Thesis

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Statement

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

October 1965 - October 1968

Signed

( E. Anderson )
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Summary

The evidence for the generally accepted mechanism of the hydrolysis of acetals, ketals and glycosides is reviewed. A brief account of the proposed mechanisms for the action of the enzyme lysozyme is given. Some of the underlying assumptions are discussed and some criticisms are offered.

Some of the more important attempts to observe "non-general" hydrolytic behaviour are discussed and the reasons for some of the failures are evaluated.

Acetals with potential neighbouring nucleophiles, where in principle assistance to bond rupture in the acid catalysed hydrolysis of the acetal group is possible, have been synthesised and the kinetics of their hydrolysis investigated. It is demonstrated that catalysis is not general and in the examples studied it is necessary to lower the polarity of the hydrolytic medium in order to observe any participation. Reasons for this are discussed.

Steric effects in the hydrolysis of 2-methoxy methoxy benzoic acid have been investigated and it is demonstrated that substituents ortho to the formal group increase the intramolecularly catalysed rate of hydrolysis irrespective of their electronic substituent effects. A satisfactory theory is developed to explain the facts.

Mixed aryl methyl acetals of benzaldehyde have been synthesised and their hydrolysis is shown to be general acid catalysed. The facts are rationalised by a development of a previous theory.

A brief section is devoted to the use of statistical methods in the calculation of rate constants and some computer programs to implement these are listed in the appendix.
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INTRODUCTION

"Studies concerned with mechanisms and catalysis for the hydrolysis of acetals, ketals, and ortho esters have been seminal in the development of a general understanding of these topics for reactions in aqueous solution. Indeed, pioneering studies of general acid-base catalysis, solvent deuterium effects, reaction kinetics in strongly acidic media, and structure-reactivity correlations have employed these substances as substrates."

E.H. Cordes

The study of the hydrolysis of acetals and related compounds has led to somewhat monotonous conclusions. The clarity of mechanism apparent in these studies, which has led to the use of these compounds as substrates for such diverse mechanistic criteria, contrasts vividly with the findings of workers in the field of ester hydrolysis. Glycosidases have stimulated a new interest in this field. The elucidation of the structure of lysozyme by Phillips and his co-workers and the general realisation that mechanistic schemes applicable to non-enzymatic glycoside hydrolysis are not satisfactory for the description of enzymatic action has led workers in this field to seek model systems where it is hoped that processes analogous to those postulated to occur in glycosidic enzymes may be observed, and hence gain a closer insight into these proposed mechanisms. Not unnaturally, a great deal of caution surrounds the interpretation of much of the more recent work, but it is becoming increasingly obvious that by careful choice of substrates non "general" behaviour may be expected. The function of this introduction will be to summarise the historical evidence for the generally accepted mechanism of hydrolysis of acetals, ketals and glycosides and to show how some of the recent work in this field extends but still embodies Cordes's quotation.

Scope of This Introduction.

This introduction consists of four sections: a historical review of the evidence for the generally accepted mechanism of acetal hydrolysis;
a brief description of the function and structure of the enzyme lysozyme; an appraisal of the more recent work to establish non-general hydrolytic behaviour; and finally a discussion of the general acid catalysed hydrolysis of ortho esters.

General Considerations.

The general subject of acetals has been reviewed by Schmitz and Eichhorn, Meerwein, and Bogdanova. The mechanisms for the hydrolysis of acetals, ketals and ortho esters have been reviewed by Cordes, and a similar review has been published for glycoside hydrolysis by BeMiller. Much of the early part of this introduction is covered in Cordes's review. The emphasis in this introduction is towards the more recent advances in acetal hydrolysis, with particular reference to intramolecular catalysis and its relation to enzymatic catalysis.

Possible Mechanisms.

The hydrolysis of acetals and ketals appears to be exclusively acid catalysed. Ortho esters may have a small term in their kinetic laws due to spontaneous hydrolysis, whilst certain glycosides undergo hydrolysis under drastic basic conditions. This introduction will be concerned only with acid catalysed mechanisms.

Cordes proposes four possible transition states for the acid catalysed hydrolysis of acetals and ketals, each of which is pictured as having arisen from the conjugate acid of the substrate.

The rate law for the hydrolysis of acetals and related species shows that a proton or its kinetic equivalent is involved in the transition state, however the location of the proton in the transition state cannot be determined from
kinetic rate laws. For the time being the question of the timing of the
of the proton transfer need not concern us and the location of the proton
needs little consideration to decide that it is on the oxygen of the C-0
bond that must break.

Returning to the possible transition states, transition states
1 and 2 are unimolecular processes (A1) and 3 and 4 bimolecular processes
(A2) and mechanisms 3 and 4 involve alkyl oxygen fission whilst 1 and 2
involve aldehyde oxygen fission.

The Site of the Bond Fission.

In transition states 2 and 4 either racemisation or inversion of
the reacting centre should occur. The first studies on this subject by
O'Gorman and Lucas\textsuperscript{10} were concerned with the synthesis and hydrolysis of
the acetal derived from D-octan-2-ol and acetaldehyde. The octanol recovered
after hydrolysis had the same configuration as the starting alcohol.

\[
\begin{align*}
\text{CH}_3\text{CHO} + \underset{\text{ROH}}{\text{H}^+} & \rightarrow \text{CH}_3\text{CHO(OH)}_2 \\
\underset{-\text{H}_2\text{O}}{\text{H}^+} & \rightarrow \text{CH}_3\text{CHO} \\
\end{align*}
\]

Cordes\textsuperscript{1} states that these findings exclude transition states 2
and 4. In the former case racemisation would be expected and in the latter
inversion. This reasoning, however, is faulty for transition state 4, since
if we assume that nucleophilic participation by water occurs in the hydrolysis
step then we should expect the reverse to occur in the formation. The net
effect of 2 inversions would be retention of configuration. O'Gorman and
Lucas do not even consider this point, arguing that the work of Skrabal and
Zlatewa\textsuperscript{11} clearly indicates extensive charge development on the aldehyde
carbon in the transition state. These authors also point out that if alkyl
oxygen fission were to occur then methanolysis of methyl acetals would yield
dimethyl ether. Garner and Lucas\textsuperscript{12} demonstrated that the diol recovered in
high yield from the hydrolysis of the acetal and formal of D(-)-butane-2,3-
diol had the same configuration as the starting diol. Similarly Boerseken
and Derx found that the hydrolysis of the acetone ketal of cis-tetrahydro-1,2-naphthalene-1,2-diol gave the original cis-diol in high yield and Hermans found the same to be true of cis-hydриndane-1,2-diol and of cis-tetrahydro-1,2-naphthalene-2,3-diol. Drumheller and Andrews investigated the possibility that certain acetals, prepared from alcohols capable of forming relatively stable carbonium ions might hydrolyze by an alkyl carbonium ion route. The alcohols chosen were methyl vinyl carbinol, phenyl vinyl carbinol and (-) phenyl ethyl alcohol. Derivatives of these alcohols are well known to undergo $S_N^1$ type displacements with either subsequent rearrangement or racemisation, where appropriate. The acetals from methyl vinyl carbinol upon hydrogenation yielded acetaldehyde di-sec-butyl acetal, which demonstrated that allylic rearrangement had occurred in the formation.

The alcohols recovered in high yield from the hydrolysis of the acetals had the same structures as the original alcohols so that, even in these compounds deliberately chosen to accentuate alkyl oxygen fission, none could be detected. The possibility that mechanism 4 might be operative was excluded by the fact that methanolysis of the acetal of (-) phenyl ethyl alcohol yielded the starting alcohol and none of the methyl ether. The whole of this work demonstrates quite clearly that the hydrolysis of acetals and ketals does not proceed via an alkyl carbonium ion. The explicit exclusion of alkyl oxygen fission mechanisms was finally performed by Bourns et al. These authors demonstrated that the synthesis of benzaldehyde di-n-butyl and di-allyl acetals from $^18O$ labelled aldehyde resulted in all the label appearing in the water formed and that the hydrolysis of these acetals in $^18O$ enriched water resulted in no incorporation of $^18O$ in the alcohols produced.

$$\begin{align*}
\text{PhCHO}^{18} + \text{ROH} & \xrightarrow{H^+} \text{PhCH(OR)}_2 + \text{H}_2\text{O}^{18} \\
\text{PhCH(OR)} + \text{H}_2\text{O}^{18} & \xrightarrow{H^+} \text{PhCHO}^{18} + \text{ROH}^{18}
\end{align*}$$

Bunton and his co-workers have investigated the hydrolysis of a large number of glycosides. From $^18O$ tracer studies they affirm that
hydrolysis proceeds via glycosyl oxygen fission. The single exception in these studies was tert-butyl β-D-glucopyranoside.

The Detailed Nature of the Mechanism.

The elucidation of the detailed nature of the mechanism has been approached from several standpoints. These fall into three broad fields: the search for and in general the failure to find, general acid catalysis, structure and reactivity correlations and semi-empirical correlations such as entropies of activation, volumes of activation and solvent isotope effects. These latter thermodynamic parameters, along with kinetic studies in strongly acidic media are being used mostly to distinguish between possible A1 and A2 mechanisms.

The Nature of the Acid Catalysis.

Although general acid catalysis is well established for orthoester hydrolysis19 no substantiated example of general acid catalysis in acetal, ketal or glycoside hydrolysis was reported prior to 1966.

Bronsted and Wynne-Jones19 observed no general acid catalysis for the hydrolysis of acetaldehyde diethyl acetal in formate buffers, nor could they observe any measurable catalysis by p-nitrophenolate or caco-dylate buffers for the hydrolysis of acetone diethyl ketal, whereas in these buffers the ethyl orthoesters of acetic, propionic and butyric acids show strong general acid catalysis. Kreevoy and Taft20 could find no ambiguous evidence for general acid catalysis by formate and acetate buffers in the hydrolysis of acetaldehyde diethyl acetal in 50% aqueous dioxan buffers. A search by Koehler and Cordes21 found that the rates of hydrolysis of acetone dimethyl ketal and acetophenone diethyl ketal were slightly depressed by increasing concentration of carboxylate buffers. This rate inhibition was interpreted as resulting from the capture of the carbonium ion by carboxylate ion to give an acylal, which it was presumed would hydrolyze
slightly more slowly than the original ketals. Smith\textsuperscript{22} studied the hydrolysis of benzaldehyde diethyl acetal and benzophenone diethyl ketal in 50% aqueous dioxan formate and acetate buffers. It was reasoned that because of the depression of the dissociation constants of carboxylic acids in the solvent chosen, and that if any general acid catalytic coefficient did not decrease to the same extent as the dissociation constant, then there would be increased opportunity to observe weak general acid catalysis. No measurable catalysis, however, could be found.

**Hydrolysis in Strongly Acid Media.**

The hydrolysis of acetals, glycosides and 1,3-dioxolanes in strongly acidic media has been extensively studied. In all reported cases a linear relationship between the logarithms of the rate constant and $H^0$ has been observed. In many cases the authors were concerned that the slope of this line was not exactly 1.0. Considering the criticisms directed at this linear free energy relationship\textsuperscript{23,24,25}, this is not surprising.

Nevertheless the workers involved were generally unanimous in assigning an A1 mechanism on the basis of their results. The following table gives a key to the literature on this subject.

**Table one.**

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Hammett Slope/comments</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depolymerisation of trioxane</td>
<td>-1.0</td>
<td>26</td>
</tr>
<tr>
<td>MeOCH$_2$OMe</td>
<td>-1.15</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Discusses salt effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>on the indicators used</td>
<td></td>
</tr>
<tr>
<td>1,3-dioxolane</td>
<td>-1.0</td>
<td>29</td>
</tr>
<tr>
<td>ClCH$_2$CH(OEt)$_2$</td>
<td>-1.0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>solvent 4% dioxan water</td>
<td></td>
</tr>
</tbody>
</table>
Inversion of sucrose

-1.0

Methyl-\(\alpha\)- and \(\beta\)-D-glucopyranosides

-0.95 and -0.91 respectively

Phenyl-\(\alpha\)- and \(\beta\)-D-glucopyranoside

-0.91 and -0.89

Solvent Deuterium Isotope Effects.

The deuterium solvent isotope effects \((k_{D2O}/k_{H2O})\) for the hydrolysis of acetals, ketals and glycosides are invariably in the range 2.0 - 3.0. A representative set of examples is given in table two.

Table two.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>T °C</th>
<th>(k_{D2O}/k_{H2O})/comments</th>
<th>ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)CH(OEt)(_2)</td>
<td>water</td>
<td>25</td>
<td>2.7 (k_{D2O}/k_{H2O})</td>
<td>1.166Exp(-521/RT)</td>
</tr>
<tr>
<td>CH(_3)CH(OEt)(_2)</td>
<td>water</td>
<td>25</td>
<td>2.66</td>
<td></td>
</tr>
<tr>
<td>CH(_3)CH(OEt)(_2)</td>
<td>50% dioxan</td>
<td>25</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>m and p subst. benzaldehyde</td>
<td>50% dioxan</td>
<td>30</td>
<td>2.8 - 3.0</td>
<td></td>
</tr>
<tr>
<td>diethyl acetals</td>
<td>water</td>
<td>25</td>
<td>3.7 (k_{D2O}/k_{H2O})</td>
<td></td>
</tr>
<tr>
<td>2-methyl-1,3-dioxolane</td>
<td>water</td>
<td>25</td>
<td>3.7 (k_{D2O}/k_{H2O})</td>
<td>1.191Exp(501/RT)</td>
</tr>
<tr>
<td>2(subst. phenyl) 1,3-dioxolanes</td>
<td>50% dioxan</td>
<td>30</td>
<td>2.9 - 3.3</td>
<td></td>
</tr>
<tr>
<td>Inversion of sucrose</td>
<td>water</td>
<td>25</td>
<td>2.05</td>
<td></td>
</tr>
<tr>
<td>methyl-(\alpha)-D glucopyranoside</td>
<td>water</td>
<td>51.2</td>
<td>1.9</td>
<td>2.17 N acid</td>
</tr>
</tbody>
</table>
A solvent isotope effect of this magnitude is commonly held to indicate a specific acid catalysed mechanism.\textsuperscript{36} Caution must be applied when using solvent isotope effects as mechanistic criteria since the location of the proton, or deuteron, in the transition state cannot be determined from these measurements.\textsuperscript{37} Nevertheless, sufficient empirical correlations exist to demonstrate that this solvent deuterium isotope effect is at least consistent with an A1 mechanism.

**Entropies of Activation.**

The use of the magnitude of entropies of activation as a mechanistic criterion for acid catalysed hydrolysis has been reviewed by Schaleger and Long.\textsuperscript{44} The values of the entropies of activation for the hydrolysis of some acetals, ketals and glycosides taken from the above review are reproduced in table 3.

**Table 3.**

<table>
<thead>
<tr>
<th>Acetal Hydrolysis in Aqueous Solution.</th>
<th>$\Delta S^#$ c.u.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dimethyl formal</td>
<td>6.8</td>
</tr>
<tr>
<td>2. Diethyl formal</td>
<td>7</td>
</tr>
<tr>
<td>3. Dimethyl acetal</td>
<td>1.3</td>
</tr>
<tr>
<td>4. Ethyl orthoformate</td>
<td>6</td>
</tr>
<tr>
<td>5. 1,3-dioxolane</td>
<td>0.6</td>
</tr>
<tr>
<td>6. 2,4,4,5,5-pentamethyl-1,3-dioxolane</td>
<td>3.8</td>
</tr>
<tr>
<td>7. 2,2-dimethyl-1,3-dioxolane</td>
<td>7.9</td>
</tr>
<tr>
<td>8. Methoxymethyl acetate</td>
<td>3.7</td>
</tr>
<tr>
<td>9. Methoxymethyl formate</td>
<td>2.7</td>
</tr>
<tr>
<td>10. Trioxane depolymerisation</td>
<td>4</td>
</tr>
<tr>
<td>11. Methyl-(\alpha)-2-deoxy-D-glucopyranoside</td>
<td>16.7</td>
</tr>
<tr>
<td>12. Methyl-(\beta)-2-deoxy-D-glucopyranoside</td>
<td>13.7</td>
</tr>
<tr>
<td>13. Methyl-(\alpha)-D-glucopyranoside</td>
<td>13.8</td>
</tr>
<tr>
<td>14. Phenyl-(\alpha)-D-glucopyranoside</td>
<td>13.2</td>
</tr>
</tbody>
</table>
The entropies of activation are all positive or slightly negative. This is often considered to be a criterion of an Al mechanism, but it is probably fair to say that it is this data, assuming that an Al mechanism is applicable, that has been used to establish this criterion. Whilst from a pictorial standpoint these results are reasonable it must be emphasised that this is not true in any strict physical sense. The commonly held views of the pictorial nature of the thermodynamic function entropy have been repeatedly challenged, so it would be safer in these cases to say that this information is at least consistent with an Al mechanism but hardly affirmative evidence for it.

Structure-Reactivity Correlations.

In this field it is perhaps difficult to decide whether the studies have been undertaken to study acetal hydrolysis or to use acetals as substrates to test more general correlations. No distinction will be drawn here between these two approaches; they will both be used to demonstrate the mechanistic features of acetal hydrolysis.

Substituents in the Alcohol Moiety.

Substituent effects for the alcohol moiety for acetal and ketal hydrolysis are generally quite small, reflecting the two step nature of the hydrolytic process. Electron releasing substituents facilitate pre-equilibrium protonation while opposing heterolysis. In the case of symmetrical acetals there is also the question of the amount of stabilisation of the alkoxy and carbonium ion. These factors turn out to be quite finely balanced and each term may become the more important in different series. Table 3a illustrates this point for a few examples.

Table 3a

<table>
<thead>
<tr>
<th>Acetal</th>
<th>Solvent</th>
<th>Temp, °C</th>
<th>( k_2 \text{ mole}^{-1} \text{ sec}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CH}_3\text{CH(OCH}_2\text{)}_2 )</td>
<td>( \text{H}_2\text{O} )</td>
<td>25</td>
<td>( 2.74 \times 10^{-1} )</td>
</tr>
<tr>
<td>( \text{CH}_3\text{CH(OCH}_2\text{H}_5\text{)}_2 )</td>
<td>( \text{H}_2\text{O} )</td>
<td>25</td>
<td>( 1.35 \times 10^6 )</td>
</tr>
</tbody>
</table>
Skrabal and Eger\textsuperscript{39} investigated the hydrolysis of formals of the type $\text{CH}_3\text{OH}_2(\text{OC}_2\text{H}_5)_2$ and reported the following relative rates: $R_{\text{CH}_3}, 1$; $\text{CH}_3\text{CH}_2, 8.5$; $(\text{CH}_3)_2\text{CH}, 47.2$; $\text{CH}_3\text{CH}_2\text{CH}_2, 9.4$; $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{H}_2, 1\times 10^3$; $\text{CH}_3\text{CH}_2\text{CH}_3, 93$. No systematic work on this topic has since been reported.

The correlation of rates of hydrolysis with substituents in phenyl glycosides has been studied in more detail. At least one attraction here is that if it is assumed that the first bond to be broken, that is the one in the rate limiting step, is the phenoxy glycosyl band and not rupture of the ring, the carbonium left will be constant throughout a reaction series and so one of the variables is set constant.

Rydon and his co-workers\textsuperscript{41} reported that electron releasing substituents facilitate the acid catalysed hydrolysis of aryl-$\beta$-$\text{D}$-glucopyranosides. A reasonably good fit was obtained for a Hammett $\xi$ plot with $\xi = 0.66$ for all substituents except a-substituents which hydrolyze faster than predicted by the substitution constant (presumably the $p$-substitution constant) by a factor of between 2 and 4. BeMiller suggests that this latter factor may be related to the steric hindrance to rotation about the glycoside linkage. The Hammett $\xi$ value for the corresponding $\alpha$ series is very low (-0.006). This large difference led Rydon\textsuperscript{42} to propose a different mechanism for the hydrolysis of the $\alpha$ anomers. In this mechanism protonation occurs on the ring oxygen followed by trans diaxial elimination.

\[
\begin{align*}
\text{HOCH}_2\text{O} & \quad \text{H}_2\text{O} & 25 & 1.27 \times 10^2 \\
(\text{CH}_3)_2\text{C}(\text{OCH}_3)_2 & \quad \text{H}_2\text{O} & 25 & 6.4 \times 10^2 \\
(\text{CH}_3)_2\text{C}(\text{OC}_2\text{H}_5)_2 & \quad \text{H}_2\text{O} & 25 & 2.3 \times 10^3
\end{align*}
\]

\*150 butyl acetal Source ref. 38
Rydon argues that such a mechanism is more likely to be under steric rather than electronic control. Timell\textsuperscript{43} however suggests that the same mechanism is operative in the α and β series and that the net effect of the substituents in these reactions is fortuitous and always small.

**Structure Reactivity Correlations in the Aldehyde Moiety.**

Electron releasing substituents in the aldehyde part of the molecule should increase the equilibrium concentration of the conjugate acid and also stabilise the carbonium ion formed; furthermore if formal conjugation between the substituent and the carbonium ion is possible then one might expect even greater stabilisation and hence rate acceleration might be expected.

The most notable early work on this topic was reported by Skrabal and his co-workers\textsuperscript{46} who found the following relative rates for the hydrolysis of pentaerythritol acetals of the type $R^1R^2\overset{\text{O}}{\text{CH}}\overset{\text{O}}{\text{CH}}\overset{\text{O}}{\text{CH}}\overset{\text{O}}{\text{CH}}\overset{\text{O}}{\text{CH}}$.

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>$k_2$ relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>7</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>H</td>
<td>6,000</td>
</tr>
<tr>
<td>CH$_2$CH$_2$</td>
<td>H</td>
<td>10,000</td>
</tr>
<tr>
<td>(CH$_3$)$_2$CH</td>
<td>H</td>
<td>4,000</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>10$^7$</td>
</tr>
</tbody>
</table>

Kreevoy and Taft\textsuperscript{47} correlated the second order constants of 24 substituted diethyl acetals and ketals, by the linear free energy relationship,

$$\log(k/k_0) = \delta \left( \Sigma \sigma^x \right) + (\Delta n)h$$

in which $\Sigma \sigma^x$ is the sum of the appropriate polar substituents and $\Delta n$ is the difference between the number of $\alpha$ hydrogen atoms in the aldehyde moiety and the number in the standard of comparison, acetone diethyl ketal and $h$ is an adjustable parameter. Acetals derived from $\alpha$-$\beta$ unsaturated and aromatic
aldehydes fall well above the correlation line indicating that where resonance stabilisation of the carbonium ion is possible a large rate increase is observed. This result, with the magnitude of $\rho = -3.5$, and the necessity of including the $(\Delta n)h$ hyperconjugation term, strongly suggests a carbonium ion transition state.

Fife and Jao\textsuperscript{48} correlated the second order rate constants for the hydrolysis of $m$-substituted benzaldehyde acetals with a conventional Hammett plot with $\sigma = -3.35$. $p$-Substituted benzaldehyde diethyl acetals and also $2$-(p-substituted phenyl)-1,3-dioxolanes gave upward curving Hammett plots with ordinary $\sigma$ values whereas the use of $\sigma^+$ values gave downward curving plots. The authors suggested that the reason for the overcompensation by the $\sigma^+$ constants may be explained if it is assumed that the transition state resembles the conjugate acid more closely than a carbonium ion. Capon, Perkins and Rees\textsuperscript{49} suggest that the reason for these curvilinear plots is that the observed rate constants are a composite of the equilibrium constant for protonation (correlated by $\sigma$) and the rate constant for heterolysis (correlated by $\sigma^+$). Cordes\textsuperscript{1} has correlated these rates by a Yukawa-Tsuno\textsuperscript{50} plot:

$$\log_{10}(k/k_0) = \rho (\sigma + r(\sigma^+-\sigma))$$

with $\rho = -3.55$ and $r = 0.5$ for the acetals and $\rho = -3.35$ and $r = 0.5$ for the dioxolanes. Although one might feel tempted to separate the two parts of this equation and assign one part to the pre-equilibrium and the other part to the heterolysis there is no necessity that these values should take on any real physical significance.

**The Work of Kankaanpera.**

The results of a detailed study of the hydrolysis of 1,3-dioxolanes have been published by Kankaanpera\textsuperscript{29}. The hydrolysis and, where applicable, the isomerisation of all the possible methyl substituted 1,3-dioxolanes was studied, with a view to the detailed understanding of the stereochemistry of the molecules. The kinetic and thermodynamic activation parameters are summarised in table 5.
Table of the Arrhenius parameters, thermodynamic functions of activation and rate coefficients at 25°C for the hydrolysis of 1,3-dioxolane and its methyl derivatives.

<table>
<thead>
<tr>
<th>Isomer</th>
<th>log A</th>
<th>$E$</th>
<th>$\Delta S$</th>
<th>$\Delta H$</th>
<th>$\Delta G$</th>
<th>$10^9 \Delta A$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3-Dioxolane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. 1,3-Dioxolane</td>
<td>13.54</td>
<td>26.17</td>
<td>+1.4</td>
<td>25.6</td>
<td>25.2</td>
<td>0.0227</td>
</tr>
<tr>
<td>2. 4-Methyl</td>
<td>13.31</td>
<td>23.65</td>
<td>+0.4</td>
<td>23.1</td>
<td>25.0</td>
<td>0.0324</td>
</tr>
<tr>
<td>3. 4,4-Dimethyl</td>
<td>12.09</td>
<td>25.75</td>
<td>-1.1</td>
<td>25.2</td>
<td>25.5</td>
<td>0.0131</td>
</tr>
<tr>
<td>4. 4,5-Dimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13.30</td>
<td>26.13</td>
<td>+0.4</td>
<td>25.5</td>
<td>25.4</td>
<td>0.0142</td>
</tr>
<tr>
<td>II</td>
<td>13.60</td>
<td>26.40</td>
<td>+1.7</td>
<td>25.8</td>
<td>25.3</td>
<td>0.0177</td>
</tr>
<tr>
<td>5. 4,5-Dimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. 4,4,5-Trimethyl</td>
<td>13.02</td>
<td>26.09</td>
<td>-0.9</td>
<td>25.5</td>
<td>25.8</td>
<td>0.00769</td>
</tr>
<tr>
<td>7. 4,4,5,5-Tetramethyl</td>
<td>13.69</td>
<td>27.33</td>
<td>+2.1</td>
<td>26.7</td>
<td>26.1</td>
<td>0.00457</td>
</tr>
<tr>
<td>8. 2-Methyl</td>
<td>14.44</td>
<td>22.25</td>
<td>+5.8</td>
<td>21.7</td>
<td>20.0</td>
<td>126</td>
</tr>
<tr>
<td>9. 2,4-Dimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13.43</td>
<td>20.66</td>
<td>+1.0</td>
<td>20.1</td>
<td>19.8</td>
<td>193</td>
</tr>
<tr>
<td>10. 2,4-Dimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13.56</td>
<td>20.95</td>
<td>-0.7</td>
<td>20.4</td>
<td>20.6</td>
<td>50.7</td>
</tr>
<tr>
<td>11. 2,4,4-Trimethyl</td>
<td>13.30</td>
<td>21.70</td>
<td>+1.3</td>
<td>21.1</td>
<td>20.7</td>
<td>50.0</td>
</tr>
<tr>
<td>12. 2,4,5-Trimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13.52</td>
<td>21.40</td>
<td>+1.4</td>
<td>20.8</td>
<td>20.4</td>
<td>68.4</td>
</tr>
<tr>
<td>13. 2,4,5-Trimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>14.52</td>
<td>22.49</td>
<td>+6.9</td>
<td>21.9</td>
<td>20.1</td>
<td>109</td>
</tr>
<tr>
<td>14. 2,4,5,5-Trimethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14.11</td>
<td>22.77</td>
<td>+4.1</td>
<td>22.2</td>
<td>21.0</td>
<td>20.5</td>
</tr>
<tr>
<td>15. 2,4,4,4-Tetramethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13.40</td>
<td>21.51</td>
<td>+0.8</td>
<td>20.9</td>
<td>20.7</td>
<td>43.3</td>
</tr>
<tr>
<td>16. 2,4,4,4-Tetramethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>14.66</td>
<td>23.59</td>
<td>+6.6</td>
<td>23.0</td>
<td>21.0</td>
<td>23.6</td>
</tr>
<tr>
<td>17. 2,4,4,4,4-Pentamethyl</td>
<td>12.40</td>
<td>20.63</td>
<td>-3.8</td>
<td>20.0</td>
<td>21.2</td>
<td>18.9</td>
</tr>
<tr>
<td>18. 2,2-Dimethyl</td>
<td>14.95</td>
<td>21.54</td>
<td>+7.0</td>
<td>21.0</td>
<td>18.6</td>
<td>1440</td>
</tr>
<tr>
<td>19. 2,2,4-Trimethyl</td>
<td>14.37</td>
<td>20.74</td>
<td>+5.2</td>
<td>20.2</td>
<td>18.6</td>
<td>1400</td>
</tr>
<tr>
<td>20. 2,2,4,4-Tetramethyl</td>
<td>14.43</td>
<td>21.87</td>
<td>+5.5</td>
<td>21.3</td>
<td>19.6</td>
<td>254</td>
</tr>
<tr>
<td>21. 2,2,4,4-Tetramethyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14.04</td>
<td>20.02</td>
<td>+3.7</td>
<td>20.3</td>
<td>19.2</td>
<td>513</td>
</tr>
<tr>
<td>22. 2,2,4,4,4-Tetramethyl</td>
<td>14.43</td>
<td>21.17</td>
<td>+5.5</td>
<td>20.6</td>
<td>18.9</td>
<td>826</td>
</tr>
<tr>
<td>23. 2,2,4,4,5-Pentamethyl</td>
<td>14.01</td>
<td>21.43</td>
<td>+3.6</td>
<td>20.8</td>
<td>19.8</td>
<td>202</td>
</tr>
<tr>
<td>24. 2,2,4,4,5,5-Hexamethyl</td>
<td>13.34</td>
<td>23.31</td>
<td>+0.5</td>
<td>22.7</td>
<td>22.6</td>
<td>1.77</td>
</tr>
</tbody>
</table>
Kankaanpera concludes after a detailed conformational analysis that the ground state conformation of the dioxolane ring is the half chair structure in figure 1.

**Figure 1.**
The Stereochemistry of the Dioxolane Ring.

If we compare the structure of the conjugate acid of the dioxolane ring with that of the carbonium ion transition state, bearing in mind that atoms $C_2$, $O_3$, and $C_4$ must be coplanar to obtain maximum resonance stabilisation of the transition state, several steric features are immediately obvious.

**Figure 2.**
Comparison of the Conjugate Acid of 1,3-Dioxolane and the T.S. for Hydrolysis.

Motion along the reaction coordinate will result in the hydrogens on $C_2$. 
rotating in such a manner that the former \( \text{e}' \) hydrogen moves into the ring and these two hydrogens become coplanar with \( \text{C}_2 \), \( \text{C}_3 \) and \( \text{C}_4 \). \( \text{C}_5 \) must twist in the opposite manner so that considerable steric interaction must occur between the two formerly \( \text{e}' \) hydrogens on \( \text{C}_2 \) and \( \text{C}_5 \). During this process the formerly \( \text{e}' \) proton on \( \text{C}_5 \) must also eclipse the \( \text{e} \) proton on \( \text{C}_4 \).

**Analysis of the Substituent Effects on the Rates of Hydrolysis.**

**i) Electronic Effects.**

Steric effects aside, one would expect the substitution of a methyl group at \( \text{C}_2 \) to cause the normal large increase in rate going from a formal to an acetal. Substitution in the 4 position should give rise to a rather small increase in rate due to the inductive stabilisation of the carbonium ion. In this case, therefore, ring scission would be expected to occur between \( \text{O} \) and \( \text{C}_5 \) in the rate limiting step.

**ii) Steric Effects.**

As noted earlier the \( \text{e}' \) substituent on \( \text{C}_2 \) rotates in towards the ring along the reaction coordinate, therefore where a substituent in this position is forced to rotate in towards the ring a large steric effect would be expected. A substituent in the 4 position may be cis to the incoming substituent on \( \text{C}_2 \), in which case a large interaction might be expected, but not so big as the effect of a methyl group on \( \text{C}_2 \). In the case of a 4 methyl substituent trans to the incoming group one would expect no steric effects other than the eclipsing of this axial methyl being eclipsed by the axial substituent on \( \text{C}_5 \).

**Effects in Individual Molecules.**

**a) One Methyl Substituent.**

2-Methyl-1,3-dioxolane hydrolyses 4,000 times as fast as 1,3-dioxolane, parallelling the trend in acyclic acetals going from formals to acetals. The 4-methyl isomer hydrolyses 30% faster than the unsubstituted dioxolane. It is expected, of course, that the methyl will be trans to the
incoming hydrogen on C_2 and therefore only the small electronic effect of a 4 substituted methyl will be felt.

2-Methyl Substituents.

Further substitution of a methyl group on C_2 of 2-methyl isomer results in only a hundredfold rate increase, much less than the 10^3 fold increase going from acetals to ketals. In this case a methyl group is obliged to rotate in towards the ring and this will result in a diminution of the rate increase expected from the inductive effect. Two 2,4-dimethyl isomers exist, the cis hydrolysing 30% faster than the 2-methyl-1,3-dioxolane and the trans hydrolysing 4 times slower.

In the case of the cis isomer it is possible for a hydrogen on C_2 to rotate in towards a hydrogen on C_4 whereas in the trans case no matter which group rotates inwards a methyl group and a hydrogen must come close together. The cis isomer of the 2,4,5-dioxolane hydrolysises about 15% faster than the trans isomer and 25% slower than the unsubstituted dioxolane, whilst the 4,4-isomer hydrolysises at about the same rate as the trans 4,5-isomer. These quite small effects demonstrate that the steric effects between the 2-hydrogen and 4 or 5-methyls are not very large.

3-Methyl Substituents.

As expected, the 4,4,5-isomer hydrolysises 3 times slower than the 1,3-dioxolane, since in this case the methyl group on C_5, which will be the site of ring fission, will be trans to the incoming hydrogen and therefore on moving along the reaction coordinate it must eclipse the a' methyl on C_4. The three isomers of 2,4,5-trimethyl-1,3-dioxolane were not fully characterised, so that no analysis of the rates is possible.

Poly Methyl Substituents.

The relative rates of the more highly substituted dioxolanes can be explained in a manner similar to the above arguments. It will, however, be instructive to look in detail at some of the more highly substituted examples.
Table 6 gives the relative rates of hydrolysis of the dioxolanes unsubstituted in the glycol residue and those with four substituents.

Table 6.

Comparison of Rates of Highly Methyl Substituted Dioxolanes at 25°.

<table>
<thead>
<tr>
<th>No. of 2-methyl groups/</th>
<th>$10^4 k_2$ for no subst. in glycol/1 mole$^{-1}$sec$^{-1}$</th>
<th>$10^4 k_2$ for 4 substituents in glycol residue/1 mole$^{-1}$sec$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0227</td>
<td>0.00457</td>
</tr>
<tr>
<td>1</td>
<td>136</td>
<td>18.9</td>
</tr>
<tr>
<td>2</td>
<td>1440</td>
<td>1.77</td>
</tr>
</tbody>
</table>

It can be seen that the effect of placing methyl substituents in the glycol residue is relatively small until both positions on C$_2$ are substituted; then an 800 fold rate increase is observed. Dreiding models show that the normal carbonium ion transition state is not sterically feasible and therefore unless a change in mechanism has occurred it would seem that the transition state must occur much earlier along the reaction coordinate, thereby denying the development of charge any effective resonance stabilisation by the oxygen. This is rather difficult to believe and a more detailed examination of this compound might provide interesting results.

A further measure of this large interaction possible between the methyl group on C$_2$ and those across the ring are conveyed in table 7.

Table 7.

Effect of the Substitution of Methyl Groups on C$_2$ of 1,3-Dioxolanes at 25°.

<table>
<thead>
<tr>
<th>Ring substituents</th>
<th>$10^4 k_2$ for no subst./1 mole$^{-1}$sec$^{-1}$</th>
<th>$10^4 k_2$ for 1 subst./1 mole$^{-1}$sec$^{-1}$</th>
<th>$10^4 k_2$ for 2 subst./1 mole$^{-1}$sec$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0.0227</td>
<td>136</td>
<td>1440</td>
</tr>
<tr>
<td>4,4-dimethyl</td>
<td>0.0131</td>
<td>50</td>
<td>254</td>
</tr>
<tr>
<td>4,4,5,5</td>
<td>0.00457</td>
<td>18.9</td>
<td>1.77</td>
</tr>
</tbody>
</table>

In all cases the introduction of the first methyl group on C$_2$ gives the normal rate increase going from a formal to an acetal ($10^4$). In the first
two cases the introduction of a second methyl group gives only an eleven fold and a threefold rate increase respectively. In the case of 4,4,5,5-substituted compound the rate decreases by a factor of nearly ten on the addition of a second methyl on C^. If we assume for the minute that the normal Al transition state is applicable then this steric interaction results in an estimated rate reduction of about $10^4 - 10^5$, assuming a methyl group increases the rate inductively by $10^3 - 10^4$. As explained earlier, this makes the assumption of the normal Al transition state seem highly unreasonable.

**Thermodynamic Correlations.**

Inspection of table 1 shows that the entropies of activation are all quite small. Three examples have slightly negative values. There seems to be no correlation between structure and rates on the one hand and whether the rate differences show up in the $\Delta S^+$ term or the $\Delta H^+$ term. Considering that three different methods were used for these rate measurements and that agreement between rates is only fair, it is quite possible that the whole range of values for $\Delta s^+$ could be accounted for by uncertainties in the rate measurements.

**More Recent Advances.**

As emphasised earlier, much of the more recent work in this field has been directed towards the investigation of acetals and glycosides which might hydrolyze by non-general mechanisms. Since a not inconsiderable amount of this work has been stimulated by the recent advances in the study of glycoside hydrolyzing enzymes, it will be appropriate to discuss briefly the enzyme lysozyme whose three-dimensional structure has been recently elucidated.

**The Enzyme Lysozyme.**

Lysozyme was discovered by Fleming in 1922. Since that time a considerable amount of work has been done to elucidate the structure, culminating in the complete three-dimensional structure of the enzyme by Phillips and his co-workers from x-ray crystallographic studies.
Substrates and Inhibitors for Lysozyme.

The natural substrate for lysozyme is the $\beta 1\rightarrow 4$ alternating polymer of N-acetylglucosamine and N-acetyl muramic acid which constitutes the cell walls of certain bacteria. Semisynthetic substrates are chitin oligosaccharides, which are $\beta 1\rightarrow 4$ linked N-acetylglucosamine oligosaccharides. These are listed below, with their relative rates of hydrolysis and cleavage pattern.\textsuperscript{52}

<table>
<thead>
<tr>
<th>Saccharide</th>
<th>$k_{rel}$ order</th>
<th>Cleavage pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>dimer</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>trimer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>tetramer</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>pentamer</td>
<td>4,000</td>
<td></td>
</tr>
<tr>
<td>hexamer</td>
<td>30,000</td>
<td></td>
</tr>
</tbody>
</table>

Heavy arrows denote major site cleavages; relief arrows minor cleavage site; under conditions of 1:1 complex saturation. Source ref. 53.

Some inhibitors are given in figure 9.
Figure 19. (a) Atomic arrangement in the lysozyme molecule in the neighbourhood of the cleft where inhibitors are bound. The main chain is shown speckled and N(H) and O atoms are indicated by line and full shading respectively. (b) Overlay showing the conformation of a hexa-N-acetyl-chitohexaose molecule bound to the enzyme. Sugar residues A, B and C are as observed in the binding of tri-NAG (and β-NAG for residue C). They occupy the sites 4, 3 and 2 respectively that were inferred at low resolution. Residues D, E and F occupy positions inferred from model building. It is suggested that the linkage hydrolysed by the action of the enzyme is between residues D and E.
Possible Modes of Action of Lysozyme.

The lysozyme catalysed glycosyl transfer between oligosaccharides derived from certain bacteria cell walls and N-acetylglucosamine proceeds with retention of configuration. If the same is true of the hydrolytic mechanism then the mechanism proposed must account for retention of configuration. Lowe proposes three possible mechanisms which could account for the action of lysozyme.
All three mechanisms account for the retention of configuration and all of them employ general acid catalysis by the un-ionised carboxyl group on glutamic acid 35. Since this carboxyl group lies in a relatively non-polar environment it is reasonable that this group should remain un-ionised whilst the carboxyl group on the aspartic acid 52 residue should be ionised.

Scheme 1) proposes synchronous general acid catalysis by the glutamic acid 35 carboxyl group and nucleophilic attack by the un-ionised acetamido group, followed by a fast general base catalysed attack of water on the protonated oxazoline.

Scheme 2) is essentially the same except that this time the attack of the acetamido group is general base catalysed by the ionised carboxyl group on the aspartic acid 52 residue. Lowe suggests in a footnote that this mechanism is unlikely. Fiszkiewicz and Bruice\(^5^5\) also make this point. From an examination of a space filling model of the enzyme they observe that when the carbonyl oxygen of the acetamido group is positioned below the anomeric carbon the proton on the nitrogen is forced to face away from the aspartate 52 residue and conversely when the amido group is rotated to a position where the carboxylate group could abstract a proton from it the carbonyl group has then been rotated 180° away from the anomeric carbon. It should be noted that these two mechanisms involve the glycoside ring taking up a boat or half boat non-formation during hydrolysis. There appears to be no evidence for or against this.

Scheme 3) involves synchronous general acid catalysis by the glutamic acid 35 carboxyl group and nucleophilic participation by the ionised aspartic acid 52 carboxyl group, followed by a fast general base catalysed attack of water on the glycal intermediate to give product with retained configuration. Vernon\(^5^7\) views this question of nucleophilic participation with some doubt, maintaining that the enzyme structure would have to undergo considerable distortion to bring the aspartate carboxylate oxygen within less than 3 Å of the anomeric carbon of residue D. He concludes that covalent bond formation would therefore be impossible. He suggests: "The simplest and
most satisfactory hypothesis is that the heterolysis of the Cl (anomeric)
carbon oxygen bond occurs under the influence of the negative charge of the
carboxyl group Asp 52. In other words the reaction proceeds, as it does
in solution by the formation of a carbonium ion. The difference is that,
whereas in free solution the carbonium ion is stabilised by interaction
with the dipoles of the solvent molecules in the enzyme, it is stabilised by
a negative charge held at a distance of 3 Å. The ion pair so formed cannot
collapse to give a normal covalent bond because the substrate is held more
or less rigidly in position by the geometry of the protein." Vernon further
claims that such an interaction should, on a straightforward point charge
basis, be worth 5 eV (≈15 k cals/mole), and that even if this approximation
is overgenerous, "sufficient energy would be gained to account for the
catalytic effort.". It is difficult to rationalise this latter point. The
imponderabilities of calculating the difference between solvation energies
and this "electrostatic interaction" and the uncertainty of how the carbonium
ion would be solvated by the considerable number of molecules that are presumably present around the active site could lead one to accept almost any
viewpoint. What seems most difficult to assess is this question of the
substrate being rigidly held in position. It is still not clear whether the
enzyme is bound in by a physical intermeshing of enzyme and substrate or
whether the substrate is held in an already reasonably defined position by
hydrogen bonds. It appears from figure ten that there are eleven possible
sites of hydrogen bonding, some of which are over considerable distances.
These should not amount to more than about 40 K cals/mole for the lot; furthermore the introduction of the inhibitor tri-N-acetyl chitotriose causes shifts
of the groups along the cleft, residue 62 moving by about 0.75 Å. It must
remain a matter of speculation what positional changes occur when the substrate is bound in the active site so that arguments like those of Vernon must be viewed with some caution. Another feature of the enzyme, the relative exposure
of the top side of the active site, also produces uncertainties. The mechanism
proposed by Bender for chymotrypsin catalysed hydrolysis of esters involves
molecules of water as transfer agents for protons. There seems to be no reason
why this should not be true at least for the aspartic acid 52 residue and
this could revive mechanism 2 as a possibility. Statements that the non
polar environment of the carboxyl group of the glutamic acid 52 residue would
cause this carboxyl group to have a high pKa (6.5) measured for one of the
acidic groups in lysozyme\textsuperscript{59} should also be viewed with some caution. It
might well be queried just how"non polar" an environment has to be to give
a pKa shift of the order of 2 for a carboxyl group. Table 9 shows the varia-
tion of the pKa of acetic acid with some common part aqueous solvent systems.

Table 9

<table>
<thead>
<tr>
<th>solvent</th>
<th>water</th>
<th>20% MeOH</th>
<th>40% MeOH</th>
<th>80% MeOH</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>4.68</td>
<td>5.068</td>
<td>5.450</td>
<td>6.633</td>
</tr>
<tr>
<td>solvent</td>
<td>20% dioxan</td>
<td>45% dioxan</td>
<td>70% dioxan</td>
<td>82% dioxan</td>
</tr>
<tr>
<td>pKa</td>
<td>5.292</td>
<td>6.307</td>
<td>8.321</td>
<td>10.509</td>
</tr>
</tbody>
</table>

Source Robinson and Stokes\textsuperscript{60}

Whilst no attempt to produce quantitative correlations will be
made, one thing at least is clear; that for the glutamic acid 35 residue
to shift its pKa to 6.5 its environment cannot be so hydrophobic.

These latter arguments tend to outline the thesis that our present
knowledge of enzyme mechanisms is far too limited for us to draw too many
parallels between enzymatic and non enzymatic reactions. Whilst there is
little doubt that the processes must be basically the same, it is not estab-
lished that our reasonings concerning such features as geometrical ordering,
simple conformational theories, and such electrostatic phenomena as solvation
can be transferred directly to the interiors of large protein molecules such
as enzymes.

It is in this latter context that attention is drawn to a remark
by Perutz in his concluding speech to the Royal Society discussion group on
lysozyme:\textsuperscript{56}

"We may now ask ourselves why chemical reactions which normally
require powerful organic solvents or strong acids or bases, can be made to
proceed in aqueous solution in the presence of enzyme catalysts. Organic solvents have the advantage over water of providing a medium of low dielectric constant, in which strong electrical interactions between reactants can take place. The non-polar interior of enzymes provides the living cell with the equivalent of the organic solvents used by chemists. The substrate may be drawn into a medium of low dielectric constant in which strong electrical interactions between it and the polar groups can occur."

Whilst one feels intuitively that this must be so, and several other authors have expressed views of this nature, examples of these phenomena have yet to be conclusively demonstrated.

Some More Recent Advances.

This section deals with some of the more recent work directed towards the observation of non-general behaviour.

A2 Mechanisms.

Following his work on the hydrolysis of substituted benzaldehyde diethyl acetics and 2-phenyl-1,3-dioxolanes, Fife studied the hydrolysis of a series of 2-(p-subst. phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes. These tetramethyl dioxolanes hydrolyze appreciably slower than the corresponding dioxolanes unsubstituted in the glycol residue; this rate deceleration is reflected almost entirely in the entropy of activation terms. The results, contrasted with the earlier work, are summarised in table 10.

Table 10.
Summary of the Work of Fife on Benzaldehyde Acetals and Phenyl-1,3-Dioxolanes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PhCH(0Et)₂</td>
</tr>
<tr>
<td>k₂ at 30⁰ 1.mole⁻¹.min⁻¹</td>
<td>29,200</td>
</tr>
</tbody>
</table>
The hydrolysis of the p-methoxy derivative was found to be weakly catalysed by formate buffers, though Fife does not discuss in detail any mechanism for the catalysis. The reduced $\rho$ value for these tetramethyl dioxolanes strongly suggest that there is less charge development in the transition state than in the case of the acyclic acetals. Furthermore Fife claims that the rates of hydrolysis of the tetramethyl dioxolanes correlate with $\sigma$ and whilst no plot of log $K_v$ vs $\sigma_v$ is given for the unsubstituted dioxolanes the text of the paper seems to suggest that $\sigma$ values alone do not give a satisfactory fit. A least squares fit of both sets of data give a similar standard of deviation of about 20% when $\sigma$ values are used and the t-test on the value for 2-(p-methoxy phenyl)-1,3-dioxolane shows that this point is acceptable at 90% confidence limits. However insufficient data is available to comment further on this. Perhaps the most convincing evidence is the Bunnett $w$ value of 1.9; this is very large by acetal standards and would certainly seem to indicate water in the transition state. Fife says:

"Each piece of evidence in this present study contains some ambiguity but taken together a consistent picture is presented of a reaction in which water is participating as a nucleophile in which either the bond being broken in the transition state is not well developed or in which an $A_1$ mechanism is still making some contribution to the observed rate."
This reasoning seems very plausible, but certain features need clarification. Firstly the solvent used in the work on the diethyl acetals and the 1,3-dioxolanes was 50% dioxan water, whereas the solvent in the case of the tetramethyl dioxolanes was water. Work reported in this thesis tends to show that this comparison may not be too unreasonable, though there is a scarcity of literature on solvent effects in acetal hydrolysis. Secondly the pHs of the solution where dioxan water was the solvent were measured by a glass electrode; again work reported in this thesis shows this to be true for the electrode used, a Radiometer type G 202 B. It should be noted that Fife quotes Marshall and Grunwald as evidence for the glass electrode giving the correct pH reading in concentrated dioxan water mixtures, but these workers measured only strong acids at high dilution. That the same relationship does not hold for acetate and formate buffers in 82% dioxan water, is demonstrated in the kinetics experimental section.

Returning to the work of Kankaanpera, it can be seen that there is nothing like this change in rate going from 2-methyl-1,3-dioxolane to 2,4,4,5,5-pentamethyl-1,3-dioxolane and even in the case the 2,2-dimethyl derivative polymethyl substitution in the glycol residue results in the rate diminution showing up essentially in the enthalpy of activation. Although it is impossible to draw a normal A1 transition for 2,2,4,4,5,5-hexamethyl-1,3-dioxolane, such a transition state is possible for 2-phenyl-1,3-dioxolane. Comparisons of the rate differences of the tetramethyl dioxolanes derived from benzaldehyde and acetaldehyde are not really fair, because of the relative inclinations of the Hammett plots for the 2-phenyl-1,3- and 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolanes. A better comparison might be between the benzaldehyde derivative and the crotonal derivative to get comparable electronic effects. Fife measured his rates spectrophotometrically by a Zeiss P M Q 11 spectrophotometer, whilst the results of Kankaanpera for the hexamethyl dioxolane were measured gas chromatographically on a Shandon "Universal" gas chromatograph. The spectrophotometrically determined rates should give entropies of activation to about 5 E U whereas any entropies of activation from the gas chromatographically
determined rates must be viewed with some scepticism. More work of higher accuracy would be very useful to establish the interrelation between these compounds. Fife draws the distinction between A1 and A2 mechanisms between the dioxolanes unsubstituted in the glycol residue and the tetramethyl substituted ones. At least as far as entropies of activation are concerned the unsubstituted dioxolanes lie between the tetramethyl substituted ones and the acyclic acetals. A possibility not considered by Fife is that the hydrolysis of dioxolanes proceeds by a mechanism different from that established for acyclic acetals.

Capon and Thacker\textsuperscript{65} propose that a different mechanism could intercede:

\[
\begin{align*}
\text{RCH}_2 \text{O} & \quad \text{H}^+ \quad \text{RCH}_2 \text{O}^+ \\
\leftrightarrow & \\
\text{RCH}^+ & \quad \text{H}_2\text{O} \quad \text{products}
\end{align*}
\]

In this scheme the heterolysis of the carbon-oxygen bond is reversible because the hydroxyl group is still in the same molecule as the carbonium ion, and furthermore the ring closure in five-membered rings is kinetically very favourable. The observed rate would then be given by:

\[
k(\text{obs}) = k_2K
\]

where \( K \) is the equilibrium constant for the equilibrium:

\[
\begin{align*}
\text{RCH}_2 \text{O} & + \text{H}_2\text{O}^+ \quad \longleftrightarrow \\
\text{RCH}^+ & \quad \text{H}_2\text{O}
\end{align*}
\]

The observed entropy of activation would then be:

\[
\Delta S^\ddagger = \Delta S^0 + \Delta S^\ddagger_2
\]

where \( \Delta S^0 \) is the standard free energy for the above equilibrium which would presumably be small and positive, whilst \( \Delta S^\ddagger_2 \), the entropy of activation of the bimolecular reaction of the carbonium ion with water, should be large and negative. The net entropy of activation would then be negative, but not so large as that normally observed for A2 mechanisms. An alternative formulation of this theory is that whilst ring opening does occur, unless a water
molecule is favourably orientated ring closure is favourable. Ring closure will then be unproductive. All one has to visualise is that the hydrolysis of all 1,3-dioxolanes involves a molecule of water but that the position of the water molecule in the transition state varies. In the case of 2-phenyl-1,3-dioxolane bond breaking is well developed before the water molecule has broken very far away from its neighbouring water structure, whereas in the case of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane the transition state is very much more like a normal A2 one, with the water molecule well along the reaction coordinate. This proposal receives indirect support from the work of Orvik who observed that the rate of hydrolysis of 2-(p-methoxy phenyl)-1,3-dioxolane is catalysed by aniline buffers and interpreted this catalysis as trapping of the carbonium ion by aniline to give a rapidly hydrolysing intermediate. Capon and Thacker favour an A2 mechanism for the hydrolysis of methyl glucuronolactones. Furanosides hydrolyze much more slowly than pyranosides and in the case of dioxolanes the entropy term is dominant in this rate deceleration. The value of $\Delta S$ is in the range $-8.0 - 11.0$ E.U. whereas the range for furanosides is $+10 - 15$ E.U.. The solvent isotope effect $k_D/k_H$ for the hydrolysis of methyl $\alpha$-D-xylofuranoside in 1 M. hydrochloric acid at $25^\circ$ is 2.5 and the Bannet $W$ values for the series are in the range $1.0 - 2.4$. The authors suggest that either an A2 mechanism applies to the hydrolysis of these five membered ring glycosides, or as discussed earlier, ring fission is reversible, with attack by water carrying the reaction to completion.

Intromolecular Catalysis.

a) General Acid Catalysis.

Bender and Silver reported that the hydrolysis of 2-(a-hydroxy substituted phenyl)-1,3-dioxanes obeys the rate law:

$$k_{obs} = k_2(Diox)(H^+) + k_1(Diox)$$

but from comparison with the corresponding $p$ compounds they concluded that
the latter term was in fact due to the kinetically equivalent,

\[ K k' (\text{H}^+) \text{(Diox)} \]

Similarly Capon and Ghosh \(^{65}\) concluded that the \( k_{\text{obs}} \text{ d - pH rate profile} \)
characteristic of intramolecular catalysis found for the hydrolysis of
2-naphthyl-\(\beta\)-D-glucuronide was also due to the different electronic substituent constants for the ionised and unionised species. The first authenticated example of intramolecular acid catalysis in glycoside and acetal hydrolysis
was reported by Capon \(^{65}\), who showed that the hydrolysis of \(\alpha\)-carboxyphenyl
\(\beta\)-D-glucoside in water at 90°C in the pH range 2 - 5 obeys the rate law:

\[ k_{\text{obs}} = k (\text{glycoside}) \]

and that this \(\alpha\)-substituted isomer hydrolyses some \(10^4\) times faster than the corresponding \(\beta\)-isomer. Two explanations are feasible for this catalysis:

![Diagram](image)

The first mechanism, similar to that postulated for lysozyme, involves
intramolecular general acid catalysis by the \(\alpha\)-carboxyl group, whilst the
second involves specific acid with nucleophilic assistance for the glycosyl protonated phenoxy bond fission, with rapid hydrolysis of the glycyal intermediate. The kinetics were rigorously first order and the spectrophotometrically determined rates were in excellent agreement with those determined polarimetrically. However, since the possible glycyal intermediate was not accessible, Capon turned to an analogous formal, 2-methoxy methoxy benzoic
acid, for which possible intermediates are accessible. Capon and Smith showed that the hydrolysis of this formal at 45° in water also obeyed a rate law of the form:

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

in the range pH 2 - 5, with an estimated rate enhancement over the p-isomer of between 400 and 650. Shown below are three possible mechanisms:

Mechanism ii) may be ruled out since the proposed intermediate is stable to hydrolysis under the conditions used. Mechanism i) was shown to be incompatible with the kinetics observed. From steady rate considerations, and knowing the rate of the hydrolysis of the intermediate acylal, it was calculated that the absorbance at the isobestic point of the formal and the products should not be constant during the hydrolysis. This was shown to be untrue and therefore only mechanism ii) is possible. Bruice and Piskiewicz criticise this interpretation suggesting that in view of Rydon’s work electronic and steric effects might be important. However an examination of the possible magnitude
of these effects shows this criticism to be completely unfounded. The same authors later accepted Capon's interpretation.

Bruce and Piskiewicz\textsuperscript{73} studied the pH-rate profiles for a series of carboxyl substituted 1,3-dioxanes and dioxolanes where, in principle, catalysis by the carboxyl group was feasible. These authors were forced to accept the view that any pH rate profiles characteristic of intramolecular general acid catalysis or specific intramolecular nucleophilic catalysis by the conjugate base, were in fact due to substituent effects. Reasons for the failure to observe intramolecular general acid catalysis in these types of systems will be discussed later, but one reason, the poor choice of substrates, will be discussed here.

The carboxyl substituted dioxanes and dioxolanes are shown in table 11.

\textbf{Table 11}

\begin{table}
\centering
\begin{tabular}{ccc}
\hline
 & 1 & 2 \\
\hline
\includegraphics[width=0.3\textwidth]{table11_1.png} & \includegraphics[width=0.3\textwidth]{table11_2.png} & \includegraphics[width=0.3\textwidth]{table11_3.png} \\
\hline
\includegraphics[width=0.3\textwidth]{table11_4.png} & \includegraphics[width=0.3\textwidth]{table11_5.png} & \includegraphics[width=0.3\textwidth]{table11_6.png} \\
\hline
\end{tabular}
\end{table}
The authors chose these substrates as models which would enable them to differentiate between the kinetically equivalent mechanisms of intramolecular catalysis and specific acid intramolecular nucleophilic catalysis by the conjugate base of the compound. Since all the compounds chosen were derived from ketones it seems very unlikely, as the authors admit in a footnote, that nucleophilic assistance to bond rupture would be needed. Several of the compounds have the carboxyl group located at the end of flexible chains, but this is not always easy to avoid. The compounds are discussed in turn, great use was made of Dreiding models to clarify steric effects and great use was made of the results of Kankaanperä and of Pihlaja to clarify the principle involved.

Compound 1) 2,2,5-Trimethyl-5-Carboxy-1,3-Dioxolane.

The measured distance (models) between the carboxyl hydrogen and the dioxolane oxygen is 1.8 Å, approximately the same as the acetal oxygen - carboxyl hydrogen distance in 2-methoxy methoxy benzoic acid. When the carbon oxygen bond proceeds to break, C2 rotates in such a manner that any 2,4 diaxial interaction is relieved, however the other methyl group must rotate in towards the ring in essentially the same manner as in dioxolane hydrolysis. At the same time, the carboxyl group must also move downwards into the ring. Examination of the model reveals that this is clearly impossible. It would seem much more likely that the preferred hydrolytic route would be:

![Similar considerations apply to compound 2).

In compound 3) the initial geometry is favourable for hydrogen bonding, the O – H distance being 1 Å, but the oxygen must move away from the carboxyl group as the C – O bond starts to break. If it is assumed that it is the carboxyl group which rotates in towards the ring, bearing in mind
that it must retain its orientation towards the oxygen on the bond breaking, the carboxyl group and the methylene group breaking away would be hopelessly intermeshed. Again a much more reasonable transition state may be proposed.

![Diagram](image)

Compound 4) is essentially the same as this.

In the case of compound 5) neither the distance between the carboxy hydrogen and the dioxolane oxygen (2.5 Å) nor the spacial orientation of these groups is favourable. Compounds 6) and 7) seem the least unreasonable. Even in these cases, if the carboxyl group is to retain its orientation to the protonated group, the carboxyl group must rotate in towards the ring and the steric consequences of this seem rather gloomy.

**Nucleophilic Catalysis.**

Only two examples of nucleophilic catalysis for the specific acid catalysed hydrolysis of acetals have been reported.

The first example, reported by Capon and Thacker \(^{73}\), though not strictly hydrolysis, was the intramolecular hydroxyl catalysed cyclisation of acyclic glucose and galactose dimethyl acetals. These acetals undergo acid catalysed ring closure to give methyl \(\alpha\) - and \(\beta\) -furanosides. N.m.r. studies of methanolysis in methanol \(\text{D}_4\) showed that ring closure and ionisation were concurrent and furthermore the ring closure of the galactose and glucose acetals was some 50 and 100 times faster respectively than the rates of hydrolysis of \(\text{D}\)-glyceraldehyde dimethyl acetal. Since the rates of hydrolysis of aliphatic acetals are retarded by hydroxyl group substitution in the aldehyde residue, this rate ratio sets a lower value for the possible rate enhancement.

The following mechanisms were proposed:
It is interesting to note that in general the thermodynamically less stable cis isomers are preferentially formed, so other than thermodynamic considerations must be important. The authors suggested that the ground state energies of the molecules could account for this and also for the much faster rate of cyclisation of the glucose acetal than the galactose acetal.

Speck et al. claim that the methyl thio group of methyl thio acetaldehyde diethyl acetal participates in the hydrolysis of the acetal.

\[
\text{CH}_3\text{S-CH}_2\text{CH(OEt)}_2 \rightleftharpoons \text{CH}_3\text{CH(OEt)}_2 + \text{H}_2\text{O} \rightarrow \text{prod}
\]

This acetal hydrolyses ten times more slowly than the parent, acetaldehyde diethyl acetal, but some 100 times faster than the corresponding methoxy acetaldehyde diethyl acetal. The authors argue that since the \( k \) values for methyl-thio and methoxyl substituents are approximately the same, this rate difference must be due to nucleophilic participation.

**Bifunctional Catalysis.**

The one recorded example of bifunctional catalysis in this field has been reported by Bruice and Piszkiwicz. They repeated the work of Capon on o-carboxy phenyl \( \beta \)-D-glucoside at 71°, and further studied the corresponding 2-carboxy phenyl-2-deoxy-2-acetamido-\( \beta \)-D-glucoside.

This compound is of course similar to the substrates for lysozyme. The authors found that further participation by the amido group resulted in a 6 fold rate increase. These workers had earlier found that the nucleo-
philic participation of the ionized amido group resulted in a very large rate enhancement. The reason for the much smaller rate enhancement by the ionized group is that in the latter case the leaving group was the ionized phenol, whereas in this case it would be the phenol itself. Since the acetyl amido group is as favourably orientated as it is likely to be in the case of lysozyme substrates, this makes mechanism i) proposed for lysozyme action seem rather unlikely. The authors claim that no buffer catalysis is observed in the hydrolysis but Capon\textsuperscript{74} has observed catalysis by formate and acetate buffer for this reaction at 65\degree and proposes the following mechanism:

\[
\begin{align*}
\text{Product} & \quad \text{Product} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\text{CH}_3\text{OH} & \quad \text{CH}_3\text{OH} \\
\text{H}_2\text{O} & \quad \text{H}_2\text{O} \\
\end{align*}
\]

This mechanism is of course similar to Lowes second mechanism and in view of the doubt surrounding Vernon's criticism of this mechanism, this must now be a serious contention.

General Acid Catalysis in Ortho Esters.

The general acid catalysed hydrolysis of ortho esters has proved difficult to rationalise. Bunton and DeWolfe\textsuperscript{75} have developed a satisfactory explanation for the observed facts. Because of the great importance of this theory to the work reported herein, their arguments will be reiterated here, with extension of some of the more important features, in order to have both a convenient source of reference and to provide a useful basis for some of the topics in the discussion section.

The hydrolyses of aliphatic ortho esters were among the first general acid catalysed reactions to be found. The hydrolysis of ethyl orthoformate is specific acid catalysed in water\textsuperscript{76} but is catalysed by both hydroxonium ion and general acids in aqueous dioxan. Most of the other aliphatic ortho esters exhibit general acid catalysis in their hydrolysis, even in water.
The general acid catalysed hydrolysis of an ortho ester could involve either nucleophilic attack on the conjugate acid by buffer components, but this is inconsistent with observed structural effects in either the catalyst or ester, or it could involve slow proton transfer from a weak acid to an oxygen atom of the ortho ester synchronous with, or prior to, carbon oxygen bond rupture or a similar decomposition of a hydrogen bonded complex of the acid and substrate.

Both of these latter two mechanisms amount to a bimolecular substitution on oxygen, giving an alkoxy carbonium ion intermediate.

\[
A - H \quad \overset{\text{OR}}{\text{CR'}}(OR)_2 \quad \rightarrow \quad \overset{\text{OR}}{\text{A}} - \quad \overset{\text{OR}}{\text{H}} - \quad \overset{\text{OR}}{\text{CR'}}(OR)_2
\]

The rate of disappearance of methyl orthobenzoate and the rate of appearance of methanol, measured by n.m.r., are identical so the conversion of the dialkoxy carbonium ion intermediate to products must be fast. There remains little doubt that the dialkoxy carbonium ions are intermediates. The derived carboniums have been characterised as their salts, and the intermediates in the hydrolysis have been trapped by hydroxylamine without altering the rates of hydrolysis.

The substituent effects for ortho ester hydrolysis are difficult to rationalise in terms of an Al mechanism. The rate limiting step in this mechanism is assumed to be the dissociation of the conjugate acid of the ester to the dialkoxy carbonium ion. All other reactions which involve the rate limiting production of a carbonium ion from a neutral species or from a conjugate acid have large substituent effects and it has been shown earlier that for acetal hydrolysis these are very large.

Substituent effects for ortho ester hydrolysis are not only small but are often in the opposite direction to what may be intuitively expected, (table 12).
Table 12.
Relative Rates of Hydrolysis of Ortho Esters.

<table>
<thead>
<tr>
<th>R in R - CH(OEt)_3</th>
<th>k rel.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1.00^1</td>
</tr>
<tr>
<td>CH₃</td>
<td>38.5</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>24.3</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>0.62</td>
</tr>
<tr>
<td>C₇H₅O</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Footnotes: 1) k^z = 5.38 x 10² l.mole⁻¹ sec⁻¹
Source ref. 75.

Furthermore the two ortho esters which yield the most stable carbonium ions are hydrolysed the most slowly. The logarithms of the rates of hydrolysis of four methyl orthobenzoates correlate well with ordinary σ values but not with σ⁺ values, indicating that there is little carbonium ion character in the transition state.

One way out of this dilemma would be to abandon the Al mechanism altogether, but as noted earlier this is inconsistent with the observed reactivity of ortho esters and the lack of participation by suitable nucleophiles. One theory is that the data could be rationalised on an Al basis by invoking a saturation effect, but this is not observed in other systems. A third explanation offered by DeWolfe and Jensen assumes that since the alkoxy carbonium ions are so much more stable than ordinary carbonium ions, the transition state lies only a short way along the transition states, and the resulting near tetrahedral geometry is geometrically unsuitable for resonance interaction with a substituent. DeWolfe freely admits this to be unlikely since the formation of the triaryl methyl carbonium ion correlates well with σ⁺ constants, demonstrating the additivity of substituent effects.

This evidence, and the very rapid hydrolysis of ortho esters
under conditions where the concentration of the conjugate acid of the ester must be vanishingly small led Bunton and DeWolfe to agree with Cordes suggestion that the hydronium catalysed hydrolysis, like the general acid catalysed hydrolysis, occurs by an SE 2 reaction.

Since it has long been accepted that proton transfer from strong acids to oxygen bases cannot be rate limiting, it is important to consider whether this proposed SE 2 mechanism is reasonable in terms of the expected rates of proton transfer to oxygen bases and their basicities. Since the basicities of aliphatic amines may be correlated by a linear free energy relationship using Taft values, with a $\sigma^*$ value of -3, and assuming that a similar relationship holds for oxygen bases, it should be possible to calculate the pKa's of acetals and ortho esters. Assuming this relationship to be true and using a $\sigma^*$ value of -3, Bunton and DeWolfe calculate the basicity of ortho esters using $\sigma^* = 0.52$ for an OMe or OEt group, 0.215 for a phenyl group, and -0.110 for a methyl or ethyl group. Taking the values of -3.8 and -3.6 for the pKa's of dimethyl and diethyl ether respectively, these authors calculate the following pKa's: -5.4 for dimethyl acetal, -7 for triethyl orthoformate, -7.6 for triethyl orthobenzoate and -8.5 for ethyl ortho carbonate.

Hydronium catalysed ortho ester hydrolysis may be represented by the following scheme:

$$S + H_2O \xrightarrow{k_1} SH^+ \xrightarrow{k_{-1}} S + H_2O$$

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

Steady state considerations then give the equation:

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

where $k_H$ is the second order rate constant for hydrolysis.

If ortho ester hydrolysis occurs by an Al mechanism, i.e. if $k_{-1} \ll k_2$ then $k_2 = k_H \times K_a$. Knowing the values of $k_H$ and using the estimated
values of $K_a$, it is then possible to calculate $k_2$ on the basis of an Al mechanism. For the acid catalysed hydrolysis of dimethyl acetal this gives a value of $k_2$ of $7 \text{ sec}^{-1}$. This value is much less than the expected value for loss of a proton from a strong conjugate acid and the conventional Al mechanism is therefore applicable.

A similar calculation of $k_2$ for triethyl orthoformate yields a value of $k_2 = 5 \times 10^9 \text{ sec}^{-1}$. It seems unlikely that in this case $k_{-1} \gg k_2$ because the value of $k_{-1}$ would be improbably high even though it involves proton transfer from a strong acid to water.

For the hydrolysis of ethyl orthoformate then the values of $k_{-1}$ and $k_2$ may well be similar and the mechanism of reaction may be on the borderline between Al and SE 2. The solvent deuterium isotope effect, $k_{H_2O}/k_{D_2O} = 0.4$ shows that transfer of the proton from hydronium ion to the substrate must be essentially complete in the transition state. If a similar treatment is applied to the hydrolysis of ethyl orthoacetate, the value of $k_2 = 2 \times 10^{11} \text{ sec}^{-1}$. Bunton and DeWolfe find it impossible to accept that the rate of loss of the proton from the conjugate acid could be greater than this rate of breakdown to products. Similar considerations apply to methyl orthobenzoate and ethyl orthocarbonate.

An SE 2 mechanism for ortho ester hydrolysis is intelligible in terms of the expected rates for proton transfer from hydronium ion to weak bases. The second order rate constants for ortho ester hydrolysis are in the range $10^2 - 10^4 \text{ l.mole}^{-1} \text{ sec}^{-1}$, which is not much smaller than the value quoted for the proton transfer between ethanol and its conjugate acid ($10^6$).

The authors then demonstrate that an acceptable value of $k_2$ for the hydronium catalysed hydrolysis of ethyl orthoacetate can be calculated on this basis. It is clear that if proton transfer is important then inductive stabilisation of the conjugate acid must outweigh resonance stabilisation of the carbonium ion, which is indeed what is observed.
DISCUSSION SECTION
Aliphatic Acetals

Attempts were made to observe intramolecular nucleophilic catalysis for the specific acid catalysed hydrolysis of acetals with neighbouring amino and carboxyl groups.

Neighbouring Amino Groups

4 Amino Butyraldehyde Diethyl Acetal

This acetal proved to be a poor choice of substrate since the pKa's of similar butylamines are around 10. Preliminary measurements at pH 5.83 at 65.0° in aqueous acetate buffers of ionic strength 0.1 showed that two mole equivalents of ethanol were formed during hydrolysis and that the rate constant, $1.35 \times 10^{-5}$ sec$^{-1}$ is not significantly different from that estimated for butyraldehyde diethyl acetal ($10^{-5}$ sec$^{-1}$) under the same conditions. No further study of this compound was made.

2 and 4 Pyridyl Methyl Amino Acetaldehyde Diethyl Acetal

The 2 isomer of this compound presents the formal possibility of nucleophilic catalysis by the pyridine nitrogen.

At pH 5.02 at 60.0° in aqueous acetate buffers of ionic strength 0.2 the relative rates of hydrolysis of the 2 and 4 isomers are 1.6:1. It was therefore concluded that no participation was observed.

Neighbouring Carboxylate Groups

The first compound chosen was succinaldehyde acid diethyl acetal. The acid itself could not be isolated (see experimental section) so the cyclohexylammonium salt was used. The acetals of this aldehydic acid are unstable, readily forming the corresponding alkoxy butyrolactones (cf experimental section). It seemed therefore that in aqueous solution the
following hydrolytic processes might be likely.

Since acylals undergo facile alkaline hydrolysis the g.l.c. work up would hydrolyze any acylal formed, and therefore methanol production would represent the disappearance of acetal. Spectrophotometric measurements on the other hand would measure only the appearance of aldehydic product.

The rates of hydrolysis, measured by g.l.c. estimation of methanol, at 30.0° in aqueous acetate buffers of ionic strength 0.2 in the range pH 3.9 - 5.2 obey the rate law

\[ k_{\text{obs}} = k_2 (H^+) \]

with \( k_2 = (3.84 \pm 0.51) \times 10^{-1} \) mole\(^{-1}\) sec\(^{-1}\), which compares with a value of \( k_2 = (4.0 \pm 0.3) \times 10^{-1} \) mole\(^{-1}\) sec\(^{-1}\) measured spectrophotometrically, for butyraldehyde dimethyl acetal under identical conditions.

The spectrophotometrically determined rate constant at pH 3.95 was not significantly different (t test at 95% confidence limits) from the g.l.c. estimated rate at that pH. No rate enhancement was therefore observed.

\[ \text{D-Threeo-Teturonic Acid Dimethyl Acetal} \]
The hydrolysis of the cyclohexylammonium salt of this acid was studied at pH 2.90 at 70.0°C in aqueous chloroacetate buffers of ionic strength 0.2. The rates were measured both polarimetrically and by g.l.c. estimation of methanol. The latter method showed that under the quenching conditions used two mole equivalents of methanol were produced during hydrolysis.

The polarimetrically determined rates fitted first order kinetics well, the first, second, and third half lives agreeing within 5% of each other. The overall rates were in good agreement with the g.l.c. estimated rates (t test at 90% confidence limits) (k_polarimetric = 2.71 \times 10^{-4} \text{ sec}^{-1}; k_{glo} = 2.54 \times 10^{-4} \text{ sec}^{-1}).

The hydrolysis of the acetal group of the methyl ester of the acid was studied as a model system. Although the methyl ester has a rate constant for hydrolysis 10 times smaller than the acid (k_{glo} = 2.28 \times 10^{-5} \text{ sec}^{-1}) it is possible that hydrolysis of the ester grouping may occur before the acetal group. Methanol estimation cannot establish the product of hydrolysis because the ester group is hydrolyzed during the g.l.c. work up. The hydrolysis could not be followed polarimetrically because the original pale amber colour of the solution deepened during hydrolysis and insufficient light was transmitted to power the servo system of the polarimeter. In view of these problems it was decided to use D-glyceraldehyde dimethyl acetal as a model compound. The rate of hydrolysis of this compound under identical conditions (k = 3.0 \times 10^{-4} \text{ sec}^{-1}) is slightly greater than the acid acetal and it was concluded that no rate enhancement was observed.

In view of the report of Capon and Thacker (see discussion) that the C_4 hydroxyl of glucose and galactose dimethyl acetals participates in the hydrolysis of these acetals it seems strange that the much more nucleophilic carboxylate anion should not participate in the hydrolysis of a structurally similar compound.

Perhaps the answer to this is that the ground state conformation of the acid is not favourable for ring closure. The following...
series of reactions may perhaps illustrate this point.

\[
\begin{align*}
\text{CHO} & \quad \text{MeOH} \quad \text{H}^+ \\
\text{CO}_2\text{H} & \quad \text{CH(OMe)}_2 \\
\text{CHO} & \quad \text{CO}_2\text{Me} \\
\text{OH} & \quad \text{OH} \\
\text{CO}_2\text{H} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

It is perhaps possible that the acids which do not exist as their cyclic forms (see experimental section) do not have ground state conformations which favour ring closure.

It was reasoned on this basis that compounds analogous to (c) would be more likely to undergo hydrolysis with nucleophilic participation of the carboxyl group. The synthesis of the following acid acetal was therefore investigated.

The key intermediate for the synthesis of this compound is the pseudo methyl ester of maleinaldehyde acid. All practicable syntheses of this compound involve the difficult photo sensitised oxidation of furan and some of its derivatives by molecular oxygen. These preparations require
either very long reaction times or elaborate photochemical equipment not available to the author. Several typical preparations were followed, but with singular lack of success. Another possibility was to condense chloromucic acid,

![Chemical Structure]

its pseudo or true methyl ester with cyclopentadiene and then proceed as for phthalaldehydic acid diethyl acetal. This however proved impossible.
Aromatic Acetals.

Potential nucleophiles ortho to benzaldehyde acetals have a favourable geometric disposition to the aldehyde carbon. This may be seen from inspection of "Dreiding Models" of the anion of 2 carboxy benzaldehyde diethyl acetal. On the other hand the derived carbonium ion is much more stabilised than the ones derived from saturated aliphatic acetals. This unfortunately is the price to be paid for the accessibility of model compounds and for the geometry of the benzene ring.

The work of Fife and his coworkers discussed in the introduction shows that 1,3 dioxolanes and especially 4,4,5,5 tetra methyl 1,3 dioxolanes hydrolyse much more slowly than the corresponding diethyl acetals. If the mechanism proposed in the introduction for dioxolane hydrolysis is correct then one might expect nucleophilic participation to be more favourable in these compounds.

o Carbamoyl Benzaldehyde Diethyl Acetal

The hydrolysis of this acetal in aqueous buffers of ionic strength 0.1 at pH's around 4 obeys first order kinetics to give 3 hydroxy phthal-amidine, the cyclic form of the amide of phthalaldehydic acid (see experimental section). Inspection of the table below shows that the rate of hydrolysis of the o isomer is not in fact as large as that of the p isomer under the same conditions.

Table 13

Comparison of the Rates Of Hydrolysis of o and p Carbamoyl Benzaldehyde Diethyl Acetal

<table>
<thead>
<tr>
<th>pH</th>
<th>o isomer</th>
<th>p isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.93</td>
<td>4.40</td>
<td>7.19</td>
</tr>
<tr>
<td>4.00</td>
<td>4.15</td>
<td>6.04</td>
</tr>
<tr>
<td>4.08</td>
<td>3.79</td>
<td>5.07</td>
</tr>
</tbody>
</table>
At higher acidities the situation is more complex. If the reaction is monitored spectrophotometrically at 254 nm the absorbance rises quickly, reaches a maximum and then more slowly decreases. Repeat scans of the UV spectrum during this process shows that an intermediate, with a broad maximum at 255.5 nm, is formed. It was hoped to analyse this curve for two consecutive first order reactions by a generalised least squares program.¹ However at the time of writing up a suitable program was not available to invert a 5×5 matrix. An almost identical curve is obtained when the hydrolysis was performed in 95% dioxan water at 25⁰ in M/250 perchloric acid.

There is no question of any rate enhancement since the half life of the initial process at pH 2.99 in chloroacetate buffers of ionic strength 0.1 at 25.0⁰ (2.5 mins.) is the same as that of the p isomer under identical conditions.

Despite this lack of rate enhancement it was felt that it would be interesting to discover what this intermediate was. The UV spectrum is quite different from that of 3-ethoxy-phthalamidine so the unlikely participation of the amide nitrogen is ruled out.

Two possible schemes are outlined below, both arising from the same carbonium ion intermediate.
The first scheme amounts to the partitioning of the intermediate between water and the amide group, followed by a slow hydrolysis of the intermediate to give the final product. The second scheme involves a slow ring closure for the amide of phthaldehydic acid. No precedent is offered for this process.

Attempts to Characterise the Intermediate.

Three approaches to the characterisation of the intermediate were made.

1. Isolation
2. Monitoring the reaction by NMR
3. Monitoring the reaction by IR

(1) As the acetal is not very soluble in water it was necessary to use acetone water as the hydrolytic medium. Aqueous buffers of pH 2.5 were diluted with an acetone solution of the amide (circa 10%) to give an approximately 5% solution of the amide. The reaction was followed on t.l.c. until all the amide had disappeared, the reaction was poured into a large excess of water and the solution extracted with a variety of organic solvents. In no case could any product be extracted. The same procedure was repeated but the reaction mixture was rapidly, but carefully, neutralised and the resultant liquor freeze dried. The only organic material that could be recovered was 3 hydroxy phthalalimidine.

(2) A solution of the amide in 50% acetone d_6 / D_2O was made up in a dry box. Two microliteres of CF_3CO_2D were added and the pH_app read from a pH meter (2.7). The solution was transferred to an NMR tube and then cooled down to 0°C. The spectrum was then scanned every few minutes.

The acetal proton resonance at 365 Hz. Rapidly disappeared (t_1/2 = 5 to 6 minutes) and was replaced by a new resonance at 621 Hz. This resonance disappeared over a period of 25 minutes and the resonance at 365 Hz. reappeared. The ethoxyl resonances were not perturbed during this time. The spectrum after the completion of the reaction was
identical with a synthetic mixture of 3-hydroxy-phthalamidine and ethanol in the molar ratio of 1:2. The former was also characterised by t.l.c. This evidence would seem to favour the acyclic amide as the intermediate. 

(2) A similar solution was used for the infra red studies except that dioxan was used for the organic component of the solvent and the CF$_3$CO$_2$D was replaced by phosphoric acid. The pH$_{app}$ of the solution was 3.0. The solution was quickly introduced into an RIIC "disposable cell" of path length 0.1 mm with silver chloride windows. After about 3 minutes the amide carbonyl absorption at 1635 cm$^{-1}$ had dissapeared and was replaced by a new band at 1690 - 1670 cm$^{-1}$. This band slowly decayed to give a new band at 1705 cm$^{-1}$, characteristic of 3 hydroxy phthalamidine. It is not possible to assign with any great confidence this band at 1690 - 1670 cm$^{-1}$, mainly because of the poor resolution resulting from the large slit widths necessary to obtain sufficient light to power the servo system of the spectrophotometer.

Taken at large the evidence would favour the acyclic amide as the intermediate, but more evidence would be required to be positive about it. However since no rate enhancement was observed it was felt that further work on this topic would prove unrewarding. 

2-(o Carbamoyl Phenyl)-1,3-Dioxolane

This dioxolane equivalent of the previous ethyl acetal proved to be rather similar in its hydrolytic behaviour to the ethyl acetal. At pH 2.99 in aqueous chloroacetate buffers of ionic strength 0.1 at 45.0$^\circ$ the reaction was complex. This time the rates of the two reactions were too similar to make any estimate of the half life of the initial process, but the time to reach a half of the maximum absorbance (12 minutes) is not that different from the half life of the p isomer under the same conditions (13.5 minutes). In M/10 HCl under otherwise identical conditions the formation of the intermediate is rapid. The UV spectrum of the intermediate is almost identical to that of the intermediate formed in the hydrolysis of the diethyl acetal. This topic was not pursued any further.
Neighbouring Carboxyl Group

The unionised amide group is a relatively poor nucleophile, a more reasonable choice of nucleophile is the carboxylate anion. The diethyl acetal, 1,3-dioxolane, and 4,4,5,5-tetra-methyl-1,3-dioxolane derivatives of phthalaldehydeic acid were synthesised and their hydrolytic behaviour compared with that of the 𝜋 isomers.

Phthalaldehydeic Acid Diethyl Acetal

This acid proved to be too unstable to isolate (see experimental section). Kinetic measurements were made on the cyclohexylammonium salt of the acid.

Behaviour in Aqueous Buffers

All buffers had ionic strength 0.1 and all kinetic runs were performed at 25.0°C. Hydrolysis at pH 4.5 to 3.5 yields 3 ethoxy phthalide, identified by its UV spectrum and by isolation (see experimental section). Under these conditions the phthalide is sufficiently stable for the reaction to be followed to ten half lives. At higher pH's the rate of hydrolysis of the phthalide is sufficiently fast to prevent following the reaction to completion. It was therefore necessary to use a variable infinity program to evaluate the rate constants.

Quite reasonable fits were obtained for first order kinetics, but probably because of the rather small absorbance changes followed the rate constants are not more reliable than ± 5%.

The rate of hydrolysis of the acetal group of the methyl ester of the acid is 12 times smaller than that of the acid at pH 3.95 and 15.5 times at pH 5.83. This is almost certainly an electronic substituent effect since at the same pH's the rate of hydrolysis of the 𝜋 acid is only 2.2 - 2.5 times slower than the ring closure reaction of the 𝜂 isomer. The pKa of the acid could not be measured because of its rapid conversion to 3-ethoxy-phthalide in water, but it should be around 3.6, so the acid would be mainly ionised in the pH range studied. This explains the moderate linear fit of the log k vs pH plot with a slope of -1.
The facts are most simply explained by the assumption that the carboxyl group does not assist bond breaking but captures the carbonium ion formed in a normal transition state with greater than 98% efficiency. This latter figure is based on the relative absorbancies at 254 and 302 nm in the UV spectra of the phthalide and phthalaldehydic acid.

Studies in 82% Dioxan / Water Buffers.

A high concentration of an inert non polar solvent, such as dioxan, in the hydrolysis medium should have two effects relevant to nucleophilic catalysis by a carboxylate anion.

The carbonium ion formed in a normal transition state would be highly destabilised by virtue of the decreased dielectric constant of the medium and the less efficient solvation of the positive centre. Secondly, this decrease in solvating power of the medium will also increase the nucleophilicity of the carboxylate anion. The depression of the dissociation constants in these solvent mixtures means that there will be increased opportunity to observe intramolecular catalysis without it being swamped by any external catalysis.

The product of reaction at 60.0°C in 82% w/w dioxan water buffers of ionic strength 0.02, made up from formate or acetate components, between the pH's 8.0-11.0 is 3-ethoxy-phthalide (UV spectrum), which is stable under the reaction conditions. The pH rate profile is characteristic of an intramolecular catalysed reaction, and obeys the rate law:

\[ k_{\text{obs}} = k_1(\text{HA}) + k_2(H^+(\text{HA})) \]

with \( k_1 = 3.31 \times 10^{-3} \text{ sec}^{-1} \); \( k_2 = 3.81 \times 10^4 \text{ mole}^{-1} \text{ sec}^{-1} \) and \( K_a = 3.28 \times 10^{-11} \text{ mole} \text{ l}^{-1} \).

The value of \( k_2 \) is not accurately defined by the pH rate profile since the reaction could not be followed satisfactorily at lower pH's. The spectrum of the unionised acid is very similar to that of phthalaldehydic acid pseudo ethyl ester. To add to this problem the absolute magnitude of the absorbancies of the species are small. Since the buffering capacity of the solvent was rather low it was necessary to use 4
cm cells, which in turn meant that dioxan absorption was significant in the spectral range used (280 - 290 nm).

The rate enhancement over the p isomer at pH 9.46 is 3000 fold and estimated to be at least $10^5$ at pH 10.8, the measured pKa of the o acid at 25°C.

Tempting though it may be, no attempt will be made to ascribe this rate enhancement to an increase in the nucleophilicity of the carboxylate group or to an increase in electrophilicity of the aldehyde carbon. The problem is that the protonating power of the medium has been reduced. The cyclisation reaction has therefore been studied at lower acidities than in aqueous solution. If we assume for the minute that the rate law is the same in totally aqueous buffers as in 82% dioxan water buffers, and using the activation parameters found by Fife and Jao for p chlorobenzaldehyde diethyl acetal (see introduction) a value of $k_1$ calculated at 25°C turns out to be much lower than that actually observed for the pseudo first order rate constant measured between pH 3.5 and pH 5. All that can be said then is that the decreased protonating power of the solvent has allowed us to observe the concerted ring closure at lower acidities. Although this reaction is much faster than the hydrolysis of p isomer under identical conditions it does not mean that we have speeded up this reaction, all that can be deduced is that we have chosen conditions where we have suppressed the normal mechanism.

Of course this does not mean that there is no real acceleration of the hydrolytic or ring closure reaction over the non concerted process, but merely that we are in no position to speculate about it.

One way out of this dilemma would be to study the effect of a series of dioxan concentrations on $k_1$. Whilst this would be of some interest in its own right it would certainly seem a lot of work to establish such a point.
At the time at which this work was undertaken the latter point was not appreciated. It was felt that a study of the dioxolane equivalents might give a further insight into nature of these processes.

However, since dioxolanes and especially 4,4,5,5-tetra-methyl-1,3 dioxolanes hydrolyze much more slowly than than their diethyl acetal counterparts it is reasonable to expect that there should be an increased opportunity to observe nucleophilic catalysis. As we shall see later this point is not as reasonable as it might at first seem.

2-(o Carboxy-Phenyl)-1,3-Dioxolane

The rates of ring closure and the subsequent hydrolysis of the 3-alkoxy-phthalide would appear to be similar in magnitude for this compound.

In the pH range 3 - 4 the reaction in aqueous buffers of ionic strength 0.1 at 45.0⁰ is complex. There appears to be no isobestic point in the UV spectra of the two products and nowhere is there sufficient difference between the absorbancies of the three species to make an analysis by the generalised least squares program for consecutive first order reactions feasible.

At 300 nm the absorbance of the starting material and 3-alkoxy-phthalides in general, are negligible, whilst phthalaldehydic acid has a relatively strong absorption. The absorbance monitored at this wavelength shows an induction period followed by a curve which after an initial acceleration approximately fits first order kinetics. A similar behaviour is observed at 255 nm.

The values quoted in the results section for the hydrolysis of this compound refer to this approximately first order curve. Whilst these values have in themselves no real physical significance, they do set limits upon the possible range that the ring closure rates could take. In view of the fact that these "first order rates" are only about ten times larger than the true rates of hydrolysis of the para isomer under identical conditions it was felt that further study of this topic would prove unrewarding. Attention was therefore directed to the tetra-methyl-dioxolane.
2 ( \( \text{p-Carboxy-Phenyl} \)) -4,4,5,5-Tetra-Methyl-1,3-Dioxolane.

**Aqueous Buffers**

This compound hydrolyses to give phthalaldehydic acid, with no evidence of an intermediate, under all conditions employed.

The rates of hydrolysis were measured in the pH range 3.1 - 5.5 in chloroacetate, formate, and acetate buffers of ionic strength of 0.1 at 65.0°. The rate of hydrolysis could not be measured below pH 3.1 because of the very close similarity of the UV spectra of the starting dioxolane and that of the unionised form of phthalaldehydic acid. The phthalide which would be formed by nucleophilic participation of the carboxylate anion proved to be too insoluble to obtain reliable kinetic data for its hydrolysis. However, if a solution of the phthalide is injected into a spectrophotometer cell containing a buffer at pH's between 3 and 5 at 65.0°, the initially turbid solution clears within 4 to 5 minutes to give a solution whose UV spectrum is identical with that of phthalaldehydic acid at the same pH. It would seem reasonable that under the hydrolytic conditions used for the dioxolane, and in view of the measured rates of hydrolysis of that compound, that if the phthalide were an intermediate in its hydrolysis it would hydrolyse rapidly.

The para isomer of this acid dioxolane, 2-(\( \text{p-Carboxy-phenyl} \))-4, 4,5,5-tetra-methyl-1,3 dioxolane, hydrolyses only 10 times more slowly at pH 3.13 and pH 3.99 than the ortho isomer under identical conditions (the complete set of results are presented in the experimental section). It is therefore unlikely that any rate enhancement due to nucleophilic participation of the carboxyl group had been observed.

**Hydrolysis in 50% Dioxan Water Buffers**

It was originally hoped to measure the rates of hydrolysis in 82% dioxan water buffers, but preliminary measurements showed that in the range of pH necessary to observe intramolecular catalysis, the reaction would be so slow that it would be highly likely that oxidation of the aldehydic products would occur.
A compromise of 50% dioxan water buffers was therefore substituted. At this concentration the pH meter gives the true pH value (see kinetics experimental section) so that direct measurements of the pH could be made.

As in aqueous buffers, the product was phthalaldehyde acid; again no evidence for an intermediate could be found. In acetate and formate buffers of ionic strength 0.05 at pH's between 5 and 7 at 95.0° the pH rate profile follows the titration curve of the acid, and obeys the rate law;

\[ k_{\text{obs}} = k \text{ (HA)} \]

or its kinetic equivalent;

\[ k_{\text{obs}} = k' K_a \text{ (H}^+\text{)(A}^-\text{)} \]

with \[ k = 1.0 \times 10^{-4} \text{ sec}^{-1} \]

and \[ pK_{a\text{app}} = 5.83 \]

The measured pKₐ at 25° is 5.83.

The intermediate expected from participation of the carboxylate anion hydrolyses rapidly to phthalaldehyde acid under these conditions. The actual rate could not be measured at 95.0°, but even at 72° the half reaction time at pH 5.8 is only 30 minutes, so that throughout the range studied the phthalide, were it an intermediate, would hydrolyse sufficiently quickly to not be observed as an intermediate.

The rate enhancement over the p isomer is 40 fold at pH 5.01 and estimated to be 300 fold at pH 5.83, the measured pKₐ of the p acid.

This is approximately two powers of 10 less than that observed for the diethyl acetal in 82% dioxan. There is no means of calculating what the rate enhancement would be in 82% dioxan water for the tetramethyl-dioxolane, but if it is assumed that the intramolecular term is independent of dioxan concentration and that the para isomer's rate of hydrolysis falls off in proportion to the acidity of the solution an
estimate of the rate enhancement can be made. If we assume that the pKa of the tetramethyl-dioxolane acid is the same as that of the diethyl acid acetal, 10.8, then an estimate of the rate enhancement in 82% dioxan water would be $10^7$. The magnitude of this estimated rate enhancement reflecting the much more $\text{A}_2$ like character of 4,4,5,5-tetramethyl dioxolane hydrolysis.

Again the problem of assigning this enhancement is essentially that of deciding whether this intramolecular term is present in totally aqueous buffers. If as Fife has shown, tetra-methyl-dioxolane derivatives of benzaldehyde hydrolyse with weak catalysis by carboxylate anions, why does an intramolecular carboxylate anion not participate in aqueous solutions.

Before answering this question it will be appropriate to return to a topic discussed in the introduction. If we apply Capon's interpretation of dioxolane hydrolysis and in view of the work of Orvik, we postulate that the initial ring opening is reversible and that the carboxonium ion is partitioned between the hydroxyl group, regenerating starting material, and solvent water, then why does the intramolecular carboxyl group not efficiently intercede?

It has been earlier established that in the case of the carbonium ion formed in the hydrolysis of phthaldehydic acid diethyl acetal the partitioning of the intermediate is exclusively by the carboxyl group. The carboxyl group captures the carbonium ion with at least 98% efficiency.

If we return to the synthesis of 2( o-carboxy-phenyl )-4,4,5,5-tetra-methyl-1,3-dioxolane it will be seen that the reaction of pinacol with phthaldehydic acid yields the tetra-methyl-dioxolane in at least 95% yield, this can only mean that the intramolecular hydroxyl group captures the carbonium intermediate considerably more efficiently than does the carboxyl group.
This presumably arises from the loading up of the dioxolane ring with methyl groups. It is also interesting to note that the formation of tetra methyl dioxolanes is just as fast as that of the unsubstituted ones, both taking only a few minutes to complete. Whilst any extrapolations from the solvent used for their synthesis (benzene) to the aqueous medium of hydrolysis must be viewed sceptically, one is struck by the oddness of the reactions of these highly substituted dioxolanes.

Since the proposed intermediate cannot be isolated its formation must remain a matter of speculation. If Capon's and Orvik's reasonings are correct and since a carboxylate ion is known to trap the intermediate carbonium ion efficiently then it is clear that in this case a free carbonium ion is unlikely.

It is of course, quite possible that the hydrolysis proceeds via an A₂ mechanism where the carboxyl group is not positioned in a manner suitable for participation. If there is still a fair amount of A₁ character in the transition state, that is, if there is a large amount of charge development on the aldehyde carbon, then for the phenyl group to provide any mesomeric stabilisation of this charge the plane of the phenyl ring must be perpendicular to the plane of the diox-
olane ring. This may be seen from the figure shown below.

Figure 71

A Mainly Transition state For the Hydrolysis of 2 (o Carboxy Phenyl) 4,4,5,5 Tetra Methyl

1,3 Dioxolane

It is quite clear from this figure that in a transition state of this structure the carboxylate anion is not able to participate directly. This of course means that to obtain any participation by the carboxylate anion it is necessary to rotate the dioxolane ring through 90°. This in turn means that any mesomeric stabilisation by the phenyl ring would be lost. These considerations apply even more forcibly for the diethyl acetal. Since a phenyl substituent, by virtue of its mesomeric effect increases the rate of hydrolysis of formal by a factor of $10^{11}$ it is necessary first to counteract this term before proceeding to give any rate enhancement. In view of this the rate enhancements in dioxan water mixtures take on a new light.

It is regrettable that this point was not appreciated when the work was being done. At least it shows some pointers to the direction to be taken.
Summary of Nucleophilic Catalysis

Intramolecular nucleophilic catalysis in the specific acid catalysed hydrolysis of acetals is not general. In order to observe this effect it would appear that several points have to be observed. Not unnaturally, it is essential to maintain efficient geometry, not only in the ground state of the molecule but great consideration must be paid to the expected structure of the transition state that will arise from participation. It is important that a powerful nucleophile be selected, and that the carbonium ion formed in a normal $A_1$ transition state be not highly stabilised. This latter state may be achieved by structural effects in the molecule or by the composition of the hydrolytic medium.

The synthesis of acetals with rigidly held groups of suitable nucleophilicity and where highly stabilised carbonium ions are not formed would be highly desirable.
STERIC EFFECTS IN THE HYDROLYSIS OF 2 METHOXY-METHOXY BENZOIC ACIDS

Smith found that the hydrolysis of 2,6-dicarboxy methoxy methoxy benzene was very fast. He was, however, unable to obtain a specimen of the acid sufficiently pure to adequately characterise the compound. The rough kinetic data showed that the rate enhancement was greater than the statistical effect of two carboxyl groups, and that since the rate did not fall off at lower pH's bifunctional catalysis was not observed.

Since substituent effects are usually small in the hydrolysis of methoxy methoxy benzenes (see results section) it was felt that some special steric effects were involved.

The dicarboxy acid was not an appealing substrate, because the separate ionisation of the two carboxyl groups would make the pH rate profile complex. Two immediate prospects were the 3-methyl and 3-nitro derivatives and possibly the 3-tertiary-butyl derivative. The latter derivative, however, proved impossible to synthesise. It was at the same time hoped to study the corresponding 6 substituted isomers, but initial attempts to synthesise these failed and sufficient time was not available to pursue this topic.

The kinetic parameters for the hydrolysis of some 2-methoxy methoxy benzoic acids are given below. The pH rate profile for the hydrolysis of these compounds obeys the kinetic law:

\[ k_{\text{obs}} = k_1 (SH^-) + k_2 (SH^+)(H^+) \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>(T^\circ)</th>
<th>I</th>
<th>pK_a</th>
<th>(k_1) sec(^{-1})</th>
<th>(k_2) l mole(^{-1}) sec(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-methoxy methoxy benzoic acid</td>
<td>45</td>
<td>.04</td>
<td>3.76</td>
<td>3.80</td>
<td>1.74 \times 10^{-3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.95 \times 10^{-2}</td>
</tr>
</tbody>
</table>
A nitro substituent in the 4 position increases \( k_1 \) by a factor of approximately 3, which is attributable to the increase in the pKa of the catalysing acid. Substituents in the 3 position increase \( k_1 \) irrespective of their electronic effects. The rate increase for the 3 nitro derivative is particularly large. This compound hydrolyses too quickly to measure any rate constants at 45°, so it was necessary to measure the rates at 20.0°. It is also interesting to note that the value of \( k_2 \) also increase in a parallel manner, and the same is also true for the methyl esters of the acids in M/10 HCl.

Before proceeding to propose an explanation of this effect some of the structural properties of aromatic ethers will be discussed.

### Structural Properties of Aromatic Methyl Ethers

#### The Geometry of Aryl Methyl Ethers

Aromatic methyl ethers in the crystal state usually have the aryl group, oxygen, and the carbon atom of the methyl group coplanar, with a C-O-C included angle of 118°, a phenyl oxygen bond length of 1.35 Å and a methyl oxygen bond length of 1.43 Å.

Some selected examples are given in table 14.
Table I:
Geometrical Parameters of Aromatic Ethers

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar-O bond length</th>
<th>Me-O bond length</th>
<th>C-O-C angle ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image 1]</td>
<td>1.36 ( \text{Å} )</td>
<td>1.45 ( \text{Å} )</td>
<td>120 °</td>
</tr>
<tr>
<td>![Image 2]</td>
<td>1.36 ( \text{Å} )</td>
<td>1.48 ( \text{Å} )</td>
<td>117.5 °</td>
</tr>
<tr>
<td>![Image 3]</td>
<td>1.38 ( \text{Å} )</td>
<td>1.52 ( \text{Å} )</td>
<td>118 °</td>
</tr>
<tr>
<td>![Image 4]</td>
<td>1.39 ( \text{Å} )</td>
<td>1.46 ( \text{Å} )</td>
<td>119.8 °</td>
</tr>
</tbody>
</table>

Although the theory of bonding in aryl and aryl alkyl ethers is not very advanced, the known bonding characteristics may be rationalised by the following simple considerations.

If aryl ethers have the same structure in solution as in the solid phase the shortness of the aryl oxygen bond would be explained by assuming that the oxygen atom is \( sp^2 \) hybridised, and that there is appreciable overlap between the the oxygen lone pair which is in a \( p \) orbital and the \( pi \) orbitals of the phenyl ring.

Figure 15
Schematic Representation of the Bonding in Aryl methyl Ethers
The reduced basicity of aromatic ethers may also be rationalised on this basis, since on protonation the oxygen atom should undergo rehybridization to give an sp\(^3\) system, losing the conjugation with the ring.

**Intramolecular Hydrogen Bonding in Salicyl Methyl Ethers**

The existence of the six membered hydrogen bonding in \(-o\) aryloxy benzoic acids and \(-o\)-methoxy benzoic acid in dilute non polar solvents is well authenticated. What is more important to this discussion is the perturbation of this hydrogen bonding by substituents adjacent to the carboxyl group and the ether group.

Oki and his coworkers\(^{100}\) have studied the effect of substituents in the 3 and 6 positions upon the hydrogen bonding in \(-o\)-methoxy benzoic acid. The infra red spectra of these acids were studied and the red shift of the OH stretching frequency of the hydrogen bonded species from the non hydrogen bonded species was taken to be a measure of the strength of the bond, whilst the integrated intensity of the absorption bands a measure of the equilibrium constant for the two species.

Substituents remote from the interacting groups modify the hydrogen bonding according to their electronic effects upon the basicity of the ether. Substituents in the 6 position completely inhibit hydrogen bonding by (presumably) forcing the carboxyl group out of the plane of the ring.

Substituents in the 3 position, that is adjacent to the ether grouping, depress the extent of the hydrogen bonding, but Oki and Hirota\(^{102}\) do not comment upon the fact that the shifts are much larger than that observed for the unsubstituted methoxy acid. A similar study by Lloyd et al\(^{103}\) shows that for these 3 substituted acids the strength of the hydrogen bond varies in the opposite sense to the ratio of the H bonded to non H bonded species. This is explained in terms of a "compression effect".

Clearly in these cases the most favourable conformations
will be those where the methyl group is out of the plane of the phenyl ring. Nevertheless, when the methyl group is in the plane of the ring it will be forced towards the carboxyl group, and the strength of the hydrogen bond will be increased.

In these planar conformations the oxygen atom of the ether is probably $sp^2$ hybridised and therefore hydrogen bonding will be to a vacant $sp^2$ hybrid orbital. In this case both the hybridisation and the geometric disposition of the lone pair is favourable. In the case where the methyl group is out of the plane of the ring two situations could arise; both of which will destroy the pi bonding of the oxygen lone pair with the $p$ orbitals of the ring. In the first case the oxygen atom could rehybridise to an $sp^3$ system, in which case no orbital is well disposed for hydrogen bonding, or it could retain its electronic configuration and hydrogen bonding could occur to a $p$ orbital. This latter system does not seem very likely and it is assumed that the first scheme which is essentially what occurs in aliphatic ethers, would be adopted.

**Hydrolysis of Methoxy Methoxy Benzenes**

The hydrolysis of methoxy methoxy benzenes should proceed via one of the following routes;

(1) $\text{PhOCH}_2\text{OCH}_3 \xrightarrow{H^+} \text{PhO}^-\text{CH}_2\text{OCH}_3 \xrightarrow{\text{slow}} \text{PhOH} + \text{CH}_2^+\text{OCH}_3$

(2) $\text{PhOCH}_2\text{OCH}_3 \xrightarrow{H^+} \text{PhOCH}_2\text{O}^-\text{CH}_3 \xrightarrow{\text{slow}} \text{PhO}^+\text{CH}_2 + \text{CH}_3\text{OH}$

The phenoxyl oxygen is much less basic than the methoxyl oxygen (see later explanation of this point), but phenol is a much better leaving group than methanol; so these two effects should tend to cancel out.

What should therefore be most important is the relative stability of the two carbonium ion intermediates. The carbonium ion formed in scheme (1) will be more highly stabilised than that in scheme (2) since in the latter case the oxygen atom is already pi bonded to the phenyl ring. To gain any mesomeric stabilisation from the oxygen
it would be necessary to destroy this conjugation.

If, as seems most probable, the mechanism is best represented by scheme (1); then protonation of the phenoxy oxygen will result in the loss of the pi bonding with the ring and therefore electron withdrawing substituents will hinder the pre-equilibrium protonation. The carbonium ion formed is not very highly stabilised so the transition state will be reached well along the reaction coordinate, and therefore much of the original pi bonding will be recovered, resulting in the near zero electronic substituent effects.

We are now in a position to discuss the reasons why the substitution of a group in the 3 position of 2-methoxy methoxy benzoic acid has such a large effect upon the rates of hydrolysis of these compounds.

It was felt at first that the likely reason for this fact was that the hydrogen bonding in these compounds might be enhanced. This is of course wrong since exactly the opposite is found to be true. Hydrogen bonding can occur to the phenoxy oxygen without perturbing the electronic state of the ether, but in the case of general acid catalysis the proton must be well transferred in the transition state. This means that the pi bonding will be in its least effective state. In view of this, comparisons with hydrogen bonding studies in dilute non polar solvents seem of rather dubious value.

These hydrogen bonding studies do however demonstrate that in the case of these 3 substituted compounds the methyl group is mostly out of the plane of the ring. This can only result in the pi bonding with the ring being either highly unfavourable or most likely completely lost.

The oxygen atom would then presumably revert to the sp^3 hybridisation found in aliphatic ethers. Thus the first half of the mechanism the protonation step has been made easier, and as the phenoxy carbon bond breaks in the transition state, the phenol formed will
gain the π bonding which was absent in the starting formal. Further to this, the phenol formed is the very stable anion of a 3 substituted salicylic acid. In the case of the esters of the acids, for which the hydrolysis of formal group is also very fast, similar considerations apply. Again, the π bonding of the phenoxyl oxygen and the phenyl ring is weakened or broken and a very stable phenol, the intra molecularly hydrogen bonded methyl ester of a 3 substituted salicylic acid, formed.

One can apply the same reasoning to the $k_2$ term in the expression for the π rate profile of the acids. This argument is intuitively correct since it lays so much stress upon the leaving capabilities of the phenol. As shall be shown later, in the case of the inter molecular catalysed hydrolysis of benzaldehyde phenyl methyl acetals the leaving group abilities of the phenol determines the relative rates of hydrolysis whereas in the case of phenyl glycosides the pre-equilibrium protonation step is the more important.

If this argument is a good representation of the facts, not only should substituents in the 6 position of 2 methoxy methoxy benzoic acids inhibit the intra molecular general acid catalysed hydrolysis of these formals, but the specific acid catalysed hydrolysis of the formal group of the methyl esters of the acids should hydrolyse at the normal rate. No examples of six substituted acids were studied, but an excellent example of this effect has been brought to my attention by Dr. N. S. Anderson of this department.

Oki and his coworkers not only studied hydrogen bonding in substituted 2-methoxy benzoic acids but also the various naphthoic acids. He found that the 2-methoxy 3-naphthoic acid had the greatest ratio of bonded species and that the 1-methoxy-2 acid was less favourable for hydrogen bonding and that the 2-methoxy 1-acid was not hydrogen bonded at all. In the latter two cases the peri hydrogen interaction is of a similar nature to the ortho interaction in 3- and 6-methoxy benzoic acids.
The 2 methoxy 1 naphthoic acid has a $k_1$ term which is about 100 times less than that of the 2,3 isomer, and the $k_2$ term is also reduced by a similar factor. The methyl ester of the acid has a second order rate constant for the hydrolysis of the formal group that is virtually the same as that found for 2 methoxy methoxy naphthalene.

Until X-ray crystallographic studies have been made of some of these compounds much of the preceding arguments must naturally be considered speculative. These proposals, of course, mean that these three substituted methoxy benzoic acids should be considerably more basic than the unsubstituted compounds. It ought to be relatively easy to check this point and this should be considered a priority experiment.

Again attention is drawn to some of the theories concerning the source of enzymes catalytic effect. Here is a system where the environment of the substrate has been modified, this time sterically, and catalysis has been made more efficient. The explanation proposed here is that the ground state free energy of the molecule has been raised by conformational considerations.
Intermolecular General Acid Catalysis in The Hydrolysis of Benzaldehyde Phenyl Methyl Acetals

At the completion of this work only one example of buffer catalysis in acetal hydrolysis had been reported. This was the specific acid nucleophilic catalysis observed for 2 (p methoxy phenyl) 4,4,5,5 tetramethyl 1,3 dioxolane, which has been discussed previously. After the completion of this work Fife and Jao reported that 2 p nitro and p chloro phenoxy tetrahydro pyran hydrolysed in 50% dioxan water with catalysis by the formate buffers.

The reasons proposed by Bunton and DeWolfe why trialkyl orthoformic esters but not acetals hydrolyse with general acid catalysis have been discussed previously. The values that these authors use for $k_2$ for the specific acid catalysed hydrolysis of acetal are wrong. The reference quoted in fact refers to formaldehyde diethyl acetal. Their arguments are, however, still correct.

Following Bunton and DeWolfe's reasoning the pKa of benzaldehyde dimethyl acetal is calculated to be -6.0, and taking the observed value for the second order hydrolytic rate constant, $2.7 \times 10^1$ mole$^{-1}$ sec$^{-1}$, this gives a value of $k_2$ of $2.7 \times 10^7$ sec$^{-1}$. This value shows that the hydronium ion catalysed reaction should proceed via the normal $A_1$ mechanism, since it is quite feasible that $k_1 > k_2$. It is not intended here that a comparison be made of a first and second order rate constant. What $k_1$ really refers to is the pseudo first order rate constant for protonation in the experimentally accessible regions of acidities directly obtained by dilute acids.

This value is marginal when compared with the value calculated for formal, 7 sec$^{-1}$, and contrasted with that for ethly orthoformate, 5 $\times$ 10$^3$ sec$^{-1}$. The very small increase in rate observed for the hydrolysis of benzaldehyde dimethyl acetal going from 0.2 M to 1.0 M acetic acid/acetate buffers at constant ionic strength could well be due to general acid catalysis. It would need some very accurate work at rather lower ionic strengths to be positive about this point.
For the acid catalysed hydrolysis of ketal (acetone diethyl ketal) the calculated pKₐ is -4.9 and using a value of $k_H^+$ of $2.3 \times 10^3$ 1 mole⁻¹ sec⁻¹ (see discussion), this gives a value of $k_2$ of $2 \times 10^7$ sec⁻¹. It is therefore not only necessary to increase the stability of the carbonium ion to achieve a value of $k_2 > 10^{10}$, which Cordes considers necessary to observe general acid catalysis, but the basicity of the acetal must be reduced.

A more pictorial approach to this problem is outlined below. The free energy versus reaction coordinate diagram for the specific acid catalysed hydrolysis of acetal is given in figure 15.

Figure 15
Free Energy versus Reaction Coordinate for The Hydrolysis of Acetal
In order to change from a specific acid to a general acid catalysed mechanism it is necessary to make transition state one of greater than, or equal free energy than transition state two. If it is assumed that these transition states closely resemble the appropriate intermediates, this can be achieved by stabilising the carbonium ion intermediate 2 or destabilising intermediate 1, or a combination of both. The latter could be achieved by making the oxygen base weaker. If this is done the two transition states will not remain static along the reaction coordinate. By Hammonds hypothesis, transition state 1 will occur later along the reaction coordinate, and transition state 2 earlier. Two distinct possibilities then arise where hydronium ion catalysis would be described as general acid catalysis.

Figure 16
The first example corresponds to the coincidence of transition states 1 and 2, where proton transfer is synchronous with bond fission. This corresponds to a concerted A⁻S⁻₂ displacement on oxygen. If, as in the latter case, the transition states are not coincident this would correspond to protonation becoming rate limiting. As pointed out by Kresge and Preto, this is not unreasonable for proton transfer between bases of widely differing strengths, since the free energy of activation must be at least equal to the free energy difference of the two conjugate acids for proton transfer from a weak acid to a weak base.

The initial calculations show that the basicity of acetals must be reduced if any general acid catalysis is to be observed. Since aryl ethers are weaker bases than alkyl ethers by a factor of approximately $2 \times 10^3$, the choice of aryl acetals seemed appropriate.

It was at first hoped to prepare the phenyl methyl acetals of acetone and crotonaldehyde, which would give highly stabilised carbonium ions. Their synthesis however proved impossible. The next best choice was benzaldehyde acetals. Both diaryl and aryl methyl acetals of benzaldehyde were prepared. The former though very weak bases, were not appealing substrates since the resulting carbonium ion

\[
\text{Ph-}^\ddagger \text{CH-OPh}
\]
would, for reasons discussed earlier, not be highly stabilised. Indeed, the second order rate constant for the hydrolysis of benzaldehyde di-
meta nitro phenyl acetal is some $10^6$ times smaller than that for the dimethyl acetal.

In the case of the mixed acetals bond fission could occur between the methoxyl or phenoxy aldehyde bond. This is of course the same problem as in the hydrolysis of methoxy methoxy benzene. For precisely the same reasons bond fission should be between the phenoxy aldehyde bond. The relative stabilities of the two possible carbonium ion intermediates are well demonstrated by the mass spectrum of the parent phenyl methyl acetal. The base peak of the spectrum is the ion $\text{Ph-CH}_2-\text{OMe}$.

and the ion which would result from the loss of $\text{OMe}$ represents much less than 1% of the base peak, and it is quite possible that this arises from trace amounts of the diaryl acetal.

If the pKa of anisole is taken as $-6.5$, and it is assumed that the second order rate constant for the hydronium catalysed hydrolysis of the phenyl methyl acetal of benzaldehyde is the same as that for the dimethyl acetal, then a value of $k_2$ of $5 \times 10^{11}$ sec$^{-1}$ is calculated. The magnitude of this rate constant is even greater than that calculated for ethyl orthoacetate.

These calculations were made after the discovery of the catalysis by general acids, and a large effect was not anticipated. Because of this it was decided to use a high buffer concentration, up to ionic strengths of 1.0. This was perhaps an unfortunate choice since it prevented the accurate determination of the intercepts of the $k$ vs (HA) plots, and as can be seen from the values of the pH's of the buffers made up from equal concentrations of acetic acid and sodium acetate at ionic strength 1.0, salt effects are very large.
The rate constants are all quite large and great care was needed to obtain satisfactory agreement between duplicates. The temperature of the buffers and their pH was checked before and immediately after each run. The exact procedure is given in the kinetics experimental section. In no case did the temperature vary more than 0.05° or the pH 0.02. The individual buffers at any given buffer ratio did not change their pH on dilution with M KCl by > 0.02 pH. It proved absolutely essential to use degassed freshly deionised water to make up buffer solutions if this pH stability was to be maintained.

The m nitro phenyl acetal proved to be rather difficult to follow, mainly because of the speed of the hydrolysis and somewhat unstable infinity values. These problems were solved when the data logging system was used to collect the data and a generalised least squares program was used to process it. In general the rates determined for duplicate runs agreed within 1-2% of each other, but the overall fits to the k vs (HA) plots were nothing like as good. The standard deviations of the slopes were all around 5% and the standard deviations of the intercepts around 10%. On reflection it would seem that the problem was due to the fact that too many duplicates were run in parallel and that slight drifts in infinity values were occurring. This latter effect is possibly due to trace amounts of the dimethyl acetal, about 1%. It is hoped that most of these runs can now be rerun on a rigorous least squares program and these small deviations corrected.

Although the precision could be improved the results are still easily good enough.

The results are considerably more impressive than was originally anticipated. The acetic acid catalysed hydrolysis of the parent phenyl methyl acetal has a rate constant of (5.94 ± 0.03) x 10^{-3} 1 mole^{-1} sec^{-1} at 20.0° at an ionic strength of 1.0, determined at 3 different buffer ratios. A plot of the intercepts of all the runs vs 10^{-pH} gave a second order rate constant for the hydronium catalysed reaction of
(4.95 ± 0.05) \times 10^{-1} \text{ mole}^{-1} \text{ sec}^{-1} \text{ under the same conditions. The intercept of this plot is essentially zero (7.4 \times 10^{-4} \text{ sec}^{-1}) and a plot of log \text{intercept vs} -pH has a slope of 0.82 ± 0.02. The m nitro derivative has a fairly large spontaneous rate of hydrolysis, measured in M/10 NaOH, which appears to be insensitive to variations of ionic strength.}

The deuterium solvent isotope effects are larger than any observed for ortho ester hydrolysis, with \frac{k_{\text{H}^3\text{O}^+}}{k_{\text{D}^3\text{O}^+}} = 1.02 ± 0.02 and \frac{k_{\text{AcOH}}}{k_{\text{AcOD}}} = 2.11±15 for the parent phenyl methyl acetal. These effects would no doubt be even larger for the m-nitro derivative.

In addition to this the Bronsted alpha value of 0.53 ± 0.08 calculated from the chloroacetic, acetic, and formic acid catalysed rates, indicates that the proton is only partially transferred in the transition state. The Hammet rho value for the acetic acid catalysed hydrolysis of the m substituted methyl, hydrogen, fluoro, and nitro derivatives, is ±0.36 ± 0.08. This is of opposite sign to that observed for the hydrolysis of phenyl-β-D-glucosides and is taken to be an indication that the leaving group ability of the phenol determines the relative rates of the general acid catalysed reaction. Unfortunately no reliable estimation of the substituent effect for the hydronium catalysed reaction can be made, because of the spontaneous rate of hydrolysis of the m-nitro derivative and the uncertainties in the intercepts of the general acid catalysis plots. It will be necessary to work at much lower buffer concentrations to obtain an accurate estimate of these values. Inspection of the results at hand suggest that the rho value is definitely positive, and small. This of course would tie in with the solvent isotope effect, indicating that the hydronium catalysed hydrolysis would best be described as an \E2 substitution on oxygen.

Just after the completion of this work Fife and Jao reported that the hydrolysis of α, α-nitro and p-chloro-phenoxy tetrahydropyran in 50% aqueous dioxan is catalysed by formic acid. The values for the second order formic acid catalysed rates were much smaller than those
found for the hydrolysis of the benzaldehyde acetals, and no general catalysis was found for \( \text{p-methoxy-phenoxy tetrahydropyran} \). No mention was made of the unsubstituted phenoxy derivative and it is assumed that no effect was observed. These authors do not state what happens in totally aqueous buffers, and as was pointed out earlier, it is more likely that general acid catalysis will be observed in dioxan water buffers than in totally aqueous ones. It is hoped that further work by these authors will clarify this point.

A value of \( k_2 \) calculated for 2-phenoxy-tetrahydro-pyran, \( 2 \times 10^4 \text{ sec}^{-1} \), is well outside the range expected for general acid catalysis and even the value calculated for the \( \text{p-nitro derivative} \) is only about \( 10^3 \text{ sec}^{-1} \). In view of the results reported in this thesis a better choice of substrate would have been the dihydropyran;

for which a very large effect might be expected to be observed.

Some Brief Suggestions for Further Work in This Field

Although the mechanism of the general acid catalysis would seem to be reasonably clear there is no doubt that further information on this novel topic would be desirable. Substituent effects in the aldehyde portion of the molecule should give a detailed picture of the transition state. One wonders if it will be possible with this system to push the deuterium solvent isotope effect through a maximum. In view of the very large substituent effects observed in acetal hydrolysis, it would be very interesting to see what the solvent isotope effects were like in the \( \text{p-methoxy-benzaldehyde phenyl methyl} \) series. It is quite possible that for this series the Bronsted alpha coefficient might be so small that water catalysis might become dominant.
SOME OVERALL CONSIDERATIONS

The work reported in this thesis has shown examples of intramolecular nucleophilic, inter, and intramolecular general acid catalysis in acetal hydrolysis. It now remains to interrelate these topics and to present some overall view of the importance of these results.

At the outset of this work the number of examples of non general behavior in acetal hydrolysis could be counted on one hand, and although much progress in this field has been made, only about a dozen examples are now known. It would be a reasonable thing to say that most of this work has been studied with the thought of lysozyme always present, and whilst no pretence is made that the results in this thesis have any direct relevance to the mechanism of action of that enzyme, many of the questions raised concerning the postulates about the mechanism have been, at least in part, answered.

No attempt will be made to manipulate values of rate enhancements observed to explain the magnitude of the catalytic effect of glycosidic enzymes, in the author's view this is futile, but one should bear in mind that interactions between effects may be large, both negative and positive. If one was asked what sort of acetal or glycoside one would pick in order to observe the maximum possible catalytic effect by neighbouring groups, one could design some very exotic compounds. This is exactly what enzymes are, very exotic compounds. It seems that when it comes to designing catalytic systems nature has us beaten, and that we would be well advised to take her lead. At the same time we must be careful to remember that what goes on in the laboratory does not necessarily have any counterpart in living systems.

It is with this latter sentiment borne well in mind that some suggestions are offered, on the basis of the work reported herein, to explain some of the features of lysozyme.

It is intended to mention only three features, nucleophilic
catalysis, general acid catalysis and general steric features which promote these. If we accept that lysozyme, or for that matter, any glycoside-hydrolysing enzyme, achieves its catalytic effect by introducing its substrate into a very accommodating environment, where acid, base, and nucleophilic catalysis is made exceptionally favourable then certain parallels might be drawn between this and some of the results in this thesis.

Firstly general acid catalysis by a carboxyl group has critical spacial requirements, and the leaving group must be either intrinsically good or modified by structural methods. This is what has been proposed for the intramolecular catalysis in 3-nitro-2-methoxy methoxy benzoic acid. Here steric effects have made the proton transfer so much more favourable by making the leaving group so much better. In aqueous solutions one is limited in the ways that one can achieve this, and necessarily steric effects must be built into the molecule. Nucleophilic participation is seen to be made favourable by increasing the nucleophilicity of the anion of a carboxyl group, by reducing its solvation. Of course, increasing the nucleophilicity of a carboxylate anion by reducing its solvation will also reduce the strength of any carboxyl group that is providing any general acid catalysis, but in an enzyme it is quite possible to arrange a situation where the groups close together see very different environments. In any case nucleophilic catalysis might make general acid catalysis of the type observed in the hydrolysis of benzaldehyde phenyl methyl acetal more likely, simply because bond breaking is facilitated. The real question is just how much interaction is possible between the catalytic groups. This is at the present very much a matter of speculation, but if anyone cares to synthesise this acetal and study its hydrolysis in 82% dioxan/water they might well get some of the answers.
RESULTS SECTION

Unless otherwise stated rate constants were calculated from data collected spectrophotometrically.
Table 15
Hydrolysis of Succinaldehyde Acid Dimethyl Acetal
T = 30.0°, I = 0.1, Acetate Buffers.
Measured by g.l.c. estimation of methanol or * spectrophotometrically

<table>
<thead>
<tr>
<th>pH</th>
<th>k * 10^5 sec^{-1}</th>
<th>obs.</th>
<th>calc</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.95</td>
<td>3.49</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>3.95*</td>
<td>3.60</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>4.18</td>
<td>1.117</td>
<td>1.554</td>
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</tr>
<tr>
<td>4.31</td>
<td>.905</td>
<td>.898</td>
<td></td>
</tr>
<tr>
<td>4.48</td>
<td>.275</td>
<td>.289</td>
<td></td>
</tr>
<tr>
<td>4.81</td>
<td>.220</td>
<td>.232</td>
<td></td>
</tr>
</tbody>
</table>

For fit to equation;

\[ k_{\text{obs}} = k_2 \left( H^+ \right) (\text{Acetal}) + k_0 \]

\[ k_2 \text{ 1 mole}^{-1} \text{ sec}^{-1} \quad \text{S.D.} \quad k_0 \text{ sec}^{-1} \quad \text{S.D.} \]

\[ 3.84 \times 10^{-1} \quad 5.6 \times 10^{-2} \quad -9.8 \times 10^{-6} \quad 4.6 \times 10^{-2} \]

D Three Teturonic Acid Dimethyl Acetal
T = 70.0°, I = 0.2, Chloroacetate buffer, pH = 2.84

\[ k_{\text{polarimetric}} = 2.71 \times 10^{-4} \text{ sec}^{-1} \]
\[ k_{\text{g.l.c.}} = * \times 10^{-4} \text{ sec}^{-1} \]

Model compounds measured under identical conditions;
Methyl ester; \[ k_{\text{g.l.c.}} = 2.28 \times 10^{-5} \text{ sec}^{-1} \]
D glyceraldehyde dimethyl acetal; \[ k_{\text{polarimetric}} = 3.0 \times 10^{-4} \text{ sec}^{-1} \]
The Hydrolysis of 2-Carboxy-Benzaldehyde Diethyl Acetal

\[ T = 25.0^\circ, I = 0.1, \text{Formate and Acetate Buffers.} \]

<table>
<thead>
<tr>
<th>pH</th>
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<tr>
<td>3.85</td>
<td>1.15</td>
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<tr>
<td>3.93</td>
<td>( 6.32 \times 10^{-2} )</td>
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<tr>
<td>4.08</td>
<td>5.39</td>
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<tr>
<td>4.31</td>
<td>3.92</td>
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<td>4.48</td>
<td>2.01</td>
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<tr>
<td>4.83</td>
<td>1.03</td>
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<tr>
<td>5.04</td>
<td>( 8.32 \times 10^{-4} )</td>
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<tr>
<td>5.83</td>
<td>3.23</td>
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The Hydrolysis of the Acetal Group of the Methyl Ester

Under Identical Conditions

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<td>( 5.14 \times 10^{-4} )</td>
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<tr>
<td>5.04</td>
<td>( 5.50 \times 10^{-5} )</td>
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The Hydrolysis of 4-Carboxy-Benzaldehyde Diethyl Acetal

Conditions as Above

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<th>pH</th>
<th>( k \text{ sec}^{-1} )</th>
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<tbody>
<tr>
<td>3.93</td>
<td>( 2.71 \times 10^{-3} )</td>
</tr>
<tr>
<td>3.95</td>
<td>( 2.63 \times 10^{-3} )</td>
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<td>4.08</td>
<td>2.22</td>
</tr>
<tr>
<td>5.83</td>
<td>( 9.00 \times 10^{-5} )</td>
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</tbody>
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Table 1
The Hydrolysis of ω-Carbamoyl-Benzaldehyde Diethyl Acetal
T = 25.0°C, I = 0.1, Acetate Buffers.

<table>
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<th>pH</th>
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<td>4.09</td>
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<td>4.08</td>
<td>3.80</td>
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Table 2
The hydrolysis of p-Carbamoyl-Benzaldehyde Diethyl Acetal
Conditions as Above

<table>
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<tr>
<th>pH</th>
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<td>6.04</td>
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<td>4.08</td>
<td>5.07</td>
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Table 21
The Hydrolysis of 2-(o-Carboxy-Phenyl)-1,3-Dioxolane
\[ T = 45.0^\circ, I = 0.1, \text{Acetate and Formate Buffers} \]
These rate constants do NOT represent the rates of hydrolysis of this compound. See the discussion for an explanation of this point.

<table>
<thead>
<tr>
<th>pH</th>
<th>( k \text{ sec}^{-1} )</th>
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<td>( 4.47 \times 10^{-4} )</td>
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<td>4.89</td>
<td>( 1.74 )</td>
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Table 22
The Hydrolysis of 2-(p-Carboxy-Phenyl)-1,3-Dioxolane
Conditions as Above

<table>
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<tbody>
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<tr>
<td>4.36</td>
<td>( 1.51 )</td>
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<tr>
<td>4.89</td>
<td>( 5.74 \times 10^{-5} )</td>
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Table 23
The Hydrolysis of 2-(o-Carboxy-Phenyl)-4,4,5,5-Tetra-Methyl-1,3-Dioxolane
\[ T = 65.0, I = 0.1, \text{Acetate and Formate Buffers} \]

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<td>( 2.00 )</td>
</tr>
<tr>
<td>4.90</td>
<td>( 1.06 )</td>
</tr>
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</table>
Table 24:  
The Hydrolysis of 2-(p-Carboxy-Phenyl)-4,4,5,5-Tetra-Methyl-1, 3-Dioxolane

<table>
<thead>
<tr>
<th>pH</th>
<th>k sec⁻¹</th>
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<tr>
<td>M/10 HCl</td>
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<tr>
<td></td>
<td>5.80 * 10⁻³</td>
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<td>&quot;</td>
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<tr>
<td>3.13</td>
<td>8.69 * 10⁻⁵</td>
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<tr>
<td>3.72</td>
<td>4.42</td>
</tr>
<tr>
<td>3.99</td>
<td>2.17</td>
</tr>
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</table>
Reactions in Aqueous Dioxan

Table 25

2-Carboxy-Benzaldehyde Diethyl Acetal

Solvent; 82% Dioxan/Water, T = 60.0°, Acetate and Formate Buffers, I = 0.02

<table>
<thead>
<tr>
<th>pH</th>
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<tbody>
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<td>8.73</td>
<td>3.365</td>
</tr>
<tr>
<td>9.46</td>
<td>3.103</td>
</tr>
<tr>
<td>9.93</td>
<td>3.03</td>
</tr>
<tr>
<td>10.43</td>
<td>2.00</td>
</tr>
<tr>
<td>10.67</td>
<td>1.23</td>
</tr>
<tr>
<td>10.82</td>
<td>0.99</td>
</tr>
<tr>
<td>10.99</td>
<td>0.721</td>
</tr>
<tr>
<td>11.13</td>
<td>0.476</td>
</tr>
<tr>
<td>11.33</td>
<td>0.360</td>
</tr>
<tr>
<td>11.43</td>
<td>0.282</td>
</tr>
<tr>
<td>11.48</td>
<td>0.266</td>
</tr>
<tr>
<td>11.53</td>
<td>0.153</td>
</tr>
</tbody>
</table>

For pH rate profile obeying equation;

\[ k_{obs} = k_1 (HA) + (H^+)(HA) \]

\[ k_1 = 3.318 * 10^{-3} \text{ sec}^{-1} \]

\[ k_2 = 5.82 * 10^4 \text{ mole}^{-1} \text{ sec}^{-1} \]

\[ K_a = 3.52 * 10^{-11} \text{ mole} \text{ l}^{-1} \]

p Isomer under identical conditions

<table>
<thead>
<tr>
<th>pH</th>
<th>k * 10^6 sec^-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.46</td>
<td>1.01</td>
</tr>
</tbody>
</table>
Table 26
The Hydrolysis of 2-(o-Carboxy-Phenyl)-4,4,5,5-tetra-Methyl-1,3-Dioxolane.
Solvent: 50% w/w Dioxan Water T, 95°C; I, 0.05; Acetate buffers.

<table>
<thead>
<tr>
<th>pH</th>
<th>$k \times 10^5$ sec$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.03</td>
<td>11.7</td>
</tr>
<tr>
<td>5.30</td>
<td>10.9</td>
</tr>
<tr>
<td>5.46</td>
<td>10.0</td>
</tr>
<tr>
<td>5.70</td>
<td>6.9</td>
</tr>
<tr>
<td>6.00</td>
<td>5.3</td>
</tr>
<tr>
<td>6.30</td>
<td>1.90</td>
</tr>
</tbody>
</table>

For fit to rate law:

$$k_{obs} = k_1 \cdot (HA)$$

$K_a = 5.88$

$k_1 = 1.00 \times 10^{-4}$ sec$^{-1}$

*p* isomer under identical conditions:

<table>
<thead>
<tr>
<th>pH</th>
<th>k sec$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/250 HClO$_4$</td>
<td>3.16 $\times$ 10$^{-4}$</td>
</tr>
<tr>
<td>5.03</td>
<td>2.5 $\times$ 10$^{-6}$</td>
</tr>
</tbody>
</table>
Table 28
Substituent Effects in The Hydrolysis of Methoxy Methoxy Benzenes
M/10 HCl at 65.0°

<table>
<thead>
<tr>
<th>Substituent</th>
<th>k * 10^5 sec⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>407 *</td>
</tr>
<tr>
<td>2-nitro</td>
<td>337 *</td>
</tr>
<tr>
<td>3-nitro</td>
<td>195 *</td>
</tr>
<tr>
<td>4-nitro</td>
<td>171 *</td>
</tr>
<tr>
<td>4-carbomethoxy</td>
<td>169 *</td>
</tr>
<tr>
<td>2-benzimidazolyl</td>
<td>318 *</td>
</tr>
<tr>
<td>4-carboxy</td>
<td>298</td>
</tr>
<tr>
<td>4-bromo</td>
<td>306</td>
</tr>
<tr>
<td>4-methyl</td>
<td>388</td>
</tr>
<tr>
<td>2-carbomethoxy</td>
<td>1070</td>
</tr>
<tr>
<td>2-carboxy</td>
<td>1441</td>
</tr>
<tr>
<td>4-methoxy</td>
<td>388</td>
</tr>
</tbody>
</table>

* Results of R. H. Dahm"
Table 27:
The Hydrolysis of 3-Methyl 2-Methoxy Methoxy Benzoic Acid

\[ T = 45.0^\circ, \ I = 0.1, \ \text{Buffers as Indicated} \]

<table>
<thead>
<tr>
<th>pH</th>
<th>( k \times 10^3 \ \text{sec}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.00 a</td>
<td>3.155</td>
</tr>
<tr>
<td>4.00 a</td>
<td>3.090</td>
</tr>
<tr>
<td>4.00 a</td>
<td>3.060</td>
</tr>
<tr>
<td>3.78 b</td>
<td>3.800</td>
</tr>
<tr>
<td>3.78 b</td>
<td>3.884</td>
</tr>
<tr>
<td>3.49 b</td>
<td>4.942</td>
</tr>
<tr>
<td>3.49 b</td>
<td>4.938</td>
</tr>
<tr>
<td>3.33 b</td>
<td>5.300</td>
</tr>
<tr>
<td>3.18 b</td>
<td>6.192</td>
</tr>
<tr>
<td>3.09 c</td>
<td>6.537</td>
</tr>
<tr>
<td>3.00 c</td>
<td>6.986</td>
</tr>
<tr>
<td>2.89 c</td>
<td>7.405</td>
</tr>
<tr>
<td>2.10 d</td>
<td>8.322</td>
</tr>
<tr>
<td>1.50 d</td>
<td>10.76</td>
</tr>
<tr>
<td>1.50 d</td>
<td>10.00</td>
</tr>
<tr>
<td>1.10 d</td>
<td>14.96</td>
</tr>
</tbody>
</table>

a = acetate buffers, b = formate buffers, c = chloroacetate buffers
d = dilute HCl, + KCl

Parameters for pH rate profile:

\[ k_1 = 7.76 \times 10^{-3} \ \text{sec}^{-1} \]
\[ k_2 = 9.10 \times 10^{-2} \ \text{mole}^{-1} \ \text{sec}^{-1} \]
\[ K_a = 1.72 \times 10^{-4} \ \text{mole}^{-1} \]

Hydrolysis of the Formal Group of the Methyl Ester at the Same Temp. and Ionic Strength

\[ \text{M/10 HCl; } k = 4.29 \times 10^{-3} \ \text{sec}^{-1} \]
\[ \text{M/100 HCl; } k = 3.63 \times 10^{-4} \ \text{sec}^{-1} \]
Table 29:
The Hydrolysis of 2-Methoxy Methoxy-3-Nitro Benzoic Acid
\[ T = 20.0^\circ, \ I = 0.1, \ \text{Buffers as Indicated} \]

<table>
<thead>
<tr>
<th>pH</th>
<th>( k \times 10^2 \text{ sec}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 a</td>
<td>9.42</td>
</tr>
<tr>
<td>1.5 a</td>
<td>8.02</td>
</tr>
<tr>
<td>2.00 b</td>
<td>7.75</td>
</tr>
<tr>
<td>2.48 b</td>
<td>5.33</td>
</tr>
<tr>
<td>2.86 c</td>
<td>4.66</td>
</tr>
<tr>
<td>2.86 c</td>
<td>4.52</td>
</tr>
<tr>
<td>2.99 c</td>
<td>3.06</td>
</tr>
<tr>
<td>2.99 c</td>
<td>3.03</td>
</tr>
<tr>
<td>3.20 c</td>
<td>2.35</td>
</tr>
<tr>
<td>3.20 c</td>
<td>2.27</td>
</tr>
<tr>
<td>3.42 d</td>
<td>1.54</td>
</tr>
<tr>
<td>3.42 d</td>
<td>1.60</td>
</tr>
<tr>
<td>3.60 d</td>
<td>0.960</td>
</tr>
<tr>
<td>3.60 d</td>
<td>0.955</td>
</tr>
<tr>
<td>3.86 d</td>
<td>0.722</td>
</tr>
<tr>
<td>3.86 d</td>
<td>0.719</td>
</tr>
<tr>
<td>4.08 e</td>
<td>0.419</td>
</tr>
<tr>
<td>4.08 e</td>
<td>0.420</td>
</tr>
</tbody>
</table>

a = dilute HCl + KCl, b = pyrophosphate buffers, c = chloroacetate buffers, d = formate buffers, e = acetate buffers.

Parameters for pH rate profile:
\[
\begin{align*}
k_1 &= 8.32 \times 10^{-2} \text{ sec}^{-1} \\
k_2 &= 1.48 \times 10^{-1} \text{ mole}^{-1} \text{ sec}^{-1} \\
K_a &= 1.54 \times 10^{-3} \text{ mole}^{-1}
\end{align*}
\]
Table 30
The Hydrolysis of The Formal Group of 2-Methoxy Methoxy 3-Nitro Methyl Benzoate.
(\(\text{HOOOH}\)) = 2 (\(\text{HOOO}^-\)), I = 1.0, Maintained with KCl, \(T = 65.0°\).

<table>
<thead>
<tr>
<th>(HA) m ole (^{-1})</th>
<th>(k \times 10^3) sec(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>4.16</td>
</tr>
<tr>
<td>1.00</td>
<td>4.18</td>
</tr>
<tr>
<td>.800</td>
<td>4.25</td>
</tr>
<tr>
<td>.800</td>
<td>4.40</td>
</tr>
<tr>
<td>.600</td>
<td>4.80</td>
</tr>
<tr>
<td>.600</td>
<td>4.82</td>
</tr>
<tr>
<td>.400</td>
<td>4.81</td>
</tr>
<tr>
<td>.400</td>
<td>4.97</td>
</tr>
<tr>
<td>.200</td>
<td>5.03</td>
</tr>
<tr>
<td>.200</td>
<td>5.14</td>
</tr>
</tbody>
</table>
GENERAL ACID CATALYSIS STUDIES

Except where otherwise stated, all kinetic measurements were made at 20.0°C and at an ionic strength of 1.0, maintained constant with KCl. The slopes are the second order rate constants for the general species catalysed reactions and the intercepts are the rates extrapolated to zero buffer concentration.

Table 31
The Acetate Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

\[( \text{CH}_3\text{COOH} ) = ( \text{CH}_3\text{COO}^- ) \], pH = 4.68

<table>
<thead>
<tr>
<th>(HA) mole(^{-1})</th>
<th>(k \times 10^3 ) sec(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>obs.</td>
</tr>
<tr>
<td>.200</td>
<td>2.98</td>
</tr>
<tr>
<td>.200</td>
<td>3.06</td>
</tr>
<tr>
<td>.400</td>
<td>4.65</td>
</tr>
<tr>
<td>.500</td>
<td>5.27</td>
</tr>
<tr>
<td>.500</td>
<td>5.27</td>
</tr>
<tr>
<td>.600</td>
<td>5.85</td>
</tr>
<tr>
<td>.600</td>
<td>6.05</td>
</tr>
<tr>
<td>.800</td>
<td>6.71</td>
</tr>
<tr>
<td>.800</td>
<td>7.00</td>
</tr>
<tr>
<td>1.00</td>
<td>8.03</td>
</tr>
<tr>
<td>1.00</td>
<td>7.91</td>
</tr>
</tbody>
</table>

Slope 1 mole\(^{-1}\) sec\(^{-1}\) S.D. Intercept sec\(^{-1}\) S.D.

5.98 \times 10^{-3} 2.6 \times 10^{-4} 2.18 \times 10^{-3} 1.8 \times 10
Table 32
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal
\((\text{CH}_3\text{COOH}) \rightarrow \text{CH}_3\text{COO}^-; \text{pH} \approx 4.36\)

<table>
<thead>
<tr>
<th>(HA) mole</th>
<th>(k \times 10^3 \text{ sec}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>.25</td>
<td>4.49 (4.80)</td>
</tr>
<tr>
<td>.25</td>
<td>4.81 (4.83)</td>
</tr>
<tr>
<td>.75</td>
<td>7.52 (7.37)</td>
</tr>
<tr>
<td>.75</td>
<td>7.63 (7.37)</td>
</tr>
<tr>
<td>1.25</td>
<td>10.0 (9.94)</td>
</tr>
<tr>
<td>1.25</td>
<td>9.59 (9.94)</td>
</tr>
<tr>
<td>1.50</td>
<td>11.6 (11.6)</td>
</tr>
<tr>
<td>1.50</td>
<td>11.0 (11.6)</td>
</tr>
</tbody>
</table>

Slope 1 mole\(^{-1}\) sec\(^{-1}\) S.D. Intercept sec\(^{-1}\) S.D.
5.14 \(\times 10^{-3}\) 2.2 \(\times 10^{-4}\) 3.52 \(\times 10^{-3}\) 1.7 \(\times 10^{-4}\)

Table 33
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal
\((\text{CH}_3\text{COOH}) = (\text{CH}_3\text{COO}^-)/2; \text{pH} = 4.96\)

<table>
<thead>
<tr>
<th>(HA) mole (^{-1})</th>
<th>(k \times 10^3 \text{ sec}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>.10</td>
<td>1.68 (1.76)</td>
</tr>
<tr>
<td>.10</td>
<td>1.60 (1.76)</td>
</tr>
<tr>
<td>.25</td>
<td>3.03 (2.65)</td>
</tr>
<tr>
<td>.25</td>
<td>2.66 (2.65)</td>
</tr>
<tr>
<td>.40</td>
<td>3.59 (3.54)</td>
</tr>
<tr>
<td>.40</td>
<td>3.50 (3.54)</td>
</tr>
<tr>
<td>.40</td>
<td>3.53 (3.54)</td>
</tr>
</tbody>
</table>
Table 34:
The Deutero Acetic Acid Catalysed Hydrolysis of Bengaldehyde Phenyl Methyl Acetal
99.7% D₂O, (CH₃COOD) = (CH₃COO⁻) * 1.6, pD = 4.84

<table>
<thead>
<tr>
<th>(DA) mol C⁻¹</th>
<th>k * 10⁻³ sec⁻¹</th>
<th>obs.</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>.640</td>
<td>3.20</td>
<td>3.18</td>
<td></td>
</tr>
<tr>
<td>.640</td>
<td>3.21</td>
<td>3.18</td>
<td></td>
</tr>
<tr>
<td>.800</td>
<td>3.61</td>
<td>3.62</td>
<td></td>
</tr>
<tr>
<td>.800</td>
<td>3.62</td>
<td>3.62</td>
<td></td>
</tr>
<tr>
<td>1.28</td>
<td>4.85</td>
<td>4.98</td>
<td></td>
</tr>
<tr>
<td>1.28</td>
<td>5.04</td>
<td>4.98</td>
<td></td>
</tr>
<tr>
<td>1.60</td>
<td>5.94</td>
<td>5.88</td>
<td></td>
</tr>
<tr>
<td>1.60</td>
<td>5.88</td>
<td>5.88</td>
<td></td>
</tr>
</tbody>
</table>

Table 35:
The Deutero Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal
99.7% D₂O, (CH₃COOD) = (CH₃COO⁻), pD = 5.10

<table>
<thead>
<tr>
<th>(DA) mol C⁻¹</th>
<th>k * 10⁻³ sec⁻¹</th>
<th>obs.</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>.500</td>
<td>4.12</td>
<td>4.13</td>
<td></td>
</tr>
<tr>
<td>.500</td>
<td>4.13</td>
<td>4.13</td>
<td></td>
</tr>
</tbody>
</table>

Slope 1 mol⁻¹ sec⁻¹ S.D. Intercept sec⁻¹ S.D.
5.92 * 10⁻³ 3.9 * 10⁻⁴ 1.17 * 10⁻³ 3.2 * 10⁻⁴
<table>
<thead>
<tr>
<th>(DA) mole l⁻²</th>
<th>k * 10³ sec⁻¹ obs.’</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>.200</td>
<td>1.36</td>
<td>1.46</td>
</tr>
<tr>
<td>.200</td>
<td>1.35</td>
<td>1.46</td>
</tr>
<tr>
<td>.500</td>
<td>2.43</td>
<td>2.30</td>
</tr>
<tr>
<td>.800</td>
<td>3.27</td>
<td>3.14</td>
</tr>
<tr>
<td>.800</td>
<td>3.12</td>
<td>3.14</td>
</tr>
<tr>
<td>1.00</td>
<td>3.50</td>
<td>3.70</td>
</tr>
<tr>
<td>1.00</td>
<td>3.68</td>
<td>3.70</td>
</tr>
</tbody>
</table>

Slope 1 mole⁻¹ sec⁻¹  S.D.    Intercept sec⁻¹  S.D.
2.80 × 10⁻³       1.8 × 10⁻⁴ 8.95 × 10⁻⁴ 1.1 × 10⁻⁴

Table 36
The Chloroacetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

( ClCH₂COO⁻ ) = ( ClCH₂COOH )/2; pH = 2.99

<table>
<thead>
<tr>
<th>(HA) mole l⁻¹</th>
<th>k * 10⁴² sec⁻¹ obs.’</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>.080</td>
<td>5.34</td>
<td>5.67</td>
</tr>
<tr>
<td>.222</td>
<td>6.96</td>
<td>6.61</td>
</tr>
<tr>
<td>.318</td>
<td>7.56</td>
<td>7.24</td>
</tr>
<tr>
<td>.444</td>
<td>7.98</td>
<td>8.07</td>
</tr>
<tr>
<td>.444</td>
<td>7.80</td>
<td>8.07</td>
</tr>
</tbody>
</table>

Slope 1 mole⁻¹ sec⁻¹  S.D.    Intercept sec⁻¹  S.D.
6.58 × 10⁻²       1.2 × 10⁻² 5.15 × 10⁻² 1.28 × 10⁻²
Table 37.
The Formic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal
\[ (\text{HCOOH}) = \frac{(\text{HCOO}^-)}{2}, \text{pH} = 3.89 \]

<table>
<thead>
<tr>
<th>(HA) mole(^{-1})</th>
<th>( k \times 10^{42}) sec(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>obs.</td>
<td>calc.</td>
</tr>
<tr>
<td>0.100</td>
<td>1.05</td>
</tr>
<tr>
<td>0.100</td>
<td>0.935</td>
</tr>
<tr>
<td>0.200</td>
<td>1.43</td>
</tr>
<tr>
<td>0.200</td>
<td>1.45</td>
</tr>
<tr>
<td>0.300</td>
<td>1.69</td>
</tr>
<tr>
<td>0.300</td>
<td>1.79</td>
</tr>
<tr>
<td>0.400</td>
<td>2.06</td>
</tr>
<tr>
<td>0.500</td>
<td>2.40</td>
</tr>
</tbody>
</table>

Slope: 1 mole\(^{-1}\)sec\(^{-1}\) S.D. Intercept: sec\(^{-1}\) S.D.
3.45 \(* 10^{-2}\) 1.93 \(* 10^{-3}\) 6.89 \(* 10^{-3}\) 1.5 \(* 10^{-3}\)

Table 38.
The Dihydrogen-Phosphate Catalysed Hydrolysis of Benzaldehyde
Phenyl Methyl Acetal
\[ (\text{H}_{2}\text{PO}_{4}^-) = 2 \times (\text{HPO}_{4}^{2-}); \text{pH} = 6.16 \]

<table>
<thead>
<tr>
<th>(HA) mole(^{-1})</th>
<th>( k \times 10^{44}) sec(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>obs.</td>
<td>calc.</td>
</tr>
<tr>
<td>0.100</td>
<td>1.97</td>
</tr>
<tr>
<td>0.100</td>
<td>1.86</td>
</tr>
<tr>
<td>0.200</td>
<td>2.81</td>
</tr>
<tr>
<td>0.200</td>
<td>2.99</td>
</tr>
<tr>
<td>0.300</td>
<td>3.70</td>
</tr>
<tr>
<td>0.300</td>
<td>3.68</td>
</tr>
<tr>
<td>0.400</td>
<td>4.38</td>
</tr>
<tr>
<td>0.400</td>
<td>4.40</td>
</tr>
<tr>
<td>HA (mole$^{-1}$)</td>
<td>$k \times 10^3$ (sec$^{-1}$)</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td></td>
<td>obs.</td>
</tr>
<tr>
<td>0.200</td>
<td>2.98</td>
</tr>
<tr>
<td>0.300</td>
<td>3.06</td>
</tr>
<tr>
<td>0.400</td>
<td>4.65</td>
</tr>
<tr>
<td>0.500</td>
<td>5.27</td>
</tr>
<tr>
<td>0.500</td>
<td>5.27</td>
</tr>
<tr>
<td>0.600</td>
<td>5.85</td>
</tr>
<tr>
<td>0.600</td>
<td>6.06</td>
</tr>
<tr>
<td>0.800</td>
<td>6.70</td>
</tr>
<tr>
<td>0.800</td>
<td>7.00</td>
</tr>
<tr>
<td>1.00</td>
<td>8.03</td>
</tr>
<tr>
<td>1.00</td>
<td>8.10</td>
</tr>
</tbody>
</table>

Table 39
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde Methyl $m$-Tolyl Acetal

$(\text{CH}_3\text{COOH}) = (\text{CH}_3\text{COO}^-)$; pH = 4.68

Slope 1 mole$^{-1}$ sec$^{-1}$ S.D.  Intercept sec$^{-1}$ S.D.
8.22 * 10$^{-4}$  3.3 * 10$^{-4}$  1.17 * 10$^{-4}$  2.83 * 10$^{-5}$
Table 40
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde m-Fluoro-Phenyl Methyl Acetal

\[
(\text{CH}_3\text{COOH}) = (\text{CH}_3\text{COO}^-), \text{pH} = 4.68
\]

<table>
<thead>
<tr>
<th>(HA) mole (^{-1})</th>
<th>(k \times 10^3 \text{ sec}^{-1}) obs.</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.200</td>
<td>2.31</td>
<td>2.33</td>
</tr>
<tr>
<td>0.200</td>
<td>2.41</td>
<td>2.33</td>
</tr>
<tr>
<td>0.400</td>
<td>4.30</td>
<td>4.11</td>
</tr>
<tr>
<td>0.400</td>
<td>4.42</td>
<td>4.11</td>
</tr>
<tr>
<td>0.600</td>
<td>5.43</td>
<td>5.89</td>
</tr>
<tr>
<td>0.600</td>
<td>5.59</td>
<td>5.89</td>
</tr>
<tr>
<td>0.800</td>
<td>7.84</td>
<td>7.67</td>
</tr>
<tr>
<td>0.800</td>
<td>7.80</td>
<td>7.68</td>
</tr>
<tr>
<td>1.00</td>
<td>9.52</td>
<td>9.45</td>
</tr>
<tr>
<td>1.00</td>
<td>9.56</td>
<td>9.45</td>
</tr>
</tbody>
</table>

Slope 1 mole \(^{-1}\) sec\(^{-1}\) S.D. Intercept sec\(^{-1}\) S.D.
8.91 \times 10\(^{-3}\) 2.9 \times 10\(^{-4}\) 5.43 \times 10\(^{-4}\) 2.1 \times 10\(^{-4}\)

Table 41
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde m-Nitrophenyl Methyl Acetal

\[
(\text{CH}_3\text{COOH}) = (\text{CH}_3\text{COO}^-), \text{pH} = 4.68
\]

<table>
<thead>
<tr>
<th>(HA) mole (^{-1})</th>
<th>(k \times 10^2 \text{ sec}^{-1}) obs.</th>
<th>calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.200</td>
<td>2.43</td>
<td>2.40</td>
</tr>
<tr>
<td>0.200</td>
<td>2.40</td>
<td>2.40</td>
</tr>
<tr>
<td>.200</td>
<td>2.41</td>
<td>2.41</td>
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<td>2.40</td>
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<tr>
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<td>2.98</td>
<td>3.01</td>
</tr>
<tr>
<td>.400</td>
<td>3.08</td>
<td>3.01</td>
</tr>
<tr>
<td>.600</td>
<td>3.53</td>
<td>3.62</td>
</tr>
<tr>
<td>.600</td>
<td>3.59</td>
<td>3.62</td>
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<tr>
<td>.800</td>
<td>4.21</td>
<td>4.22</td>
</tr>
<tr>
<td>.800</td>
<td>4.18</td>
<td>4.22</td>
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<tr>
<td>1.00</td>
<td>4.91</td>
<td>4.83</td>
</tr>
<tr>
<td>1.00</td>
<td>5.08</td>
<td>4.83</td>
</tr>
</tbody>
</table>

**Slope 1 mole^{-1} sec^{-1} S.D. Intercept sec^{-1} S.D.**

\[
3.03 \times 10^{-2} \quad 5.1 \times 10^{-4} \quad 1.80 \times 10^{-2} \quad 3.9 \times 10^{-4}
\]

\[k\] in M/10 NaOH at 20.0°C = 9.21 \times 10^{-4} sec^{-1} S.D. = 0.4%.

**Sundry Plots for The General Acid Catalysed Hydrolysis of Benzaldehyde Aryl Methyl Acetals.**

**Plot of Intercepts vs \(10^{-pH}\) of all phenyl methyl runs;**

Slope = 4.96 \times 10^1 1 mole^{-1} sec^{-1}
Intercept = 7.42 \times 10^{-4} sec^{-1}, S.D. = 2.6 \times 10^{-3}

for \(\text{log}_{10}\) intercepts vs \(-pH;\)
Slope = .82, S.D. = .025

**Bronsted plot for the acetic( 3 ), formic, and chloroacetic catalysed hydrolysis;**

\[\alpha = .597, \text{ S.D.} = .066\]

**Hammett plot for the m-methyl, -fluoro, -nitro, and hydrogen (3) acetic acid catalysed rates;**

\[\rho = .89, \text{ S.D.} = .08\]
Deuterium Solvent Isotope Effects.

\[
\frac{k_{H_2O}}{k_{D_2O}} = 1.01 \pm 0.03
\]

\[
\frac{k_{\text{CH}_3\text{COOH}}}{k_{\text{CH}_3\text{COOD}}} = 2.14 \pm 0.03
\]

---

**Table 41**

The Hydrolysis of Benzaldehyde Dimethyl Acetal Under The Same Conditions as The Phenyl Methyl Acetal

(conditions as in table 31)

<table>
<thead>
<tr>
<th>(HA) mole (l^{-1})</th>
<th>(k \times 10^4 \text{ sec}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>.20</td>
<td>7.0</td>
</tr>
<tr>
<td>.20</td>
<td>6.6</td>
</tr>
<tr>
<td>1.00</td>
<td>8.3</td>
</tr>
<tr>
<td>1.00</td>
<td>8.7</td>
</tr>
</tbody>
</table>

---

**Table 42**

The Hydrolysis of 2- and 4-Pyridylmethylamino-Acetaldehyde Diethyl Acetal

\(T = 60.0^\circ, I = 0.2, \text{ Acetate Buffers, G.L.C estimated, pH = 5.02}\)

<table>
<thead>
<tr>
<th>Isomer</th>
<th>(k \times 10^5 \text{ sec}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>.54</td>
</tr>
<tr>
<td>2</td>
<td>.91</td>
</tr>
</tbody>
</table>
Graph 1

Graph of $1/(H^+)$ vs $1/k$ for the Hydrolysis of 2-Carboxy Benzaldehyde Diethyl Acetal in 82% Dioxan/Water.

$T = 60.0^\circ$
Graph 2.

pH Rate Profile for the Hydrolysis of 2-Carboxy-Benzaldehyde Diethyl Acetal in 82% Dioxan/Waten

T = 60°
Graph 3
pH - Rate Profile for The Hydrolysis of 3-Nitro 2Methoxy Methoxy Benzoic Acid.

T = 20.0°, I = 0.1
Graph 4
pH - Rate Profile for The Hydrolysis of 3-Methyl 2-Methoxy Methoxy
Benzoic Acid.
$T = 45.0^\circ$, $I = 0.1.$
Graph 5
The Acetic Acid Catalyzed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal.

\[(HA) = 2.5 \,(A^-), \, T = 20.0^\circ, \, pH = 4.36.\]
Graph 6
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

\[(HA) = (A^-), \ pH = 4.68, \ T = 20.0^\circ C.\]
Graph 7
The Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

\[(HA) = (A^-)/2, \; \text{pH} = 4.96, \; T = 20.0^\circ\]
The Deuterio Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

$(DA) = 1.6(A^-), \ pD = 4.84, \ T = 20.0^\circ$
Graph 9

The Deuterio Acetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

$[DA] = \left[\mathcal{A}^{-}\right]$, $pD = 5.18$, $T = 20.0^\circ C$
Graph 10

The Dihydrogen Phosphate Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

\[ (HA) = 2 (A^-), \quad pH = 6.16, \quad T = 20.0 \]
Graph 11
The Formic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal

\[(\text{HA}) = (\text{A}^-)/2, \quad \text{pH} = 3.89, \quad T = 20.0^\circ\]
Graph 12
The Chloroacetic Acid Catalysed Hydrolysis of Benzaldehyde Phenyl Methyl Acetal
\[(HA) = (A^-)/2, \quad \text{pH} = 2.99, \quad T = 20.0^\circ\]
Graph 13

The Acetic Acid Catalysed Hydrolysis of Benzaldehyde m-Tolyl Methyl Acetal

\[(HA) = (A^-), \quad pH = 4.68, \quad T = 20.0^\circ C\]
Graph 14

The Acetic Acid Catalysed Hydrolysis of Benzaldehyde \( m \)-Fluoro-Phenyl Methyl Acetal

\((HA) = (A^-), \quad pH = 4.68, \quad T = 20.0^\circ C\)

\((CH_3CO_2H) \text{ Mole } l^{-1}\)
Experimental Section

Part 1; preparative experimental.

The literature source of well authenticated compounds prepared by simple procedures are not cited. The melting and boiling points of these compounds were obtained from the standard compilations of these data.
GENERAL PROCEDURES.

Several general procedures have been employed in the synthetic work involved in this thesis. These are described below and are referred to by the title given.

Preparation of Acetals by the "Tri Alkyl Orthoformate" Method.

\[ RCHO + HC(OR')_3 \xrightarrow{H^+} R\text{CHO} + HC\text{O}_2R' \]

The procedure is described by Fife and Jao.\(^1\)

Preparation of 1,2-Dioxolanes from the Corresponding Aldehyde.

\[ RCHO + HOCH_2\text{-CH}_2\text{OH} \xrightarrow{H^+} R\text{CH}_2\text{O} + 2\text{H}_2\text{O} \]

The procedure is described by Fife and Jao.\(^1\) Toluene was used exclusively as the entraining solvent.

Preparation of 1,2-Dioxolanes from the Corresponding Dimethyl Acetal.

\[ R\text{CH}_3\text{O} + (\text{CH}_2\text{-CH}_2\text{-CH}_3)_2 \xrightarrow{H^+} R\text{CH}_2\text{O} + 2\text{MeCH} \]

The acetal, in a threefold excess of ethylene glycol and a trace of p-toluene sulphonlic acid, was heated in a Claisen flask until the theoretical quantity of methanol had been collected. The mixture was poured into 2% sodium carbonate solution, the dioxolane extracted with ether, the extract washed with water, dried, and the solvent removed in vacuo. The residue was distilled under reduced pressure to yield the appropriate dioxolane.

Preparation of 4,4,5,5-Tetramethyl Dioxolanes from the Corresponding Aldehyde.

\[ RCHO + HO\text{Me}_2\text{C}_2\text{Me}_2\text{OH} \xrightarrow{H^+} R\text{CH}_2\text{O} \]

The procedure is described by Fife.\(^2\)
Preparation of Methoxy, Methoxy Benzene Derivatives.

\[
\text{IMP} \\
\begin{align*}
\text{ArCH} + \text{NaH} & \rightarrow \text{ArO}^+ + \text{Na}^+ \\
\text{ArO} + \text{ClCH}_3\text{OCH}_3 & \rightarrow \text{ArOCH}_3\text{OCH}_3 + \text{Cl}
\end{align*}
\]

Several solvent systems have been used for this reaction. The author found the following procedure the most useful, yields being almost quantitative even in the case of severely sterically hindered and unreactive phenols.

The phenol (0.1 mole) in dried dimethyl formamide (10 ml.) was added dropwise to a cooled stirred suspension of sodium hydride (0.1 mole) in dried dimethyl formamide (30 ml.) in a flask equipped with an efficient reflux condenser. When hydrogen ceased to be evolved, chloromethyl ether (0.1 mole) was added dropwise over five minutes to the solution. The cooling bath was removed, the solution allowed to warm to room temperature and left to stand for 30 minutes, poured into 2% sodium carbonate solution, extracted with ether, washed thoroughly with N/10 sodium hydroxide (to remove unchanged phenol) then washed several times with water (to remove any residual dimethyl formamide). The ethereal extract was dried, evaporated in vacuo, and the residue either distilled or purified by preparative g.l.c.

This procedure was also used to prepare mixed phenyl alkyl acetals by the reaction of the corresponding α-chloroether with the appropriate phenoxide.

Example.

Preparation of Methyl Esters by the "Diazomethane Method".

\[
\text{CH}_2\text{N}_2 + \text{RCO}_2\text{H} \rightarrow \text{RCO}_2\text{CH}_3
\]

Ethereal diazomethane was prepared by the method of Backer and deBoer. The acid was suspended in ether and the ethereal diazomethane poured in slowly until the solution was no longer acid. The ether was removed under reduced pressure. The residual ester is sufficiently pure for further synthetic work.
Preparation of Esters by the "Methanol Method".

\[
\begin{align*}
\text{RCO}_2\text{H} + \text{MeOH} & \rightarrow \text{RCO}_2\text{Me} + \text{H}_2\text{O} \\
\text{H}^+ & \\
\end{align*}
\]

A solution of the acid in a twentyfold excess of 5% methanolic sulphuric acid was heated under reflux until no carboxylic acid could be detected by t.l.c.. Most of the excess methanol was then removed on a rotary evaporator and the residue poured into cold water. The ester was extracted with an appropriate solvent, the extract dried and the solvent removed in vacuo. The ester was then purified by distillation or recrystallisation, where appropriate.

Preparation of Cyclohexylammonium Salts of Acid Acetals.

\[
\begin{align*}
\text{RCO}_2\text{Me} & \xrightarrow{\text{a)Ba(CH)}} \text{Ba(CN)}_2 \\
\text{b)(C}_6\text{H}_{11}\text{NH}_3 \text{SO}_4 & \rightarrow \text{RCO}_2\text{C}_6\text{H}_{11}\text{NH}_3 \\
\end{align*}
\]

Approximately 1g. of the ester was accurately weighed in a tared flask. An exactly equivalent volume of standardised barium hydroxide solution (ca. 0.4N) was introduced from a burette. The solution was shaken mechanically until clear and neutral. An exactly equivalent amount of N/10 cyclohexylammonium sulphate solution was added from a burette and the precipitated barium sulphate removed by centrifuging and decantation. The aqueous solution of the salt was freeze-dried and the residual salt recrystallised, usually from methanol-ether.

This technique is very useful where the acid acetal is too unstable to be isolated by acidifying the solution resulting from alkaline hydrolysis. Furthermore this procedure gives a useful increase in molecular weight when handling small quantities and the salts are usually highly crystalline, but have rather indefinite melting points.

Preparation of Aromatic Nitriles.

\[
\begin{align*}
\text{CuCN} & \\
\text{ArBr} & \rightarrow \text{ArCN} \\
\text{IMF} & \\
\end{align*}
\]

The procedure of Friedman and Schechter was employed. It was found to be very important to follow the reaction to completion by t.l.c., since prolonged reaction times gave large amounts of evil-smelling black tars.
Preparation of Aliphatic Nitriles.

\[
\text{RCN} \quad \begin{array}{c} \text{DMSO} \\ \text{Im SO} \end{array} \quad \text{NaCN} \quad \rightarrow \quad \text{RCN} \quad \text{NaCl}
\]

The procedure of Friedman and Schechter\(^6\) was used, except that the washing with 6N HCl was omitted.

Preparation of Amides from Nitriles.

\[
\begin{array}{c}
\text{RCN} \\
\text{H}_2\text{O} / \text{NaOH/EtOH} \\
60^\circ
\end{array} \quad \rightarrow \quad \text{RCONH}_2
\]

This method of the hydrolysis of aromatic nitriles is described by Vogel\(^{17}\) in the preparation of \(\alpha\)-toluamide.

4-Aminobutyraldehyde Diethyl Acetal.

a) \(\text{ClCH}_2\text{CH}_2\text{CH(OEt)}_2 \quad \text{NaCN} \quad \text{DMSO} \quad \rightarrow \quad \text{NCCH}_2\text{CH}_2\text{CH(OEt)}_2\)

b) \(\text{NCCH}_2\text{CH}_2\text{CH(OEt)}_2 \quad \text{Na} \quad \text{EtOH} \quad \rightarrow \quad \text{H}_2\text{NCH}_2\text{CH}_2\text{CH(OEt)}_2\)

a) 3-Chloropropionaldehyde diethyl acetal was converted to the nitrile by the general method for aliphatic nitriles:

\[b^6 86-87^\circ \text{ (lit.}^7, b^5 84^\circ)\]

IR (neat) \(\nu \text{ cm}^{-1}\)

2220m (\(\text{C} = \text{N} \) str.); 1190, 1120, 1050 (v.s.) (acetal \(\text{C-O-C} \) str.).

The nitrile was reduced to the amine by sodium and ethanol.\(^8\)

The separation of the amine from unreduced nitrile by fractional distillation was very difficult, so the distillate was subjected to the reducing conditions once more, distillation again gave a centre cut \(b^9 81-81.5^\circ \) (lit.\(^9, b^{10-11} 83-83.7^\circ\) which showed no nitrile peak in the i.r. spectrum.

IR (neat) \(\nu \text{ cm}^{-1}\)

3375m, 3290m, 3280 str. (primary \(\text{NH} \) str.); 1120v.s., 1050v.s., 1000v.s. (acetal \(\text{C-O-C} \) str.).
**NMR (neat)**

\[
E \quad F \quad E \quad D \quad C \quad B' \quad A
\]

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Multiplet Type</th>
<th>Coupling Constants (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67Hz</td>
<td>triplet</td>
<td>( J_{ab} ) (8)</td>
</tr>
<tr>
<td>7Hz</td>
<td>triplet</td>
<td>( J_{ab} ) (2)</td>
</tr>
<tr>
<td>157Hz</td>
<td>triplet</td>
<td>( J_{ab} ) (1)</td>
</tr>
<tr>
<td>180-225Hz</td>
<td>complex</td>
<td></td>
</tr>
<tr>
<td>265Hz</td>
<td>triplet</td>
<td></td>
</tr>
</tbody>
</table>

Attempted Preparation of Succinaldehydic Acid Diethyl Acetal from the Nitrile.

The crude potassium salt of the acid was prepared by the hydrolysis of the nitrile by the method of Wohl and Schweizer\(^\text{10}\). The salt was dissolved in chloroform and the resultant solution washed with 0.1M HCl, water, dried and evaporated *in vacuo* at room temperature. The resultant oil showed only a carboxylic acid carbonyl absorption in the region 2000-1600 cm\(^{-1}\) in the i.r. and distillation in a molecular still gave a liquid whose i.r. and n.m.r. spectra were consistent with those expected for the acid acetal. Titration of the acid gave an equivalent weight consistent with the structure. However, analyses were both variable and inconsistent. I.r. spectra showed that the acetal decomposed slowly to \(\gamma\)-ethoxy \(\gamma\)-butyrolactone over several days. Fire\(^\text{11}\) and Motoki et al.\(^\text{7}\) have shown that this transformation proceeds readily at slightly elevated temperatures.

**Preparation of the Cyclohexylammonium Salt of Succinaldehydic Dimethyl Acetal.**

a) \[
\text{MeOH} \rightarrow \begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
\end{array}
\]

b) \[
\text{SOCl}_2 \rightarrow \begin{array}{c}
\text{OCH}_3 \\
\text{Cl} \\
\end{array}
\]

c) \[
\text{Rosemund redn.} \rightarrow \begin{array}{c}
\text{OCH}_3 \\
\text{CHO} \\
\end{array}
\]

d) \[
\text{HC(OMe)}_3 \stackrel{\text{MeOH/H}}{\rightarrow} \begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
\end{array}
\]

e) \[
\text{Ba(OH)}_2 \rightarrow \begin{array}{c}
\text{OCH}_3 \\
\text{OCH}_3 \\
\text{C}_6\text{H}_{11}\text{NH}_3 \\
\end{array}
\]

\(i\) \(\text{Ba(OH)}_2\) 

\(i\text{i} \) \(2(C_6\text{H}_{11}\text{NH}_3)\text{SO}_4\)
Steps a), b), and c) were carried out by the procedures given in Organic Syntheses.\textsuperscript{12} The Rosemund reduction of the acid chloride was very difficult, and even with no catalyst poison, reduction was slow and incomplete. In an attempt to separate the aldehyde from unchanged acid chloride by fractional distillation extensive polymerisation occurred. Similar difficulties in the Rosemund reduction of succinic acid half-ester acid chlorides have been encountered by other workers.\textsuperscript{13} The residue from a second reduction was flash-distilled and the aldehyde converted to the acetal by the "triethyl orthoformate method" and separated from the dimethyl succinate resultant from the reaction of the acid chloride present with solvent, by fractional distillation.

Overall yield 10\% \( b_{11} \) 80-81°C (lit.\textsuperscript{14} \( b_{11} \) 79-80.5°C)

e) The ester was converted to the cyclohexylammonium salt of the acid by the general procedure, m.p. 77-79°C

\( \text{IR (Nujol mull) } \nu \text{ cm}^{-1} \)

1620\( \text{cm}^{-1} \) (NH\textsuperscript{+}); 1540s, broad (CO\textsuperscript{-}); 1150s, 1050s (acetal C-O-C str.)

\( \text{NMR (DMSO-}d_6) \)

50-130Hz. (ca. 15 protons); cyclohexylammonium and NH\textsuperscript{+} protons; 193Hz. (6) methoxyl protons; solubility and viscosity problems prevented the assignment of the protons of the acetal chain.

(Found: C, 58.2; H, 9.95; N, 5.55 C\textsubscript{12}H\textsubscript{25}NO\textsubscript{4} requires: C, 58.3; H, 10.1; N, 5.65 %)

Butyraldehyde Dimethyl Acetal.

Butyraldehyde (0.1 mole), methanol (300 ml.) and p-toluene sulphonic acid (1 g.) were heated under reflux for 30 minutes after which g.l.c. showed that about 75% conversion had taken place. Saturated sodium carbonate solution (50 ml.) was added to neutralise the acid, excess methanol was removed on a rotary evaporator, the residue taken up in ether, washed with water, dried, and the ether removed on a water bath. The residue was distilled through a 30 theoretical plate spinning band column and a centre cut \( b_{750} \) 114-114.2°C (lit.114°C) was taken.
2-Pyridyl Methyl Amino Acetaldehyde Diethyl Acetal.

This was supplied by the Aldrich Chemical Company and was distilled before use.

\[ \text{NMR (CDCl}_3\text{)} \]

Triplet 69Hz., \( J_{ab} \) 7Hz.(6), 10; 146Hz.(1), 6; complex multiplet 212Hz.(4), 9a and 9b; 230Hz.(2), 5; triplet 273Hz., \( J_{ab} \) 6Hz.(1), 8; complex multiplet 448Hz.(3), 2, 3 and 4; hyperfinely split doublet 517Hz.(1), 1.

4-Pyridyl Methyl Amino Acetaldehyde Diethyl Acetal.

This was supplied by the Aldrich Chemical Company and was distilled before use.

\[ \text{NMR (CDCl}_3\text{)} \]

Triplet 71Hz., \( J_{ab} \) 7Hz.(6), 10; broad unsymmetrical doublet 161Hz.(3), 7 and 6; complex multiplet 217Hz.(2), 5; 228Hz.(2), 5; triplet 273Hz., \( J_{ab} \) 6Hz.(1), 8; hyperfinely split doublet 441Hz.(2), 3 and 4; broad doublet 527Hz.(2), 1 and 2.

The Cyclohexylammonium Salt of D-Threo Tetruronic Acid Dimethyl Acetal.

The methyl ester dimethyl acetal was made by the method of Gorin and Perlin\(^{15}\) and converted to the cyclohexylammonium salt of the acid by the general procedure. The salt crystallises from methanol but is extremely hygroscopic.

\[ \text{IR (Nujol mull)} \text{ } \nu \text{ cm}^{-1} \]

3400, \( \nu \) broad (OH str.); 1600, broad (OH def. and \( \tilde{\nu} \) and \( \tilde{\nu}_2 \) carbonyl str.); 1125s, 1060s, 1000, (acetal C-O-C str.).
NMR (Pyridine)

The peaks in the spectrum were very broad, probably due to the high viscosity of the solution. 50-120 Hz. (11) cyclohexyl protons; 120-160 Hz. (5) OH and NH protons exchanging; 206 Hz. (6), OCH protons; 265-305 (3) protons of aliphatic chain.

A satisfactory and consistent analysis could not be obtained, possibly due to its extremely hygroscopic nature. A quantitative estimation of the methanol produced on hydrolysis gave a molecular weight (assuming 2 moles of MeOH produced per mole of substrate) of 245.3; C_{12}H_{25}NO_4 requires 247.0.

D-Glyceraldehyde Dimethyl Acetal.

This was prepared by Dr. D. Thacker of Birkbeck College, London University.

α-Car bamoyl Benzaldehyde Diethyl Acetal.

\[
\begin{align*}
\text{CHO} & \quad \text{HC(OEt)_3} \quad \text{EtOH/H+} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{CH(OEt)_2} & \quad \text{CuCN} \quad \text{DMF 140°} \\
\text{Br} & \quad \text{CN}
\end{align*}
\]

\[
\begin{align*}
\text{CH(OEt)_2} & \quad \text{NaOH/H_2O_2} \quad \text{EtOH} \\
\text{CN} & \quad \text{NH}_2
\end{align*}
\]

a) α-Bromobenzaldehyde was converted to the diethyl acetal in quantitative yield by the "triethyl orthoformate method".

b) 95-98°

IR (neat) \nu cm⁻¹

1110, 1050, 1015 (acetal C-O-C str.); 750 (α-disubstituted benzene).

NMR (neat)

Triplet 70 Hz., J_{ab} 7 Hz. (6), CH₃ of ethyls; quartet 215 Hz., J_{ab} 7 Hz. (4), CH₂ of ethyls; 343 Hz. (1), acetal proton; typical substituted aromatic pattern 415-478 Hz. (4).
b) The bromo acetal was converted to the nitrile (65-75%) by the general method for the preparation of aromatic nitriles. I.r. and n.m.r. spectra were satisfactory for this compound but analyses were not. G.I.c. of the product showed that about 10% of starting halide was present. This proved impossible to remove on the small scale employed, (0.05 mole), and the crude material was used in the next step.

c) The nitrile was partially hydrolysed by the general procedure for the preparation of aromatic amides, to give α-carbamoyl benzaldehyde diethyl acetal (65%) m.p. 104-104.5° from ether-petrol.

IR (Nujol mull) ν cm^−1

3350m, 3160m (amide NH str.); 1645m, 1620m (amide bands I and II); 1595m, 1575m (aromatic C=O str.) 1115s, 1060s, 1020s (acetal C-O-C str.)

NMR (CDCl_3)

Triplet 70Hz., J_αβ 7Hz. (6), CH_3 of ethoxyls; quartet 228Hz., J_αβ 7Hz. (4), CH_2 of ethoxyls; 346Hz. (1), acetal proton; broad singlet 423Hz. (2), amide NH; 420-460Hz. (4), α-disubstituted benzene pattern.

(p-Carbamoyl Benzaldehyde Diethyl Acetal.

\[
\text{CHO} \quad \text{HO(OEt)}_3 \quad \text{CN} \quad \text{NaOH/H}_2\text{O}_2/\text{EtOH} \quad \text{CONH}_2
\]

\[
\text{CH(OEt)}_2 \quad 60^\circ \quad \text{CH(OEt)}_2
\]

(p-Cyanobenzaldehyde (0.01 mole) was converted to the diethyl acetal by the "triethyl orthoformate method" and the crude acetal used in the next step. The nitrile acetal was converted to the amide, (90% overall), using the normal procedure.

(m.p. 104-105° from benzene.)
IR (Nujol mull) ν cm⁻¹

3370m, 3165m (amide NH str.); 1650s, 1622s (amide bands I and II); 1571 (aromatic C=C); 1215s, 1195s, 1075s (acetal C-O-C str.); 850s (α-subst.).

NMR (CDCl₃)

Triplet 74Hz., Jₜₑₜ 7Hz.(6), CH₃ of ethoxyls; quartet 215Hz., Jₜₑₜ 7Hz.(4), CH₂ of ethoxyls; 332Hz.(1), acetal proton; broad singlet 400Hz.(2), amide protons; A' A'B' B' system centred on 463Hz.(4), aromatic protons.

(Found: C, 64.2; H, 7.35; N, 6.25; C₁₂H₁₇NO₃ requires C, 64.55; H, 7.65; N, 6.3 %)

3-Hydroxynaphthalimidine.

This was prepared by the reduction of phthalimide with magnesium and ammonium chloride in methanol according to the procedure of Dunet and Willemart.¹⁸

m.p. 171-172°

IR (KBr disc) ν cm⁻¹

3350m (CH str.); 3180m, 3075 (NH str. of imide); 1705s (5-membered ring lactam C=O str.); 1615s (aromatic C=C str.); 1060s (C-O str. of C=O-H).

3-Ethoxynaphthalimidine.

This was prepared by the method of Dunet and Willemart.¹⁹

M.p. 104-104.5° from ethanol water.

IR (KBr disc) ν cm⁻¹

3300-3000m (NH str. of imide); 1710s (C=O str. of 5-membered ring lactam); 1620m, 1605w (aromatic C=C); a complex of 8 sharp symmetrical peaks centred on 1090m. and sₜₑₜ,(C-O-Et stretching modes); 750s (α-subst.).

NMR (CDCl₃)
Triplet $7\text{Hz.}, J_{ab} 7\text{Hz.}(3)$, $a$; quartet $211\text{Hz.}, J_{ab} 7\text{Hz.}(2)$, $b$; $347\text{Hz.}(1)$, $c$; complex pattern $430-475\text{Hz.}(4)$, $e$, $f$, $g$ and $h$. The NH proton resonance appeared to be lost in the noise.

**Attempted Preparation of α-Carboxy Benzaldehyde Diethyl Acetal from the Amide.**

α-Carbamoyl benzaldehyde diethyl acetal (0.01 mole) was heated under reflux with a fivefold excess of N/10 sodium hydroxide until the solution was homogeneous and ammonia no longer evolved. The solution was cooled in ice salt, covered with ether, very rapidly stirred and acidified to pH 3.6 with N/10 hydrochloric acid. The ethereal layer was separated, dried and the ether removed at 0°C in vacuo to leave a mixture of phthalaldehydic acid and its 1-ethyl ester (t.l.c. and i.r.). A similar attempt to prepare the barium salt by hydrolysis with barium hydroxide solution, followed by removal of excess barium hydroxide with carbon dioxide and freeze-drying of the centrifuged supernatent liquor gave 3-ethoxyphthalide as the only recognisable organic material.

In view of the difficulties encountered in trying to isolate the acid or an inorganic salt, it was decided to prepare totally organic salts.

**Preparation of the Cyclohexylammonium Salt of 2-Carboxy Benzaldehyde Diethyl Acetal.**

a) Methyl 2-formylbenzoate was prepared by the method of Bender et al. except that it was found more convenient to separate the true ester from any 3-methoxyphthalide formed by fractional distillation rather than fractional freezing.

$125$ \begin{align*}
\begin{array}{ccc}
\text{OH} & \xrightarrow{\text{CH}_2\text{N}_2} & \text{CHO} \\
& & \text{Con}_{2}\text{Me} \\
\text{CO}_2\text{Me} & \xrightarrow{\text{HCl(OEt)}_2} & \text{CH(OEt)}_2 \\
\text{CO}_2\text{Me} & \xrightarrow{\text{Ba(OH)}_2} & \text{CH(OEt)}_2 \\
& \xrightarrow{\text{C}_{6}\text{H}_{11}\text{NH}_3\text{SO}_4} & \text{C}_{6}\text{H}_{11}\text{NH}_3 \\
\end{array}
\end{align*}

b) $135-133°$ (lit. 136-138°)
b) The aldehyde was converted to the diethyl acetal by the "triethyl orthoformate method".

\[ \delta_{0.3} 104 - 105^\circ \]

IR (neat) \( \nu \) cm.\(^{-1} \)

1715s (C=O str. of aromatic ester); 1270s (C-OR str. of aromatic ester); 1100s, 1050s, 1015s (acetal C-O-C str.).

NMR (neat)

Triplet 72Hz., \( J_{\text{ab}} 7 \text{Hz.}(6) \), \( \text{CH}_3 \) of ethoxyls; quartet 217Hz., \( J_{\text{ab}} 7 \text{Hz.}(4) \), \( \text{CH}_2 \) of ethoxyls; 231Hz.(3), \( \text{CH}_3 \) of ester; 372Hz.(1), acetal proton; Substituted pattern 435-476Hz.(4), aromatics.

(Found: C,65.2; H,7.8. \( \text{C}_{13}\text{H}_{18}\text{O} \) requires C,65.55; H,7.6 %)

c) The ester was converted to the cyclohexylammonium salt of the acid by the general procedure.

M.p. 191-192° from methanol-ether.

IR (Nujol mull) \( \nu \) cm.\(^{-1} \)

1625m (NH\(_3\)); 1520 (carbonyl str. of carboxylate ion); 1115, 1080, 1045, 1020 (acetal C-O-C str.); partially resolved doublet 735-750 (\( \gamma \)-subst.).

NMR (DMSO-\( d_6 \))

Triplet 63Hz., \( J_{\text{ab}} 6 \text{Hz.}, \) \( \text{CH}_3 \) of ethoxyls; superimposed on broad absorption 30-190Hz. (20 in all) due to cyclohexylammonium resonances; apparent octet, 210Hz.(4), \( \text{CH}_2 \) of ethoxyls; 376Hz.(1), acetal proton; typical \( \gamma \)-subst. pattern 430-470Hz.(4), aromatics.

(Found: C,66.75; H,8.85; N,4.35. \( \text{C}_{23}\text{H}_{29}\text{NO} \) requires C,66.85; H,8.95; N,4.35 %)
127

3-Ethoxyphthalide.

This was prepared by the method of Bender et al., substituting ethanol for methanol.

M.p. 64.5-65° from ethanol-water. Lit. 64-65°

Terephthalaldehyde Diethyl Acetal, Cyclohexylammonium Salt.

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{HO(OEt)}_3} \text{Ba(OH)}_2 \\
\text{EtOH/H}^+ & \text{Ba(OH)}_2 \\
\end{align*}
\]

a) Terephthalaldehyde acid ethyl ester diethyl acetal was prepared from the ethyl ester aldehyde by the "triethyl orthoformate method:"

\[
\text{B}^0.3 \text{ 110-112°}
\]

IR (neat) \( \nu \text{cm}^{-1} \)

1722s (C=O str. of ester); 1260s (C-O-R str. of aromatic ester); 1110s, 1050s, 1020m (acetal C-O-C str.); 760m (\( \alpha \)-subst.).

NMR (neat)

Apparent quartet consisting of 2 exactly overlapping triplets at 71Hz. and 78Hz., both \( J_{\text{ab}} \) 7Hz.(9), acetal \( \text{CH}_3 \) 71Hz. and ester \( \text{CH}_3 \) 78Hz.; quartet 211Hz., \( J_{\text{ab}} \) 7Hz.(4), \( \text{CH}_2 \) of acetal ethyls; quartet 255Hz.(2), \( \text{CH}_2 \) of ester ethyl; 330Hz.(1), acetal proton; A A' B' system, 448Hz., 456Hz., 478Hz., 486Hz. (aromatics).

(Found: C,66.7; H,7.95. C_{14}H_{20}O_4 requires C,67.1; H,8.1 %)

b) The ester was hydrolysed to give the cyclohexylammonium salt by the standard procedure.

M.p. 117-120°

IR (KBr disc) \( \nu \text{ cm}^{-1} \)

2960m (\( \text{CH}_2 \) str.); 3220-2500m (\( \text{NH}_3^+ \) str.); 1618m (\( \text{NH}_3^+ \)); 1540m, broad (carbonyl str. of carboxylate ion); 1400s (\( \text{CH}_2 \) def.); 1120s, 1060s, 1020s (acetal C-O-C str.).
NMR (DMSO-d_6 at 60°)

Triplet 1.16 ppm., J_{ab} 7 Hz., (CH_3 of ethyl acetal) superimposed on broad absorption 0.3 to 2.2 ppm., CH_2's of cyclohexyl ring, (17 in all); quartet 3.6 ppm., J_{ab} 7 Hz., (4), CH_2 of ethyl acetal; 5.55 ppm., (1), acetal proton; A 'X X' system centred on 7.75 ppm., (4), aromatics.

(Found: C, 66.7; H, 8.8; N, 4.3. C_{25}H_{29}NO requires C, 66.85; H, 8.95; N, 4.35 %)

2-Phenyl-1,3-dioxolane.

This was prepared by the method of Fife and Jao; its n.m.r. and i.r. are discussed in the section dealing with acetal characterisation.

2-(o-Carbamoylphenyl)-1,3-Dioxolane.

a) o-Bromobenzyl bromide (95%) was prepared by the photo-bromination of o-bromotoluene in carbon tetrachloride.

b) CuCN

d) H_2O_2, NaOH

e) Br, 72.8. C_{15}H_{14}Br_3 requires C, 25.5; H, 1.52; Br, 73.0 %)
b) α-Bromobenzal bromide (0.5 mole) was added cautiously to a stirred solution of sodium methoxide (1.0 mole) in methanol (600 ml.). The solution was heated under reflux overnight. The then neutral solution was filtered from the precipitated sodium bromide and excess methanol removed on a rotary evaporator. The residual oil was dissolved in chloroform and the resultant solution washed several times with water, dried, the solvent removed in vacuo and the residue distilled to give α-bromobenzaldehyde dimethyl acetal (90%). B° 96°

IR (neat) $\nu \text{ cm}^{-1}$

2920s (CH str. of methoxyl); 2800w (CH str. of acetal proton); 1105s, 1075s, 1015s (C=O-C str. of acetal); 750s (α-subst.).

NMR (neat)

295Hz.(6), methoxyl; 333Hz.(1), acetal proton; 410-470Hz.(4), aromatics.

(Found: C,46.9; H,4.93; Br,34.71. C$_{9}$H$_{11}$BrO$_{2}$ requires C,46.75; H,4.75; Br,34.65%)

c) α-Bromobenzaldehyde dimethyl acetal (0.1 mole) was converted into 2-(α-bromophenyl)-1,3-dioxolane by the standard procedure and on distillation gave a forerun of α-bromobenzaldehyde, followed by a main fraction (50%) of the dioxolane, B° 90-92°

IR (neat) $\nu \text{ cm}^{-1}$

1121s, 1085s, 1040s, 1020s (dioxolane ring C=O-C str.); 750 (α-subst.).

(Found: C,47.1; H,4.05; Br,34.9. C$_{9}$H$_{9}$BrO$_{2}$ requires C,47.15; H,3.9; Br,34.95%)

d) The bromo-dioxolane was converted to the cyano-dioxolane by the standard procedure.

B° 122° M.p. 30-31° from petrol.

IR (melt between NaCl plates) $\nu \text{ cm}^{-1}$

2220s (nitrile); complex peaks 1120-1000 all strong (dioxolane C=O-C str.); 760s (α-subst.).
NMR (CDCl₃)

Decet 246Hz.(4), dioxolane CH₂ protons; 359Hz.(1), acetal proton; 230-27Hz.(4), aromatics.

(Found: C,68.5; H,5.25; N,7.05. C₁₀H₇NO₂ requires C,68.56; H,5.18; N,8.00 %).

e) The nitrile was converted to the amide by the standard procedure.

M.p. 131-132° from methylene chloride.

IR (Nujol mull) \(\nu\) cm⁻¹

3480m, 3380m, 3200m (amide NH str.), 1615m broad, (amide carbonyl str.)

NMR (acetone-d₆)

Complex multiplet 24CH₂.(4), dioxolane CH₂ protons; 373Hz.(1), acetal proton; 395-429Hz.(2), amide NH₂ proton; 435-468Hz.(4), \(\alpha\)-subst., aromatics.

(Found: C,62.2; H,5.8; N,7.25. C₁₀H₉NO₂ requires C,62.15; H,5.8; N,7.25 %).

2-(\(\alpha\)-Carbamoylphenyl)-1,2-Dioxolane.

\[
\begin{align*}
\text{CHO} & \quad \text{CH₃} \\
\text{C=N} & \quad \text{CH₂} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

a) \(p\)-Cyanobenzaldehyde was converted to the dioxolane by the standard procedure and the crude product used in the next step.

b) The nitrile was converted to the amide by the standard procedure, m.p. 158-158.5° from methylene chloride.

IR (Nujol mull) \(\nu\) cm⁻¹

3485m, 3180m (NH str. of amide); 1645m (amide C=O str.); 1028s (C-O-C of dioxolane ring); 850 (\(p\)-subst.).
NMR (acetone-d$_6$)

243Hz. (4), CH$_2$s of dioxolane ring; 350Hz. (1), acetal proton; A $\Delta'X\ X'$ system, 450-476Hz. (4), p-subst. aromatics.
(Found: C, 61.8; H, 5.85; N, 7.1. C$_{10}$H$_{11}$NO$_3$ requires C, 62.15; H, 5.8; N, 7.25%).

2-(a-Carboxyphenyl)-1,3-Dioxolane. Cyclohexylammonium Salt.

a) 2-(a-Carbomethoxyphenyl)-1,3-dioxolane was prepared from methyl 2-formylbenzoate by the standard procedure and the crude ester converted to the cyclohexylammonium salt of the derived acid by the standard procedure.
M.p. 173-174° from methanol ether.

IR (KBr disc) cm$^{-1}$

3200-2500s (CH$_2$ and NH$_3$ str.); 1630 (NH$_3$); 1560m (carbonyl str. of carboxylate); 1375s (CH$_2$ scissoring); 1110s, 1070s (C-O-C str. of dioxolane ring); 750 (o-disubst.).

NMR (DMSO-d$_6$)

40-130Hz. (14), CH$_2$s and NH$_3$ of cyclohexylammonium; broad doublet 235Hz., $\delta$3Hz. (4), CH$_2$s of dioxolane ring; 320-465Hz. (5), aromatics and acetal proton.
(Found: C, 65.5; H, 8.2; N, 4.85. C$_{16}$H$_{23}$NO$_4$ requires C, 65.5; H, 8.2; N, 4.8%).

2-(p-Carboxyphenyl)-1,3-Dioxolane.
a) 2-(p-Carboxyphenyl)-1,3-dioxolane (90%) was prepared by the method of Fieser, Fields and Lieberman. The ester (1.0 g.) was shaken with N/10 sodium hydroxide (75 ml.) until the solution was clear. The solution was cooled in ice, covered with ether, vigorously stirred and the solution acidified with N/10 hydrochloric acid to pH 3.0. The ether layer was separated, dried, the solvent removed in vacuo and the residue recrystallised from ether (90%). M.p. 168-169°.

IR (Nujol mull) \(\nu\) cm\(^{-1}\)

1690s (C=O str. of CO\(_2\)H); 1295s (C=O str. of CO\(_2\)H); 1073s, 1020s (C-O-C str. of dioxolane ring); 850s (p-subst.).

NMR (CDCl\(_3\))

246Hz.(4), dioxolane CH\(_2\)s, 305Hz.(1), acetal proton; A A' B' system 436, 444, 453, 461Hz.(4), p-subst. aromatics; 667Hz.(1), removed on shaking with D\(_2\)O, CO\(_2\)H proton.

(Found: C,61.8; H,5.35. C\(_{10}\)H\(_{10}\)O\(_4\) requires: C,61.85; H,5.2 %)

2-(p-Carboxyphenyl)-4,4,5,5-Tetramethyl-1,3-Dioxolane.

All attempts to prepare the methyl ester of this compound by the standard procedure, from methyl 2-formylbenzoate and pinacol, failed. The following route was devised.

a)  

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{\text{pinacol}} \quad \text{Br} \\
\text{Br} & \quad \xrightarrow{H^+} \quad \text{Br}
\end{align*}
\]

b)  

\[
\begin{align*}
\text{Br} & \quad \xrightarrow{i) \text{Mg/THF}} \quad \text{CHO} \\
\text{CHO} & \quad \xrightarrow{\text{ii) OC(OEt)}_2} \quad \text{Br}
\end{align*}
\]

c)  

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \xrightarrow{i) \text{NaOH}} \quad \text{CHO} \\
\text{CHO} & \quad \xrightarrow{\text{ii) HCl}} \quad \text{CO}_2\text{Et}
\end{align*}
\]
a) o-Bromobenzaldehyde was converted to the corresponding tetramethyl dioxolane (90%) by the standard procedure and purified by distillation. The distillate solidified in the receiver.

\[ \text{B.p. 112-113}^\circ \text{ M.p. 67-69}^\circ \text{ from 40/60 petrol.} \]

IR (CCl\textsubscript{4}) ν cm\textsuperscript{-1}

The i.r. spectrum is extremely complex; the most characteristic peak is at 2880 cm\textsuperscript{-1}, the CH stretching frequency of an acetal CH.

NMR (CCl\textsubscript{4})

Apparent doublet 75 and 78 Hz. (12), CH\textsubscript{2}s of tetramethyl dioxolane; 373 Hz. (1), acetal proton; multiplet 416-460 Hz. (4), \( \alpha \)-subst. aromatics.

(Found: C, 54.85; H, 5.95; Br, 28.25. \( \text{C}_{13}\text{H}_{17}\text{BrO}_2 \) requires: C, 54.75; H, 5.95; Br, 28.05 %)

b) This method for the preparation of esters from the Grignard reagents of bulky \( \alpha \)-substituted bromobenzenes is described in Organic Syntheses. Considerable difficulty was encountered in this preparation; the Grignard reagent could not be prepared in ether and went only to 50% completion, using THF as solvent. The incomplete reaction mixture was decanted from the unreacted magnesium and ethyl carbonate added. In contrast to a control preparation of ethyl \( \alpha \)-toluate, where the reaction is extremely exothermic, this reaction was very slow. The reaction mixture was heated under reflux overnight and worked up using saturated ammonium chloride solution to decompose the magnesium complexes. The crude product was fractionally distilled under reduced pressure, but it proved impossible to separate the desired product from the unreacted bromo-dioxolane.

The i.r. spectrum showed a typical aromatic ester carbonyl absorption at 1720 cm\textsuperscript{-1} and the n.m.r. a typical ethyl ester triplet and quartet at 73 and 256 Hz. (J\textsubscript{ab} 7 Hz.) respectively. It was estimated from the integrated spectrum that the distilled product contained approximately 70% of the required ester. This was confirmed by g.l.c. of the mixture.
c) The crude ester (2.5 g.) was shaken with sufficient N/1 carbonate-free sodium hydroxide solution to react with the estimated amount of ester present until the mixture was neutral to brilliant orange indicator paper (pH 9-9.5). The residual organic material was removed with ether and the resultant clear solution cooled to 0°, acidified with N/10 hydrochloric acid to pH 3-2, rapidly extracted with ether, the ethereal extract dried and evaporated to yield the required acid (30% overall), m.p. 67-68°.

IR (CCl₄) \(\text{cm}^{-1}\)

Broad absorption 3520-2900s, (CH and OH str. of carboxylic acid); 1700s, (dimeric aromatic carboxylic acid C=O str.); 1460s, (asymmetric methyl bending); 1400s (symmetric methyl bending); 1300s, (asymmetric C-O-C str. of aromatic ester); 1150s (symmetric C-O-C str. of aromatic ester); 1100, 1060, 1000s, (dioxolane ring C-O-C str.).

NMR (CDCl₃)

Apparent doublet 74 and 79Hz. (12), CH₃s of dioxolane ring; 405Hz. (1), acetal proton; multiplet 421-490Hz. (4), \(\text{a-subst. aromatics}\); 619Hz. (1), broad, removed on shaking with D₂O, OH of carboxylic acid.

(Found: C, 67.05; H, 7.25. C₁₄H₁₈O₂ requires C, 67.15; H, 7.25 %)

2-(p-Carboxyphenyl)-4,4,5,5-Tetramethyl-1,3-Dioxolane.

a) Methyl 4-formylbenzoate was converted to the tetramethyl dioxolane by the standard procedure.

M.p. 53-54° from petrol.
IR (CCl₄) $\tilde{\nu}$ cm⁻¹

2980 and 2950m (asymmetric CH₃ str.); 2865w (symmetric CH₃ str.); 1720s (aromatic ester C=O str.); 1430m, sharp (asymmetric CH₂ def.); doublet 1396, 1370m (geminal CH₂s); 1275 and 1260s (asymmetric and symmetric C–O–C str. of aromatic ester); 1110, 1080, 1020s (acetal C–O–C–O–C str.).

NMR (CDCl₃)

Apparent doublet 72 and 77JHz (12) CH₃s of dioxolane ring; 233Hz. (3), methyl ester; 361Hz. (1) acetal proton; A A'B' B' system 451, 459, 461, 489Hz. (4), p-subst. aromatics.

(Found: C, 68·0; H, 7·6. C₁₅H₁₉O₄ requires: C, 68·15; H, 7·65 %)

b) The ester was converted to the corresponding acid by the standard procedure.

M.p. 168–170° from cyclohexane.

IR (KBr disc) $\tilde{\nu}$ cm⁻¹

3500–2800 (OH and CH str.); 1700s (C=O str. of dimeric aromatic carboxylic acid); 1450m (asymmetric methyl def.); 1290m (asymmetric C–O–C str. of aromatic ester); 1150m (symmetric C–O–C str. of aromatic ester); 1080, 1020m (C–O–C–O–C str. of dioxolane ring); 860m (p-subst. aromatics).

NMR (CDCl₃)

Apparent doublet 75 and 78JHz. (12) CH₃s of dioxolane ring; 363Hz. (1) acetal proton; A A'B' B' system 453, 462, 485, 495Hz. (4), p-subst. aromatics; 619Hz. (1), broad, removed on shaking with D₂O, carboxylic acid proton.

(Found: C, 67·0; H, 7·35. C₁₄H₁₈O₄ requires: C, 67·2; H, 7·25 %)

3-(2-Hydroxy-1,1,2,2-Tetramethyl Ethoxy) Phthalide.

\[ \text{pinacol/H}^+ \text{ toluene} \]
Phthalaldehydic acid (0.03 mole), pinacol (0.03 mole), p-toluene-sulphonic acid (1 mg.) and toluene (10 ml.) were heated under reflux in a Dean and Stark apparatus. Immediately after the stoichiometric amount of water had been collected, (5 min.), the heater was turned off and the solution allowed to cool to ambient temperature. The white crystalline solid which formed was filtered to give a near quantitative yield of 2-(α-carboxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane (m.p. and i.r. comparison). This is one of the few reported examples of the formation of a "normal" derivative of phthalaldehydic acid. The reaction was repeated using benzene as the entraining agent and the reaction refluxed for several hours. Samples were withdrawn every hour and the i.r. spectrum recorded, the carboxylic acid dimer carbonyl absorption decreasing with time and a typical 6-lactone absorption at 1785 cm⁻¹ appearing and increasing. When the reaction was complete, (ca. 7 hours), the solution was allowed to cool overnight. The desired product crystallised (60%), m.p. 242-3°. The same product may be obtained by sublimation of the initially formed acid at 180°.

IR (KBr disc) 2υ cm⁻¹

Broad peak, 3500m (OH str.); doublet 1760, shoulder at 1780, (definitely 5-membered ring lactone 0=0 str. but complexity uncertain).

NMR (CDCl₃)

Apparent doublet 92 and 96Hz (12), CH₃'s of aliphatic chain, moved 10Hz. down field from corresponding ring compounds; 40Hz. (1), proton at 0-3; multiplet 450-490Hz.; the spectrum was too noisy to locate the hydroxyl proton resonance.

Mixed Methyl Aryl Acetals.

Reaction of Benzal Chloride with Sodium Phenoxides in Methanol.

Benzal chloride reacts with sodium phenoxide in refluxing methanol to give a mixture of benzaldehyde dimethyl, methyl phenyl, and diphenyl acetals. The following scheme is proposed:
In this reaction scheme the dimethyl acetal arises from initial solvolysis to form the O- -chlorobenzyl methyl ether which undergoes an $S_{N}1$ reaction to give exclusively the dimethyl acetal. This reaction is paralleled by the exclusive formation of bromoacetaldehyde methyl ethyl acetal from the reaction of 1,2-dibromodiethyl ether with sodium phenoxide in methanol.

In reaction path b) one chloride ion is substituted by a phenoxide ion and the resultant O- -chlorobenzyl phenyl ether then undergoes a rapid $S_{N}1$ reaction. The derived cation reacts either with the solvent, methanol, or phenoxide ion. If this scheme is correct then the ratio of phenyl methyl to diphenyl acetal should be sensitive to the stability of the carbonium ion formed and to the nucleophilicity and concentration of the phenoxide ion. If the carbonium ion is very stable one would expect to find exclusive formation of the diaryl acetal. These considerations and the difficulty of separating the products limits the usefulness of this method of preparation of mixed aryl methyl acetals.
Benzaldehyde Methyl Phenyl Acetal.

Sodium (0.2 mole) was added to dried methanol (250 ml.) in a flask equipped with an efficient condenser and nitrogen inlet. Phenol (0.2 mole) in dried methanol (50 ml.) was added, followed by benzal chloride (0.1 mole). The solution was heated under reflux until all the benzal chloride had reacted (t.l.c.). The reaction was worked up in a manner identical to that used for the preparation of methyl aryl formals. The resultant oil, which showed three components on t.l.c., was fractionally distilled in vacuo to yield three fractions:

1) b. 50-55°, 5 ml.
2) b. 50-120°, 1 ml.
3) b. 120-130°, 5 ml.

Fraction 1) was identical to an authentic sample of benzaldehyde dimethyl acetal (g.l.c., retn. time, i.r., n.m.r.). The third fraction was the desired mixed acetal, but was contaminated with about 15% of the dimethyl acetal. An analytically pure sample was obtained by repeated distillation, taking a 50% centre cut each time. The pure sample contained less than 0.2% of the dimethyl acetal (g.l.c. estimation in Apiezon 1 column) and had b. 125-126°.

IR (neat) v cm⁻¹

2920m (CH₃ str.); 2880w (CH str. of acetal) 1600, 1590s (aromatic C=C str.); 1450m (asymmetric CH₃ def.); 1350 (symmetric CH₃ def.); 1065, 1050, 1025, 1010, 990m (C-O-C-O-C str. of mixed acetal); 750, 690m (mono-subst.).

NMR (neat)

189Hz.(3), methoxyl; 363Hz.(acetal proton); multiplet 400-460Hz.

(10) aromatic protons.

(Found: C, 78.4; H, 6.65. C₁₄H₁₄O₂ requires: C, 78.35; H, 6.65 %)
Benzaldehyde p-Bromophenyl Methyl Acetal.

This was similarly prepared, with the substitution of p-bromo-phenol for phenol. The crude mixture of acetals was distilled in a modified Hickmann still. The bulk of the dimethyl acetal was removed from the mixture using ice-salt as the coolant and air as the heating medium.

A second fraction was collected by replacing the ice-salt with solid CO$_2$-acetone and heating the still in a silicone oil bath. The pressure, measured on a Macleod gauge was between $10^{-4}$ and $10^{-5}$ torr. This fraction was further fractionated in a semimicro short path distillation apparatus at $10^{-4}$ torr. to yield the required product (15%).

$\text{b}0.001 = 150-160^\circ$

IR (CCl$_4$) $\nu$ cm$^{-1}$

1590s (aromatic C=C str.); 1470m (asymmetric CH$_3$ def.); 1400w (symmetric CH$_3$ def.); 1035, 1075, 1010, 985m (C-O-C-O-C str.).

NMR (CCl$_4$)

200Hz. (3), methoxyl protons; 363Hz. (1), acetal proton; 450-460Hz. (9), aromatic protons.

(Found: C,57.21; H,4.45; Br,27.55. C$_{14}$H$_{13}$BrO$_2$ requires: C,57.3; H,4.3; Br,27.3 %)

Attempted Preparation of Benzaldehyde Methyl m-Nitrophenyl Acetal.

The same procedure as above was adopted substituting m-nitrophenol for p-bromophenol. During the removal of the dimethyl acetal, most of the remaining material crystallised. The crystals were filtered and recrystallised from ethanol to yield benzaldehyde di-m-nitrophenyl acetal (15%), m.p.120-122°.

IR (KBr disc) $\nu$ cm$^{-1}$

1530v.s. (asymmetric NO$_2$ str.); 1350v.s. (symmetric NO$_2$ str.); 1100w, 1080, 1050, 1005, 995m (C-O-C-O-C str. of acetal).
NMR (CDCl₃)

415Hz. (1), aromatic diaryl acetal proton; multiplet 430-465Hz. (6), m-nitrophenoxy protons broad singlet 465-490Hz. (5), phenyl protons.

(Found: C, 62.3; H, 3.95; N, 7.6. C₁₉H₁₄N₂O₆ requires: C, 62.3; H, 3.85; N, 7.65 %)

T.l.c. examination of the combined residues showed no product at the r.f. expected for the mixed acetal, which was prepared by an alternative method.

**Attempted Preparation of Phthalaldehydic Acid Methyl Ester Methyl, Methyl Salicyl Acetal.**

a)

\[ \text{MeCO}_2\text{H} \quad \text{Br}_2 \quad \text{hν} \quad \text{MeCO}_2\text{H} \]

b)

\[ \text{MeCO}_2\text{H} \quad \text{Br}_2 \quad \text{MeOH} \quad \text{MeCH} \]

a) Methyl α,α'-dibromo-α-toluate (95%) was prepared by the method of Elieel and Burghstahler and had the quoted m.p. of 42-43°C.

b) Methyl α,α'-dibromo-α-toluate (0.1 mole) was added to a solution of the sodium salt of methyl salicylate (0.2 mole) in dried methanol (150ml.). The solution was heated under reflux overnight and the reaction mixture worked up in a similar manner to that of the previous series of experiments.

The product, distilled from a molecular still, consisted of two fractions:

i) bath temp. 100°C (8g.)

ii) bath temp. 150-100°C (8g.)

The first fraction appeared to be mainly the dimethyl acetal (n.m.r.), the second fraction crystallised on cooling. The crystals were recrystallised from petrol to give the diaryl acetal (25%), m.p. 53-54°C.
IR (CCl₄)  ν cm⁻¹

3000w (aromatic CH str.); 2900w (CH₃ str. of methoxyl); 2820v.w. (acetal CH str.); 1720s (aromatic ester C=O str.); 1460m (asymmetric CH₂ def.); 1290s (asymmetric C-O-C str. of aromatic ester); 1120s (symmetric C-O-C str.) 1090s, 1025, 970m, (acetal C-O-C-O-C str.).

NMR (CCl₄)

235Hz. (9), methyl ester protons; 489Hz. (1), diaryl acetal proton.

Multiplet 460-500Hz. (12), aromatics.

(Found: C, 66.8; H, 5.2. C₁₂₂H₂₂₂O₁₂ requires: C, 66.65; H, 4.9 %)

b) ii) In an attempt to reduce the rate of capture of the benzyl arylxy carbonium ion by phenoxide ion and thereby to increase the chance of capture of the ion by methanol, the methanolic solution of the sodium salt of methyl salicylate was added in small portions, only when the solution was near neutral; the products were again the dimethyl acetal and the diaryl acetal in an essentially unchanged ratio.

b) iii) It was felt that a reduction in nucleophilicity of the phenoxide ion might favour the formation of the mixed acetal. Since the lithium salt of methyl saliclylate might be expected to be more associated in methanolic solution than the corresponding sodium salt, and hence less nucleophilic, the reaction was repeated using the lithium salt. The reaction was indeed much slower, but resulted only in the formation of more dimethyl acetal at the expense of the diaryl acetal.

Methyl Aryl Acetals from α-Chloro Ethers.

The reaction of α-halo ethers with sodium phenoxides gives excellent yields of mixed acetals, and where the α-halo ether is accessible this is the preferred synthetic method.

The subject of α-halo ethers has been reviewed by Summers. Three general methods for the preparation of α-halo ethers are discussed by this author:
i) The addition of a hydrogen halide to a vinyl ether gives excellent yields, but places limitations upon the structure of the halo ether.

ii) This method is restricted to lower aliphatic aldehydes and aliphatic alcohols; it is the normal method for the preparation of α-chloro methyl alkyl ethers.

iii) This is probably the most useful general method for the preparation of α-chloro ethers. A more recent adaptation of this method is that of Black and Landor who prepared a large series of α-chloro alkyl ethers by the reaction of boron trichloride on acetals:

\[ \text{RCH(OR')}_2 + \text{BCl}_3 \rightarrow \text{RCH} - \text{Cl} + \text{B(OR')}_3 \]

Generally speaking, secondary α-halo ethers are too unstable for convenient manipulation.

A tempting synthesis of α-bromo benzyl ethers is the free radical bromination of benzyl methyl ethers:

\[ \text{PhCH}_2\text{OMe} \xrightarrow{\text{Br/h\text{I}}} \text{PhCH} - \text{Br} + \text{HBr} \]

the intermediate radicals of the type PhCHOMe however give the benzaldehyde and methyl bromide by attack of a bromine atom on the methyl carbon rather than the aldehyde carbon.
\( \text{\textalpha-} \text{Chloro Benzyl Methyl Ether.} \)

\[
\text{PhCH(OMe)}_2 + \text{SOCl}_2 \rightarrow \text{PhCH}_2\text{Cl} \quad \text{PhCH}_2\text{OMe}
\]

Benzaldehyde dimethyl acetal (0.5 mole) was mixed with an equal volume of thionyl chloride in a flask equipped with nitrogen inlet and efficient reflux condenser. Considerable heat was evolved in the reaction and the solution refluxed vigorously for several minutes. The reaction was allowed to cool and left to stand overnight. Excess thionyl chloride was removed in vacuo at room temperature and the residue rapidly fractionated under reduced pressure to yield \( \text{\textalpha-} \text{chloro benzyl methyl ether} \) (80\%).

\[
\text{b}_{1.0} \ 68-70^\circ, \text{lit.} 32^\circ \text{b}_{0.1} \ 68-70^\circ
\]

There is a large disparity between the boiling point found and that recorded in the literature, but the same authors later report the boiling point of the p-nitro isomer as \( b_{1.0} 107^\circ \) which seems incompatible with a \( b_{0.1} \) of 68-70\(^\circ\) of the unsubstituted compound. N.m.r. showed conclusively that the compound obtained was indeed that required.

NMR (neat)

206Hz. (3), methoxyl; 332Hz. (1), the chemical shift calc. for proton on carbon bearing 1 phenyl group, 1 methoxyl and 1 chloro is 375Hz.; multiplet 423-476Hz. (5), aromatics.

The following benzaldehyde methyl \( m \)-substituted phenyl acetals were prepared from \( \text{\textalpha-} \text{chlorobenzyl methyl ether} \) and the appropriate sodium phenoxide by the standard procedure.

Benzaldehyde \( m \)-Fluorophenyl Methyl Acetal.

IR (neat) \( \nu \) \( \text{cm}^{-1} \)

3000\( \nu \), (aromatic CH str.); 2900\( \nu \), (CH\( _3 \) str.); 2680\( \text{sh} \), (acetal CH str.); 1440\( \nu \), (asymmetric CH\( _2 \) def.); 1350\( \nu \), (symmetric CH\( _2 \) def.); 1150, 1100, 1080, 1030, 1000\( \nu \), (acetal C-O-C-O-C str.).
NMR (neat)

190Hz. (3), methoxyl protons; 363Hz. (1), aryl methyl acetal proton; multiplet 390-460Hz. (9), aromatics.

$^{19}$F NMR (56.4 MHz)

Broad singlet 31 KHz. down field from $\text{C}_6\text{F}_6$.

(Found: C, 72.7; H, 5.85; F, 8.05. $\text{C}_{14}\text{H}_{13}\text{FO}_2$ requires: C, 72.4; H, 5.6; F, 8.2 %)

Benzaldehyde m-Chlorophenyl Methyl Acetal.

IR (neat) $\nu$ cm$^{-1}$

3000v.w., (aromatic CH str.); 2900w., (CH$_3$ str.); 2820v.w. (acetal CH str.); 1600s (aromatic C=C str.); 1495s; 1475m.s. (asymmetric CH$_3$ def.);

1360s, (symmetric CH$_3$ def.) 1118, 1090, 1070, 1018, 955s (acetal C-O-C-O-C str.).

NMR (neat)

193Hz. (3), methoxyl; 363Hz. (1), acetal proton; multiplet 417-460Hz. (9), aromatics.

(Found: C, 67.4; H, 5.35; Cl, 14.5. $\text{C}_{14}\text{H}_{13}\text{ClO}_2$ requires: C, 67.6; H, 5.25; Cl, 14.3 %)

Benzaldehyde Methyl m-Nitrophenyl Acetal.

M.p. 41-43° from petrol.

IR (CCl$_4$) $\nu$ cm$^{-1}$

3000v.w., (aromatic CH str.); 2950m.w., (CH$_3$ str.); 2810sh., (acetal CH str.); 1595s (aromatic C=C str.); 1520v.s., (asymmetric NO$_2$ str. under weak CCl$_4$ absorption); 1450s, (asymmetric CH$_3$ def.); 1340v.s., (symmetric NO$_2$ str.); 1110, 1090, 1070, 1000, 990s, (acetal C-O-C-O-C str.).

NMR (CCl$_4$)

196Hz. (3), methoxyl; 372Hz. (acetal proton). Multiplet 430-460Hz. (9), aromatics.
Benzaldehyde Methyl m-Tolyl Acetal.

IR (neat) $\nu \text{ cm}^{-1}$

$3000w,$ (aromatic CH str.); $2950m w.$ (CH$_3$ str.); $2820sh$, (acetal CH str.); $1595s,$ (aromatic C-C str.); $1480s,$ (asymmetric CH$_2$ def.); $1235s,$ (symmetric CH$_2$ def.); $1090, 1075s, 1005$ broad s, (acetal C-O-C-O-C str.).

NMR (CDCl$_3$)

$138Hz.$ (3), benzylic CH$_2$; $194Hz.$ (3), acetal methoxyl; $366Hz.$ (1), acetal proton; $390-463Hz.$ (9), aromatic protons.

Attempted Preparation of Acrolein Phenyl Methyl Acetal.

a) $\text{ClCH}_2\text{CH}_2\text{CH(OMe)}_2 \xrightarrow{\text{BCl}_3} \text{ClCH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$

b) $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{OCH}_3 \xrightarrow{\text{NaOPh}} \text{ClCH}_2\text{CH}_2\text{CH}_2\text{OPh}$

c) $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{OPh} \xrightarrow{\text{DEN}} \text{CH}_2\text{CH}_2\text{CH}_2\text{OPh}$

a) 3-Chloropropionaldehyde dimethyl acetal was converted to 1,3-dichloropropyl methyl ether by the procedure of Black and Lendor.$^{30}$ Consistent analyses could not be obtained, probably due to the extreme ease of hydrolysis of this compound; however the mass spectrum gave the correct parent ions in the correct ratios for the formula C$_4$H$_8$Cl$_2$O (peaks at m/e 142, 144, 146 in the relative intensities of 9:6:1).

NMR (neat)

Quartet $148Hz.$, $J_{ab} 7Hz.$ (2), a; $210Hz.$ (3), d; triplet $215Hz.$, $J_{ab} 6Hz.$ (2), b; triplet $341Hz.$, $J_{ab} 7Hz.$ (1), c.
b) The α-chloro ether was converted to the methyl phenyl ether by the standard procedure.

**NMR (neat)**

![Chemical Structure]

Quartet 127Hz, J\text{ab} 7Hz, (2), b; 191Hz, (3), d; triplet 210Hz, J\text{ab} 7Hz, (2), a; triplet 315Hz, J\text{ab} 6Hz, (1), c; multiplet 400-443Hz, (5), aromatics.

This compound proved to be unstable, polymerising within a few days. Attempts to dehydrohalogenate it with diazabicyclo 4.3.0 non-5-ene merely accelerated the polymerisation.

Attempts to prepare the phenyl methyl acetics of crotonaldehyde and acetone by the following route:

a) \[ \text{CH}_3\text{CH} = \text{CH} - \text{CH(O)Me}} \xrightarrow{\text{BCl}_3} \text{CH}_3\text{CH} = \text{CH} - \text{CH(O)Me} \]

b) \[ \text{CH}_3\text{CH} = \text{CH} - \text{CH} - \text{CH(O)Me}} \xrightarrow{\text{NaOPh, IMF}} \text{CH}_3\text{CH} = \text{CH} - \text{CH(O)Me} \]

resulted in violent reactions in step a) with extensive charring of the organic reactant.

**Aryl Methyl Formals (Methoxy Methoxy Benzenes).**

The following p-substituted methoxy methoxy benzenes were prepared by the standard procedure. All yields were between 85 and 95%. The compounds were purified by distillation unless otherwise stated.

**p-Methoxy Methoxy Anisole.**

b.p. 97-98°

**IR (neat) cm\(^{-1}\)**

3005v,w., (aromatic CH str.); 2950m, (CH\(_2\) str.); 2850m, (symmetrical CH\(_2\) str.); 1505s, (aryl formal peak, see characterisation section); doublet 1460, 1440m, (asymmetric CH\(_3\) bend and CH\(_2\) scissoring); 1105m, 1080, 1018,
1005s, (acetal C-O-C-O-C str.); 930s, (CH$_2$ rocking mode); 860s, (p-subst.).

NMR (neat)

200Hz,(3), formal CH$_2$; 215Hz,(3), ether CH$_2$; 307Hz,(2), formal CH$_2$; A A'B B' system 402, 412, 416, 427Hz.(4), p-subst. aromatics.

(Found: C, 71.0; H, 7.9. C$_7$H$_{12}$O$_2$ requires: C, 71.0; H, 7.95 %)

p-Bromo Methoxy Methoxy Benzene.

This was purified by preparative g.l.c. (6ft. 3/8", 20% SE 30 on Chromosorb W, temp. 160°, flow rate 100ml./min. of N$_2$). The retention time was 15 min. These parameters were invariably used for gas chromatographic purification of methoxy methoxy compounds.

IR (CCl$_4$) 14 cm$^{-1}$

The CH stretching region of this compound is discussed in the characterisation section.

1610m, 1585m.w., (aromatic C=C str.); 1522sh, 1510s, (aryl formal); 1450m (asymmetric CH$_2$ def.); 1235s, 1150s (possibly CH$_2$ twisting); 1085, 1015 (acetal C-O-C-O-C str.); 930s, sharp, (CH$_2$ rocking); 860m, (p-subst.).

NMR (neat)

202Hz,(3), formal CH$_2$; 301Hz,(2), formal CH$_2$; singlet 417Hz.(4), accidentally degenerate p-subst. aromatics.

(Found: C, 44.1; H, 4.4; Br, 36.7. C$_8$H$_9$BrO$_2$ requires: C, 44.25; H, 4.15; Br, 36.85 %)

p-Methyl Methoxy Methoxy Benzene.

This was purified by preparative gas chromatography.

IR (neat) 14 cm$^{-1}$

3005v.w., (aromatic CH str.). The CH$_3$ and CH$_2$ stretching region was not resolved; 1605, 1595m, (aromatic C=C str.); 1505s, (aryl formal); 1230s, (uncertain); 1150s, 1030, 1020s, (acetal C-O-C-O-C str.); 950m, (CH$_2$ rocking); 860s, (p-subst.).
NMR (CDCl₃)

146Hz.(3), "toluene" CH₃; 204Hz.(3), formal CH₃; 302Hz.(2),
formal CH₂; A A'B' system 406, 415, 417, 426Hz.(4), p-subst. aromatics.
(Found: C,70.85; H,8.05. C₉H₁₂O₂ requires: C,71.0; H,7.95 %)

p-Carbomethoxy Methoxy Benzene.

IR (neat) υ cm⁻¹

3000w,(aromatic CH str.); 2950w,(CH₃ str.); 2810w,(symmetric
CH₂ str.); 1720s,(aromatic ester carbonyl); 1605, 1595m,(aromatic C=C str.);
1510s,sharp,(aromatic formal); 1440s,(asymmetric ester CH₂ def.); 1280s,
(asymmetric C-O-C str. of aromatic ester); 1250s,(uncertain); 1180s,
(symmetric C-O-C str. of aromatic ester); 1160s; 1110, 1090, 1000s,(C-O-C-O-C
str. of acetal); 930s,(CH₂ rocking); 860s,(p-subst.).

NMR (CDCl₃)

204Hz.(3), CH₃ of formal; 227Hz.(3), CH₃ of ester; 306Hz.(2),
CH₂ of formal; A A'B' system 414, 423, 470, 479Hz.(4), p-subst. aromatics.

p-Nitro Methoxy Methoxy Benzene.

This was supplied by Dr. N. S. Anderson of Leicester University
and had the following properties:
b₀ 5 72-75°

IR (neat) υ cm⁻¹

3000-2900w,(aromatic CH and CH₃ str.); 2840w,(CH₂ str.); 1608,
1592s,(aromatic C=C str.); doublet 1510, 1425s,(aromatic C=C str.); 1345s,
(asymmetric NO₂ str.); 1250s, 1100, 1085s,(acetal C-O-C-O-C str.); 960s,
(CH₂ rocking); doublet 860, 850, (p-subst.).
NMR (CDCl₃)

206Hz.(3), formal CH₃; 315Hz.(2), formal CH₂; A A'B B' system
421, 431, 486, 496Hz.(4), p-subst. aromatics.

(Found: C,52.4; H,5.1; N,7.65. C₈H₇NO₄ requires: 0,52.4; H,4.95; N,7.65%)  

Cyclohexylammonium Salt of 2-Methoxy Methoxy 3-Nitrobenzoic Acid.

a) 3-Nitrosalicylic acid (10 g.) was esterified by the methanol method, m.p. 141-2°C, lit. 141-2°C
b) The phenolic ester was converted to the methoxy methoxy derivative (80%) by the standard procedure.
   m.p. 41-43°C from petrol.

IR (CCl₄) U cm⁻¹

3010v.w.,(aromatic CH str.); 2960m,(asymmetric CH₂ str.); 2650w, (symmetric CH₂ str.); 1745s,(aromatic ester O=O str.); 1610m,(aromatic C=C str.); 1335s,(asymmetric aromatic NO₂ str.); 1460, 1440s,(overlapping asymmetric CH₃ def. and CH₂ bend.); 1370s,(symmetric NO₂ str.);
1300, 1270s, (asymmetric C-O-C str. of aromatic ester); 1170s, (symmetric C-O-C str. of aromatic ester); 1150s, 1080s, (acetal C-O-C-O-C str., much less complicated than usual); 930s, (CH<sub>2</sub> rocking).

NMR (CDCl<sub>3</sub>)

209Hz. (3), formal CH<sub>2</sub>; 237Hz. (3), ester CH<sub>2</sub>; 310Hz. (2), formal CH<sub>2</sub>; 20Hz. ABX system 430-493Hz. (3), 1, 2, 3-subst. aromatics.

(Pound: C, 49.5; H, 4.6; N, 5.85. \( C_{10}H_{11}NO_6 \) requires: C, 49.8; H, 4.6; N, 5.8 %)

c) The ester was converted to the cyclohexylammonium salt of the acid (85%) by the standard procedure. The salt has an ill defined m.p. and is thermally unstable.

IR (KBr disc) \( \nu \text{cm}^{-1} \)

2930m, (CH<sub>2</sub> str.) typical cyclohexylammonium absorption 3300, 2400; 1620m, (NH<sub>2</sub> def.); 1550s, (asymmetric CO<sub>-</sub>- str.); 1520s, (aromatic nitro asymmetric str.); 1400s, (CH<sub>2</sub>); 1360v.s., (symmetric NO<sub>2</sub> str.); 1080s, (C-O-C-O-C str.); 945s, (CH<sub>2</sub> rocking).

NMR (DMSO-d<sub>6</sub>)

50-130Hz. (16), typical cyclohexylammonium residue; 207Hz. (3), formal CH<sub>2</sub>; 311Hz. (2), formal CH<sub>2</sub>; 410-460Hz. (3), aromatics.

(Pound: C, 55.25; H, 6.7; N, 8.65. \( C_{15}H_{22}N_2O_6 \) requires: C, 55.2; H, 6.8; N, 8.6 %)

Cyclohexylammonium Salt of 2-Methoxy Methoxy 3-Methyl Benzoate.

This salt was prepared by a method analogous to that of the above compound, starting from 3-methylsalicylic acid.

The physical properties of the intermediates are:

**Methyl 3-Methyl Salicylate**

\( b_1 \) 102-3°; lit. b<sub>1</sub> 111°; \( \nu_{\text{C}=\text{O}}(\text{CCl}_4) \), 1680; lit. \( \nu_{\text{C}=\text{O}}(\text{CCl}_4) \), 1681.
Methyl 2-Methoxy 3-Methyl Benzoate.

IR (CCl$_4$, cm$^{-1}$)

3000w, (aromatic CH str.); 2950m, (CH$_3$ str.); 2930sh, (asymmetric CH$_2$ str.); 2850w, doublet, (symmetric CH$_2$ str.); 1725s, (aromatic ester C=O str.); 1600m, (aromatic C=C str.); 1460, 1435 (overlapping asymmetric CH$_3$ def. and CH$_2$ bend.); 1295, 1265s, (symmetric C-O-C str. of aromatic ester); 1160s, (symmetric C-O-C str.); 1150s; 1070s, (acetal C-O-C-O-C str.); 960s, (CH rocking).

NMR (neat)

138Hz. (3) "toluene" CH$_3$ (3), formal CH$_3$; 224Hz. (3), ester CH$_3$; 301Hz. (2), formal CH$_2$; AB$_2$ system 400-470Hz. (3), 1,2,3-subst. aromatics.

(Found: C, 62.6; H, 6.9. C$_{11}$H$_{14}$O requires: C, 62.65; H, 6.7 %)

Cyclohexylammonium Salt.

MP, 102-103° from methanol-ether.

IR (KBr disk, cm$^{-1}$)

2930, (CH$_2$ str.); typical cyclohexylammonium residue 3300-2400; 1620, (NH$_3$ def. ); 1550 as, CO$_2^-$ str.; 1400, (CH$_2$ ); 1080, (C$_{10}$C str.); 945, (CH$_2$ rock).

NMR (DMSO d$_6$)

50-130 Hz. (16), typical cyclohexylammonium residue; 132 Hz. (3), Ar CH$_3$; 203 Hz. (3), formal CH$_3$; 302 Hz. (2), formal CH$_2$; 400-450 Hz. (3), aromatic protons.

(Found C, 65.0; H, 8.65; N, 4.7. C$_{16}$H$_{25}$NO$_4$ requires: C, 65.0; H, 8.55; N, 4.75%.)
The Structure of Acid Aldehydes

The opposing spectrum of chloromucic acid clearly shows its cyclic structure, with the lactone carbonyl band at 1745 cm$^{-1}$. This is confirmed by its NMR spectrum in DMSO $d_6$ which shows a resonance for the "aldehyde" proton at 363 Hz. Esterification with methanol and sulphuric acid yields the pseudo ester with a carbonyl band in the IR spectrum at 1760 cm$^{-1}$. Succinaldehydic acid on the other hand shows a broad band from 1735-1695 cm$^{-1}$, due to the overlapping aldehyde and carboxyl bands. Furthermore the UV spectrum shows a maximum around 260 nm with an absorbancy of 70-80, characteristic of an aliphatic aldehyde. Fife has shown that in acidic ethanol the pseudo ester of this compound is smoothly converted to the ethyl ester diethyl acetal. Esterification of succinaldehydic acid with methanol gives the methyl ester dimethyl acetal as the sole product (g.l.c. comp. with an authentic specimen).

The reported IR of hexahydro-3-hydroxy 3a methyl 4,7 methylene phthalide shows carbonyl absorption in the IR at 1735 cm$^{-1}$, and similarly the compound without the 3a methyl shows absorption at 1760 cm$^{-1}$. The pseudo ethyl ester of the 5-6 dehydro derivative of the latter compound has been reported and typical compounds of this structure yield pseudo esters on reaction with acid methanol.
EXPERIMENTAL SECTION

Part 2; kinetic procedures.
Rate constants were calculated from data collected spectrophotometrically, polarimetrically, and by g.l.c. estimation of methanol or ethanol.

**Solutions**

All chemicals used for the preparation of buffers and for other kinetic solutions were of the highest commercial grade available. Dioxan was purchased from Merck ("spectrograde") and stored at 5°. Unless otherwise stated all buffers had ionic strength 0.1. Where dilute HCl was used as the buffer the ionic strength was adjusted, where necessary, with potassium chloride. For general acid catalysis studies the ionic strength of the buffers was also maintained constant with KCl.

Dioxan buffers were made up by volume, but were corrected to give the correct w/w ratios using the stated density of the dioxan at 20.0°.

**pH Measurements**

The pH of all buffer solutions was measured at the temperature of the kinetic measurements with a Radiometer TTT 1 titrator equipped with scale expansion facilities. The TTT 1, along with the same manufacturer's SBU 2 burette and Titrigraph was used to measure the pKa's of acids by titration with N/10 "carbonate-free" sodium hydroxide, or by back titration of their cyclohexylammonium salts with N/10 hydrochloric acid.

At temperatures less than 55° a type G 202 B, or C Radiometer glass electrode was used, with a type K401 calomel electrode. Above this, a type G 202 EH glass electrode was substituted. Above 65° the calomel electrode became unstable and it proved necessary to use a salt bridge.

THE pH meter was standardised against commercial buffer preparations to BS 1647, 1961.

**Standardisation of The Glass Electrode in Aqueous Dioxan**

The procedure chosen was to measure the apparent pH of a solution of a half neutralised acid, whose pKa had been determined conductimetrically. The pKa of benzoic acid has been determined in 50% dioxan water by Dunsmore and Speckman. Fortunately, these workers determined this value at several ionic strengths so a direct comparison was possible.
In this case the pH meter reading is not significantly different from the pKa of the acid (t test at 99% significance). Thus, no correction is necessary.

The pKa's of formic and acetic acid have been measured in 82% dioxan water by Earned and his coworkers. A tabulation of these results can be found in ref. 36. Since these values are for zero ionic strength a value of 0.02 was chosen for the ionic strength of the buffers. A correction of +2.50 + .02 was determined. Over the range pH 8.5-11 the response of the electrode was linear to within the accuracy of the measurements. If further work is done on this system it is recommended that this calibration method be more deeply evaluated.

The response of the high temperature electrode in 82% dioxan at 60° is not very satisfactory. It was therefore necessary to check the pH's of the solutions at 25° and to correct the pH's to 60° by using the temperature coefficients of the pKa's of the acids given in reference 36.

G.I.G. Estimation of Methanol and Ethanol

The principles involved are well known and therefore no attempt will be made to discuss them here.

Equipment

A Perkin Elmer F11 flame ionisation instrument was used, with a Honeywell Brown "Electronik 15" recorder, equipped with a disc integrator. For the bulk of the work a 2 metre by 1/8" od stainless steel column packed with 10% carbowax 400 on 100/120 celite was used. Under optimum conditions methanol and ethanol can be resolved from the internal standard, n propanol. Some difficulties were experienced with tailing, and it proved more practicable to use peak heights rather than integrated areas for analysis.

The optimum precision with this system is around 1.5%, whereas under normal working conditions one could expect to obtain about 2%. The instrument is more reproducible than this but reproducibility should
not be confused with absolute accuracy.

Later, a 1 mto "poropak Q" column was packed. This cross linked divinyl benzene styrene copolymer affords incredible resolution. All the lower alcohols can be resolved from each other at temperatures as high as 170°, at any feasible carrier gas flow rate. Virtually no tailing was observed, and this, along with the almost zero background from the column allowed working concentrations as low as $2 \times 10^{-3}$ M to be used.

**Kinetic Procedure.**

The hydrolysis may be followed in a volumetric flask sealed with a serum cap. Above 65° ampoules are advisable, and at 95° mandatory. Any quantities quoted should be treated solely as guides.

The buffer containing the internal standard (n-propanol) is introduced into a volumetric flask and allowed to equilibrate in a water bath. After a suitable time interval the acetal is added, the flask resealed, vigorously shaken, and returned to the bath. Optimum results were obtained by using sufficient acetal to give a final ethanol concentration of $10^{-2}$ M and the same concentration of internal standard. Samples were withdrawn at appropriate intervals with a hypodermic syringe through the serum cap, and quenched by adding to solid sodium carbonate (0.2 mls. onto 50 mgs.). 0.5 microlitres of this solution were then injected into the chromatograph. For reactions with $t_{1/2} > 1$ hour the samples were sealed and kept at 4-5° until all the samples could be analysed consecutively. It was always established that any procedures used did not result in any deterioration of the samples.

The data were processed by the normal first order least squares program, using the ratio of the ethanol to propanol peak heights, or integrated areas as the dependant variable.

**Polarimetrically Determined Rates.**

Polarimetrically monitored rates were followed on a Perkin Elmer 141 automatic polarimeter. The jacketted 10 cm cell supplied with the instrument was used to thermostat the sample. Water was circulated
through the jacket of the cell from a water bath regulated to $\pm 0.02^\circ$. The output from this instrument was regulated to 2.5 mv / 0.5° (the maximum), and this analogue signal recorded on a potentiometric recorder, or the data logging system. This procedure is described later.

Spectrophotometric Data

Three spectrophotometers were used in this work, a Unicam SP 800, a Hilger-Gilford reaction kinetics spectrophotometer, and a Zeiss PQQ 11. These instruments are adequately described in the manufactures literature. Only one common feature of these instruments will be described, their thermostating arrangements.

The Hilger uses two large plates, through which water is circulated, which form the two ends of the cell compartment. The heat transfer medium is therefore air, and this is not satisfactory. This instrument could only be used, therefore, at temperatures close to ambient. This problem was eventually overcome by using "Helma" thermostattable cells and circulating water around these also.

The Unicam has a large aluminium block, through which water is circulated, which results in very good thermal contact between the cell and the block. Unfortunately water circulation is not particularly good and this results in a large temperature differential between the cell and the water bath. This can be as high as 3° at 65°, and the exact magnitude of this difference is sensitive to changes in ambient temperature.

With the Zeiss water can be circulated around both the cell compartment and the cell block, and although the thermal contact is not particularly good, when the temperature does settle down the differential between cell and bath is less than 0.1°, even at 65°. This instrument, which is of course the most accurate of the three, was used for the general acid catalysis studies. The following procedure was found to give the best results.
The cell holder accommodates 4 cells. In cell 4 was placed a thermometer and bung, and 3 ml of buffer. Cells 3, 2, and 1 were filled with 3 ml of buffer and sealed with a rubber bung. The top of the compartment was covered with cotton wool, to simulate the conditions with the lid down. When the temperature had settled down any readjustments were made to the temperature and this cycle repeated until the temperature was within 0.02°C of the required temperature. Once this had been set it was seldom necessary to make any changes over periods of several weeks. All thermometers used for this procedure were either NPL standardised, or calibrated by the author for 3cm immersion, against NPL ones.

When the temperature had finally settled down the pH of cell 3 (that is the buffer) was checked with a previously equilibrated Radiometer type GK 2024 C combined glass/reference electrode. For other runs where temperatures in excess of 45°C were employed an equivalent Beckmann electrode was used. The cells were again allowed to reach thermal equilibrium, and then the instrument was set up at 100% T on cell 1. 30 microlitres of a dioxan solution of the substrate were injected into cell 2 and the cell vigorously shaken, and returned to the cell holder. For very fast runs it is best to inject the solution through the rubber bung with a Hamilton Syringe and to shake the cell holder containing the cell. A few seconds were allowed to pass, in order to allow air bubbles to clear and the taking of readings was commenced.

One cell can be monitored for up to at least 1 hour with no fears of drift. However if the instrument was used with the tungsten filament lamp as light source it was best to use it manually. After the termination of the run the 100% T value was adjusted if necessary and the "infinity" value recorded. The pH's of the buffer in cells 2 and 1 were measured and the temperature of cell 2 measured. Virtually no discrepancies were found in pH values and seldom did the temperature vary by > 0.05°C. As was stated earlier this latter point was not always so on the SP 800, and unsatisfactory runs were rejected.
If this procedure is rigidly followed, and no extraneous effects occur, a reproducibility of better than 1.2% can be expected. With the Zeiss output may be either in transmittance or absorbance, the former though probably the most reliable is limited by the readability of the scale at low transmittances. Reproducibility of runs on the SP 800 was seldom much better than 3%

Data Acquisition and Processing

Since all rate constants were calculated by least squares computer programs the data collection systems used will be briefly discussed. The g.l.c. system has been described. The output from all these instruments is in the form of a 10mv analogue signal. The problem is therefore a question of converting this analogue signal into digital form in a computer compatible input form.

Automatic processing of data was achieved with a Solartron Compact Data Logger, with output onto 5 hole perforated tape in Ferranti code. This equipment is described in the manufactures technical literature and therefore no description will be attempted here. It will suffice to say that time information can be generated to one part in $10^6$ and that absorbance or transmittance can be recorded to an accuracy significantly greater than the noise level of the spectrophotometers.

Manual processing of the data was achieved by recording the signal on a 10 mv recorder ( either a Honeywell Electronic 15 or a Servoscribe ) and punching selected values onto paper tape or cards. It was normal to use about 200 values on the logger system and about 30-40 manually.

Calculation of Rate Constants

The methods used by the author in this work have developed considerably with time, it would be rather difficult to discuss them in
any great detail. In general, the earlier work was done using non
weighted linear least squares methods. This involves manipulating the
equations into a linear form and then fitting that equation. As is exp­
lained in the next section, this is not always satisfactory. It still
represents a considerable improvement over graphical procedures.

Some Considerations on Curve Fitting

Any discussion of the methods used to extract kinetic parameters
from raw data must centre on two points, what is required of the data,
and just how good the data is. It makes no sense to criticise the vast
number of methods available, because they all have their place. What is
really important is to assess what methods one should use in order to
obtain the highest precision. Just how much effort is worthwhile is very
much a matter for the individual worker, but it would be fair to say
that where further parameters are to be calculated from the rate const­
ants one should choose a method in which such matters as covariance
errors are at least evaluable. This is especially true of such things
as isokinetic plots, where parameters are obtained through several sets
of transformations. In these cases it is absolutely necessary to take
the most stringent care to avoid any chance of bias, or non random
errors.

This question of bias is of course, fundamental to least squares
curve fitting. This problem is clearly demonstrated by the following
example.

Consider the method of calculating first order rate constants
by evaluating the function;

\[ \log \left[ \frac{A_{\inf} - A_o}{A_{\inf} - A_t} \right] / T \]

and averaging the values. It is immediately recognised that the overall
accuracy is strictly limited by the accuracy of the value of the denomi­
nator in the logarithmic expression.
A better way to calculate $k$ is to plot the function:

$$\log(A_{\infty} - A_t) = -kT + \log(A_{\infty} - A_0)$$

whence this constant term is an evaluated parameter. Graphical methods are of course open to possible personal bias, and the better way is to recourse to least squares methods. Even this has its problems. The greatest of these is the rather vexed problem of weighting. Again inspection of the equation shows that when $A_t$ is comparable in magnitude to $A_{\infty}$ a small deviation in either of these will result in a very large change in the value of the expression. This means that when rather more than 2.5 half-lives are exceeded errors in both parameters will dominate the residuals. This is because the least squares method minimises the absolute not relative $\sum y^2$ values. This in turn means that the least reliable data points carry most weight. A quotation from a text by Deming is appropriate to this context.

"It is customary amongst computers to fit the exponential curve $y = ae^{-bx}$ by taking logarithms and treating it as linear in $\log y$ and $x$, but it is not so usual for them to change the weightings to correspond to logarithms. The neglect of the factor $(2.303 y)^2$ not only distorts the results for $a$ and $b$, but also invalidates the reciprocal matrix and all calculations made with it on the standard error of the parameters..."

There can be little doubt that the solution to this problem lies in the use of rigorous least squares procedures. It must however, be acknowledged that these procedures are laborious in the extreme, and that writing computer programs to do this automatically is not easy.

Throughout the period of time that this thesis represents a steady appreciation of these points has been reached. In the end, when a Fortran implementing data processing system was available generalised least squares programs were written.

Although a great deal of experience with this program has not
yet been acquired, several points can still be made. They will be restricted to first order fitting.

The relative standard errors in $A_{\text{inf}}$ are usually rather less than half those in $k$. The covariance errors between these two parameters are not always insignificant, and when this occurs, usually because the reaction has not been followed long enough, $A_{\text{inf}}$ must be fixed. When this is done the estimates of the standard deviations in $k$ are essentially meaningless, the true uncertainties are reflected in $A_{\text{inf}}$. It is therefore necessary to be certain that no drift or other non-random errors are present. This may seem trivial, but how often can one exactly superimpose an infinity spectrum upon a synthetic mixture of the products. The propagation of errors from $A_{\text{inf}}$ to $k$ can be very serious and one can be quite certain that the factor of 2 previously mentioned represents a minimum value. This means that for a reaction where an absorbance change of 0.8 occurs, it is necessary to measure $A_{\text{inf}}$ with an accuracy of .003 to obtain an uncertainty in $k$ of 1%. This is probably the limit of many spectrophotometers used to measure reaction kinetics. In contrast with this the rest of the data points need only be measured to .7% to obtain this magnitude of uncertainties.

One point that needs clarification is that the assumption that a curve passes through a fixed point (say by fixing $A_{\text{inf}}$) results in a better fit to the data, judged by the standard deviations of the parameter and the reproducibility between duplicates. This will always be true if the difference between the fixed point and its least squares adjusted value is statistically insignificant. The reason for this is that the assumption that a curve passes through a point contributes information that was not available when this was not so, or to put it another way, the curve is restricted in its variation because it must pass through the point in question. For a first order equation then, the assumption that the infinity value is explicitly known will very often result in a much better fit. If one does this one must be absolutely certain that no bias.
exists in its determination.

All other kinetic and thermodynamic parameters, such as Hammett rho values, Bronsted plots, slopes and intercepts of general acid catalysis plots, and other miscellaneous plots, were evaluated by linear least squares procedures. pH rate profiles were analysed by a program written by Dr. Capon, my supervisor, which varied all three parameters until a best fit to the data was found. This program will be superceded by a rigorous least squares procedure.

Some selected computer programs written in Fortran IV are included in the appendix. Only a minimum amount of information is included with them, so anyone wishing to make use of these should contact the author for a description of their use and the facilities which they offer.
CHARACTERISATION SECTION

The most satisfactory methods for the characterisation of acetal are their NMR and IR spectra.

Infra Red Spectra

Numbers quoted refer to the maxima of absorption bands in reciprocal cms.

Acetals

Acetals of the type RCH(OR')₂ where R' is aliphatic show a characteristic sharp CH stretching band at 2810-2820. The C-O-C stretching region usually shows three broad intense bands at 1115, 1060, and 1020. The former band is due to a perturbed CH deformation band. Conley states that bands appear at 1190-1160, 1195-1125, and 1098-1063, these bands were seldom seen. Benzaldehyde phenyl methyl acetals show bands at 1085, 1050, 1025, 1010, and 990. Sometimes a band at 1150 occurs, but this does not appear to be characteristic. Diaryl acetals of benzaldehyde all show strong bands in the region 1110-950, but there would seem to be little correlation between complexity and position, and structure.

1,3-Dioxolanes

2-phenyl-1,3-dioxolanes show characteristic absorption in the C-O-C stretching region, but the situation is quite complex. The spectra of thin films or mulls show two or three bands, but in dilute CCl₄ solution, these bands can be resolved into several bands. In the case of tetra-methyl dioxolanes as many as ten bands are noted, and if the spectra are recorded on a high resolution spectrophotometer, such as a Perkin Elmer 225, the complexity of the spectra increase with increasing resolution. It would seem that any assignments made previously for these compounds must be considered oversimplified.
Methoxy Methoxy Benzenes

The IR spectra of these compounds are quite characteristic, but these compounds are better characterised by their NMR spectra. In dilute CCl₄ solution with a grating instrument, a Perkin Elmer 237 was used, all the various CH stretching modes can be resolved (see facing spectrum). The strong band which appears in the spectra of these compounds at 1500-1505 is probably one of the aromatic C=C stretching modes. The C-O-C stretching region is similar to that observed for acetals but the bands are less intense, and less broad. The most characteristic band in the spectra of these formals is the CH₂ rocking mode, which is always very strong, but varies in position in the range 980-920.

The typical bands of acetals are well tabulated in all the standard texts, some key references to the original literature are given in ref. The assignment of the bands of other functional groups was made with the aid of that excellent text by Conley.

NMR Spectra

All spectra were recorded on a Varian A 60 A instrument at 60 mHz. Quoted shifts are Hz. downfield from TMS or TMPSA, both internal.

Diethyl Acetals

The ethyl methylene absorption in aliphatic diethyl acetals is complex. This is of course a typical example of magnetic non-equivalence. This pattern has been fully analysed for acetal itself. Surprisingly, the methylene absorption in aromatic diethyl acetals is a simple quartet.

Methyl Acetals

The position of the methoxyl resonance for several types of methyl acetals is summarised below.
NMR Spectrum of 2 Phenyl 1,3 Dioxolane of the CH₂ protons
Table 42
Methoxyl Resonance In Various Methyl Acetals

<table>
<thead>
<tr>
<th>Acetal</th>
<th>ArCH(OMe)_2</th>
<th>ArCH(OMe)_2</th>
<th>ArCH(OMe)_2</th>
<th>PhCH,OMe,OArl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shift</td>
<td>200 ± 1</td>
<td>196 ± 2</td>
<td>190-196</td>
<td>189-195</td>
</tr>
</tbody>
</table>

The methylene absorption of methoxy methoxy benzenes occurs at 300 ± 3

Dioxolanes

The absorption of the 4 protons on the 4 and 5 positions of 2 phenyl 1,3 dioxolane is a symmetrical decet (see facing page). Substituted phenyl dioxolanes show varying degrees of complexity, but all retain the symmetry of the parent compound. This pattern is a typical AA'BB' one and the spectrum of 2 methyl 1,3 dioxolane has been analysed on this basis. 4,4,5,5 Tetra methyl 1,3 dioxolanes show two methyl absorptions, which represent the methyls cis and trans to the phenyl group. Four resonances are not observed because of the fast pseudo rotation of the ring. Temperature studies of this system might give some information on the magnitude of the eclipsing strain induced in the hydrolysis of these compounds.

The position of the acetal proton resonance in several types of acetals is summarised below.

Table 43
The Position of The Resonance of The Acetal Proton in Some Different Types of Acetals

<table>
<thead>
<tr>
<th>Type of Acetal</th>
<th>ArCH(OMe)_2</th>
<th>ArCH(OMe)_2</th>
<th>ArCH(OMe)_2</th>
<th>ArCH(OMe)_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shift</td>
<td>270 ± 3</td>
<td>270 ± 3</td>
<td>335 ± 3</td>
<td>335 ± 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ArCH-CMe</th>
<th>ArCH-O</th>
<th>ArCH-O</th>
<th>PhCH-CMe</th>
<th>PhCH(OMe)_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>387 ± 5</td>
<td>340-390</td>
<td>340-405</td>
<td>360-370</td>
<td>varies widely from 420-480</td>
</tr>
</tbody>
</table>
All other assignments were made with the aid of Shoolery rule tables.
Three computer programs are listed. They all conform to ASA Fortran (Fortran 4) except that there may be an occasional mixed mode expression. Input is from logical device 7 and output on device 2.

The first program gives a non weighted linear least squares solution for the following things.

First order rates with data from a strip chart recorder in the form of transmittance or absorbance, or absorbance readings from data collected manually, General acid catalysis plots, Hammett plots, Bronsted plots, and a subroutine to evaluate $k_2$ and $n$ from plots of the type:

$$k_2 = k_{\text{obs}} \times (H^+)^n$$

The second one gives a rigorous generalised least squares solution for first order kinetics with data in the form of absorbance or transmittance, and all that needs modifying for other forms of data processing is for the weighting to be adjusted accordingly. The author also has a subroutine for the analysis of pH rate profiles.

The third program is designed to handle equations with up to ten parameters, and a subroutine for the analysis of first order consecutive rates is given.

It is strongly recommended that anyone interested in using these programs should contact the author to discuss their application.
C MAIN CALLING PROGRAM

INTEGER RUNNUM, CLIENT(20)
COMMON/DELTA/RUNNUM, MODE, CLIENT
DIMENSION K(12)
READ(7,1010)(K(I), I=1,12)

1010 FORMAT(12A4)
70 READ(7,10) RUNNUM, MODE
10 FORMAT(I3, A4)

IF(RUNNUM.EQ.999) GO TO 60
READ(7,11)(CLIENT(I), I=1,20)

11 FORMAT(20A4)
WRITE(2,1000)

1000 FORMAT(I11)
DO 100 I=1,12
IF(MODE.NE.K(I)) GO TO 100
GOTO(30,40,20,40,30,1,2,3,4,30), I

100 CONTINUE
WRITE(2,21)

21 FORMAT(1HO, 69H A NON RECOGNISABLE MODE HAS BEEN PUNCHED, TRY AGAIN
  FOR A PRIZE)

20 CALL G1C
GOTO 70
30 CALL UVM1
GOTO 70
40 CALL UVM2
GOTO 70
1 CALL GENACD
GOTO 70
2 CALL HAMMET
GOTO 70
3 CALL BRONST
GOTO 70
4 CALL SECOND
GOTO 70

60 STOP
END
SUBROUTINE UVM2
REAL INCEPT, CALABS(50)
DIMENSION X(50), Y(50), TIME(50,3), OD(50), ABC(50)
COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE
COMMON/ALPHA/X, Y, NVAL, ABC
J=0
20 J=J+1
READ(7,30) OD(J), (TIME(J, I), I=1, 3)
30 FORMAT(F4.3, F3.0, 2F2.0)
IF(TIME(J,1) .LT. 0.0) GO TO 100
100 NVAL=J-1
DO 40 I=1, NVAL
ABC(I)=ABS(OD(I) - OD(J))
Y(I)=ALOG(ABC(I))
X(I)=TIME(I,1)*3600. + TIME(I,2)*60. + TIME(I,3)
40 CONTINUE
CALL LESQR
RATE=-RATE
DO 61 I=2, NVAL
CALABS(I)=EXP(CALABS(I))
61 CONTINUE
CALL OUTPUT
RETURN
END

SUBROUTINE UVM1
DIMENSION X(50), Y(50), TIME(50), OD(50), ABC(50)
REAL INCEPT, CALABS(50)
COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE
COMMON/ALPHA/X, Y, NVAL, ABC
READ(7, 11) CNVN, BASE
11 FORMAT(F4.0, F4.2)
J=0
20 J=J+1
50 READ(7, 30) TIME(J), OD(J)
IF(BASE .NE. 0.0) OD(J)=ALOG10(BASE/OD(J))
30 FORMAT(F3.1, F4.2)
IF(TIME(J) .LT. 0.0) GO TO 20
IF(BASE .NE. 0.0) WRITE(2, 60) BASE
60 FORMAT(1H, 74H THE DATA WAS OBTAINED BY TRANSMITTANCE MEASUREMENTS
1 , THE BASE LINE WAS , F5.1, 8H PERCENT )
NVAL=J-1
DO 40 I=1, NVAL
ABC(I)=ABS(OD(I) - OD(J))
Y(I)=ALOG(ABC(I))
X(I)=TIME(I)*CNVN
40 CONTINUE
CALL LESQR
RATE=-RATE
DO 61 I=2, NVAL
CALABS(I)=EXP(CALABS(I))
61 CONTINUE
CALL OUTPUT
RETURN
END
SUBROUTINE LESQR

C A SUBROUTINE FOR THE BEST FIT OF A STRAIGHT LINE

REAL INCEPT, NDP

DIMENSION X(50), Y(50), ABC(50), CALABS(50), CMNT(20)

COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE

COMMON/ALPHA/X, Y, NVAL, ABC

SUMX=0.0
SUMY=0.0
SUMXX=0.0
SUMYY=0.0
SUMXY=0.0

DO 10 I = 2, NVAL
SUMY = Y(I) + SUMY
SUMX = X(I) + SUMX
SUMXX = X(I)**2 + SUMXX
SUMXY = X(I) * Y(I) + SUMXY
SUMYY = Y(I)**2 + SUMYY

10 CONTINUE

NDP = NVAL - 1
DENOM = NDP * SUMXX - SUMX**2
INCEPT = (NDP * SUMXY - SUMX * SUMY) / DENOM
RATE = (NDP * SUMXY - SUMX * SUMY) / DENOM

DO 20 I = 1, NVAL
CALABS(I) = (INCEPT + RATE * X(I))

20 CONTINUE

VARNCY = SUMY - (SUM**2) / NDP - ((SUMXY - SUMX * SUMY / NDP)**2) * NDP / DENOM
SDDEV1 = SQRT((VARNCY * NDP) / (DENOM * (NDP - 2)))
SDDEV2 = SDDEV1 * SQRT(SUMXX / DENOM)

RETURN
END
SUBROUTINE LESQR

C A SUBROUTINE FOR THE BEST FIT OF A STRAIGHT LINE

REAL INCEPT, NDP

DIMENSION X(50), Y(50), ABC(50), CALABS(50), CMNT(20)

COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE
COMMON/ALPHA/X, Y, NVAL, ABC

SUMX=0.0
SUMY=0.0
SUMXY=0.0
SUMYY=0.0
DO 10 I=2, NVAL
  SUMY=Y(I)+SUMY
  SUMX=X(I)+SUMX
  SUMXX=X(I)**2+SUMXX
  SUMXY=X(I)*Y(I)+SUMXY
  SUMYY=Y(I)**2+SUMYY
10 CONTINUE

NDP=NVAL-1

DENOM = NDP*SUMXX-SUMX**2
RATE = (NDP*SUMXY-SUMX*SUMY)/DENOM
INCEPT = (SUMY*SUMXX-SUMX*SUMXY)/DENOM

DO 20 I=1, NVAL
  CALABS(I)= (INCEPT+RATE*X(I))
20 CONTINUE

VARNCY=SUMYY-(SUMY**2)/NDP-((SUMXY-SUMX*SUMY/NDP)**2)*NDP/DENOM
SDDEV1 = SQRT((VARNCY*NDP)/(DENOM*(NDP-2))
SDDEV2=SDDEV1*SQRT(SUMXX/DENOM)

RETURN
END
SUBROUTINE OUTPUT
C A SUBROUTINE FOR THE OUTPUT FROM KINETIC PROGRAMES
REAL INCEPT
INTEGER CMNT, RUNNUM
DIMENSION X(50), Y(50), ABC(50), CALABS(50), CMNT(20)
COMMON/ALPHA/X, Y, NVAL, ABC
COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE
COMMON/DELTA/RUNNUM, MODE, CMNT
WRITE(2,10)(CMNT(I), I=1, 20)
10 FORMAT(1H0, 20X, 20A4)
WRITE(2, 20)
20 FORMAT(1HO, 76H RUN MODE RATE CONSTANT S.D. IN K INTERCEPT S.D. OF INTERCEPT)
WRITE(2, 30) RUNNUM, MODE, RATE, SDDEV1, INCEPT, SDDEV2
30 FORMAT(1HO, X, I3, 4X, A4, 4X, 1PE10.4, 5HSEC-1, 2X, 1PE9.3, 2X, 1PE10.3
2, 6X, 1PE9.3)
WRITE(2, 50)((ABC(I), CALABS(I)), I=1, NVAL)
50 FORMAT(1H, (12(0PG11.4)))
RETURN
END
SUBROUTINE GLC
RETURN
END
SUBROUTINE GENACD
DIMENSION X(50), Y(50), ABC(50), SPEED(50), CONC(50), CALABS(50),
1XI(50), Y1(50)
REAL INCEPT
COMMON/ALPHA/X, Y, NVAL, ABC
COMMON/BETA/CALABS, SDDEV1, SDDEV2, INCEPT, RATE
EQUIVALENCE(Y(1), SPEED(1)), (X(1), CONC(1))
J=0
20 J=J+1
READ(7, 30) CONC(J), SPEED(J)
ABC(J)=Y(J)
IF(Y(J)) 40, 40, 20
30 FORMAT(F5.3, E8.3)
C
C
40 CONTINUE
NVAL=J-1
C
CALL LESQR
CALL OUTPUT
RETURN
END
SUBROUTINE HAMMET
DIMENSION X(50),Y(50),ABC(50),RATE(50),SIGMA(50)
REAL INCEPT,CALABS(50)
COMMON/ALPHA/X,Y,NVAL,ABC
COMMON/BETA/CALABS,SDDEV1,SDDEV2,INCEPT,RAT
J=0
20 J=J+1
READ(7,30) SIGMA(J),RATE(J)
30 FORMAT(F5.3,E8.4)
IF(RATE(J))40,40,20
40 CONTINUE
NVAL=J-1
DO 50 J=1,NVAL
ABC(J)=RATE(J)
Y(J)=ALOG10(ABC(J))
X(J)=SIGMA(J)
50 CONTINUE
CALL LESQR
DO 60 1=2,NVAL
CALABS(I)=10.0**CALABS(I)
60 CONTINUE
CALL OUTPUT
RETURN
END

SUBROUTINE BRONST
REAL INCEPT,CALABS(50)
DIMENSION X(50),Y(50),ABC(50),RATE(50),PKA(50)
COMMON/ALPHA/X,Y,NVAL,ABC
COMMON/BETA/CALABS,SDDEV1,SDDEV2,INCEPT,RAT
J=0
20 J=J+1
READ(7,30) PKA(J),RATE(J)
30 FORMAT(F5.3,E8.4)
IF(RATE(J))40,40,20
40 CONTINUE
NVAL=J-1
DO 50 J=1,NVAL
ABC(J)=RATE(J)
Y(J)=ALOG10(ABC(J))
X(J)=-PKA(J)
50 CONTINUE
CALL LESQR
DO 60 1=1,NVAL
CALABS(I)=10.0**CALABS(I)
60 CONTINUE
CALL OUTPUT
RETURN
END
SUBROUTINE SECOND
DIMENSION X(50), Y(50), ABC(50), RATE(50), PH(50)
COMMON PH
COMMON/BETA/CAIABS, SDDEV1, SDDEV2, INCEPT, RAT
COMMON/ALPHA/X, Y, NVAL, ABC
REAL INCEPT, CALABS(50)

J = 0
20 J = J + 1
READ(7, 30) PH(J), RATE(J)
IF (RATE(J)) 40, 40, 20
30 FORMAT(F5.3, E8.4)
40 CONTINUE
NVAL = J - 1
DO 50 I = 1, NVAL
   ABC(I) = RATE(I)
   Y(I) = ABC(I)
   X(I) = 10.0**(-PH(I))
50 CONTINUE
CALL LESQR
CALL OUTPUT
DO 60 I = 1, NVAL
   X(I) = -PH(I)
   Y(I) = ALOG10(Y(I))
60 CONTINUE
CALL LESQR
CALL OUTPUT
DO 70 I = 1, NVAL
   CALABS(I) = 10.0**CALABS(I)
70 CONTINUE
CALL OUTPUT
RETURN
END
SUBROUTINE LOGGER
RETURN
END
C MAIN CALLING PROGRAM FOR OPENENDED GENERALISED LEAST SQUARES PROGRAM

C THE NORMAL CALLING PROCEDURE IS USED READING IN THE
C NAMES OF THE ROUTINES REQUIRED THEN ENTERING A LOOP TO CALL
C TO THE ROUTINE WHICH WILL CALCULATE THE WEIGHTS AND DERIVATIVES

INTEGER CMNT(20),J(20), RUNNUM
READ(7,20)(J(I),I=1,10)
2 READ(7,10)RUNNUM,MODE
10 FORMAT(I3,A4)
C NUMBER RUN SERIES TERMINATOR IS USED RUN NUMBER 999
IF(RUNNUM.EQ.999) STOP
READ(7,20)(CMNT(I),I=1,20)
20 FORMAT(20A4)
WRITE(2,30) RUNNUM,MODE
30 FORMAT(10H RUN NUMBER,15,26H THE MODE OF THE DATA WAS ,A4)
WRITE(2,40)(CMNT(I),I=1,20)
40 FORMAT(20X,20A4)
DO 50 I=1,10
50 WRITE(2,55)MODE
55 FORMAT(44H YOU HAVE PUNCH AN UNRECOGNISABLE MODE*** ,A4,28H THE
RUN HAS BEEN TERMINATED )
STOP
60 GOTO(70,80,90,100,100,100,100,100,100,100 ),I
70 CALL CONSEC
GOTO 2
80 CALL GENUVA
GOTO 2
90 CALL PHPROF
GOTO 2
100 WRITE(2,110) MODE
110 FORMAT(7H MODE ,A4,24H HAS NOT BEEN ALLOCATED )
STOP
END
SUBROUTINE PH PROF
RETURN
END
SUBROUTINE GENUVA
RETURN
END
SUBROUTINE GELSQ2
LOGICAL DECIDE
REAL MATRIX(10,10) ,L(200)
DIMENSION F(10,200),FO(200),X(200),Y(200),PRMTER(10),COEF(10),
1 DELTA(10) ,ERROR(10)
COMMON WINT,NVAL,F,FO,X,Y,NIT,DECIDE,L,N,PRMTER
NN=N
DO 20 I=1,N
DO 10 J=1,N
MATRIX(I,J)=0.0
10 CONTINUE
COEF(I)=0.0
20 CONTINUE
FOI=0.0
C THIS INITIALISES THE ARRAYS BEFORE THE SUMMATIONS
DO 40 K=1,N
DO 60 M=1,N
DO 50 I=2,NVAL
MATRIX(K,M)=MATRIX(K,M)+F(K,I)*F(M,I)/L(I)
50 CONTINUE
60 CONTINUE
40 CONTINUE
WRITE(2,990) ((MATRIX(I,J),I=1,5),J=1,5) ♦
CALL ORTO2 ( MATRIX,NN,N) ♦
990 FORMAT(1H ,5E14.3) ♦
WRITE(2,990) ((MATRIX(I,J),I=1,5),J=1,5) ♦
DO 70 I=2,NVAL
FOI=FOI+FO(I)**2/L(I)
70 CONTINUE
DO 80 J=1,N
COEF(J)=COEF(J)+F(J,I)*FO(I)/L(I)
80 CONTINUE
DO 90 I=1,N
DELTA(I)=0.0
90 CONTINUE
DO 110 I=1,N
DELTA(I)=DELTA(I)+MATRIX(I,J)*COEF(J)
110 CONTINUE
DO120 I=1,N
PRMTER(I)= PRMTER(I)- DELTA(I)
120 CONTINUE  
SEXT=0.0  
DO 130 I=1,N  
SEXT=SEXT-COEF(I)*DELTA(I)  
130 CONTINUE  
C NOW CALCULATE THE F VALUES AND THE STANDARD DEVIATIONS  
VAL=NVAL-1  
T=SEXT/(VAL*WINT**2)  
DIV=VAL*FLOAT(NV)  
DO 140 I=2,NVAL  
ERROR(I)=(MATRIX(1,1)/(DIV*WINT))**0.5  
140 CONTINUE  
DO 150 I=1,N  
DECIDE=DELTA(I).LT.0.1*ERROR(I)  
IF(.NOT.DECIDE) GOTO 175  
150 CONTINUE  
175 DECIDE= NIT.EQ.10 .OR.DECIDE  
C NOW CALCULATE THE PERCENTAGE ERRORS  
DO 160 I=1,N  
ERROR(I)=ERROR(I)/PRMTER(I)*100.0  
160 CONTINUE  
IF(NIT.EQ.1)WRITE(2,170)  
170 FORMAT(IHO,25X,36H CORRECTED VALUES OF COEFFICIENTS )  
WRITE(2,180)(PRMTERd), I=1,N)  
180 FORMAT(IIH PARAMETERS,10(1PE12.4))  
WRITE(2,190)(ERROR(I),I=1,N)  
190 FORMAT(15H PERCENT ERRORS,3X,(10(0PF5.2,7X)) )  
IF(.NOT. DECIDE)RETURN  
C IF THE ITERATIONS ARE COMPLETE WRITE OUT THE INVERSE MATRIX  
C NOTE THAT ASIMPLE IMPLIED LOOL IS NOT USED BECAUSE THE EXACT SIZE  
C OF A LINE CANNOT BE EZPLICITLY STATED  
DO 200 J=1,N  
WRITE(2,210)( MATRIX(I,J),I=1,N)  
210 FORMAT(IHO, 10(1PE13.4))  
200 CONTINUE  
RETURN  
END
SUBROUTINE CONSEC
C A SUBROUTINE FOR CONSECUTIVE FIRST ORDER REACTIONS DET BY UV
C MEASUREMENTS
REAL L(200) ,K1,K2 ,K21
DIMENSION F(10,200),FO(200),X(200),Y(200),TIME(200),RECORD(200)
LOGICAL DECIDE
COMMON WINT,NVAL,F,FO,X,Y,NIT,DECIDE,L,N,K2,K1,C,B,A
COMMON/FRED/WX,WY
DECIDE=.FALSE.
NIT=1
N=5
READ(7,10) SCALE,OFFSET,CNVN
10 FORMAT(3F4.0)
C THIS READS IN THE ABSORBANCE SCALE USED THE BACK OFF THE APPROXIMATE
C CONCENTRATION AND THE TIME CONVERSION FROM INCHES TO SECONDS
J=0
20 J=J+1
READ(7,30) TIME(J),RECORD(J)
30 FORMAT(F3.1,F4,2)
C THIS READS IN THE X AND Y AXIS OF THE RECORDER
C THEN WE CAN CONVERT THE TIME TO SECONDS AND THE RECORDER VALUES
C TO ABSORBANCES
X(J)=TIME(J)*CNVN
Y(J)=OFFSET+RECORD(J)*SCALE
IF (TIME(J)) 40,20,20
40 CONTINUE
NVAL=J-1
A=Y(1)
C=Y(J)
READ(7,50) NTIME,NTIME,K1,K2
50 FORMAT(I3,2E7.3)
B=Y(NTIME)
C THIS READS IN THE NTTH VALUE AT WHICH THE MAXIMUM OD IS OBSERVED
C THIS IS TAKEN TO BE THE OD OF THE INTERMEDIATE
C THE SAME CARD ARE PUNCHED THE ESTIMATES OF K1 AND K2
60 FORMAT(3F4.0)
DO 60 I=2,NVAL
EXPK1T=EXP(-K1* X(I) )
62 K21 = K2- K1
WINT=K21
WX=K21/(.10 * CNVN )
COEF1 = A * K21 + B * K1 - C * K2
COEF2 = C * K1 - B * K1
DO 60 I=2,NVAL
EXPK1T=EXP(-K1* X(I) )
EXPK2T = EXP(-K2*(X(I)))
FX = -K1 * EXPK1T * COEF1 - K2 * EXPK2T * COEF2
FY = -K21
L(I) = (FX/WX)**2 + (FY/WY)**2
FO(1) = -Y(I) * K21 + EXPK1T * COEF1 + EXPK2T * COEF2 + C*K21
F(5,I) = K21*EXPK1T
F(4,I) = K1 * EXPK1T - K1 * EXPK2T
F(3,I) = -K2 * EXPK1T + K1 * EXPK2T + K21
F(2,I) = Y(I)-C*(B-A)*EXPK1T-X(I)*EXPK2T*COEF1+(C-B)*EXPK2T
F(1,I) = -Y(I) + C + (A-C) * EXPK1T -X(I) *EXPK2T*COEF2

60 CONTINUE
WRITE(2,997)(((F(J,I),J=1,5),FO(I),L(I)),I=2,NVAL)
997 FORMAT(1H , (7E15.3))
CALL GELSQ2
IF(DECIDE) RETURN
NIT=NIT+1
GOTO 62
END

For this program the subroutine MATINV has been retitled ORTO2
all other features of this matrix inversion program are unchanged
DIMENSION J(6)

C MAIN CALLING PROGRAM

INTEGER RUNNUM, MODE, CMNT(20)
READ(7,2)(J(I), I=1,6)
2 FORMAT(6A4)
1 READ(7,10) RUNNUM, MODE
10 FORMAT(I3,A4)

C NORMAL RUN SERIES TERMINATOR
IF(RUNNUM.EQ.999) STOP

30 FORMAT(1HORON NUMBER, I8, 28H THE MODE OF THE DATA WAS , A4)
WRITE(2,30) RUNNUM, MODE
READ(7,20)(CMNT(I), I=1,20)
20 FORMAT(20A4)
WRITE(2,40)(CMNT(I), I=1,20)
40 FORMAT(1H0, 20X, 20A4)
DO 50 I=1,3
IF(MODE.NE.J(I)) GOTO 50
GOTO(60,70,80), I
50 CONTINUE
60 CALL GENUVM
GOTO 1
70 CALL PHPROF
GOTO 1
80 WRITE(2,81)
81 FORMAT(12H MODE ERROR )
STOP
WRITE(2,90) MODE
90 FORMAT(40H THE MODE PUNCHRD IS NOT RECOGNISABLE, A4)
STOP
END
SUBROUTINE PHPROF
RETURN
END
SUBROUTINE GENUVM
C A SUBROUTINE FOR DATA IN THE FORM OF ABSORBANCE VS TIME FOR GENERAL
C LEAST SQUARES FITTING
REAL L
EQUIVALENCE(OD,Y),(TIME,X)
LOGICAL DECIDE
DIMENSION FA(50),FB(50),FC(50),FO(50),FX(50),FY(50),L(50),TIME(50)
1,OD(50),X(50),Y(50)
COMMON/SHAMUS/FA,FB,FC,FO,A,B,C,NVAL,L,NIT,DECIDE
DECIDE=.FALSE.
NIT=1
READ(7,10)CNVN,BASE
C THIS READS IN THE CONVERSION FACTOR FOR DIVISIONS TO SECONDS.
C IF THE MEASUREMENTS ARE IN TRANSMITTANCE CONVERSION WILL BE NON ZERO
IF(BASE.EQ.0.0)GOTO 20
CALL GENUV2(CNVN,BASE)
RETURN
C NOTE THE USE OF THIS RETURN STATEMENT SO THAT WHEN THE ROUTINE
C RETURNS TO HERE IT IMMEDIATELY RETURNS TO THE MAIN PROGRAM
10 FORMAT(F4.0,F4.1)
20 CONTINUE
J=0
30 J=J+1
READ(7,40)TIME(J),OD(J)
TIME(J)=TIME(J)*CNVN
40 FORMAT(F3.1,F4.2)
IF(TIME(J))50,30,30
C THE TERMINATOR FOR A DATA SEQUENCE IS A NEGATIVE TIME, THE OD IS THE
C GUESSED INFINITY VALUE, THEN THE ESTIMATE OF THE RATE CONSTANT IS
C READ IN
50 CONTINUE
NVAL=J-1
READ(7,60)B
60 FORMAT(E11.4)
A=OD(J)
C=OD(1)
62 AC=A-C
DO 61 I=2,NVAL
EXPCT = EXP (-B * X(I))
$F_O(I) = -A \cdot Y(I) + AC \cdot EXPKT$

$FA(I) = -1.0 \cdot EXPKT$

$FB(I) = -AC \cdot EXPKT \cdot X(I)$

$FC(I) = -EXPKT$

$FX(I) = -AC \cdot EXPKT \cdot B$

$L(I) = (FX(I) \cdot 0.1)^2 + 0.5$

CONTINUE

CALL GELSQR

IF(DECIDE) RETURN

NIT = NIT + 1

GOTO 62

END
SUBROUTINE GENUV2(CNVN,BASE)

REAL L
LOGICAL DECIDE

DIMENSION FA(50),FB(50),FC(50),FO(50),FX(50),FY(50),L(50),TIME(50)
1,TRANS(50),X(50),Y(50)
COMMON/SHAMDS/FA,FB,FC,FO,A,B,C,NVAL,L,NIT,DECIDE
EQUIVALENCE(TRANS,Y),(TIME,X)

DECIDE=.FALSE.
NIT=1
J=0
30 J=J+1
READ(7,40) TIME(J),TRANS(J)
TIME(J)=TIME(J)*CNVN
40 FORMAT(F3.1,F4.2)
IF(TIME(J)>50,30,30
50 CONTINUE

C THE TERMINATOR FOR A DATA SEQUENCE IS A NEGATIVE TIME, THE OD IS THE
C GUESSED INFINITY VALUE, THEN THE ESTIMATE OF THE RATE CONSTANT IS

READ(7,60) B
60 FORMAT(E11.4)
A=TRANS(J)
C=TRANS(1)
NVAL=J-1
62 AC=ALOG(C/A)
DO61 I=2,NVAL
EXPBX=EXP(-B*X(I))
FA(I)=(1.0-EXPBX)/A
FB(I)=-X(I)*EXPBX*AC
FC(I)=EXPBX/C
FO(I)=AC*EXPBX-ALOG(Y(I)/A)
L(I)=(B*EXPBX*AC/10.)**2*(1.0/(01.3*Y(I)))**2
61 CONTINUE
CALL GELSQR
IF(DECIDE)RETURN
NIT=NIT+1
GOTO 62
RETURN
END
SUBROUTINE GELSQR
LOGICAL DECIDE
REAL MATRIX,INVERT,L (50)
DIMENSION MATRIX(3,3),INVERT(3,3),DELTA(3),COEF (4),FA(50),FB(50),
IFC(50),FX(50),FY(50),FO(50),VARNCE(6),ERROR(3)
DIMENSION VARNC(6)
EQUIVALENCE(VARNCE,VARNC)
EQUIVALENCE(MATRIX,INVERT)
COMMDN/SHAMUS/FA,FB,FC,FO,A,B,C,NVAL,L,NIT,DECIDE
DO 20 I=1,3
DO 10 J=1,3
MATRIX(I,J)=0.0
COEF(I)=0.0
20 CONTINUE
FOI=0.0
C THIS SETS THE ELEMENTS OF THE ARRAYS TO ZERO BEFORE THE SUMMATIONS
DO 90 I=2,NVAL
MATRIX(1,1)=MATRIX(1,1) +FA(I)*FA(I)/L(I)
MATRIX(1,2)=MATRIX(1,2) +FA(I)*FB(I)/L(I)
MATRIX(1,3)=MATRIX(1,3) +FA(I)*FC(I)/L(I)
MATRIX(2,2)=MATRIX(2,2) +FB(I)*FB(I)/L(I)
MATRIX(2,3)=MATRIX(2,3) +FB(I)*FC(I)/L(I)
MATRIX(3,3)=MATRIX(3,3) +FC(I)*FC(I)/L(I)
FOI=FOI+FO(I)**2/L(I)
COEF(I)=COEF(I)+FA(I)*FO(I)/L(I)
COEF(2)=COEF(2)*FB(I)*FO(I)/L(I)
90 CONTINUE
C NOW WE CAN SET THE OTHER ELEMENTS OF THE ARRAY TO THEIR VALUES
DO 110 I=1,3
DO 100 J=1,3
MATRIX(J,I)=MATRIX(I,J)
100 CONTINUE
110 CONTINUE
CALL MATINV(MATRIX,3,3)
DO 120 I=1,3
DELTA(I)=0.0
120 CONTINUE
DO 150 I=1,3
DO 140 J=1,3
DELTA(I)=DELTA(I)-INVERT(I,J)*COEF(J)
140 CONTINUE
150 CONTINUE
A = A - DELTA(1)
B = B - DELTA(2)
C = C - DELTA(3)

C The following statements could be dispensed with but they will be
C useful where the weight of unit variance is not unity and the
C propagation coefficients are desired

VARNC(1) = INVERT(1,1)
VARNC(2) = INVERT(2,2)
VARNC(3) = INVERT(3,3)
VARNC(4) = INVERT(1,2)
VARNC(5) = INVERT(2,3)

C

C Now we can test to see if a satisfactory convergence has been
C reached
C

SEXT = FOI
DO 160 I = 1, 3
  SEXT = SEXT - COEF(I) * DELTA(I)
160 CONTINUE

VAL = NVAL
F = SEXT / (VAL - 3.0)
IF (NIT .NE. 1) WRITE (2, 170)
170 FORMAT (10SH NIT PARAMETER A PERCENT ERROR PARAMETER B PERCENT ERRO
1R PARAMETER C PERCENT ERROR SIGMAEXT/SIGMAINT    )

C Now test for convergence

DIV = ((VAL - 3.0) * VAL)
DO 171 I = 1, 3
  ERROR(I) = (VARNC(I) / DIV) ** 0.5
171 CONTINUE

DO 172 I = 1, 3
  DECIDE = DELTA(I) .LT. .25 * ERROR(I)
  IF (.NOT. DECIDE) GOTO 175
172 CONTINUE

175 DECIDE = NIT .EQ. 10 .OR. F .LT. 0.010 .AND. DECIDE
  ERROR(1) = ERROR(1) / A * 100
  ERROR(2) = ERROR(2) / B * 100
  ERROR(3) = ERROR(3) / C * 100
  WRITE (2, 180) NIT, A, ERROR(1), B, ERROR(2), C, ERROR(3), F
180 FORMAT (1H , 12, 2X, (3(1PE11.4, 2X, 0PF7.2, 6X), F8.4))
  IF (NIT .EQ. 10) WRITE (2, 200)

200 FORMAT (95H After ten iterations a satisfactory convergence could
1not be obtained, the run was abandoned    )
RETURN
END
SUBROUTINE MATINV(A,M,N)
DIMENSION A(M,N),B(40)
M1=M-1
N1=N-1
N2=0
DO 7 I=1,M
B(N)=1.0/A(1,1)
N2=N2+1
3 DO 5 K=1,N1
5 B(K)=A(1,K+1)*B(N)
DO 6 I=1,M1
A(I,N)=-B(N)*A(I+1,1)
DO 6 J=1,N1
6 A(I,J) = A(I+1,J+1) -B(J)*A(I+1,1)
DO 7 J=1,N
7 A(M,J) = B(J)
RETURN
END
REFERENCES TO THE EXPERIMENTAL SECTION

10) A. Wohl and H. Schweizer, Ber. 39, 890 (1906).
17) ref. 8 p789.
27) C. K. Ingold, "Structure and Mechanism in Organic Chemistry",
REFERENCES TO THE DISCUSSION AND INTRODUCTION SECTION.

19) See for example;
37) see reference 2 for a discussion of this point.
40) For a discussion of this point see ref. 7 pp28-9.
45) For a lucid and somewhat entertaining discussion of this and related topics see "The Use and Misuse of Thermodynamics", Inaugural Lecture in the University of Exeter, January 1965, University of Exeter Press.


56) ref. 53 p

57) ref. 54 p 383.

58) See section on chymotrypsin in ref. 2

59) ref 53 p 448.


74) B. Capon private communication.
76) See ref. 19 in ref. 1.
J. Wiley and Sons, N.Y., 1961, P 213.
81) ref. 79 and uncited work in reference 75.
85) For an early discussion of this point see; J. N. E. Day and C. K. Ingold, Trans Farad. Soc., 37, 686(1941); R. P. Bell, Trans.
Farad. Soc., 37, 705(1941).
88) R. P. Bell, "The Proton in Chemistry", Cornell University Press,
Ithaca, N.Y., 1959, p 118.
91) See for example K. F. Alder and F. Farina, Anales. Real Soc. Espana
Fis y Quim(Madrid), 54B, 689-9(1958).
92) ref 64.
94) B. Capon private communication.
95) T. N. Polynova, N. G. Bolzii and M. A. Poraikoshits, Zh. Struct.
Chim., 6B, 878(1965), see C.A. 64, 11978.