontaneous reaction of IV is water catalysed, which discards mechanism 1. Mechanism 4 postulates fast, reversible, unassisted ring opening with the carboxyl group trapping the carbonium ion in a slow step. If this were so then one would expect a term in the rate law, proportional to the undissociated

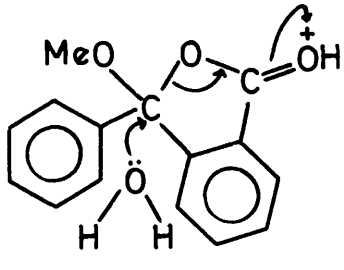
Fig. 18



acid only, resulting from the ionised carboxyl group trapping the carbonium ion in competition with an undissociated phenolic group. The latter would surely be a less effective nucleophile than the phenoxide ion. This mechanism is also therefore excluded. This sort of mechanism is of interest with reference to the recent suggestions that the rate limiting step in S_N1 reactions is destruction of an initially formed ion-pair,[262,101] and that all nucleophilic substitutions at saturated carbon are initiated by ionisation not by nucleophilic attack.[101] For acetal hydrolysis, in general, the intermediate carbonium ion is an ion-neutral molecule pair, and the normal electrostatic stabilisation brought about by the gegen ion is absent in this system. It is therefore difficult to accept this hypothesis for the specific acid catalysed hydrolysis of acetals, and for the general acid catalysed reactions impossible.

Mechanism 2 represents nucleophilic attack of the carboxylate group, on the developing electron deficient centre, concerted with proton transfer from a water molecule. Mechanism 3 has the normal rate limiting step for these compounds, the rate enhancement arising from the carboxylate group providing a more stable carbonium ion, which subsequently collapses in a fast step to the acylal.

Such stabilisation could arise from electrostatic solvation, or the solvated carboxylate group may alter the local dielectric constant of the medium and hence make the neighbouring water molecules more effective at stabilising the carbonium ion, and the transition state leading to it. Is there a distinction between electrostatic solvating function of a species and its nucleophilic function, which is responsible for covalency formation? Is solvation an ion-dipole interaction or does it involve orbital overlap?[262,263] Distinguishing between these two mechanisms is analogous to the problem of carboxylate nucleophilic participation versus electrostatic stabilisation of an incipient carbonium ion in the hydrolysis of α-haloacetates.[264] Intra-molecular nucleophilic assistance by o-carboxy groups in the hydrolysis of benzhydryl bromides has been suggested.[265] The reverse of the concerted nucleophilic attack mechanism would be rate limiting expulsion of the carboxyl group, from the acetal carbon, by the phenolic group. It is of interest that the acylal shown below hydrolyses via nucleo-



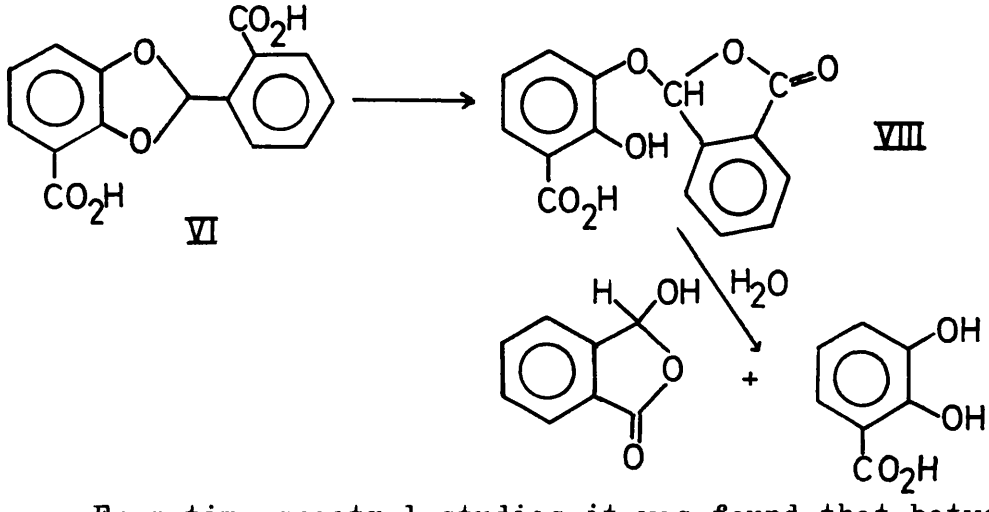
philic attack on the ketal carbon, even under acid conditions.[260,266]

On the principle that catalysis occurs where it is most needed,[246] nucleophilic participation by the carboxylate group is unexpected in this case in view of the arguments put forward to explain the observation of intermolecular general acid catalysis.

Models of the o-carboxy derivative, IV, show that, for co-linear rear-side attack of the carboxylate group, participation is possible if little bond breaking has occurred. As bond breaking moves ahead of bond making the carboxylate group can only participate at the expense of loss of delocalisation energy of the incipient carbonium ion with the phenyl ring. If the free carbonium ion has oxygen, the aldehydic carbon and the phenyl ring co-planar, then orbital overlap of the oxygen orbitals of the carboxylate group with the vacant p orbital of the carbonium ion is not possible. At present it is not possible to distinguish between mechanisms 2 and 3.

Bifunctional Catalysis

In an attempt to observe bifunctional catalysis in acetal hydrolysis the o-carboxybenzaldehyde acetal of 2,3-dihydroxy benzoic acid, VI, was synthesised and its rate of reaction compared to that of the p-carboxy derivative, VII. The possible intermediate acylal, VIII, was also prepared.

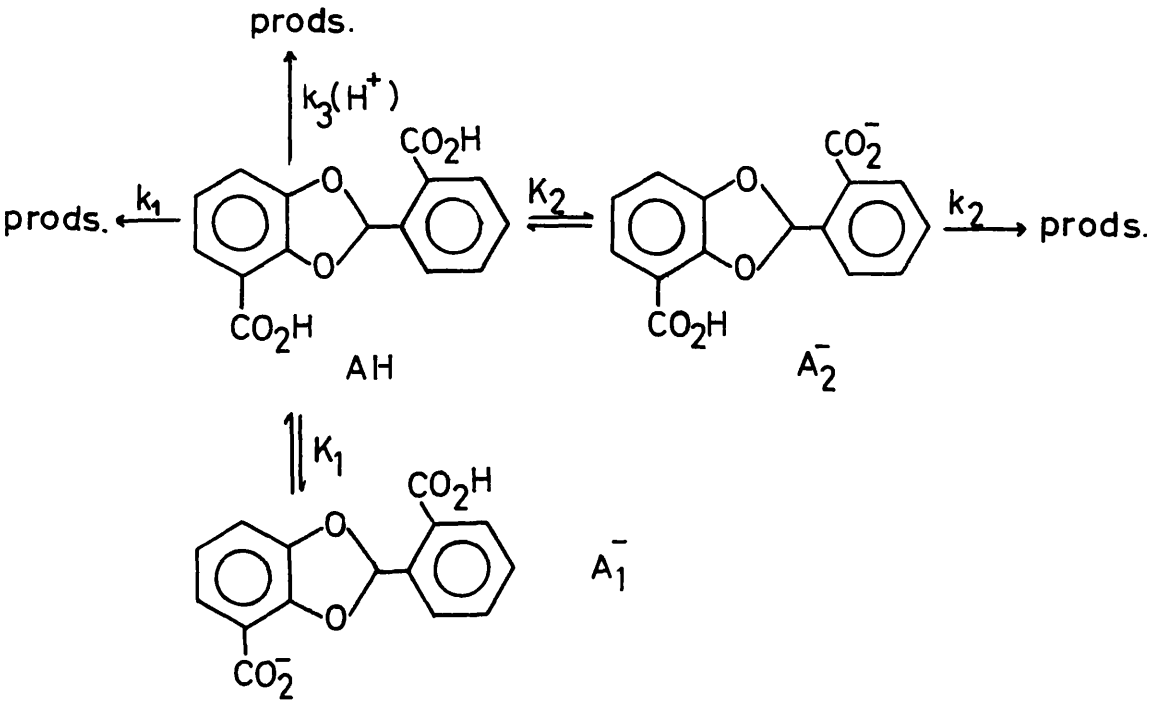


From time spectral studies it was found that between pH 2 and 5 at 55°C the acetal, VI, is converted directly to the acylal which is stable under these conditions, and is only very slowly converted to the hydrolysis products. As with the monosubstituted derivatives the U.V. absorption spectra of the acetal, acylal and hydrolysis products are not very different (Fig. 19) but careful analysis on a Carey 14 spectrophotometer leaves no doubt that the acylal is the product formed under these conditions. This was also confirmed by extracting the acylal in 90% yield from the

reaction mixture at pH 3·8 after 10 half-lives, which gave a product identical with an authentic sample as shown by m.pt., mixed m.pt., t.l.c., i.r. and, of course, U.V. spectra. At, and below pH 0 the acetal is converted directly to the hydrolysis products, and, under these conditions, the acylal is hydrolysed slower than the di-acid.

The reaction showed no buffer catalysis and the pH-rate profile is shown in Fig. 20 and the relevant data in Table 36. The dominating feature of the graph is the characteristic 'bell-shape', and the rate maximum at pH 3·75 is in the region where the concentration of the mono-anion is expected to be at a maximum. Although at first sight this looks indicative of bifunctional catalysis, with the mono-acid form of the di-acid as the reactive species, enthusiasm is dampened when the pH-rate profile is compared with that of the p-carboxybenzaldehyde derivative, VII, (Fig. 20, Table 37). This also shows a maximum in the same pH region. The rate difference between the two compounds at pH 3·75 is 3! The 'bell-shape' pH-rate profile is therefore probably an artifact of the different electronic effects of an undissociated and dissociated carboxyl group. The plateau region between pH 0 and 2 is the intra-molecular general acid catalysed reaction of the

completely undissociated species, similar to that discussed earlier. As the pH increases, the species with an undissociated carboxyl group in the phenolic residue but dissociated in the aldehydic portion of the molecule becomes more reactive, presumably due to the formation of a more stable carbonium ion (σ for p CO_2H = 0·41, σ for p CO_2^- = 0·12).[66] The rate then decreases as the unreactive dianion becomes the predominant species. The solid line in the graph is that generated by the following scheme, with the overall rate given by:



$$\text{Rate} = k_1(AH) + k_2(A_2^-) + k_3(AH)(H^+)$$

The observed rate constant will then be given by:

$$k_{obs} = \frac{k_2K_2(H^+) + k_1(H^+)^2}{((H^+) + K_1)((H^+) + K_2)} + k_3(H^+)$$

the constants used for VI were $K_1 = 1{\cdot}00 \times 10^{-4}$ M, $K_2 = 2{\cdot}50 \times 10^{-4}$ M, $k_1 = 3{\cdot}50 \times 10^{-4}$ sec^{-1} and $k_2 = 5{\cdot}20 \times 10^{-3}$ sec^{-1}. Similarly those used to generate the solid line in Fig. 20 for the p-carboxy derivative, VII, were with $K_1 = 1{\cdot}00 \times 10^{-4}$ M, $K_2 = 2{\cdot}50 \times 10^{-4}$ M, $k_1 = 2{\cdot}50 \times 10^{-4}$ sec^{-1} and $k_2 = 1{\cdot}60 \times 10^{-3}$ sec^{-1}. For comparison, the equivalent rate constant, k_o, for 2,3 - benzylidene dioxy benzoic acid, II, is $4{\cdot}94 \times 10^{-3}$ sec^{-1} at the same temperature. Using the previously cited σ values this date would give an approximate rho value of -3 to -4, for para substitution. At all acidities up to pH 4·5 the rate of autolysis of VI is slower than the rate of hydrolysis of II, but above this pH the rates are similar.

It is of interest to note that the rate of the ring closure reaction of the o-isomer, VI, is similar to that of hydrolysis of the p-isomer, VII. The uncomplicated explanation of this is that the carboxylate group simply traps the carbonium ion in a fast product determining step of the reaction. In 1-5 M $HClO_4$, the rates of hydrolysis of the two isomers are almost identical (Tables 36,37).

If the carboxylate group does indeed provide anchimeric assistance in the hydrolysis of o-carboxy-

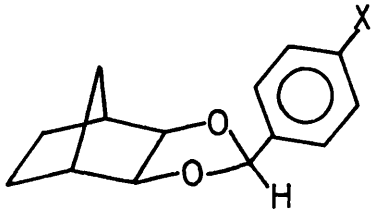
benzaldehyde acetal of catechol, IV, why does it not in the di-acid derivative, VI? As mentioned in the introduction (p. 45) a similar phenomenon has been reported by Bruice and Piskiewicz[166] in their study of o-carboxy-phenyl glucoside and o-carboxyphenyl-2-deoxy-2-acetamido glucoside. These authors were disturbed that the effects were not additive, and tried to explain the lack of bifunctional catalysis in terms of the unfavourable entropy of bringing the catalytic groups together. Even if these doubtful arguments are correct (see p. 81) their data, from a 3 point Arrhenius plot does not support their reasonings. Recalculation of their data taking the highest and medium, and then the medium and the lowest temperature values give entropies of activation differing by 16 e.u., and enthalpies varying by 5·3 Kcal.mole^{-1}. The authors were trying to 'explain' differences of 6 e.u.

A protonated phenoxy compound is a better leaving group than an unprotonated species, presumably partial proton transfer in the transition states gives an entity of intermediate ability. The driving force for the rapid rates of hydrolysis of these o-carboxyphenyl derivatives is that there is a very good leaving group, the salicyl monoanion. Whether in these compounds proton transfer is rate determining or whether there is a pre-equilibrium

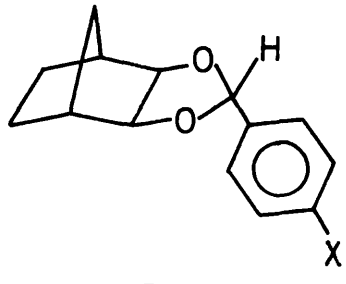
proton transfer does not matter in this argument. For the latter formation of the conjugate acid of the acetal, provides an even better leaving group than a protonated phenol. The inherent stability of the salicyl anion will mean there is less carbon-oxygen bond cleavage in the transition state for these compounds, the incipient carbonium ion will be less electrophilic and hence there will be less need for nucleophilic participation.

The A-2 Mechanism

As a sequel to the studies of catechol benzaldehyde acetal and also in an effort to detect reversible ring opening in the hydrolysis of 1,3-dioxolanes, several substituted benzaldehyde acetals of 2,3-exo-norbornanediol were prepared. These compounds were obtained isomerically



isomer I



isomer II

with X = NO_2, Cl, H and OMe

pure (see experimental section) but an unambiguous assignment of their configuration was not possible. The isomers were separated by column chromatography, and in the arbitrary assignment given above, isomer I refers to the compound with the highest R_F value, and hence the isomer which was collected first. There is a large difference in the n.m.r. spectra of these compounds (Table 38) and the chemical shift of the benzylidene proton of isomer I is consistently at lower field, about 0·55 - 0·75 p.p.m., than that of isomer II. This is an extremely large difference, and

presumably reflects the anisotropy of the aromatic residue, as supported by the broader signal of the latter for isomer II. This could arise from restricted rotation of the aromatic ring due to severe interaction with the 7-*syn* hydrogen in the isomer with the 'exo' aryl group, especially when the 'envelope flap' of the 1,3-dioxolane ring is 'up'. There is also a difference, about 0·05 - 0·15 p.p.m., in the chemical shifts of the C-2 *endo* hydrogens. The U.V. spectra of the *p*-nitro derivatives are also different, λ_{max} for the $\pi \rightarrow \pi^*$ transition occurring at 272 nm. for isomer I and at 264·3 nm. for isomer II, the extinction coefficients are similar. This indicates that the π cloud of the aromatic ring is disturbed in one of the isomers, and this could be due to the interactions discussed above. The red shift could also be due to overlap between the lone pair orbitals of the oxygen atoms and the aromatic π orbitals.[267]

The melting points for the solid compounds were always lower for isomers I.

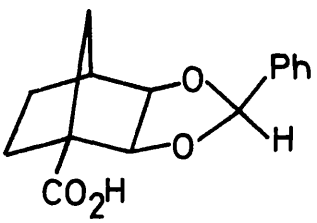
Baggett and co-workers[268] have assigned the configuration to various *cis* and *trans* substituted derivatives of 2-phenyl 1,3-dioxolane on the basis of the magnitude of the chemical shift of the benzylidene proton in the n.m.r. spectra. According to these authors the chemical shift of

the benzylidene proton occurs at lower field for the isomer in which this proton is 'cis' to a 4 or 5 substituent, isomer II in our arbitrary assignment. This was thought to be due to mutual deshielding of these entities. The assignment of configuration has been supported by chemical evidence.[269]

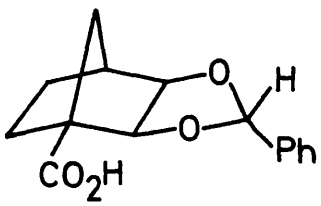
Eliel and Willy[270] have also found that in some 2,4,5-trisubstituted 1,3-dioxolanes the n.m.r. signal of the 2 proton assigned the syn configuration occurs at higher field than the corresponding anti isomer. The authors suggest that to minimise the vicinal interaction at the 4 and 5 positions, the ring adopts a half-chair configuration. The latter is, of course, not possible in a 1,3-dioxolane system fused to a norbornane structure.

If this diagnosis were applicable to the system under consideration, then the arbitrary assignment given would be reversed. It appears to the present author that the chemical shift could just as likely be affected by aryl-substituent interactions as hydrogen-substituent interactions across the ring. Intuitively the arbitrary assignment given seems reasonable, since the equilibrium constant favours isomer II (Table 39) and the probable greater dipole moment of the latter is reflected in the higher melting points and lower t.l.c. and v.p.c. R_F values for this isomer.

In an attempt to observe intra-molecular general acid catalysis in the hydrolysis of a none-salicylic acid derivative, the benzaldehyde acetal isomers of 1-carboxy 2,3-exo-norbornanediol were also prepared.



isomer I



isomer II

In Table 39 is shown the percentage of the isomers at thermodynamic equilibrium in toluene.

Preliminary experiments with the unsubstituted aryl isomers indicated that isomerisation occurred during the hydrolysis of these acetals. This was shown by t.l.c. of the organic material extracted from the aqueous reaction mixture. The generalised least squares program used to analyse the kinetic results, outputs the calculated absorbance values for the 'best fitting' rate constant. For isomer I the initial calculated absorbance values were always lower than the observed values, showing the reaction had a slight induction period i.e. the rate started off

slower than expected from the rest of the first order curve. Under certain conditions isomer II showed an 'initial burst' as indicated by the calculated absorbance values being higher than expected. This phenomenon was only just detectable by inspection of the absorbance/time graph generated on a chart recorder.

Isomerisation was investigated more quantitatively by extracting the unreacted acetal from the reaction mixture of the pure isomers, after certain periods of hydrolysis, and measuring the ratio of the isomers by n.m.r. spectroscopy. The results are given in Tables 40 - 42. For the p-methoxy derivative isomerisation occurs much faster than hydrolysis and is complete for isomer I before 10% hydrolysis has occurred. Isomer I of the unsubstituted derivative isomerises only slightly faster than it hydrolyses. Whereas for the p-nitro derivative the rate of hydrolysis is faster than isomerisation.

These results show that the rate of isomerisation is more sensitive to substitution than is the rate of hydrolysis i.e. the latter has a less negative rho value.

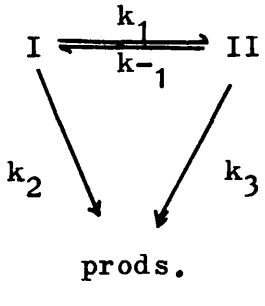
The only conceivable mechanism, apparent to the author, for acid catalysed isomerisation of 1,3-dioxolanes is fission of the carbon-oxygen bond followed by ring closure to form the other isomer. If this occurs at a rate faster

or comparable to that of hydrolysis, then the rate limiting step for the latter cannot be cleavage of the carbon-oxygen bond. As seen in the introduction, another step must therefore be rate controlling for hydrolysis. This could either be nucleophilic attack of water on the conjugate acid of the acetal, or water trapping the carbonium ion in competition with the intra-molecular hydroxyl group.

Kinetic results for the hydrolysis of these isomers will now be discussed in turn.

I p-methoxy derivative

The rates of hydrolysis of the two pure isomers were studied under various conditions. For runs with half-lives less than 10 minutes, the measured rate constants for the two isomers were identical and identical with that of an equilibrium mixture of the acetals (Table 43) within experimental error; the calculated absorbance values were in excellent agreement with the observed values. Even those runs with half-lives greater than 1 hour gave rate constants varying by only 10% and the 'fit' to the first order calculation was reasonable.



Scheme 1

For the system on the preceding page, if it is assumed that equilibrium is maintained throughout the reaction i.e. that the rate of interconversion of I and II is fast compared with their rate of reaction, then the observed rate constant is given by:

$$k_{obs} = \frac{k_2 + k_3K}{1 + K} \qquad \text{where } K = \frac{k_1}{k_{-1}}$$

So, even knowing the value of K, the rate constants for the individual isomers are not extractable from the available data.

These composite first order rate constants for the p-methoxy derivative are given in Table 43. There is no detectable buffer catalysis in acetic or chloro-acetic acid buffers (Table 44). In aniline buffers, the reaction was accompanied by precipitation, a purple colouration, and a decrease in acidity. The logarithm of the observed rate constant is proportional to the pH, and of unit slope. The rates are about 5% faster in 1·0 M $HClO_4$ than in 1·0 M HCl, which is similar, but of smaller magnitude, to catechol benzaldehyde acetal but in the opposite direction to that narmally observed in acetal hydrolysis. The solvent isotope effect on the observed rate constant is $k_{D^+}/k_{H^+} = 2{\cdot}30$ at 25°C (Table 43). If the equilibrium constant is inde-

pendent of H_2O or D_2O as solvent, and the rate constants for the individual isomers, k_2 and k_3, have similar S.I.E., then this value is that of these constants. If only the first condition holds then the observed S.I.E. is the average of the latter on k_2 and k_3.

II p-nitro derivative

The n.m.r. experiments showed that, especially for isomer II, hydrolysis was faster than isomerisation. This was supported from the kinetic results of hydrolysis of the p-nitro compounds. For isomer II the absorbance data gave the same rate constant, within ±4%, using the values for $1\frac{1}{2}$ to $3\frac{1}{2}$ half-lives. The residuals between the calculated and the observed absorbance values were satisfactory. These rate constants are given in Table 45. Isomer II hydrolyses about 15 times faster than isomer I in 1 M hydrochloric acid at 45°C (Tables 45, 46). The observed rate constant obtained by following the production of p-nitrobenzaldehyde, at a wavelength where the isomers have the same absorbance, is therefore considered to be the true hydrolytic constant, k_3, for hydrolysis of isomer II.

The hydrolytic rate 'constants' for isomer I are reported in Table 46. For this isomer the 'constants' varied depending on the number of half-lives the reaction was followed. Also the calculated absorbance values were

lower than the observed values. This may be due to the fact that, at the wavelength at which the reaction was studied, the absorbance of isomer II was slightly greater than that of I. The apparent 'initial burst' may therefore have been due to the conversion of isomer I to II. But this appears unlikely since even for isomer I the rate of hydrolysis is twice as fast as that for isomerisation (Table 42). Also the same phenomenon occurred with isomer I of the phenyl derivative.

The solvent isotope effect for isomer II is k_{D^+}/k_{H^+} = 2·32 at 65·5°C (Table 45). The entropy of activation for isomer II, calculated from only two temperatures, is -7·0 e.u. and $\Delta H^{\ddagger}$ is 21·80 Kcal.mole^{-1} (Table 45). The rate constant for the p-nitro derivative obtained from 1 M $HClO_4$ was also about 10% higher than that from 1 M HCl.

The hydrolysis of the p-nitro isomers was studied as a function of increasing concentration of perchloric acid at 45°C (Tables 45, 46). The plot of log k_{obs} for isomer II versus log $[HClO_4]$ is curved whereas the plot of log k_{obs} versus $-H_o$ is linear of slope 0·96, the value determined in 5 M acid showing a slight deviation (Fig. 21). A plot of (log k_{obs} + H_o) for isomer II versus log a_{H_2O} gives a w value of zero or slightly positive. Generally, highly negative values are observed for acetal hydrolysis.[17]

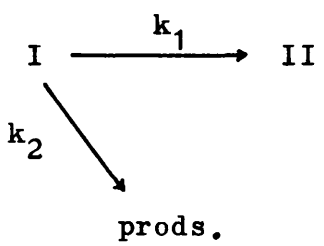
The same values are of course obtained for φ from a plot of $(\log k_{obs} + H_o)$ against $(H_o + \log (H^+))$.[223]

Isomer I hydrolyses 15 times slower in 1 M hydrochloric acid at 45°C than isomer II, and 13 times slower in the same acid concentration at 65·5°C. However as the concentration of mineral acid increases the rate differences between the isomers decreases (Tables 45, 46), and I is only 5 times slower in 5 M $HClO_4$. As mentioned earlier, the initial calculated absorbance values for isomer I are slightly lower than the observed values ($\sim$10%), when the rate constant is calculated by using less half-lives, the rate constant decreases and the 'fit' becomes better. This phenomenon is more pronounced the higher the acid concentration of the solution, and only has a small effect upon the rate constants determined in 1 and 2 M $HClO_4$ (Table 46). When the logarithm of the constants obtained from the initial slopes are plotted against -Ho, a straight line correlation is obtained of slope 1·22 (Fig. 21).

The rate of a reaction involving water in the transition state would be expected to increase less acutely than an A-1 process as the acid concentration is increased. In general, as the latter occurs the activity of water decreases, these factors will tend to oppose one another for an A-2 mechanism. One would therefore anticipate the

rate of isomerisation to increase more rapidly than hydrolysis with increasing acid concentration. This has indeed been shown for the unsubstituted derivatives reported in the next section. The difference in slopes between the isomers for the H_o correlations could be real, or simply that as H_o decreases the conversion of isomer I to isomer II increases rapidly, and therefore the observed rate constants for the hydrolysis of I contain a contribution from the hydrolysis of II.

A full analysis of the rate data was not possible with the limited figures available. The constants k_1, k_{-1}, k_2 and k_3 in scheme 1 (p. 179) could probably be evaluated as follows. By monitoring the production of aldehyde at a wavelength where the two isomers have the same extinction coefficient, the initial slopes would give k_2 and k_3 for each pure isomer. The initial reaction for isomer I may be represented as:



$$-\frac{d(I)}{dt} = (k_1 + k_2)(I)$$

If the reaction was followed at a wavelength where the two isomers have considerably different absorbances, the initial slopes would give $(k_1 + k_2)$. Hence k_1 could be determined. The value of k_{-1} could be found from a similar study using isomer II or by calculation from the equilibrium constant.

III Unsubstituted phenyl derivative

Unfortunately, the kinetic study of the hydrolysis of these isomers was performed before it was realised isomerisation was taking place. Rather it was these results which lead to the detection of isomerisation during hydrolysis.

Both isomers were studied as a function of temperature (Tables 47, 49) and of high acid concentration (Tables 48, 50). For isomer II all the studies conducted in solutions more concentrated than 3 M $HClO_4$, and also those at 65°C, the residuals between the calculated and actual absorbance values were satisfactory, the data giving a good 'fit'. At lower temperatures and acidities the observed values for II were slightly less (< 3%) than the calculated values. The rate starts off faster than expected from the rest of the data. Removing these initial values or following the reaction to fewer half-lives has very little effect upon the observed rate constant. For isomer I the observed

absorbance values were greater (< 10%) than the calculated values.

The rate is initially slower than that expected considering the later data. In 4 and 5 M $HClO_4$ solutions both isomers gave the same rate constant for hydrolysis. Under all other conditions, isomer I gave a lower value, but by removing the initial absorbance values the rate constant increases towards that of isomer II, and the calculated data gives a better 'fit' to the observed values (Tables 49, 50).

Following isomerisation during hydrolysis by n.m.r. showed that for isomer I the rate of hydrolysis is similar to that of isomerisation, whereas the latter for isomer II is about 1·5 times slower than hydrolysis (Table 40).

A system such as scheme 1 (p. 179) has been analysed,[271] and a method of computing the constants given:[272,273,275]

$$\text{Abs} = ae^{-\lambda_2 t} + be^{-\lambda_3 t}$$

where $\lambda_1 + \lambda_2 = k_1 + k_{-1} + k_2 + k_3$

$$\lambda_1\lambda_2 = k_2k_{-1} + k_2k_3 + k_1k_3$$

The final rate constant for hydrolysis is accurately known since most of the reaction proceeds at this rate. This constant is equal to λ_2 in the above equation. The difference in the initial absorbance values between those

predicted by λ_2 and the observed values is small (< 0·020 O.D. unit) and there are not enough values to allow a satisfactory analysis. So again the evaluation of all the constants in scheme 1 is not possible.

The present observations show that any extensive future study of this system using 'classical' monitoring techniques will have to involve substrates with electron-withdrawing substituents and preferably with a chromophore such that the absorption spectrum of the isomers are different. Alternatively the reaction may be followed by a careful kinetic study using n.m.r. to measure the rates of isomerisation. The latter method will obviously require substantial quantities of the substrate, which will present synthetic problems.

The observed rate constants for the hydrolysis of isomer II give a good Arrhenius plot, (Fig. 22) and the derived values are $\Delta S^{\ddagger}$ = -10·6 e.u. at 25°C, and $\Delta H^{\ddagger}$ = 18·2 Kcal.mole^{-1} (Table 47). A plot of log k_{obs} against the logarithm of the concentration of perchloric acid is curved, but linear and of slope +0·89 against $-H_o$. Again the value determined in 5 M $HClO_4$ has a slight negative deviation from this plot (Fig. 23). A plot of (log k_{obs} + H_o) against the logarithms of the activity of water in these solutions is curved, but definitely of

positive slope, w^{17} about $1\pm\cdot4$.

The solvent isotope effect on the observed rate constant for the hydrolysis of isomer II is $k_{D^+}/k_{H^+} = 2\cdot62$ at 25°C (Table 51).

The observed rate constants showed no buffer catalysis in formic and chloro-acetic acid solutions, in fact they decrease slightly with increasing buffer concentration (Table 52). The logarithm of the observed rate constant is proportional to the pH and of unit slope for isomer II (Table 53).

Benzaldehyde acetal of 1-carboxy 2,3-exo-norbornanediol

The immediate precursor in the synthetic steps towards this compound was the t-butyl ester. There is very little of isomer I present in this acetal (7·5% at equilibrium) and since this was the stage at which the isomers were separated, only isomer II was obtained in sufficient quantity to study isomerisation. Attempts to separate the isomers of the carboxylic acid acetals by chromatography were not successful.

I.r. dilution studies of the carboxy acetal in carbon tetrachloride and chloroform showed an intra-molecularly hydrogen bonded hydroxyl group at 3320 cm^{-1} (see experimental section). The pre-requisite for facile proton transfer, from the carboxyl group to the acetal oxygen, is therefore at least possible without large geometrical changes occurring in

the molecule.

To see if the neighbouring carboxyl group facilitated the rate of hydrolysis of the acetal, the latter was studied as a function of pH. The results are given in Table 55, and may be compared with the data for the unsubstituted compound in Table 53. Again these experiments were performed before it was realised isomerisation was taking place, but the kinetic data gave a satisfactory 'fit' to a first order calculation. The data reported in Table 55 are these observed rate constants for hydrolysis. The reaction was followed between pH 1 and 4, and a plot of log k_{obs} against the pH is linear of slope 1·01. The rate of hydrolysis of this acetal is about 2·5 times slower than isomer II of the benzaldehyde acetal of 2,3-exo-norbornanediol. There is thus no evidence of participation and the 1-carboxyl group does not enhance the rate of hydrolysis. In retrospect, since the acetal hydrolyses by an A-2 mechanism, for the carboxyl group to facilitate hydrolysis it would have to act as a general acid with proton transfer occurring synchronously with attack of water on the acetal carbon. Alternatively it could stabilise the conjugate acid of the acetal and hence favour the pre-equilibrium step of an A-2 mechanism. Since no enhancement is observed these mechanisms do not represent favourable reaction paths.

The carboxyl group could conceivably enhance the rate of ring opening, and hence isomerisation. A mechanism involving pre-equilibrium proton transfer would require any enhancement to result from stabilisation of the conjugate acid or the leaving group. This type of interaction would be possible for hydrolysis, therefore any facilitation of isomerisation would have to result from a mechanism involving rate limiting proton transfer concerted with ring opening.

The rate of isomerisation of isomer II was studied as a function of pH and the results are given in Table 56. In 1 M $HClO_4$ the rate of isomerisation is about 5 times greater than its hydrolysis, and about 3 times greater than isomerisation for isomer II of the unsubstituted derivative It is of interest to note this with the 2·5 times greater rate of hydrolysis of the unsubstituted acetal over that of the 1-carboxy compound. However, from Table 56, there is no plateau in the pH-rate data, and therefore there appears to be no significant term in the rate law proportional only to the acetal with an undissociated carboxyl group. The pK_a of 1-carboxy-norbornane in water at 25°C is 4·88.[274] If the present compound has a pK_a of similar magnitude, and allowing for electronic effects, the carboxyl group is not completely dissociated in the pH region studied for isomer-

isation.

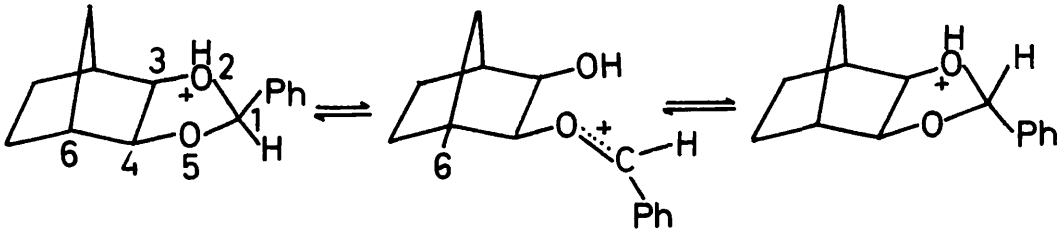
Mechanism and Discussion

As mentioned in the introduction the only previous reasonably substantiated example of an A-2 mechanism occurring in acetal hydrolysis is that of aryl - 4,4,5,5- tetramethyl - 1,3-dioxolanes,[14,27] The main evidence for assigning this mechanism to the hydrolysis of this series of compounds is a non-linear plot of log k_{obs} against H_o, but a linear one against log (H^+) of slope 2·0. More important, was the reported large rate retardation produced on substituting the acetal hydrogen with a 2-methyl group. The empirical nature of the acidity dependence criteria is shown in this work, since a linear plot of log k_{obs} against H_o is observed and yet water is definitely involved in the transition state. There have been two contrasting reports of the hydrolysis of aryl - 1,3 - oxathiolanes based on conflicting data. Fife and Jao[276] favour an A-1 mechanism, whereas De and Fedor[277] have assigned an A-2 mechanism to the hydrolysis of these compounds. The experimental evidence consisted of solvent isotope effects, activation parameters, rho value and the effect of 2-methyl substitution.

Returning to the norbornyl system under study, the carbon atom of the aldehydic group has approximately sp^3 hybridisation and is roughly tetrahedral. As fission of the C-O bond occurs it undergoes a change in hybridisation

to sp^2 and becomes approximately planar with 120° bond angles. Using these arguments the following deductions may be made by studying Fieser models of this system.

Ring opening of the benzaldehyde acetal of 2,3-exo norbornanediol involves the phenyl group moving 'out' and the hydrogen 'in' towards the ring. The opposite motion leads to severe interaction between the aryl moiety and the residue of the norbornanediol system. The plane of the aryl ring must be at an angle of 20° to the aldehydic hydrogen atom for maximum delocalisation of the charge developing on the incipient carbonium ion. If the C_1-O_2 bond breaks the phenyl group in the intermediate carbonium ion will be cis to the C_6 substituent. Because of the

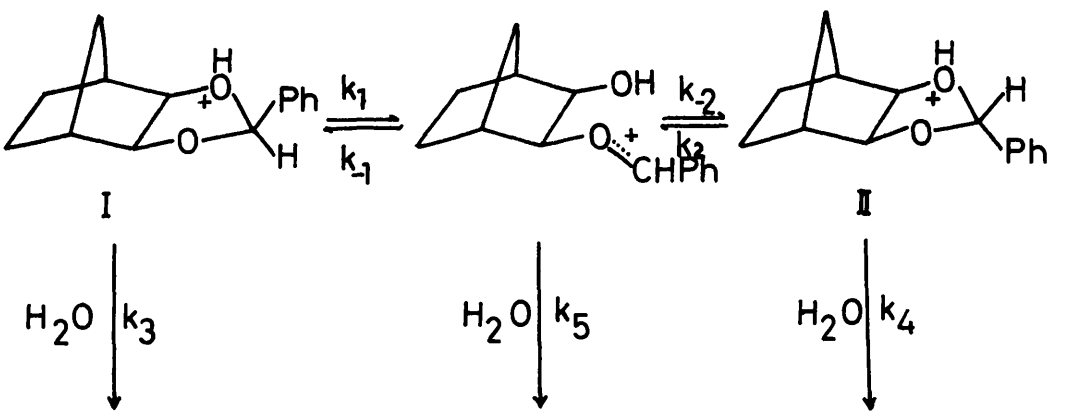


restrictions mentioned above, both isomers give the same carbonium ion. For isomerisation to occur therefore it is unnecessary for rotation to take place round the C_1-O_5 bond. Which isomer is formed depends simply on whether the phenyl

group folds up or down on ring closure.

It has been estimated that an energy of activation of 11 Kcal.mole^{-1} exists for rotation about the central carbon-oxygen bond in trimethoxy-methyl-carbonium ion, arising from the double bond character of this bond.[278] hindered rotation about the C-O bond in protonated carbonyl compounds has been observed on the n.m.r. time scale at low temperatures in non-nucleophilic media.[279]

Since it is established that isomerisation occurs during hydrolysis, what is the mechanism of the latter reaction of these acetals? The reaction path could involve rate limiting attack of water on the reversibly formed carbonium ion, k_5, or attack of water on the conjugate acid, k_3 and k_4.



Even if k_5 was diffusion controlled this could still be

the rate limiting step, since it is preceded by an unfavourable equilibrium i.e. the carbonium ion is captured intra-molecularly many more times than it is by solvent. If k_5 is the hydrolytic pathway then initially the rate of hydrolysis of I will be given by:

$$\text{Rate} = \overset{h}{k_I}.I = \frac{k_1.k_5(H_2O).K.I}{k_{-1} + k_{-2} + k_5(H_2O)}$$

and that for isomerisation by:

$$\text{Rate} = \overset{i}{k_I}.I = \frac{k_1.k_{-2}.K.I}{k_{-1} + k_{-2} + k_5(H_2O)}$$

where K = equilibrium-constant for acetal conjugate-acid formation.

The effect of substituents may distinguish between these mechanisms. It has been found that the rate of isomerisation is more dependent on the substituent than is the rate of hydrolysis, the latter has a less negative rho value. If hydrolysis occurs via step k_5, then the ratio of the rate of isomerisation to hydrolysis is given by $k_{-2}/k_5(H_2O)$. Presumably these two rate constants have similar sunstituent dependencies. It is therefore anticipated that both isomerisation and hydrolysis, via step k_5, will have similar rho values. However, if k_3 and k_4 are the rate limiting steps, even with bond breaking being more

important than bond making, one would anticipate the reaction to be less dependent on the electronic properties of the substituent. The observed dependence of isomerisation and hydrolysis therefore indicates that the rate limiting step for the latter is the nucleophilic attack of water on the conjugate acid of the acetal, k_3 and k_4. The intermediate carbonium ion does not lie on the reaction path for hydrolysis.

For the p-nitro derivative, using an equilibrium constant of 3·55 for II/I and taking the rate difference for hydrolysis of 15 between the isomers, shows that the transition state for isomer II is 2·4 Kcal.mole^{-1} more stable than that for isomer I. This is probably a reflection of the interaction between the 7-syn proton and the aromatic residue during ring opening in isomer I.

Why is ring opening reversible in the benzaldehyde acetals of 2,3-exo-norbornanediol but not in the case of benzylidene catechol, I? Why does solvent water capture the carbonium ion faster than the intra-molecular phenolic group, and yet the intra-molecular hydroxyl group can compete favourably with water for the intermediate in the norbornyl system? Either ring closure is unfavourable in the aryl acetal, or reaction of the carbonium ion with water in the norbornyl derivative is inhibited. The latter presumably

amounts to steric inhibition of solvation of the carbonium ion.

The following ad hoc explanations come to mind. In aryl ethers one of the lone pairs of the oxygen atom is delocalised into the aromatic ring, as is shown by the shorter C-O bond lengths and planarity of the system in the solid state.[245,280] The basicities of aryl ethers are also less than that of the corresponding alkyl ethers.[226] The aromatic acetal also forms a more stable intermediate, an o-hydroxy phenoxy carbonium ion. All of those suggestions will lead to ring closure in the aromatic acetal being of relative higher energy than that for the norbornyl derivative. Another reason could be not the unfavourable rate of ring closure of the aryl acetal but the facile former pathway for the norbornyl acetal.

Why does the neighbouring carboxyl group not facilitate hydrolysis or isomerisation? Geometrically, it is more favourably disposed for proton transfer to the acetal oxygen than is benzylidene 2,3-dioxy benzoic acid. It would be interesting to know if the pKa of 1-carboxy 2-exo-norbornanol is similar to the unsubstituted compound. It has been postulated [281] that at the active site of an enzyme there is a critical alignment of catalytic groups and substrate which is necessary for activity. The

observations reported here indicate that factors other than having the catalytic groups suitably oriented are also important.

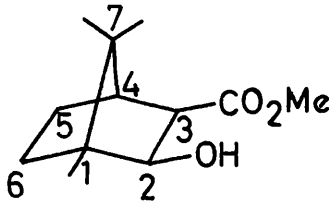
Some Studies of Ester Hydrolysis

A series of aliphatic 2-hydroxy esters was synthesised in which the dihedral angle between the hydroxyl and the ester groups varied. This was in an attempt to elucidate the exact nature of enhanced rates of hydrolysis of certain esters containing neighbouring alcoholic functions (see introduction). The following esters were prepared, 2-hydroxybutyrates, the *cis* and *trans* isomers of 2-carbethoxy cyclopentanol and cyclohexanol, aryl *cis* and *trans* 2-hydroxy cyclopentane carboxylates, *cis* and *trans* 3-carbmethoxy 2-norbornanol, and *cis* and *trans* 3-carbmethoxy 2-bornanol.

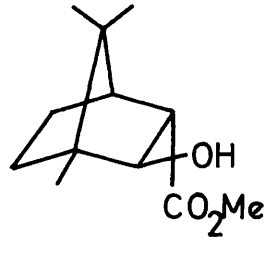
2-Bornanol 3-carboxylic acid esters

Treatment of camphor with sodium naphthalide and then carbon dioxide gave a β-keto-acid of sharp melting point, 133-134·5°C, but containing a mixture of *endo*-and *exo*-carboxylic acid. Two isomeric hydroxy esters were extractable, by chromatography, from borohydride reduction of the methyl esters of these keto-acids or of the acids themselves, followed by esterification. I.r. dilution studies in carbon tetrachloride showed that one isomer had the *cis* configuration since it was strongly intra-molecularly hydrogen bonded, between the hydroxyl and the carbonyl of the carboxylate group. Whereas under the same conditions the other isomer, assigned a *trans* configuration, showed

only the normal bands associated with non-hydrogen bonded carbonyl and hydroxyl groups. From n.m.r. studies the trans isomer has the 2-hydroxyl group exo and the 3-carboxy group endo, in the cis derivative both of these groups are exo. This assignment is in contrast to a recent study which reported that the hydroxyl group was endo in both isomers and the carboxylic acid exo or endo, based mainly on chemical tranformations to compounds of known stereochemistry.[281,282]



'cis'



'trans'

A first order interpretation of the n.m.r. spectra is in good agreement with the observed lines, bearing in mind that accidental equivalence may lead to "deceptively simple" spectra.[283] For the trans isomer H-2 is a doublet at 3·95 δ with $J_{2endo,3exo}$ = 4·0 Hz. This small coupling constant supports the trans assignment of the two groups. An exo H-2 would also be coupled to exo H-6. H-3 is a doublet of triplets centred on 3·00 δ, $J_{3exo,2endo} = J_{3exo,4}$

= 4·0 Hz. and $J_{3exo,5exo}$ = 1·4 Hz. An endo H-3 would give just a doublet, coupling occurring only between H-2 and H-3. H-4 is a triplet at 2·00 δ with $J_{4,2exo}$ and $J_{4,5exo}$ = 4 Hz. If the carbmethoxy group were exo H-4 would be just a doublet, coupling occurring only between H-4 and H-5exo.

In the cis isomer, H-2 at 3·95 δ is a doublet with $J_{2endo,3endo}$ = 8·2 Hz., supporting the cis stereochemistry. H-3 is also a doublet at 2·60 δ with $J_{3endo,2endo}$ = 8·2 Hz. An exo H-3 would also be coupled to H-4 and H-5exo. H-4 is at 2·28 δ and a doublet with $J_{4,5exo}$ = 4·0 Hz. Again were the carbmethoxy group endo H-4 would be a triplet being coupled also to H-3exo. Spin decoupling confirmed the above assignments. Long range w-form coupling has been previously established in relationship to the bicyclo [2,2,1] heptanes, leading papers to this and the n.m.r. spectra, in general, of norbornyl systems are given in references 284-291.

During a preliminary study of these esters it was found that isomerisation occurred during hydrolysis! Extraction of the organic non-acid material during the hydrolysis of the cis isomer, in 20% dioxan 0·1 N sodium hydroxide solution at room temperature, showed that both cis and trans isomers were now present. This was shown by t.l.c.

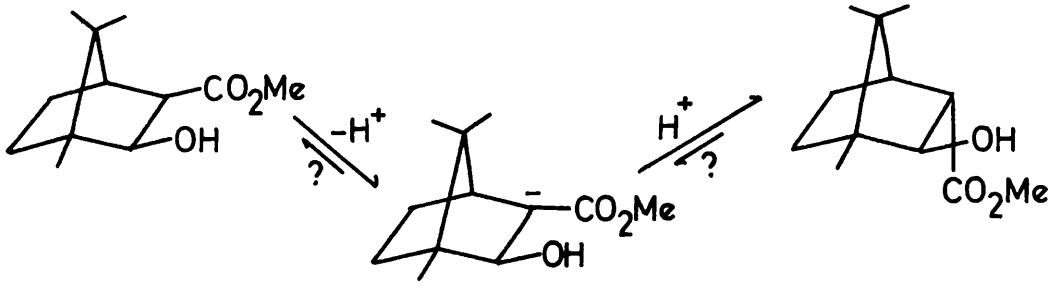
of the extracted material, there was also present a small quantity of an unsaturated compound which decolourised bromine water. N.m.r. showed that the ratio of *cis* to *trans* was about 1:1. After 48 hours in 20% dioxan carbonate buffer of pH 10 at room temperature the *cis* hydroxy ester isomerised also under these conditions. But no isomerisation occurred in 20% dioxan buffer of pH 9·7 after 4 hours at room temperature. The hydrolysis product contained the *trans* acid, identified by m.pt., n.m.r. and t.l.c., and another unidentified saturated carboxylic acid.

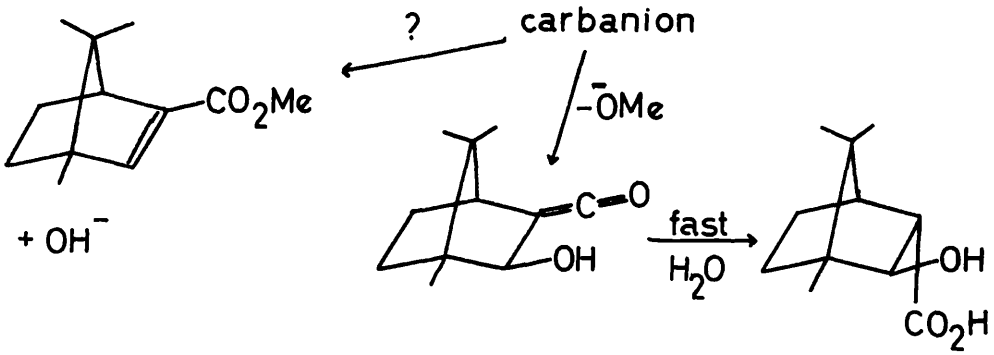
Similar experiments with the *trans* hydroxy ester in 20% dioxan 0·1 N sodium hydroxide solution at room temperature showed no evidence of the *cis* isomer being present after 2 hours of hydrolysis. However, t.l.c. of the organic non-acid material showed the presence of at least two other compounds of R_F 0·8 in benzene. This material contained no hydroxyl or ester groups and decolourised bromine water. The hydrolysis product contained only the *trans* hydroxy acid.

The most plausible mechanism for isomerisation would seem to involve base abstraction of the C-3 *endo* proton to form the carbanion. *Exo* reprotonation of this intermediate would give the *trans* isomer. Alternatively, isomerisation could result from dehydration followed by hydration of the

unsaturated ester, but under the conditions used this is extremely unlikely. It seems very surprising, if the carbanion mechanism is the pathway for isomerisation, that the reaction is so facile. Usually strongly basic conditions are required to epimerise carbmethoxy groups. Refluxing a mixture of cis and trans carbmethoxy cyclohexanol in 6 N sodium hydroxide for 36 hours gives the pure trans acid.[292] 6-endo carbmethoxy norcamphor is isomerised with sodium methoxide in methanol at 130°C.[293,294] This facile isomerisation is presumably due to severe interaction between the 7-syn methyl and the carbmethoxy group.

The question naturally arises of the mechanism of hydrolysis for these esters. It has been suggested that certain esters possessing ionisable protons adjacent to the carbonyl function may hydrolyse in alkaline solution via a pathway involving a ketene[295] or isocyanate[296] as an intermediate. For the ester under consideration the following reaction paths are possible. Kézdy[297] and Kaiser[298] have used solvent isotope effects to distinguish between the





above type of mechanisms.

The present system obviously requires further study.

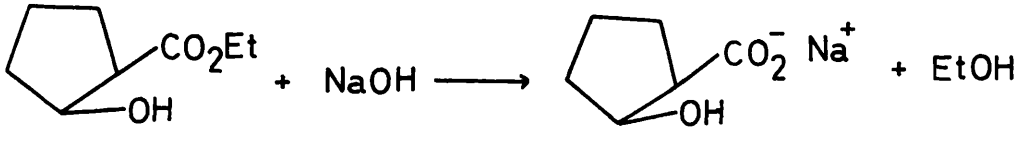
2-carboxy cyclopentanols

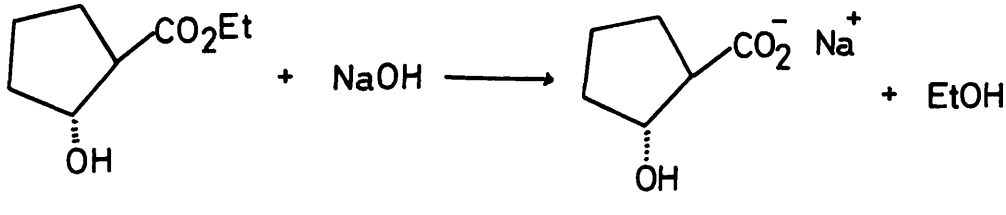
The literature preparation of the cis and trans isomers of 2-carbethoxy cyclopentanol by fractional recrystallisation of derivatives was not reproducible. The chemical methods used by the author for the specific synthesis of the individual isomers were also not successful (see experimental section).

The cis and trans isomers of the ethyl ester were separated by preparative v.p.c. The isomer collected first was assigned the cis configuration, since it exhibited intramolecular hydrogen bonding, between the hydroxyl and the carbonyl of the carboxylate group, as shown by i.r. dilution studies in carbon tetrachloride. There was no evidence of hydrogen bonding in the trans isomer. The observed spectra agreed reasonably with the previously reported study, using samples obtained by the fractional recrystallisation procedure (see experimental section). The n.m.r. spectra

of these isomers and derivatives are slightly different and details are given in the experimental section.

The pure cis isomer was dissolved in 20% dioxan 0·01 N sodium hydroxide solution at 25°C for ten minutes. V.p.c. analysis of the non-acid material after this time showed the presence of only the isomerically pure cis ester. Similar results were obtained using 0·1 N solution hydroxide under the same conditions. Identical experiments using the trans isomer showed that this compound was also stable under these conditions. The isomerically pure hydroxy-acids were the sole acid products of hydrolysis.





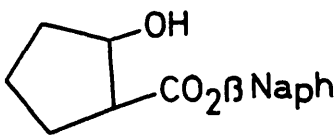
The rate of alkaline hydrolysis of the isomeric ethyl esters and ethyl cyclopentane carboxylate were studied as a function of the percentage of dioxan in the solution at

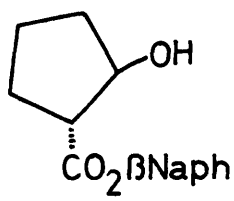
30·5°C (Table 57). A plot of log k_{obs} against the mole fraction of dioxan is given in Fig. 24. The trans hydroxy ester hydrolyses twice as fast as the cis isomer in pure aqueous solution. The unsubstituted ester is not soluble enough to follow the reaction by u.v. spectroscopy, but extrapolation from the rates determined in dioxan solutions (Fig. 24) shows that its rate of hydrolysis is similar to that of the cis isomer. As the mole fraction of dioxan increases the rate of hydrolysis of the unsubstituted ester decreases. It decreases 7 fold on going from about 10% to 70% dioxan. However, the cis isomer's rate of hydrolysis is almost independent of the dioxan concentration between about 0 and 70% dioxan, the rate varying only by $\pm$10%. k_{obs} for the trans isomer is less dependent than the unsubstituted ester upon dioxan concentration, but its rate decreases by about 2 on going from 0 to 70% dioxan. This means that in 70% dioxan solution the cis and trans isomers hydrolyse at approximately the same rate, but about 10 times faster than the unsubstituted ester. The reaction could not be followed in solutions of higher dioxan concentration because of immiscibility of the solvents at this ionic strength. It has been reported that the cis ethyl hydroxy ester hydrolyses 37 times faster than the unsubstituted compound, but no conditions were given.[141]

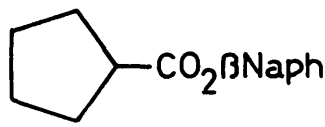
The discussion of these results will be deferred till after the report of a similar study with aryl esters of 2-hydroxy acids.

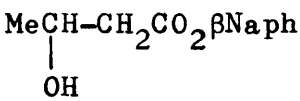
Aryl esters of 2-hydroxy acids

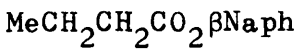
The 2-naphthyl esters of cis and trans 2-hydroxy cyclopentane carboxylic acid, cyclopentane carboxylic acid, 2-hydroxy butyric acid and butyric acid were prepared.











I.r. dilution studies in carbon tetrachloride showed that the hydroxyl group of the cis ester was intramolecularly associated with the carbonyl of the carboxylate group, whereas the trans ester is not. Similarly the hydroxy butyrate shows weak intra-molecular hydrogen bonding.

The rate of hydrolysis of these esters was studied as a function of pH and buffer type in 20% w/w dioxan. The reactions were followed by repeat scans of the u.v. spectrum, and the rate constants given in Table 60 were taken from

the half-lives of these reactions. They are therefore probably only accurate to ±10%.

The only reaction which shows a substantial enhanced rate of hydrolysis for the hydroxy ester over the unsubstituted derivative is the borate catalysed hydrolysis. The largest effect is found in the butyrate and hydroxy butyrate derivatives, the latter hydrolysing 25 times faster than the former in the particular borate buffer used. Complex formation between borate ions and hydroxyl groups is well substantiated and similar kinetic observations in salicyl ester derivatives has lead to speculation about the nature of the involvement of the complexed borate group.[299,300] The present study shows that a rigid stereochemistry of the alcohol and ester function is not necessary to observe this phenomenon.

The acid catalysed hydrolysis of the hydroxy esters is slower than that of the parent compound, and the small effect is that expected of a neighbouring substituent. Replacing one of the two water molecules suggested to participate in the mechanism of acid catalysed hydrolysis of esters[301] by a neighbouring hydroxyl group has no effect. Such participation in the present case would involve the formation of a β-lactone in two of the mechanisms proposed.[301]

The 2-hydroxy group has apparently no substantial

effect upon the buffer catalysed reaction with imidazole.

The rates of methanolysis of these esters were also studied, and the results are given in Table 59. The 2-hydroxy butyrate is solvolysed 7 times faster than the parent compound, and a similar ratio is found for the trans isomer. A slightly smaller enhancement is observed for the cis isomer.

The rates of hydrolysis of the hydroxy esters were also studied as a function of dioxan concentration at 30·5°C and ionic strength 0·01 M, and the results are given in Table 61. A plot of log k_{obs} against the mole fraction of dioxan is given in Fig. 25. The form is very similar to that obtained for the ethyl esters, but with the lower ionic strength used the rates could be followed up to about 90% dioxan, k_{obs} for the unsubstituted esters steadily decreases as the mole fraction of dioxan in the solution increases. The rates are 20-25 times slower in about 90% dioxan than they are in aqueous solution. However, the hydroxy esters again show rates of hydrolysis which are almost idenpendent, ±20%, of the dioxan concentration between about 30 and 80% dioxan. At higher dioxan concentrations the rates of these esters also decreases. In pure aqueous solution the rate of hydrolysis of the 2-hydroxy butyrate is 3 times that of the butyrate ester.

This rate difference increases as the mole fraction of dioxan increases and reaches a value of about 20 in 80 and 90% dioxan solutions. Very similar results are shown by the cis and trans esters relative to the parent cyclopentyl system.

A similar effect was found in glycine buffers although the rate differences were less marked (Table 62).

Discussion

Under the conditions which the esters were studied, the difference in rates of hydrolysis of the cis 2-hydroxy cyclopentyl carboxylates and the unsubstituted ester is not due to direct interaction between the hydroxyl and the ester groups. This is because the trans isomer, in which the hydroxyl is held rigidly away from the ester group, and the 2-hydroxy butyrate, which presumably has relatively free rotation around the C-C bond connecting the functional groups, also show this phenomenon. There is no evidence of the type of interaction found in the salicyl esters.[134,135]

One would anticipate any substantial facilitation by the direct interaction of the hydroxyl with the ester group in the cis isomer to be observed in methanolysis or dilute aqueous dioxan solutions. Water itself can act as an effective acid and base catalyst, and is also a good solvent

for polar reactions reflecting its hydrogen-bonding capacity. Therefore intra-molecular acid or base catalysis or 'internal solvation' of the transition state would be expected to be less dramatic in pure water.

One of the noticeable features of Figs. 24 and 25 is the point of inflection for all the esters occuring around 0·92 mole fraction of water. In an extension of their work on solvent polarity parameters, Winstein and Fainberg[302] investigated the solvolysis of t-butyl chloride in mixed solvents. All the mixtures studied showed inflection points when plotted against Y values.[303] For dioxan-water this occurred at 0·93 and 0·49 mole fraction of water, the former value is similar to that found in this work.

On further study[59] it was found that there is a considerable diversity of behaviour of the thermodynamic quantities of activation with the solvent composition of several binary solvent systems. In aqueous solvent mixtures involving a non-hydroxylic solvent e.g. water-dioxan, the principal contribution to the increase in rate is made by $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$ remaining approximately constant. But both quantities show small minima and maxima as solvent composition is varied. The situation is more complex when both components are hydroxylic; e.g. ethanol-water, $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ pass through sharp minima at about 0·85 mole fraction of

water for this system.[59] The solvolysis of t-butyl chloride has been further investigated and the heat capacity of activation also passes through extreema.[60b] Similar phenomena have been found in the solvolysis of benzyl chloride,[304] for which the volume of activation also passes through a maximum as the composition of the ethanol-water solvolysing medium is changed.[305] Arnett has suggested that most of the complexity of Winstein and Fainbergs results in ethanol-water is due to solvent effects on the t-butyl chloride initial state, while the transition state is following much simpler behaviour like that exhibited by ordinary uni-univalent electrolytes.[62a] Large changes in the heats of solution of both electrolytes and non-electrolytes have been found as the solvent composition is varied, and the maxima occur in exactly the same composition region where $\Delta H^{\ddagger}$ minima for t-butyl chloride solvolysis occurs.[62a,306] These phenomena are even more enhanced when the temperature of the solution is lowered.[62b] Many other physical properties pass through extreema as the solvent composition of ethanol-water systems is varied.[307] There is a negative excess entropy and enthalpy of mixing ethanol to water. The heat evolution is explained by more and better hydrogen bonds being formed.[307] The mechanism by which increased order is produced by the addition of small

amounts of alcohol or other co-solvents to water is not clear. The extra hydrogen bonding could result from alcohol-water molecules or just between water molecules yielding larger clusters. The degree of 'structuredness' must increase until it passes through a maximum, beyond this composition the highly ordered solvent structure begins to collapse, and the system behaves like an ordinary binary.[307]

Using the above arguments, Arnett[61] has rationalised the extreema found by considering the effect of the solute on the more 'structured' medium, containing the non-aqueous co-solvent, relative to its effect on water. For non-electrolytes the solution process is exothermic when structure promotion is possible, but when the latter is exhausted the process becomes less favourable. Salts are assumed to have more structure to break in the binary of higher order, leading to a higher endothermic process.

In some respects dioxan in its aqueous solutions behaves very differently from alcohols. In particular, water-dioxan mixtures do not show the characteristic maxima in sound adsorption-composition curves shown by water-alcohol mixtures, which are considered to arise from structural effects.[307] Dioxan-water mixtures show a maximum in a viscosity-concentration graph, similar to

ethanol-water, but the first derivatives of the curves $d\eta/dc$ decreases with increasing dioxan concentration yet increases with increasing ethanol concentration.[308] The partial molar enthalpy of solution, $\Delta\bar{H}_s$, of sodium tetraphenylboride in dioxan-water, gives a maximum at about 0·93 mole fraction of water.[309] The authors concluded that the contours for all aqueous binaries follow the general rules:

(1) endothermic maxima, relative to $\Delta\bar{H}_s$ in water, are found for all solutes regardless of their size, charge or substituent groups;

(2) the position of the endothermic maxima in a given binary depends primarily on the particular non-aqueous co-solvent and are nearly independent of the nature of the solute.

The observed inflection in the plots of log k_{obs} against composition of the dioxan-water medium in Figs. 24 and 25 at least has precedents even if the exact nature of the phenomenon is not understood. The observations would appear to be a function of the medium and not of the solute. It would be of interest to see if the activation parameters for hydrolysis pass through extreema around this composition. It is of interest to note in passing that large changes in the λ_{max} for electronic transitions have been observed on

changing the solvent composition in highly aqueous t-butanol.[310] This enhanced effect is thought to be due to the excited Franck-Condon state not being in equilibrium with its enviroment. One wonders if a similar phenomenon would be observed in $A_{SE}2$ reactions where it is often assumed that the transition state may not be in solvation equilibrium with its environment.

The observation that the rate constant of hydrolysis of the hydroxy esters is almost independent of dioxan concentration, between about 30 and 80% dioxan, and yet that for the unsubstituted ester decreases steadily will now be considered. The macroscopic dielectric constant for water-dioxan falls almost linearly from 78 to 30 as the mole fraction of water changes from 1·0 to 0·8, and then decreases exponentially to about 2.[307] However, the rates of hydrolysis of esters and many ionic reactions cannot be quantitatively correlated with the dielectric constant of the medium.[302,311] For the alkaline hydrolysis of esters, the variation of k_{obs} with solvent composition is not in accord with the Hughes-Ingold[58] theory of solvent action, developed for the solvolysis of alkyl halides.[312] Of course, as seen earlier, a smooth change in the free-energy of activation may be the result of random changes in the enthalpy and entropy of activation.

The change in the free-energy of activation with variation of solvent composition is given by: (see p. 58)

$$d\Delta G^{\ddagger} = d\Delta G_{s}^{\ddagger} - dG_{v}^{o}$$

i.e. the difference in the free-energy of solvation of the initial and transition state. This does not imply that there is a single transition whose solvation is varying from one medium to another. The actual nature of the T.S. and its position along the reaction co-ordinate must vary from one solution to another as the effective solvation changes.

The observed constant activation free-energy could be the result of variations in the energy of the initial and transition states (I.S. and T.S. respectively) but which cancel each other. Conversely, it could reflect a true constant free-energy of activation i.e. the energy of the I.S. and T.S. could remain the same as the solvent composition is varied. Intuitively, the latter explanation seems more satisfactory.

The rationale for this phenomenon which comes to mind is that the solvent shell of the hydroxy ester remains constant despite changes in the composition of the bulk phase. Solvent sequestering by the alcoholic function leads to a cybotactic region of different composition to that of the main phase of the medium. Since the composition of the kinetically important microscopic solvation sphere

does not change, the energy of the states likewise remains constant.

This interpretation has been suggested before for other reactions and has been called 'solvent sorting.'[313] Many authors have proposed the possibility of specific solvation of solutes in binary solvent mixtures.[314,315] Salomaa suggested that in the alcoholysis of 1-haloethers in benzene-alcohol mixtures, the T.S. was preferentially solvated by the more polar component of the solvent, alcohol.[316] It has been shown that silver ions in solutions of silver nitrate in acetonitrile-water mixtures are preferentially solvated by acetonitrile molecules, while the nitrate ions tend to be solvated by the water molecules.[317] The hydronium ion in water-dioxan mixtures may be associated with 2 or 3 molecules of dioxan.[318] The exchange of solvent molecules in and out of the cybotactic region is probably very fast, but the possibility exists that solvent sorting could lead to different products. From careful product studies of solvolysis reactions in the extreema region of highly aqueous solutions, there was found no evidence that the composition of the solvent shell around the T.S. is different from that in the bulk solvent.[319]

The frequently observed maxima or minima through which solvolytic activation parameters pass as binary solvent

mixture composition is varied has been interpreted in terms of the differences in specificity of solvation of the I.S. or T.S. by one or other components of the binary solvent system.[313] The degree to which the particular state can specifically select its solvation shell components would be expected to be temperature dependent. This should be reflected in the maximum or minimum observed in the activation energy at different temperatures. For benzyl chloride solvolysis in ethanol-water, the difference in $\Delta E^{\ddagger}$ between that at the minimum and that in pure water changes from 2·2 Kcal.mole^{-1} at 37°C to 1·6 Kcal.mole^{-1} at 65°C.[304,320]

It would be of interest to study the solvolysis of the esters under consideration as a function of temperature. If the interpretation of solvent sorting is correct, as the temperature is raised the additional thermal energy will make it more difficult for the solute, in both I.S. and T.S., to maintain the specificity of solvation. As the mole fraction of dioxan is increased together with the temperature the solvent independent region should diminish, and the rate difference between the hydroxy and unsubstituted esters should decrease.

Solvent sorting by the hydroxyl group could arise from interaction with the water or dioxan molecules by hydrogen

bonding, or from the dispersion forces as suggested by Grunwald.[57a] It is worth noting that it has been suggested that the peculiar properties of water-alcohol mixtures probably owe more to the hydrophobic alkyl group than to the hydrophilic hydroxyl function, and are related to the structure promoting tendencies of solutes possessing exposed non-polar surfaces.[307]

Grunwald found evidence from the partial pressures of the solvent components that alkali cations in dioxan-water mixtures are associated with two dioxan molecules in addition to a small but unknown amount of water.[322] Feakins[324] has interpreted the facts somewhat differently, which in turn has been criticised by Bates.[323] Feakins has interpreted the behaviour of dioxan-water mixtures in terms of the enhanced or reduced basicity of water. Water molecules hydrogen bonded to the ethereal oxygens of dioxan will have more basic oxygens than free-water molecules, which in turn affects the latter's solvating ability.[325] The solvent-system dioxan-water has been reviewed by Franks,[321] and the author has collected the relevant data on the suggested interactions between dioxan and water. These range from 1:1 to 1:6 dioxan:water associations and proposals suggesting that dioxan promotes and breaks water structure.

Since the properties of dioxan-water mixtures are not understood it may seem rather nebulous to suggest that the observed phenomenon with the hydroxy esters is due to solvent sorting. A simpler explanation could be that the composition of the solvation shell of the ester is the same as that of the bulk solvent, but that the neighbouring hydroxyl group interacts with these solvent molecules to make them a better solvating media for the reaction. Between about 30-80% dioxan this interaction is independent of solvent composition.

RESULTS

TABLE 1

Rates of hydrolysis of benzylidene 2,3-dioxy benzoic acid, II, at 55·0°C and I = 0·10 M

Buffer	pH_{55}	$k_{obs}\ 10^3\ sec^{-1}$	$k_{calc}\ 10^3\ sec^{-1}$
1·00 M HCl		12·0	
0·10 M HCl	1·29	5·39, 5·38	5·49
0·01 M HCl	2·21	4·87, 4·99	4·93
chloro-acetate	2·63	4·70, 4·75	4·76
"	3·07	4·14, 4·60	4·42
formate	3·34	4·00, 4·10	4·02
"	3·65	3·31, 3·35	3·41
"	3·88	2·86, 3·00	2·82
"	4·05	2·24, 2·30	2·34
acetate	4·45	1·28	1·29
"	5·05	0·248, 0·300	0·40
"	5·31	0·182, 0·179	0·21
"	5·35	0·154, 0·161	0·23
malonate	5·83	0·0529	0·072

TABLE 2

Test for buffer catalysis in the hydrolysis of benzylidene 2,3-dioxy benzoic acid, II at 55·0°C I = 0·50 M

[AcOH]	[OAc^-]	pH_{55}	$k_{obs}\ 10^3\ sec^{-1}$
0·080	0·020	4·09	1·85
0·160	0·040	4·07	1·83
0·240	0·060	4·08	1·87
0·320	0·080	4·07	1·83
0·400	0·100	4·09	1·95

TABLE 3

The dissociation constant of 2,3-dioxy benzoic acid, II, at 55·0°C was determined spectrophotometrically by measurement of the optical density at zero time at 326 nm in 0·1 N HCl, 0·1 N NaOH and at 10 pH's around pH 4.

$$pK_a = 3·98 \pm 0·03$$

TABLE 4

Solvent isotope effect for the hydrolysis of benzylidene 2,3-dioxy benzoic acid at 55·0°C I = 0·10 M $\%H^+$ reaction at pH 2·1 is < 1%.

0·100 M HCl pH = 2·11 k_{obs} = 5·20, 5·21 x 10^{-3} sec^{-1}

0·103 M DCl pD = 2·02[a] k_{obs} = 4·08, 4·07, 4·10 x 10^{-3} sec^{-1}

$$k_{H_2O} / k_{D_2O} = 1·28$$

a pD = pH meter glass electrode reading +0·40 (ref. 326).

TABLE 5 (see Fig. 12)

Rate of spontaneous hydrolysis of 2,3-benzylidene dioxy benzoic acid, II, as function of temperature 0·01 M HCl, I = 0·05 M, pH = 2·20. $\%H^+$ reaction at this pH is < 1% at 55°C.

Temp °C	k_{obs} sec^{-1}	$\Delta H^{\ddagger}$ $Kcal.mole^{-1}$	$\Delta S^{\ddagger}$ e.u.
65·20	$1·24 \times 10^{-2}$		
	$1·23 \times 10^{-2}$		
	$1·24 \times 10^{-2}$		
55·12	$5·23 \times 10^{-3}$		
	$5·25 \times 10^{-3}$	18·22 ± 0·01	−13·62 ± 0·25
	$5·19 \times 10^{-3}$		
45·61	$2·01 \times 10^{-3}$		
	$2·02 \times 10^{-3}$		
	$1·99 \times 10^{-3}$		
35·06	$7·67 \times 10^{-4}$	18·88 ± 0·08	−11·32 ± 0·20
	$7·70 \times 10^{-4}$		
	$7·69 \times 10^{-4}$		
25·44	$2·73 \times 10^{-4}$		
	$2·76 \times 10^{-4}$		
	$2·76 \times 10^{-4}$		

TABLE 6

Hydrogen-bonding studies of benzylidene 2,3-dioxy benzoic acid, II, and related cpds., determined on a Perkin-Elmer 225 spectrometer.

Compound	Solvent	Conc. M	$\nu_{C=O}$ cm^{-1}	ν_{OH} cm^{-1}
Benzylidene 2,3-dioxy benzoic acid	CCl_4	0·084	1697, 1740 (sh. 1763)	3533 (sh. 3510)
		0·003	a	
Benzylidene 2,3-dioxy benzoic acid	$CHCl_3$	0·016	1700, 1735	3520 (asymm.)
		0·003	a	
Methylene 2,3-dioxy benzoic acid	CCl_4	satd.	1705, 1736	3540
		< 0·002 M		
Benzylidene 3,4-dioxy benzoic acid	CCl_4	satd.	1742, 1695	3551
Benzylidene 3,4-dioxy benzoic acid	$CHCl_3$	0·015	1730, 1693	3529
		0·003	a	
o-methoxy benzoic acid	CCl_4	0·003	1710(w), 1750(s)	3366(s) 3533(w)

a = intensity of monomer peak at higher ν increases relative to that at lower ν on dilution.

sh = shoulder; asymm. = asymmetric peak; s = strong

w = weak

TABLE 7

Data for the hydrolysis of benzylidene 3,4-dioxy benzoic acid, III, as a function of pH I = 0·50 M at 55·0°C.

Buffer	pH_{55}	k_{obs} or k_{int} sec^{-1}
1·00 M HCl	~0·08	$1·98, 1·96 \times 10^{-3}$
0·10 M HCl	1·17	$1·59, 1·56 \times 10^{-4}$
0·010 M HCl	2·11	$2·94, 2·95 \times 10^{-5}$
formate	3·08	$1·67 \times 10^{-5}$
acetate	4·06	$1·03 \times 10^{-5}$

$[HCO_2H]$ M	pH_{55}	k_{obs} 10^5 sec^{-1}	k_{calc} 10^5 sec^{-1}
0·083	3·07	2·04	2·02
0·166	3·08	2·38	2·37
0·249	3·08	2·66	2·72

$k_{int} = 1·67 \times 10^{-5}$ sec^{-1}

$k_{HA} = 4·2 \times 10^{-5}$ M^{-1} sec^{-1}

[AcOH] M	pH_{55}	k_{obs} 10^5 sec^{-1}	k_{calc} 10^5 sec^{-1}
0·080	4·07	1·13	1·13
0·160	4·05	1·24	1·23
0·240	4·06	1·32	1·33
0·320	4·05	1·42	1·43

$k_{int} = 1·03 \times 10^{-5}$ sec^{-1} $\quad k_{HA} = 1·26 \times 10^{-5}$ M^{-1} sec^{-1}

TABLE 8

Formic acid catalysed hydrolysis benzylidene catechol, I, at 65·10°C in water I = 0·50 M

$[HCO_2H] : [HCO_2^-] = 9·0 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·090	2·73	4·17, 4·37	4·28
0·180	2·71	5·64, 5·61	5·63
0·270	2·72	6·98, 7·01	6·98
0·360	2·73	8·08, 7·91	8·33
0·450	2·79	8·44, 8·51	9·68

$$k_{int} = 2·93 \times 10^{-5}\ sec^{-1}$$

$$k_{HA} = 1·50 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

TABLE 9

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 65·10° in water I = 0·50 M

$[HCO_2H] : [HCO_2^-] = 4{\cdot}90 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·083	3·09	2·67, 2·74	2·69
0·166	3·10	3·77, 3·81	3·82
0·249	3·10	4·97, 4·95	4·95
0·332	3·10	5·91, 5·95	6·08
0·415	3·10	6·99, 7·03	7·21

$k_{int} = 1{\cdot}56 \times 10^{-5}\ sec^{-1}$

$k_{HA} = 1{\cdot}36 \times 10^{-4}\ M^{-1}\ sec^{-1}$

TABLE 10

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 65·12°C, in water I = 0·50 M

$[HCO_2H] : [HCO_2^-] = 1·50 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·060	3·53	1·60, 1·61	1·62
0·120	3·54	2·40, 2·35	2·35
0·180	3·55	3·07, 2·97	3·07
0·240	3·55	3·88, 3·81	3·79
0·300	3·59	4·45, 4·44	4·51

$$k_{int} = 9·06 \times 10^{-6}\ sec^{-1}$$

$$k_{HA} = 1·20 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

TABLE 11

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 65·14°C, in water I = 0·50 M

$[HCO_2H] : [HCO_2^-] = 0{\cdot}666 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·040	3·71	1·60	1·58
0·080	3·74	2·08	2·10
0·120	3·76	2·67	2·62
0·160	3·76	3·06	3·14
0·200	3·79	3·74	3·76

$k_{int} = 1{\cdot}06 \times 10^{-5}\ sec^{-1}$

$k_{HA} = 1{\cdot}30 \times 10^{-4}\ M^{-1}\ sec^{-1}$

TABLE 12

Acetic-acid catalysed hydrolysis of benzylidene catechol, I, at 65·10°C, in water I = 0·50 M

[AcOH] : [AcO^-] = 4·0 : 1

[AcOH] M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·080	4·09	1·08, 1·09	1·09
0·160	4·07	1·50, 1·52	1·51
0·240	4·08	1·88, 1·84	1·94
0·320	4·07	2·17, 2·21	2·37
0·400	4·09	2·37, 2·44	2·80

$k_{int} = 6{\cdot}58 \times 10^{-6}\ sec^{-1}$

$k_{HA} = 5{\cdot}32 \times 10^{-5}\ M^{-1}\ sec^{-1}$

TABLE 13

Acetic acid catalysed hydrolysis of benzylidene catechol, I, at 65·10°C, in water I = 0·50 M

[AcOH] : [AcO^-] = 10·0 : 1

[AcOH] M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·200	3·58	2·09, 2·09	2·09
0·400	3·58	3·11, 3·11	3·11
0·600	3·58	4·06, 3·99	4·13
0·800	3·58	4·69, 4·66	5·15
1·000	3·57	5·53, 5·45	6·17

$k_{int} = 1{\cdot}07 \times 10^{-5}\ sec^{-1}$

$k_{HA} = 5{\cdot}10 \times 10^{-5}\ M^{-1}\ sec^{-1}$

TABLE 14

Chloro-acetic acid catalysed hydrolysis of benzylidene catechol, I at 65·10°C, in water I = 0·50 M

$[ClCH_2CO_2H] : [ClCH_2CO_2^-] = 3·0 : 1$

$[ClCH_2CO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·075	2·41	5·73, 5·54	5·66
0·150	2·40	8·08, 8·18	8·17
0·225	2·40	10·2, 10·2	10·7
0·300	2·41	12·0, 12·2	13·2
0·375	2·45	13·7,13·8,14·0	15·7

$$k_{int} = 3·11 \times 10^{-5}\ sec^{-1}$$

$$k_{HA} = 3·34 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

TABLE 15

Chloro-acetic acid catalysed hydrolysis of benzylidene catechol, I, at 65·10°C, in water I = 0·50 M

$[ClCH_2CO_2H] : [ClCH_2CO_2^-] = 5{\cdot}0 : 1$

$[ClCH_2CO_2H]$ M	pH_{65}	$k_{obs}\ 10^4\ sec^{-1}$	$k_{calc}\ 10^4\ sec^{-1}$
0·100	2·25	1·16, 1·17	1·25
0·200	2·15	1·64, 1·65	1·65
0·300	2·13	2·04, 2·09	2·05
0·400	2·11	2·45, 2·42	2·45
0·500	2·10	2·84, 2·84	2·85

$$k_{int} = 8{\cdot}50 \times 10^{-5}\ sec^{-1}$$

$$k_{HA} = 3{\cdot}99 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

TABLE 16

Phosphoric-acid catalysed hydrolysis of benzylidene catechol, I at 65·10°C, in water, I = 0·50 M $[H_3PO_4] : [H_2PO_4^-] = 4·0 : 1$

$[H_3PO_4]_{stoich}$	$[H_3PO_4]_{calc}$ [a]	pH_{65}	$k_{obs}\ 10^4\ sec^{-1}$	$k_{corr}\ 10^4\ sec^{-1}$ [b]	$k_{cal}\ 10^4\ sec^{-1}$
0·080	0·020	1·80	2·87, 2·95	4·41, 4·33	4·36
0·161	0·050	1·71	4·72, 4·91	5·92, 5·73	5·81
0·241	0·088	1·64	6·69, 6·55	7·13, 7·27	7·26
0·322	0·131	1·59	7·95, 8·07	8·30, 8·25	8.71
0·402	0·175	1·56	9·53, 9·71	9·71, 9·53	10·2

$k_{HA} = 1·81 \times 10^{-3}\ M^{-1}\ sec^{-1}$ $k_{int} = 2·91 \times 10^{-4}\ sec^{-1}$

b $k_{corr} = k_{obs} - k\Delta H^+$ correcting to pH 1·56; a calculated from $K_{HA}/\gamma_{\pm}^2 = K'_{HA}$

where $\gamma_{\pm}$ = antilog $\left(\frac{-I\sqrt{I}}{1 + I^{\sqrt{2}}}\right)$ (see ref. 200)

a Using these values to calculate k_{HA} gives a curve of initial slope $4·92 \times 10^{-3}\ M^{-1}\ sec^{-1}$

TABLE 17

The formic acid catalysed hydrolysis of catechol benzaldehyde acetal, I, Temp = 65·0°C I = 0·05 M

$[HCO_2H]$ M	$[HCO_2^-]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·009	0·01	3·69	0·794, 0·794	0·794
0·018	0·02	3·68	0·901, 0·912	0·913
0·027	0·03	3·67	1·03, 1·05	1·03
0·036	0·04	3·68	1·14, 1·12	1·15
0·045	0·05	3·68	1·26, 1·26	1·27

$k_{HA} = 1{\cdot}32 \times 10^{-4}\ M^{-1}\ sec^{-1}$

$k_{int} = 6{\cdot}75 \times 10^{-6}\ sec^{-1}$

TABLE 18

The chloro-acetic acid catalysed hydrolysis of catechol benzaldehyde acetal, I, Temp = 65·0°C I = 0·05 M

$[ClCH_2CO_2H]$ M	$[ClCH_2CO_2^-]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·005	0·01	3·03	1·14	1·12
			1·10	
0·010	0·02	3·00	1·33	1·32
			1·33	
0·015	0·03	2·98	1·49	1·52
			1·54	
0·020	0·04	2·97	1·69	1·72
			1·75	
0·025	0·05	2·97	1·89	1·92
			1·95	

$k_{HA} = 3{\cdot}99 \times 10^{-4}\ M^{-1}\ sec^{-1}$

$k_{int} = 9{\cdot}25 \times 10^{-6}\ sec^{-1}$

TABLE 19

The acetic acid catalysed hydrolysis of catechol benzaldehyde acetal, I, Temp = 65·0°C I = 0·05 M

[AcOH] M	[AcO⁻] M	pH_{65}	k_{obs} 10^5 sec	k_{calc} 10^5 sec^{-1}	
0·00562	0·0007	3·76	0·625 0·628	0·626	
0·01125	0·00125	3·74	0·663 0·659	0·660	
0·0225	0·0025	3·74	0·732 0·729	0·729	$k_{int} = 5·92 \times 10^{-6}$ sec^{-1}
0·045	0·005	3·73	0·872 0·854	0·866	$k_{HA} = 6·12 \times 10^{-5}$ M^{-1} sec^{-1}
0·090	0·010	3·73	1·10 1·12	1·14	
0·135	0·015	3·72	1·27 1·31	1·41	
0·180	0·020	3·72	1·48 1·50	1·69	
[illegible]	0·025	3·72	1·68 1·65	96	

TABLE 20

Data for hydrolysis of benzylidene catechol, I, as a function of pH at 65·10°C in water I = 0·50 M

Buffer	pH_{65}	k_{obs} or k_{int} sec^{-1}
1·00 M HCl	~0·09	1·19, 1·25, 1·24 x 10^{-2}
0·10 M HCl	1·19	9·06, 8·93 x 10^{-4}
0·010 M HCl	2·11	9·72, 9·58 x 10^{-5}
chloro-acetate	2·13	8·50 x 10^{-5}
"	2·41	3·11 x 10^{-5}
formate	2·73	2·93 x 10^{-5}
"	3·10	1·56 x 10^{-6}
"	3·55	9·06 x 10^{-6}
"	3·75	1·06 x 10^{-5}
acetate	3·58	1·07 x 10^{-5}
"	4·08	6·58 x 10^{-6}
phosphate	7·27	3·66, 3·76 x 10^{-6}
0·10 M NaOH	~13	5·17 x 10^{-6}

$$k_{H^+} = 1{\cdot}24 \times 10^{-2} \ M^{-1} \ sec^{-1}$$

TABLE 21

Solvent isotope effects believed to involve rate limiting proton transfer to oxygen.

Compound	Solvent	Temp °C	k_H/k_D	Ref.
2-**p**-nitrophenyl tetrahydropyran	50% dioxan-water	30	$H_3O^+/D_3O^+ = 0{\cdot}75$	160
benzaldehyde phenyl methyl acetal	water	25	AcOH/AcOD = 1·86	231
2-(2,2,2 trifluoroethoxy) tetrahydropyran	water	25	$H_3O^+/D_3O^+ = 0{\cdot}78$	197
tropone diethyl ketal	water	15	tris H^+/tris D^+ = 1·49 H_2O/D_2O = 1·16	204
ortho-ester hydrolysis	water	15 - 35	$H_3O^+/D_3O^+ = 0{\cdot}4 - 0{\cdot}5$	3
ethyl ortho carbonate	water	?	$H_3O^+/D_3O^+ = 0{\cdot}71$ AcOH/AcOD = 1·43	230

TABLE 22

Solvent Isotope Effects

	Compound	Solvent	Temp °C	k_H/k_D
1.	catechol benzaldehyde acetal I	water	65·0	H_3O^+/D_3O^+ = 0·92
2.	ditto	ditto	65·0	AcOH/AcOD = 1·33
3.	ditto	ditto	75·2	H_2O/D_2O = 1·61
4.	benzaldehyde diphenyl acetal XV	0·0519 M.F. dioxan-water	15·0	H_3O^+/D_3O^+ = 0·67
5.	2,3-benzylidene dioxy-benzoic acid II	water	55·0	H_2O/D_2O = 1·28

2. see Table 23

3. see Table 27

5. see Table 4

1. Determined in 1·04 M HCl and DCl

k_{obs} HCl = 1·41, 1·41, 1·44 x 10^{-2} sec^{-1}

k_{obs} DCl = 1·29, 1·30, 1·26 x 10^{-2} sec^{-1}

4. Determined in 0·0102 N HCl and DCl, both 0·0519 mole fraction in dioxan.

k_{obs} HCl = 6·65, 6·75 x 10^{-3} sec^{-1}

k_{obs} DCl = 9·81, 9·80 x 10^{-3} sec^{-1}

TABLE 23 (c.f. Table 23a)

Deutero-acetic acid catalysed hydrolysis of benzylidene catechol, I, at 65·00°C, in water I = 0·05 M

[AcOD] : [AcO^-] = 10 : 1

pD = pH meter reading using glass electrode + 0·27 (ref. 327, 328).

[AcOD]	pD_{65}	$k_{obs}\ 10^6\ sec^{-1}$	$k_{calc}\ 10^6\ sec^{-1}$
0·010	4·09	4·06	4·06
0·020	4·06	4·52	4·52
0·030	4·05	4·92	4·98
0·040	4·05	5·28	5·44
0·050	4·06	5·62	5·90

$k_{int} = 3{\cdot}60 \times 10^{-6}\ sec^{-1}$

$k_{DA} = 4{\cdot}60 \times 10^{-6}\ M^{-1}\ sec^{-1}$

$k_{AcOH}/k_{AcOD} = 1{\cdot}33$

TABLE 23a

Deutero-acetic acid catalysed hydrolysis of benzylidene catechol, I, at 65·10°C, in water I = 0·50 M

[AcOD] : [AcO$^-$] = 10·0

[AcOD]	pD_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·204	3·94	1·21, 1·20	1·20
0·408	3·93	1·88, 1·91	1·89
0·612	3·91	2·45, 2·52	2·58
0·816	3·92	2·94, 3·00	3·27
1·019	3·93	3·33, 3·30	3·96

$k_{int} = 5{\cdot}14 \times 10^{-6}\ sec^{-1}$

$k_{DA} = 3{\cdot}38 \times 10^{-5}\ M^{-1}\ sec^{-1}$

$k_{HA}/k_{DA} = 1{\cdot}51$

TABLE 24

Data for hydrolysis of benzylidene catechol, I, as a function of H_o, in water at 25·14°C.

Molarity $HClO_4$	% $HClO_4$ w/w	$-H_o$ [a]	a_{H_2O} [b]	k_{obs} sec^{-1}
1·000	9·52	0·30	0·9545	2·94, 2·95 x 10^{-4}
2·000	18·11	0·85	0·9165	1·11, 1·13 x 10^{-3}
2·995	25·78	1·33	0·8590	3·61, 3·73 x 10^{-3}
3·947	32·35	1·76	0·7951	1·16, 1·15 x 10^{-2}
5·021	39·26	2·32	0·7135	4·39, 4·46 x 10^{-2}

a from ref. 329 and 17

b from ref. 330

L. L. Sq. plot $\log_{10} k_{obs}$ against $-H_o$ = 1·08

TABLE 25

Data for hydrolysis of benzylidene catechol, I, as a function of catalysing acid and electrolyte at 65·0°C in water.

Acid	k_{obs} sec^{-1}	$k_{obs}/[H^+]$
1·00 M HCl	1·25, 1·24 x 10^{-2}	1·24 x 10^{-2}
1·00 M $HClO_4$	1·64, 1·67 x 10^{-2}	1·65 x 10^{-2}
0·50 M H_2SO_4	6·26, 6·22 x 10^{-3}	1·25 x 10^{-2}

$[HCO_2H]$ M	NaCl M	NaBr M	pH_{65}	k_{obs} 10^5 sec^{-1} I = 0·50 M
0·083	0·483	0	3·09	2·70
0·083	0	0·483	3·08	2·59
0·332	0·432	0	3·10	5·91
0·332	0	0·432	3·08	6·07

TABLE 26

Hydrolysis of benzylidene catechol, I, as a function of temperature in 1·00 M $HClO_4$ in 1·0% dioxan-water

Temp °C	k_{obs} sec^{-1}
65·00	1·73, 1·67, 1·64 x 10^{-2}
55·00	6·54, 6·54, 6·58 x 10^{-3}
45·00	2·48, 2·50, 2·51 x 10^{-3}
35·00	8·79, 8·75, 8·88 x 10^{-4}
25·14	2·98, 2·94, 2·95 x 10^{-4}

L. L. Sq. treatment of

data yields

$\Delta H^{\ddagger}$ = 19·67 ± 0·02 Kcal.mole^{-1}

$\Delta S^{\ddagger}$ = -8·78 ± 0·18 e.u. at 25°C

= -8·94 ± 0·04 e.u. at 65°C

TABLE 27

Rate of spontaneous hydrolysis of benzylidene catechol, I, as functiom of temperature. Phosphate buffer

pH = 7·85 I = 0·028 M

Temp °C	k_{obs} sec^{-1}	
85·24	$2·38 \times 10^{-5}$	
	$2·39 \times 10^{-5}$	
75·17	$9·95 \times 10^{-6}$	
	$9·99 \times 10^{-6}$	
65·00	$3·80 \times 10^{-6}$	
	$3·84 \times 10^{-6}$	
75·17	$6·15 \times 10^{-6}$	in D_2O pD = 7·90
	$6·25 \times 10^{-6}$	

TABLE 28

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 65·25°C, in water I = 0·05 M

$[HCO_2H] : [HCO_2^-] = 5·0 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·010	3·23	1·13, 1·10	1·13
0·020	3·18	1·26, 1·28	1·27
0·030	3·16	1·39, 1·43	1·41
0·040	3·14	1·53, 1·56	1·55
0.050	3·14	1·69, 1·65	1·70

$$k_{int} = 9·90 \times 10^{-6}\ sec^{-1}$$

$$k_{HA} = 1·41 \times 10^{-4}\ M^{-1}\ sec^{-1}$$

TABLE 28 (Contd.)

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 60·50°C in water I = 0·05 M

$[HCO_2H] : [HCO_2^-] = 5 : 1$

$[HCO_2H]$ M	pH_{60}	$k_{obs}\ 10^5\ sec^{-1}$	$k_{calc}\ 10^5\ sec^{-1}$
0·010	3·24	0·870	0·901
0·020	3·17	0·995	1·00
0·030	3·15	1·12	1·11
0·040	3·13	1·22	1·22
0·050	3·12	1·32	1·33

$k_{int} = 7{\cdot}95 \times 10^{-6}\ sec^{-1}$

$k_{HA} = 1{\cdot}06 \times 10^{-4}\ M^{-1}\ sec^{-1}$

TABLE 28 (Contd.)

Formic acid catalysed hydrolysis of benzylidene catechol, I, at 55·18°C in water I = 0·05 M

$[HCO_2H] : [HCO_2^-] = 5 : 1$

$[HCO_2H]$ M	pH_{55}	$k_{obs}\ 10^6\ sec^{-1}$	$k_{calc}\ 10^6\ sec^{-1}$
0·010	3·22	5·55, 5·44	5·57
0·020	3·16	6·23, 6·37	6·31
0·030	3·14	7·02, 7·04	7·05
0·040	3·12	7·73, 7·89	7·79
0·050	3·12	8·55, 8·46	8·53

$k_{int} = 4·83 \times 10^{-6}\ sec^{-1}$

$k_{HA} = 7·38 \times 10^{-5}\ M^{-1}\ sec^{-1}$

TABLE 28 (Contd.)

Formic-acid catalysed hydrolysis of benzylidene catechol, I, at 50·48°C in water I = 0·05 M

$[HCO_2H] : [HCO_2^-] = 5{\cdot}0 : 1$

$[HCO_2H]$ M	pH_{50}	$k_{obs}\ 10^6\ sec^{-1}$	$k_{calc}\ 10^6\ sec^{-1}$
0·010	3·21	3·16, 3·11	3·25
0·020	3·14	3·74, 3·82	3·76
0·030	3·13	4·30, 4·35	4·27
0·040	3·11	4·68, 4·76	4·78
0·050	3·10	5·17, 5·20	5·29

$k_{int} = 2{\cdot}74 \times 10^{-6}\ sec^{-1}$

$k_{HA} = 5{\cdot}10 \times 10^{-6}\ M^{-1}\ sec^{-1}$

TABLE 29

Activation parameters for the hydrolysis of benzylidene catechol in 1% dioxan-water.

Catalyst	Standard State	Temp. Range °C	No. of Temp.	$\Delta H^{\ddagger}$ Kcal.mole^{-1}	$\Delta H^{\ddagger}$ e.u. (T°C)
H_3O^+	1 M H_3O^+	25 - 65	5	19·6±0·02	-8·78± 0·18(25°) -8·94± 0·04(65°)
HCO_2H	1 M HCO_2H	50 - 65	4	14·70±0·9	-33·1± 2·7(60°)
H_2O	1 M H_2O	65 - 85	3	21·2±0·15	-29·1± 0·50(75°)
H_2O	unimolecular	65 - 85	3	21·2±0·15	-21·1± 0·50(75°)

TABLE 30

The formic acid catalysed hydrolysis of benzaldehyde diphenyl acetal, XV, Temp. 65.0°C 20% W/W dioxan - water I = 0·50 M

$[HCO_2H] : [HCO_2^-] = 3{\cdot}0 : 1$

$[HCO_2H]$ M	pH_{65}	$k_{obs}\ 10^3$ sec^{-1}	$k_{calc}\ 10^3$ sec^{-1}	
0·114	3·56	2·60	2·62	
		2·66		
0·228	3·53	2·86	2·90	$k_{int} = 2{\cdot}34 \times 10^{-3}\ sec^{-1}$
		2·92		
0·343	3·52	3·20	3·19	$k_{HA} = 2{\cdot}50 \times 10^{-3}\ M^{-1}\ sec^{-1}$
		3·26		
0·457	3·52	3·53	3·48	
		3·48		
0·571	3·52	3·67	3·75	
		3·72		

TABLE 31

The acetic-acid catalysed hydrolysis of benzaldehyde diphenyl acetal, XV, Temp. = 65·0°C 20% W/W dioxan - water I = 0·50 M

[AcOH]:[AcO$^-$] = 3 : 1

[AcOH] M	pH_{65}	$k_{obs}\ 10^4$ sec^{-1}	$k_{calc}\ 10^4$ sec^{-1}	
0·133	4·61	2·30	2·30	
		2·28		
0·266	4·63	2·59	2·62	$k_{int} = 1·98 \times 10^{-4}\ sec^{-1}$
		2·63		
0·533	4·64	3·17	3·24	$k_{HA} = 2·38 \times 10^{-4} M^{-1} sec^{-1}$
		3·19		
0·799	4·65	3·65	3·86	
		3·62		
1·066	4·66	4·12	4·48	
		4·09		
1·332	4·68	4·35	5·10	
		4·39		

TABLE 32

Chloropropionic acid catalysed hydrolysis of benzaldehyde diphenyl acetal, XV, Temp. = 65·0°C 20% W/W dioxan-water I = 0·50 M

$[ClCH_2CH_2CO_2H] : [ClCH_2CH_2CO_2^-] = 3 : 1$

$[ClCH_2CH_2CO_2H]$ M	pH_{65}	$k_{obs}\ 10^3$ sec^{-1}	$k_{calc}\ 10^3$ sec^{-1}	
0·107	3·65	1·24	1·23	
		1·22		
0·214	3·65	1·37	1·37	$k_{int}=1·09\times10^{-3}sec^{-1}$
		1·40		
0·321	3·66	1·53	1·51	$k_{HA}=1·35\times10^{-3}M^{-1}sec^{-1}$
		1·55		
0·428	3·67	1·65	1·65	
		1·68		
0·534	3·68	1·83	1·79	
		1·77		

TABLE 33

Data for the hydrolysis of the acylal, IX, at 65·0°C and I = 0·50 M. The runs in HCl were followed at 206 nm., and all the others at 256 nm.

Buffer	pH_{65}	k_{obs} sec^{-1}
1·0 M HCl		$5·8 \times 10^{-4}$
0·10 M HCl	1·11	$1·04, 1·10 \times 10^{-4}$
chloro-acetate	2·74	$1·2 \times 10^{-5}$
formate	3·53	$1·01, 1·10 \times 10^{-5}$
acetate	4·08	$2·50, 2·48 \times 10^{-5}$
"	4·59	$6·51 \times 10^{-5}$
"	5·14	$1·44, 1·39 \times 10^{-4}$
"	5·64	$3·39, 3·44 \times 10^{-4}$
phosphate	6·05	$7·82, 7·77 \times 10^{-4}$
"	6·48	$2·10, 2·09 \times 10^{-3}$
"	7·01	$6·51, 6·83 \times 10^{-3}$
borate	7·85	$4·52, 4·43 \times 10^{-2}$

TABLE 33 (Contd.)

Test for buffer catalysis I = 0·50 M

[AcOH]	pH_{65}	k_{obs} sec^{-1} x 10^5
0·100	4·59	6·51
0·200	4·60	6·77
0·300	4·64	6·97
0·400	4·67	7·03
0·500	4·69	7·27

Effect of ionic strength at pH 4·08

I = 0·1, k_{obs} = 1·82 x 10^{-5} sec^{-1}; I = 0·4, k_{obs} = 2·42 x 10^{-5} sec^{-1}

TABLE 34

Data for the disappearance of the o-carboxybenzaldehyde acetal of catechol, IV, at 65·0°C and I = 0·50 M

Buffer	pH_{65}	k_{obs} or k_{int} sec^{-1}
1·0 M HCl		1·16, 1·10 x 10^{-3}
0·10 M HCl	1·11	1·02, 0·997 x 10^{-4}
0·010 M HCl	2·11	1·50, 1·51 x 10^{-5}
chloro-accetate	2·13	1·62 x 10^{-5}
formate	2·74	1·59 x 10^{-5}
formate	3·10	2·34 x 10^{-5}
"	3·53	3·90 x 10^{-5}
acetate	4·08	6·61 x 10^{-5}
	4·63	8·52 x 10^{-5}
"	5·15	1·23 x 10^{-4} I = 0·20 k_{obs} = 1·24x10^{-4}
"	5·70	1·40 x 10^{-4}
phosphate	6·50	9·15 x 10^{-5}
"	7·26	7·35 x 10^{-5}
carbonate	9·66	8·27 x 10^{-5}

TABLE 34 (Contd.)

Buffer catalysis in the disappearance of o-carboxybenzaldehyde acetal of catechol, IV, at 65.0°C and I = 0.50 M

$[ClCH_2CO_2H]$	pH_{65}	$k_{obs} \times 10^5$ sec^{-1}	$k_{calc} \times 10^5$ sec^{-1}
0.100	2.25	1.73	1.77
0.200	2.15	1.91	1.92
0.300	2.13	2.03	2.07
0.400	2.11	2.21	2.22

$k_o = 1.62 \times 10^{-5}$ sec^{-1}

$k_{HA} = 1.50 \times 10^{-5}$ M^{-1} sec^{-1}

$[HCO_2H]$	pH_{65}	$k_{obs} \times 10^5$ sec^{-1}	$k_{calc} \times 10^5$ sec^{-1}
0.090	2.73	1.76	1.69
0.180	2.71	1.80	1.79
0.270	2.72	1.89	1.89
0.360	2.73	2.00	1.99
0.450	2.79	2.04	2.08

$k_o = 1.59 \times 10^{-5}$ sec^{-1}

$k_{HA} = 1.1 \times 10^{-5}$ M^{-1} sec^{-1}

$[HCO_2H]$	pH_{65}	$k_{obs} \times 10^5$ sec^{-1}	$k_{calc} \times 10^5$ sec^{-1}
0.083	3.09	2.48	2.51
0.166	3.10	2.73	2.68
0.249	3.10	2.88	2.84
c.f. 0.01	3.17	1.95	I = 0.05

$k_o = 2.34 \times 10^{-5}$ sec^{-1}

$k_{HA} = 2.0 \times 10^{-5}$ M^{-1} sec^{-1}

TABLE 34 (Contd.)

$[HCO_2H]$	pH_{65}	$k_{obs} \times 10^5$ sec^{-1}	$k_{calc} \times 10^5$ sec^{-1}
0·060	3·53	4·06	4·09
0·120	3·54	4·22	4·28
0·180	3·55	4·56	4·47
0·240	3·55	4·69	4·65
0·300	3·59	4·88	4·84

$k_o = 3{\cdot}90 \times 10^{-5}$ sec^{-1}

$k_{HA} = 3{\cdot}10 \times 10^{-5}$ M^{-1} sec^{-1}

[AcOH]	pH_{65}	$k_{obs} \times 10^5$ sec^{-1}	$k_{calc} \times 10^5$ sec^{-1}
0·08	4·09	6·75	6·77
0·16	4·07	6·98	6·93
0·24	4·08	7·06	7·09

$k_o = 6{\cdot}61 \times 10^{-5}$ sec^{-1}

$k_{HA} = 2{\cdot}0 \times 10^{-5}$ M^{-1} sec^{-1}

TABLE 35

Data for the hydrolysis of the p-carboxybenzaldehyde acetal of catechol, V, at 65·0°C I = 0·50 M

Buffer	pH_{65}	k_{obs} sec^{-1}
1·0 M HCl		7·77, 7·67 x 10^{-4}
0·10 M HCl	1·11	5·57, 5·61 x 10^{-4}
0·01 M HCl	2·11	8·17, 8·22 x 10^{-4}

$[HCO_2H]$	pH_{65}	k_{obs} x 10^6 sec^{-1}	k_{calc} x 10^6 sec^{-1}
0·09	2·71	3·71	3·71
0·18	2·71	4·45	4·52
0·27	2·72	5·36	5·33

k_o = 2·90 x 10^{-6} sec^{-1} k_{HA} = 9·0 x 10^{-6} M^{-1} sec^{-1}

0·120	3·53	5·03	5·03
0·160	3·53	5·55	5·55

k_o = 3·47 x 10^{-6} sec^{-1} k_{HA} = 1·3 x 10^{-5} M^{-1} sec^{-1}

0·083	3·10	3·45	3·45
0·249	3·10	5·30	5·30

k_o = 2·54 x 10^{-6} sec^{-1} k_{HA} = 11·0 x 10^{-6} M^{-1} sec^{-1}

[AcOH]	pH_{65}	k_{obs} 10^6 sec^{-1}	k_{calc} 10^6 sec^{-1}
0·100	4·60	4·36	4·36
0·300	4·63	6·14	6·14

k_o = 3·48 x 10^{-6} sec^{-1} k_{HA} = 8·9 x 10^{-6} M^{-1} sec^{-1}

phosphate	7·30	2·28 x 10^{-6}

TABLE 36

Data for the disappearance of the o-carboxybenzaldehyde acetal of 2,3-dihydroxy benzoic acid, VI, at 55·0°C and I = 0·10 M

Buffer	pH_{55}	$k_{obs}\ 10^3\ sec^{-1}$	$k_{calc}\ 10^3\ sec^{-1}$
5·021 M $HClO_4$		9·43, 9·50	
2·995 M $HClO_4$		2·44, 2·48	
2·00 M $HClO_4$		1·28, 1·24	
1·00 M HCl		0·466, 0·514	
0·10 M HCl	1·11	0·323, 0·324	0·352
0·01 M HCl	2·11	0·493, 0·484	0·531
chloro-acetate	2·72	0·952, 0·958	0·960
formate	3·10	1·42, 1·39	1·38
"	3·32	1·71, 1·69	1·68
"	3·59	1·95, 1·93	1·96
acetate	3·84	1·97, 1·98	2·01
"	4·06	1·78, 1·84	1·81
"	4·23	1·60, 1·58	1·57
"	4·47	1·20, 1·18	1·18
"	4·71	0·920, 0·922	0·80
"	5·08	0·388, 0·363	0·37
"	5·68	0·160, 0·153	0·13

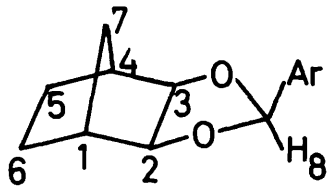
TABLE 37

Data for the hydrolysis of the p-carboxybenzaldehyde acetal of 2,3-dihydroxybenzoic acid at 55.0°C and I = 0.10 M

Buffer	pH_{55}	$k_{obs}\ 10^4\ sec^{-1}$	$k_{calc}\ 10^4\ sec^{-1}$
5.021 M $HClO_4$		86.8, 86.5	
1.00 M HCl		4.36, 4.21	
0.10 M "	1.11	2.54, 2.54	
0.01 M "	2.11	2.74, 2.68	2.70
chloro-acetate	2.72	3.71, 3.75	3.78
formate	3.10	5.00, 5.09	4.98
"	3.59	5.96, 5.85	6.35
acetate	3.84	6.49, 6.50	6.60
"	4.27	5.57, 5.64	5.21
"	4.70	2.87, 2.96	2.72
"	5.21	1.29, 1.22	1.05
"	5.68	0.294	0.26

TABLE 38

N.m.r. spectral data for the benzaldehyde acetals of exo 2,3-norbornanediol.

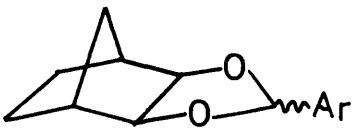


Ar	Isomer	τ value H_1	H_2 d	H_8	H_7	Ar
p-C_6H_4OMe	I	7·64	6·05	3·84	8·20	2·63, 3·13
	II	7·58	6·00	4·50	8·10	2·57, 3·13
p-$C_6H_4NO_2$	I	7·60	6·08	3·82		1·82, 2·42
	II	7·57	5·93	4·38		1·78, 2·34
p-C_6H_4Cl	I	7·65	6·12	3·88		2·67
	II	7·58	5·98	4·48		2·60
C_6H_5	I	7·64	6·12	3·85		2·68
	II	7·60	6·04	4·54		2·70

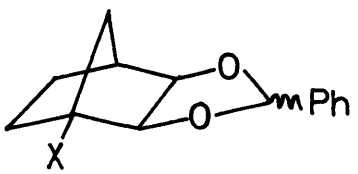
d = doublet; $J_{2endo,7anti}$ = 1·4 c/s

TABLE 39

Thermodynamic Equilibrium Composition of the benzaldehyde acetals of 2,3-exo-norbornanediol in toluene.



Ar	% isomer I	% isomer II
C_6H_5	31	69
p-$C_6H_4NO_2$	22	78
p-C_6H_4OMe	19·5	80·5



X		
CO_2H	31	69
$CO_2{}^tBu$	7·5	92·5

TABLE 40

Percentage of isomerisation occurring during the hydrolysis of benzaldehyde acetal of 2,3-exo-norbornanediol in water.

$$\% \text{ other isomer present} = \frac{\text{conc. of other isomer}}{\text{total conc. of both isomers}} \times 100$$

Isomer I

Acid	Time (mins)	Temp °C	Calc % Hydrolysis	% other isomer present
1·0 M HCl	5	22	30	30
1·0 M HCl	10	23	45	35
1·0 M HCl	20	23	70	61

Isomer II

1·0 M HCl	5	22	30	6
1·0 M HCl	10	23	45	9
1·0 M HCl	20	23	70	17

TABLE 41

Percentage of isomerisation occurring during the hydrolysis of the p-methoxybenzaldehyde acetal of 2,3-exo-norbornanediol in water.

Isomer I

Acid	Time (mins)	Temp °C	Calc % Hydrolysis	% other isomer present
0·1 N HCl	5	22	12	80
0·01 N HCl	2·5	25	< 1	53

Isomer II

0·1 N HCl	5	22	12	13
0·01 N HCl	2·5	25	< 1	12

TABLE 42

Percentage of isomerisation occurring during the hydrolysis of p-nitrobenzaldehyde acetal of 2,3-exo-norbornanediol in water.

Isomer I

Acid	Time (mins)	Temp °C	Calc % Hydrolysis	% other isomer present
4 M $HClO_4$	40	25	23	13
4 M $HClO_4$	90	25	44	17•5

Isomer II

4 M $HClO_4$	10	25	35	< 2 ?
4 M $HClO_4$	25	25	65	4

TABLE 43

The rates of hydrolysis of the p-methoxybenzaldehyde acetal of 2,3-exo-norbornanediol in water.

Buffer	Temp °C	Isomer II k_{obs} sec^{-1}	Isomer I k_{obs} sec^{-1}
2·00 M $HClO_4$	25·0	$2·49 \times 10^{-2}$	$2·44 \times 10^{-2}$
		$2·50 \times 10^{-2}$	$2·35 \times 10^{-2}$
1·00 M $HClO_4$	25·0	$9·69 \times 10^{-3}$	$9·49 \times 10^{-3}$
		$9·66 \times 10^{-3}$	$9·19 \times 10^{-3}$
1·00 M HCl	25·0	$9·26 \times 10^{-3}$	
		$9·39 \times 10^{-3}$	
1·04 M HCl	25·0	$9·39 \times 10^{-3}$	
		$9·40 \times 10^{-3}$	
1·04 M DCl	25·0	$2·15 \times 10^{-2}$	
		$2·17 \times 10^{-2}$	
0·10 M HCl	44·96	$3·85 \times 10^{-3}$	
		$3·84 \times 10^{-3}$	
0·10 M HCl	25·0	$5·89 \times 10^{-4}$	$6·23 \times 10^{-4}$
		$6·06 \times 10^{-4}$	$6·03 \times 10^{-4}$

An equilibrium mixture of the two isomers in 1·0 M HCl at 25·0°C gave a k_{obs} of $9·37 \times 10^{-3}$ sec^{-1}.

TABLE 44

Tests for buffer catalysis of p-methoxybenzaldehyde acetal of 2,3-exo-norbornanediol in water. Isomer II

I = 0·50 M

$[ClCH_2CO_2H]$	pH	Temp °C	$k_{obs}\ 10^5\ sec^{-1}$
0·100	2·13	25·0	7·63, 7·58
0·200	2·02	25·0	8·01, 8·09
0·300	2·00	25·0	8·00, 8·22
[AcOH]			
0·200	3·55	64·93	7·75
0·400	3·55	"	7·92
0·800	3·55	"	7·66
1·000	3·54	"	7·62

TABLE 45

The rates of hydrolysis of the p-nitrobenzaldehyde acetal of 2,3-exo-norbornanediol in water. Isomer II

Acid	Temp °C	k_{obs} sec^{-1}
1·00 M $HClO_4$	44·96	2·49, 2·52 x 10^{-4}
2·00 M $HClO_4$	"	8·04, 8·24 x 10^{-4}
2·995 M $HClO_4$	"	2·50, 2·46 x 10^{-3}
3·947 M $HClO_4$	"	6·38, 6·56 x 10^{-3}
5·021 M $HClO_4$	"	1·88, 1·86 x 10^{-2}
1·00 M HCl	"	2·30, 2·35 x 10^{-4}
1·03 M HCl	65·55	2·02, 1·97 x 10^{-3}
1·03 M DCl	65·55	4·59, 4·68 x 10^{-3}
3·947 M $HClO_4$	25·00	6·53, 6·42 x 10^{-4}
2·00 M $HClO_4$	"	7·73, 7·90 x 10^{-5}

TABLE 46

The rates of hydrolysis of the p-nitrobenzaldehyde acetal of 2,3-exo-norbornanediol in water. Isomer I

Acid	Temp °C	k_{obs} sec^{-1} 3 x $t_{\frac{1}{2}}$	2 x $t_{\frac{1}{2}}$
1·00 M HCl	44·96	1·58, 1·61 x 10^{-5}	1·50, 1·52 x 10^{-5}
1·00 M $HClO_4$	"	1·69, 1·67 x 10^{-5}	1·60, 1·58 x 10^{-5}
2·00 M $HClO_4$	"	7·80 x 10^{-5}	7·42 x 10^{-5}
2·995 M $HClO_4$	"	3·23, 3·12 x 10^{-4}	2·89, 2·93 x 10^{-4}
3·947 M $HClO_4$	"	1·08, 1·14 x 10^{-3}	9·10 x 10^{-4}
5·021 M $HClO_4$	"	5·14, 5·24 x 10^{-3}	4·43, 4·52 x 10^{-3}
1·03 M HCl	65·55	1·93, 1·94 x 10^{-4}	1·89, 1·92 x 10^{-4}
1·03 M DCl	65·55	4·99, 4·89 x 10^{-4}	4·88, 4·81 x 10^{-4}
3·947 M $HClO_4$	25·00	9·69, 9·48 x 10^{-5}	8·43, 8·17 x 10^{-5}

An equilibrium mixture of the two isomers gave the following rate constants.

Acid	Temp °C	k_{obs} sec^{-1}
5·021 M $HClO_4$	44·96	1·17, 1·22 x 10^{-2}
3·995 M $HClO_4$	44·96	4·17, 4·09 x 10^{-3}

TABLE 47

Data for the rate of hydrolysis of the benzaldehyde acetal of 2,3-exo-norbornanediol, isomer II, as a function of temperature in 1·00 M perchloric acid.

Temp °C	k_{obs} sec^{-1}
65·00	5·61, 5·62, 5·60 x 10^{-2}
55·00	2·32, 2·31, 2·33 x 10^{-2}
45·00	1·01, 0·949, 0·953 x 10^{-2}
35·00	3·67, 3·66, 3·65 x 10^{-3}
25·14	1·30, 1·31, 1·33 x 10^{-3}

$\Delta S^{\ddagger} = -10·63 \pm 0·25$ e.u. at 25°C,

$\Delta H^{\ddagger} = 18·21 \pm 0·007$ Kcal.mole^{-1}

TABLE 48

Rate of hydrolysis of the benzaldehyde acetal of 2,3-exo-norbornanediol, isomer II, as a function of acid concentration at 25·14°C.

Molarity $HClO_4$	% $HClO_4$ w/w	H_o	k_{obs} sec^{-1}
1·00	9·52	-0·30	1·30, 1·31 x 10^{-3}
2·00	18·11	-0·85	3·82, 3·82 x 10^{-3}
2·995	25·78	-1·33	1·00, 1·00 x 10^{-2}
3·947	32·35	-1·76	2·45, 2·46 x 10^{-2}
5·021	39·26	-2·32	6·76, 6·80 x 10^{-2}

TABLE 49

Rate of hydrolysis of the benzaldehyde acetal of exo-2, 3-norbornanediol, isomer I, as a function of temperature in 1·00 M $HClO_4$.

Temp °C	k_{obs} sec^{-1}	k_{obs} sec^{-1} after removing 0·5 of 1st half-life
65·00	5·29, 5·40, 5·44 x 10^{-2}	5·40, 5·51, 5·61 x 10^{-2}
55·00	2·25, 2·19, 2·13 x 10^{-2}	2·29, 2·22, 2·19 x 10^{-2}
45·00	7·06, 7·06, 7·09 x 10^{-3}	
35·00	2·69, 2·79, 2·81 x 10^{-3}	
25·14	9·07, 9·19 x 10^{-4}	

TABLE 50

Rate of hydrolysis of the benzaldehyde acetal of 2,3-exo-norbornanediol, isomer I, as a function of acid concentration at 25·14°C.

Molarity $HClO_4$	k_{obs} sec^{-1}	removing 1st $0{\cdot}5 \times t_{\frac{1}{2}}$	removing 1st $t_{\frac{1}{2}}$
1·00	$9{\cdot}07, 9{\cdot}19 \times 10^{-4}$		
2·00	$3{\cdot}39, 3{\cdot}15 \times 10^{-3}$	3·50, 3·31	3·53, 3·35
2·995	$9{\cdot}65, 9{\cdot}58 \times 10^{-3}$	9·81, 9·74	9·84, 9·78
3·947	$2{\cdot}46, 2{\cdot}44 \times 10^{-2}$	2·46, 2·44	
5·021	$6{\cdot}87, 6{\cdot}77 \times 10^{-2}$		

TABLE 51

Rate of hydrolysis of the benzaldehyde acetal of exo-2,3-norbornanediol, isomer II.

Acid	Temp °C	k_{obs} sec^{-1} 10^3
1·03 M HCl	25·00	1·33, 1·34, 1·40
1·03 M DCl	25·00	3·49, 3·49, 3·55

$$k_{D_3O^+}/k_{H_3O^+} = 2{\cdot}62$$

TABLE 52

As Table 51, I = 0·50 M

$[HCO_2H]$	pH_{65}	Temp °C	k_{obs} 10^5 sec^{-1}
0·083	3·09	65·05	4·97
0·249	3·10	65·05	4·64
0·415	3·10	65·05	4·58

$[ClCH_2CO_2H]$	pH_{65}	Temp °C	k_{obs} 10^4 sec^{-1}
0·075	2·41	65·05	2·66
0·150	2·39	"	2·72
0·225	2·39	"	2·62
0·300	2·40	"	2·19
0·375	2·45	"	2·66

TABLE 53

As Table 51, pH-rate data.

Buffer	pH_{65}	k_{obs} sec^{-1}
HCl	1·16	$4·38, 4·63 \times 10^{-3}$
chloro-acetate	2·41	$2·50 \times 10^{-4}$
formate	2·73	$1·19 \times 10^{-4}$
"	3·09	$4·97 \times 10^{-5}$
"	3·71	$1·32 \times 10^{-5}$

A linear least squares plot of log k_{obs} against pH gives a slope of 1·00.

After 48 hours in 0·10 N NaOH at 80°C about 5% hydrolysis occurred.

TABLE 54

Rate of hydrolysis of the benzaldehyde acetal 2,3-exo-norbornanediol, isomer I, at 65·05°C, I = 0·50 M.

Buffer	pH_{65}	k_{obs} sec^{-1}
HCl	1·16	$2·69, 2·77 \times 10^{-3}$
chloro-acetate	2·41	$1·31, 1·31 \times 10^{-4}$
formate	2·73	$7·00 \times 10^{-5}$
"	3·71	$6·82 \times 10^{-6}$

$[HCO_2H]$	pH_{65}	k_{obs} sec^{-1} 10^5
0·090	2·73	7·00
0·270	2·73	6·21
0·450	2·78	5·98

These are the observed calculated rate constants, using all the data including the initial absorbance values.

TABLE 55

Rate of hydrolysis of the benzaldehyde acetal of 1-carboxy 2,3-exo-norbornanediol, isomer II, as a function of pH.

Buffer	pH_{65}	Temp °C	k_{obs} sec^{-1}
HCl	1·16	65·05	$1·78, 1·78 \times 10^{-3}$
chloro-acetate	2·41	"	$9·06, 9·00 \times 10^{-5}$
formate	2·73	"	$4·14 \times 10^{-5}$
"	3·71	"	$5·97 \times 10^{-6}$

Linear least squares plot of log k_{obs} against pH gives a slope of 1·01

TABLE 56

Percentage of isomerisation occurring during hydrolysis of the benzaldehyde acetal of 1-carboxy 2,3-exo-norbornanediol in water. Isomer II.

	Time (mins)	Temp °C	Calc % Hydrolysis	% other isomer present
1 M $HClO_4$	5	25	12	16
1 M $HClO_4$	15	25	32	25
0·1 M $HClO_4$	15	25	4	10
0·010 M $HClO_4$	25	25	<1	<3

TABLE 57

Rate of hydrolysis of cis and trans ethyl 2-hydroxy cyclopentane carboxylate and ethyl cyclopentane carboxylate as a function of dioxan concentration in dioxan-water mixtures. 0·10 N sodium hydroxide at 30·50°C I = 0·10.

Mole Fraction Water	k_{obs} sec^{-1} cis	trans	cyclopentyl
1·000	$6·98,6·82 \times 10^{-3}$	$1·41,1·45 \times 10^{-2}$	
0·977	$7·99,8·23 \times 10^{-3}$	$1·33,1·39 \times 10^{-2}$	$4·60,4·56 \times 10^{-3}$
0·950	$7·02,7·62 \times 10^{-3}$	$1·26,1·20 \times 10^{-2}$	$3·27,3·35 \times 10^{-3}$
0·917	$7·15,7·33 \times 10^{-3}$	$1·05,1·06 \times 10^{-2}$	$2·60,2·67 \times 10^{-3}$
0·877	$7·70,7·57 \times 10^{-3}$	$9·82,9·76 \times 10^{-3}$	$1·70,1·82 \times 10^{-3}$
0·760	$7·67,7·80 \times 10^{-3}$	$7·88,7·95 \times 10^{-3}$	$8·65,8·87 \times 10^{-4}$
0·671	$7·27,7·34 \times 10^{-3}$	$7·07,7·17 \times 10^{-3}$	$6·46,6·58 \times 10^{-4}$

TABLE 58

Rate of hydrolysis of cis and trans ethyl cyclopentane carboxylate as a function of pH in water at 30·5°C.

	k_{obs} sec^{-1}	
Alkali	cis	trans
1·00 N NaOH	8·90, 9·08 x 10^{-2}	1·58, 1·62 x 10^{-1}
0·10 N NaOH	6·98, 6·82 x 10^{-3}	1·41, 1·45 x 10^{-2}
0·01 N NaOH	7·25, 7·35 x 10^{-4}	1·56, 1·60 x 10^{-3}

(I = 0·10)

TABLE 59

Rates of methanolysis of 2-naphthyl esters of 2-hydroxy acids at 25°C 10^{-4} M NaOMe/MeOH. k_{obs} sec^{-1}.

butyrate	1·6 x 10^{-3}	cis 2-hydroxy cp. carboxylate	2·3 x 10^{-3}
2-hydroxy butyrate	1·2 x 10^{-2}	trans 2-hydroxy cp. carboxylate	5·8 x 10^{-3}
		cp. carboxylate	9·0 x 10^{-4}

TABLE 60

Rates of hydrolysis of 2-naphthyl esters of 2-hydroxy acids in 20% w/w dioxan at 60·0°C. cp. = cyclopentyl.

Buffer	pH	butyrate	2-hydroxy butyrate	cis-2 hydroxy cp. carboxylate	trans-2 hydroxy cp. carboxylate	cp. carboxylate
glycine	9·5	$3·9 \times 10^{-4}$	$9·3 \times 10^{-4}$	$5·0 \times 10^{-4}$	$7·5 \times 10^{-4}$	$2·9 \times 10^{-4}$
borate	9·6	$9·0 \times 10^{-4}$	$2·3 \times 10^{-2}$	$9·8 \times 10^{-3}$	$5·9 \times 10^{-3}$	$7·1 \times 10^{-4}$
imidazole	6·7	$5·1 \times 10^{-4}$	$4·8 \times 10^{-4}$	$1·8 \times 10^{-4}$	$5·8 \times 10^{-4}$	$4·7 \times 10^{-4}$
5 M HCl		$6·3 \times 10^{-3}$	$2·3 \times 10^{-3}$	$1·3 \times 10^{-3}$	$3·9 \times 10^{-3}$	$6·3 \times 10^{-3}$

TABLE 61

Rates of hydrolysis of 2-naphthyl esters of 2-hydroxy acids as a function of dioxan concentration in dioxan-water mixtures. 0·010 N NaOH at 30·50°C I = 0·01 cp. = cyclopentyl.

Mole Fraction Water	k_{obs} sec^{-1} Butyrate	2-hydroxy butyrate	cis-2-hydroxy cp. carboxylate	trans-2-hydroxy cp. carboxylate	cp. carboxylate
1·000	$1·38,1·44x10^{-2}$	$4·39,4·43x10^{-2}$	$5·76,5·80x10^{-2}$	$5·40,5·48x10^{-2}$	
0·977	$1·15,1·17x10^{-2}$	$4·13,4·17x10^{-2}$	$4·40,4·50x10^{-2}$	$4·36,4·40x10^{-2}$	$1·03,1·07x10^{-2}$
0·917	$7·55,7·63x10^{-3}$	$3·79,3·92x10^{-2}$	$3·10,3·18x10^{-2}$	$3·30,3·36x10^{-2}$	$6·04,6·14x10^{-3}$
0·877	$5·00,5·14x10^{-3}$	$3·20,3·28x10^{-2}$	$2·53,2·61x10^{-2}$	$2·60,2·71x10^{-2}$	$3·85,3·91x10^{-3}$
0·760	$3·29,3·33x10^{-3}$	$3·03,3·04x10^{-2}$	$2·10,2·22x10^{-2}$	$2·30,2·36x10^{-2}$	$2·40,2·42x10^{-3}$
0·671	$2·72,2·68x10^{-3}$	$3·32,3·44x10^{-2}$	$2·78,2·86x10^{-2}$	$2·66,2·73x10^{-2}$	$1·88,1·91x10^{-3}$
0·543	$1·84,1·85x10^{-3}$	$3·27,3·31x10^{-2}$	$2·64,2·68x10^{-2}$	$2·33,2·36x10^{-2}$	$1·29,1·33x10^{-3}$
0·345	$6·20,6·31x10^{-4}$	$1·18,1·21x10^{-3}$	$8·29,8·33x10^{-3}$	$8·01,8·10x10^{-3}$	$3·87,3·92x10^{-4}$

TABLE 62

Rates of hydrolysis of 2-naphthyl esters of 2-hydroxy acids in glycine buffers at 65·0°C I = 0·05 k_{obs} sec^{-1}.

Medium	Butyrate	2-hydroxy butyrate	cis-2-hydroxy cp. carboxylate	trans-2-hydroxy cp. carboxylate	cp. carboxylate
water	$1·06 \times 10^{-3}$	$2·62 \times 10^{-3}$	$2·83 \times 10^{-3}$	$2·76 \times 10^{-3}$	
20% w/w dioxan	$2·79 \times 10^{-4}$	$7·00 \times 10^{-4}$	$6·48 \times 10^{-4}$	$6·01 \times 10^{-4}$	$2·19 \times 10^{-4}$
70% w/w dioxan	$1·55 \times 10^{-5}$	$5·77 \times 10^{-5}$	$4·99 \times 10^{-5}$	$5·32 \times 10^{-5}$	$1·00 \times 10^{-5}$

Fig 2

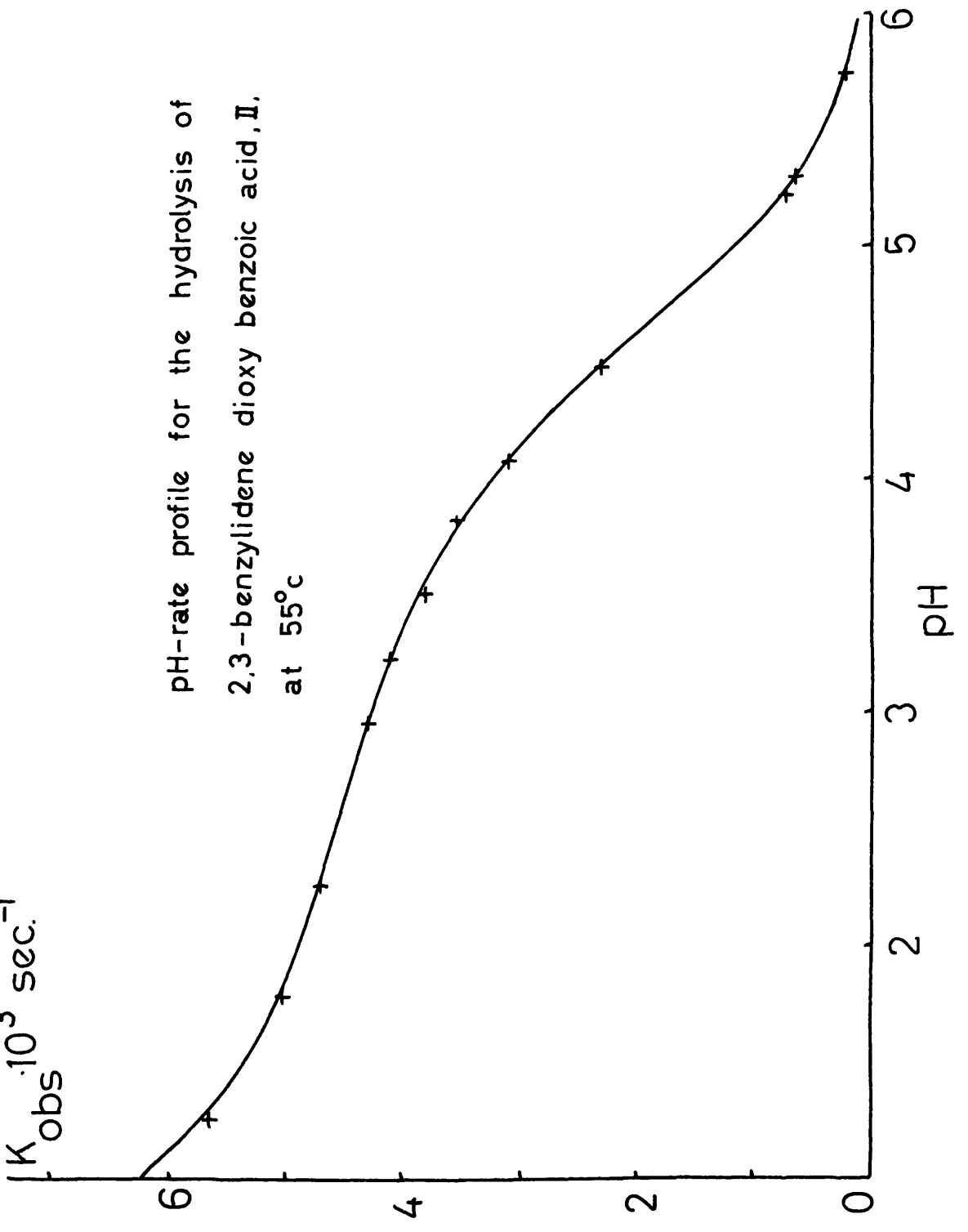

pH-rate profile for the hydrolysis of
2,3-benzylidene dioxy benzoic acid, II,
at 55°c
$K_{obs} \cdot 10^3$ sec.$^{-1}$
0
2
4
6
2
3
4
5
6
pH

Fig 3

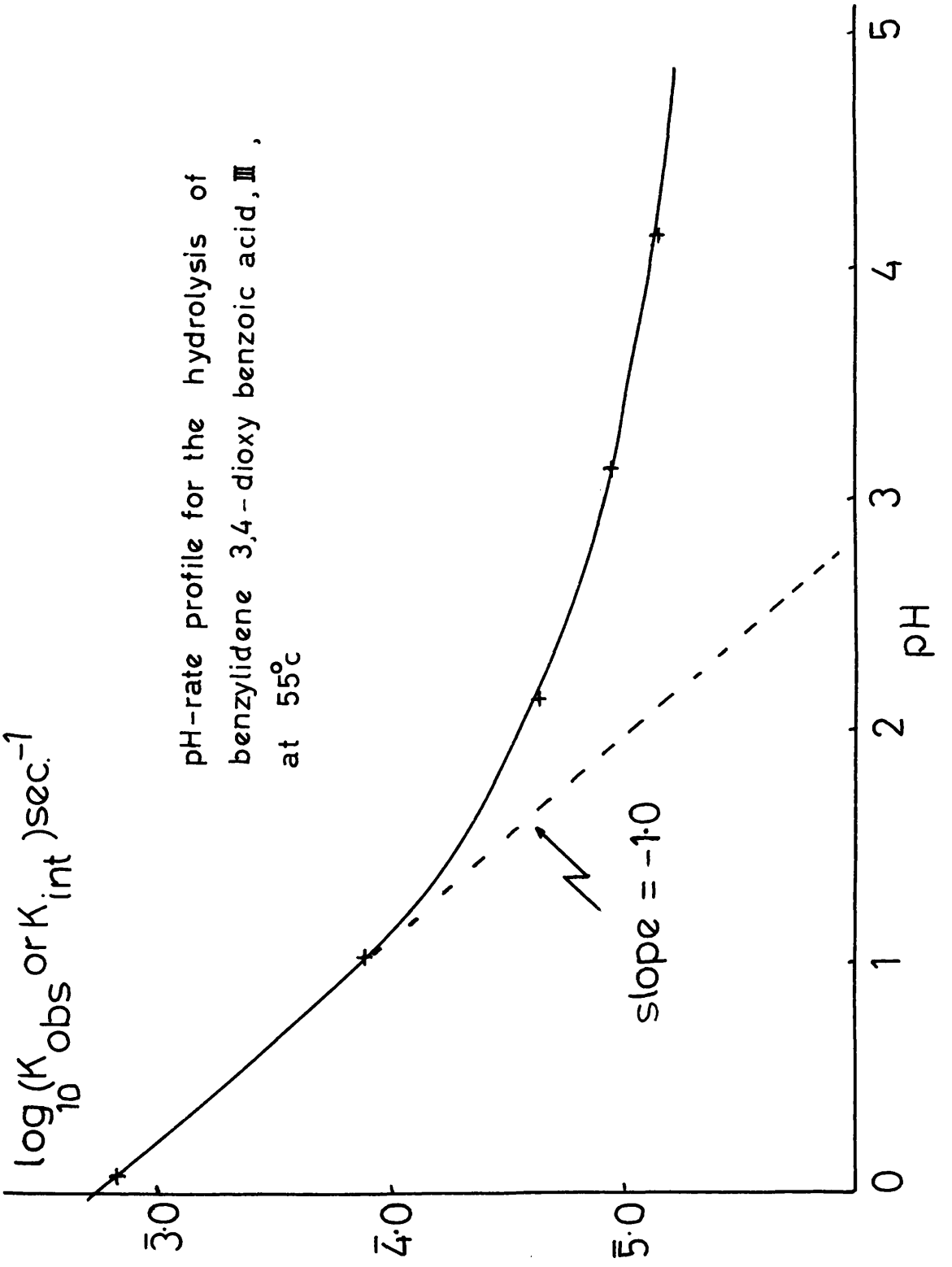
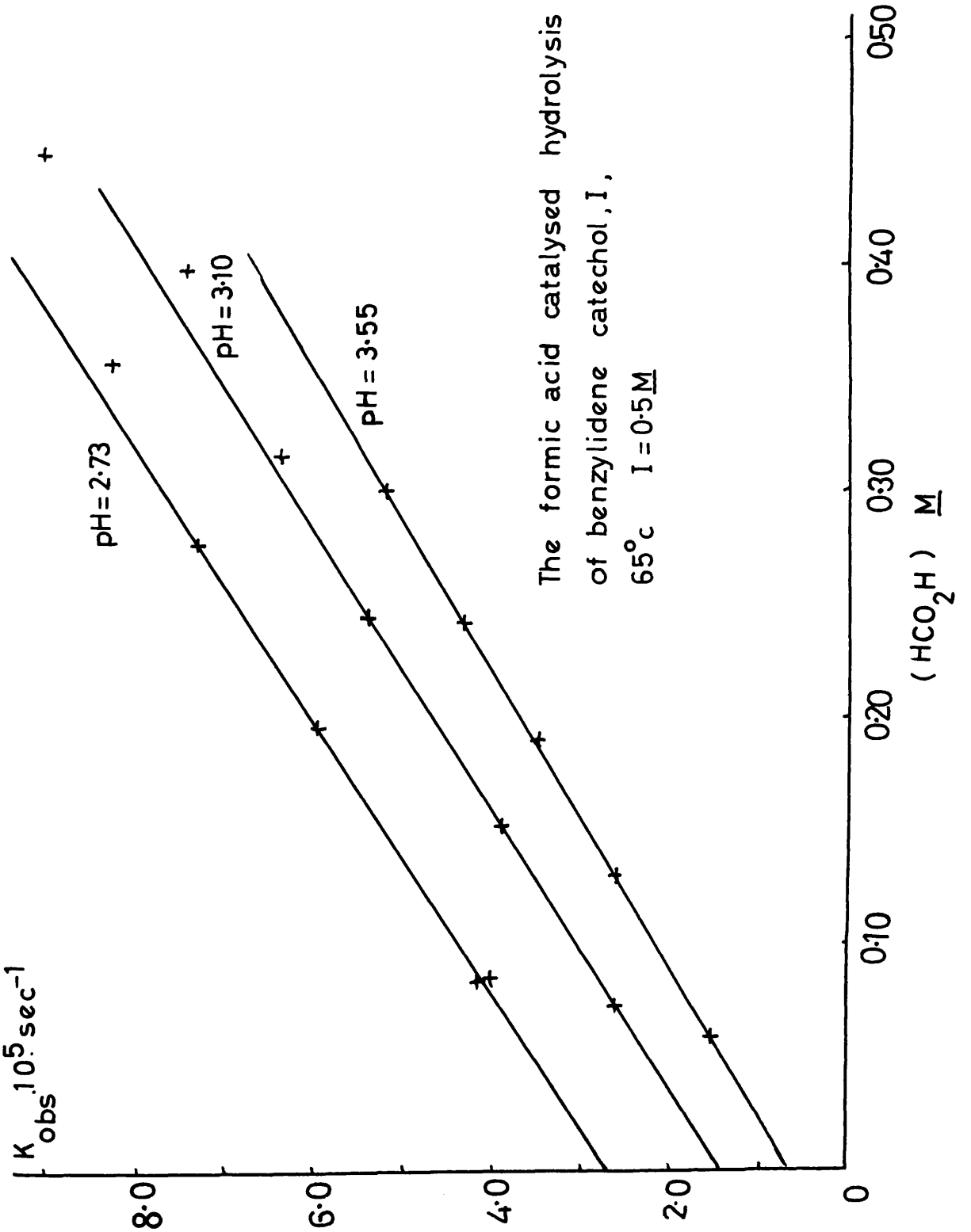

pH-rate profile for the hydrolysis of benzylidene 3,4-dioxy benzoic acid, III, at 55°c
log (K obs or K int) sec.-1
3·0
4·0
5·0
0
1
2
3
4
5
pH
slope = -1·0

Fig. 5


The formic acid catalysed hydrolysis of benzylidene catechol, I, 65°c I = 0·5 M
pH = 2·73
pH = 3·10
pH = 3·55
$K_{obs}.10^5 sec^{-1}$
8·0
6·0
4·0
2·0
0
0·10
0·20
0·30
0·40
0·50
(HCO_2H) M

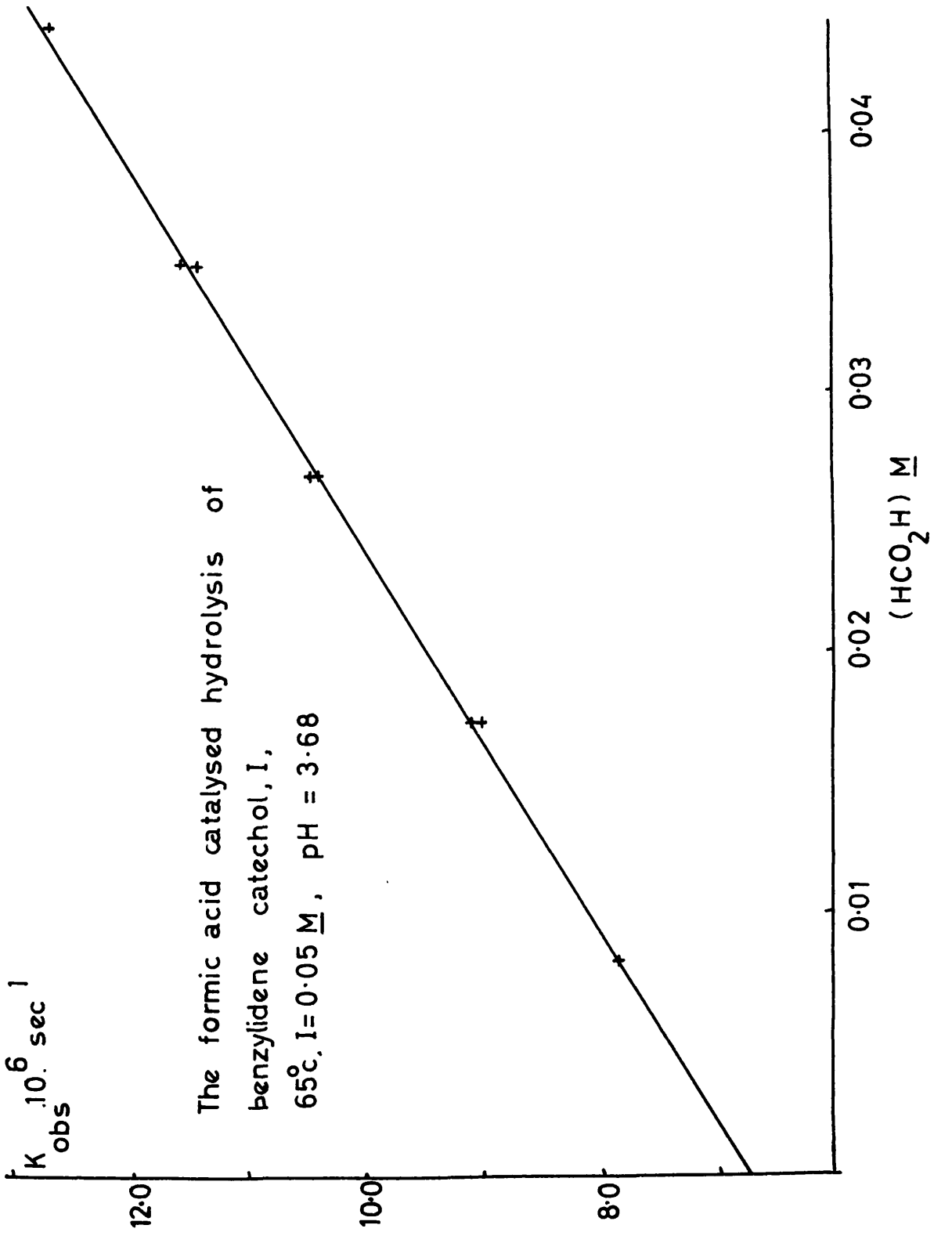


Fig 5a
$K_{obs}.10^6$ sec^{-1}
12·0
10·0
8·0
The formic acid catalysed hydrolysis of benzylidene catechol, I,
65°c, I= 0·05 M, pH = 3·68
0·01
0·02
0·03
0·04
(HCO_2H) M

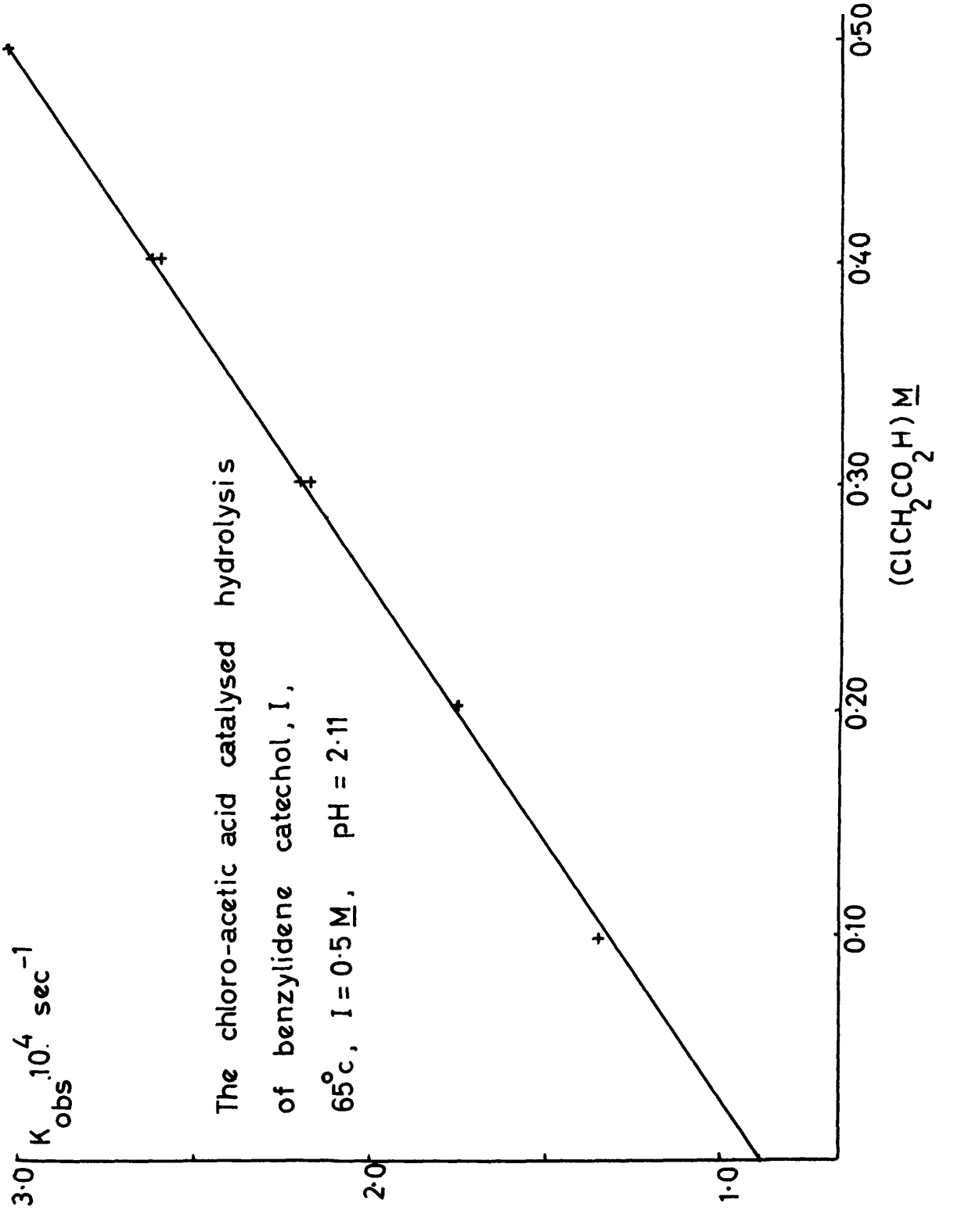
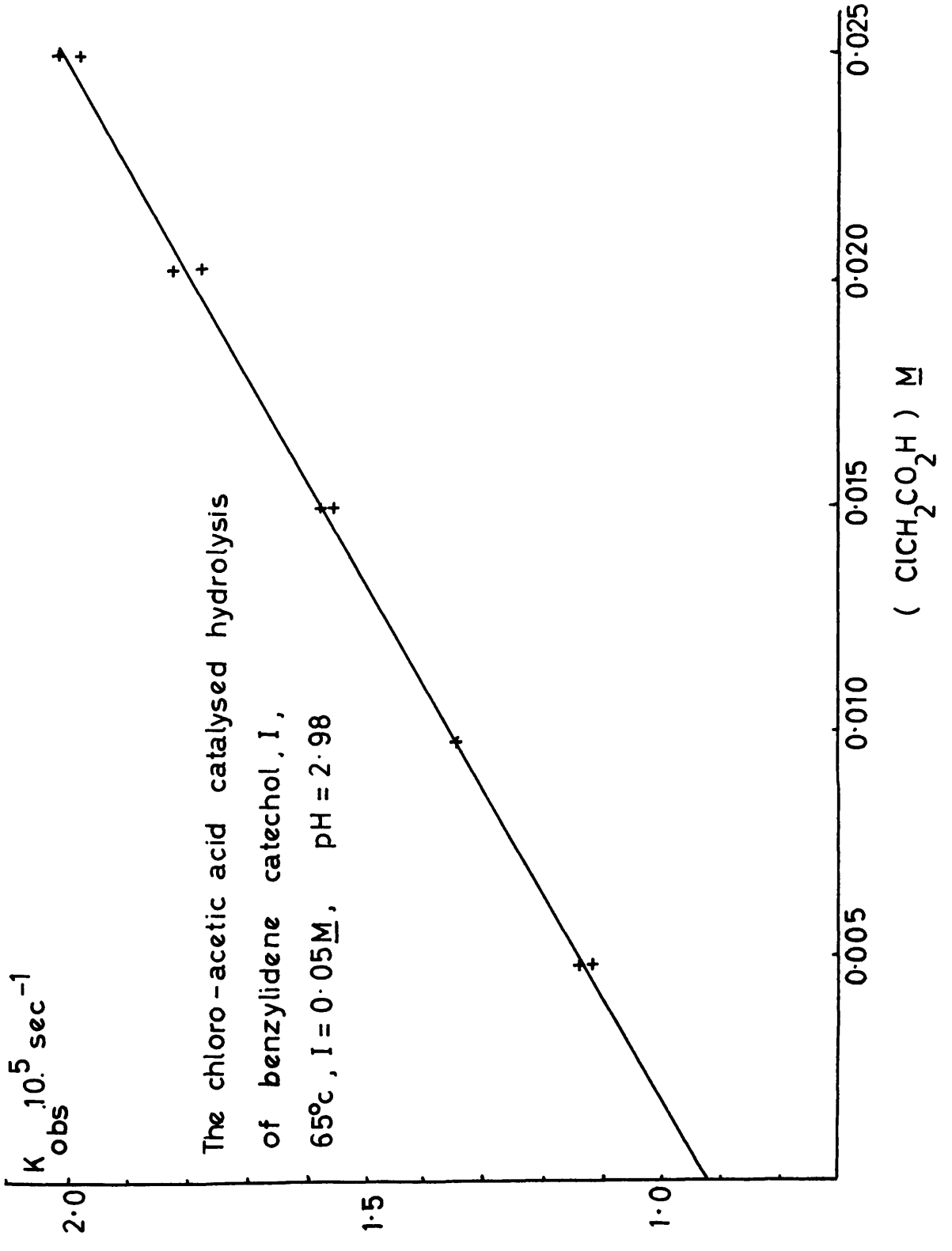


Fig 6
The chloro-acetic acid catalysed hydrolysis of benzylidene catechol, I, 65°c, I = 0·5 M, pH = 2·11
$K_{obs}.10^4$ sec^{-1}
3·0
2·0
1·0
0·10
0·20
0·30
0·40
0·50
$(ClCH_2CO_2H)$ M

Fig. 6a


$K_{obs}.10^5$ sec^{-1}
2·0
1·5
1·0
The chloro-acetic acid catalysed hydrolysis
of benzylidene catechol, I,
65°c, I = 0·05M, pH = 2·98
0·005
0·010
0·015
0·020
0·025
($ClCH_2CO_2H$) M

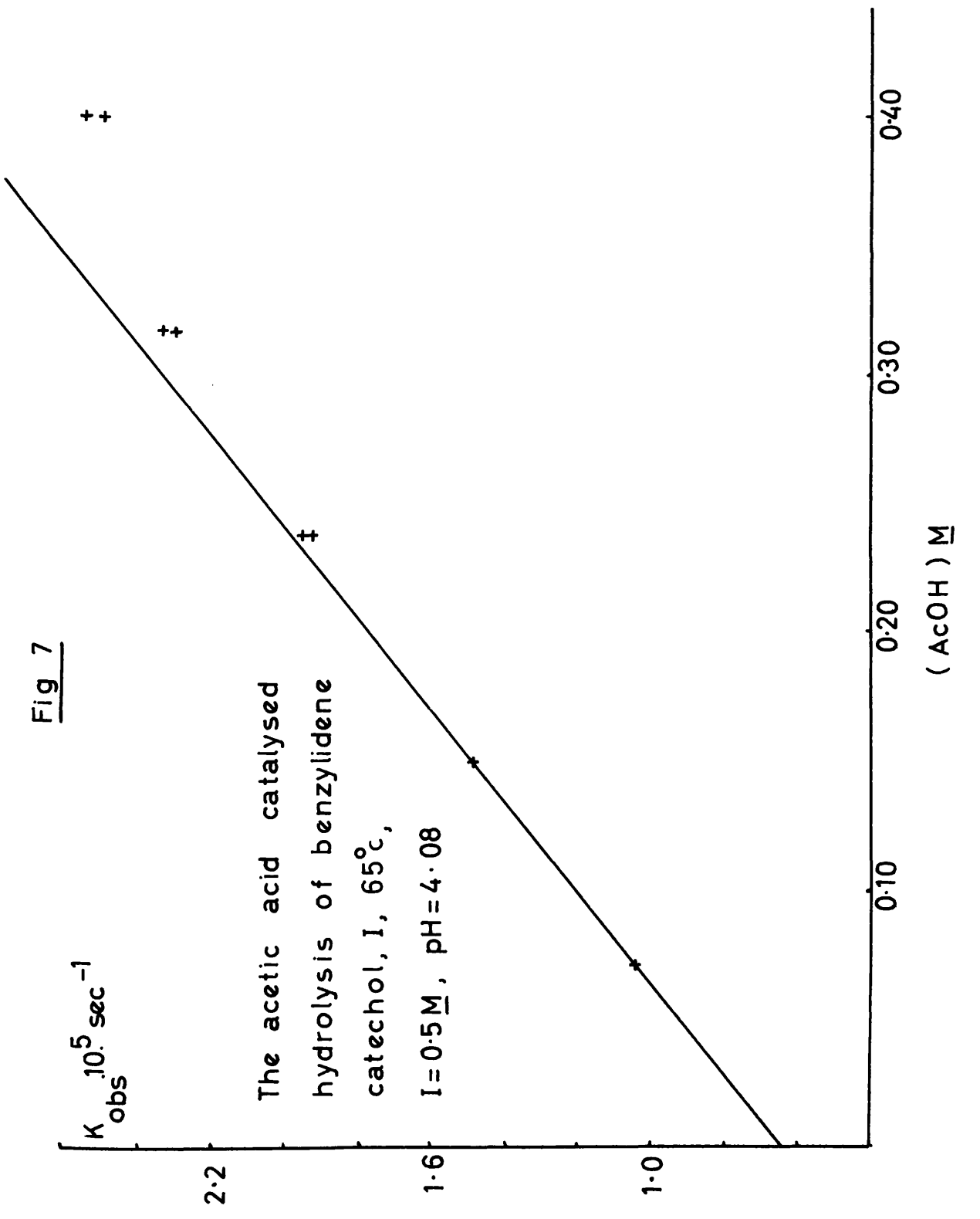


Fig 7
$K_{obs}.10^5\ sec^{-1}$
The acetic acid catalysed hydrolysis of benzylidene catechol, I, 65°c, I= 0·5 M, pH=4·08
2·2
1·6
1·0
0·10
0·20
0·30
0·40
(AcOH) M

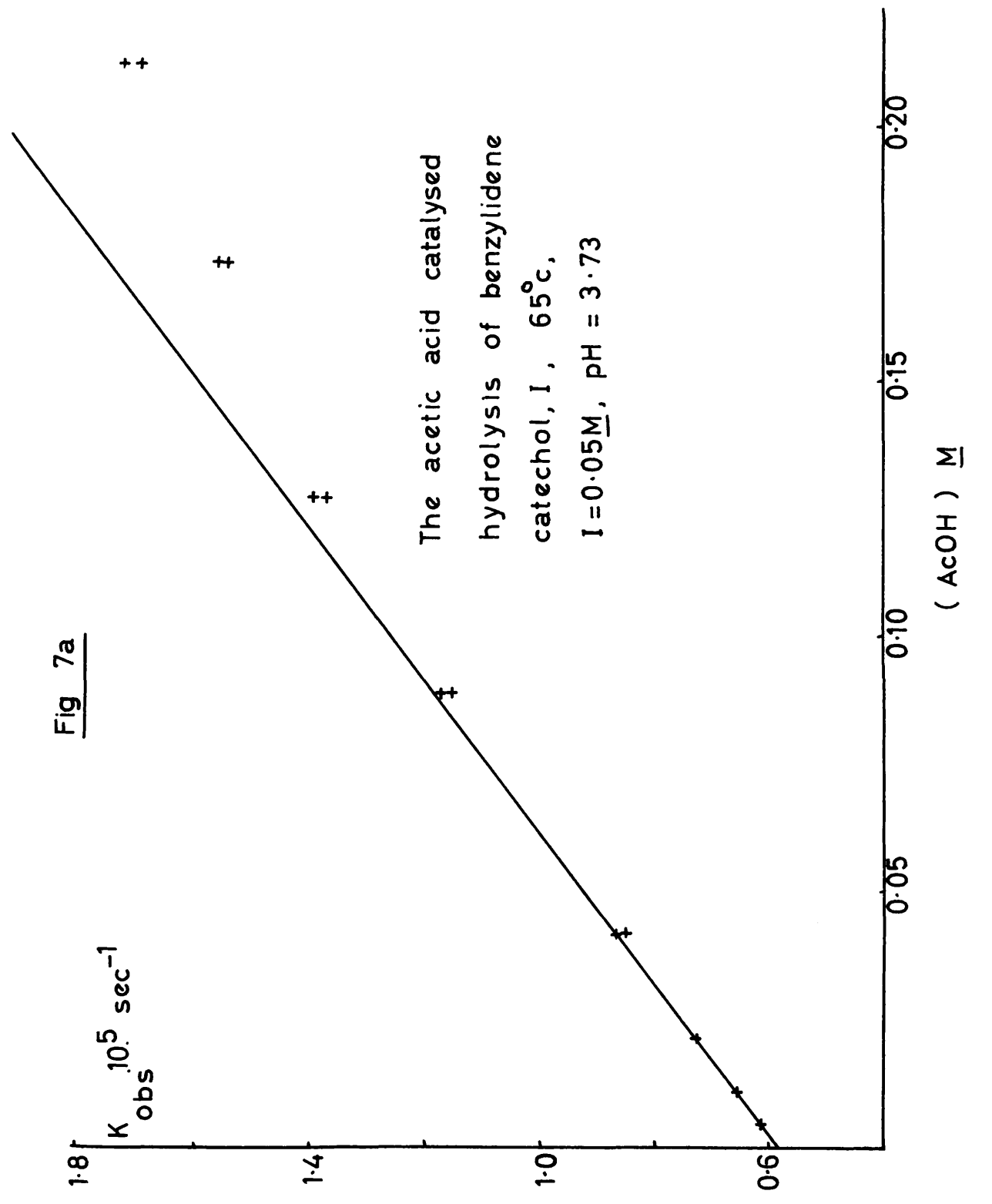


Fig 7a
The acetic acid catalysed hydrolysis of benzylidene catechol, I , 65°c, I=0·05M, pH = 3·73
$K_{obs}.10^5$ sec^{-1}
1·8
1·4
1·0
0·6
0·05
0·10
0·15
0·20
(AcOH) M

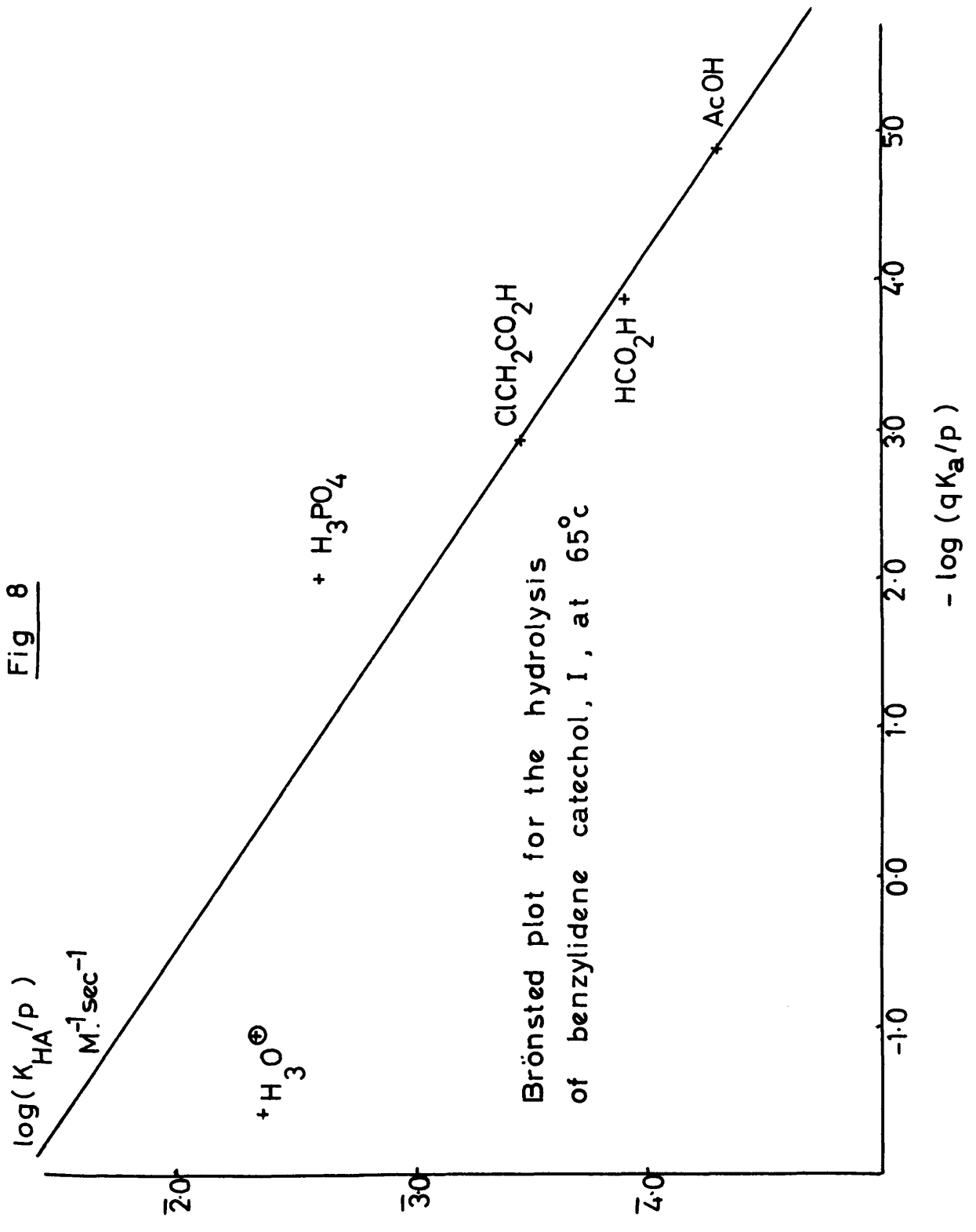
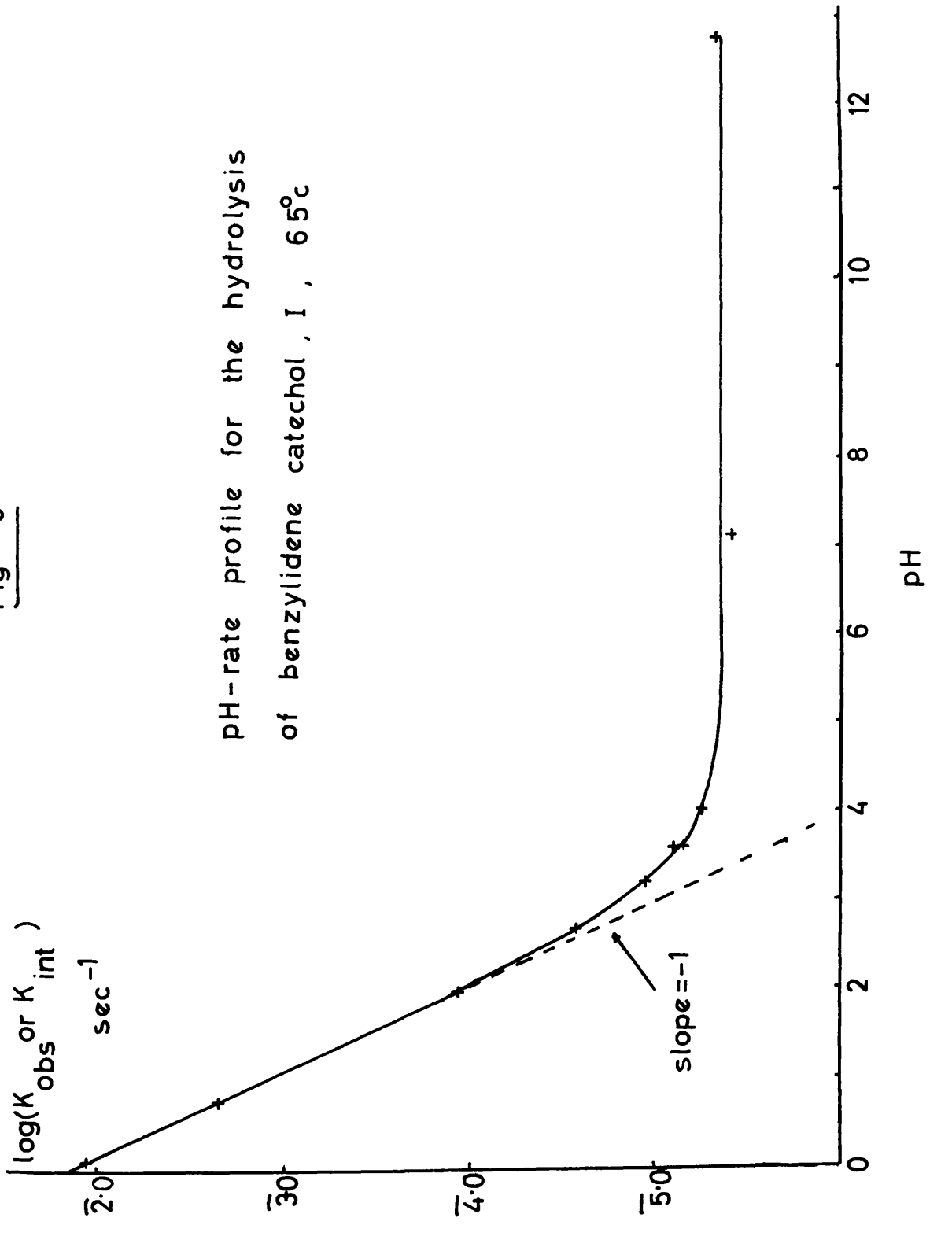


Fig 8

Brönsted plot for the hydrolysis of benzylidene catechol, I, at 65°c

Fig 9


pH-rate profile for the hydrolysis of benzylidene catechol, I, 65°c
log(K obs or K int) sec⁻¹
-2·0
-3·0
-4·0
-5·0
slope=-1
0
2
4
6
8
10
12
pH

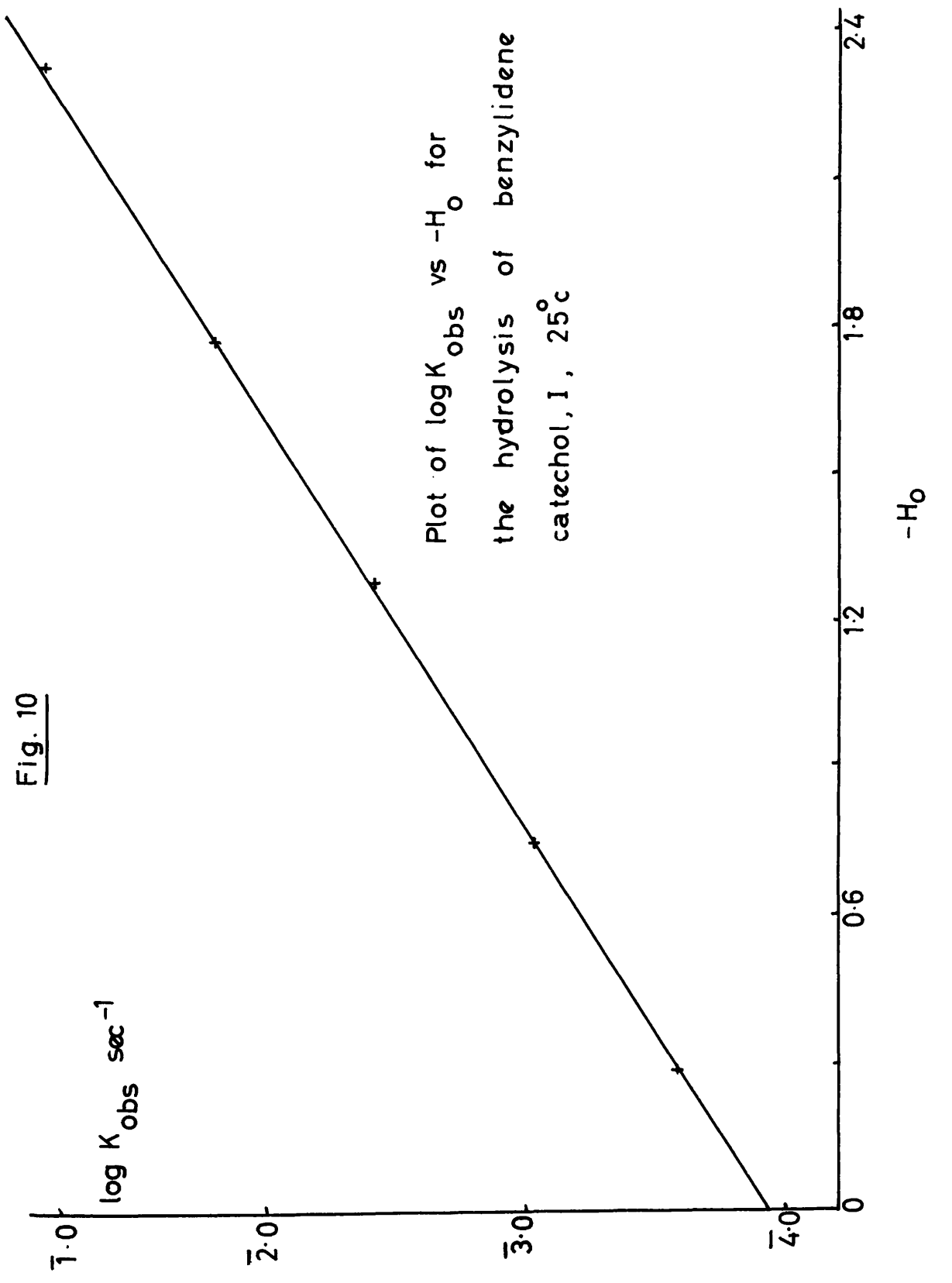


Fig. 10
Plot of log K_{obs} vs $-H_o$ for the hydrolysis of benzylidene catechol, I, 25°c
log K_{obs} sec^{-1}
$\bar{1}\cdot0$
$\bar{2}\cdot0$
$\bar{3}\cdot0$
$\bar{4}\cdot0$
0
0·6
1·2
1·8
2·4
$-H_o$

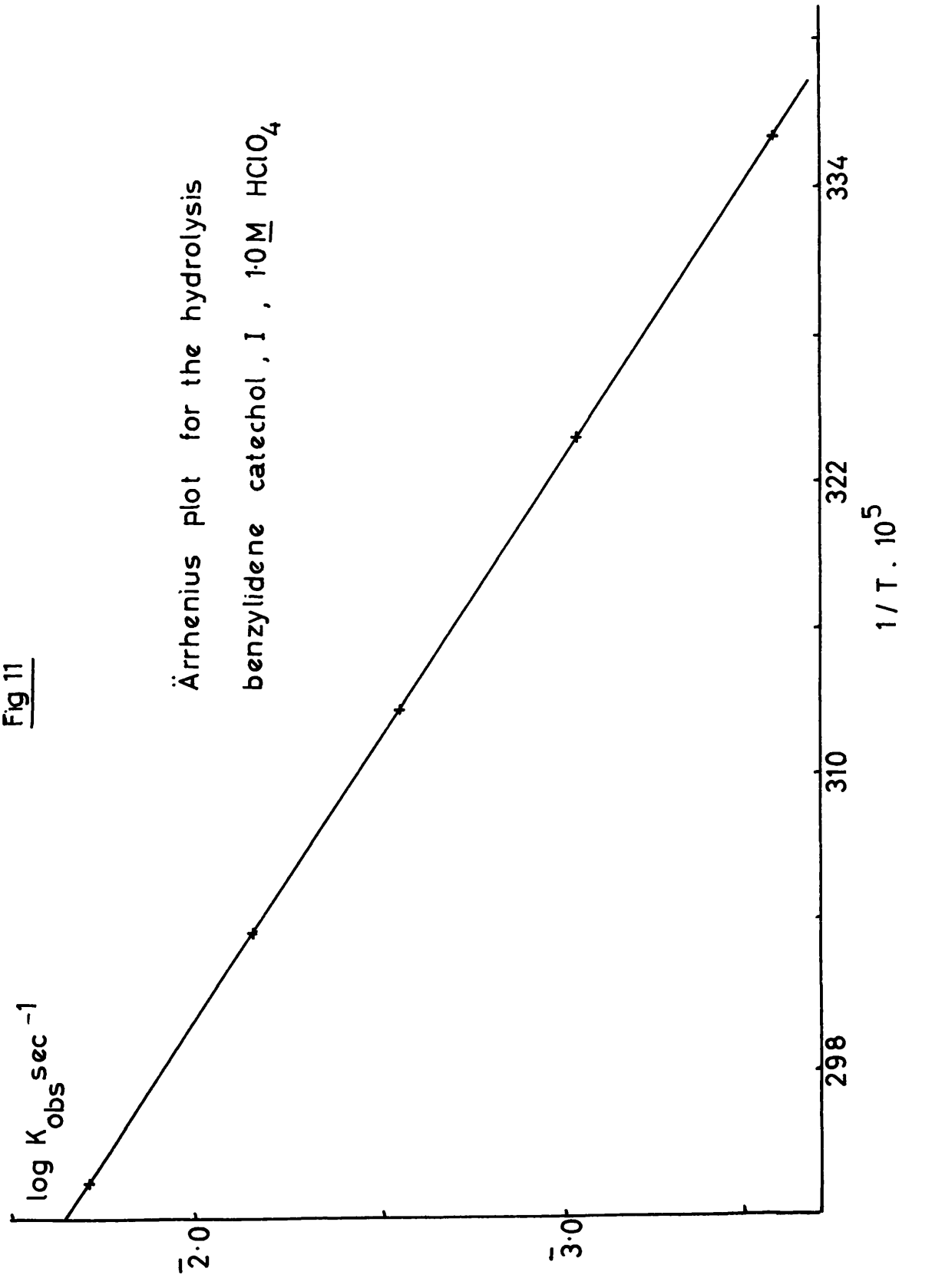


Fig 11

Ärrhenius plot for the hydrolysis benzylidene catechol, I, 1·0 M $HClO_4$

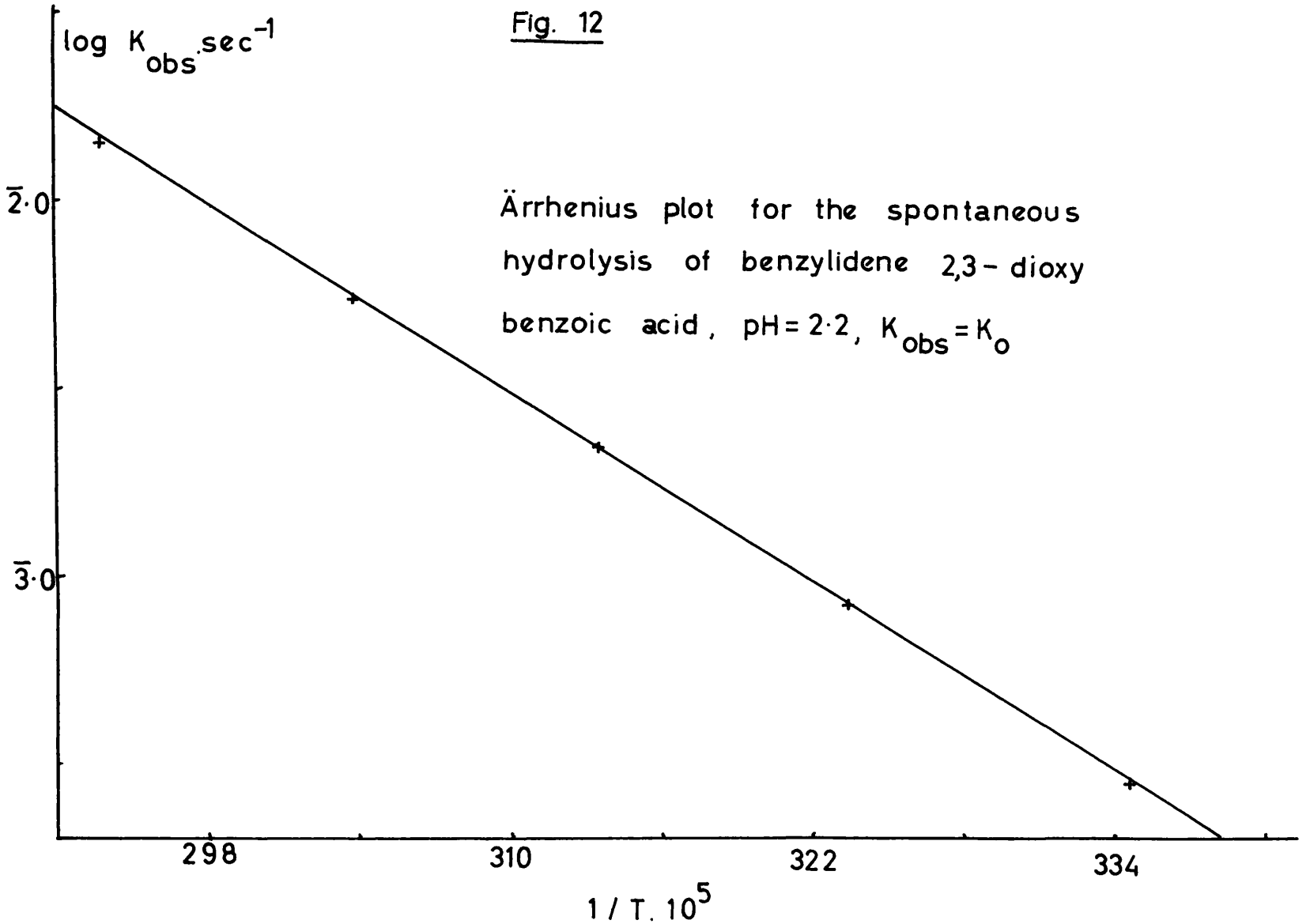
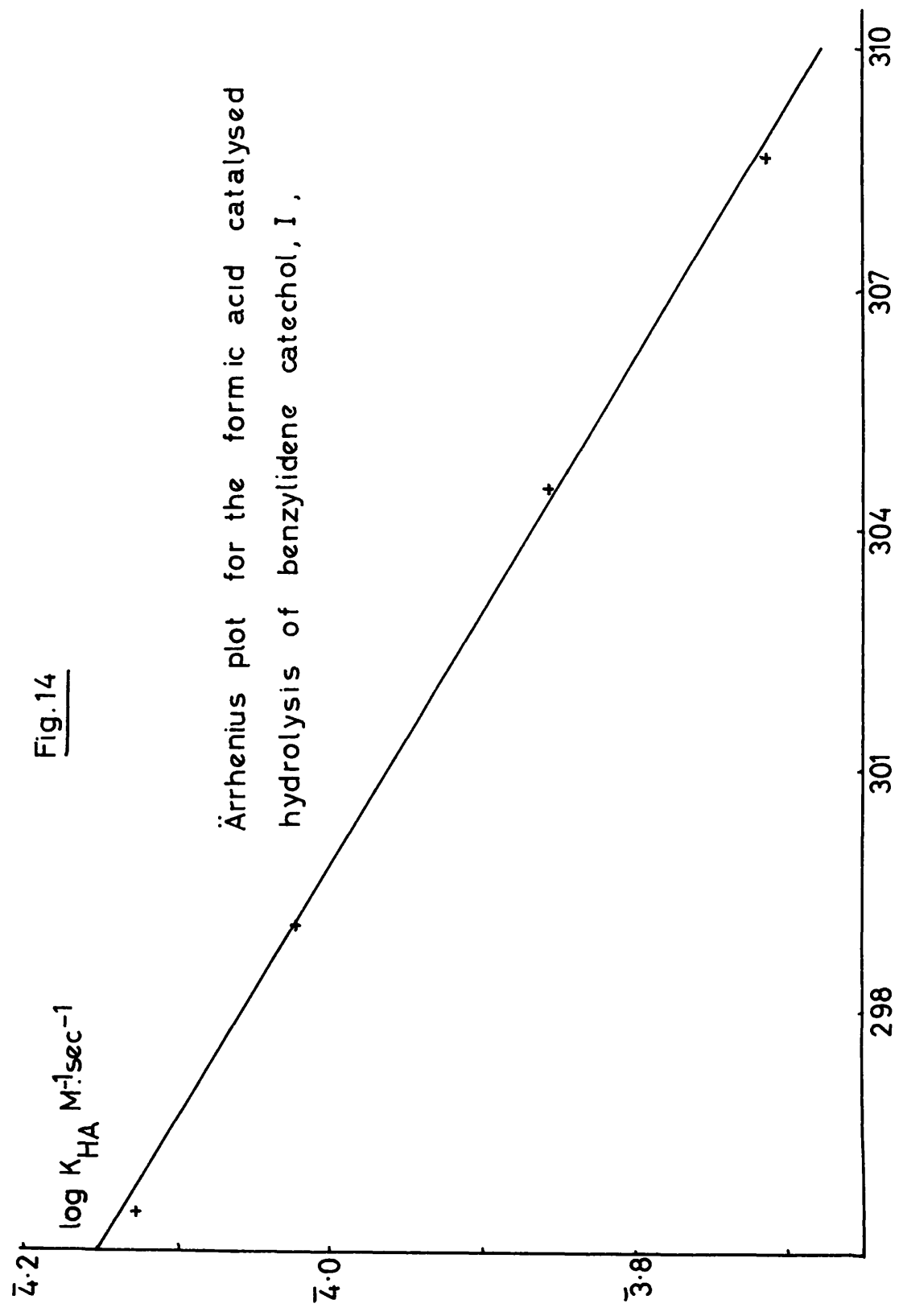

log K_{obs}.sec^{-1}
Fig. 12
Ärrhenius plot for the spontaneous hydrolysis of benzylidene 2,3 - dioxy benzoic acid, pH = 2·2, $K_{obs} = K_o$
$\bar{2}$·0
$\bar{3}$·0
298
310
322
334
1 / T. 10^5

Fig.14

Ärrhenius plot for the formic acid catalysed hydrolysis of benzylidene catechol, I ,



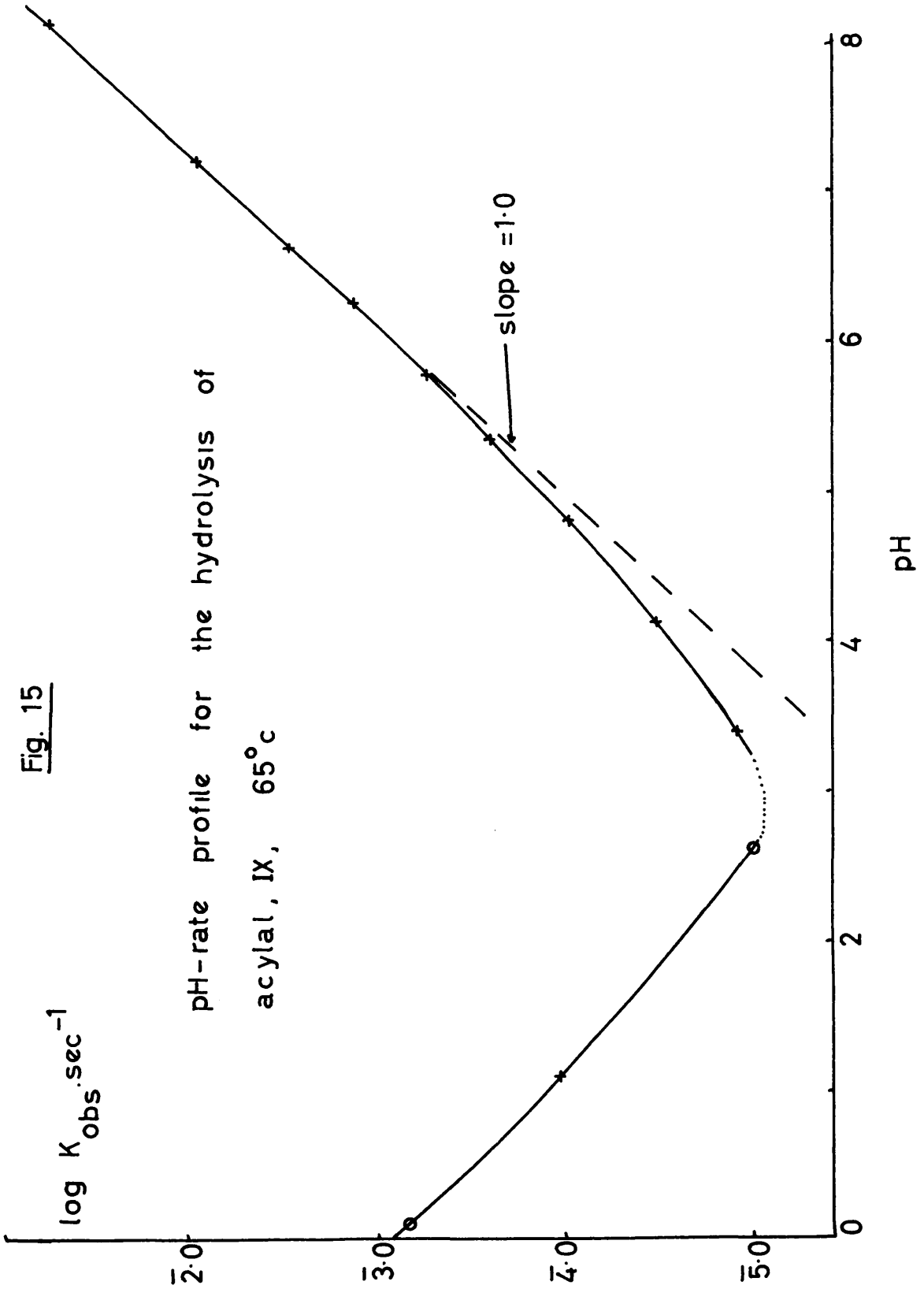
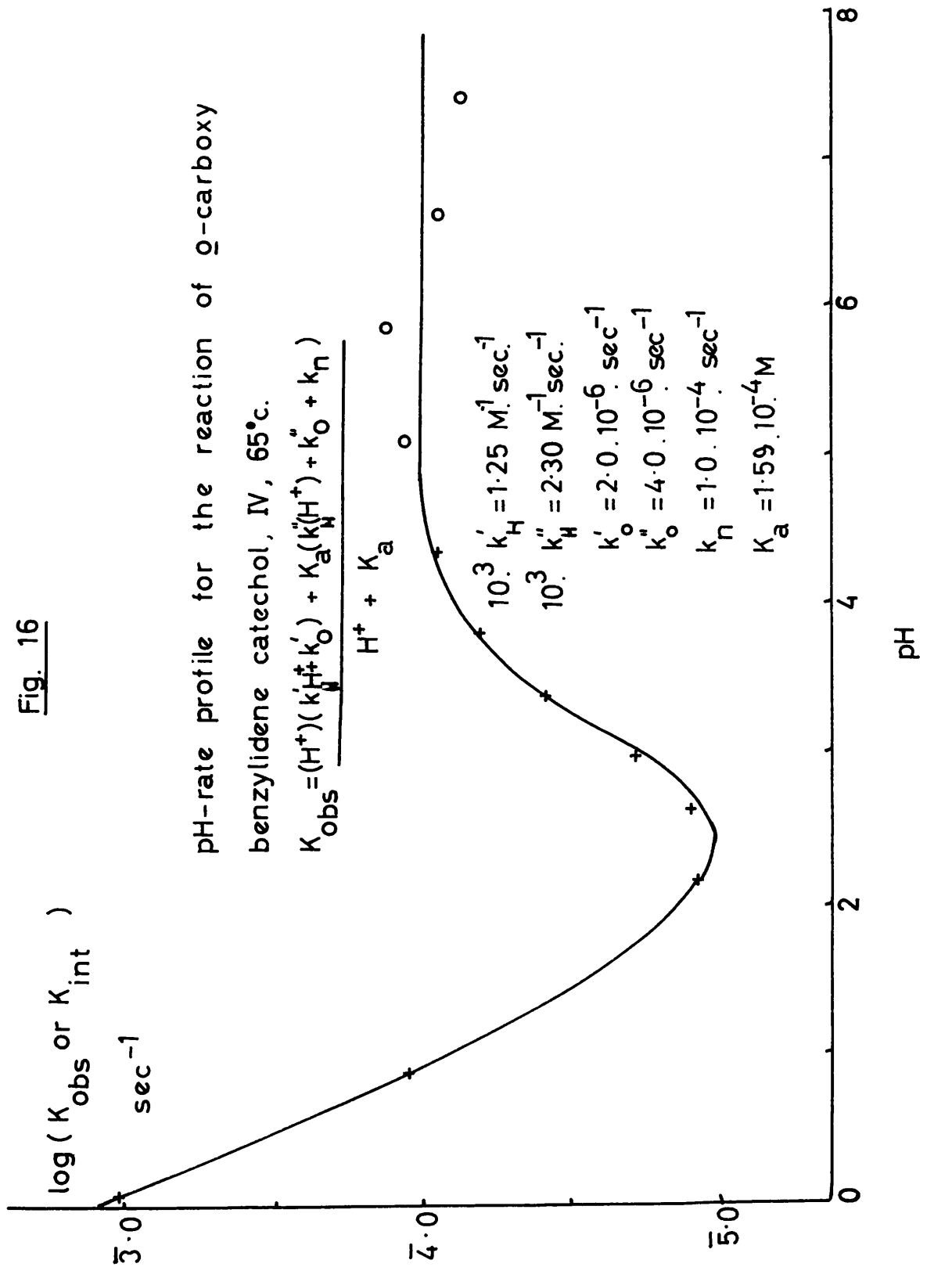


Fig. 15

pH-rate profile for the hydrolysis of acylal, IX, 65°c

Fig. 16


pH-rate profile for the reaction of o-carboxy benzylidene catechol, IV, 65°c.
$K_{obs}=\frac{(H^+)(k'_H H^+ + k'_o) + K_a(k''_H(H^+) + k''_o + k_n)}{H^+ + K_a}$
$10^3\ k'_H = 1{\cdot}25\ M^{-1}.sec^{-1}$
$10^3\ k''_H = 2{\cdot}30\ M^{-1}.sec^{-1}$
$k'_o = 2{\cdot}0.10^{-6}\ sec^{-1}$
$k''_o = 4{\cdot}0.10^{-6}\ sec^{-1}$
$k_n = 1{\cdot}0.10^{-4}\ sec^{-1}$
$K_a = 1{\cdot}59.10^{-4} M$
log (K_{obs} or K_{int}) sec^{-1}
$\bar{3}{\cdot}0$
$\bar{4}{\cdot}0$
$\bar{5}{\cdot}0$
0
2
4
6
8
pH

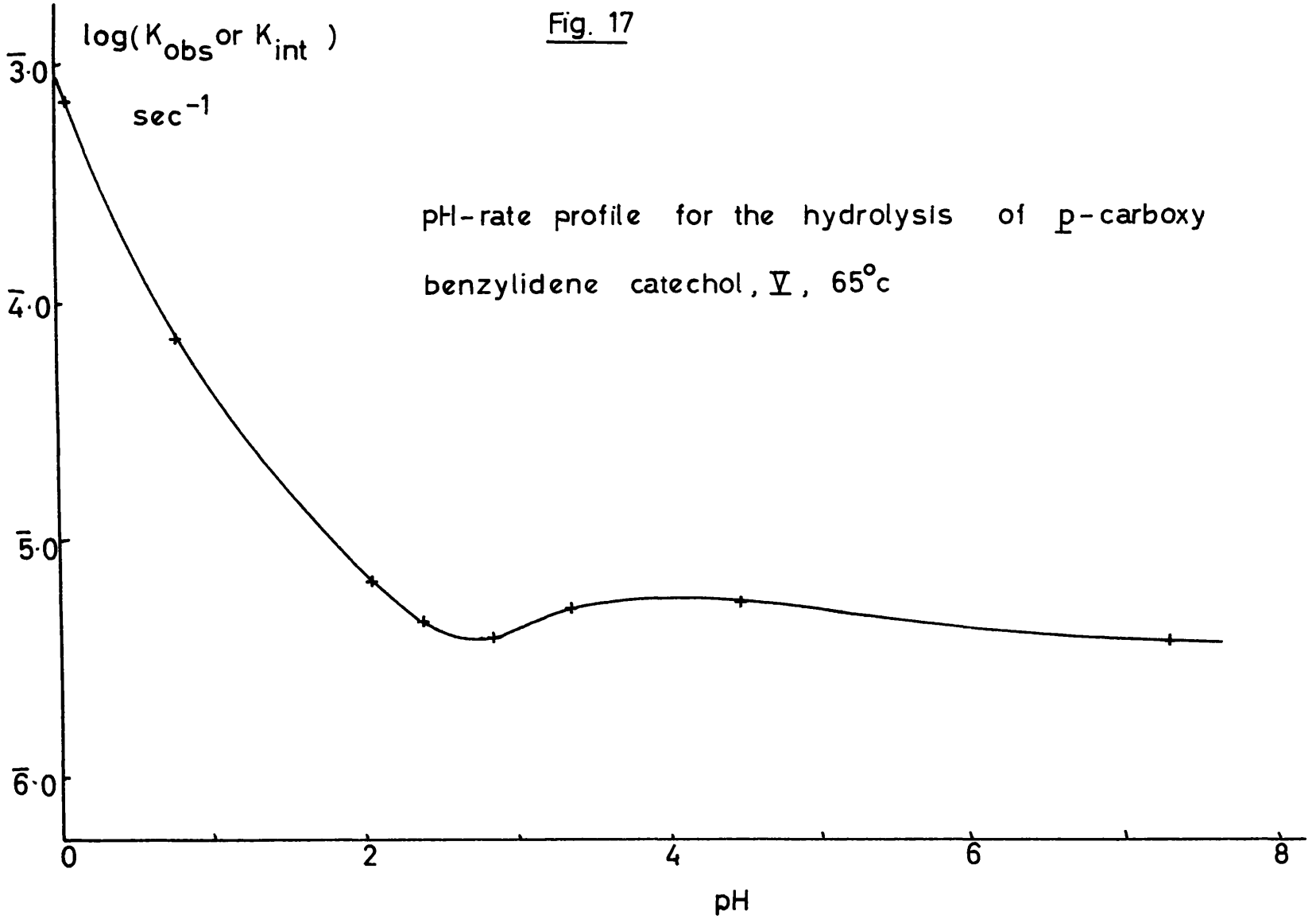


Fig. 17

pH-rate profile for the hydrolysis of p-carboxy benzylidene catechol, V, 65°c

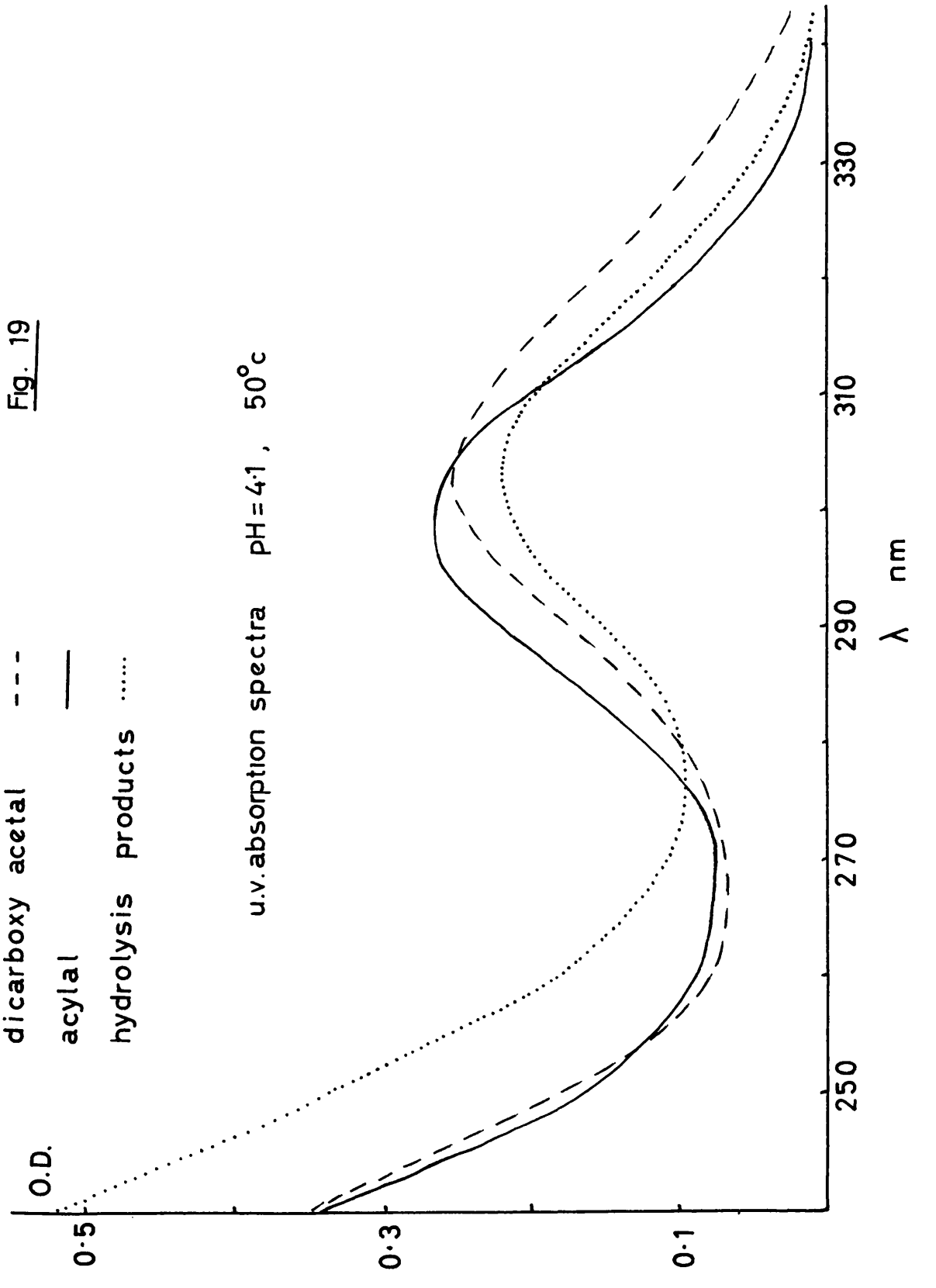
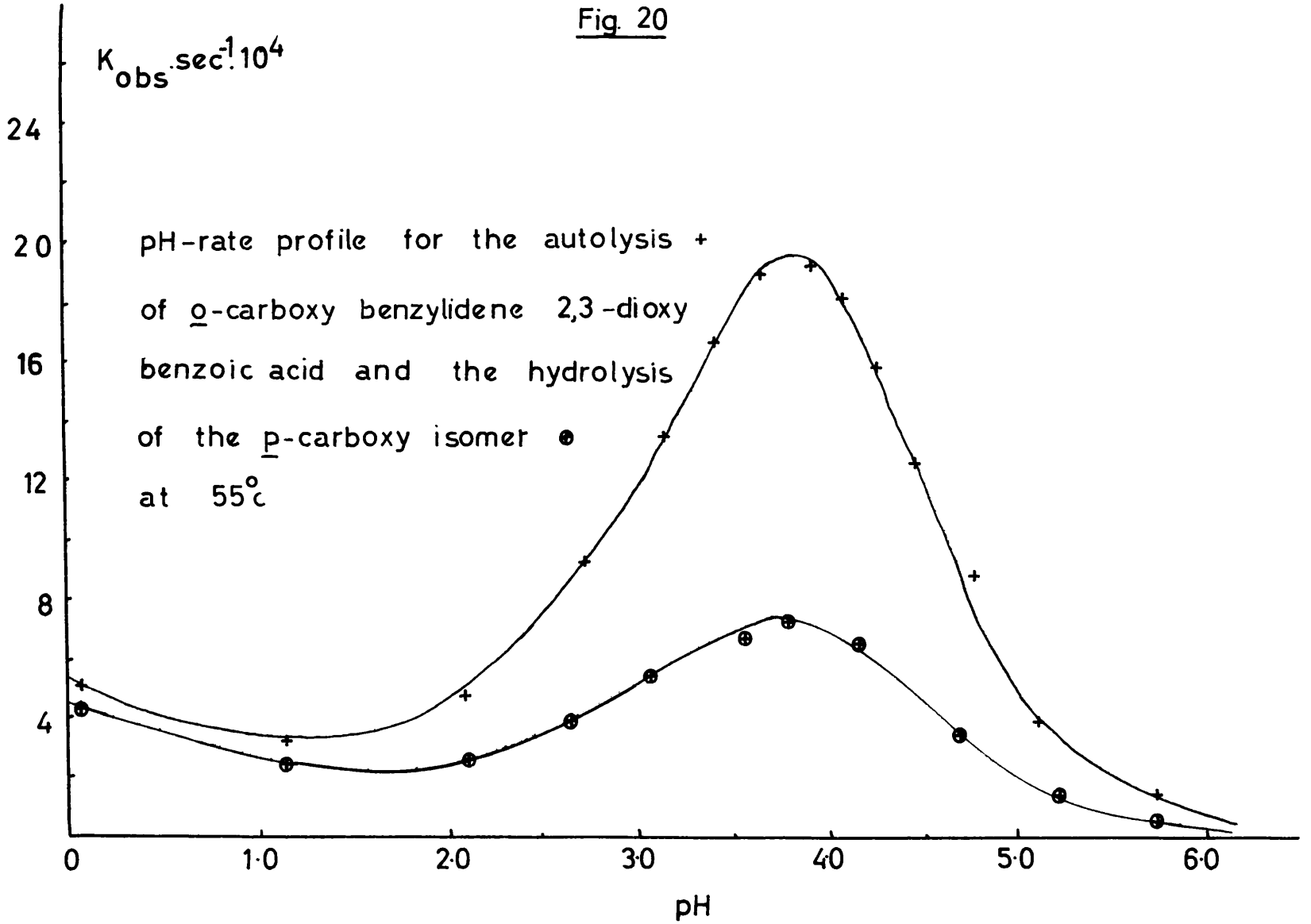

dicarboxy acetal ---
acylal ——
hydrolysis products .....
u.v. absorption spectra pH = 4·1, 50°c
O.D.
0·5
0·3
0·1
250
270
290
310
330
λ nm

Fig. 19

Fig. 20


$K_{obs}.sec^{-1}.10^4$
24
20
16
12
8
4
pH-rate profile for the autolysis +
of o-carboxy benzylidene 2,3-dioxy
benzoic acid and the hydrolysis
of the p-carboxy isomer ⊕
at 55°c
0
1·0
2·0
3·0
4·0
5·0
6·0
pH

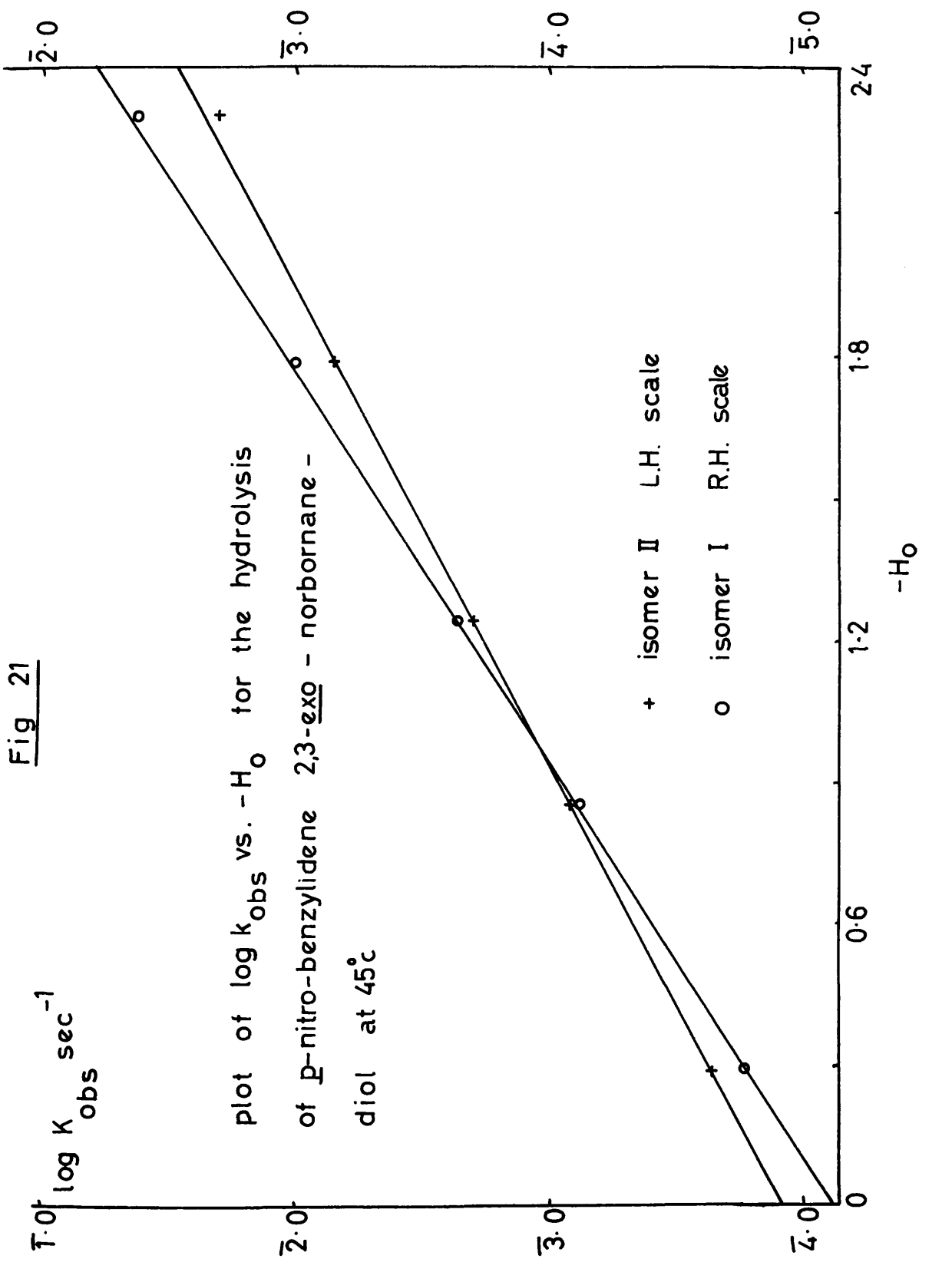
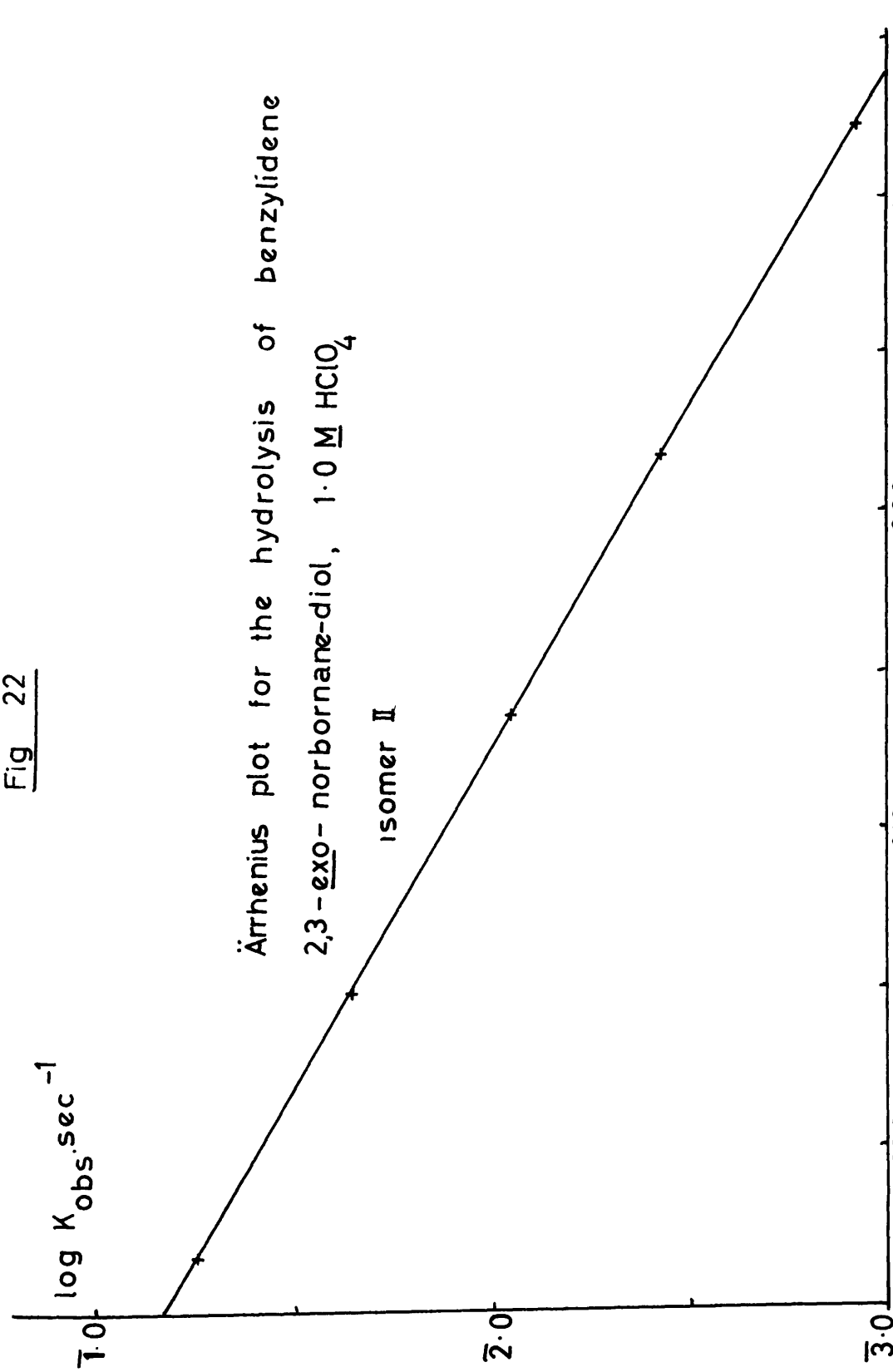


Fig 21
plot of log k_{obs} vs. $-H_o$ for the hydrolysis of p-nitro-benzylidene 2,3-exo - norbornane - diol at 45°c
log K_{obs} sec^{-1}
$\bar{1}\cdot0$
$\bar{2}\cdot0$
$\bar{3}\cdot0$
$\bar{4}\cdot0$
$\bar{2}\cdot0$
$\bar{3}\cdot0$
$\bar{4}\cdot0$
$\bar{5}\cdot0$
0
0·6
1·2
1·8
2·4
$-H_o$
+ isomer II L.H. scale
o isomer I R.H. scale

Fig 22


Ärrhenius plot for the hydrolysis of benzylidene
2,3-exo- norbornane-diol, 1·0 M HClO4
isomer II
log Kobs.sec-1
1·0
2·0
3·0
298
310
322
334
1/T.10^5

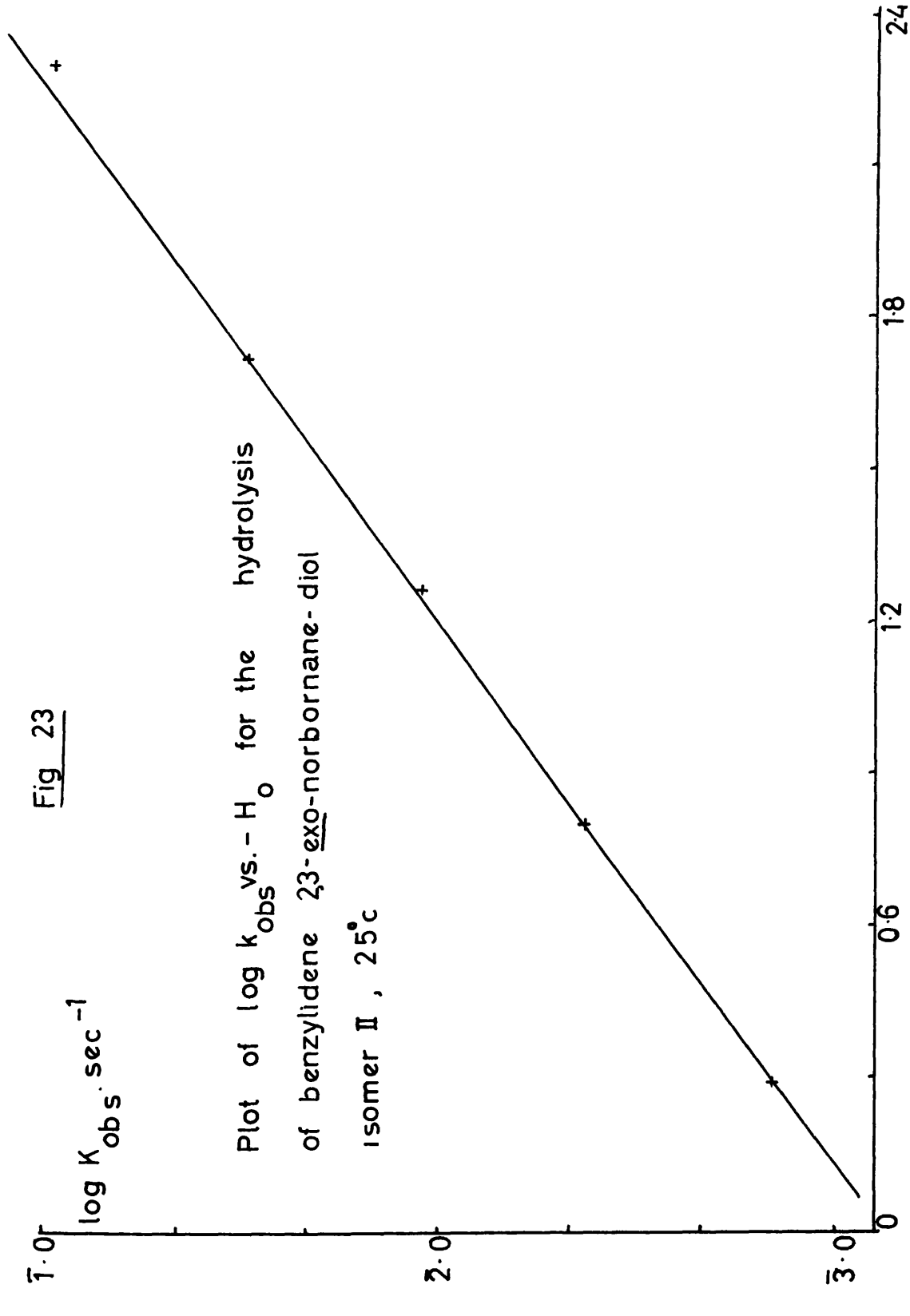


Fig 23
Plot of log k_{obs} vs. $-H_o$ for the hydrolysis of benzylidene 2,3-exo-norbornane-diol isomer II, 25°c
log K_{obs}. sec^{-1}
-1·0
-2·0
-3·0
0
0·6
1·2
1·8
2·4
$-H_o$

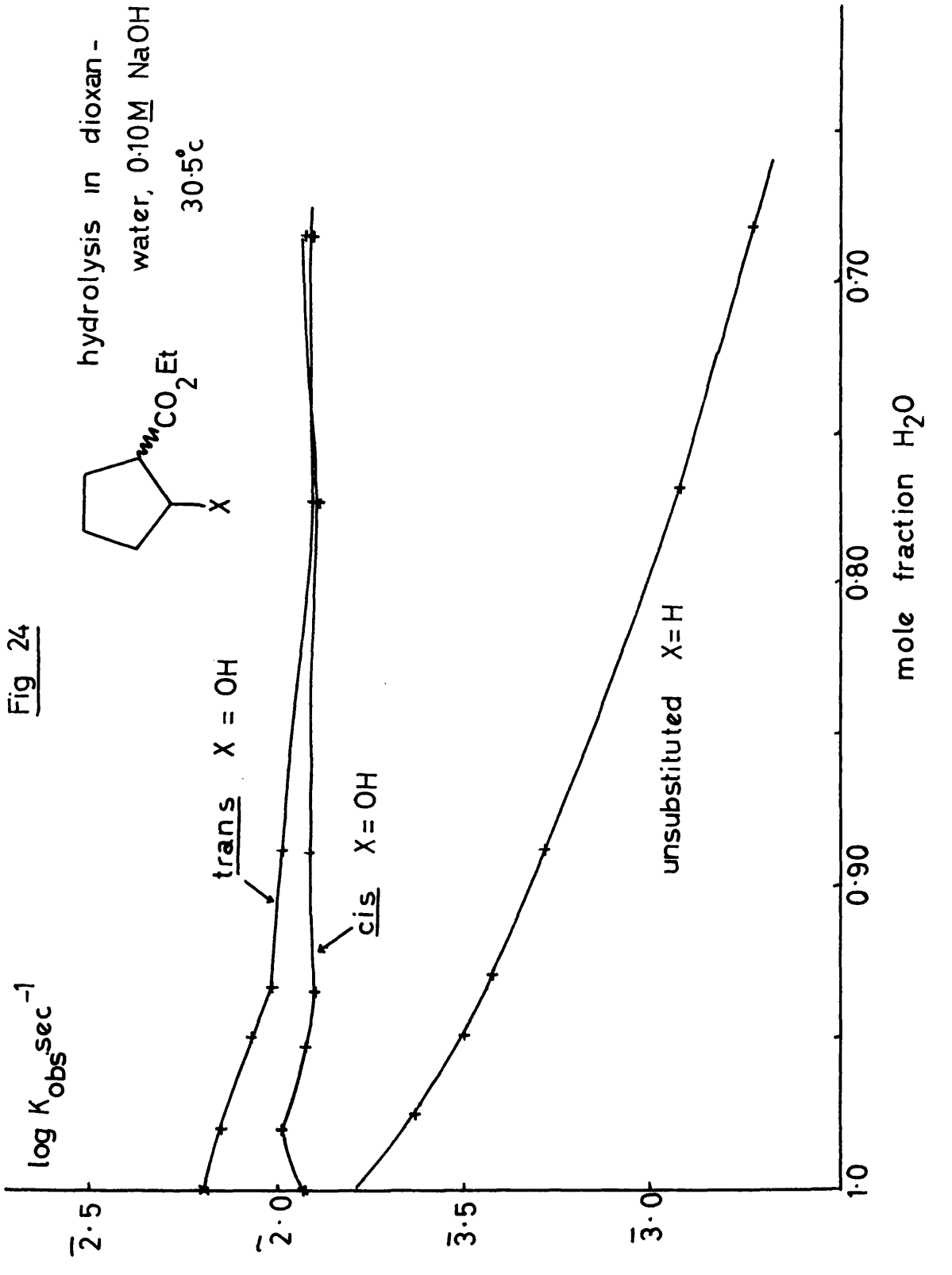


Fig 24
hydrolysis in dioxan-water, 0·10M NaOH 30·5°c
log $K_{obs}^{sec^{-1}}$
trans X = OH
cis X = OH
unsubstituted X = H
mole fraction H_2O
2·5
2·0
3·5
3·0
1·0
0·90
0·80
0·70
CO_2Et
X

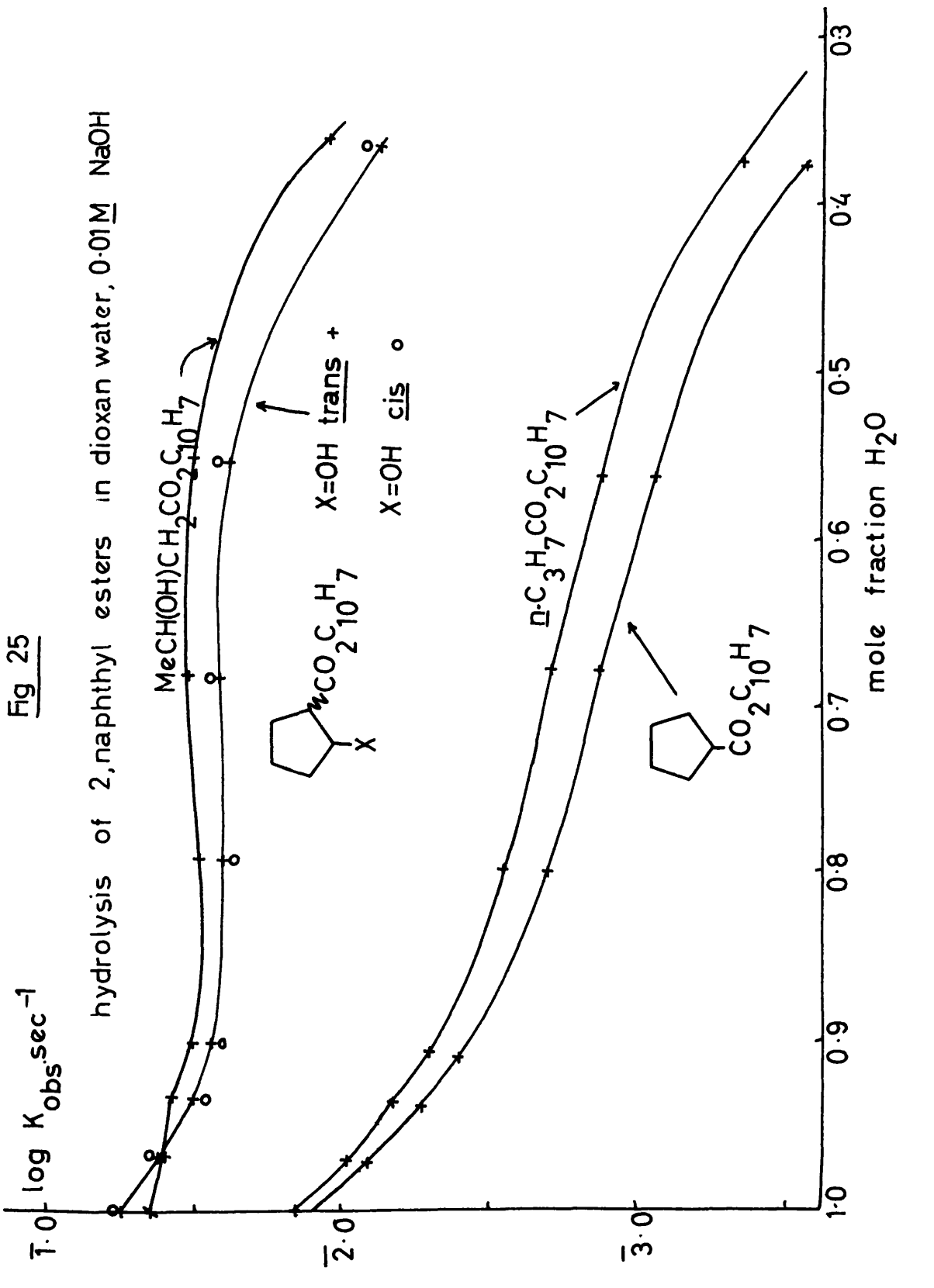


Fig 25
hydrolysis of 2,naphthyl esters in dioxan water, 0·01M NaOH
log K_{obs}.sec^{-1}
1·0
2·0
3·0
MeCH(OH)CH$_2$CO$_2$C$_{10}$H$_7$
X=OH trans +
X=OH cis o
CO$_2$C$_{10}$H$_7$
X
n-C$_3$H$_7$CO$_2$C$_{10}$H$_7$
CO$_2$C$_{10}$H$_7$
0·9
0·8
0·7
0·6
0·5
0·4
0·3
mole fraction H$_2$O

EXPERIMENTAL

Preparative Experimental

Details of readily prepared, well authenticated, compounds are not reported.

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

I.r. spectra were determined generally using a Unicam SP 200 or a Perkin-Elmer 237 spectrometer, and were calibrated with a polystyrene film. Detailed spectra were performed on a Perkin-Elmer 225.

N.m.r. spectra were determined as approximately 10% solutions on 60 MHz. instruments, a Varian T-60 or A-60 and a Perkin-Elmer R-10, unless otherwise stated. 100 MHz. spectra were performed on a Varian HA-100. Chemical shifts were measured downfield from internal T.M.S., and are quoted as tau values. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, and the chemical shift quoted for the latter is the centre of the multiplet.

Mass spectral (M.S.) analysis were performed on an AEI MS 12 mass spectrometer.

A Perkin-Elmer F 11 was used for the vapour phase chromatography (v.p.c.) experiments. T.l.c. were performed on silica unless otherwise stated.

Elemental analysis were determined by Mr. J. Cameron,

of the University of Glasgow, and are quoted as percentages.

Preparation of benzylidene catechol

The acid catalysed condensation of catechol and benzaldehyde or the reaction of the mono- and di-anion of catechol with benzylidene chloride in D.M.F. or methanol did not yield the desired product. The following method was suggested by Dr. G. Sankey.

0·10 mole of recrystallised catechol were dissolved in 100 mls. of dry pyridine, added 0·10 mole of freshly distilled benzylidene chloride in 50 mls. of dry pyridine. The mixture was refluxed under nitrogen for 12 hrs. Evaporated off the pyridine, dissolved residue in methylene chloride and washed successively with water, 0·01 N hydrochloric acid or saturated cadmium chloride, many times with 0·5 N sodium hydroxide and finally with water. The organic layer was dried, the solvent evaporated and the residue recrystallised twice from aqueous ethanol.

Yield = 50%

m. pt. = 49-50°C

t.l.c. R_F 0·5 5% ether-petrol.

Analysis: 79·06 C, 5·26 H; $C_{13}H_{10}O_2$ requires 78·77 C, 5·09 H.

N.M.R. ($CDCl_3$) acetal H 3·07 s, catechol H 3·17 s, benzaldehyde aromatics 2·55 m.

I.R. (KBr disc) 3060, 2880, 1623, 1600, 1480, 1350, 1230, 1097, 1029, 1012, 905 cm^{-1}.

m.s. parent ion 198, M-1 equal intensity, metastable 196, C_6H_5CO 105, C_6H_5 77, $C_6H_5CO_2$ 121.

Preparation of benzylidene 2,3-dioxy benzoic acid

Methyl 2,3-dihydroxy benzoate (m.pt. 79-80°C) (20 mmoles) was reacted with 20 mmoles of benzylidene chloride and worked up as for the preparation of benzylidene catechol. The methyl ester was distilled on a diffusion pump at 180°C.

Yield = 60%

Analysis 70·42 C, 4·60 H; $C_{15}H_{12}O_4$ requires 70·31 C, 4·72 H.

N.M.R. CCl_4 acetal H 3·00 s, aldehyde aromatics and H o to CO_2Me 2·62 m, catechol aromatics 3·15 $J_{1,2}$ = 8 Hz., $J_{1,3}$ = 2 Hz., ester CH_3 6·05 s.

The methyl ester was hydrolysed to the acid by shaking with 2 equivalents of 0·1 N sodium hydroxide for 2 weeks at room temperature. After this time the non-acid material was extracted from the alkaline aqueous solution. The ice-cold solution was then carefully acidified with ice-cold 0·1

N HCl with stirring and extracting with $CHCl_3$ to pH 3. Extracted 3 times with $CHCl_3$, washed combined layers with water, dried and evaporated off the solvent. Recrystallised residue twice from benzene. m.pt. = 179-181·5°C.

Analysis 69·26 C, 4·11 H; $C_{14}H_{10}O_4$ requires 69·42 C, 4·16 H.

N.M.R. d_6 DMSO acetal H 2·67 s, C_6H_5 2·38 s.

I.R. mull 2400-3600, 1680, 1633, 1598, 1305 (see also Table 6) 1245, 1053, 1018 cm^{-1}.

m.s. parent 242, M-1 241, 198 (loss CO_2), 197, 165 (loss C_6H_5).

Preparation of benzylidene 3,4-dioxy benzoic acid

Methyl 3,4-dihydroxy benzoate is very soluble in water, the sulphuric acid used in the esterification of the acid was removed with barium carbonate. The acetal was prepared using a similar procedure to that for the 2,3-derivative. Yield 40% after distillation on a diffusion pump at 180°C.

Analysis 70·51 C, 4·55 H; $C_{15}H_{12}O_4$ requires 70·31 C, 4·72 H.

N.M.R. CCl_4 acetal H 3·05 s, H m to CO_2Me 3·27 d $J_{1,2}$ = 8·5 Hz., ester CH_3 6·23 s, rest m 2·6.

The ester was not hydrolysed by refluxing in aqueous

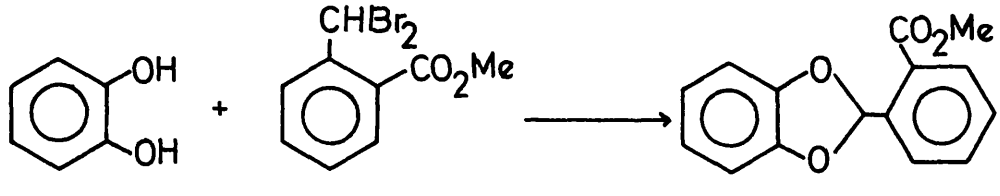
0·1 N NaOH. Dissolved 1·4 mmoles of ester in 50 mls. DMSO added 35 mmoles NaOH in 10 mls. of water. Shook for 12 hours at R.T. Worked up as for the 2,3-derivative. Recrystallised twice from benzene. m.pt. = 179·5 - 181°C (mixed m.pt. with 2,3-cpd. ~ 160°C).

Analysis 69·34 C, 4·14 H; $C_{14}H_{10}O_4$ requires 69·42 C, 4·16 H.

I.R. mull 2400-3200, 1680, 1622, 1609, 1263 (see also Table 6) 1032, 1018 cm^{-1}

N.M.R. d_6 DMSO acetal H 2·63 s, H m to acid 2·90 d $J_{1,2}$ = 8 Hz., rest m 2·42.

Preparation of o-carboxy benzaldehyde acetal of catechol



+ 2 HBr

Methyl α,α-dibromo-o-toluate was prepared (90%) from methyl-o-toluate using the photo-bromination technique of Eliel and Rivard.[331] Recrystallised from petrol m.pt. = 52 - 53°C. 0·19 moles of recrystallised catechol and 0·17 moles of the dibromide were treated and worked up as for benzylidene catechol. The residue was recrystallised from benzene/methanol, the resulting solid was a lactone

(C = O 1780 cm^{-1}) and did not melt up to 300°C. The filtrate was chromatographed on a silica column, eluting with ether.

Yield = 40%

N.M.R. $CDCl_3$ acetal H 2·13 s, catechol aromatics 3·17 s, aldehyde aromatics 2·27 m, CH_3 of ester 6·12 s.

I.R. mull 1720, 1433, 1088, 1020 cm^{-1}

The ester was dissolved in dioxan, added an equal volume of 1 N NaOH, and the solution shaken for 4 days at room temperature. Worked up as for the other carboxy acetals. Recrystallised twice from methanol, and four times from benzene.

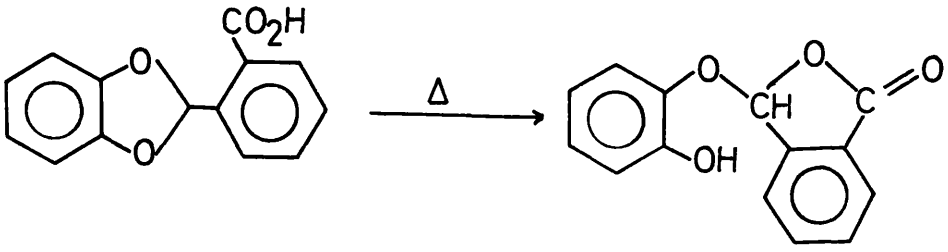
Analysis 69·12 C, 4·31 H; $C_{14}H_{10}O_4$ requires 69·42 C, 4·16 H.

I.R. KBr disc 2400-3300, 1693, 1579, 1480, 1268, 1231, 1020 cm^{-1}.

N.M.R. d_6 acetone acetal H 2·03 s, catechol aromatics 3·13 s, aldehyde aromatics 2·20 m.

m.s. parent ion 242, 197 (loss CO_2H), 134 (loss $C_6H_4O_2$), 105 (C_6H_5CO), 110 ($C_6H_6O_2$)

The corresponding acylal was prepared by simply subliming the acid.



m.pt. = 145 - 146·5°C

Analysis 69·47 C, 4·25 H; $C_{14}H_{10}O_4$ requires 69·42 C, 4·16 H.

N.M.R. d_6 DMSO aldehydic aromatics 2·12 m, rest 2·90 - 3·15.

I.R. KBr disc 3390, 1760, 1597, 1515, 1380, 1288, 1235, 1120, 1055, 935 cm^{-1}

m.s. parent ion 242, 196, 181, 133 ($C_8H_5O_2$), 141, 109 ($C_6H_5O_2$).

Preparation of the p-carboxy benzaldehyde acetal of catechol

0·19 mole methyl α,α-dibromo-p-toluate, recrystallised twice from petrol (m.pt. 68 - 69°C), was refluxed with 0·17 mole of catechol as previously. Charcoal treatment and recrystallisation twice from methanol gave desired product.

M.pt. = 80·5 - 81·5°C Yield = 30%

Analysis 70·51 C, 4·78 H; $C_{15}H_{12}O_4$ requires 70·3 C, 4·72 H.

N.M.R. $CDCl_3$ acetal H 3·07 s, catechol aromatics 3·19 m,

H o to CO_2Me 1·92 d $J_{1,2}$ = 8·5 Hz.,
H m to CO_2Me 2·41 d $J_{1,2}$ = 8·5 Hz.,
CH_3 of ester 6·14 s.

I.R. mull 1713, 1489, 1283, 1245, 1047, 1024 cm^{-1}

The ester was hydrolysed by dissolving in dioxan, adding an equal volume of 1 N NaOH and shaking for one week at room temperature. Worked up as for previous examples. Recrystallised twice from benzene.

m.pt. = 198 - 199°C

Analysis 69·50 C, 4·17 H; $C_{14}H_{10}O_4$ requires 69·42 C, 4·16 H.

N.M.R. d_6 DMSO acetal H 2·73 s, catechol aromatics 3·05 m, H o to CO_2H 1·88 d $J_{1,2}$ = 8·5 Hz., H m to CO_2H 2·30 d $J_{1,2}$ = 8·5 Hz.,

I.R. mull 2500 - 3400, 1681, 1628, 1582, 1240, 1042, 1022 cm^{-1}

Preparation of the o-carboxy benzaldehyde acetal of 2,3-dihydroxy benzoic acid

30 mmoles of methyl α,α-dibromo-o-toluate were reacted with 33 mmoles of methyl 2,3-dihydroxy benzoate, and worked up using a similar procedure to that for benzylidene catechol. Recrystallised residual oil from ether. This solid was a lactone (C = O 1780 and 1720 cm^{-1}). The mother liquor was chromatographed on a silica column eluting with

ether t.l.c. showed 2 compounds still present. Recrystallisation from methanol gave the desired product.

M.pt. = 94 - 95°C Yield = 15%

Analysis 64·67 C, 4·68 H; $C_{17}H_{14}O_6$ is 64·96 C, 4·49 H.

N.M.R. $CDCl_3$ acetal H 1·96 s, phenolic aromatics 3·10 m, aldehydic aromatics and H o to CO_2Me in catechol residue 2·25 m, CH_3 of ester 6·10 s and 6·05 s.

I.R. mull 1722, 1253, 1148, 1032, 1008 cm^{-1}.

Hydrolysed ester (1 mmole) in 20 mls. dioxan and 50 mls. 1 N NaOH. Shook for 5 days. Worked up as for other carboxy acetals. Recrystallised twice from methanol.

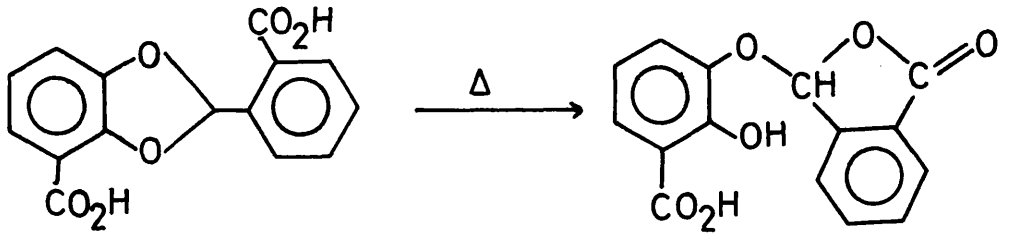
Yield = 80%

Analysis 63·08 C, 3·52 H; $C_{15}H_{10}O_6$ requires 62·94 C, 3·52 H.

I.R. KBr disc 2200 - 3300, 1683, 1630, 1578, 1467, 1415, 1300, 1243, 1053, 1025 cm^{-1}.

m.s. parent ion 286, 242, (loss CO_2), 197 (loss $2CO_2$ + H), 154 ($C_7H_6O_4$), 133 ($C_8H_5O_2$), 105 (C_6H_5CO), 77 (C_6H_5), 44 (CO_2).

The corresponding acylal was again prepared by simply subliming the di-acid at 120°/0·5 mm Hg.



Ring opening occurs in the position shown since the acylal has as an ionisable group of $pK_a \sim 3$ (u.v. spectrum at various pH's) and also gives a blue colouration with neutral ferric chloride solution, typical of salicylic acid derivatives.

Analysis 62·84 C, 3·47 H; $C_{15}H_{10}O_6$ requires 62·94 C, 3·52 H.

I.R. KBr disc 2500 - 3300, 1790, 1660, 1615, 1463, 1445, 1372, 1245, 1040, 1068, 965 cm^{-1}

m.s. identical with the di-acid.

Preparation of the p-carboxy benzaldehyde acetal of 2,3-dihydroxy benzoic

The usual method of preparation and work up yielded only p-carbmethoxy benzaldehyde.

39 mmoles of methyl α,α-dibromo-p-toluate and 33 mmoles of methyl 2,3-dihydroxy benzoate in 100 mls. of dry pyridine, refluxed for 12 hrs. under dry nitrogen. Evaporated off solvent, dissolved residue in ether, washed

6 times with 0·5 N NaOH, then twice with brine. Dried, and evaporated off the solvent t.l.c. showed the aldehyde to be present. Chromatographed immediately on a silica gel column eluting with 1:1 ether:petrol. Recrystallised the solid from methanol, three times.

M.pt. = 108 - 109°C Yield = 20%

Analysis 64·97 C, 4·49 H; $C_{17}H_{14}O_6$ requires 64·97 C, 4·50 H.

N.M.R. $CDCl_3$ acetal H 2·90 s; H o to p CO_2Me 1·94 d $J_{1,2}$ = 8·8 Hz., H m to p CO_2Me 2·40 d $J_{1,2}$ = 8·8 Hz., H o to phenolic CO_2Me 2·58 d of d $J_{1,2}$ = 8·2 Hz., $J_{1,3}$ = 2·8 Hz. rest 3·0 m, CH_3 of CO_2Me 6·09, 6·07 both s.

I.R. mull 1720, 1292, 1240, 1200, 1025, 1010 cm^{-1}

t.l.c. R_F 0·3 in 3:1 petrol:ether.

Dissolved 3 mmoles of di-ester in 30 mls. of dioxan, added 150 mls. of N NaOH and shook for 24 hrs. at room temperature. Worked up as with previous examples.

Yield = 60%

Recrystallised twice from ethanol.

Analysis 63·14 C, 3·63 H; $C_{15}H_{10}O_6$ requires 62·94 C, 3·52 H.

N.M.R. d_6 DMSO acetal H 2·60 s, H o to p CO_2H 1·93 d $J_{1,2}$ = 8·8 Hz., H m to p CO_2H

2·30 d $J_{1,2}$ = 8·8 Hz., rest 2·8 m.

I.R. mull 2600 - 3400, 1699, 1303, 1252, 1040, 1020 cm^{-1}.

Preparation of benzaldehyde diphenyl acetal

Attempts to prepare this compound from sodium phenoxide and benzal chloride in D.M.F. failed, as did the normal procedure in pyridine.

α,α-dibromo toluene (0·02 mole) prepared from the photo-bromination of toluene, was reacted with phenol (0·10 mole) in pyridine in the normal manner and worked up as described previously. T.l.c. of the crude product showed at least a dozen compounds. This mixture was chromatographed and the fraction collected having R_F 0·35 in 3% ether petrol. Distilled residue at 100°C/0·8 mm, to remove impurities, recrystallised non-distilled material from petrol.

M.pt. = 55 - 56°C Yield = 0·7%

Carrying out the reaction with sodium phenoxide in methanol, DMSO or DMF and benzal bromide did not improve the yield, but the latter two solvents gave fewer impurities.

Analysis 82·83 C, 6·01 H; $C_{19}H_{16}O_2$ requires 82·58 C, 5·84 H.

I.R. KBr disc 3030, 3050, 1595, 1585, 1360, 1205, 1080, 1062, 1024, 1007, 990 cm^{-1}

N.M.R. $CDCl_3$ acetal H 3·34, rest multiplet 2·7.

m.s. parent ion 276, very intense PhCHOPh at 183, 165, 155, 106 (C_6H_5CHO), 105 (C_6H_5CO).

Attempted preparation of benzaldehyde o-methoxy diphenyl acetal

Attempts to prepare this compound from o-methoxy phenol or its sodium salt and benzal chloride or benzal bromide in DMF or pyridine failed. The only acetal extracted from the reaction mixture was benzylidene catechol as proved by t.l.c., n.m.r., mass spectrum and mixed m.pt.

Preparation of p-methoxy benzylidene catechol

p-methoxy benzal bromide,[346] from the photobromination of p-methoxy toluene, and catechol in pyridine were reacted in the usual manner, but without refluxing. Vigorous reaction, left at room temperature 3-4 hrs. Usual work up t.l.c. showed anisaldehyde, acetal and other compounds present. Chromatographed on silica column eluting with 10% EtOAc/petrol. Washed desired fraction with saturated $NaHSO_3$, washed with NaOH, w/w. Dried and evaporated off solvent. Yellow oil.

I.R. liq. 1613, 1590, 1498, 1255, 1238, 1040, 1015 cm^{-1}.

N.M.R. $CDCl_3$ OMe 6·24 s, H o to OMe 2·50 d of m $J_{1,2}$ = 8 Hz., C_6H_4 3·18 s, rest 3 - 3·2 m.

On exposure to air this compound turned purple and t.l.c. and i.r. showed that it had hydrolysed to catechol

and p-methoxy benzoic acid.

Preparation of cis and trans 2-carbethoxy cyclopentanol

Carbethoxy cyclopentanone was prepared by a standard procedure. It has been reported that the β-keto ester may be preferentially reduced to form a pure hydroxy isomer.[332] These methods were tried and the refractive index agreed with that reported for the cis isomer,[333] and t.l.c. in a variety of solvents showed only 1 spot. However, v.p.c. analysis of the hydroxy esters showed both isomers to be present, n.m.r. showed the CH_2 of the ethyl group to be two sets of quartets. Pure trans isomer is reported to be the sole product when the keto ester is hydrogenated in ethanolic sodium ethoxide and Raney nickel at 100 atmosphere.[324] This was not reproducible.

The separation of the isomers was attempted by fractional recrystallisation of the 3,5-dinitrobenzoate derivatives, as has been reported.[333] Recrystallisation of 140 g. of this derivative 5 times from 1·5 l. of absolute ethanol gave a compound of constant m.pt. 116·5 - 117°C in 51% yield. Hydrolysis of this material as described[333] gave the cis hydroxy ester containing 3 - 5% of the trans iosmer, as shown by v.p.c. Fractional recrystallisation procedures on the mother liquors did not produce any dinitrobenzoate of constant m.pt., the lowest m.pt. material on hydrolysis gave the trans ester containing

15% of the cis isomer.

The following chemical methods were tried:

(1) cyclopentane bromo-hydrin[335] was treated with sodium cyanide in DMSO using the procedure of Friedman and Shecter.[336] Alkaline hydrolysis of the resulting cis 2-hydroxy nitrile gave an unsaturated carboxylic acid;

(2) cyclopentane epoxide was reacted with sodium cyanide in water to give the trans 2-hydroxy nitrile, which, upon alkaline hydrolysis, also gave an unsaturated carboxylic acid;

(3) attempted hydroxylation of cyclopentene-1-carboxylic acid, obtained from heating the hydroxy acid, by the oxy-mercuration method[338] gave no identifiable products;

(4) alkaline hydrolysis of the unsaturated acid also gave no hydroxy acid.

Separation of the isomeric hydroxy esters

A mixture of the isomers was obtained by hydrogenation of the keto-ester under 3-4 atm. of hydrogen using PtO_2 at room temperature.

Using a 20% carbowax column and a column temperature of 150°C the cis isomer has a retention time of 28 mins. and the trans 50 mins. The column temperature must be at 150°C or below since at 190°, or with the injection block temperature too high, the pure compounds isomerise.

The pure isomers were separated by preparative v.p.c. using an Aerograph autoprep Model A-700. The stationary phase was 30% carbowax 20-M 45/60 chrom. W and acid washed. Column 20' x 3/8". Column temperature 170°C, injection temperature 195°C. Flow rate 10 mls./3 sec. nitrogen 30 lbs. in^{-2}. Under these conditions the cis isomer had a retention time of 80 mins. and the trans 140 mins. These conditions were used since the automatic injector was not working, and it was more efficient to inject another sample immediately after the cis isomer had been collected, rather than collect both isomers before further injection under conditions to produce smaller retention times.

I.R. data

The v.p.c. pure samples were dissolved in 'AR' carbon tetrachloride, and their I.R. spectra measured as a function of dilution.

The absorption spectra of the trans isomer changes on dilution and confirms the configuration since it is not a favourable geometry to show intra-molecular hydrogen bonding. The cis derivative, however, shows a symmetrical hydroxyl absorption, unchanged on dilution at 3512 cm^{-1}. This lower frequency is due to hydrogen bonding. The normal mode of H-bonding between alcohols and esters involves

Compound	Conc. M	$\nu_{C=O}$ cm^{-1}	ν_{C-O} cm^{-1}	ν_{OH} cm^{-1}
ethyl cyclopentane carboxylate	3×10^{-2}	1730, (sh. 1740, 1734, 1717)	1183, 1155	
<u>trans</u>-ethyl 2-hydroxy cp. carboxylate	0·15	1730, (sh. 1735, 1720)	1182, 1155	3610, (sh. 3500)
	0·015	1729, (sh. 1738, 1715)	1180, 1155	3618
	0·0015	1727, (sh. 1738, 1734, 1715)		3617
<u>cis</u>-ethyl 2-hydroxy c.p. carboxylate	0·13	1709, (sh. 1718, 1700, 1735)	1185, (sh. 1205) 1156	3510
	0·013	"	1186, 1158	3513
	0·0013	"		3512

the more basic carbonyl rather than the alcoholic oxygen, especially when this forms a 6-membered ring.[339] When the latter is not possible e.g. in 1,3-diols H-bonding may take place between the hydroxyl group and the alcoholic oxygen, as shown by a raising of the carbonyl and a lowering of the C - O stretching frquencies.[137] An i.r study of the methyl esters of the present cyclopentane system has been reported,[340] but since they were prepared by the fractional recrystallisation method, the experiments were repeated. The conclusion that the cis isomer is H-bonded but not the trans was also reached by these workers. They also assigned a shoulder at 1739 cm^{-1} in the cis isomer to the presence of some alcohol oxygen H-bonded species.[340] But the present results show that this is not reflected in the C - O frequency, and all the esters studied show a shoulder at higher frequency than the carbonyl maximum. One may have also expected 2 hydroxyl peaks were there two H-bonded species present.[341] The present evidence therefore appears to suggest only carbonyl H-bonded species present in CCl_4 solutions.

The H attached to the C - OH group has a smaller band-width in the cis isomer than in the trans derivative. The band-width was measured between the first and last lines of the multiplet. Similar results in the same system have been reported.[343] In view of the effect of electro-

N.M.R. $CDCl_3$

Compound	H - COH		H - C - CO_2X	
	Chem. Shift τ	Band-width Hz.	Chem. Shift τ	Band-width Hz.
cyclopentanol	5·82	17·5		
carbethoxy-cyclopentane			7·37	22
carboxy-cyclopentane			7·28	25
cis-2 carbethoxy cylcopentanol	5·60	11	7·30	23
trans-2-carbethoxy cyclopentanol	5·63	18	7·38	25
cis-2-carboxy cyclopentanol	5·48	11	7·24	25
trans-2-carboxy cylcopentanol	5·58	19	7·25	24

negativities of substituents on coupling constants, and other variables affecting the band-width,[342] detailed inter-

pretation of this phenomenon is not warranted.

Preparation of cis and trans hydroxy acids

The v.p.c. pure ester was shaken with 1·5 equivalents of 0·5 N NaOH for 30 mins. at room temperature. Cooled in ice, acidified with ice-cold N HCl, saturated with NaCl, and extracted 5 times with ether. Washed combined layers with satd. NaCl, dried and evaporated off the solvent.

trans recrystallised twice from ether, m.pt. (sealed tube) = 67 - 68°C (lit. 68 - 69[332]).

I.R. mull 2300 - 3700, 3330, 1700, 1215, 1083, 1055 cm^{-1}.

cis this isomer could not be crystallised, and is extremely hygroscopic.

Determination of pK_a of cis and trans 2-hydroxy cyclopentane carboxylic acid

Approximately 3 mmoles of each acid was titrated against B.D.H. carbonate-free 0·10 N NaOH solution, using a Radiometer TT1 titrator equipped with an SBU burette and Titrigraph.

pK_a of cis isomer at 24°C in water = 4·83 ± 0·01

pK_a of trans isomer at 24°C in water = 4·74 ± 0·02

Preparation of trans 2-naphthyl 2-hydroxy cyclopentane carboxylate

The trans hydroxy acid (3·85 mmoles) and 2-naphthol (3·85 mmoles) were dissolved in 25 mls. of methylene

chloride and ice-cooled. Slowly added ice-cold methylene chloride solution of N,N-dicylcohexylcarbodiimide (DCCI) stirred overnight. Evaporated off solvent, took up in ether, filtered off acyl urea. Washed ice-cold ethereal soln. 3 times with ice-cold 0·01 N NaOH, and 3 times with water. Dried, evaporated off solvent, t.l.c. in 3:2 benzene:ether showed 4 spots R_F 0·9, 0·8, 0·5, and 0·3. The mixture was chromatographed and the fraction with R_F 0·5 was the desired product. Distilled 120°C/0·4 mm, then recrystallised distillate from petrol-benzene.

M.pt. = 59 - 60°C Yield = 20%

Analysis 75·07 C, 6·19 H; $C_{16}H_{16}O_3$ requires 74·98 C, 6·29 H.

N.M.R. naphthyl 2·4 m, H - COH 5·41 m bandwidth 18 Hz., H - C - CO_2Ar 7·00 m bandwidth 24 Hz., cyclopentyl residue 8·0 m.

I.R. CCl_4 3617, 3060, 2965, 2873, 1750, 1628, 1597, 1208, 1153, 1135 cm^{-1}.

m.s. parent ion 256, M-1 255, 238 (loss H_2O) 144, 115 (C_9H_7) 95, 67.

Preparation of cis-2-naphthyl 2-hydroxy cyclopentane carboxylate

The procedure was similar to that for the trans ester, t.l.c. of the initial product in 3:2 benzene:ether showed

about a dozen compounds present. This was chromatographed and the fractions with $R_F \sim 0{\cdot}6$ in the above solvent system collected t.l.c. of this material in 10% EtOAc: benzene showed 5 compounds R_F 0·8, 0·75, 0·7, 0·65 and 0·6. This was further chromatographed eluting with 5% EtOAc:benzene, to give a product of R_F 0·3 and 0·25 in this solvent system. The latter were separated on a prep. plate using 2% EtOAc benzene as eluent, the higher R_F value corresponding to the desired product. Distillation 80°C/ 0·2 mm gave the pure cis hydroxy ester.

Yield = 2%

Analysis 74·58 C, 6·17 H; $C_{16}H_{16}O_3$ requires 74·98 C, 6·29 H.

t.l.c. 10% EtOAc benzene R_F 0·7.

N.M.R. naphthyl 2·5 m, H - COH 5·62 m bandwidth 13 Hz., H - C - CO_2Ar 7·1 m, cyclopentyl 8·0 m.

I.R. CCl_4 3540, 3060, 1731, 1628, 1597, 1205, 1152 cm^{-1}.

m.s. parent ion 256, 223, 115 (naphthyl), 144, 149.

Preparation 2-carbethoxy cyclohexanols

2-carbethoxy cyclohexanone was hydrogenated with PtO_2 to yield to isomeric alcohols. The isomers were separated by preparative v.p.c. as described for the cyclopentyl system.

trans N.M.R. $CDCl_3$ H - COH 6·25 m, bandwidth 23 Hz.,

H - CCO_2Et 7·14 m bandwidth 15 Hz.,

cis N.M.R. $CDCl_3$ H - COH 5·82 m, H - CO_2Et 7·50 m bandwidth = 20 Hz.

Preparation of 2-naphthyl cyclopentane carboxylate

Cyclopentane carboxylic acid and 2-naphthol were reacted with DCCI in methylene chloride as previously described. Evaporated off solvent, dissolved in ether, filtered, evaporated off filtrate. Recrystallised residue 3 times from methanol.

M.pt. = 54·5 - 55°C Yield = 70%

Analysis 79·56 C, 6·57 H; $C_{16}H_{16}O_2$ requires 79·97 C, 6·71 H.

N.M.R. $CDCl_3$ naphthyl 2·7 m, H - C - CO_2Ar 7·00 m bandwidth 23 Hz., rest 8·2 m.

I.R. CCl_4 3060, 2960, 2870, 1750, 1628, 1597, 1152, 1137 cm^{-1}.

Preparation of 2-naphthyl butyrate

Prepared from the acid chloride and 2-naphthol. Recrystallised from ether.

M.pt. = 24 - 25°C

Analysis 78·63 C, 6·49 H; $C_{14}H_{14}O_2$ requires 78·48 C, 6·59 H.

N.M.R. $CDCl_3$ CH_3 9·00 t, $MeCH_2$ 8·25 sextet, CH_2CO_2Ar 7·45 t, aromatics 2·1 - 2·9 m.

I.R. CCl_4 3060, 2965, 1757, 1628, 1597, 1207 1153 cm^{-1}.

Preparation of 2-naphthyl 3-hydroxy butyrate

3-hydroxy butyric acid, from the reduction and then hydrolysis of ethyl acetoacetate, and 2-naphthol were reacted with DCCI and worked up as previously described. The reaction mixture was chromatographed, and the hydroxy ester recrystallised from benzene then sublimed.

M.pt. = 95 - 96°C Yield = 30%

Analysis 73·27 C, 6·31 H; $C_{14}H_{14}O_3$ requires 73·03 C, 6·13 H.

N.M.R. $CDCl_3$ naphthyl 2·7 m, CH_3 8·70 $J_{1,2}$ = 7 Hz., CH_2 7·24 d $J_{1,2}$ = 6 Hz., CH 5·67 m.

I.R. 3565, 3060, 2970, 2925, 1749, 1628, 1597, 1212, 1155 cm^{-1}.

Hydrogen bonding studies of 2-naphthyl esters

The CCl_4 solutions of the esters gave the i.r. data shown on the following page.

The cis, but not the trans, hydroxy ester shows intramolecular hydrogen bonding between the hydroxyl and the carbonyl of the ester group. Similarly, the hydroxy butyrate ester. Ethyl 3-hydroxy butyrate has been shown to exhibit hydrogen bonding in CCl_4.[341]

Compound	Conc. M	$\nu_{C=O}$ cm^{-1}	ν_{C-O} cm^{-1}	ν_{OH} cm^{-1}
2-naphthyl cp. carboxylate	3×10^{-2}	1750	1152, 1137	
2-naph. trans 2-hydroxy cp. carboxylate	$2{\cdot}2 \times 10^{-2}$	1750	1153, 1135	3617, 3480
	$2{\cdot}2 \times 10^{-3}$	1750		3617
cis 2-naph. 2-hydroxy cp. carboxylate	$1{\cdot}7 \times 10^{-2}$	1731, (sh. 1755, 1740, 1715)	1152, (sh. 1170) 1138	3545
	$1{\cdot}7 \times 10^{-3}$	"		3540
2-naphthyl butyrate	$2{\cdot}6 \times 10^{-2}$	1757	1153, (sh. 1146)	
2-naph. 3-hydroxy butyrate	$2{\cdot}5 \times 10^{-2}$	1749	1155	3565
	$2{\cdot}5 \times 10^{-3}$	1749	1155	3565

Preparation of the benzaldehyde acetals of exo 2,3-norbornane diol

2,3-exo-norbornanediol was prepared by the potassium permanganate hydroxylation of norbornene as described by Sable and Katchian,[343] except that magnesium sulphate was added.[344] However, using this procedure gave many side products and the yield was only 20%. A better method is that of Wiberg, using $KMnO_4$ in aqueous t-butanol.[345]

M.pt. = 139·5 - 141°C Yield = 40% (lit. 138 - 140[343])

N.M.R. $CDCl_3/D_2O$ H - CO 6·36 d $J_{2endo,7anti}$ = 1·7 Hz., bridgehead 7·88 m.

From symmetry considerations, the two hydroxyl groups are cis related. Also, were they endo, endo the 2 and 3 exo protons would show a coupling of about 4 Hz. to the bridgehead protons.

Two techniques were used to condense the aldehyde and diol. Equimolar quantities of the diol and aldehyde were dissolved in dry toluene, and a few crystals of p-toluene-sulphonic acid were added. If the reaction was done on a large scale (> 0·01 M), then the mixture was refluxed and the water continuously removed using a Dean and Stark apparatus. On a smaller scale, the mixture was refluxed with molecular sieves, type 5A, in a sauxhlet trap to remove the condensed water. Usually after 4 or 5 hours refluxing

the reaction was complete, (t.l.c.).

The reaction mixture was worked up by adding ether, washing twice with 0·1 N NaOH, twice with water. Dried and evaporated off solvent. Yields of product from this procedure were about 90% n.m.r. and t.l.c. showed that the product contained two isomers which were separated by column chromatography or an a 'prep-plate'.

Benzaldehyde acetals

isomer 1 t.l.c. 1:9 ether:petrol R_F = 0·6

v.p.c. pure apiezon column 150°C ret. time = 8 min.

Distilled at 80°C/0·5 mm colourless liquid.

Analysis 77·84 C, 7·64 H; $C_{14}H_{16}O_2$ requires 77·75 C, 7·46 H.

I.R. 3050, 1325, 1212, 1085, 1063 cm^{-1}.

N.M.R. $CDCl_3$ acetal H 3·85 s, H - C - O 6·12 d $J_{2n,7s}$ = 1·4 Hz., bridgehead 7·64 m, aromatics 2·68 m, 7-syn 8·22 d of m $J_{7,7}$ = 10 Hz., rest 8·8 m.

m.s. parent ion 216, 215, 187 (loss C_2H_4) 169, 159, 139 (loss C_6H_5) 77 (C_6H_5).

isomer 2 t.l.c. 1:9 ether:petrol R_F = 0·55

v.p.c. pure apiezon column 150°C ret. time = 12 min.

Distilled at 80°C/0·5 mm, then recrystallised from petrol,

M.pt. = 31·5 - 32°C

Analysis 77·62 C, 7·37 H; $C_{14}H_{16}O_2$ requires 77·75 C, 7·46 H.

I.R. 3070, 1390, 1135, 1085, 1063, 1025, 1000, 925 cm^{-1}.

m.s. identical with that of isomer1.

N.M.R. $CDCl_3$ acetal H 4·54 s, H - CO 6·04 d $J_{2n,7s}$ = 1·4 Hz., bridgehead 7·60 m, aromatics 2·70 m, 7-syn 8·3 d of m $J_{7,7}$ = 10 Hz., rest 8·8 m.

The above assignments were confirmed at 100 MHz.:

isomer 1 H at 8·22 is 7-syn since irradiation at H-2,3 does not affect splitting. This appears as a doublet of triplets $J_{7s,7a}$ = 10·2 Hz., $J_{7s,1}$ = $J_{7s,4}$ = 1·7 Hz. This may be deceptively simple, there apparently being no coupling between H5, H6 endo and H-7-syn. However, on irradiation at H1 and H4, the doublet of triplets remains but the peaks are a lot sharper, so there is coupling between 7-syn and 5,6 endo. H1 and H4 is a 6 line absorption which collapses to a triplet on irradiation at 7-syn. Width of aromatic absorption at half-height = 10 Hz.

isomer 2 H-2,3 doublet collapses to singlet on irradiation at 8·8, the H-7anti proton. H-7-syn at 8·3 is doublet of triplets $J_{7s,7a}$ = 10·2 Hz. H1 and 4 is again a 6 line absorption.

p-nitro-benzaldehyde acetals

isomer 1 t.l.c. 10% ether:petrol R_F 0·5 recrystallised from petrol m.pt. = 99 - 99·5°C.

Analysis 64·31 C, 5·96 H, 5·23 N; $C_{14}H_{15}O_4N$ requires 64·36 C, 5·79 H, 5·36 N.

I.R. mull 1603, 1520, 1195, 1133, 1095 cm^{-1}.

N.M.R. $CDCl_3$ acetal H 3·82 s, H - CO 6·08 d $J_{2endo,7anti}$ = 1·4 Hz., bridgehead 7·60 m, norbonyl residue 8·6 m, H o to NO_2 1·82 d $J_{1,2}$ = 9 Hz., H m to NO_2 2·42 d $J_{1,2}$ = 9 Hz.

isomer 2 t.l.c. 10% ether:petrol R_F 0·4 recrystallised from petrol m.pt. = 105 - 106°C.

Analysis 64·43 C, 5·86 H, 5·30 N; $C_{14}H_{15}O_4N$ requires 64·36 C, 5·79 H, 5·36 N.

N.M.R. $CDCl_3$ acetal H 4·38 s, H - CO 5·93 d $J_{2,7}$ = 1·4 Hz., bridgehead 7·57 m, norbornyl residue 8·6 m, H o to NO_2 1·78 d $J_{1,2}$ = 9 Hz., H m to NO_2 2·34 d $J_{1,2}$ = 9 Hz.

p-methoxy-benzaldehyde acetals

isomer 1 t.l.c. 10% ether:petrol R_F 0·6 distilled 90°/0·5 mm and recrystallised from petrol m.pt. = 53 - 55°C.

Analysis 73·36 C, 7·40 H; $C_{15}H_{18}O_3$ requires 73·15 C, 7·37 H.

N.M.R. $CDCl_3$ acetal H 3·84 s, H - CO 6·05 d $J_{2,7}$ = 1·7 Hz., CH_3O 6·20 s, bridgehead 7·64 m, bridge 7-syn 8·20 d of m $J_{7,7}$ = 12 Hz., rest norbornyl 8·8 m, aromatics 2·63 d $J_{1,2}$ = 9 Hz., 3·13 d, $J_{1,2}$ = 9 Hz., OMe usually exerts the same chemical shift difference on protons o, m and p to itself.

This isomer isomerises in the solid state and in dioxan solutions on standing for long periods, ~ 4 weeks.

isomer 2 t.l.c. 10% ether:petrol R_F 0·5 recrystallised from petrol m.pt. = 62 - 63°C.

Analysis 73·38 C, 7·51 H; $C_{15}H_{18}O_3$ requires 73·15 C, 7·37 H.

I.R. mull 1615, 1590, 1312, 1250, 1165, 1063, 1035, 840 cm^{-1}.

N.M.R. $CDCl_3$ acetal H 4·50 s, H - CO 6·00 d $J_{2,7}$ = 1·7 Hz., CH_3O 6·22 s, bridgehead 7·58 m, bridge 7-syn 8·10 d of m $J_{7,7}$ = 10 Hz., rest norbornyl 8·8 m, aromatics 2·57 d $J_{1,2}$ = 9 Hz., 3·13 d $J_{1,2}$ = 9 Hz.

This compound also isomerises after about 2 months in dioxan solution.

p-chloro-benzaldehyde acetal

isomer 1 t.l.c. 10% ether petrol R_F 0·8 distilled 100°C/0·5 mm.

Analysis 67·18 C, 6·17 H; $C_{14}H_{15}O_2Cl$ requires 67·13 C, 6·03 H.

N.M.R. $CDCl_3$ acetal H 3·85 s, H - CO 6·12 d, bridgehead 7·64 m, aromatics 2·68 m.

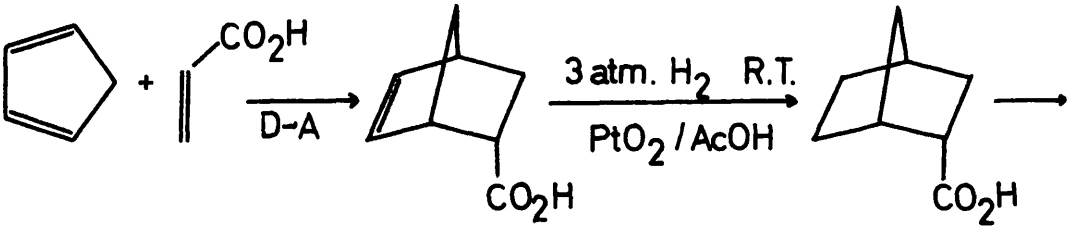
isomer 2 t.l.c. 10% ether petrol R_F 0·75 recrystallised from petrol m.pt. = 95 - 96°C.

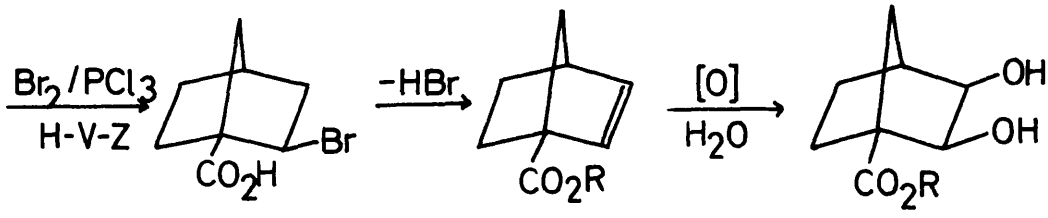
Analysis 67·09 C, 6·00 H; $C_{14}H_{15}O_2Cl$ requires 67·13 C, 6·03 H.

N.M.R. $CDCl_3$ acetal H 4·48 s, H - CO 5·98 d, bridgehead 7·58 m, aromatics 2·60 m.

Preparation of benzaldehyde acetal of 1-carboxy 2,3-exo-norbornanediol

1-carboxy 2-exo-bromo-norbornane was prepared by the methods of Boehme[347] and Kwart and Null.[348]





It was found that the 5-endo-carboxy norbornene derivative was formed exclusively to its epimer providing the temperature of the reaction was maintained below 30°C.

It had been reported that dehydrobromination of this acid gave exclusively 2-carboxy norbornene,[349] however the following procedure gave a mixture of isomers.

50 mmoles of bromo-acid were added to 61 mmoles of potassium t-butoxide in 50 mls. t-butanol. Refluxed for 24 hrs. Evaporated off t-BuOH, dissolved in ether, extracted with sodium carbonate soln., acidified latter with HCl, extracted with ether, washed with water. Dried, evaporated off solvent. The pale yellow, viscous, foul smelling oil polymerised on strong heating. N.m.r. showed the presence of two compounds. The mixture of acids were esterified with diazomethane. V.p.c. of esters on apiezon column, 140°C, showed two isomers, 29% of methyl norbornen-1-carboxylate and 71% of methyl norbornene-2-carboxylate. I.r. C = C 1600 cm^{-1}, C = O 1710 and 1740, n.m.r. CCl_4: 2-carboxylate, vinyl H 3·2 d bridgehead 6·80 m and 7·02 m;

1-carboxylate vinyl H 3·9 m.

Similar observations have since been reported.[350] 1-carboxy 2-exo-bromo-norbornane was esterified with dimethyl sulphate by the method of Wilt et al.[350] 0·48 mole of the ester was refluxed with 1·09 moles of potassium t-butoxide in 1·7 l. of t-butanol under nitrogen for 48 hrs. Evaporated off t-butanol, dissolved in ether, washed with 0·1 N NaOH, then with brine. Dried, evaporated off solvent. Distilled residue and collected t-butyl-norbornene-2-carboxylate at 94°C/14 mm. Yield = 63% The pleasant odourous liquid appears to be a heart stimulant on smelling.

I.R. neat 1720, 1570, 1395, 1365, 1312 cm^{-1}.

CCl_4 1730, 1395, 1370, 1317 cm^{-1}.

N.M.R. CCl_4 vinyl H 3·97 m, bridgehead 7·10 m, t-Bu 8·55 s.

Hydroxylations of the olefin with permanganate or osmium tetroxide and hydrogen peroxide gave mainly ring-cleaved products.[351,352]

Dissolved 5·9 mmoles of olefin in 50 mls. of dry ether, added 5·9 mmoles of osmium tetroxide in 80 mls. of dry ether. Added 1 ml. dry pyridine, stoppered flask and protected from the light, stirred at room temperature for 6 hrs. Stirred with saturated solution of sodium meta-

bisulphite for 2 hrs. Continuously extracted with ether, washed twice with saturated brine. Dried and evaporated off solvent. A small sample was chromatographed, and used as seed to recrystallise the diol from petrol.

Yield = 77%

Sublimed sample M.pt. = 88·5 - 89·5°C

Analysis 63·08 C, 8·68 H; $C_{12}H_{20}O_4$ requires 63·14 C, 8·83 H.

N.M.R. $CDCl_3/D_2O$ H - CO 6·21 d of d $J_{2n,7a} = J_{3n,7a}$ = 1·8 Hz., t-butyl 8·55 s, rest 7·9 - 8·9 m.

I.R. CCl_4 0·002 M C = O 1703, 1738 cm^{-1} ratio 3:1, OH 3530, 3400 cm^{-1} ratio 2:1, t-Bu 1396, 1373 cm^{-1}.

2,3-exo-norbornane diol shows ν_{OH} at 3632, 3529 cm^{-1}.[353]

The present system does not show any free hydroxyl absorption. The 2-exo-hydroxyl is hydrogen bonded to the carbonyl of the ester group, and also the the 3-exo-hydroxyl group.

The diol was reacted with benzaldehyde as previously described.

isomer 1 t.l.c. 4% EtOAc petrol R_F 0·35

N.M.R. $CDCl_3$ acetal H 3·78 s, H - CO 5·95 m, aromatics 2·63 m, t-butyl 8·53 s.

isomer 2 t.l.c. 4% EtOAc petrol R_F 0·3 recrystallised from petrol m.pt. = 108·5 - 109·5°C.

Analysis 72·28 C, 7·75 H; $C_{19}H_{24}O_4$ requires 72·13 C, 7·65 H.

N.M.R. $CDCl_3$ acetal H 4·38 s, H - CO two d 5·81 and 5·84 $J_{2n,7a} = J_{3n,7a}$ = 1·5 Hz., bridgehead 7·64 m, 7-syn 7·92 d $J_{7,7}$ = 12 Hz., t-butyl 8·54 s, aromatics 2·61 m.

I.R. mull 1726, 1406, 1368, 1343, 1305, 1160, 1025, 1000 cm^{-1}

CCl_4 C = O 1736 cm^{-1}.

Hydrolysed ester of isomer 2 in DMSO/1 N sodium hydroxide solution by shaking for 1 week at room temperature. Worked up as for other carboxy acetals. Recrystallised from benzene.

M.pt. = 172 - 173°C.

Analysis 69·39 C, 6·14 H; $C_{15}H_{16}O_4$ requires 69·22 C, 6·20 H.

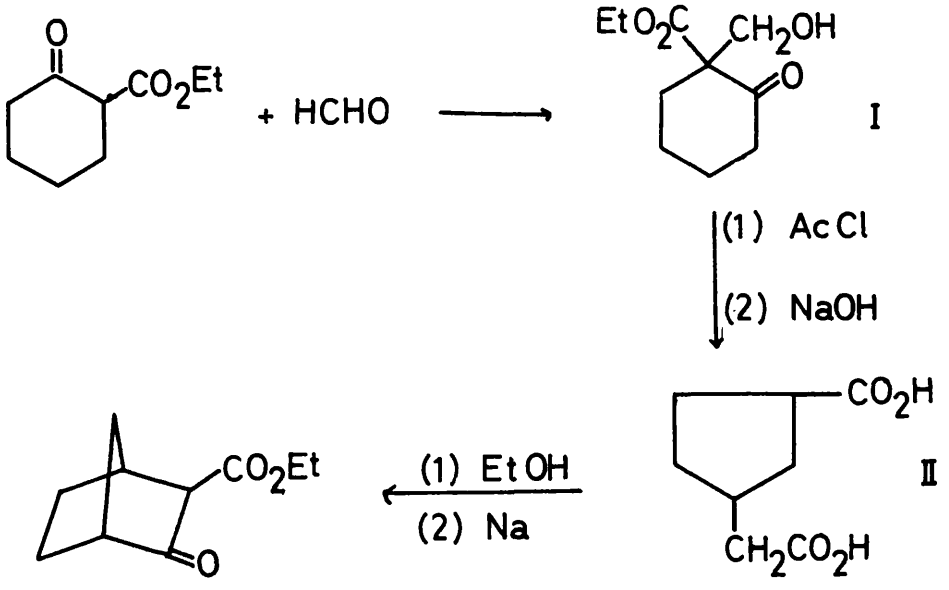
N.M.R. $CDCl_3$ acetal H 4·44 s, H - CO 5·84 m, aromatics 2·68 m, bridgehead 7·62 m.

I.R. CCl_4 0·0018 M monomeric OH 3530, intra-molecularly H-bonded OH 3360, C = O 1760, 1710 cm^{-1}.

$CHCl_3$ (0·014, 0·003 M) C = O 1755, 1710, OH 3500, 3300 ratio unchanged on dilution.

Attempted preparation of 2-hydroxy 3-norbornane carboxylic acid.

The following sequence is reported in the literature.[354]



N.m.r. of I showed it to be the 2,6-cyclohexanone derivative. II was $CH_2 = CH(CO_2H)(CH_2)_4CO_2H$ which on reduction gave 2-methyl pimelic acid as shown by i.r. n.m.r. and m.pt.

2-norbornene carboxylic acid could not be prepared from norbornene carbanion and CO_2.[355] It was prepared by the method described earlier. Hydroxylation by the oxymercuration method failed.[338] An unidentified 2,3-hydroxy acid in the norbornane series has been reported by Tobler

and Foster.[356] The yields were found to be poor and the hydroxy acid was not the desired compound.

Attempts to enter the series by reacting camphor with NaOEt/diethyl oxalate, NaH/diethyl carbonate, NaOEt/diethyl carbonate yielded only unreacted ketone.

The trichloro-acetate of 2-exo-hydroxy 3-exo-norbornane carboxamide was prepared by the method of Smith et al.[357] On hydrolysis with 0·01 N NaOH at room temperature this gave 2-exo-norbornane carboxamide. M.pt. = 135 - 136°C, i.r. 1680, 1660, 3250, 3440, 3380 cm^{-1}. 61·42 C, 8·36 H, 8·62 N; $C_8H_{13}O_2N$ is 61·91 C, 8·44 H, 9·03 N. However this could not be hydrolysed to the hydroxy acid by refluxing in ethanolic NaOH, nitrous acid treatment or with aqueous cobalt II chloride at pH 6.

Preparation of 3-carboxy camphor

The carbonation procedure of Normant was used.[358]

To 0·5 mole of naphthalene in 400 mls. of dry THF was added 0·5 mole of sodium in small pieces. Mixture stirred for 3 hrs. under nitrogen. Added 0·5 mole of camphor in ether dropwise to vigorously stirred solution. Green solution turned red and did not decolourise until all the ketone had been added. Addition took 1 hr., solution gets warm. Added crushed solid CO_2 to solution, vigorous reaction. Added 200 mls. water, then acetic acid and HCl

till acid. Extracted with EtOAc, washed with water, dried and evaporated off solvent. Dissolved in ice-cold sodium carbonate, extracted with ether, acidified aq. layer with ice-cold 0·1 N HCl, extracted with EtOAc, washed w/w, dried and exaporated off solvent. Recrystallised from benzene.

Yield = 30%

M.pt. = 133 - 134·5°C (lit. 128°[282])

Analysis 67·54 C, 8·27 H; $C_{11}H_{16}O_3$ requires 67·32 C, 8·22 H.

1 spot t.l.c. polyamide R_F I·6 ($CHCl_3$) R_F 0·8 (MeOH) silica R_F 0·5 (3:1 benzene:EtOAc 4% AcOH).

N.M.R. $CDCl_3$ shows cpd. to be a mixture of 67% endo and 33% exo carboxy.

3 exo carboxy CH_3 8·98, 9·05, 9·12 s, H-3 endo 7·08 s, bridgehead 7·28 d $J_{4,5x}$ = 4 Hz.

3 endo carboxy H-3 exo 6·60 d $J_{3x,4}$ = 5 Hz., bridgehead 7·50 t, irradiation at bridgehead collapses H-3 d to s.

I.R. CCl_4 ($1·5 \times 10^{-3}$ M) C = O 1780, 1750, 1730, 1708 cm^{-1}, OH 3530, broad peak at 3300 cm^{-1}.

3-carbmethoxy camphor

Ethereal diazomethane treatment of acid gave an unsaturated ester as well as expected exo and endo esters,

purified by chromatography, t.l.c. R_F 0·6 1:1 ether:petrol.

N.M.R. $CDCl_3$ again showed presence of two isomers.

3-exo-carbmethoxy H-3 endo 7·12 s, bridgehead 7·33 d $J_{4,5x}$ = 4 Hz., CH_3 of ester 6·37 s, CH_3's 9·01, 9·08, 9·14 s.

3-endo-carbmethoxy H-3 exo 6·67 d of d $J_{3x,4}$ = 4·8 Hz., $J_{3x,5x}$ = 1·2 Hz., bridgehead 7·57 t.

I.R. mull 1760, 1725 cm^{-1}.

2-exo-hydroxy 3-endo-carboxy bornane

Keto-acid was not reducible with PtO_2/H_2, but was reduced in methanol with sodium borohydride. The pure isomer could be recrystallised from the worked up reduction mixture in toluene, and more product was obtained by chromatographing the mother liquor on silica gel column eluting with 3:1 benzene:EtOAc, 1% AcOH.

M.pt = 169 - 170°C (lit. 170 - 171°[282])

N.M.R. d_6 acetone CH_3's 8·90, 9·10, 9·13 s, H-2 endo 6·12 d $J_{2n,3x}$ = 4·0 Hz., H-3 exo 7·04 d of t $J_{3x,2n}$ = $J_{3x,4}$ = 4·0 Hz., $J_{3x,5x}$ = 1·6 Hz.

I.R. mull 3550, 2500 - 3500, 1718, 1195, 1050 cm^{-1}.

2-exo-hydroxy 3-endo-carbmethoxy bornane

This was prepared from reduction of the mixture of keto esters with sodium borohydride, t.l.c. of worked up reaction mixture showed about 6 compounds. The desired

ester was separated by chromatography. Esterification of the corresponding acid with diazomethane gave the same product without the need for chromatographic purification. Recrystallised from petrol. M.pt. = 56·5 - 57·5°C.

Analysis 67·89 C, 9·36 H; $C_{12}H_{20}O_3$ requires 67·89 C, 9·50 H.

t.l.c. 10% ether benzene R_F 0·25

N.M.R. $CDCl_3$ H-2 endo 6·05 d $J_{2n,3x}$ = 4·0 Hz., H-3 exo 7·00 d of t $J_{3x,2n}$ = $J_{3x,4}$ = 4·0 Hz. $J_{3x,5x}$ = 1·4 Hz., bridgehead 8·00 t $J_{4,3x}$ = $J_{4,5x}$ = 4·0 Hz, CH_3 of ester = 6·34 s, CH_3's 9·15, 9·10, 8·93.

Irradiation at 8·4 collapsed the d of t of H-3 to t. Irradiation at 7·0 decoupled H2 with H3.

I.R. CCl_4 ($2·5 \times 10^{-2}$ M) C=O 1740, OH at 3635, and small peak at 3500 which disappears on dilution.

2-exo-hydroxy 3-exo-carbmethoxy bornane

From chromatographic separation of the mixture from borohydride reduction of the isomeric keto esters. Distilled 50°C/0·5 mm.

Analysis 67·87 C, 9·51 H; $C_{12}H_{20}O_3$ is 67·89 C, 9·50 H.

t.l.c. 10% ether benzene R_F 0·4

N.M.R. H-2 endo 6·07 d $J_{2n,3n}$ = 8·2 Hz., H-3 endo 7·40 d $J_{3n,2n}$ = 8·2 Hz., bridgehead 7·72 d $J_{4,5x}$ = 4·0 Hz. CH_3 of ester 6·27 s, CH_3's 9·02, 9·08, 9·15.

I.R. CCl_4 (3 x 10^{-2} and 3 x 10^{-3} M) C=O 1755, 1715 OH 3505 (sh. 3610) unchanged on dilution.

3-carboxy norcamphor

Prepared by a similar procedure to that for the camphor derivative.

Yield = 25%

recrystallised from benzene M.pt. = 110 - 111°C.

Analysis 62·39 C, 6·47 H; $C_8H_{10}O_3$ requires 62·33 C, 6·54 H.

N.M.R. $CDCl_3$ H-3 endo 6·92 s, bridgehead H1 6·95 m, H2 6·78 m, rest 2·3 m.

I.R. CCl_4 (6 x 10^{-3} M, 1·2 x 10^{-3} M) 1773, 1749 (sh. 1755) 1738, 1710 on dilution 1710 decreases, 1749 increases.

Isolation of product of autolysis of o-carboxy benzaldehyde acetal of 2,3-dihydroxy benzoic acid

3·0 mg. of acetal in 1 ml. of dioxan were added to 50 mls. of formate buffer pH 3·8 at 55°C and left for 90 mins. (10 half-lives). Cooled in ice acidified with

ice cold HCl to pH 0, extracted 5x with 100 mls. ether. Washed combined layers w/w, dried and evaporated off solvent.

Yield = 2·7 mg. (89%) M.pt. = 228 - 230°C

Mixed m.pt. with genuine sample of acylal = 226 - 227°C. M.pt. of acylal = 226 - 228°C, m.pt. of equimolar mixture of expected hydrolysis products = 91 - 96°C.

The i.r. spectrum was identical with that of an authentic sample of the acylal. Characteristic peaks at 1790, 1660, 1445, 1040, 965 cm^{-1} (KBr disc). An equimolar mixture of the hydrolysis products and acetal have no absorption at these frequencies. T.l.c. on silica and polyamide-pulver identical R_F value to acylal. The u.v. spectrum is also identical with that of the acylal.

Extraction of intermediate acylal in the hydrolysis of o-carboxy benzylidene catechol

4·4 mg. of the acetal in 1 ml. of dioxan added to 50 mls. of formate buffer pH 3·55 at 65°C and left for 5 hours. Cooled in ice, acidified with HCl to pH 1, extracted 5 times with 100 mls. of ether. Washed combined extracts with water, dried and evaporated off solvent.

Yield = 4·3 mg.

I.R. (KBr disc) showed peaks at 1760, 1380 and 935 cm^{-1},

as does the acylal. Neither an equimolar mixture of the hydrolysis products or the acetal has absorptions at these frequencies.

Continuous scanning of the u.v. spectrum of the solvolysis of the acetal also showed the intermediacy of the acylal. At pH 3·4 and at 65°C the extinction coefficients of the acylal and hydrolysis products are similar at 284 nm., but at 257 nm. that of the acylal and acetal are similar. The optical density at 284 nm. changes 50% of that expected in 4 hours, but at 257 nm. there is less than 5% change of that expected for hydrolysis in this time interval. Following the absorbance change at 257 nm. shows a long induction period followed by the expected change of optical density for hydrolysis. Similar results were obtained at pH 2·9, 4·9 and 4·0. At the latter pH there is 17% O.D. change at 286 nm. but only 1·5% at 257 in the same time interval. Also at pH 4·0 the O.D. decreases then increases with time at 274 nm. All these observations are consistent with the intermediacy of the acylal.

Isomerisation of the acetals

About 50 mg. of the isomerically pure acetal in 20 mls. of dioxan were added to about 2 l. of the aqueous solution. The reaction was stopped by quickly adding excess alkali.

The acetal was then extracted many times with ether. The combined extracts washed with water, dried and the solvent evaporated. The product was then analysed by t.l.c. and n.m.r. For the 1-carboxy norbornyl derivative, after initial alkalination the solution was carefully re-acidified to about pH 2.

Kinetic Experimental

Solutions and Buffers

All chemicals used for the preparation of buffered and other solutions were of 'AnalaR grade'. Formic acid was standardised against 0·1 N sodium hydroxide (89·95% pure), as was phosphoric acid (90·48%). For formic and chloro-acetic acid, standard B.D.H. carbonate-free sodium hydroxide solution was used for the neutralisation of buffers. For buffer catalysis a stock solution of buffer at a particular ionic strength was diluted with a stock solution of sodium or potassium chloride at the same ionic strength. Diluted HCl solutions were also maintained at constant ionic strength by the addition of sodium chloride. Perchloric acid solutions were prepared by dilution of 'AR' 72% $HClO_4$. Weighed samples of these were titrated against standard sodium hydroxide, and thence the corresponding H_o value taken from ref. 330. All solutions used for the study of acetals contained 10^{-4} M EDTA, which had no effect upon the observed rate constant. Without this the products were unstable. Merck 'spectrograde' dioxan, stored in a refrigerator, was used for the preparation of aqueous dioxan buffers and also for the stock solution of the substrate.

Deuterated buffers

D_2O and 20% DCl were purchased from Koch-Light, and NaOD and deutero-acetic acid from Ciba. For the acetate buffers, sodium acetate was fused and potassium chloride heated to remove moisture. The purity of the solutions was checked before and after the kinetic run, by adding dioxan as a standard and measuring the quantity of H_2O by n.m.r. which was always $< 1\%$.

pH measurements

The pH of all buffer solutions was measured at the temperature of the kinetic experiment with a Radiometer TTT1 titrator and expansion scale, or a Radiometer Model 26 pH meter, with an external temperature compensator. Below 55°C a Radiometer type G202C glass electrode was used together with a type K401 calomel electrode. Above 55°C a type G202BH glass electrode was used. The pH meter was standardised against commercial standard buffers complying to BS 1647, 1961.

Spectrophotometric rate determinations

The bulk of the reported rate constants were determined on a Cary Model 14 spectrophotometer. Occasionally a Zeiss PMQ II or a Unicam SP 800 spectrophotometer was used. The former was used for the measurement of O.D. for all runs determined in sealed tubes. The latter were used

for runs with half-lives greater than 15 hours and were performed in a thermostatted bath kept at constant temperature ± 0·005°C by an efficient relay system. The Cary Model 14 was fitted with a five cell compartment, and thermostatting arrangements. Constant temperature was achieved by using a Lauda electronic thermostatting bath to circulate water through the central spindle of the cell holder, then through channels in the cell compartment and finally around the reference cell holder. The temperature 'drop' between the cell and the water bath is about 1° at 65°C. The temperature was measured in the cell with an N.P.L. calibrated thermometer. All five cells were at the same temperature ± 0·01°. The temperature was measured before and after each run and was constant to ± 0·03°C.

10 mm. Spectrosil quartz u.v. cells were used. 2·5 mls. of buffer were added to the cells and at least 30 minutes was allowed for temperature equilibration. 25 µl. of the stock dioxan solution of the substrate were injected into the solution. All reported rate constants for aqueous solutions therefore relate to 1% dioxan. The cell was then removed, vigorously shaken and immediately returned to the cell holder. For fast runs ($t_{\frac{1}{2}} < 10$ mins.) the solutions were stirred with a glass rod equilibrated at the

same temperature, giving rate constants about 3-5% higher than those determined by 'shaking'. A period of time, depending on the rate of the reaction, was allowed to pass before reading the absorbance changes.

The pen-recorder slide wire on the spectrophotometer drove a highly linear potentiometer, across the ends of which was applied a constant voltage from a Mallory type RM-42 R 1·35 v battery. The output from this potential-divider was fed to a Solartron Compact Data Logger which digitised the absorbance reading. The latter could then be transferred on to 5-channel paper tape, via a Creed punch, at convenient time intervals. Usually 100 - 700 values were taken, but for kinetic measurements read off the chart recorder, or those obtained manually, only about 40 absorbance readings were used.

The first-order rate constants were determined using a generalised least-squares program, written by Dr. B. Capon, following the procedure of Wentworth[359] and Deming.[360] Evaluation was performed on an English Electric KDF9 computer. The slopes and intercepts of plots of k_{obs} against buffer concentration and the pH-rate profile for II were also determined by a generalised least-squares procedure. All other kinetic and thermodynamic parameters were evaluated by an unweighted least-squares procedure.

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