THE GENERATION AND PROPERTIES OF TETRAHEDRAL INTERMEDIATES

by

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TO

MY PARENTS

AND

HELEN

STATEMENT

This project was carried out in the Chemistry Department of the University of Glasgow, with the guidance of Professor B. Capon. There is no part being submitted concurrently for another degree.

October 1975 - September 1978

Signed:

DUNCAN McLEAN ALLAN GRIEVE

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Duncan Grieve,
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University of Glasgow.

October 1978

ABSTRACT

The study of "tetrahedral intermediates" is reviewed.

Studies by proton nuclear magnetic resonance spectroscopy (N.M.R.), of several ortho ester derivatives (acetoxy-dimethoxy-methane, acetoxy-diethoxy-methane, 2-acetoxy-1,3-dioxolan, 2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan and 2-chloroacetoxy--4,4,5,5-tetramethyl-1,3-dioxolan) have shown the existence of the postulated tetrahedral intermediates likely to be obtained from loss of the acetoxy or chloroacetoxy group followed by reaction with water. These intermediates have been shown to be observable over long periods at low temperatures and the rate constants for their decomposition have been calculated. The observation of one intermediate, 2-hydroxy--4,4,5,5-tetramethyl-1,3-dioxolan has also been carried out using ^{13}C N.M.R.

Attempts to synthesise other acetoxy species and other possible precursors (phenoxy and p-nitro-phenoxy derivatives, etc.) have all met with failure. Studies on the hydrolyses of other compounds have not resulted in the detection of any tetrahedral intermediates. Also no intermediates were detected in the reactions of various carbenium salts.

The hydrolyses of 2,2-dimethoxytetrahydropyran and 2,2-diethoxytetrahydropyran yield δ-valerolactone, the alcohol (methanol or ethanol) and methyl or ethyl 5-hydroxyvalerate, indicating that the reaction is not specific as thought by Deslongchamps.

The kinetics of the hydrolysis of benzaldehyde di-t-butyl acetal and α-acetoxy-α-t-butoxy-toluene has been studied in several acetate and one imidazole buffers. Both have been shown to hydrolyse by rate limiting decomposition of the hemiacetal at low pH by general buffer catalysis. Whereas no change in the rate determining step is observed for α-acetoxy-α-t-butoxy-toluene the hydrolysis of benzaldehyde di-t-butyl acetal shows complex two step kinetics (i.e. an induction period) over a very large pH range (ca 4-7) with a change in the rate determining step to hydrolysis of the acetal. No general buffer catalysis was observed at the higher pHs in the buffer used (imidazole).

C O N T E N T S

C O N T E N T S (Cont'd)

INTRODUCTION

The Moral of the Tale

"It is interesting to speculate why certain compounds have resisted discovery for long periods of time, only to be synthesised quite painless once the initial breakthrough has been made. Although reasons can be given that are peculiar to each system, the general pattern seems to be an initial unsuccessful effort to make a compound, followed by detailed rationalisation of the failure. Thereafter the rationalisation tends to be accepted, and little or no effort is made to refute it".

Non Existent Compounds.

E.H. Appelman Acc. Chem. Res. (1973) 113.

Historical Introduction

Hydrolyses and Esterification Reactions

The study of esterifications and related reactions have, from the first investigations by Berthelot and Péan de Saint-Gilles[1] (over 100 years ago) to present day research, produced a wealth of explanations and deductions for what appear initially to be some of the simplest reactions in chemistry. The possible reaction mechanisms[2] are generally sub-divided according to the type of bond fission, acyl-oxygen (AC) or alkyl-oxygen (AL), the nature of the rate determining step, unimolecular (1) or bimolecular (2) and finally whether the ester (B) or conjugate acid (A) is involved.

The evidence favouring particular reaction mechanisms stems from basically three sources (a) the use of isotopes, (b) the determination of products and (c) the effects on kinetics by structural changes in the substrate.

It is not altogether obvious at this stage that only two of the possible mechanisms, $B_{AC}2$ and $A_{AC}2$, could generate possible tetrahedral intermediates in their reactions and so evidence for the other mechanisms will be included, in part, for consideration. The definition of a "tetrahedral intermediate" will become obvious in the later discussions.

Hydrolysis reactions involve the incorporation of water into the products (esterifications are effectively the reverse). One of the main possible uses of isotopes, therefore, can be the use of labelled ^{18}O water and the resulting incorporation or non-incorporation into products.

The use of ^{18}O water was first used by Polanyi and Szabo[3] in the investigation of the alkaline hydrolysis of n-amyl acetate. They showed that the incorporation of ^{18}O from the solvent appeared in the acid product but not in the alcohol. Further studies on a variety of esters; γ-butyrolactone,[4] methyl 2,4,6-triphenylbenzoate,[5] diphenylmethyl and 9-fluorenyl acetates,[6] methyl trifluoroacetate,[7] phenyl and diphenylmethyl trifluoroacetates,[8] bornyl and isobornyl acetates,[9] ethyl, isopropyl and t-butyl benzoates[10] have all shown similar results, i.e. acyl-oxygen fission in alkaline solution.

The acid hydrolyses of methyl hydrogen succinate,[13] diphenylmethyl formate,[14] γ-butyrolactone,[4] methyl,[7] and phenyl fluoroacetates,[8] bornyl acetate,[9] phenyl acetate, ethyl acetate and methyl formate[15] all show oxygen incorporation into the acid function i.e. acyl-oxygen fission. The esterification[16] of methanol and benzoic acid, the reverse of hydrolysis, also showed exchange to the carbonyl function.

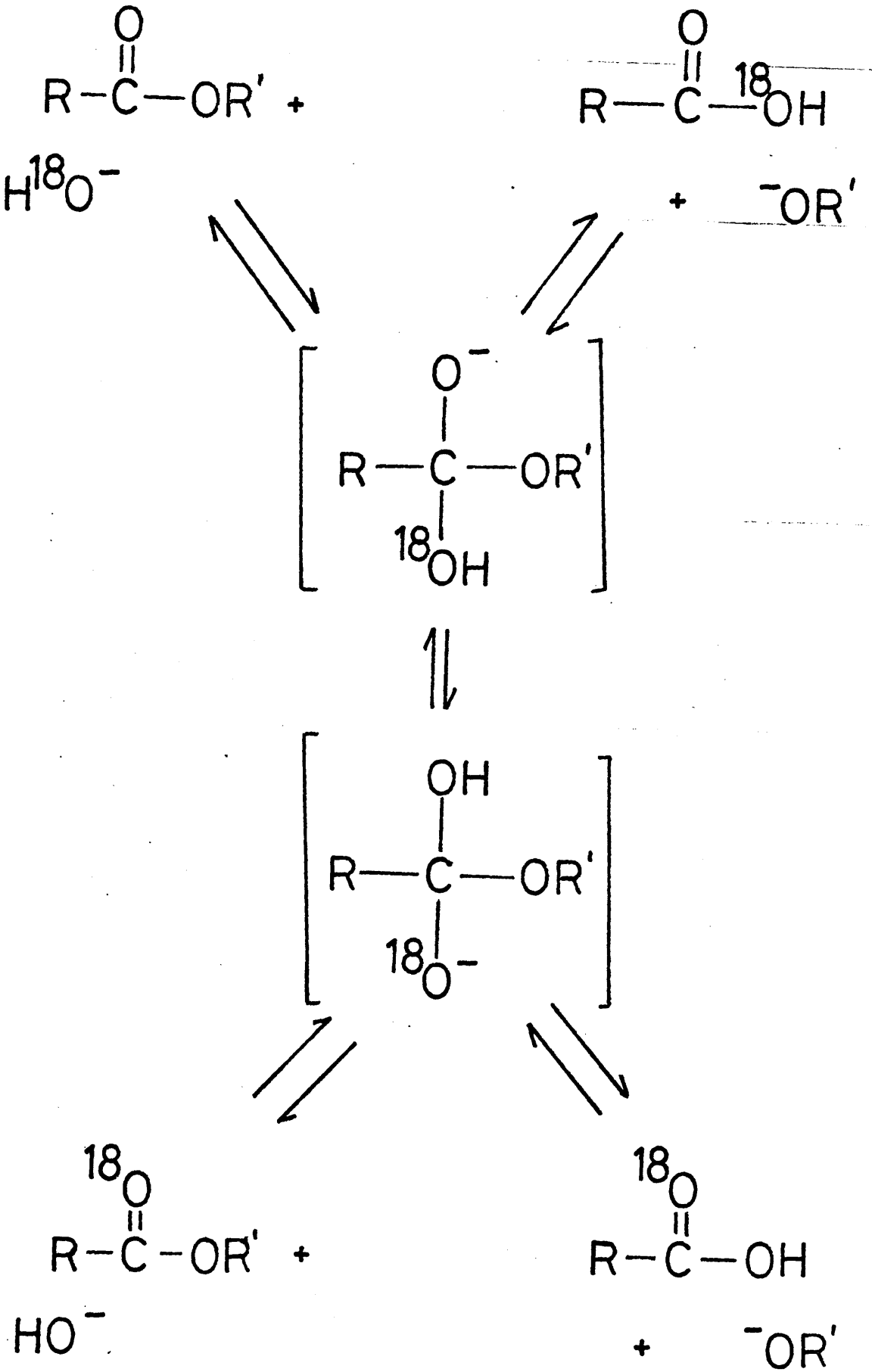
The incorporation of ^{18}O into the alcohol function has been observed for the acid hydrolysis of t-butyl acetate,[17,18] diphenylmethyl trifluoroacetate,[8] p-methoxy-diphenylmethyl acetate[19] and triphenylmethyl acetate[20] which are all hydrolysed by the $A_{AL}1$ mechanism.[21] Hydrolysis of β-butyrolactone[22] in neutral solution led to ^{18}O incorporation in the alkyl function ($B_{AL}2$ mechanism).[21]

A modification to the above method where the label is incorporated into the ester, in the alkyl oxygen, has been studied for ethyl propionate[23] and shown to produce ethanol containing excess ^{18}O.

Product analysis has played a large part in the comparison of acyl-oxygen versus alkyl-oxygen cleavage but not as a direct method for evidence for or against tetrahedral intermediates. It has served, however, to eliminate a number of hydrolysis reactions from possible consideration by the simple fact that if alkyl-oxygen cleavage occurs an S_N type displacement takes place with no tetrahedral intermediate being possible (see later).

The first evidence for acyl-oxygen fission, from product analysis, was produced by Holmberg[40] from the study of the alkaline hydrolysis of acetoxysuccinic acid which yielded the alcohol with the same relative configuration as that in the starting material. This early attempt, however, was

Fig. 1


R—C—OR' +
H18O−
R—C—18OH
+ −OR'
O−
R—C—OR'
18OH
OH
R—C—OR'
18O−
18O
R—C—OR' +
HO−
18O
R—C—OH
+ −OR'

flawed in that participation of the carboxylate ion of the acid could occur, i.e. an intramolecular reaction, giving retention of configuration with alkyl-oxygen cleavage. Later work using methyl allyl acetates[41] and neopentyl esters[42] has shown no rearrangement whereas with certain asymmetrical allyl[43,44] alcohol esters have shown rearrangement and racemisation to occur.

The observation of ethers[45] during alcoholysis and the formation of alkenes during hydrolysis reactions[5,46] have also pointed to alkyl-oxygen fission.

In the reactions in which acyl-oxygen cleavage takes place two possible extremes of mechanism are possible summarised as direct S_N type displacement (both S_N1 and S_N2). In the case of S_N2 displacement, i.e. the bimolecular reaction, the possibility arises of a discrete intermediate species. The evidence obtained of incorporation of ^{18}O from the solvent into the unreacted starting material could be regarded as evidence for such an intermediate, having a finite lifetime, in which proton transfer occurred faster than the breakdown to products (see fig. 1). If this rate of ^{18}O exchange was much slower than the rate of hydrolysis, however, it could be argued that the ^{18}O exchange was a side-reaction and was not involved in the hydrolysis step.

If one assumes a tetrahedral species does exist three factors would be important in determining the ratio of the rate of hydrolysis to the rate of exchange (k_H/k_e). These are (A) the relative rate of the initial equilibrium step (attack, for example, by $^{\ominus}OH$) as against the rate of loss of alkoxide (B) the basicities of alkoxide (or more generally X) versus hydroxide (C) and the relative stabilities of the cationic products. It can be seen, therefore, that the values of k_H/k_e may be expected to vary. (Phenylacetate[15] k_H/k_e = 120, ethyl acetate[15] k_H/k_e = 5, isobornyl acetate[9] k_H/k_e = ~ 0,5). In one case, at least, the rate of ^{18}O exchange for ethyl trifluoroacetate,[24] has been shown to be similar to that of hydrolysis.

It should be noted, at this stage that if proton transfer is slow, or the lifetime of the intermediate is short, no exchange may occur. This does not necessarily have to mean no intermediate on the reaction pathway. The hydrolysis of phenyl benzoate,[11] p-methoxy and p-chlorobenzyl benzoates[12] have shown no measurable incorporation.

Other possible interpretations can be viewed from this data either the "intermediate" is in fact a transition state where exchange can occur to some extent but not necessarily complete bond formation or fission during the intermediate period of the reaction, or that some other mechanism could in fact be operative.

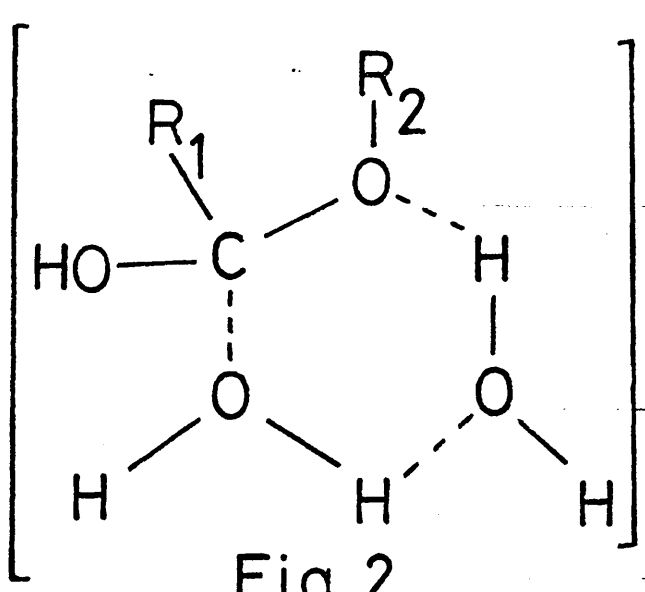


Fig. 2

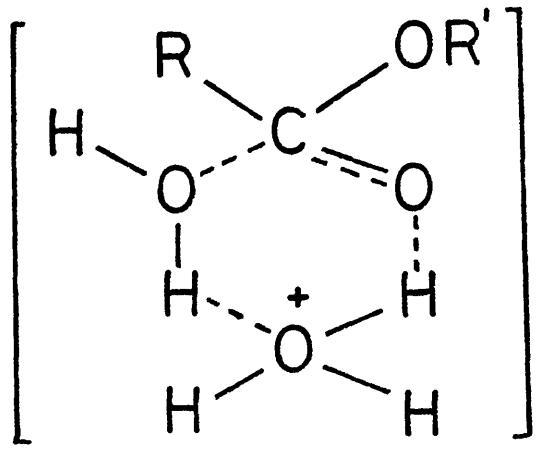


Fig. 3

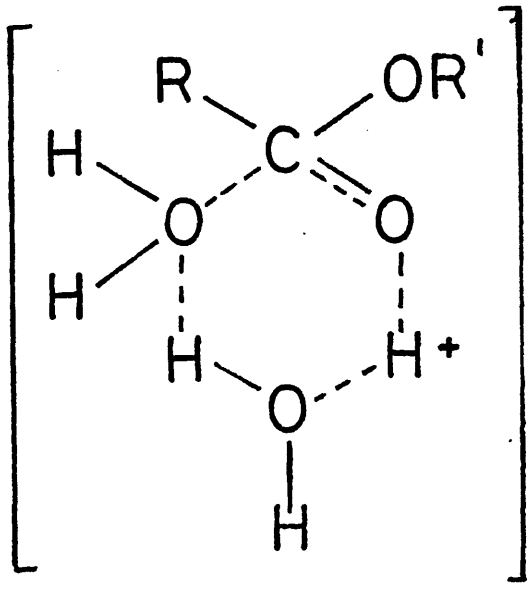
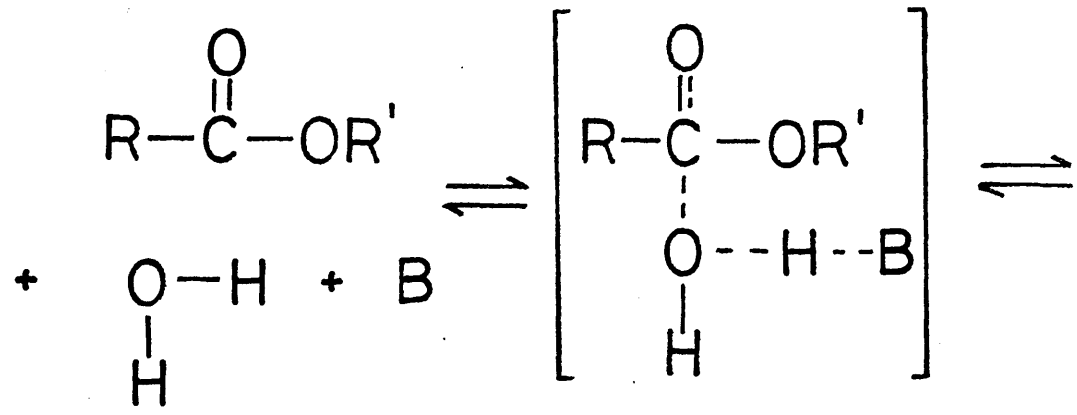
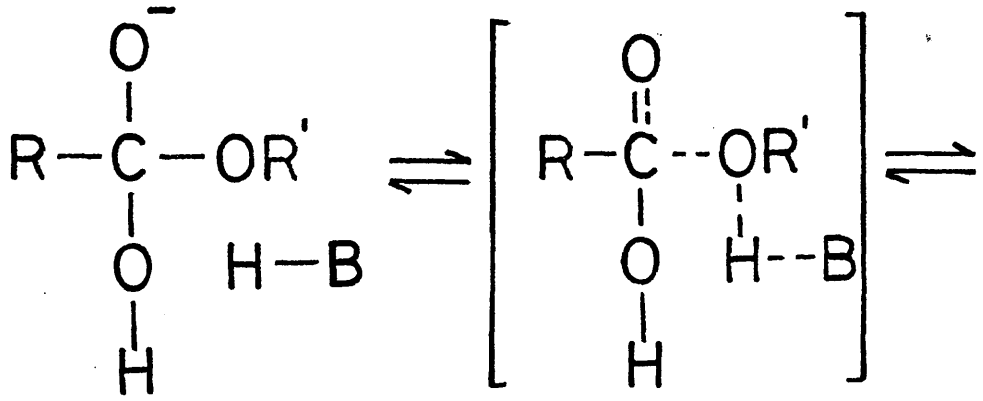


Fig. 4





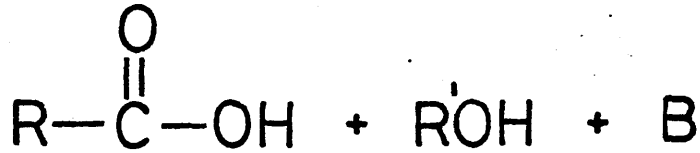


Fig. 5

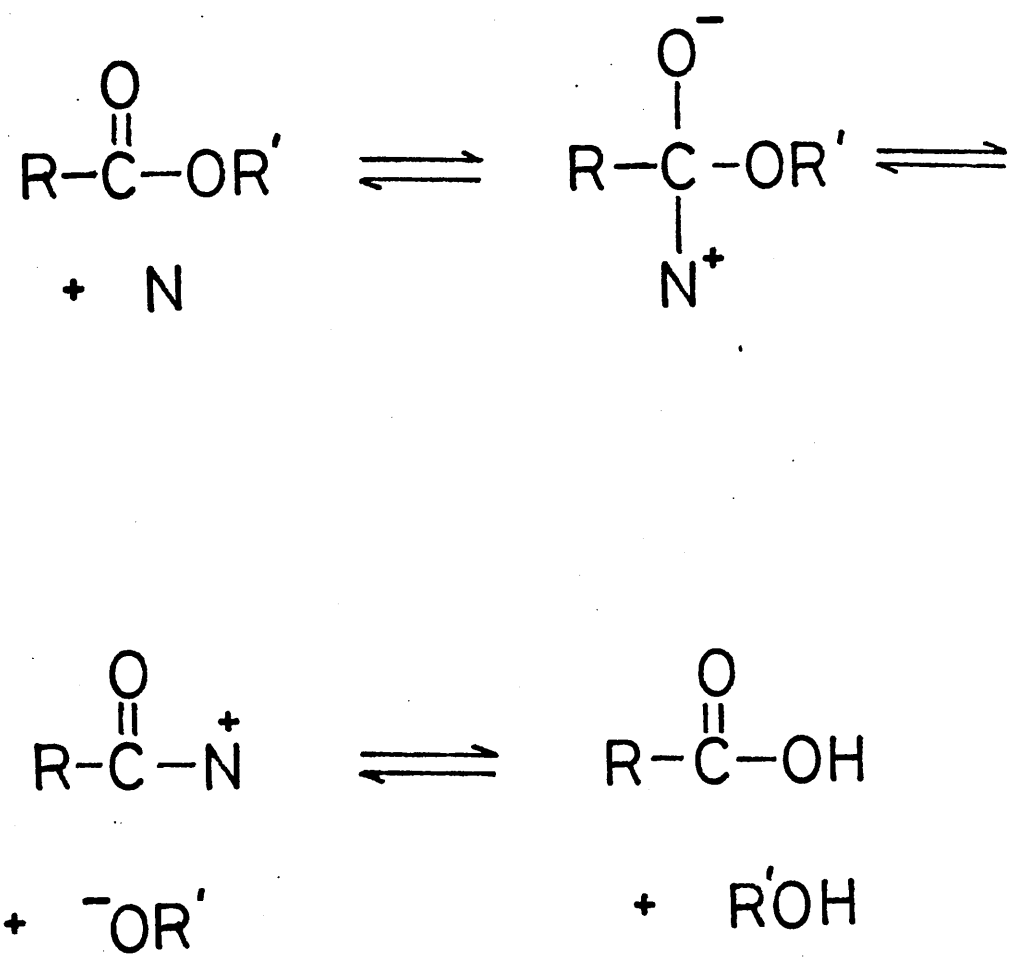


Fig. 6

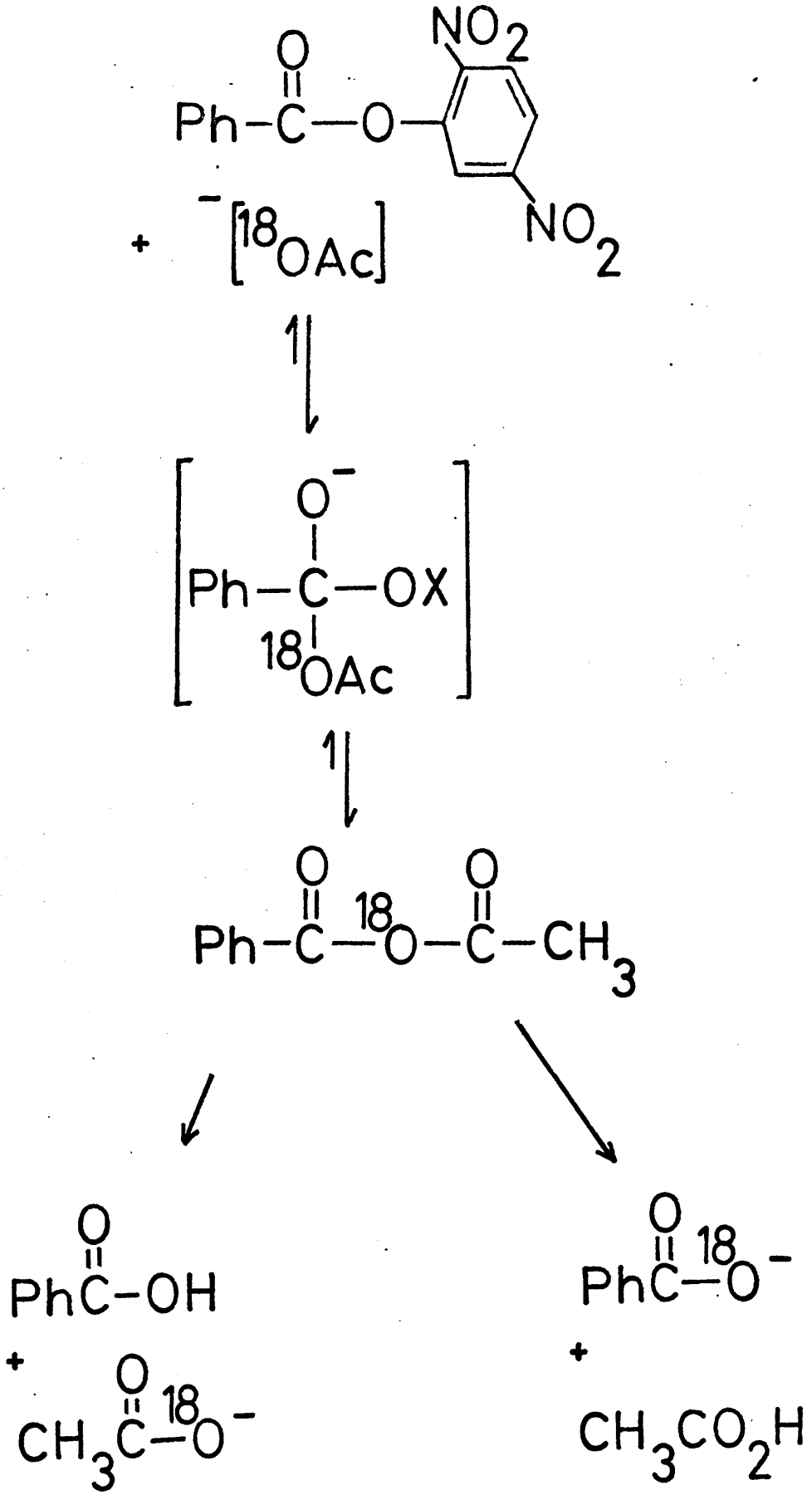


Fig. 7

The hydrolysis of esters[25] in concentrated acid (a different mechanism may exist in alkaline or neutral solution since it is known that kinetic equations change as pH changes) was explained by the transition state shown in figure 2. Other proposed transition states include figures 3[26] and 4[27].

An added complication of ester hydrolysis in buffer solutions is that of participation[28,31,32,33,34] of bases in either general base or nucleophilic catalysis. General base catalysis[28,29,30] can be represented as shown in fig. 5 where B can represent any base including hydroxide. The reaction can be seen to be represented as a two step process where proton transfer could be either a concerted or semi-concerted mechanism. The intermediate expected to be derived from nucleophilic catalysis, however, is not the species derived from attack of water as the nucleophile on the ester. Evidence for nucleophilic catalysis (fig. 6) is based mainly on the isolation or observation of the other intermediate $RC(=O)N^{\oplus}$, for example the hydrolysis[35] of 2,4-dinitrophenyl benzoate in ^{18}O labelled acetate resulted in a 75% incorporation of the ^{18}O into the benzoic acid product presumably by the mechanism shown (fig. 7). In the imidazole-catalysed hydrolysis of p-nitrophenyl acetate[36] it was possible to observe spectrophotometrically the formation of both p-nitrophenol and N-acetylimidazole during the reaction. In fact

many hydrolyses involve a change from general base catalysis to nucleophilic catalysis[33,34] or vice versa depending, for example, on the pKa of phenols in the hydrolysis of substituted phenyl acetates.

The analysis of the effect of deuterium oxide on the rates of hydrolysis are generally difficult to interpret as compared to the use of ^{18}O labelling. Generally, however, neutral hydrolysis[38] (action by water itself) has $k_{D_2O}/k_{H_2O} \approx 0.5\text{-}1.2$ as compared to acid[36,37] ($A_{AC}2$) catalysis $k_{D_2O}/k_{H_2O} \approx 1.3\text{-}1.68$ and base catalysis[28,29(b)] generally less than 0.5.

Structural reactivity correlations can play an important part in some cases in confirming the evaluation of the mechanisms of hydrolysis and esterification type reactions since they relate the effect of changes in the reactivity of a substrate by the addition of electron-attracting or donating species to the change in activation energy of the intermediate species. The use of Hammett,[47,49] Bronsted,[36] Taft and Bunnett[48] type relationships and plots have succeeded, to a certain extent, in suggesting the possible presence of tetrahedral intermediates and cationic species in acyl-oxygen and alkyl-oxygen changes by confirming views held on the effect of stabilisation and destabilisation of these species by substitution in both the acyl[49] and alkyl functions.[33] For

a much more detailed account of these effects on each of the possible mechanisms the works of Bender,[36], Johnson,[39(b)] Euranto,[39(a)] Ingold,[2(b)] Gold[50] and Bruice[51] should be consulted.

The Hydrolysis of Amides

There are many similarities in the hydrolysis of amides and that of esters. These can be summarised as the modes of hydrolysis of amides are effectively $B_{AC}2$ and $A_{AC}2$ mechanisms since the rate of hydrolysis[52] in moderately acidic or basic solution is proportional to the amide concentration and acid or base concentration respectively. The fact that for hydrolysis acyl-nitrogen cleavage must occur is obvious and so eliminates the other mechanisms. The effects of substituents[52] on alkaline hydrolysis is in the expected manner, where electron attracting groups accelerate and electron donating groups retard the rate of hydrolysis. The effects of substituents on the rate of acid hydrolysis[52] are, as expected, very slight; while steric effects slow the rate of hydrolysis in both acidic and basic solutions.[53] The exchange of the carbonyl oxygen of benzamide[54] with the solvent during its hydrolysis has shown that the tetrahedral species exists long enough to undergo a reaction other than breakdown to products or reversion to the starting materials. However the very high rate of hydrolysis versus exchange shows that either the relative rate of partitioning to products versus reactant is quite high, or that the lifetime is short.

In the study of amide hydrolysis in higher acid concentrations the rate is observed to go through a maximum[55] but is generally different for each amide. This maximum has been explained as being due to competitive protonation until saturation (i.e. all amide protonated) and declining activity of water as the acid strength increases. This effect has been studied by the consideration of acidity functions[56] and has tended to suggest a transition state with at least 3 water molecules involved.

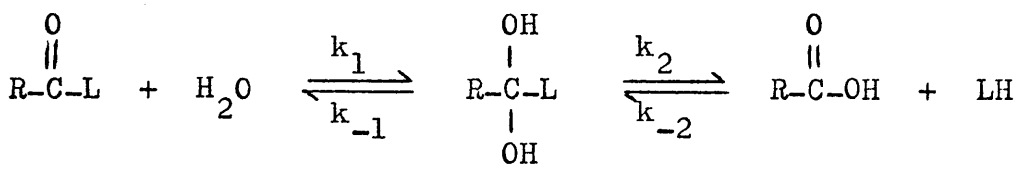
As with the ester hydrolysis added complications of competing pathways have been shown to exist, for example via the kinetic data.[55(b)] This type of situation will be discussed in a later section.

The hydrolysis of much more sterically hindered N-t-alkyl-substituted amides[57] in concentrated acid solutions have shown that the products, tertiary alcohols and olefins must be explained by alkyl-nitrogen fission contrary to the previous assumption but these systems may be expected to be exceptional cases.

Breaks in pH rate profiles and buffer concentration rate Curves

1) Partitioning of the Intermediate[39(b)]

Assuming the existence of tetrahedral intermediates the simplest possible mechanism for the reaction of a basic species with a carbonyl compound can be represented as



It can be seen therefore that the generation and decomposition of the tetrahedral intermediate can either be symmetrical or asymmetrical situation, where the symmetrical mechanism partitioning of tetrahedral intermediate occurs by a similar catalysis, k_2 and k_{-1}, in opposite directions. The asymmetrical mechanism similarly requires different catalysis in each direction.

Probably the most obvious deduction from the above considerations is that if the asymmetrical mechanism occurs in a particular reaction then a change in the type and rate of catalysis will become apparent in both the pH rate profile and buffer concentration rate curves. However in a symmetrical mechanism, where the entering and leaving groups are similar, the resulting plots should show no such change or break in the profiles.

Taken to extremes the apparent symmetrical mechanism may in fact produce an asymmetrical situation if the concentrations

TABLE 1 Kinetic behaviors of general acid-base catalyzed ester reactions

(Ref (39b))

No.	X_1	X_2	X_{-1}	k_{obs}	Kinetic Behavior [b]	
					Low Buffer Concentration	High Buffer Concentration
1	B	B	BH^+	$\frac{k_1 k_2 [B]^2}{k_{-1}[BH^+]+k_2[B]}$	No levelling off, however the pH of the system affects the kinetics low pH high pH	 $K[OH^-][B]$ $K[B]$
2	BH^+	BH^+	B	$\frac{k_1 k_2 [BH^+]^2}{k_{-1}[B]+k_2[BH^+]}$	No levelling off, however the pH affects the kinetics low pH high pH	 $K[BH^+]$ $K[H^+][BH^+]$
3	BH^+	B	B	$\frac{k_1 k_2 [B][BH^+]}{(k_{-1}+k_2)[B]}$	No levelling off	$K[BH^+]$
4	B	BH^+	BH^+	$\frac{k_1 k_2 [B][BH^+]}{[k_{-1}+k_2][BH^+]}$	No levelling off	$K[B]$
5	B	OH^-	BH^+	$\frac{k_1 k_2 [B][OH^-]}{k_{-1}[BH^+]+k_2[OH^-]}$	$K[B]$	$K[OH^-]^2$

TABLE 1 (Contd.)

No.	X_1	X_2	X_{-1}	k_{obs}	Kinetic Behavior [b]	
					Low Buffer Concentration	High Buffer Concentration
6	OH^-	B	H_2O	$\frac{k_1k_2[OH^-][B]}{k_{-1}+k_2[B]}$	$K[OH^-][B]$	$K[OH^-]$
7	B	H_3O^+	BH^+	$\frac{k_1k_2[B][H^+]}{k_{-1}[BH^+]+k_2[H^+]}$	$K[B]$	K
8	H_3O^+	B	H_3O^+	$\frac{k_1k_2[H^+][B]}{k_{-1}[H^+]+k_2[B]}$	$K[B]$	$K[H^+]$
9	H_3O^+	BH^+	H_2O	$\frac{k_1k_2[H^+][BH^+]}{k_{-1}+k_2[BH^+]}$	$K[H^+][BH^+]$	$K[H^+]$
10	BH^+	H_3O^+	B	$\frac{k_1k_2[BH^+][H^+]}{k_{-1}[B]+k_2[H^+]}$	$K[BH^+]$	$K[H^+]^2$
11	B	H_2O	BH^+	$\frac{k_1k_2[B]}{k_{-1}[BH^+]+k_2}$	$K[B]$	$K[OH^-]$

TABLE 1 (Contd.)

No.	X_1	X_2	X_{-1}	k_{obs}	Kinetic Behaviour [b]	
					Low Buffer Concentration	High Buffer Concentration
12	H_2O	B	H_2O	$\frac{k_1k_2[B]}{k_{-1}+k_2[B]}$	K[B]	K
13	H_2O	BH^+	H_2O	$\frac{k_1k_2[BH^+]}{k_{-1}+k_2[BH^+]}$	K[BH^+]	K
14	BH^+	H_2O	B	$\frac{k_1k_2[BH^+]}{k_{-1}[B]+k_2}$	K[BH^+]	K
15	OH^-	BH^+	H_2O	$\frac{k_1k_2[OH^-][BH^+]}{k_{-1}+k_2[BH^+]}$	K[B]	K[OH^-]
16	BH^+	OH^-	B	$\frac{k_1k_2[BH^+][OH^-]}{k_{-1}[B]+k_2[OH^-]}$	K[BH^+]	K
17	H_3O^+	B	H_2O	$\frac{k_1k_2[H^+][B]}{k_{-1}+k_2[B]}$	K[BH^+]	K[H^+]

TABLE 1 (Contd.)

No.	X_1	X_2	X_{-1}	k_{obs}	Kinetic Behaviour [b]	
					Low Buffer Concentration	High Buffer Concentration
18	H_3O	BH^+	H_3O^+	$\frac{k_1 k_2 [H^+] [BH^+]}{k_{-1}[H^+] + k_2 [BH^+]}$	$K[BH^+]$	$K[H^+]$

Expressed in a rate equation of the general form $\frac{k_1 k_2 [X_1] [X_2]}{k_{-1}[H^+] + k_2 [BH^+]}$. [b] In this Table K refers to a combination of rate or equilibrium constants.

of the catalysing species are increased high enough.

The table 1 (of Johnson 39(b)) effectively summarises all the possible general acid-base catalysed mechanisms which could be observed for simple carbonyl addition reactions.

2) Rate Profiles and Concentration Curves. (Indirect evidence for tetrahedral intermediates).

While direct evidence for tetrahedral intermediates by their direct observation is rather sparse the amount of data on reactions which fit kinetic equations for rate determining breakdown of tetrahedral intermediates, and hence demonstrates the possibility for their intervention, is vast.

The hydrolyses of the cleavage of diethyl acetylmalonate and its related precursor diethyl acetylethylmalonate have, for example, been interpreted[58] from their pH rate profiles as rate determining hydration of the carbonyl at high pHs and rate determining cleavage, i.e. breakdown of an intermediate by carbon-carbon bond breakage, at low pHs.

The cyanolysis[59] of ethyl thiolacetate and the hydrolysis of benzoyl cyanide,[60] acetyl cyanide[61] and propionyl cyanide[61] have all sigmoidal pH rate profiles and the former, at least, can be interpreted as reversible formation of a tetrahedral intermediate with acid catalysed expulsion of the thiol group.

As previously stated the alkaline hydrolysis of amides[62] can consist of both first and second order terms in hydroxide.

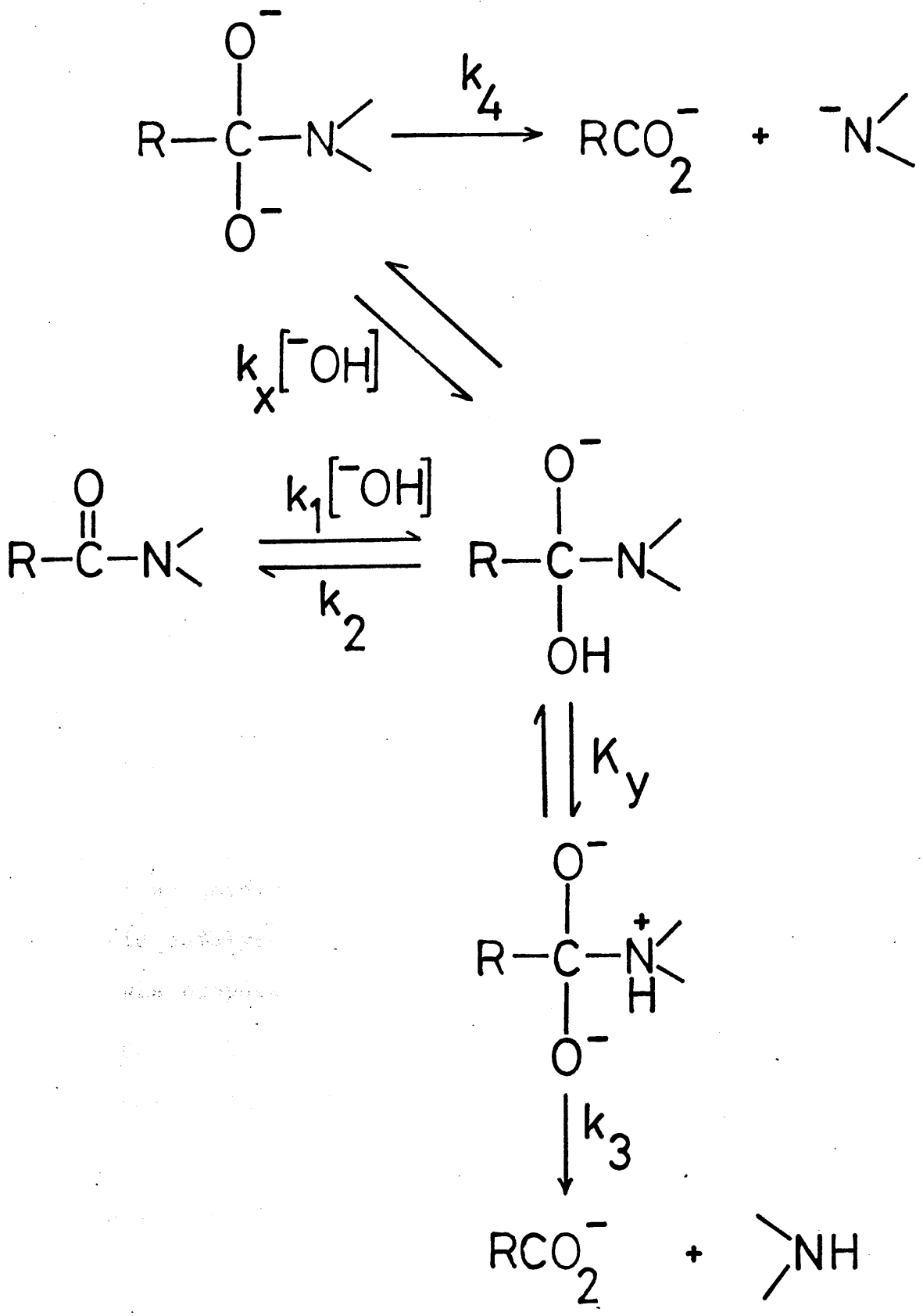


Fig. 8

While this could be explained by a mechanism involving a double attack of hydroxide, the second attacking the first as it in turn attacks the carbonyl, a more reasonable mechanism is that a complicated partition system where the tetrahedral intermediate is in equilibrium with its other ionic forms (fig 8). The hydrolyses of several amides[62,63] with breaks in their pH rate profiles have been shown to fit the derived rate equation for this mechanism. The general mechanism is now thought to be rate determining breakdown of the tetrahedral intermediate at low pH and rate limiting formation of tetrahedral intermediate at high pH.

While the hydrolyses of the thiol esters of acetic,[64] formic[65] and benzoic acids[66] exhibit acid catalysis while the hydrolyses of progressively electron withdrawing[67,68] thiol esters show inhibition at low pH. The curved pH rate plots obtained for trifluoroacetate were explained by Fedor and Bruice[67] as involving formation of a tetrahedral intermediate with acid catalysed formation of thiol ester. A similar scheme was proposed for ethyl trifluoroacetylmercaptoacetate.

$$CF_3\overset{\overset{O}{\|}}{C}SR + H_2O \underset{k_2[H^{\oplus}]}{\overset{k_1}{\rightleftharpoons}} CF_3\overset{\overset{O^{\ominus}}{|}}{\underset{\underset{OH}{|}}{C}}SR \xrightarrow{k_3} CF_3CO_2H + RSH$$

Work by Bender and Heck,[69] via ^{18}O exchange, also suggested the mechanism and involved asymmetric partitioning. Later work by Herschfield and Schmir[68] has suggested a much more

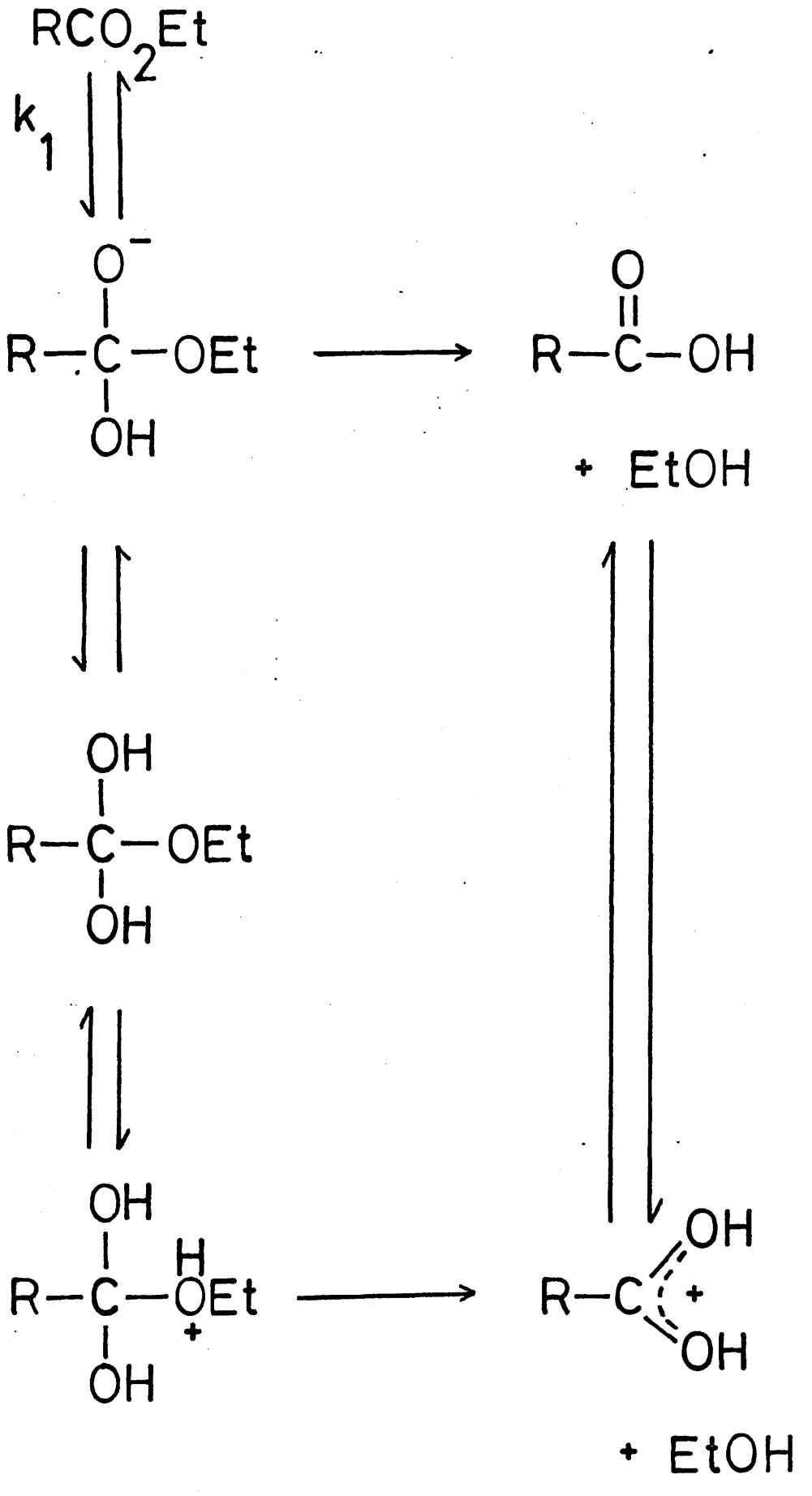
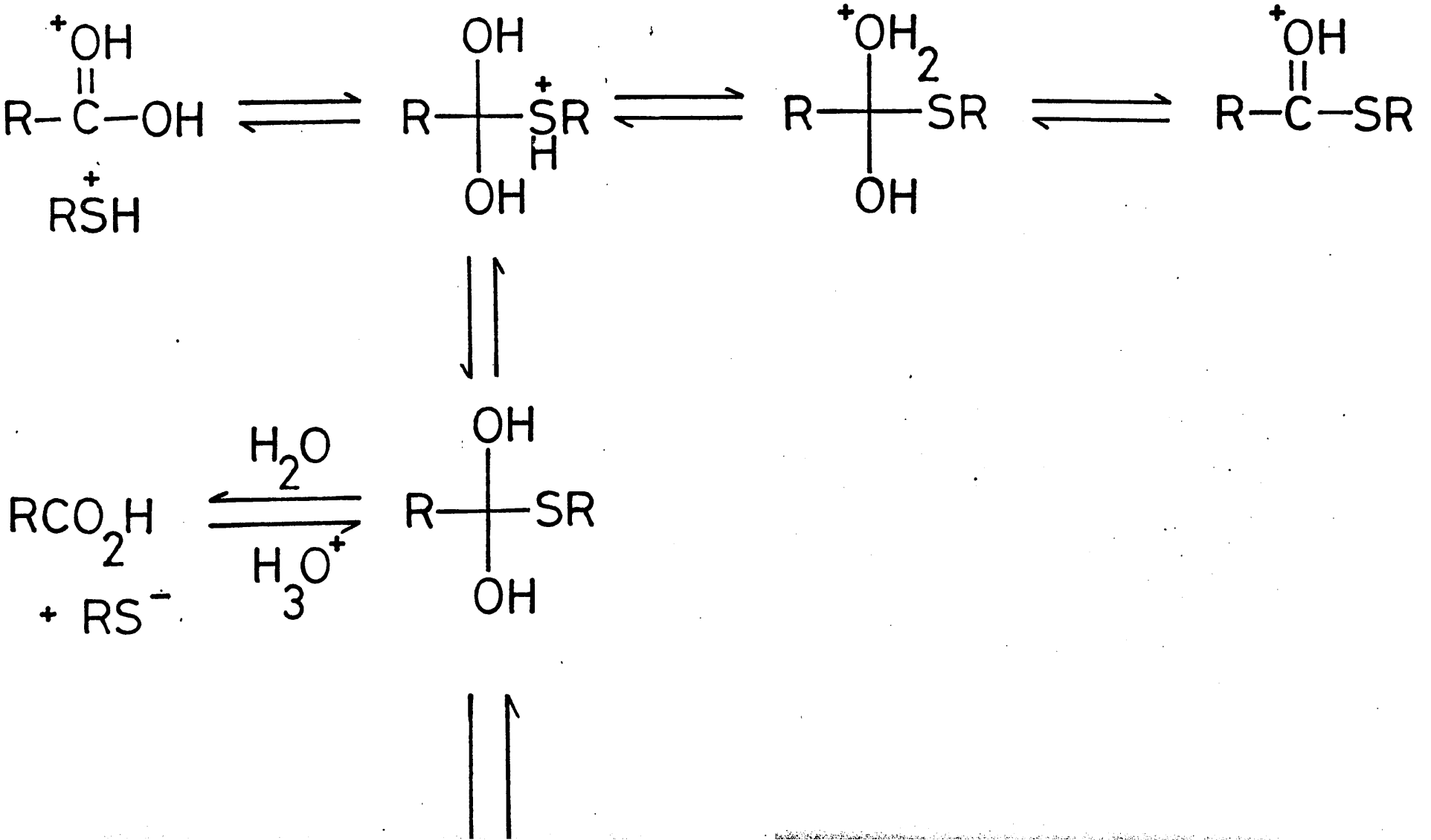

RCO2Et
k1
k2
O⁻
R—C—OEt
OH
O
R—C—OH
+ EtOH
OH
R—C—OEt
OH
OH
R—C—H
OEt+
OH
OH
R—C
+
OH
+ EtOH

Fig. 9



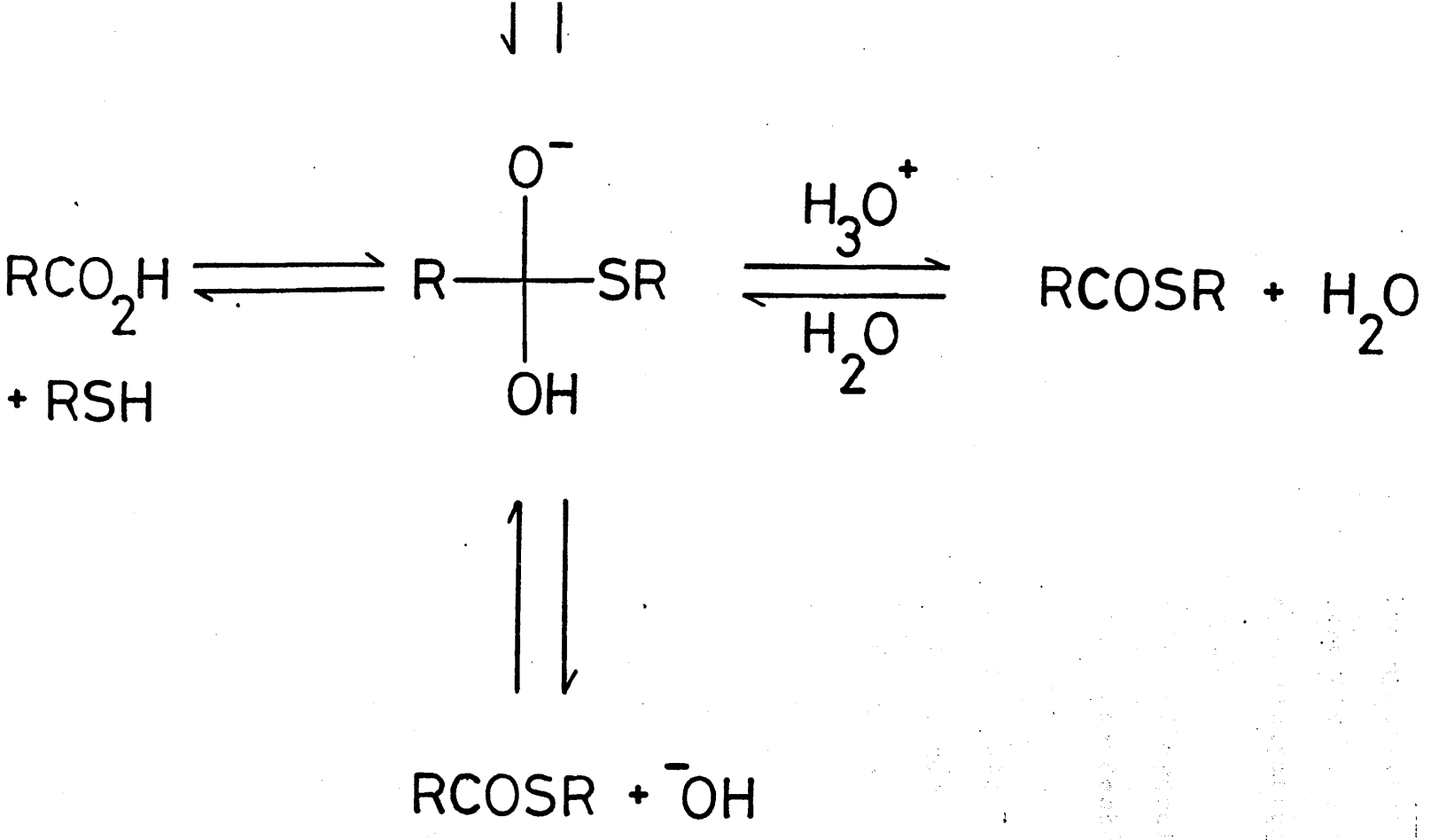


Fig. 10

complex mechanism the acid inhibition being directly related to the ratio of the rate constants for the breakdown of the intermediates to products and reactants.

The pH-rate profiles for the hydrolyses of ethyl trichloroacetate and trifluoroacetate[70] are also non linear and have been interpreted with a similar participation of tetrahedral intermediates (see figures 9 and 10).

The observation that the rates of hydrolysis of some ketene[71] acetals show a non linear dependence of rate on buffer concentrations at constant pH is in accord with a mechanism which involves initial rate determining proton transfer to the olefin at low buffer concentrations and rate determining decomposition of the carbonium ion at high concentrations. The expulsion from the mixed ketene acetals of alcohol functions in very acidic solutions and thio functions in less acidic solutions has been taken for evidence for further intermediates on the reaction pathway, these considerations resulting in the mechanism which included tetrahedral intermediates.

Studies on the hydrolysis of substituted maleamic[143] and maleanilinic acids[144] has shown that the amide hydrolyses by intramolecular participation. The mechanism is thought to be as in fig. 11 with rate determining decomposition of the tetrahedral intermediate (4) in most substituted species but rate determining diffusion away of the general acid (3) $\rightleftharpoons$ (4) in the case of di-isopropyl-maleamic acid. The hydrolysis of

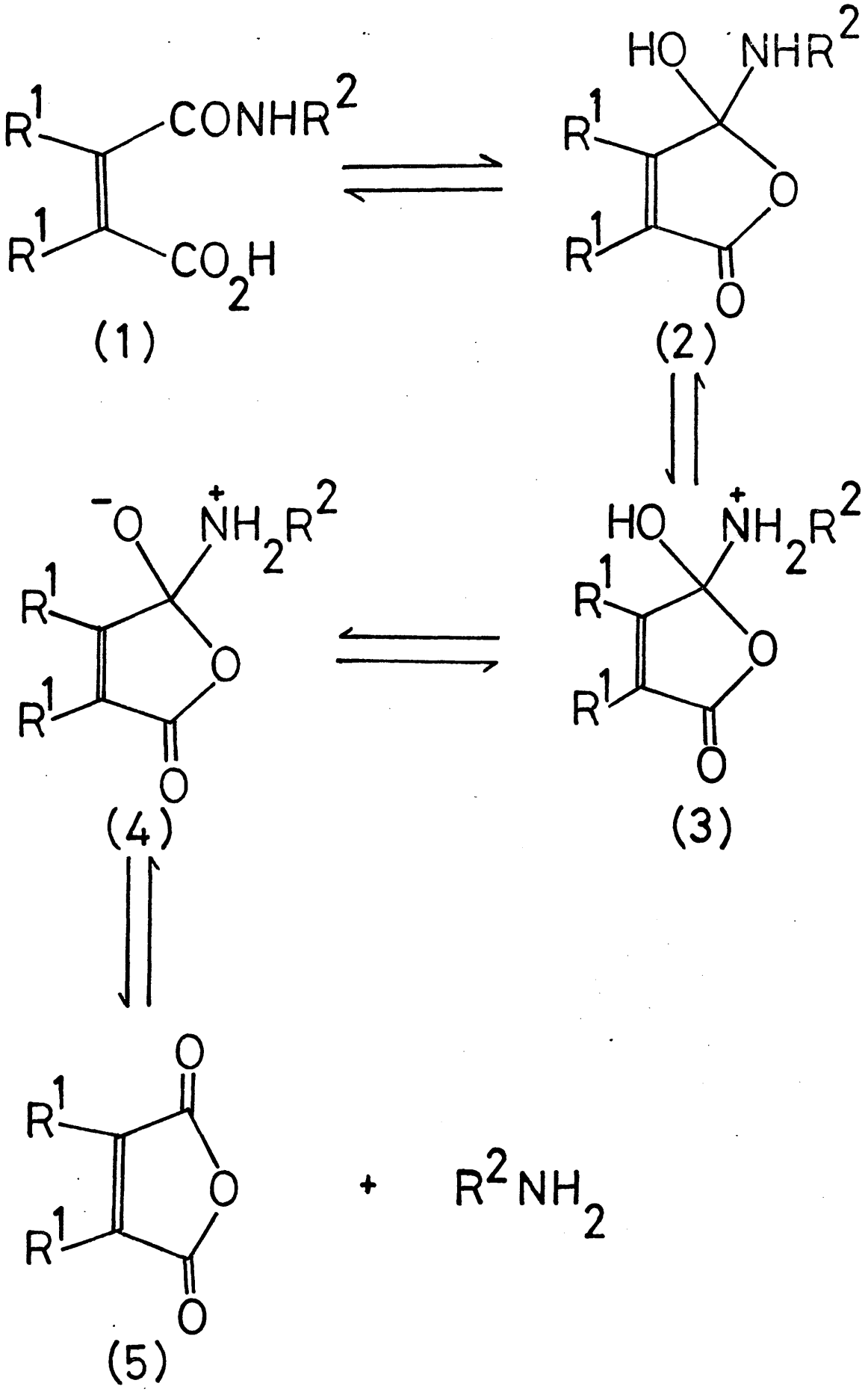

R1
CONHR2
R1
CO2H
(1)
HO
NHR2
R1
O
R1
O
(2)
-O
+NH2R2
R1
O
R1
O
(4)
HO
+NH2R2
R1
O
R1
O
(3)
R1
O
R1
O
(5)
+
R2NH2

Fig. 11

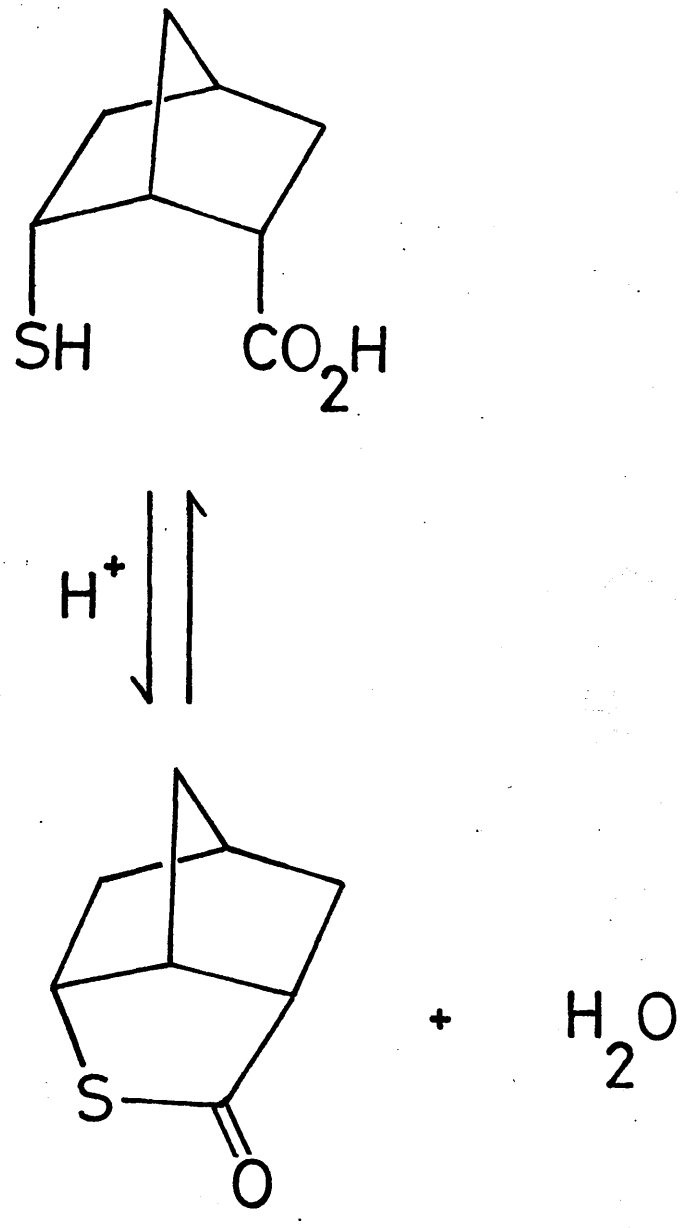
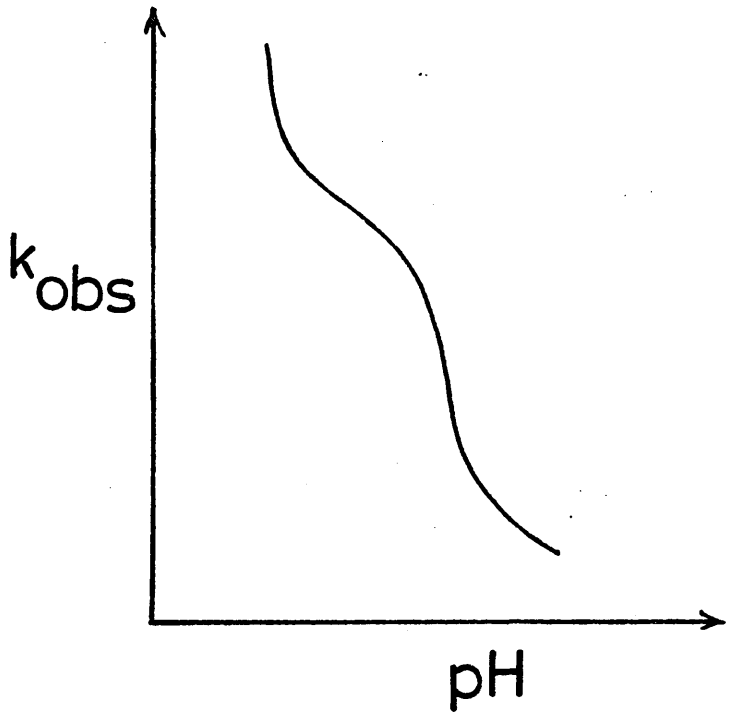


Fig. 12


k_{obs}
pH

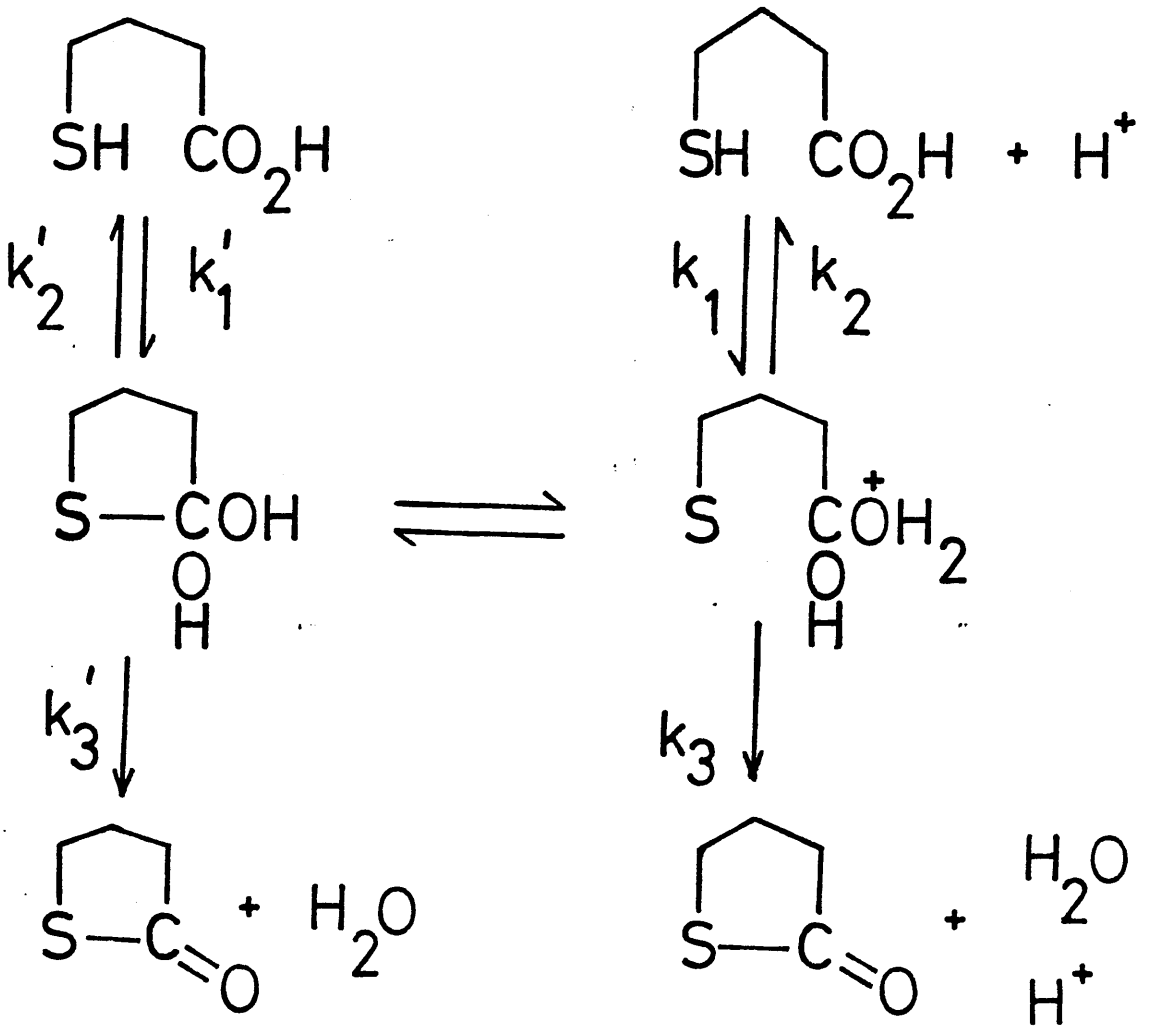

SH CO2H
SH CO2H + H+
k'2
k'1
k1
k2
S—COH
O
H
S COH2
O
H
k'3
k3
S—C=O + H2O
S—C=O + H2O
H+

Fig. 13

the corresponding esters, alkyl hydrogen dialkylmaleates has been interpreted in a similar manner.[145]

The study[72] of the bicyclic thiol (fig. 12) by acid esterification has also been shown to have a non linear pH rate profile and has been interpreted as involving a partially similar mechanism (fig. 13) with rate limiting decomposition of the tetrahedral intermediate at pH > 3 and rate determining formation at lower pHs.

The hydrolysis[73] of 2-methyl-Δ^2-thiazole to the two products, 5-acetylmercaptoethylamine and N-acetylmercaptoethylamine has been demonstrated by Martin et al to have a bell shaped rate profile with changing pH. It is subject to general base catalysis above pH 2.3 but not below this value. This apparent change in mechanism was explained by involving a tetrahedral intermediate species which subsequently broke down in either direction to the products (fig. 14). The change in rate determining step was explained as initial rate determining attack of water on the protonated thiazoline above pH 3 and rate determining breakdown of the tetrahedral intermediate below this value. Evidence from further work[73] on the equilibration of the thiol/amine placed this explanation in doubt. In addition Jencks and Barnett,[74] who observed that neither step is completely rate determining over most of the pH range, have since explained these results

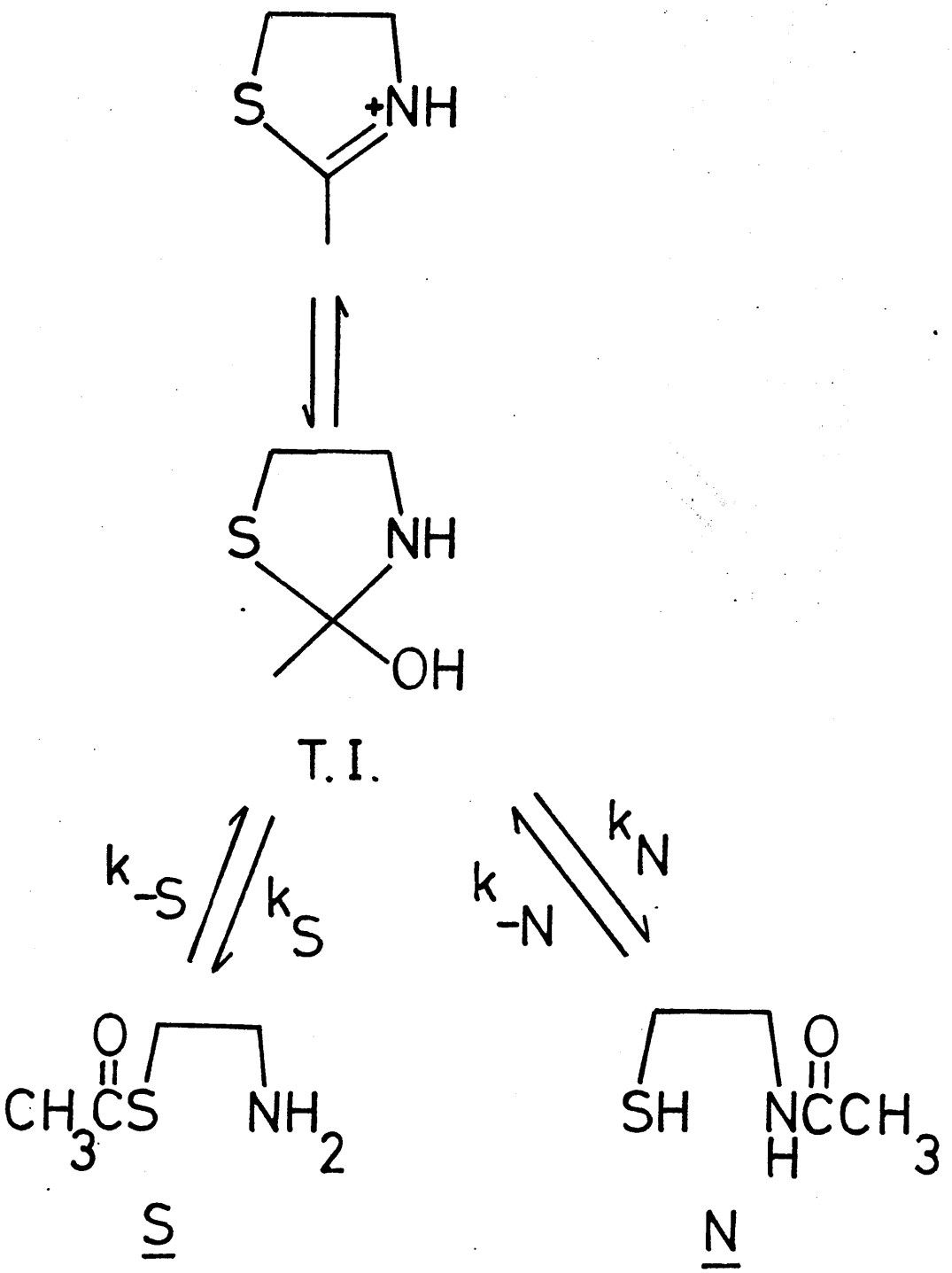


Fig. 14

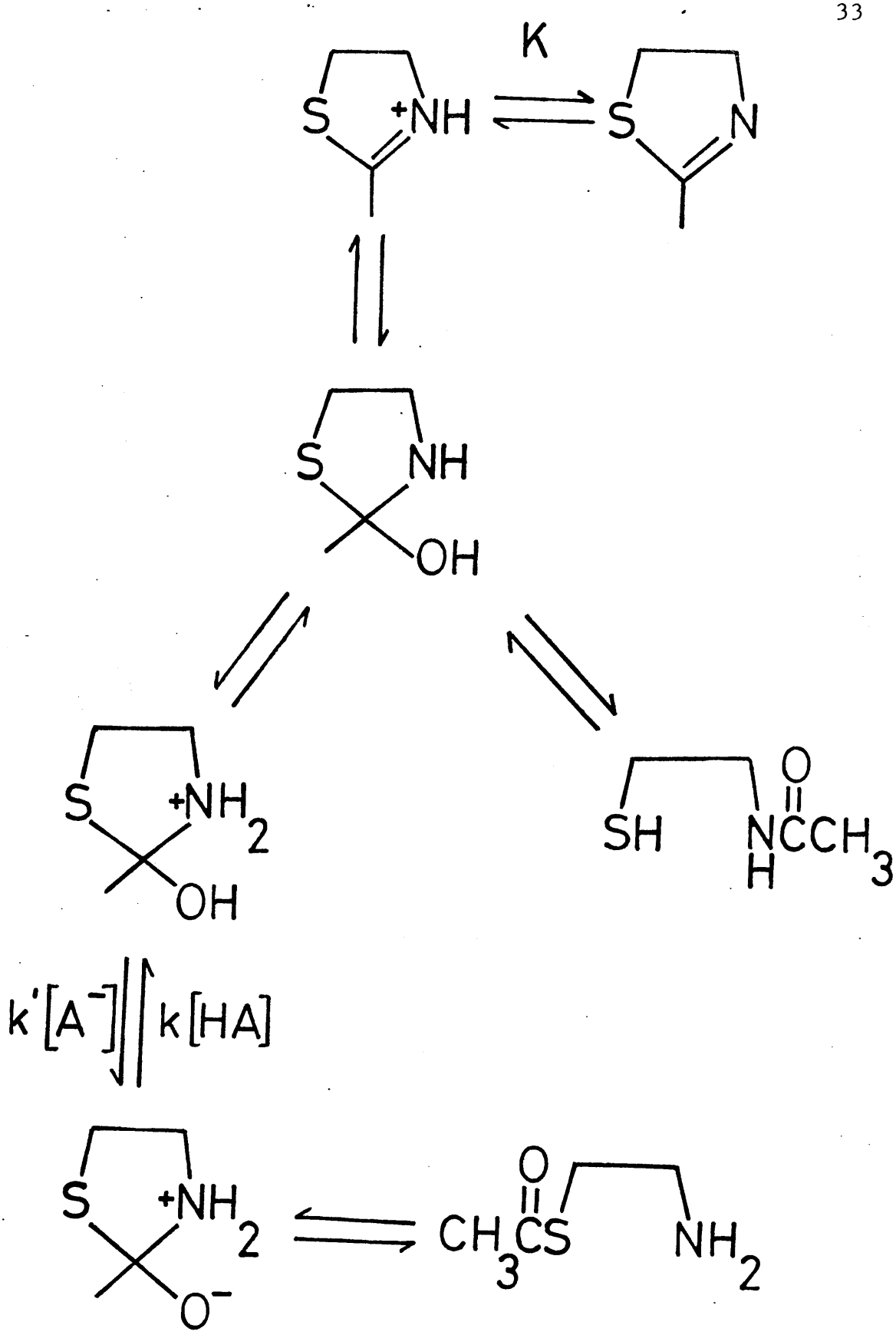


Fig. 15

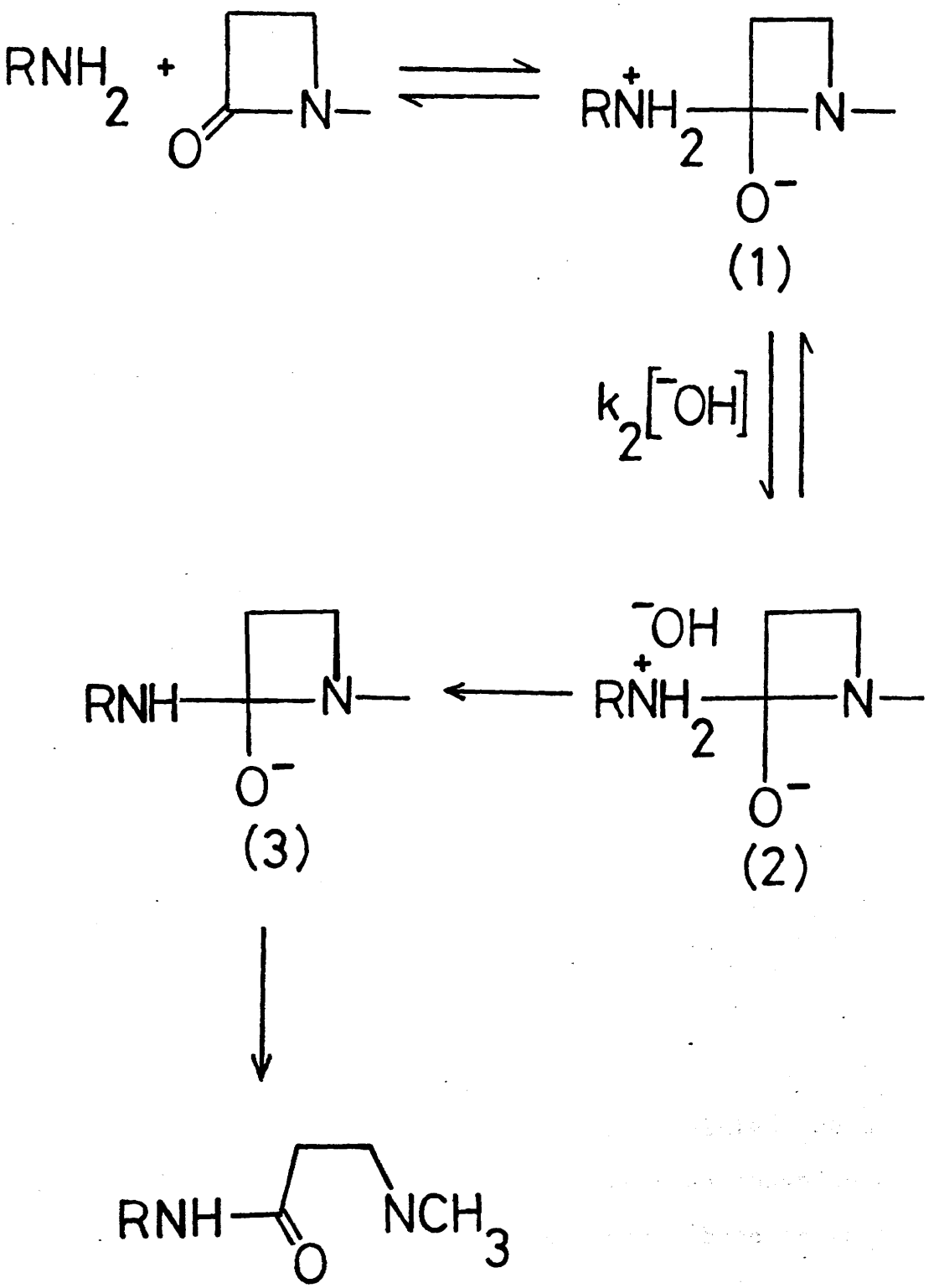


Fig.16

by considering there is rate determining proton transfer above pH 2.3 (fig. 15) (for work on similar compounds see ref. 75).

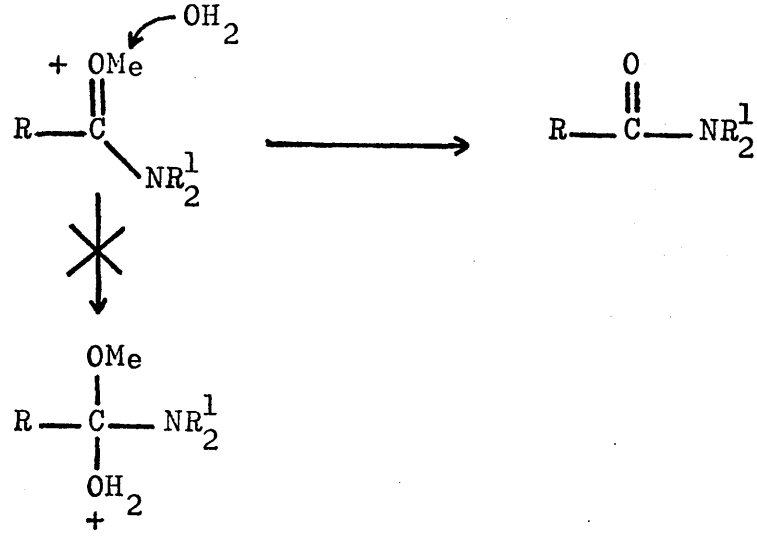
One of the most studied areas is that of the reactions of amino compounds with aldehydes,[76] ketones[76] and esters[77] where non-linear pH rate profiles have been analysed in great detail. Non-linear Bronsted plots[78] have also been observed for many reactions and have been interpreted as involving tetrahedral intermediates. The observation of several changes in the rate profiles are not unknown.

Possibly the most recent addition to the study of aminolysis reactions is that of the observation of non-linear dependence of the rate[146] of aminolysis of benzylpenicillin upon hydroxide ion concentration. The reaction has been interpreted as rate determining diffusion of the hydroxide and tetrahedral intermediate (2) together at low hydroxide concentrations and rate determining decomposition of the tetrahedral intermediate (3) at high hydroxide concentrations. (see fig. 16 : cf. ref. 145).

Similarly the alkaline and acid hydrolyses of imidate,[79] thioimidate[80] esters, Schiff bases[81] and related precursors[79] have all been studied extensively, have been shown to have non-linear pH rate profiles and have hence been shown to fit the complicated kinetics involving a number of changes in the rate determining step. The resulting products of hydrolysis

have also been shown to be pH dependent. A summary of the "relative families" of rate profiles has been given by Mesli.[82]

The participation of tetrahedral intermediates in the hydrolyses of imidates[83] in concentrated acid, at least, has been called to question by the observation of alkyl-oxygen cleavage by ^{18}O solvent incorporation into the alcohol function rather than at the carbonyl.



Similarly the hydrolyses[84] of ethyl thiolbenzoate and ethyl thionbenzoate have been shown to undergo different hydrolysis mechanisms in concentrated acid. While ethyl thiolbenzoate undergoes an $A_{AC}1$ mechanism, ethyl thionbenzoate undergoes an $A_{AC}2$ mechanism.

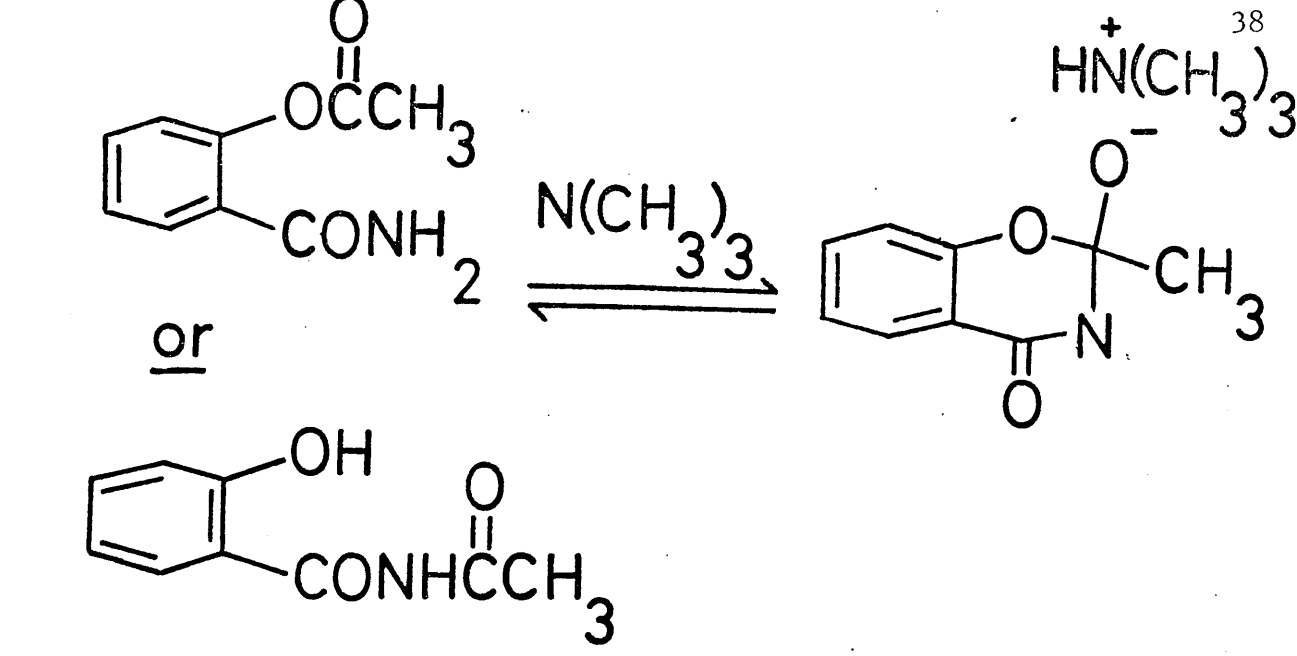
Direct Spectroscopic Observation of Tetrahedral Intermediates.

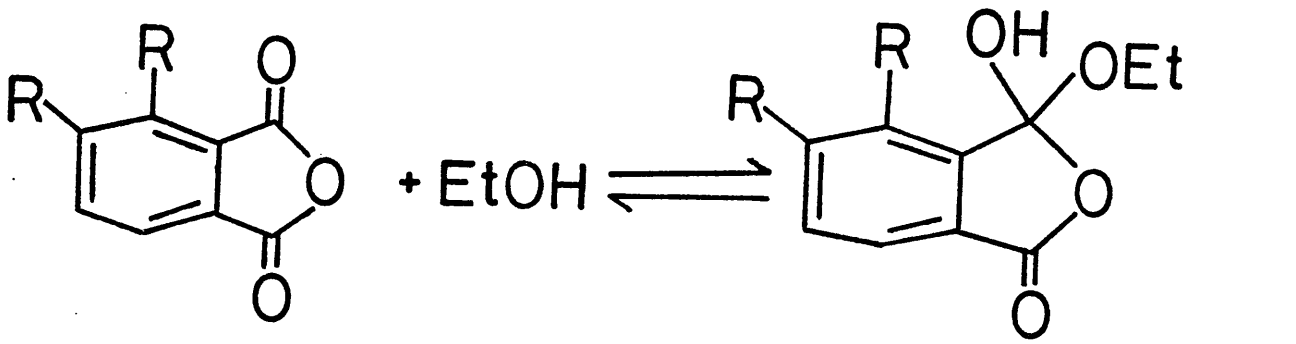
There are, as has just been described, many reactions fitting kinetic equations where tetrahedral intermediates have been postulated. Direct observation of transient intermediates, however, has in itself been fraught with difficulties and the resulting misinterpretations.

It should be generally accepted that the majority of "older" work[120] should be taken and interpreted with care. In his review Bender[101] gives several examples of possible tetrahedral intermediate equilibria from rather sparse evidence, e.g. personal communications, to support them. Ideally these reactions (fig. 17) should be repeated in view of the greater advancements in instrument technology.

Other studies for example of the two step hydrolysis of the orthoester[85] 2,2,-dimethoxy-3-phenyl-2H-chromene (fig. 18) by U.V. spectroscopy has shown the presence of a transient intermediate. It is, however, much more likely that such a transient intermediate is the carboxonium ion in view of the possible resonance stabilisation present in the molecule.

The conversion of 2,2,5-trisubstituted-1,3-oxothioles into 1-acylthio-2-alkanones in acid solution[92] has been shown to have a rate constant independent of whether R" = CH_3 or Et. This fact combined with the observation of immediate formation of methanol (by N.M.R.) at the start of the reaction, led to


OCCH3
O
CONH2
N(CH3)3
HN(CH3)3
O
O
CH3
N
O
or
OH
O
CONHCCH3


R
O
O
O
+EtOH
R
OH
OEt
O
O

R = CH_3

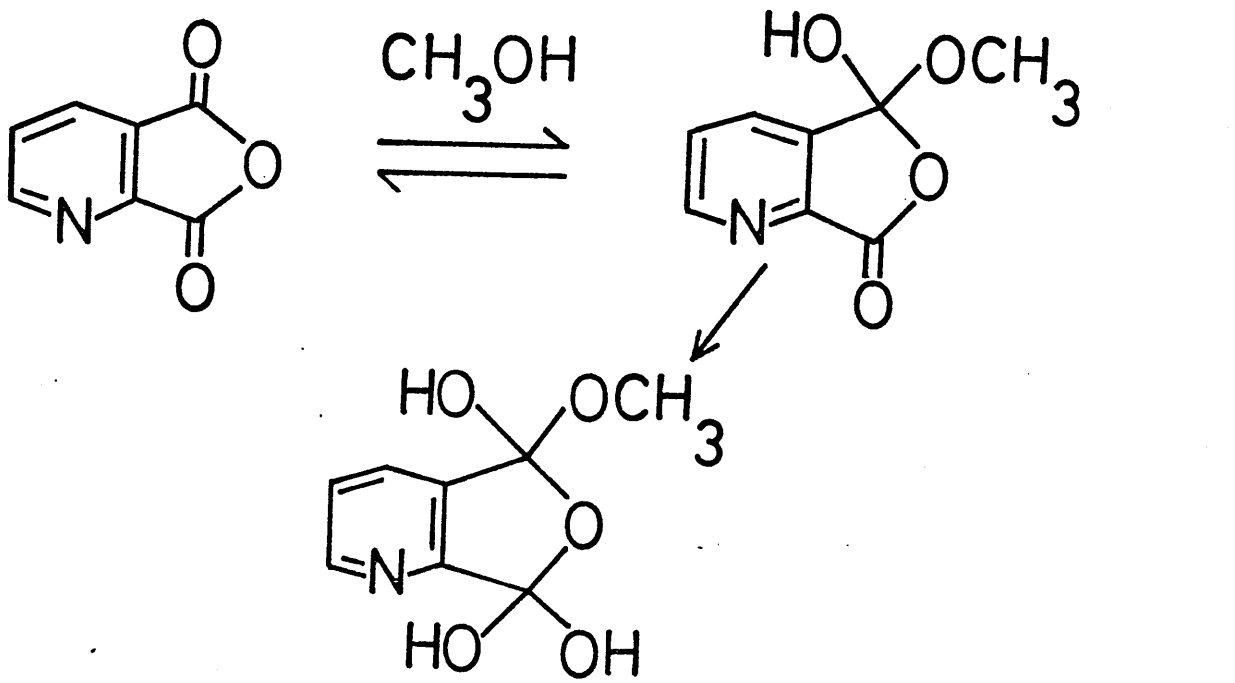
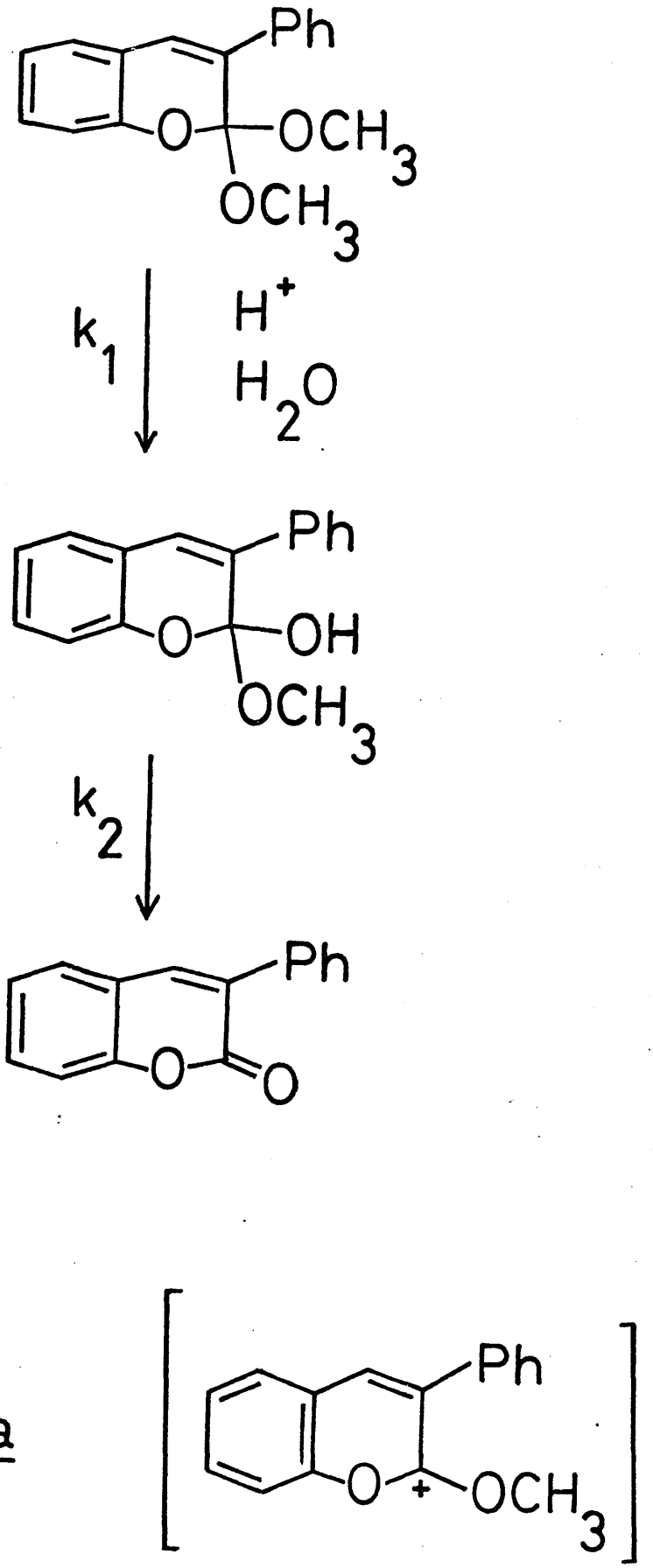

O
O
N
O
CH3OH
HO
OCH3
O
N
O
HO
OCH3
O
N
HO
OH

Fig.17



via

Fig.18

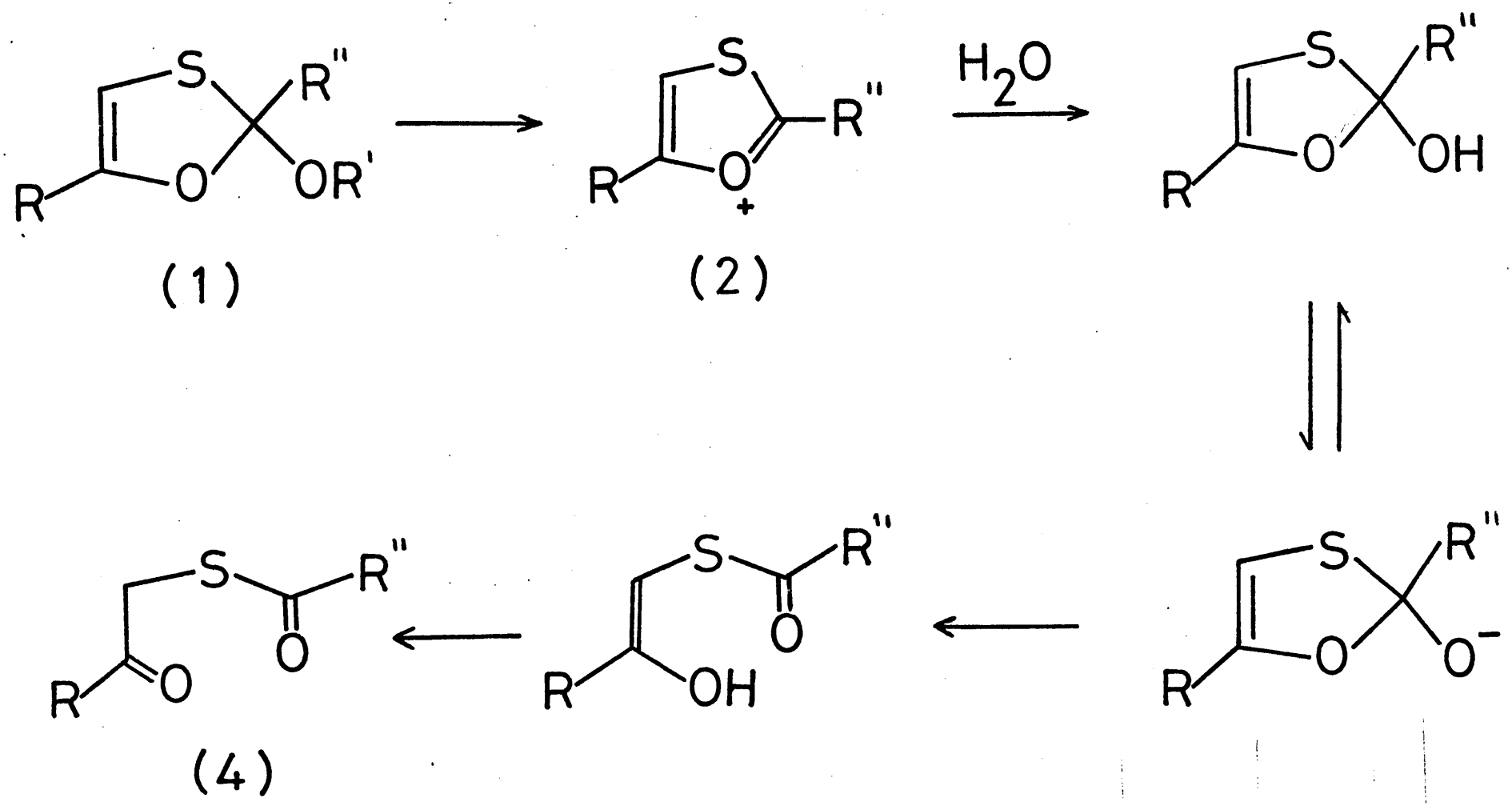


Fig. 19

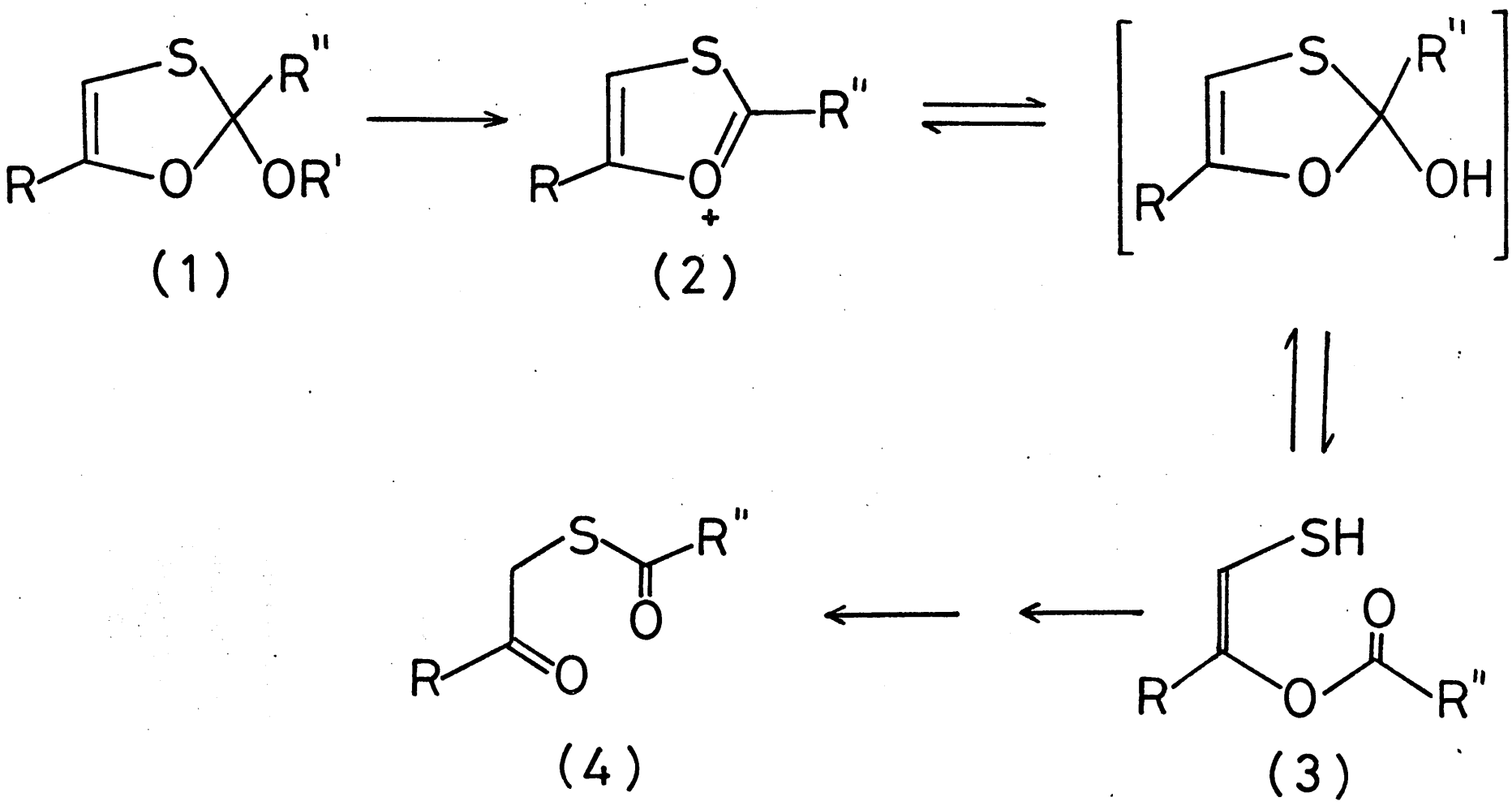
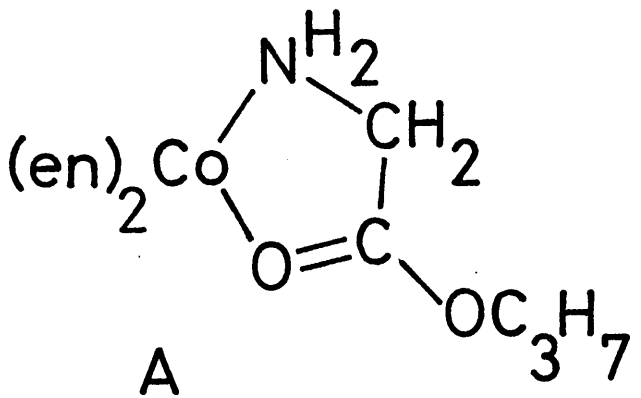


Fig. 20

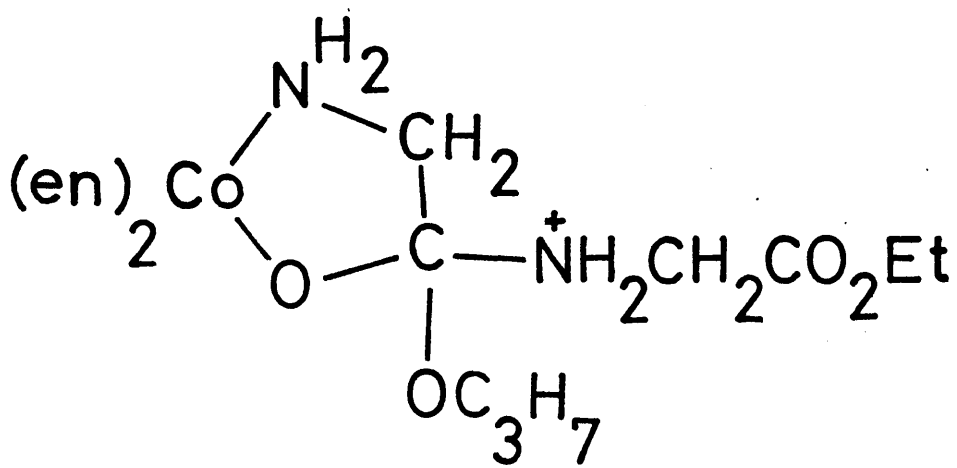
the conclusion that the initial fast step is that of formation of a tetrahedral intermediate (fig. 19). The rate of the slow step was found to be proportional to the activity of the hydroxide ions present which suggested that an initial proton transfer occurred before the tetrahedral intermediate broke down. The question of how stable the positive ion initially formed compared to that of the tetrahedral intermediate cast some doubt as to whether the decomposition of the tetrahedral intermediate was in fact rate determining however, since the aromatic character of the ion may result in poor nucleophilic attack to produce the tetrahedral intermediate. Further work[92(c)] therefore, was carried out and it was shown that the initial fast step was that of formation of (2) with a subsequent slow reaction where (2) is in equilibrium with compound (3); thought originally not to be on the reaction pathway (fig. 20). Compounds (2) and (3) were isolated and characterised and (3) was shown to undergo subsequent fast reactions to product (4).

The reaction[86] between isopropylglycinate bis(ethylenediamine)cobalt III perchlorate (fig. 21(A)) and glycine ethyl ester in dimethyl sulphoxide has also been shown to be a two step reaction. Observation of an initial increase in optical density followed by a slower decrease has led to the assignment, with I.R. data, of this initial product as a tetrahedral intermediate stabilised by a metal ion. Several other examples exist where such stabilisation by metal ions have been suggested e.g. the alcoholysis of ethyl fluoroacetates,[94] aryl benzoates[95] and related precursors.[96]



A

+ $NH_2CH_2CO_2Et$



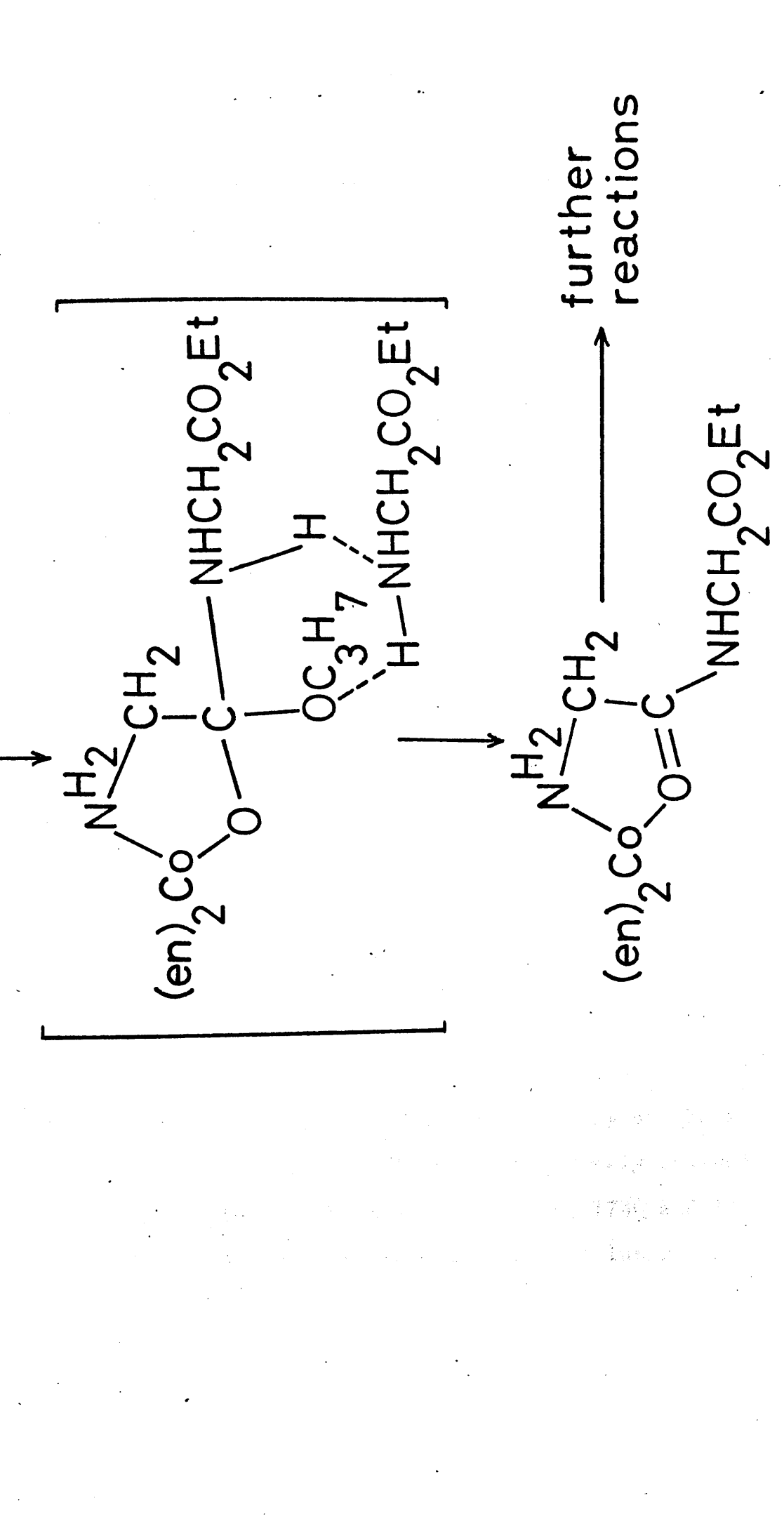

NHCH2CO2Et
H
NHCH2CO2Et
OC3H7
CH2
C
NH2
O
(en)2Co
further
reactions
CH2
C
NH2
NHCH2CO2Et
O
O
(en)2Co

Fig. 21

The mechanism proposed, for the cobalt stabilised reaction, is shown in figure 21, the initial step being first order in amine and the second one being general acid catalysed. No separation of individual rate constants was possible in this study due to the overall complexity of the reaction. The possibility of some other unforseen pathway leads the author to question the probability of the initial step being that of the observation of a tetrahedral intermediate.

Probably the most doubtful example of a tetrahedral intermediate is the study by some Russian workers,[93] of the I.R. spectra of several lactams in various concentrations of potassium deuteroxide solution where it was observed that changes occurred in the carbonyl region. In the case of γ-butyrolactone the carbonyl band at 1650 cm^{-1} in deuterium oxide decreased with increasing concentration of the alkali and a new band at 1555 cm^{-1} initially formed followed by further bands at 1740 and 1395 cm^{-1} in more concentrated solutions. Consideration of the I.R. spectrum of strontium carbonate which showed similar carbonyl bands, at 1740, 1555 and 1400 cm^{-1}, resulted in the assigning of the initial new peak, 1555 cm^{-1}, to that of the negatively charged tetrahedral intermediate and the two other bands, 1740 and 1395 cm^{-1}, to that of the doubly ionised tetrahedral intermediate. The

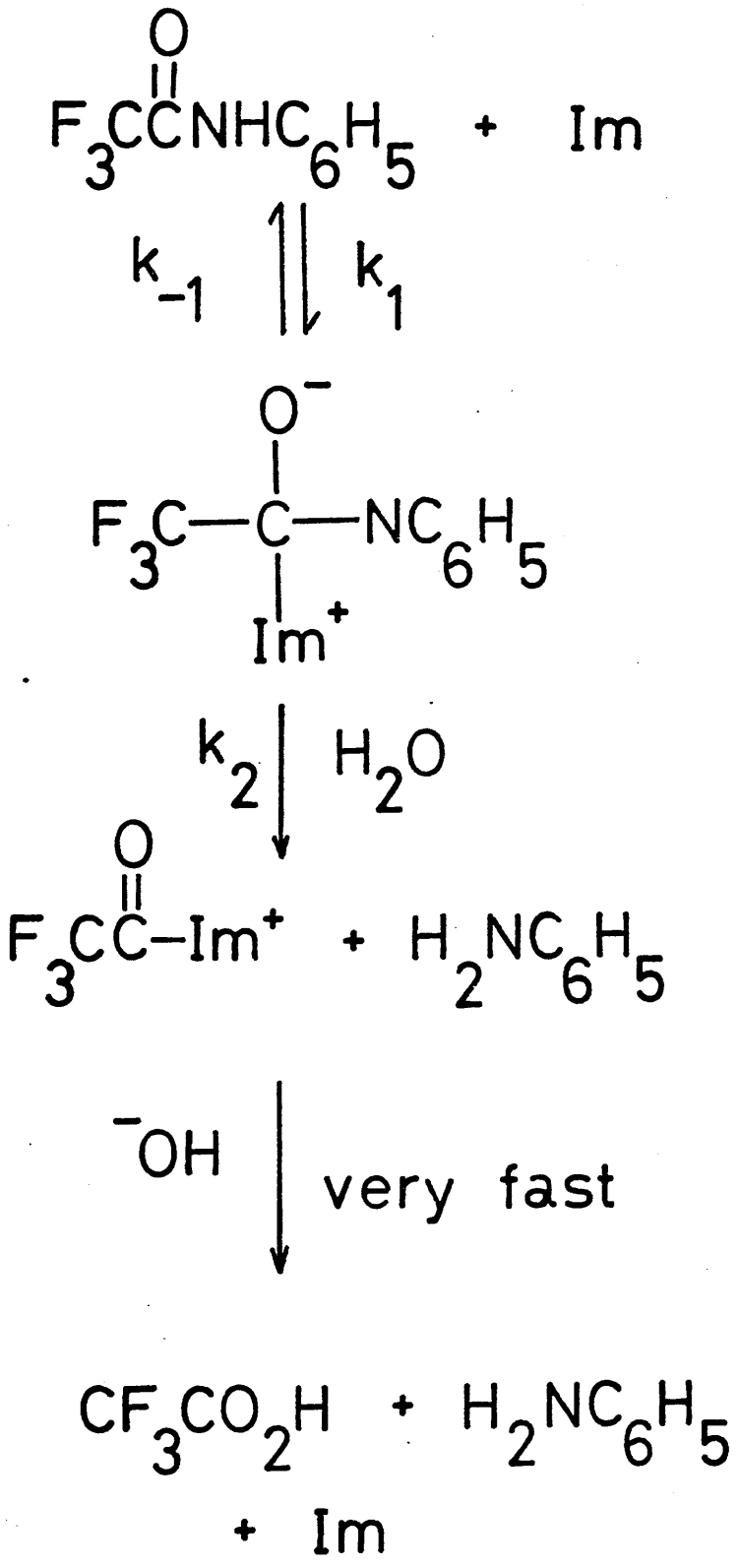

O
F3CCNHC6H5 + Im
k-1
k1
O−
F3C—C—NC6H5
Im+
k2
H2O
O
F3CC–Im+ + H2NC6H5
−OH
very fast
CF3CO2H + H2NC6H5
+ Im

Fig. 22

lactam anion, due presumably to the loss of a proton from the nitrogen, was proved not to correspond to any of the new I.R. bands, by measuring the I.R. spectrum of the lactam sodium salt. While some of the I.R. bands could be argued as being due to acid formation no real evidence is forthcoming to argue against the direct observation of the tetrahedral intermediates in the solution. The study of much more related species than strontium carbonate may add more light on the subject.

Stauffer claimed[147] that the hydrolysis of trifluoroacetanilides gave a build up, of approximately 30%, of a tetrahedral intermediate but this was shown to be incorrect by ^{19}F N.M.R. studies by Guthrie.[148] A further study of the hydrolysis of substituted trifluoroacetanilides in imidazole buffer by Stauffer[149] showed the presence of an initial increase in U.V. absorbance, during the reaction which is proportional to the concentration of imidazole present, followed by a slow decrease over a longer time interval. The mechanism proposed is shown in fig. 22 and has been interpreted as direct nucleophilic attack of the imidazole on the carbonyl of the amide with the resulting formation of a tetrahedral intermediate followed by a slow breakdown of this species to products. The hydrolysis of transient amide formed is reported to be extremely fast under the conditions

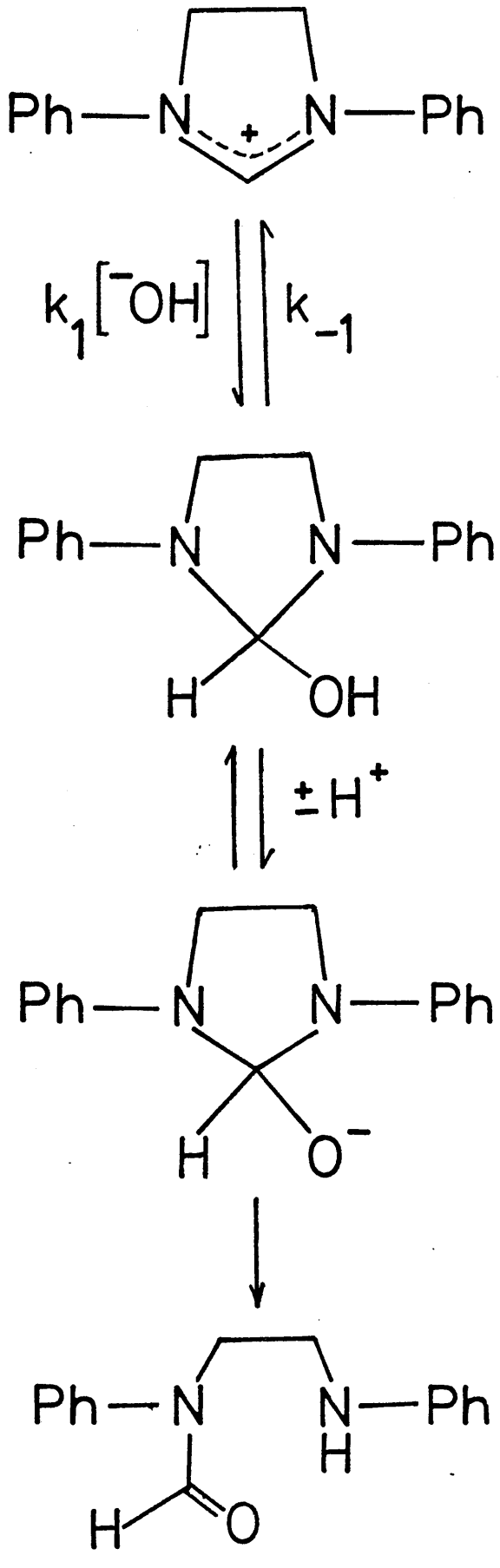
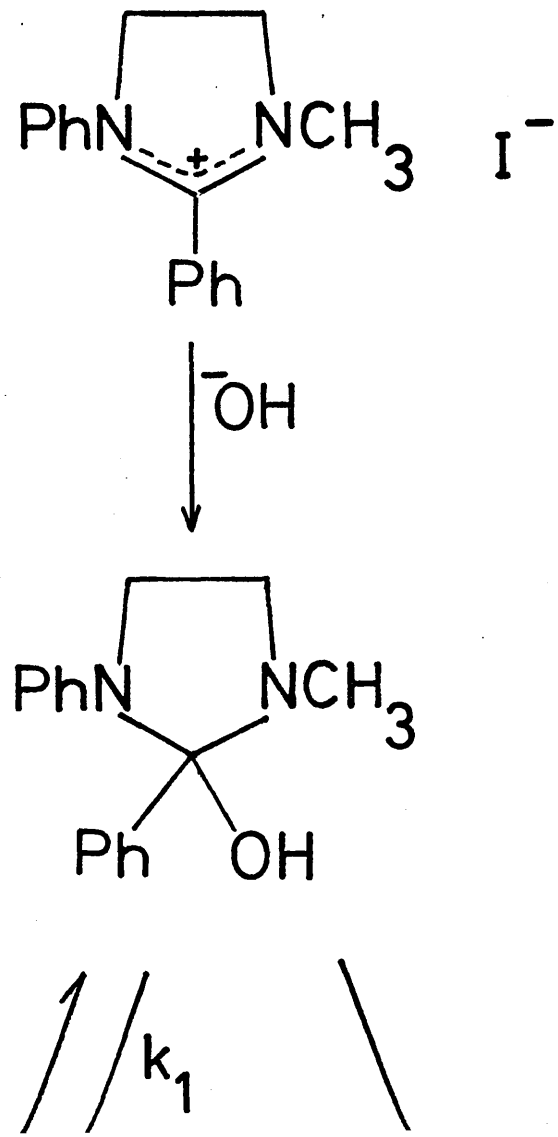


Fig. 23


PhN
NCH3
I−
Ph
−OH
PhN
NCH3
Ph
OH
k−1
k1

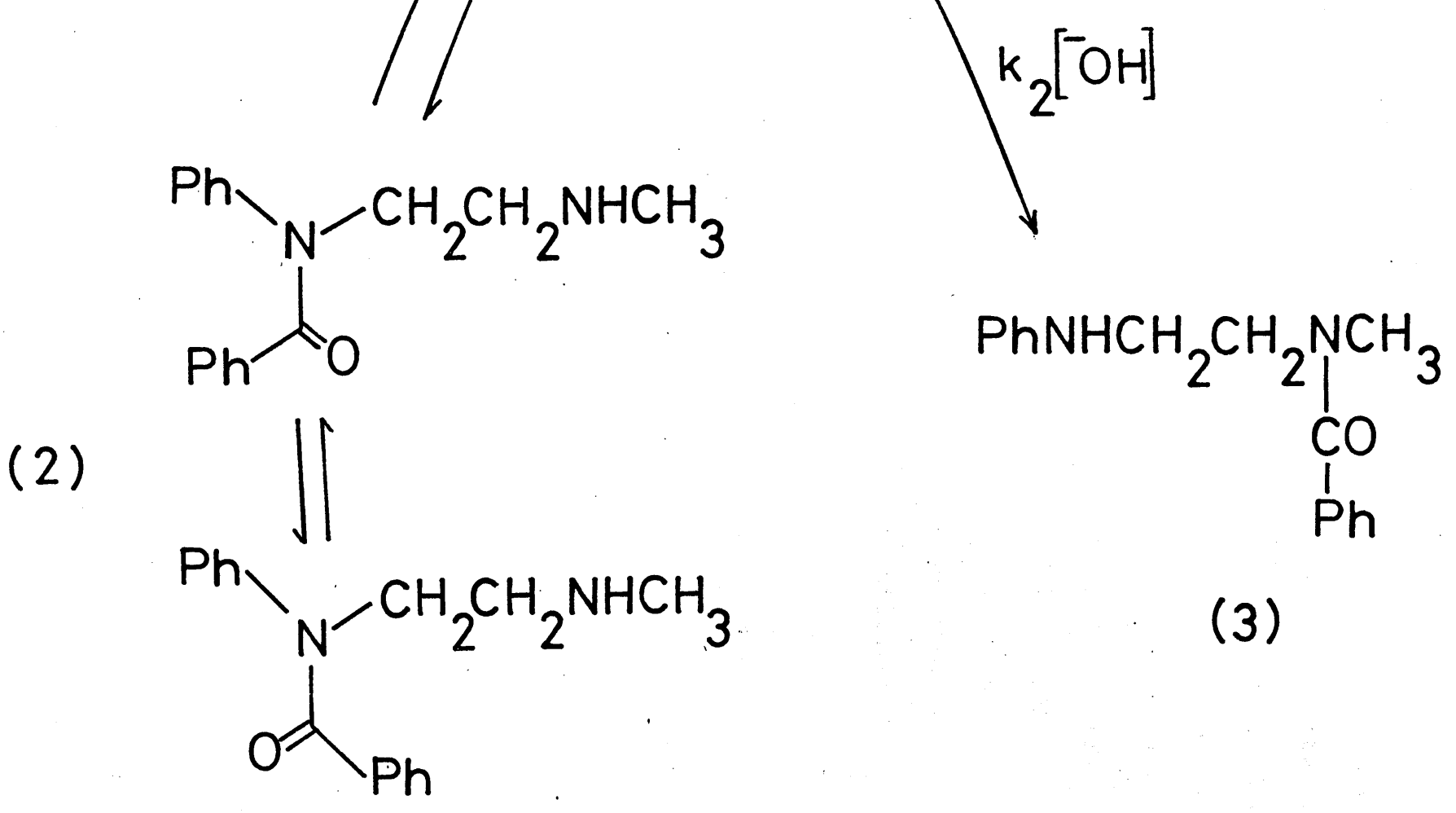

k2[⁻OH]
Ph
N
CH2CH2NHCH3
Ph
O
(2)
Ph
N
CH2CH2NHCH3
O
Ph
PhNHCH2CH2NCH3
CO
Ph
(3)

Fig. 24

studied. However it may have been that this transient amide was the species being studied in the first step.

Work on the hydrolysis[88] of a formamidinium compound, diphenylimidazolinium chloride, where non-linear pH rate profiles have been observed, have shown the presence of an intermediate by stopped flow spectroscopy. The initial increase in U.V. absorption followed by a slower decrease characteristic of a two step reaction was observed, the initial increase being very susceptible to pH. The results have been interpreted as an initial reversible, pH sensitive, reaction, forming a tetrahedral intermediate, with a slower decay to products with general acid catalysis (fig. 23). In view of the next example this assignment of the transient intermediate as the tetrahedral intermediate during the reaction should be called to question.

A rather startling example, of a misinterpreted suggestion[135] of a tetrahedral intermediate, is the observation in the hydrolysis of 1,2-diphenyl-3-methylimidazolinium iodide of initially, by thin layer chromatography (T.L.C.), a single spot $R_f \approx 0$; the appearance of a second spot after 2-3 minutes, R_f 0.1, and finally the observation of a third spot, the final product after approximately 1 hour. The observation of the second spot (the first was starting material) at a few minutes time interval was taken as being that of the

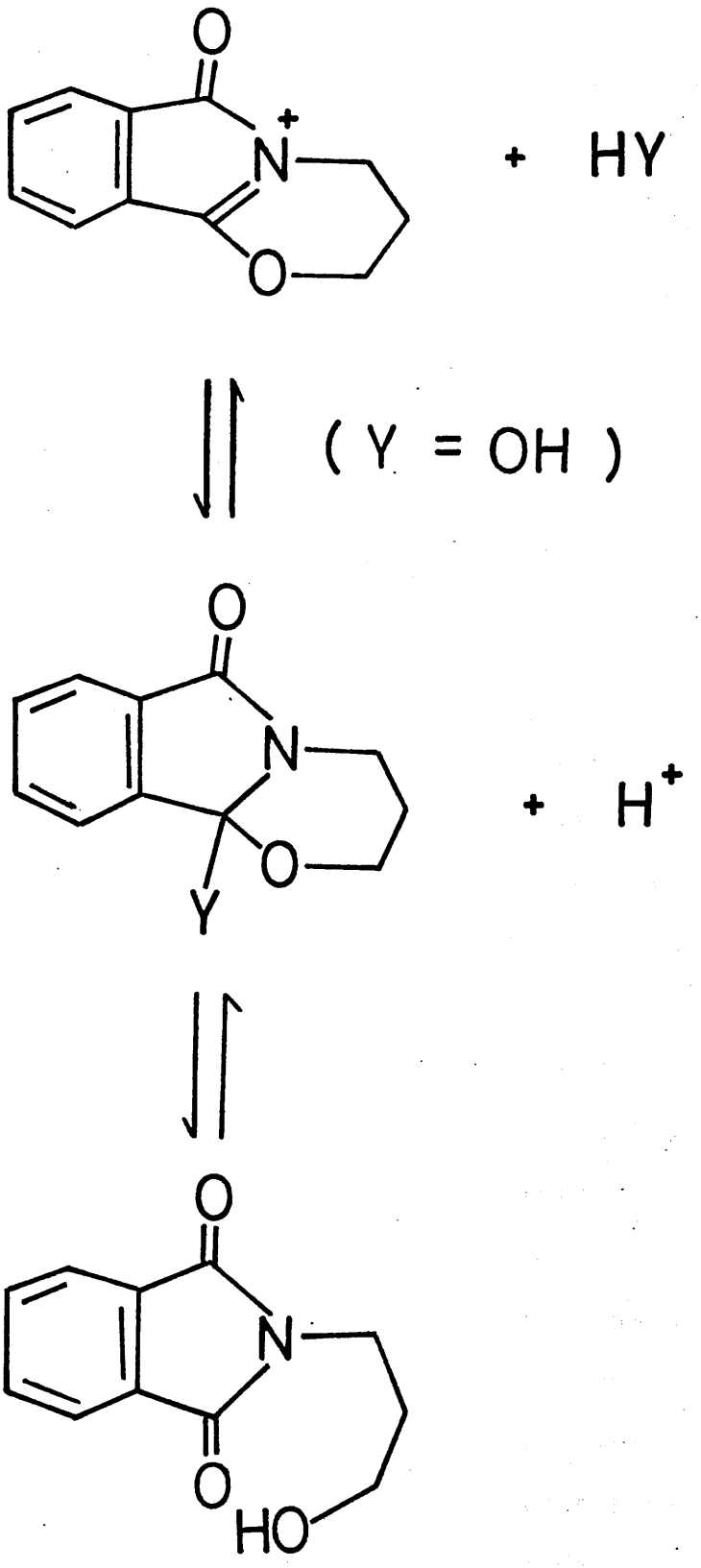


Fig. 25

tetrahedral intermediate by referring to the work on a similar compound[88] where the tetrahedral intermediate had been observed by stopped flow. It would seem likely, however, that in both cases the observation of a transient intermediate is probably due to one of the syn- and anti-type configurations of the amide being formed first followed by a slower formation of the thermodynamically more stable isomer. In the latter example[135] the possibility of further rearrangement is (fig. 24) apparent (i.e. product (3)).

A similar observation, and one of the most detailed studies, is the reaction[87] of phthalimidium perchlorate in weakly acidic solutions where it has been observed by U.V. that an initial rapid loss of absorbance due to starting material is followed by a much slower appearance of product. The spectrum obtained after the initial fast disappearance of substrate was found to be very similar to that of the isolated stable adducts (Y = alcohol) and was therefore assigned a tetrahedral intermediate structure. The mechanism for this reaction is shown in fig. 25.

In the study of enzyme catalysis Richards et al[153] have observed by stopped flow spectroscopy a transient intermediate, in the hydrolysis of Ac-L-Ala-L-Pro-L-Ala-p-nitroanilide by the serine proteinases elastase and α-lytic proteinase, which has been interpreted as being the tetrahedral intermediate formed during the reaction.

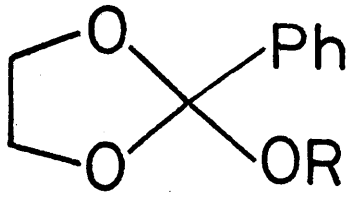


Fig.26

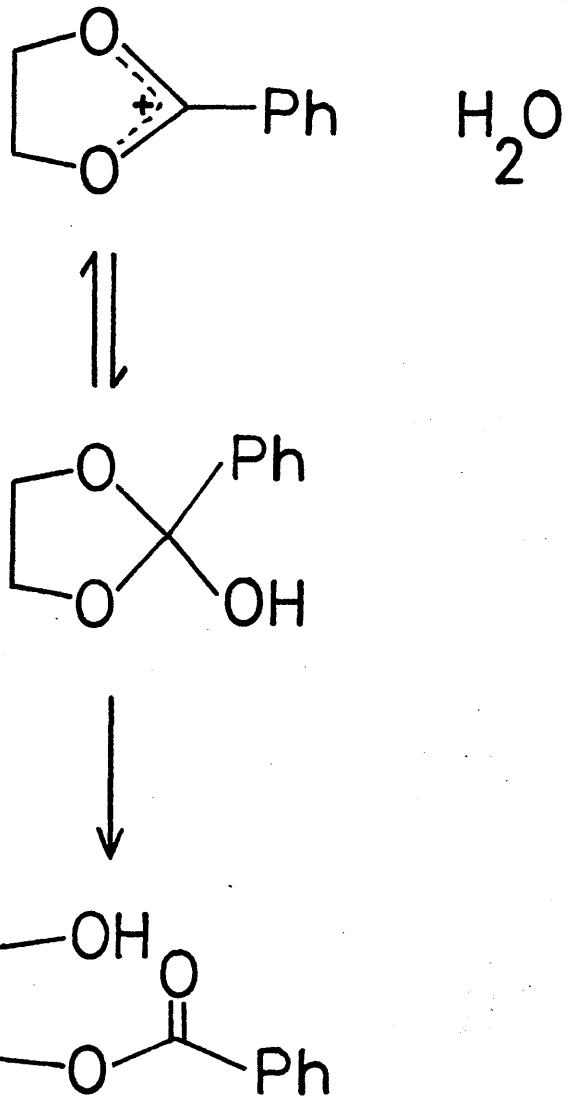


Fig.27

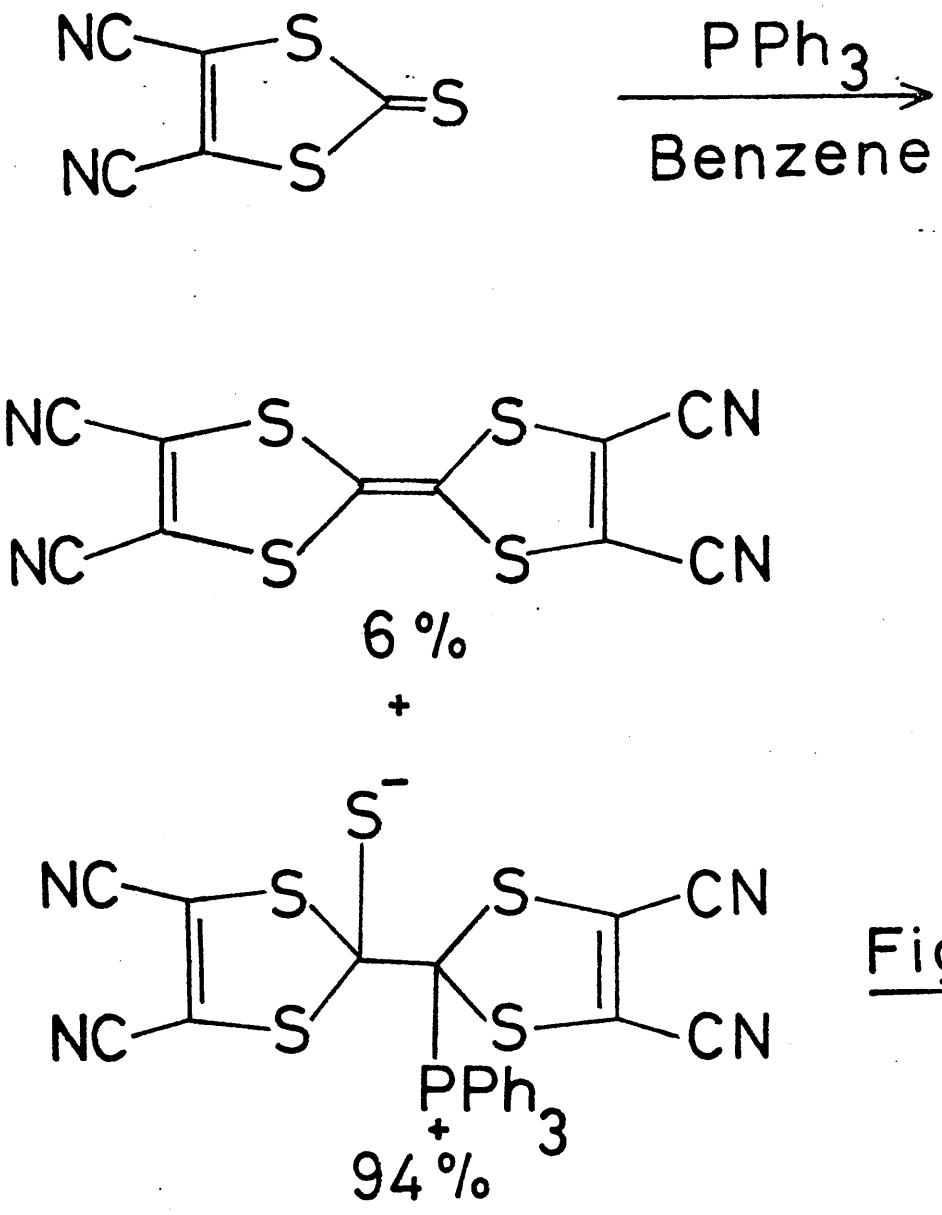

NC
S
S
NC
S
PPh3
Benzene
NC
S
S
CN
NC
S
S
CN
6 %
+
S−
NC
S
S
CN
NC
S
S
CN
PPh3
+
94 %

Fig. 28

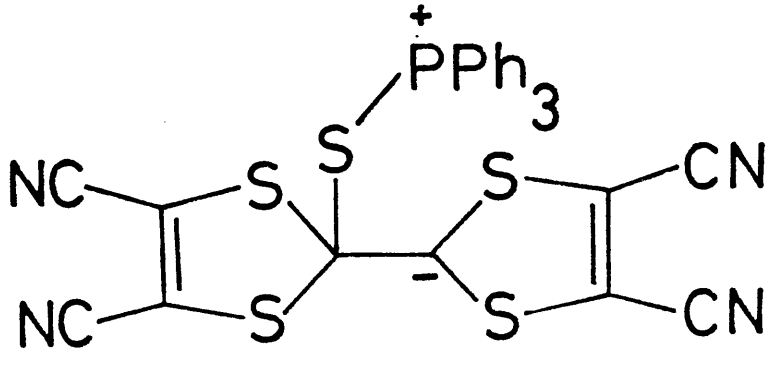
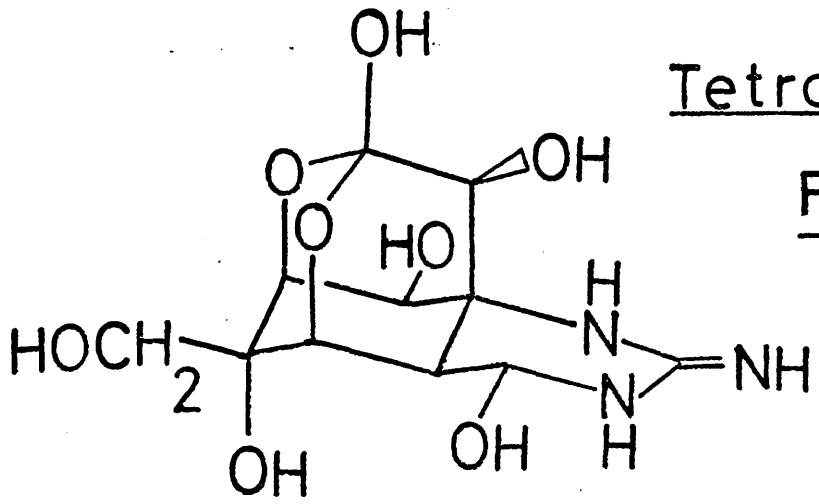

+
PPh3
S
NC
S
S
CN
NC
S
−
S
CN

Fig. 29

The study by stopped flow methods of the acid catalysed hydrolysis of orthoesters has been shown by Kresge et al[90] to hydrolyse at similar rates for differing alkyl substituents (fig. 26), at high acid concentrations. At lower acid concentrations an induction period for the reaction kinetics was observed. Studies on the dioxolenium ions have also shown an initial fast change in the U.V. absorption followed by a slower decrease. The above data has been interpreted as rate determining decomposition of the tetrahedral intermediate at high acid concentrations in the case of the orthoester systems and equilibrium formation of the intermediate with the salt in the dioxolenium salt hydrolysis (fig. 27).

The "free" utilisation of tetrahedral intermediates is no more apparent than in the example, derived as a side product of the synthesis of tetracyanotetrathiofulvalene. Initially this "by product" was given a tetrahedral intermediate structure[119] (fig. 28) but in a later paper[150] was given a completely different structure (fig. 29). Neither of these structures have been proved or disproved!

The largest most complicated stable tetrahedral intermediate observed to date is tetrodotoxin (fig. 30) whose structural illucidation was not straightforward and immediately obvious.[125] Conformation of its structure was finally obtained by X-ray studies[126] and direct synthesis.[127] Many



Tetrodotoxin

Fig. 30

- Proposed Structure -

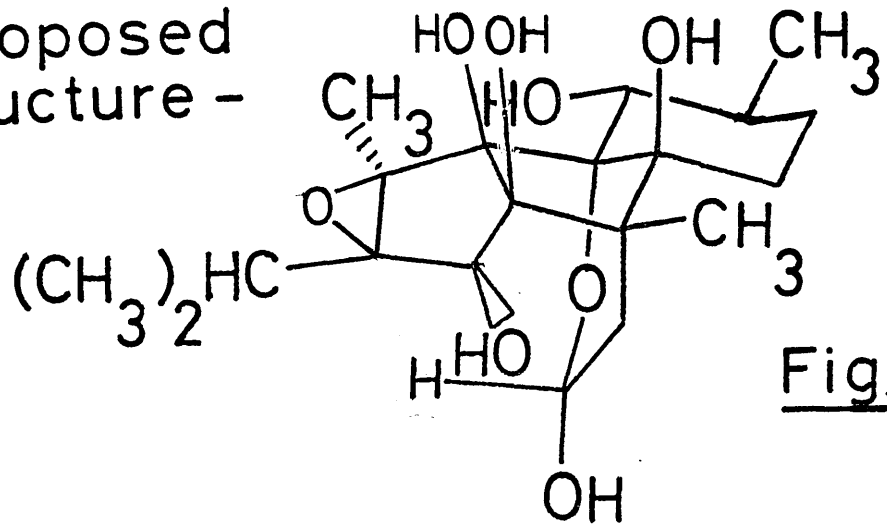
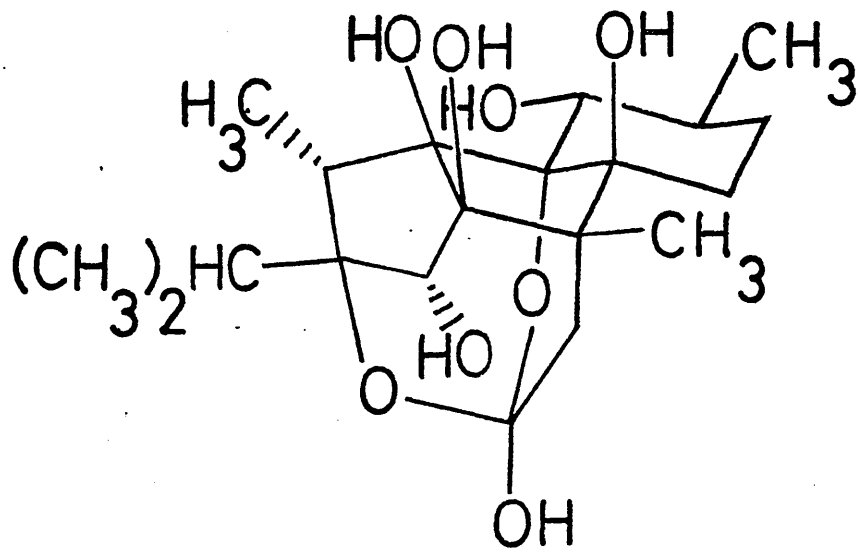
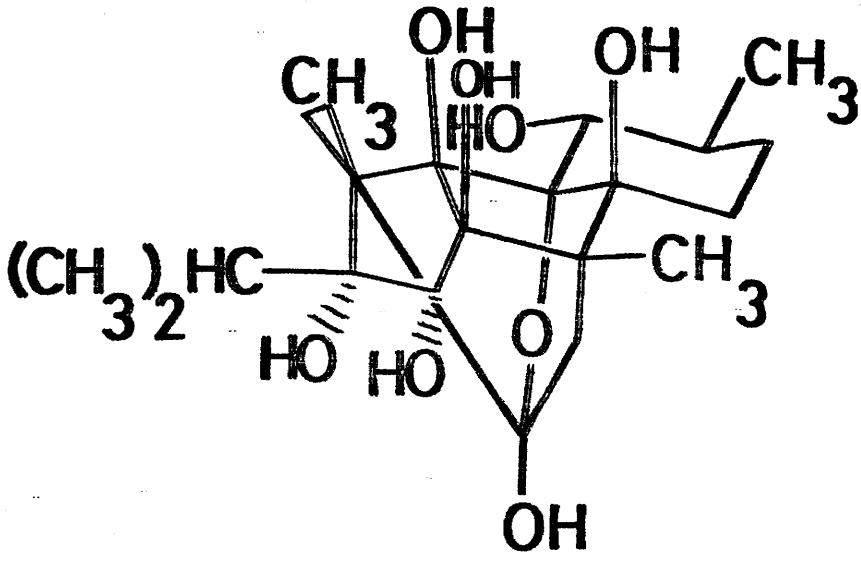


Fig. 31



Revised ?

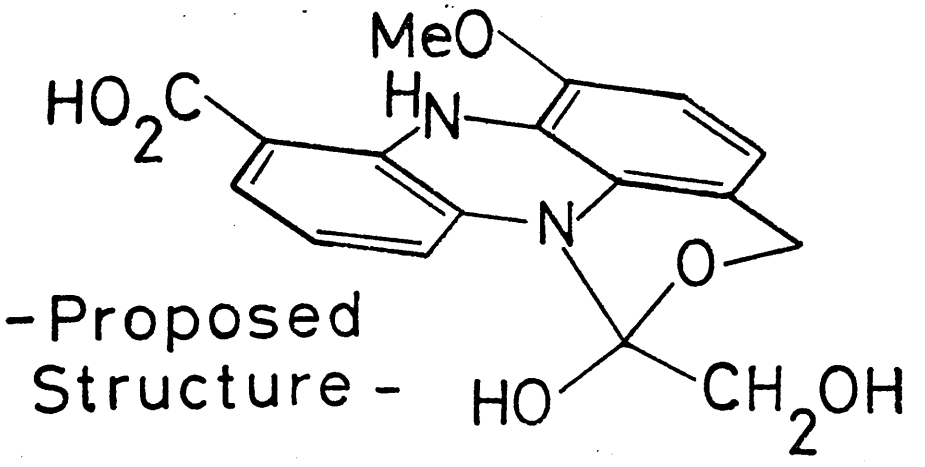
Fig. 32(a)



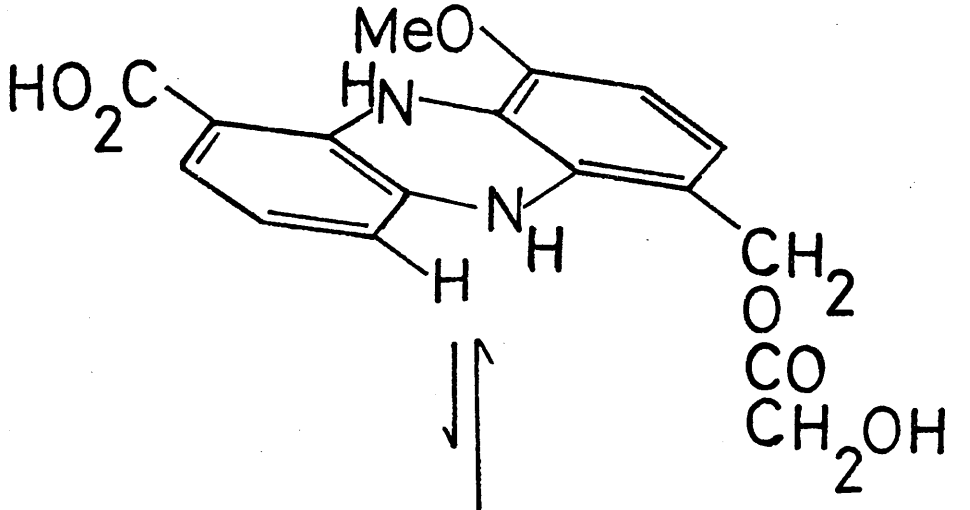
Revised ?

Fig.32 (b)

Ryanodol

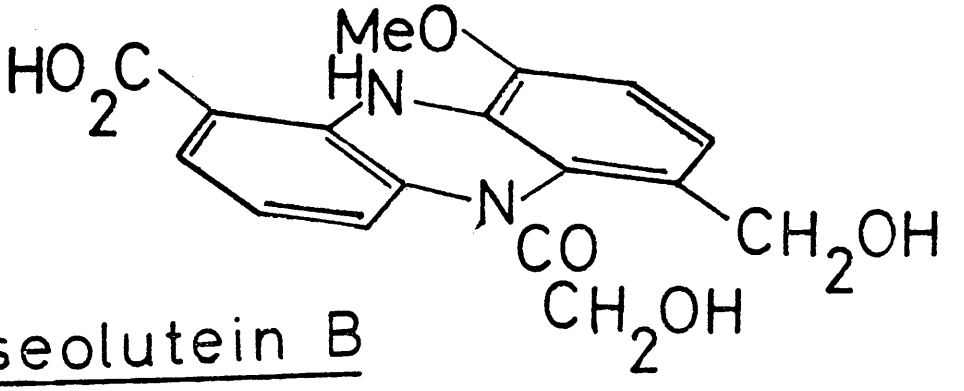


-Proposed Structure-



Revised.

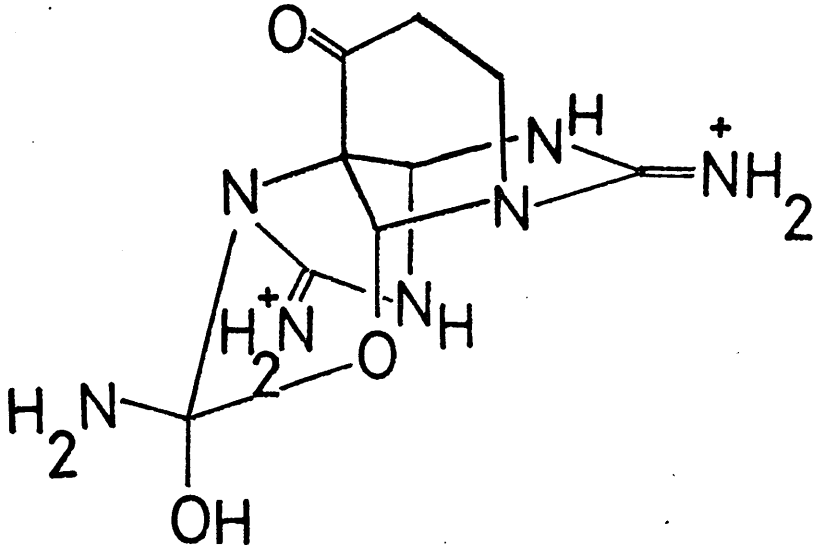
?

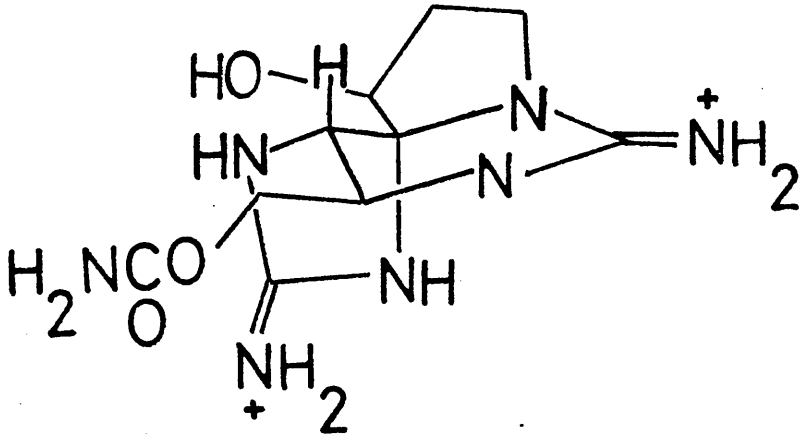


Griseolutein B

Fig.33

-Proposed Structure-





Revised.

Saxitoxin

Fig.34

other cases, in carbohydrate[130] and natural product chemistry, which were initially thought to be tetrahedral intermediates have refuted, however, in later work. Both the structures of ryanodol[131] and griseolutein B (figs. 31, 32 and 33) have been questioned[132] and probably do not exist in the tetrahedral form; although the latter may be an equilibrium mixture of open and closed chain forms. The initial isolation[125] and characterisation of saxitoxin suggested a tetrahedral intermediate type structure but this has since been revised (fig.34 by the preparation of crystalline derivatives[125,133] and subsequent X-ray work. Whether the formation of the crystalline material resulted in the loss of the tetrahedral intermediate structure is questionable.

While I.R. spectroscopic data suggests the hemiorthoester structure[134] of the formyl derivative of 3α-benzylamino-5β-progname-20β,21-diol (fig. 35) it seems an unlikely structure in view of the lack of any stabilising factors following the cyclic structure over the normal open chain ester/alcohol. Structural considerations of steric interactions by the use of models would appear to disfavour any likely cyclisation and in view of the work carried out in this thesis on the 2-hydroxy-1,3-dioxolan system the acyclic structure seems the more likely.

While the monochloroacetic acid ester of ethylene glycol[97] showed only ester character the dichloro[97] and trichloroacetic[98]

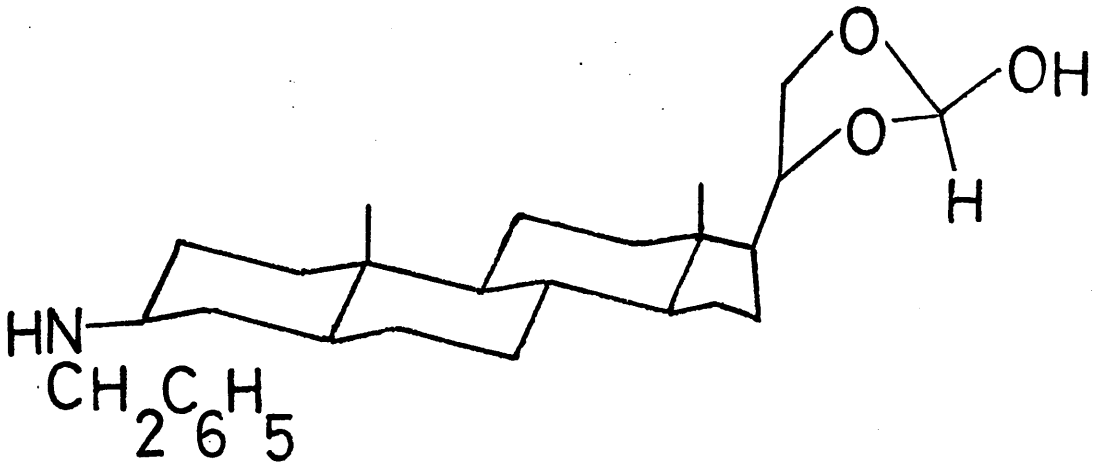
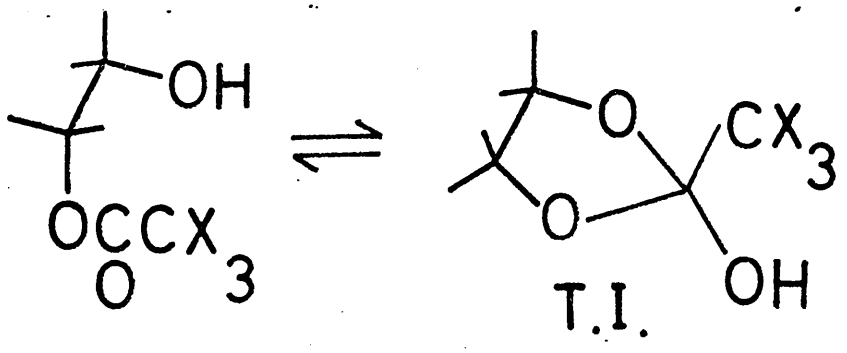


Fig. 35



X = F

Solvent	% of T.I.
1,4-dioxan	95
CH_3CN	95
CCl_4	60
Benzene	72

X = Cl

CH_3CN	13
CCl_4	7

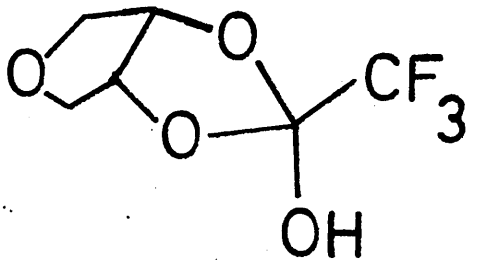
Fig.36

acid esters have shown chemical properties, e.g. reaction with diazomethane,[97,99] which suggest that they exist in equilibrium with the hemiorthoester species. The extent of this equilibrium in favour of the tetrahedral intermediate is, however, questionable considering that a slight displacement in the equilibrium, e.g. the reaction with diazomethane, could result in an unfair analysis of its properties via the formation of 2-methoxy-1,3-dioxolan. The subsequent study of pinacol[100] esters of trichloro and trifluoroacetic acids by N.M.R., however, have shown quite conclusively that this equilibrium does exist, with the solvent playing a very important part in deciding the partitioning (fig. 36).

The related precursor (fig. 37) has been studied in a similar manner and has been shown to exist predominantly in the tetrahedral intermediate form.[117]

Direct N.M.R. and U.V. spectral data have also provided evidence for the appreciable hydration[105] of N-trifluoroacetylpyrrole in aqueous acetonitrile (fig. 38). In acetonitrile only two signals in the N.M.R. exist for the protons on the pyrrole ring. In aqueous acetonitrile, however, a further two signals are observed initially which cannot be attributed to the products obtained from slow hydrolysis. The U.V. spectrum also contained an extra peak which cannot

Fig.37



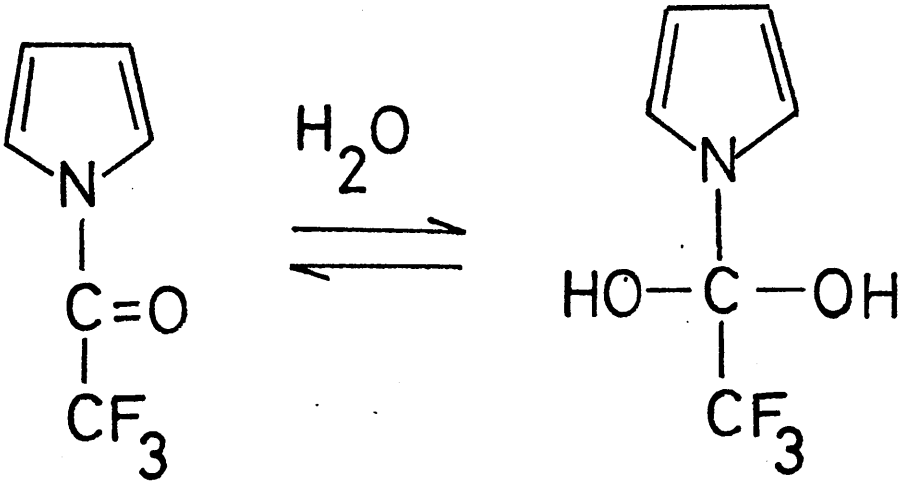


Fig.38

be assigned to the hydrolysed material. This data was therefore attributed to the hydrated species which should be present as a reactive intermediate on the reaction pathway.

While oxygen → nitrogen acyl migration,[106,107] and similar reactions, have been postulated to occur via T.I.s the direct evidence for this assumption has been slim. The observation and isolation, therefore, of the T.I. involved in the acyl transfer has been the first direct evidence. The equilibrium is such that direct isolation and characterisation could be carried out (see fig. 39).

The T.I. obtained from the intramolecular acyl transfer[108] of mono-5-acylated 1,8-naphthalenedithiol (fig. 40) has also been isolated but has been found only to be stable in the solid crystalline form. Whereas the I.R. spectrum of the solid shows a strong hydroxyl bond and no carbonyl or thiol stretches the corresponding spectrum in chloroform shows the reverse. It was concluded, therefore, that since the N.M.R. showed only a thiol peak and no alcohols except when immediately recrystallised from methanol that the crystallisation was enough to stabilise the tetrahedral intermediate form. Further work with substituents on both the benzene and naphthalene rings should confirm this by possibly stabilising the tetrahedral intermediate further.

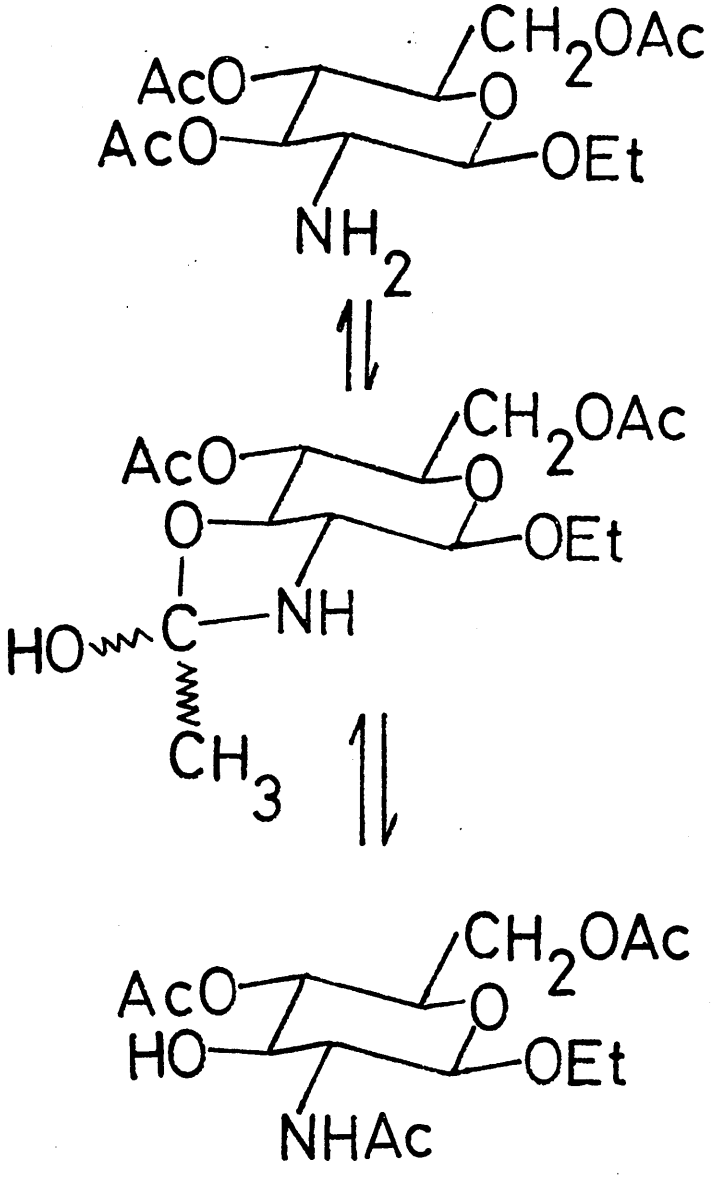

CH2OAc
AcO
O
AcO
OEt
NH2
CH2OAc
AcO
O
O
OEt
HO
C
NH
CH3
CH2OAc
AcO
O
HO
OEt
NHAc

Fig.39

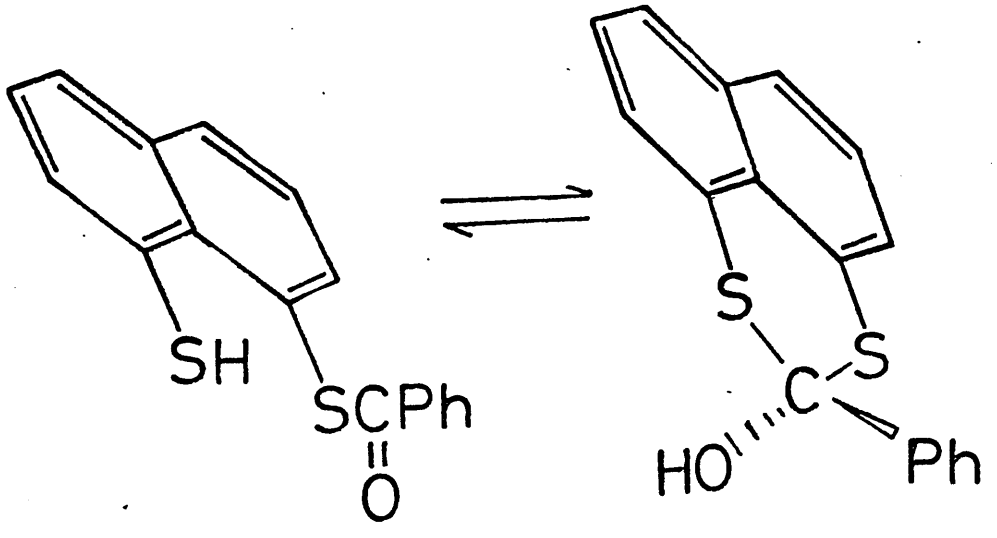

SH
SCPh
O
S
S
C
HO
Ph

Fig.40

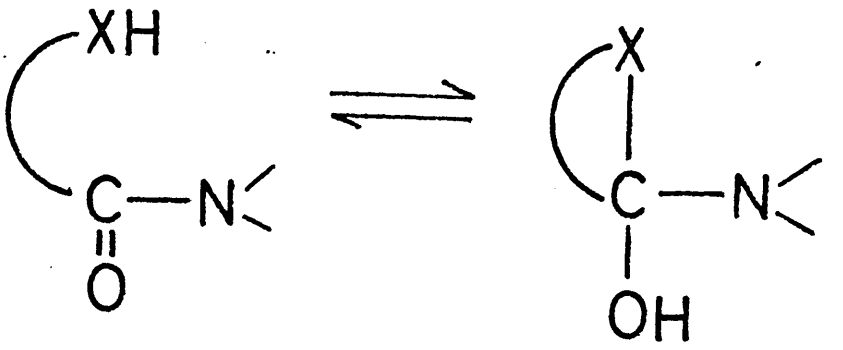
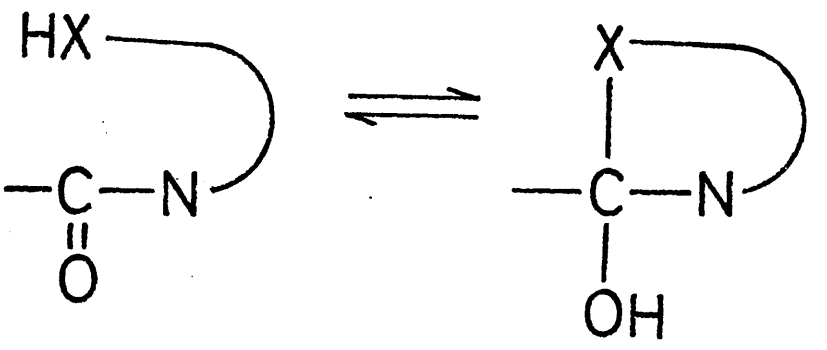
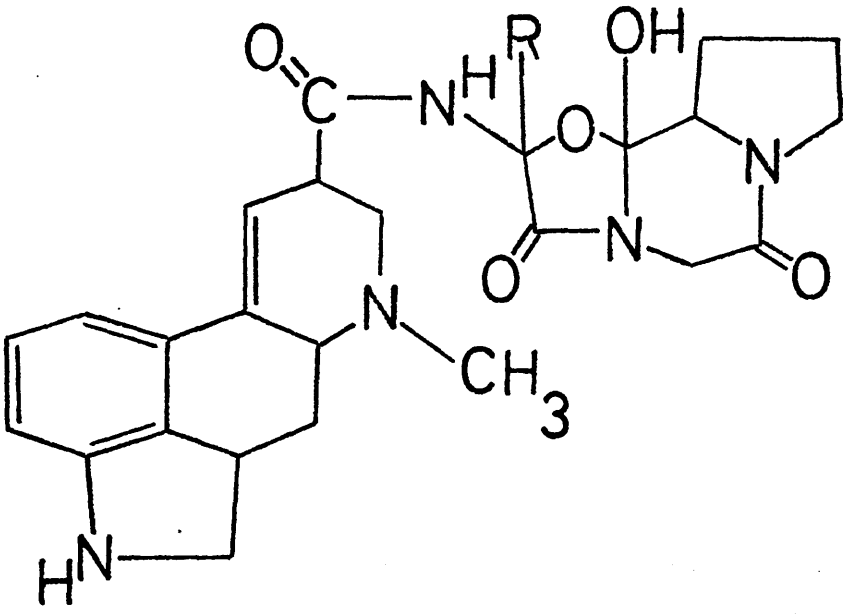


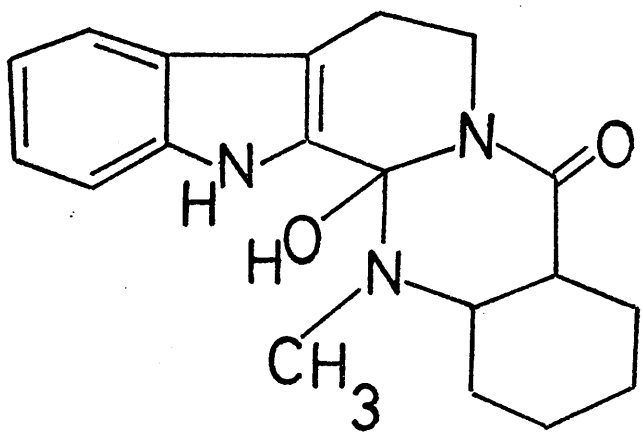
Fig.41





General structure of the Ergot Alkaloids

Fig. 42



Rhetsinene

Fig.43

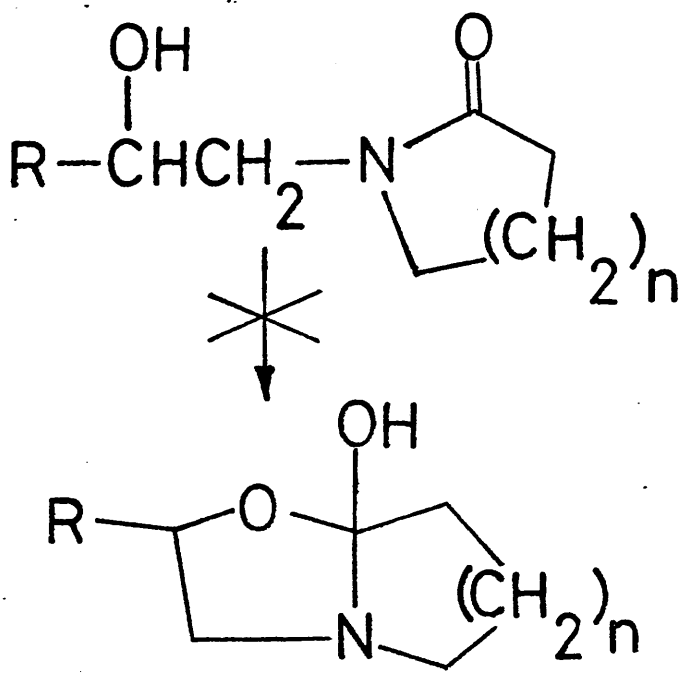


Fig.44

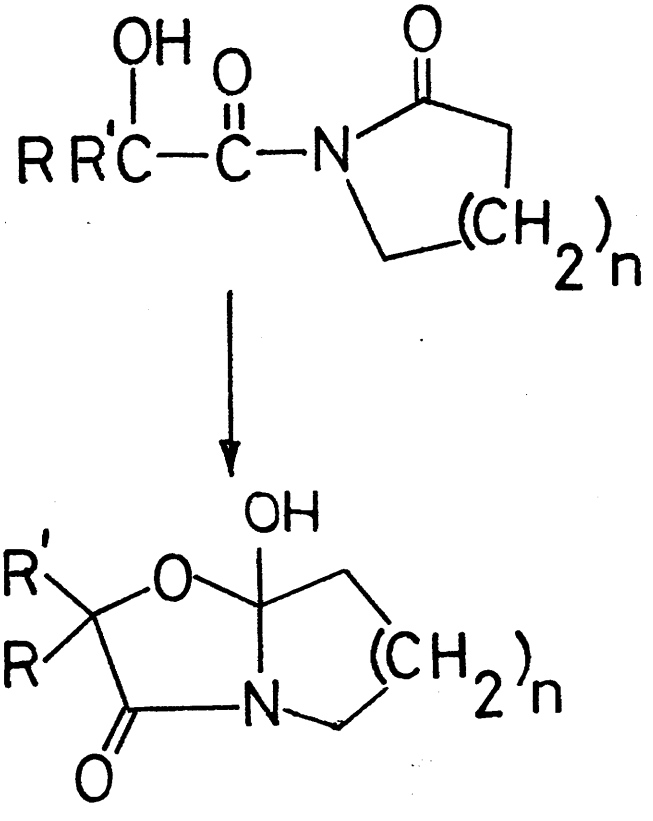
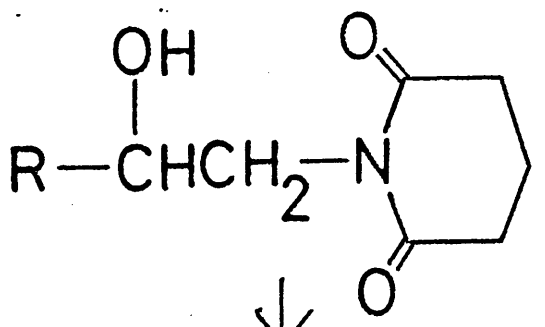


Fig.45



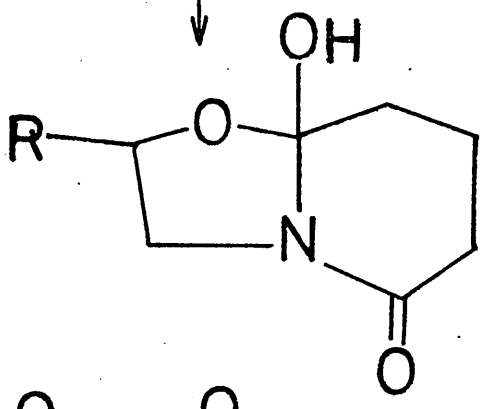
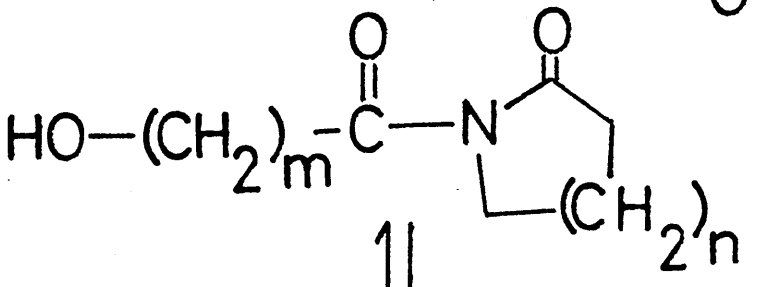


Fig.46



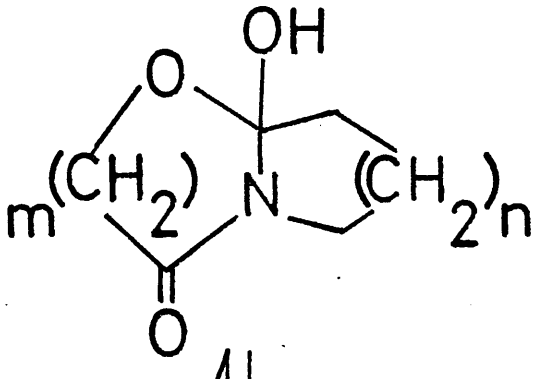
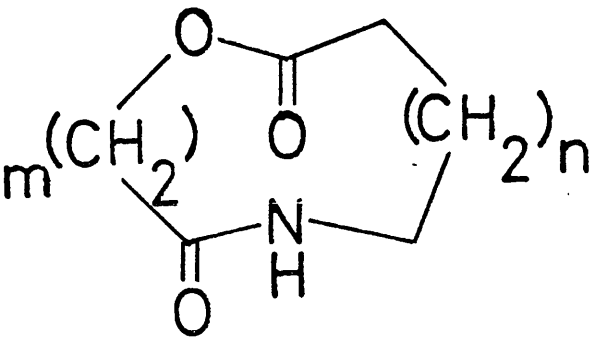


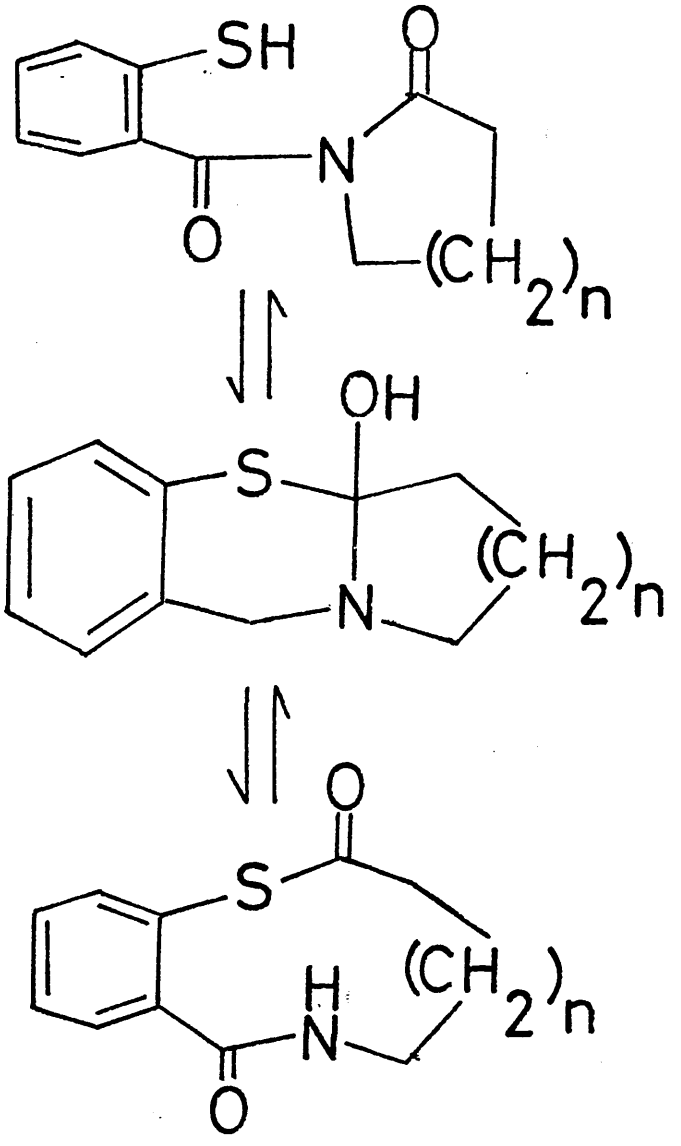
Fig.47



The study of N-hydroxyalkyl carboxamides and their resulting cyclisation by intramolecular addition has been effectively summarised by De Wolfe.[109]

While most cyclised forms of the type shown, (see fig. 41) are unstable, as compared to the open chain form, several examples exist where stabilisation results in the equilibrium being displaced partly or completely towards the tetrahedral intermediate form. Probably the best known examples of these stable tetrahedral intermediates (cyclols) are the ergot alkaloids[109,113] and rhetsinene[114] which have been demonstrated to have the general structures shown (figs. 42 & 43) Work by several experimentalists on structural factors affecting the equilibrium and isomerisation between the various species have resulted in the deductions that the presence of a carbonyl exocyclic to lactam ring stabilises the cyclol as compared to the open chain form (see fig. 45). The lack of this activating species (fig. 44) or the presence of it in the same ring as the lactam (fig. 46) results in no cyclisation. The sizes of both rings (values of m,n) greatly affect the stability of the cyclol and can result in no isomerisation if both m and n are small or the formation of the macrocycle if m and n are large (generally occurs when there are more than 11 atoms in the ring). The observation of equilibrium mixtures occurs in the intervening period with the possible

Fig.48



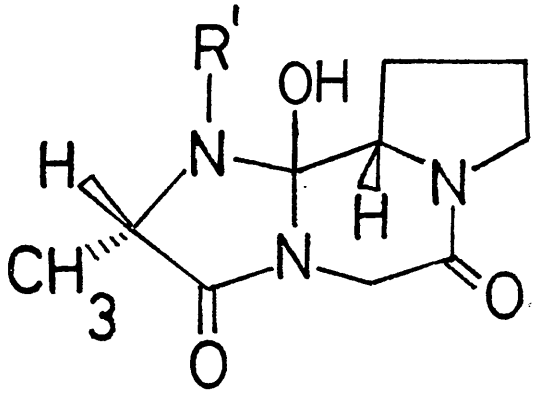
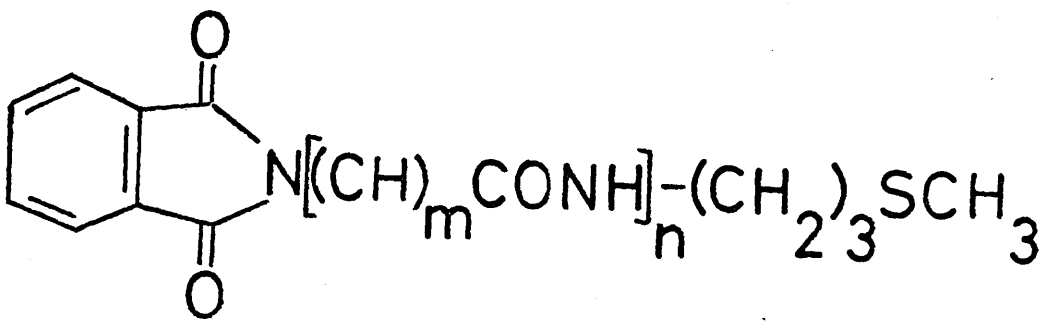
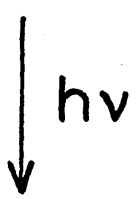


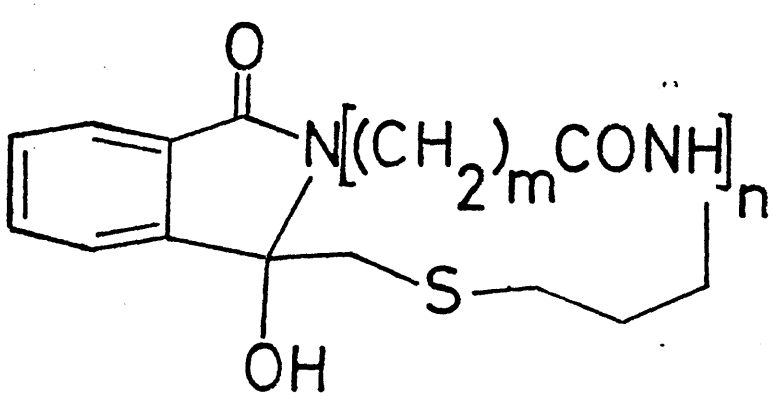
Fig.49

R' = $PhCH_2OCO$

= p-$BrPhCH_2OCO$







m = 1, n = 1
m = 2, n = 2
m = 5, n = 2

Fig. 50

preferred stabilisation of cyclol (fig. 47). The general lack of reactivity of the smaller ringed systems is probably due to a combination of steric effects and reduced electrophilicity of the carbonyl characteristic of 5 and smaller membered rings. The isolation of cyclol systems where X is sulphur[110] or nitrogen[111] has produced many other interesting stable species (see figures 48 and 49). The generation of similar novel compounds,[112] which are not tetrahedral intermediates, by irradiation, emphasises the stabilising effect of the carbonyl (see fig. 50).

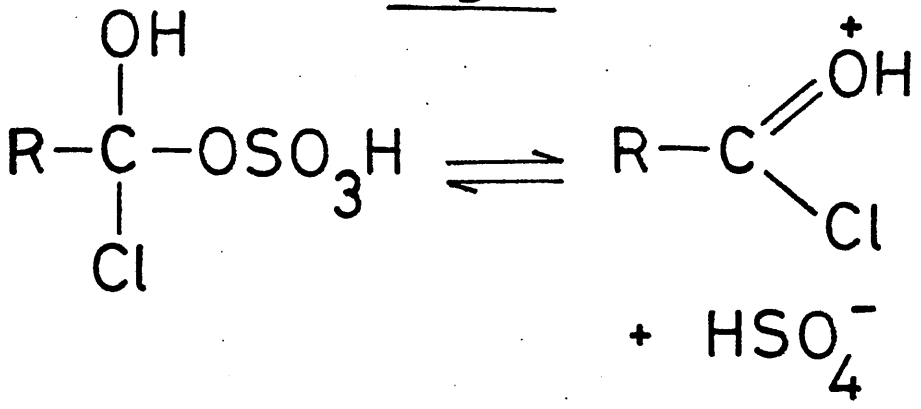
With the advent of modern analytical techniques the evidence for the occurrence of tetrahedral intermediates has increased. The Raman spectra of solutions of benzoyl chloride and sulphuric acid has permitted the demonstration of the equilibrium[151] of the addition intermediate with its salt (fig. 51). A similar type of reaction has shown the presence of solely the addition intermediate[116] (fig. 52).

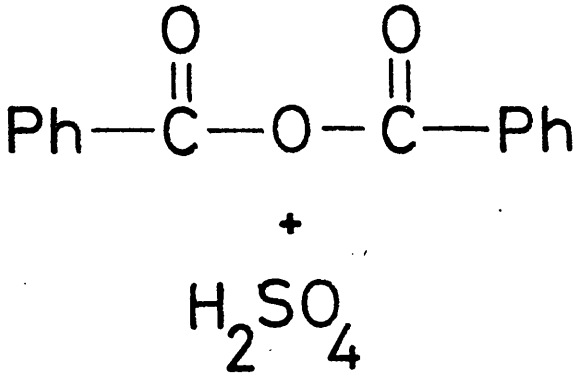
The structures of several other tetrahedral intermediates are summarised in figures 53 to 57.

The reactions of thiols with carbonyl cyanide[123] has produced a very interesting intermediate species (fig. 58) dicyanolhydrins) which in some cases have been isolated in a crystalline form.

Finally the isolation of methanetrithiol[124] (the trithioorthoformic acid) by stepwise deacylation of methanetrithiol,

Fig.51





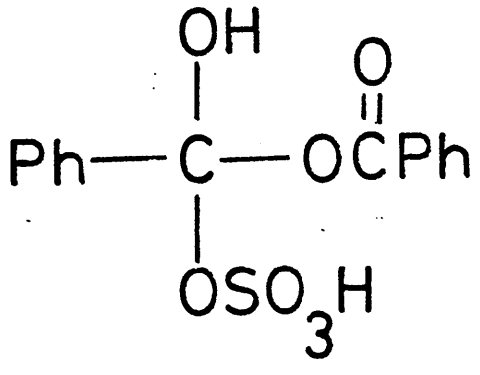
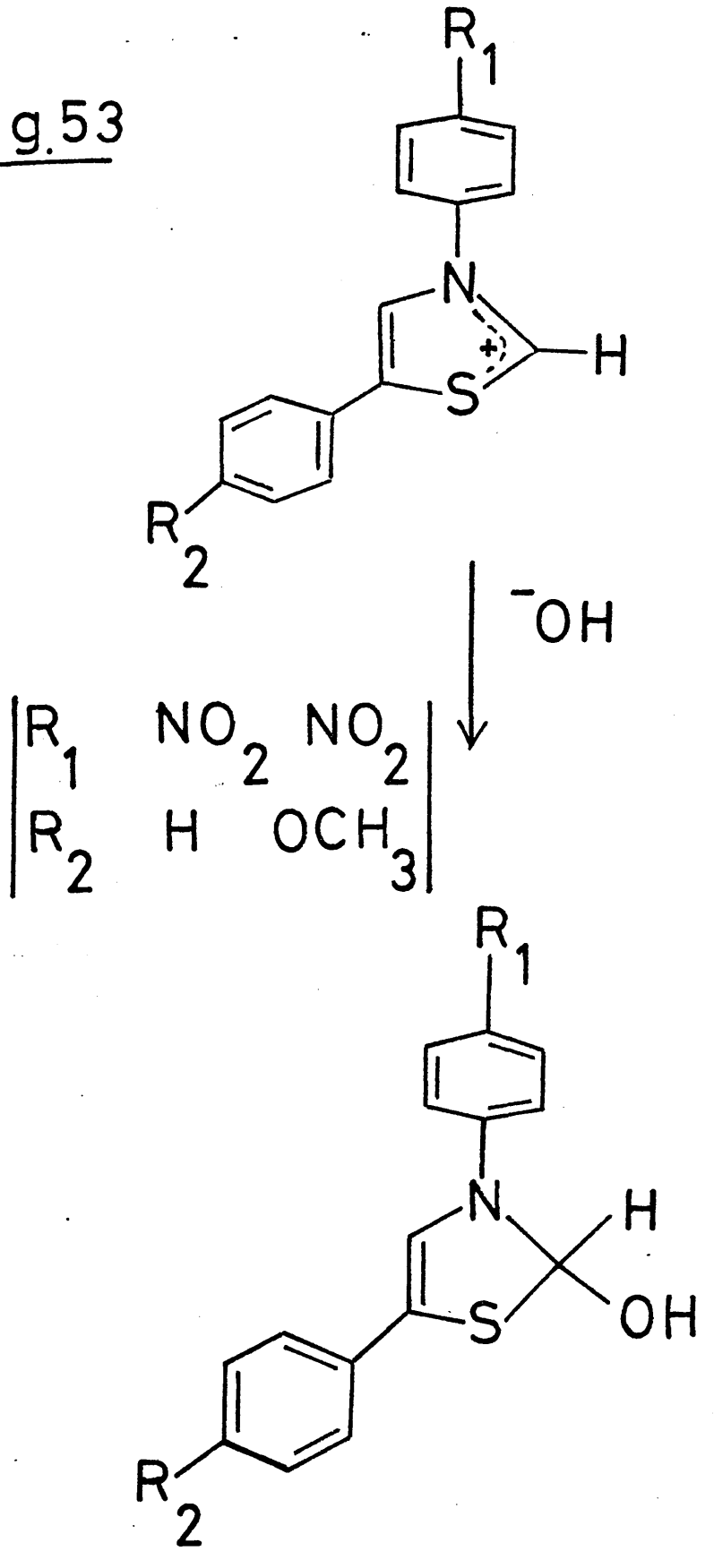


Fig.52

Fig.53



Ref. 115

Ref. 122(b)

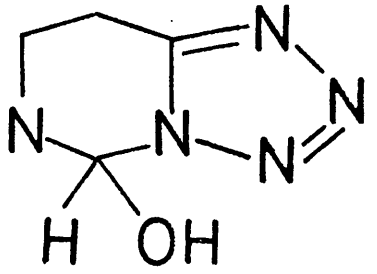
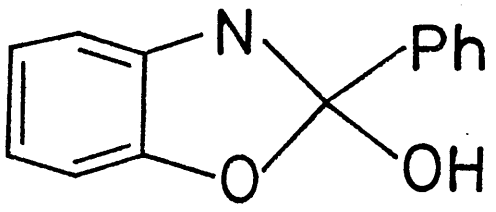
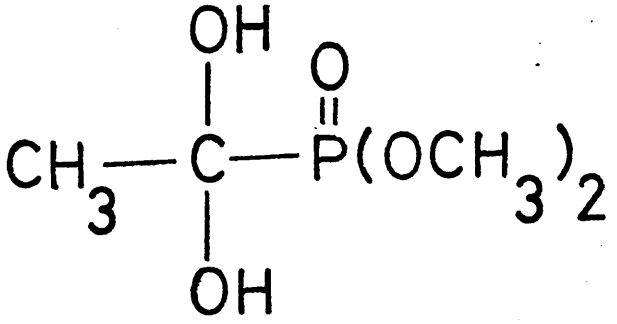


Fig.54



Ref. 118

Fig.55



Ref. 154

Fig.56

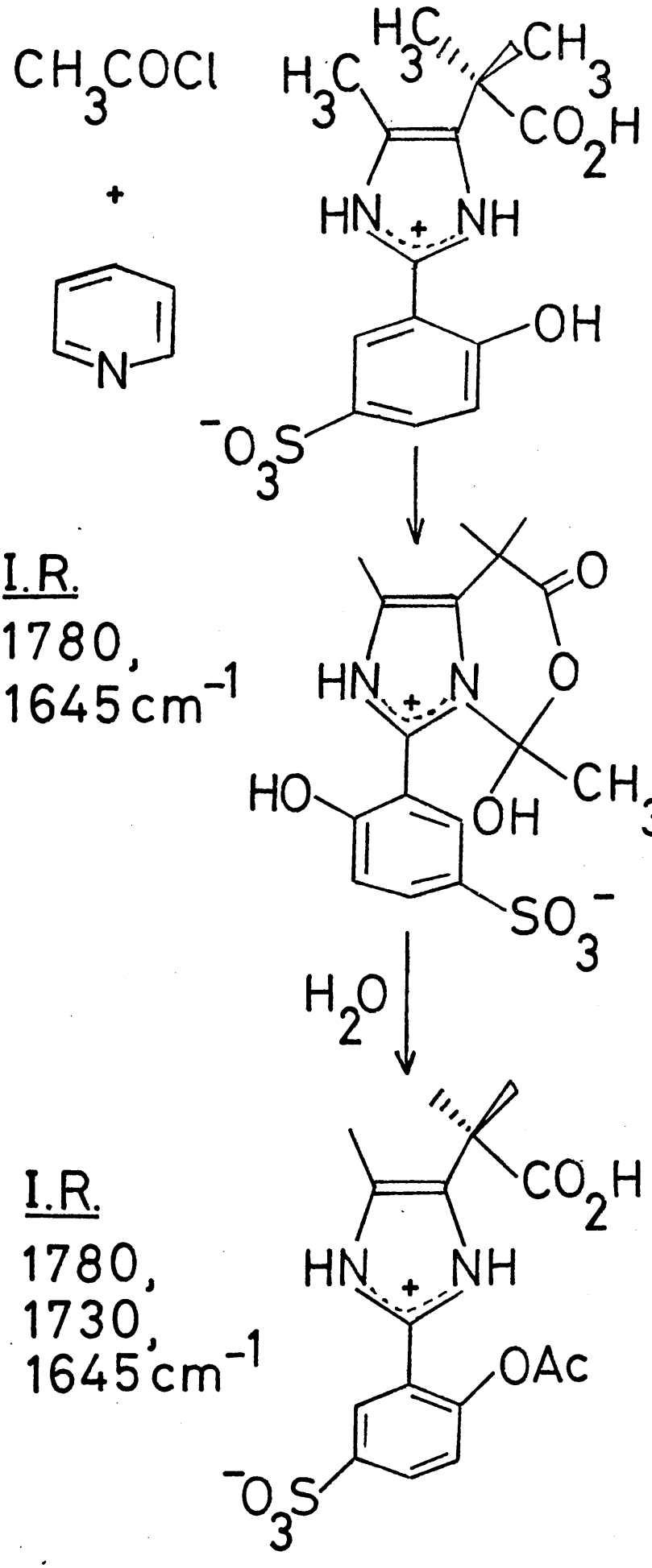
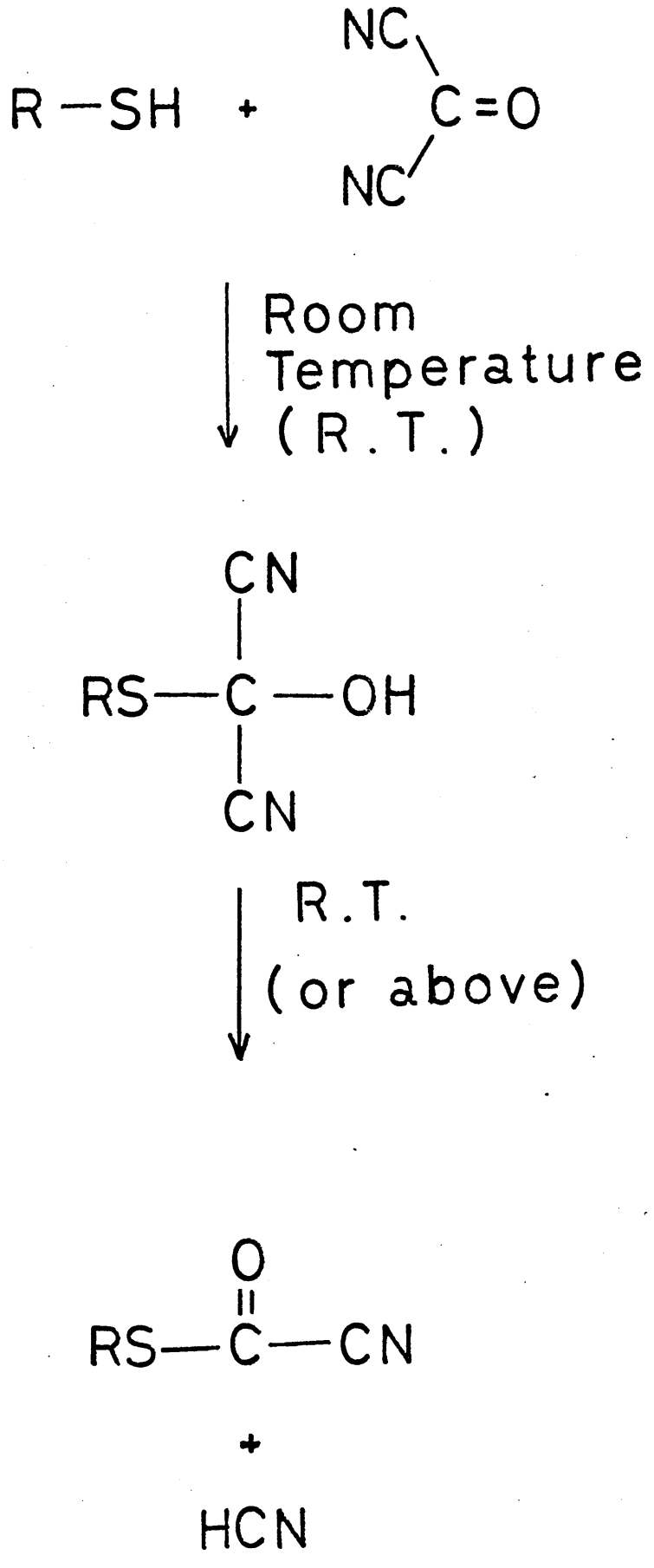


Fig. 57

Ref. 121

Fig.58

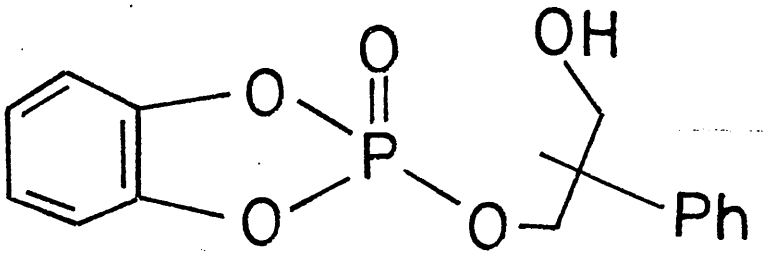

R—SH
NC
C=O
NC
Room
Temperature
(R.T.)
CN
RS—C—OH
CN
R.T.
(or above)
O
RS—C—CN
+
HCN

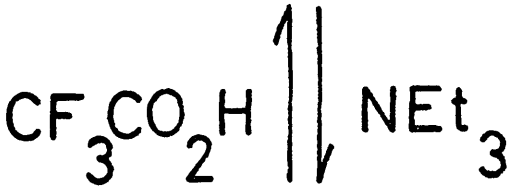
at -30°C, is probably the first example of the observation and characterisation of an orthoacid, these species having been often postulated as low concentration unstable species.

While not directly relevant to the study of tetrahedral intermediates the nucleophilic addition equilibrium of alkoxide to phosphorous to give a pentacovalent species,[104] analogous to a tetrahedral intermediate has been suggested to have been observed as an acid/base equilibrium by ^{31}P N.M.R. (fig. 59). Similar studies of two other pentavalent intermediates[152,122(a)] have also been postulated (figs. 60 and 61). While a good correlation of the ^{31}P N.M.R. chemical shifts for the first two species[104,152] can be seen, the latter species, isolated as the salt[122(a)] differs greatly from the other phosphorous intermediate[104] reputed to be stabilised by triethylamine (table 2). These results, therefore, may be slightly in question.

TABLE 2

	^{31}P shift of pentavalent intermediate	Open Chain Species
Ref 104	28	- 12
Ref 152	27	- 6.7
Ref 122(a)	-50.5 (stabilised as ion)	





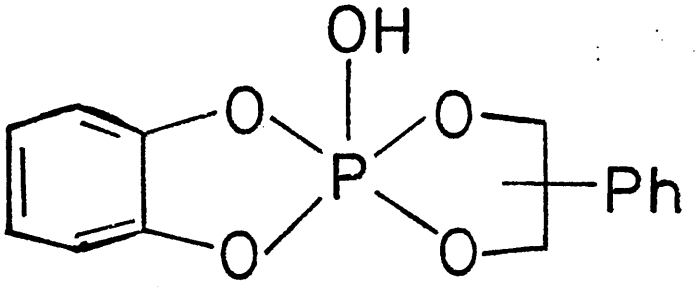


Fig.59

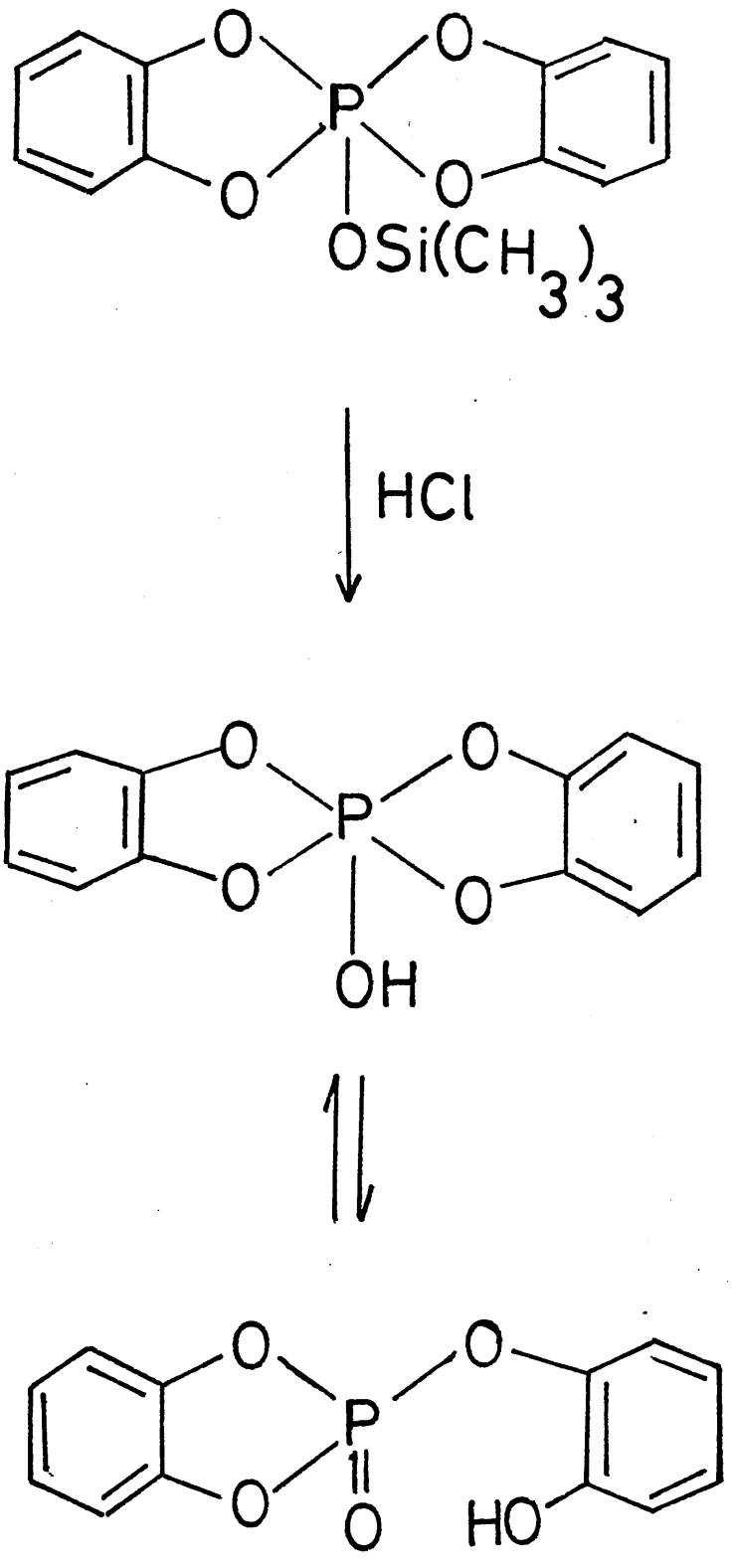


Fig.60

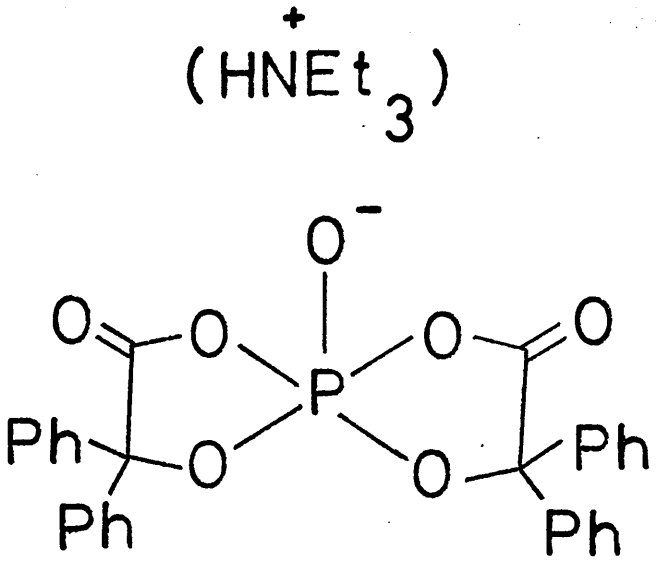
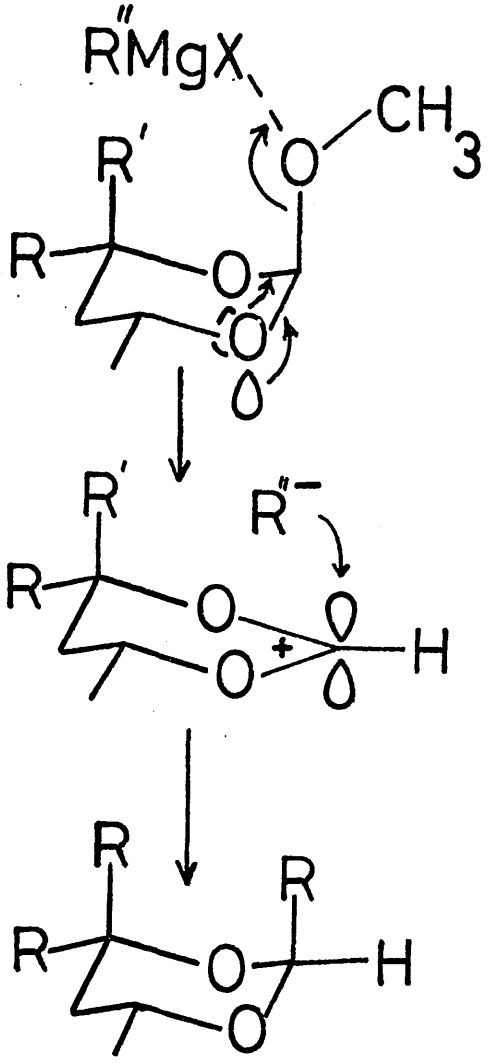


Fig.61

Stereoelectronic Control of Products

The observation by Eliel and Nader[137] that the reaction of substituted-2-alkoxy-1,3-dioxanes with Grignard reagents resulted in preferential reaction of the orthoester which had a fixed axial group, rather than the equatorial isomer, led to an interpretation of these results as assistance, by the lone pairs of the 1,3-dioxane oxygens, of the loss of the alkoxy function (fig. 62 and table 3). The apparent lack of reactivity of the equatorial 2-alkoxy group, under non-forcing conditions, could then be rationalised as the lack of oxygen pairs anti-parallel (antiperplanar) to the leaving group. This effect can be viewed as being similar to an E2 type mechanism where the effective kicking out of the group is observed (fig. 63).

King and Allbutt,[139] in their study of fused dioxolenium ions, observed that the reaction with halide ions resulted in predominantly the diaxial isomer rather than the diequatorial species by attack at positions 4 and 5 of the dioxolan ring. (The dioxolan rings are numbered to give the oxygens the lowest possible values i.e. in this case 1,3-dioxolan). The reactions of alcohol and water, however, gave the products obtained from attack at position 2 with breakdown to predominantly the axial ester when water was the nucleophile (fig. 64). Attack of the ROH function on the C-1 carbon was considered to occur initially perpendicular to the common



Trans

I R,R' = H

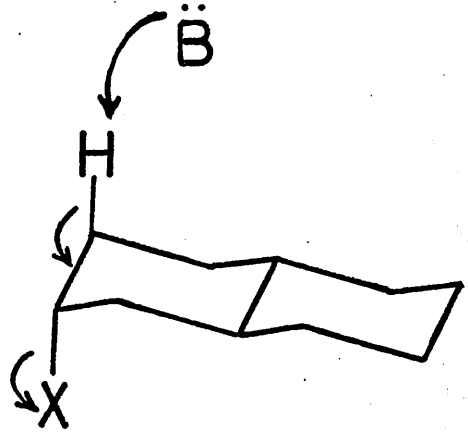
III R = CH_3

V R,R' = CH_3

Fig.62

TABLE 3

				% Yield
trans I	CH_3MgI	86% trans	14% cis	67%
trans III	"	90% trans	10% cis	70%
trans V	"	88% trans	12% cis	62%
mixed I (69% trans) (31% cis)	"	88% trans	12% cis	51%
cis III	"	0		-
cis V	"	0		-



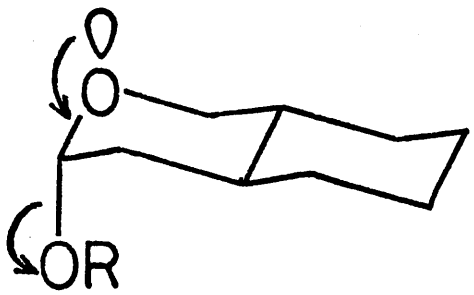


Fig.63

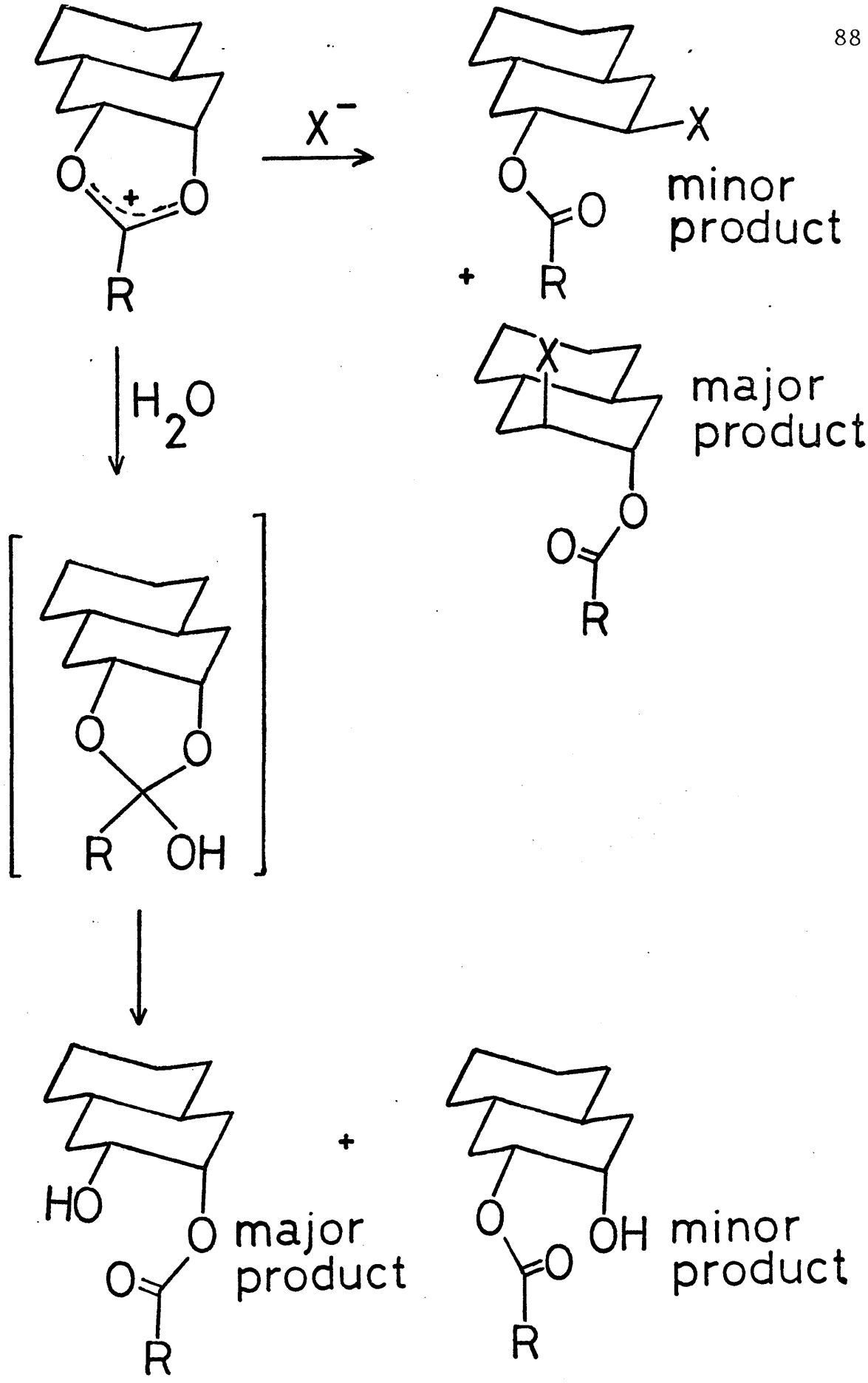

X⁻
minor product
major product
H₂O
major product
minor product

Fig.64

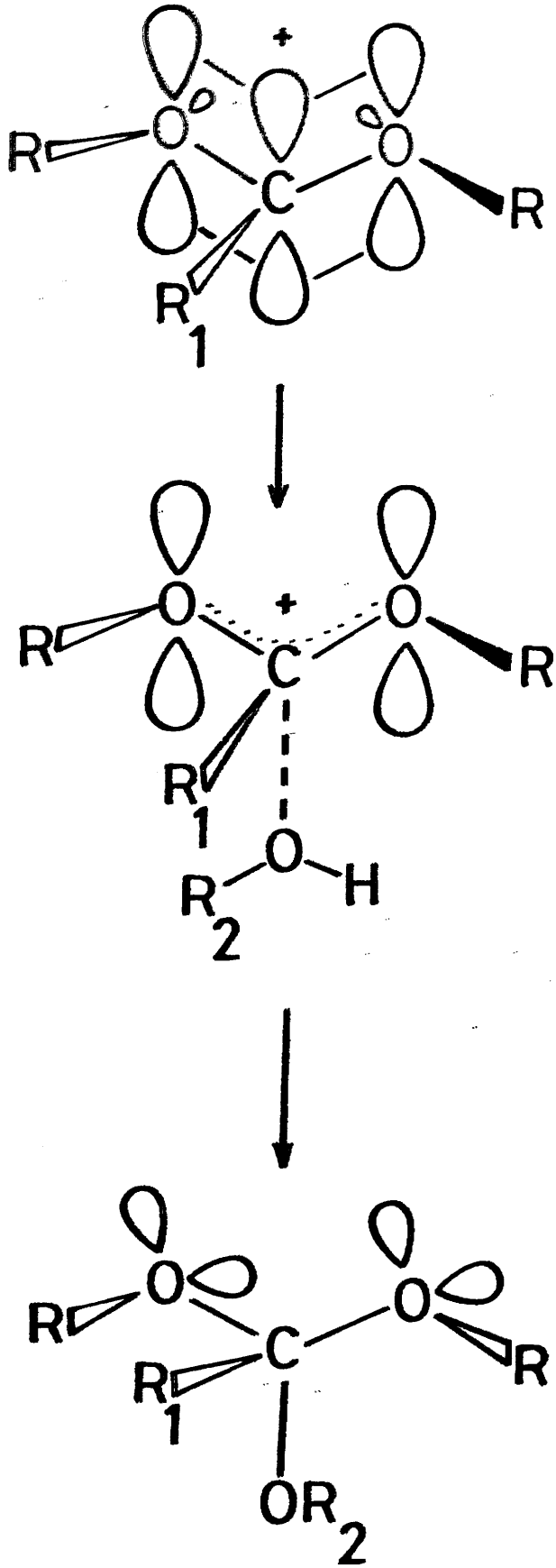


Fig 65

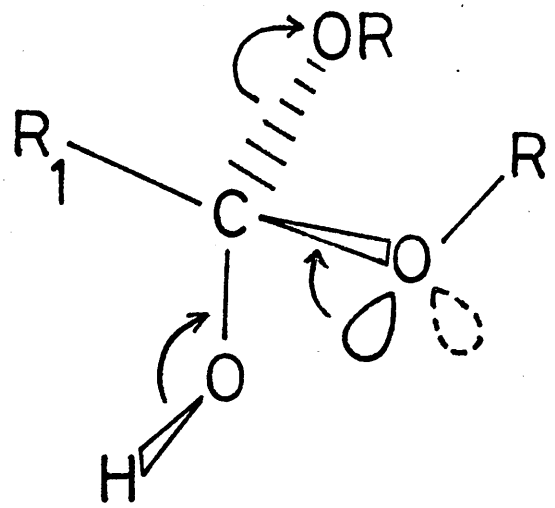


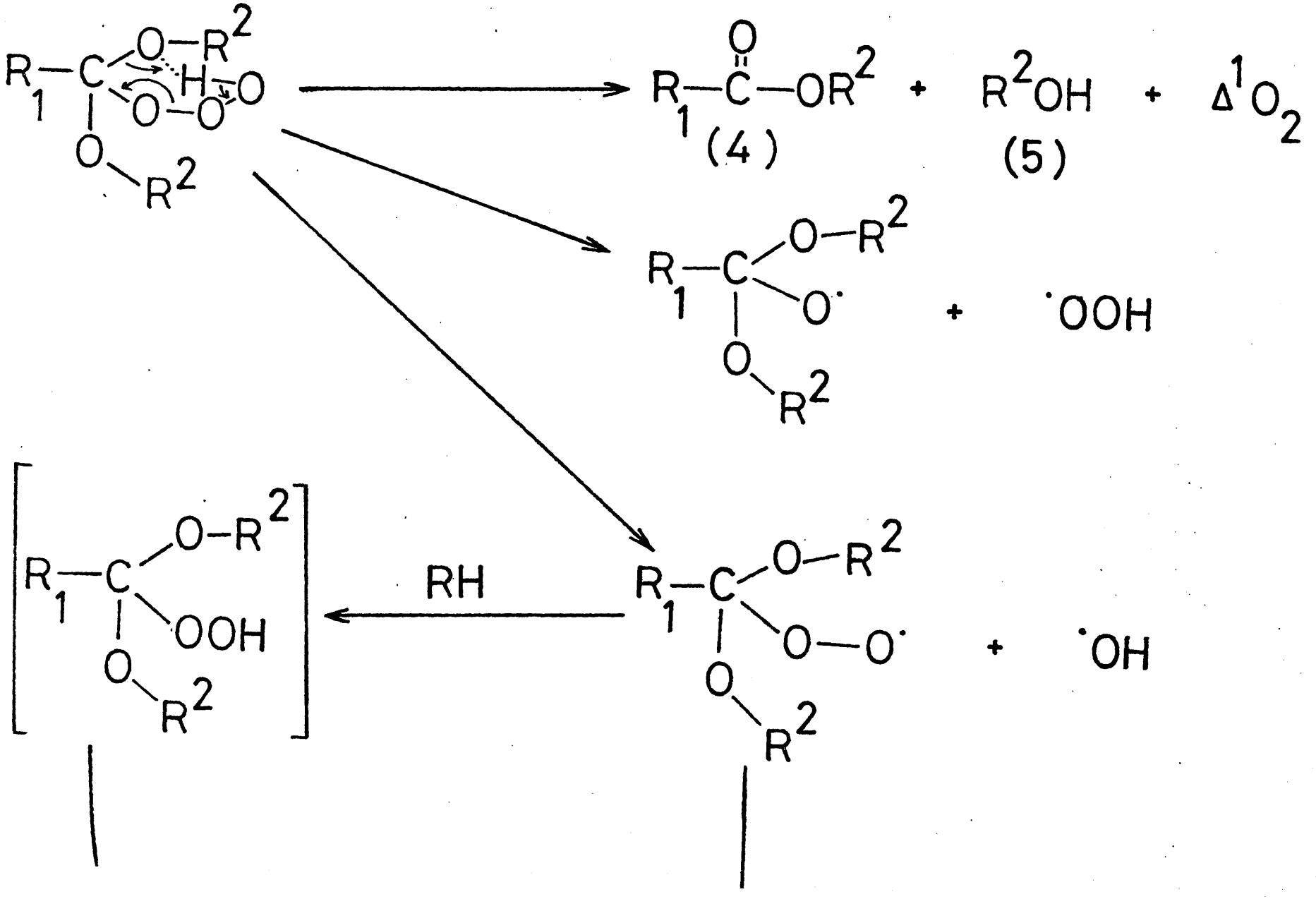
Fig.66

plane of the carbon and oxygens so that the initial and final transition states are as shown in fig. 65. A simple reverse of this reaction would necessarily involve the lowest possible energy and hence the maximum stabilisation of any charge would be required. This is obtained by having oxygen electron pairs anti (antiperiplanar) to the leaving group so that the reverse steps reach maximum stability (fig. 66).

This idea that participation of antiperiplanar orbitals giving greater stability has been the basis of the work of Deslongchamps[136] which is divided up into a number of different areas.

The ozonolysis of acetals results in the formation of ester and alcohol functions. In his first paper, Deslongchamps assumes the existence of an intermediate from the insertion of ozone into the C-H bond of the acetal:

"It is assumed that this reaction proceeds via insertion of ozone in the C-H bond of the acetals to give a hydrotrioxide intermediate.....which then gives the corresponding ester and alcohol functions".[136(a)] This assumption is used, together with a further assumption that a tetrahedral intermediate is equivalent to the hydrotrioxide species, in all the ozonolysis work. In one paper three variations of this idea are presented:


R1
C
O
R2
H
O
O
O
R2
R1
C
OR2
O
(4)
+
R2OH
(5)
+
Δ1O2
R1
C
O
R2
O·
O
R2
+
·OOH
RH
R1
C
O
R2
OOH
O
R2
R1
C
O
R2
O
O·
O
R2
+
·OH

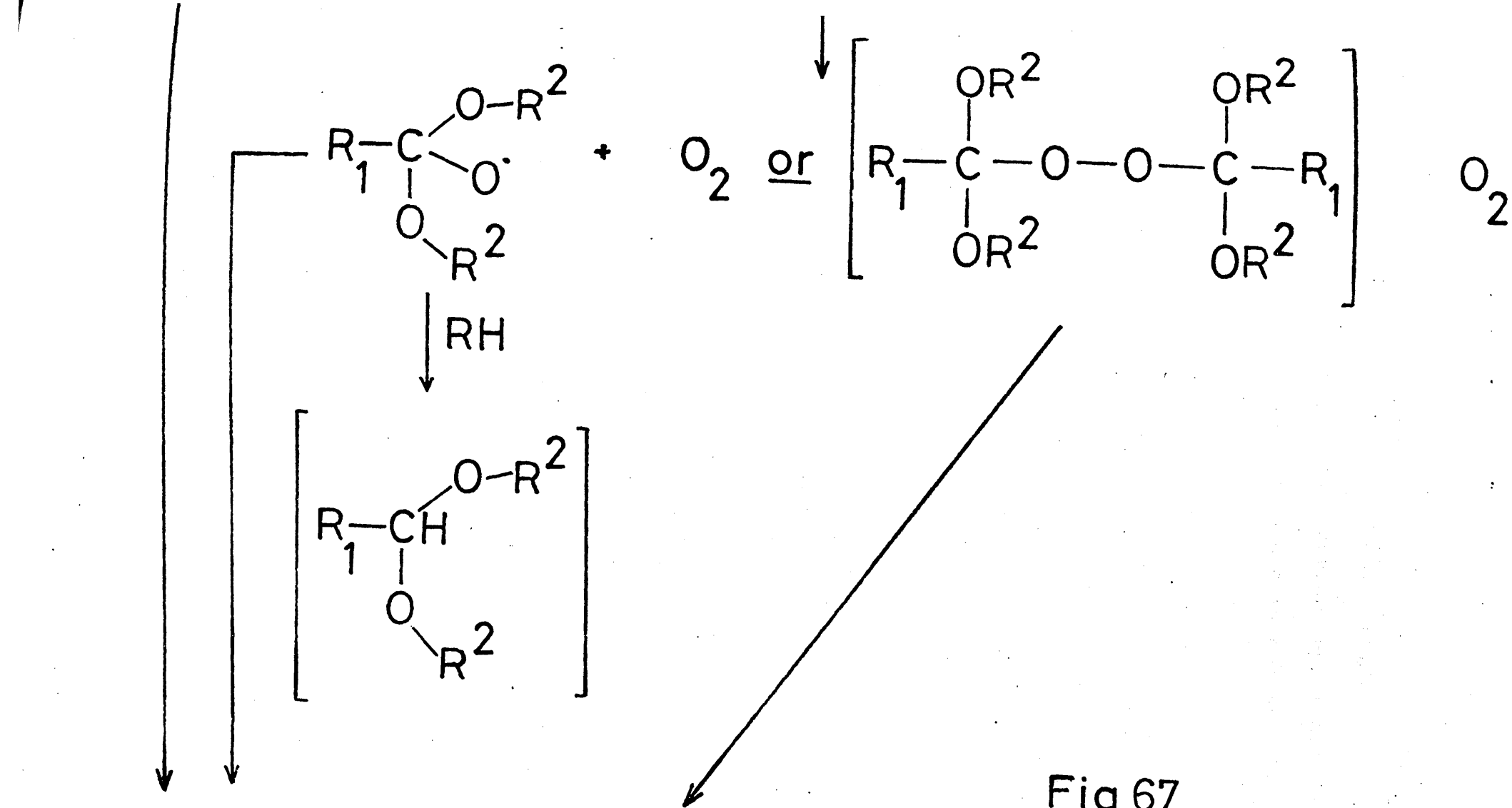


Fig.67

"We have recognised very early during our work that the intermediate which is formed during the oxidation of acetals is either identical or equivalent to a hemiorthoester which is the tetrahedral intermediate formed during the transesterification of esters".

"It is likely that it proceeds via the insertion of ozone into the C–H bond of the acetal forming an intermediate....".

"We conclude that the ozonolysis of acetals doubtless proceeds via the formation of an intermediate analogous to a hemiorthoester".[136(d)]

It is only recently that the existence of hydrotrioxides[140] has been shown and has, partly, quelled the argument of possible radical mechanisms.[141] The stability of these hydrotrioxides are such that they are observed only at lower temperatures, up to -10°C, and have been shown to be intramolecularly hydrogen bonded. It is therefore possible that the orientation of the lone pairs and hence the breakdown is controlled by this intramolecular bonding.

The ozonolysis of some acetals[142(b)] has been shown to give a variety of products and this has led to the suggestion that breakdown of the expected hydrotrioxide occurs via both a cyclic non-radical pathway and also via a radical process (fig. 67).

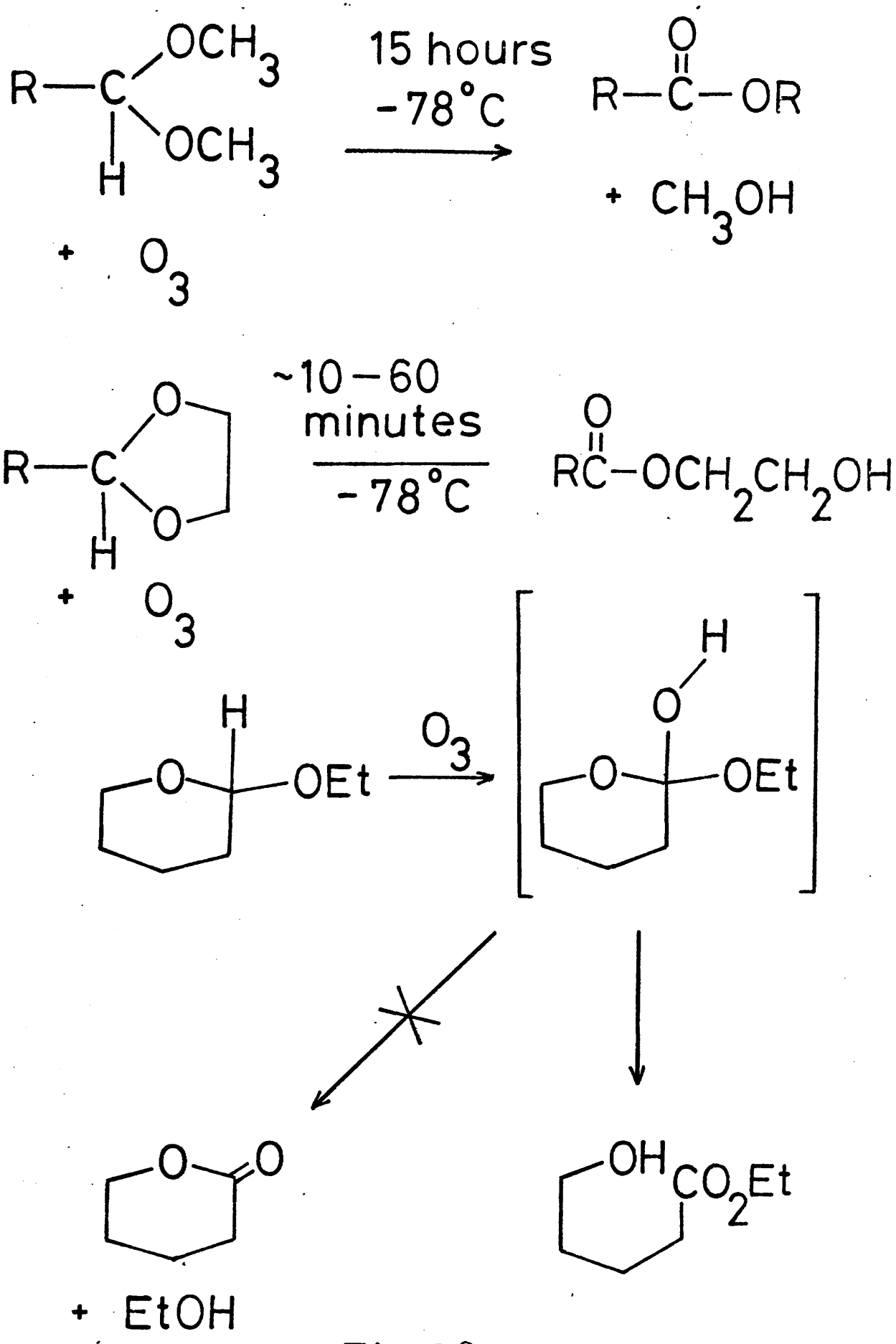

R—C(OCH3)(OCH3)(H)
15 hours
-78°C
R—C(=O)—OR
+ CH3OH
+ O3
~10-60 minutes
-78°C
RC(=O)—OCH2CH2OH
+ O3
OEt
O3
OEt
OH
CO2Et
+ EtOH

Fig. 68

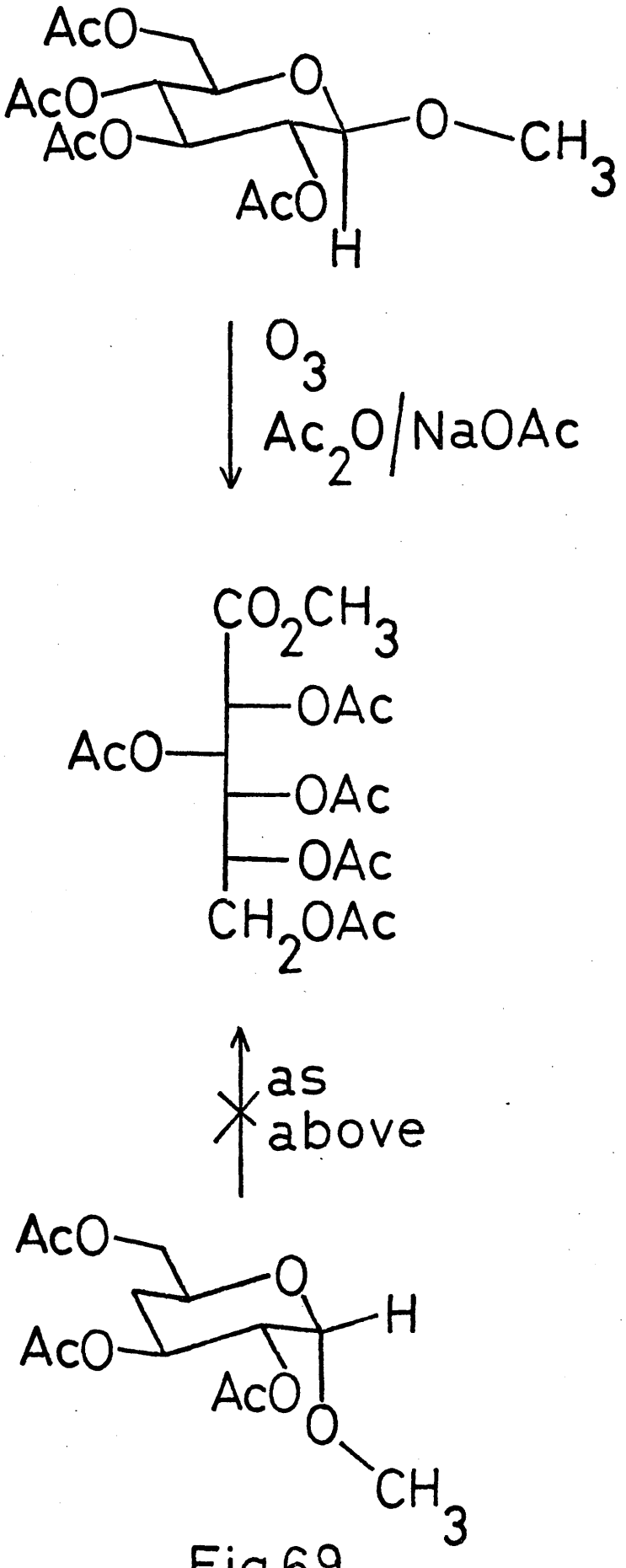
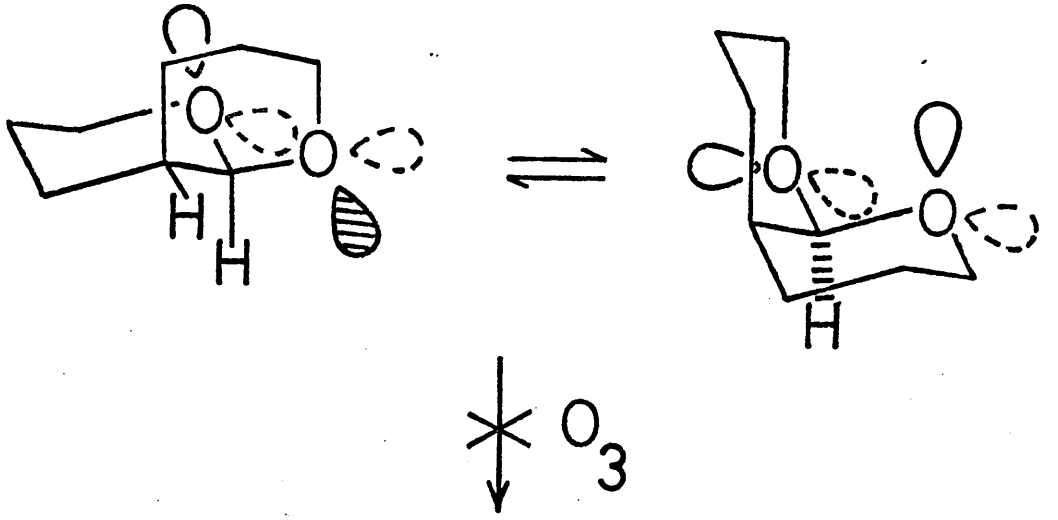

AcO
AcO
AcO
AcO
O
O
CH3
H
O3
Ac2O/NaOAc
CO2CH3
OAc
AcO
OAc
OAc
CH2OAc
as
above
AcO
AcO
AcO
O
H
O
CH3

Fig.69



No reaction.

Fig.70

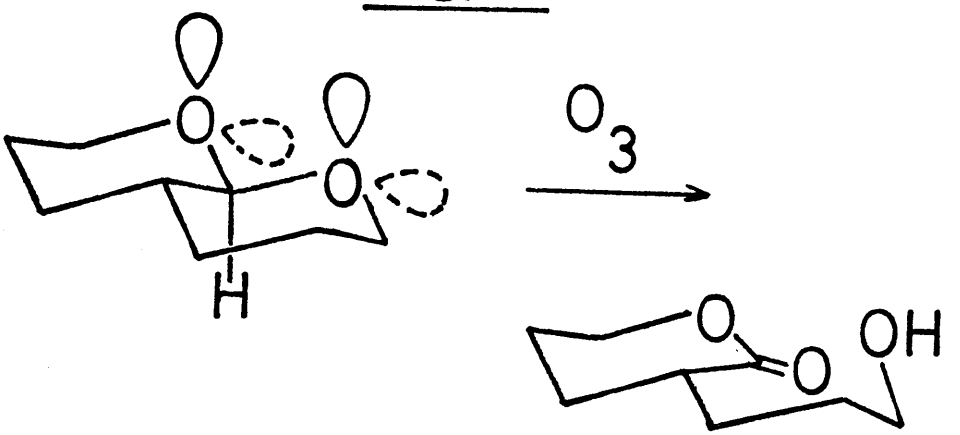


Fig.71

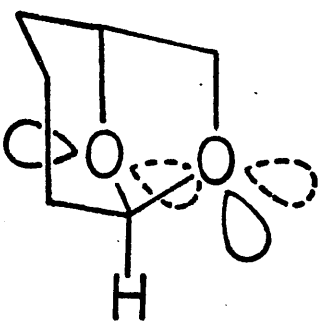


Fig.72

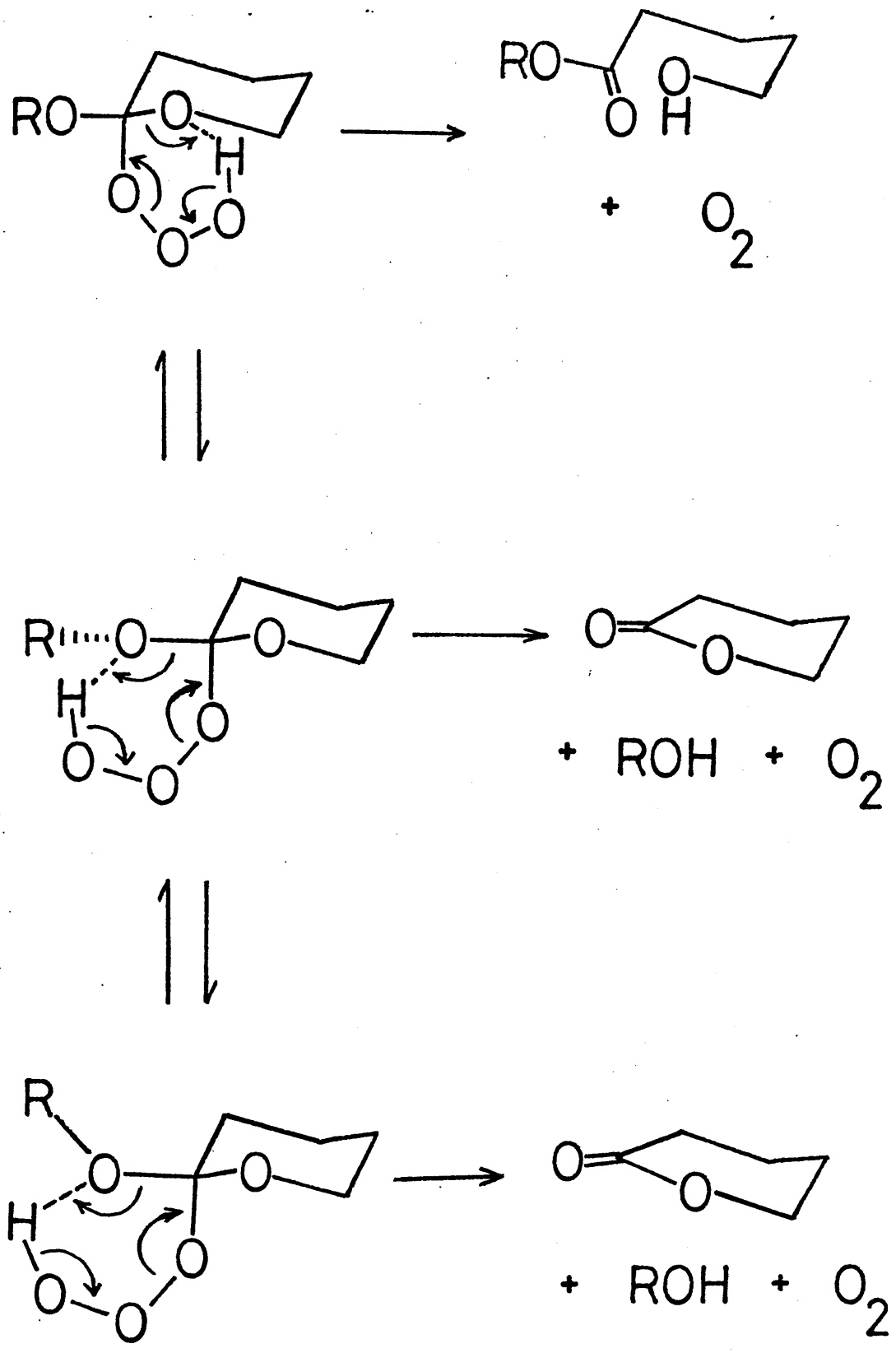


Fig.73

Deslongchamps has studied the ozonolysis of both cyclic and acyclic acetals, the former being found to react much more rapidly (fig.68). The only product for the ozonolysis of 2-ethoxytetrahydropyran was the open chain ester. Similarly in the reaction of ozone with α- and β-acetylated glucopyranoxides only the β-anomer reacted (fig. 69). Consideration of all the possible stereochemistries of the acetals and of the ozonolysis of several model compounds (figs. 70-72) resulted in the postulation of the requirement that each acetal oxygen was required to have a lone pair antiperiplanar to the C-H bond which was broken. Similarly, since the reaction of 2-ethoxytetrahydropyran gave only one product the intermediate formed must breakdown in a stereospecific manner.

While the Deslongchamps' theory requires that any transition state/intermediate does not exist long enough for any molecular rotation to take place, the observation of relatively stable hydrogen-bonded hydrotrioxides easily accommodates all the preceding evidence given that the hydrogen-bonding is more likely to occur in a rigid rather than "freely rotating" system. In the case of 2-ethoxytetrahydropyran any hydrogen-bonding will only occur into the cyclic system (fig. 73); the likelihood of exocyclic hydrogen bonding being thermodynamically unstable. The resultant products will therefore be only or <u>very</u> predominantly the

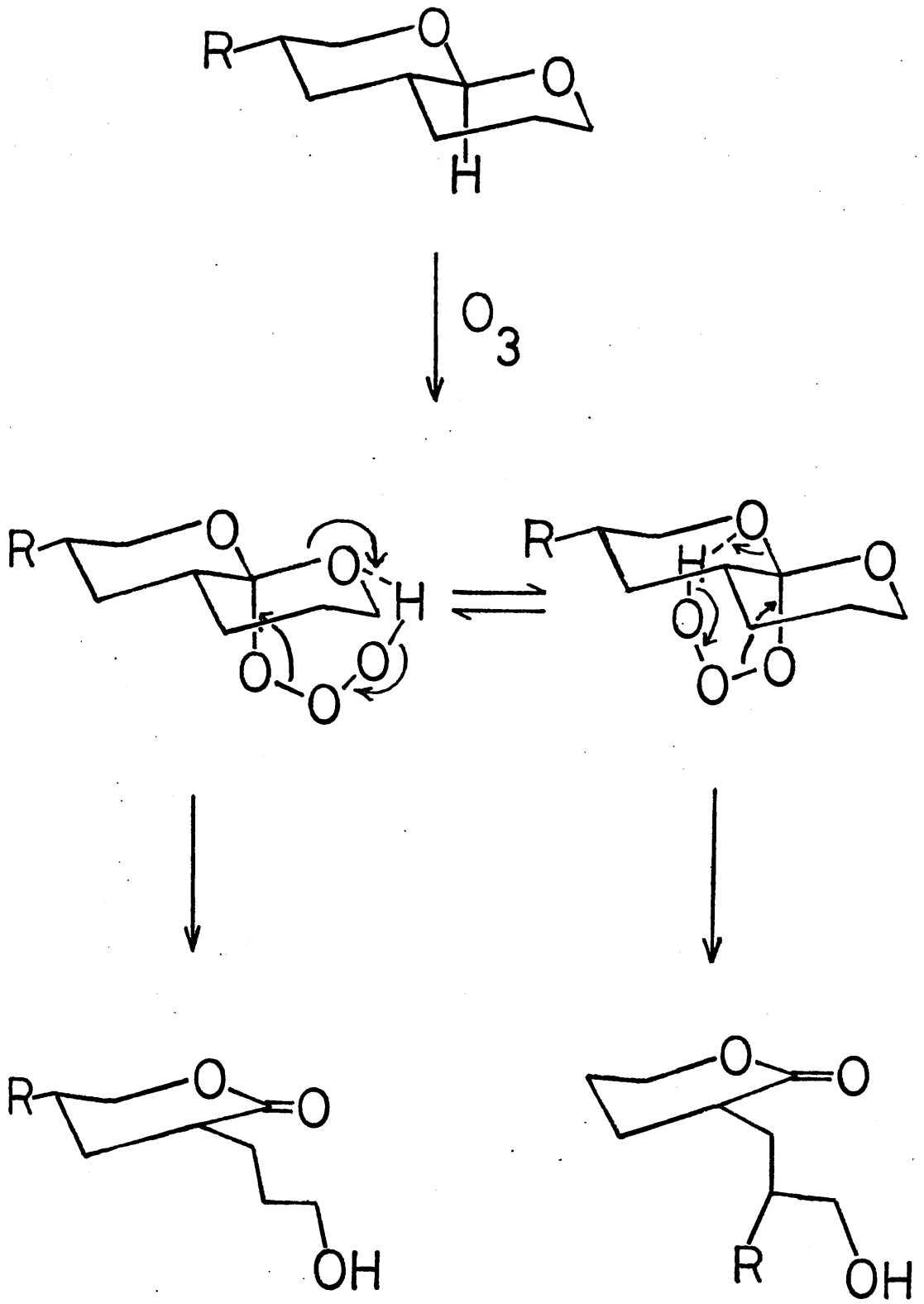


Fig. 74

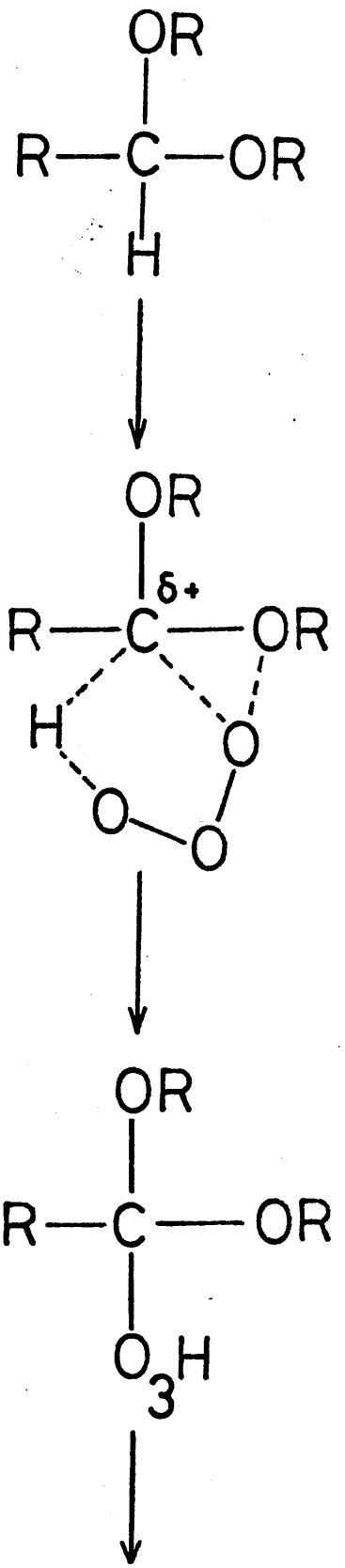
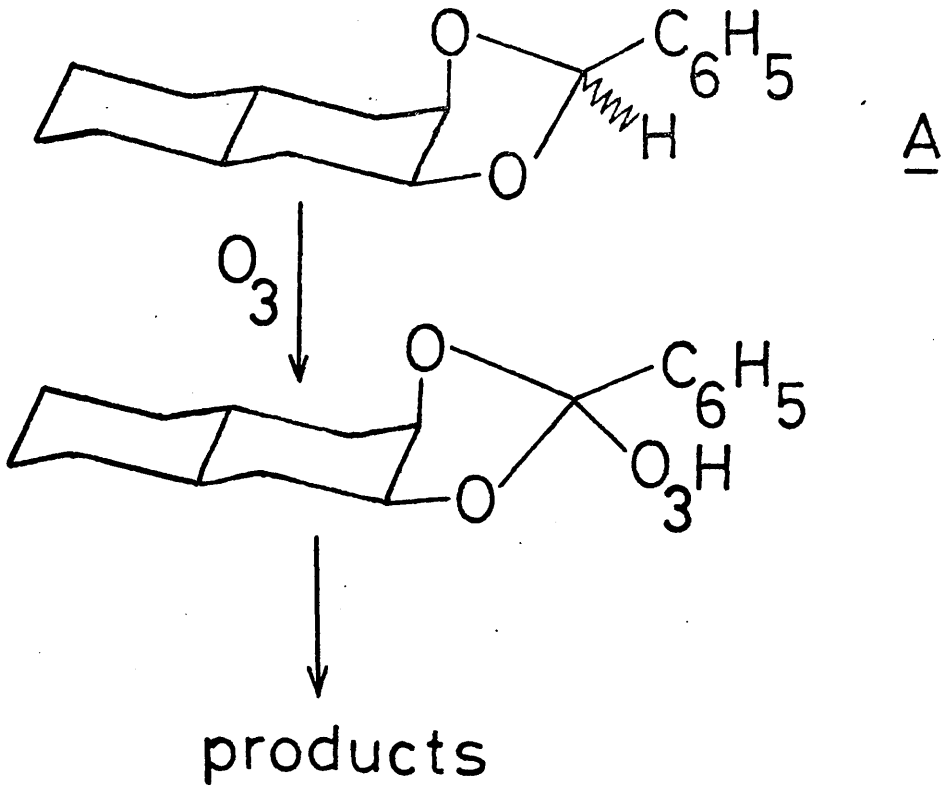
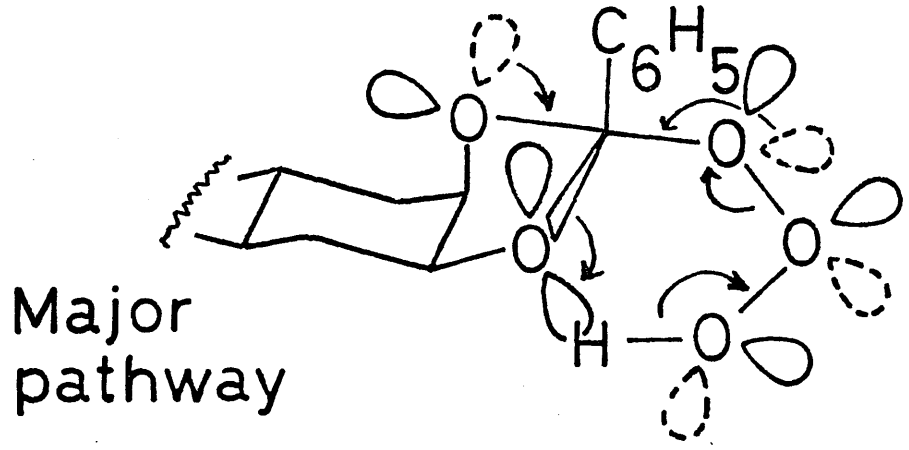


Fig.75


O
C6H5
H
O
A
O3
O
C6H5
O
O3H
O
products


C6H5
O
O
O
O
H
O
Major
pathway

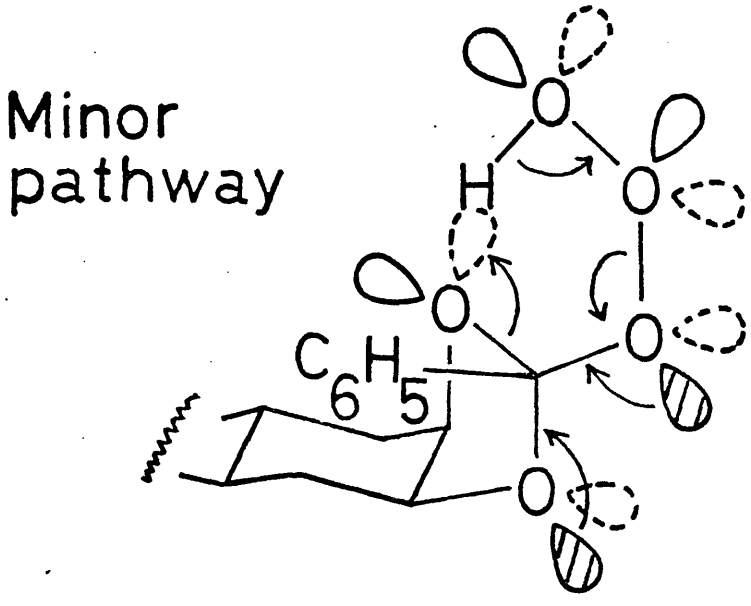
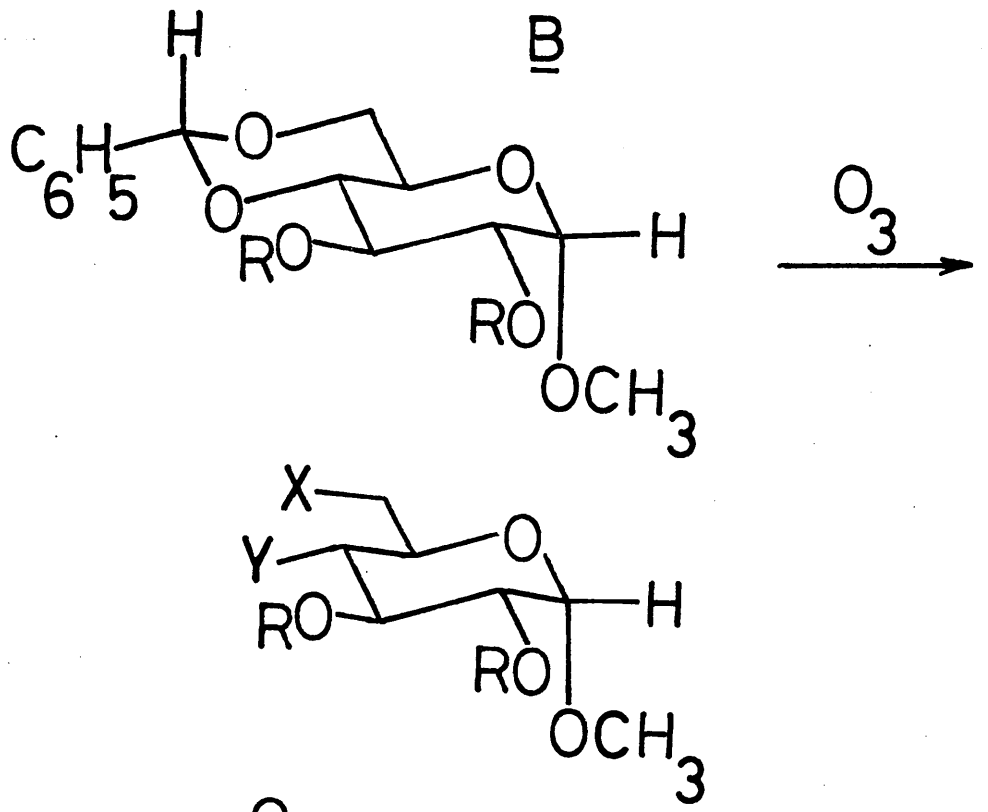

Minor
pathway
O
H
O
O
O
C6H5
O

Fig. 76


B
H
C6H5
O
O
O
RO
H
RO
OCH3
O3
X
Y
O
RO
H
RO
OCH3

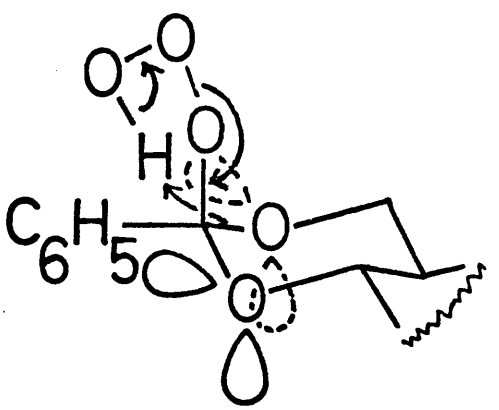

O
O
O
H
O
C6H5
O

Fig. 76

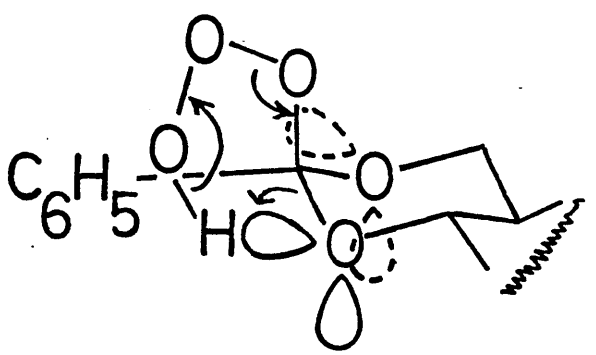

O
O
O
C6H5
O
H
O

TABLE 4

	X	Y	% *	solvent
R = CH_3	PhCO	OH	60	$CC\ell_4$
	OH	PhCO	40	
R = CH_3CO	PhCO	OH	85	glacial acid acid
	OH	PhCO	15	
R = $CH_3C_6H_4SO_4$	PhCO	OH	0	glacial acid acid
	OH	PhCO	100	

* No other products were noted: Total yield per reaction ≈100%.

R = CH_3

B_1 ⟶ X = OH; Y = PhCO

B_2 ⟶ X = PhCO; Y = OH main product

R = CH_3CO

B_1 ⟶ X = OH; Y = PhCO

B_2 ⟶ X = PhCO; Y = OH main product

R = $CH_3C_6H_4SO_2$

B_1 ⟶ X = OH; Y = PhCO main product

B_2 ⟶ X = PhCO; Y = OH

open chain form (fig. 73). The stabilisation energy required to stop rotation about the exocyclic oxygen-alkyl bond would be very much less than any gained from formation of the ring. Synthesis of a structure similar to the trans-1,8-dioxaoctahydronaphthalene would show cleavage of both C-O bonds by the observation of two different products from the two different cleavages of the bicyclic rings (see fig. 74) but would not resolve the situation.

Initial addition of ozone can be considered as heterolytic cleavage too for a carbenium and hydride ion (the hydride ion being possibly bonded to the ozone) in which case the conditions of antiperiplanar orbitals apply (see work of Eliel and nader, etc.)[137] or the mechanism of Price and Tumolo[142(a)] could take place where partial effects of antiperiplanar orbitals assist cleavage (see fig. 75). While it has been said that molecules where only one antiperiplanar orbital is present do not react with ozone, it is likely that under more forcing conditions they will in fact react when further steric factors occur.

Ozonolysis of the rigid bicyclic systems (fig. 76) (A) and (B) can be explained by the utilisation of hydrotrioxides. The results of ozonolysis of (B) are given in table 4. While the data is far from complete one can rationalise the results as being due to two considerations, (a) the ease of

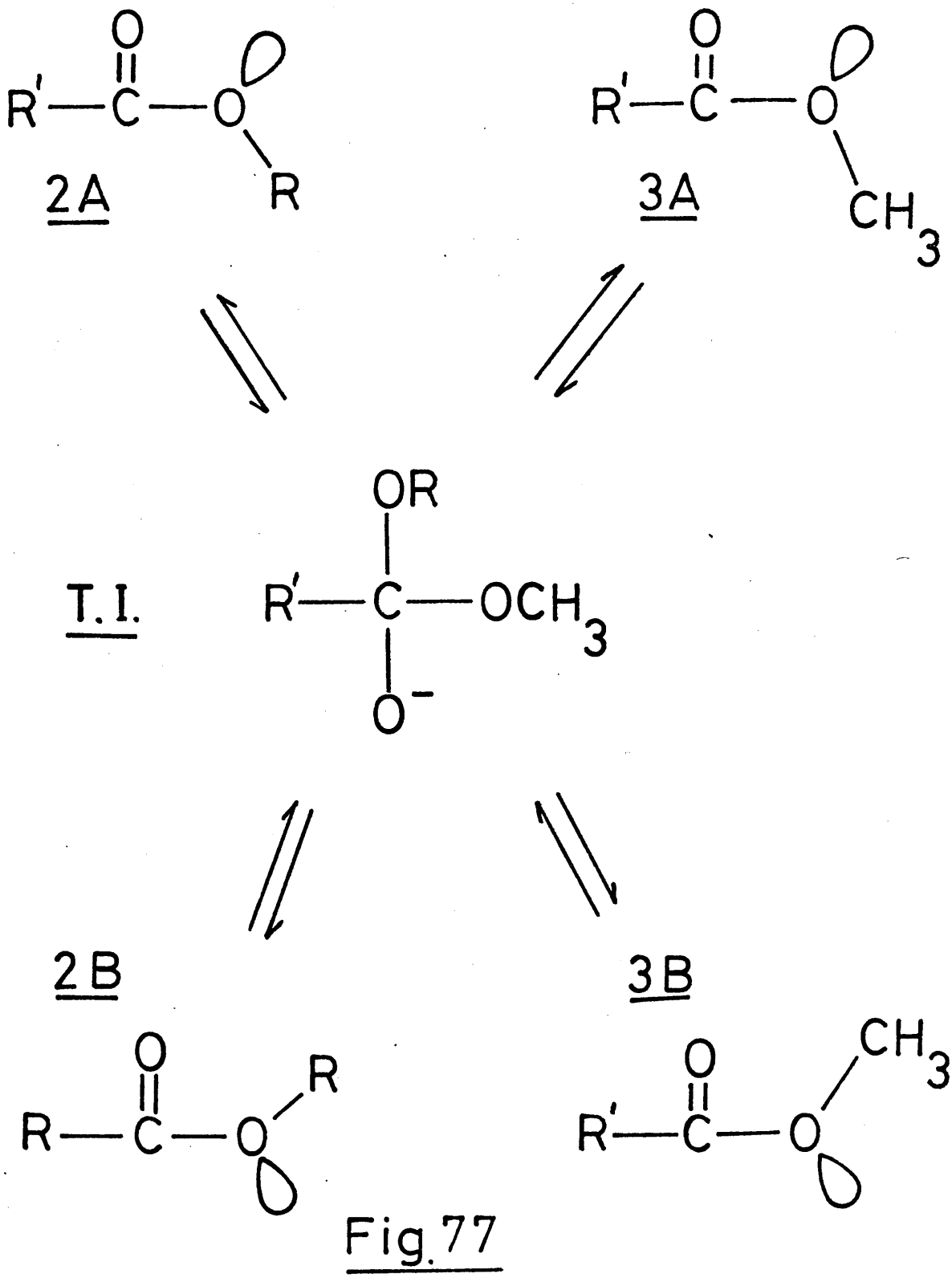
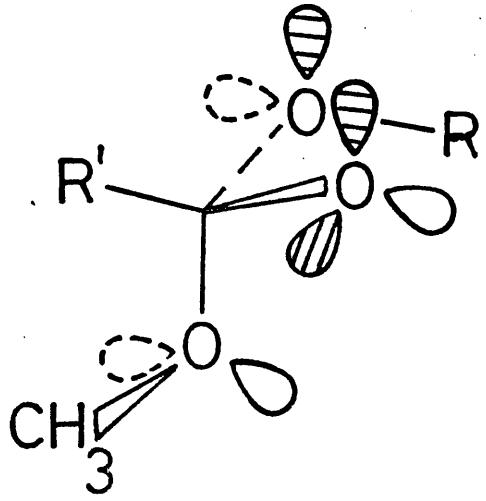
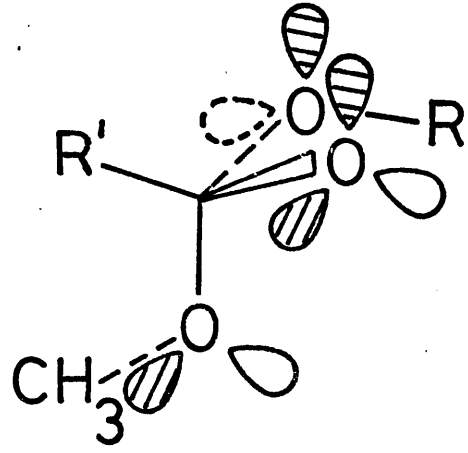


Fig. 77

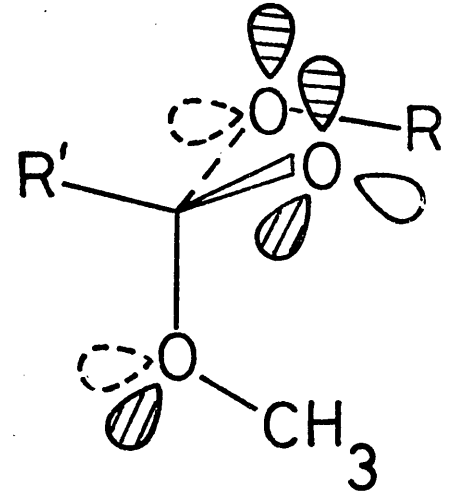
A



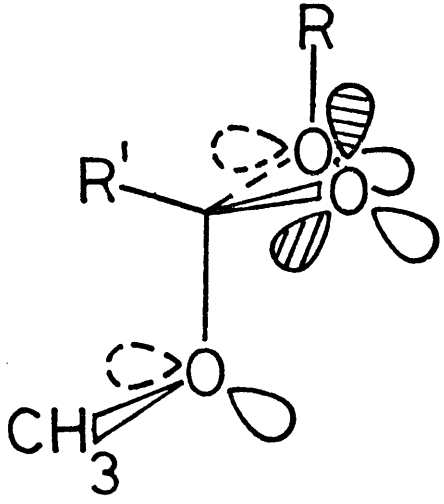
B



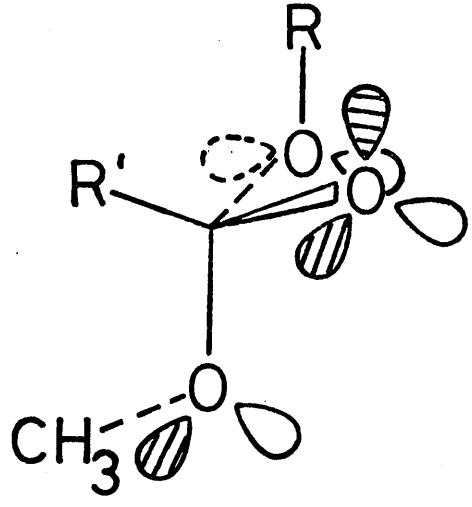
C



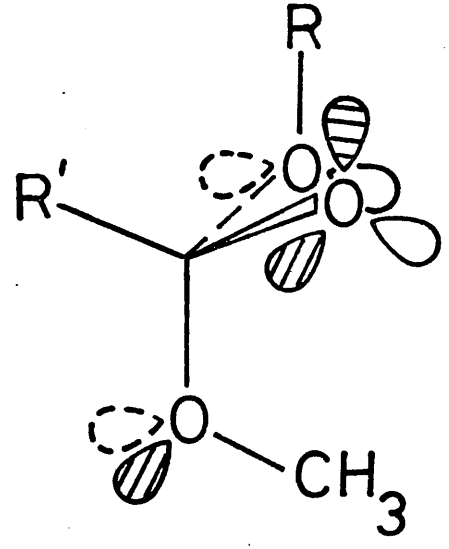
D

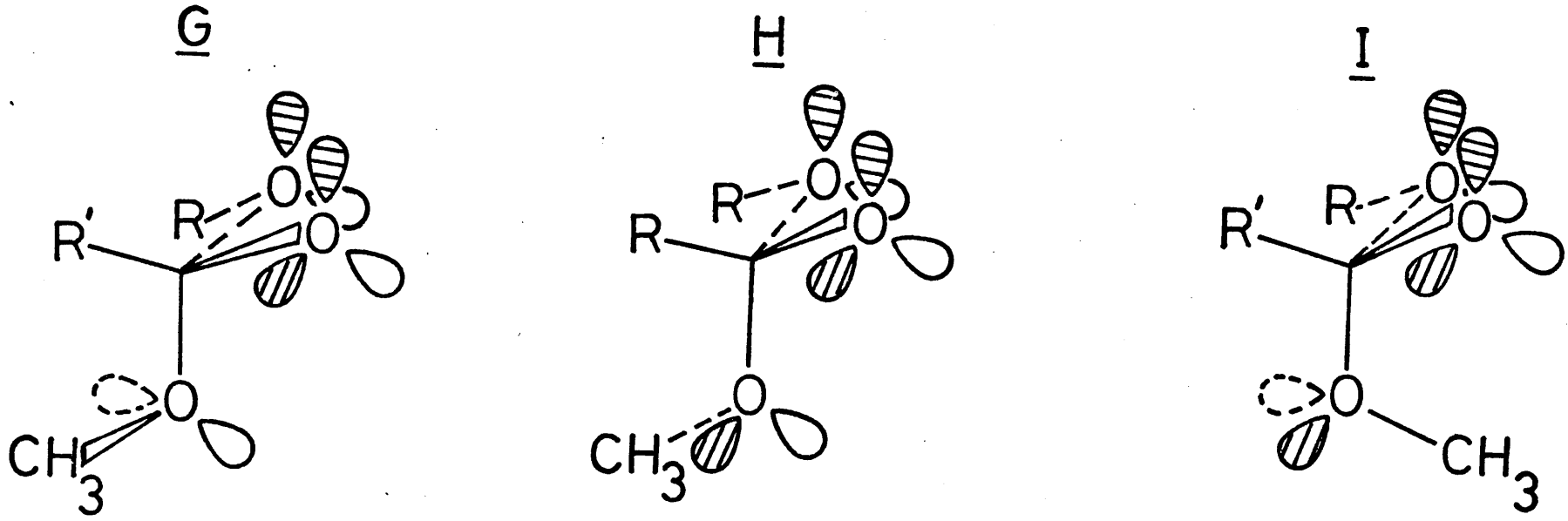


E



F



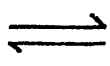
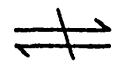
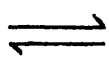
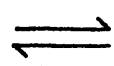
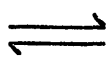
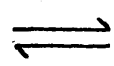
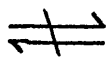
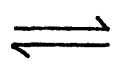
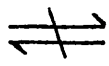
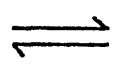
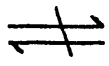
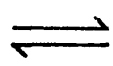
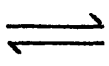
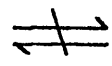
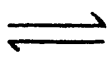
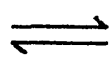
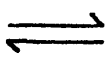
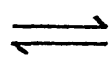


A, B, E are mirror images of F, I, G

Fig. 78

TABLE 5

Summary of Specific Cleavages

Ester 2		Conformer (T.I.)		Ester 3
Transoide		A		
Transoide		B		Cisoide
Transoide		C		Transoide
		D		Cisoide *
		E		Cisoide
		F		Transoide
Cisoide		G		
Cisoide		H		Cisoide
Cisoide		I		Transoide

* Will only occur as a higher energy species

formation of the hydrogen bond of the hydrotrioxide to the ring oxygens and (b) the stabilisation gained from loss of steric interactions. The formation of the hydrotrioxide B_1 would be expected to result in a smaller increase in energy due to loss of steric interactions than would B_2 where the benzoate ester formed would be further from the unreactive ring. Similarly any hydrogen bonding in B_2 would be decreased as steric and bulk effects of the R groups increased. When R = CH_3 and CH_3CO the difference in bulk effects is very small the stronger driving force would then be maximum stabilisation of the product i.e. route B_1. When R = $CH_3C_6H_4SO_2$ however the ability to form B_2 is very well impaired by this large group so that B_1 would be the main mechanism. (Note. No account has been taken of inductive or any other effects and for any true consideration a much more detailed study is required).

In the study of orthoester hydrolysis the postulated hemi-orthoester is generally suggested as being as in fig. 77. By considering all the possible modes of breakdown Deslongchamps showed that there were 9 different conformations (which incidentally can also result from an alcoholysis reaction on an ester) and of these 9 examples he reasoned that, assuming the requirement of antiperiplanar orbitals to the leaving group, only certain conformers would be reactive (see table 5 & fig. 78).

The general assumptions put forward were, 1) any tetrahedral intermediate formed did not exist for any period long enough to undergo rotation. 2) The generation of tetrahedral intermediates from orthoesters occurred by microscopic reversibility of the OR cleavage resulting in a tetrahedral intermediate of similar conformation. 3) If the orbitals are aligned antiperiplanar breakdown must occur. In view of the previous considerations of tetrahedral intermediates from stable species to others with lifetimes as short as transition states some cases only would appear to justify the first and third assumptions. The second point can be viewed from considerations that initially the alkoxy bond to the centre carbon is broken generating a carbenium ion; the alkoxy group then diffuses away before attack by hydroxide occurs. Whether the hydroxide attacks either side of the carbenium ion the same product (mirror images) is obtained if rotation or change of configuration of the chain takes place. In cases where no configurational changes can occur attack in the reverse direction must occur. A further assumption by Deslongchamps that an oxygen-hydrogen bond is equivalent in effect to a lone pair rules out any possibility of differing reactions for oxygen hydrogen position.

Hydrolysis of several cyclic orthoesters and isolation of the products (see fig. 80 and table 6) gave complete endo-

cyclic ring cleavage (this author does not necessarily agree - see experimental section). By considering the 9 possible conformers of diethoxytetrahydropyran Deslongchamps discounted five on steric grounds. One of the remaining four, C, was discounted by a rather unconvincing argument. The tricyclic orthoester (fig. 79) which had the same configuration as conformer C was found not to be reactive in acid solution and therefore it was generalised that all C type conformers were unreactive. The unreactivity of conformer in the tricyclic case is, however, probably due to the fact that the central carbon will incur great strain on the molecule if formation of a carbenium ion was to take place. Detailed consideration of the three possibly reactive conformers, A, E and F resulting in the observation that while A and F gave solely hydroxyester E could also give lactone (fig. 81). Previous observations on the hydrolysis of the cyclic orthoesters suggested no lactone formation and so therefore it was concluded that the reactive conformer E could be eliminated. In his search for a single mechanism for the breakdown of tetrahedral intermediates of cyclic orthoesters the study of rigid bicyclic orthoesters having different alkoxy groups showed that loss of the axial group always occurred resulting in the conclusion that reaction occurred through conformer A. (It should be noted conformer E does not necessarily have to produce large quantities of

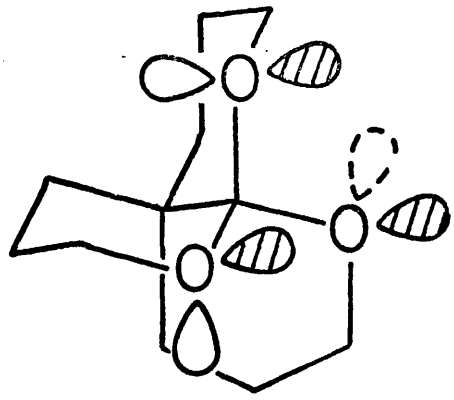


Fig.79

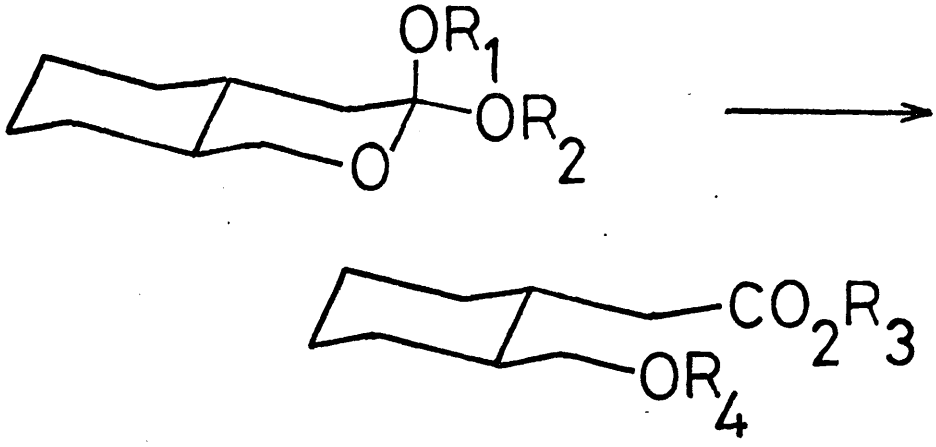
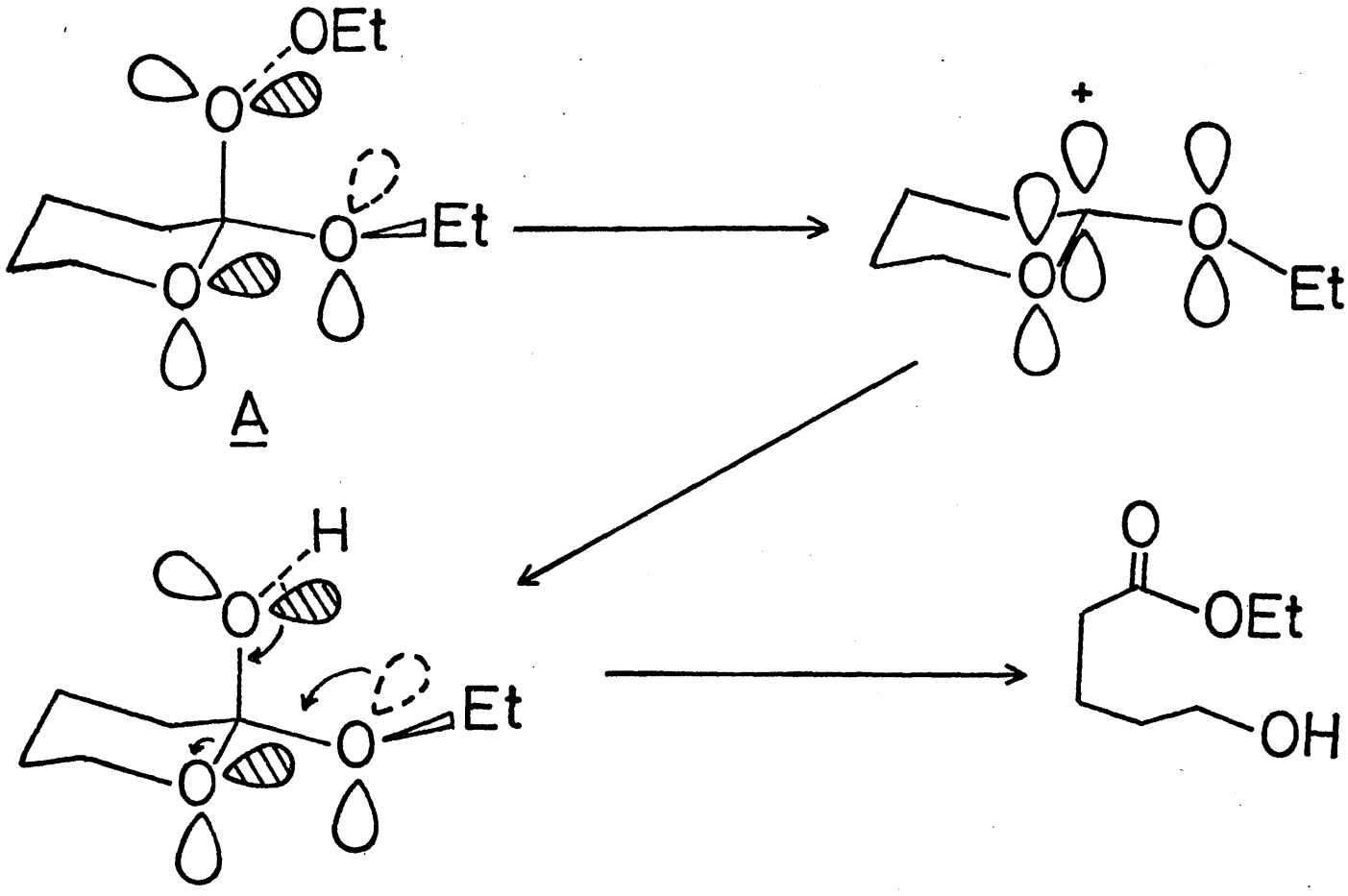


Fig.80

TABLE 6

R_1	R_2	R_3	R_4
CH_3	CH_3	CH_3	CH_3CO
Et	Et	Et	ditto
CH_3	Et	Et	ditto
Et	CH_3	CH_3	ditto
CD_3	CH_3	CH_3	ditto
CH_3	CD_3	CD_3	ditto


OEt
Et
A
+
Et
H
Et
O
OEt
OH

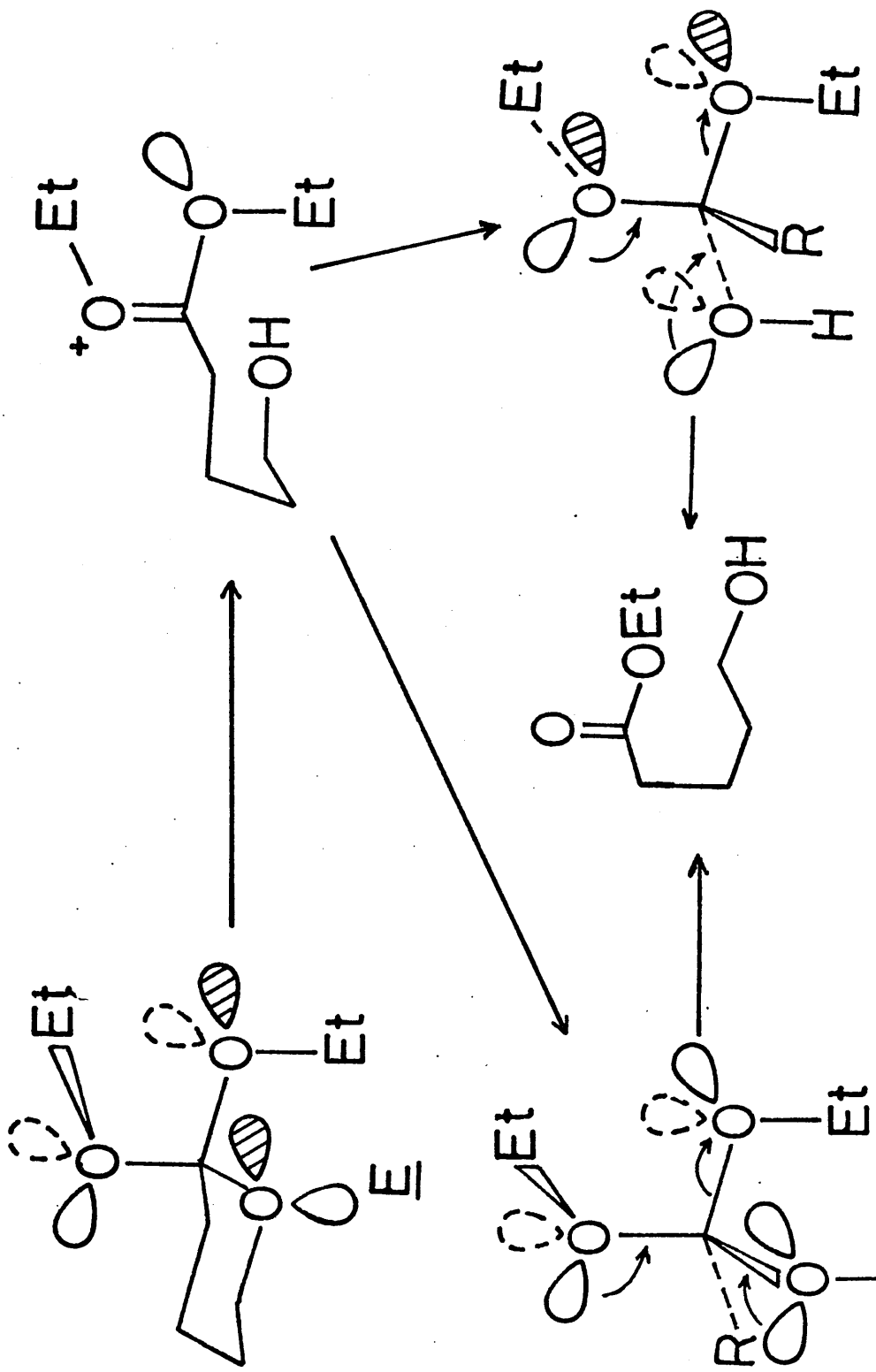
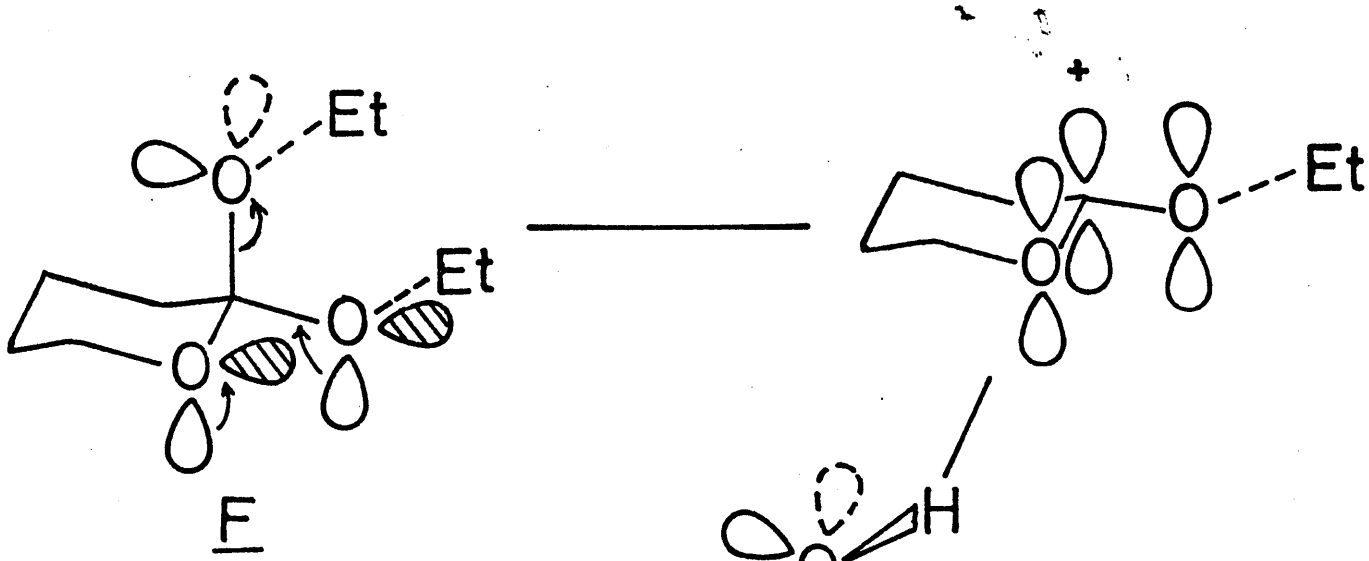


Fig. 81



F

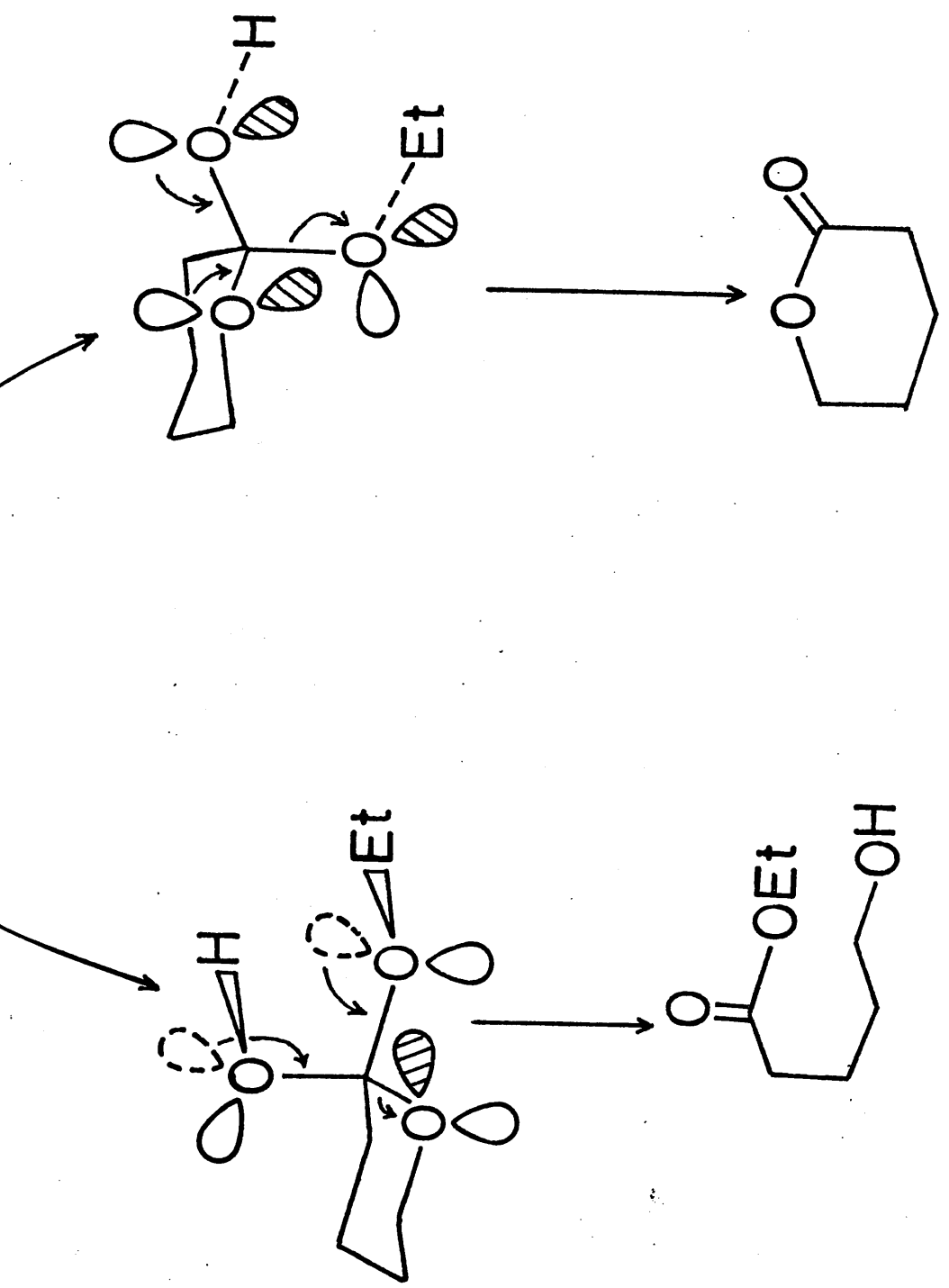
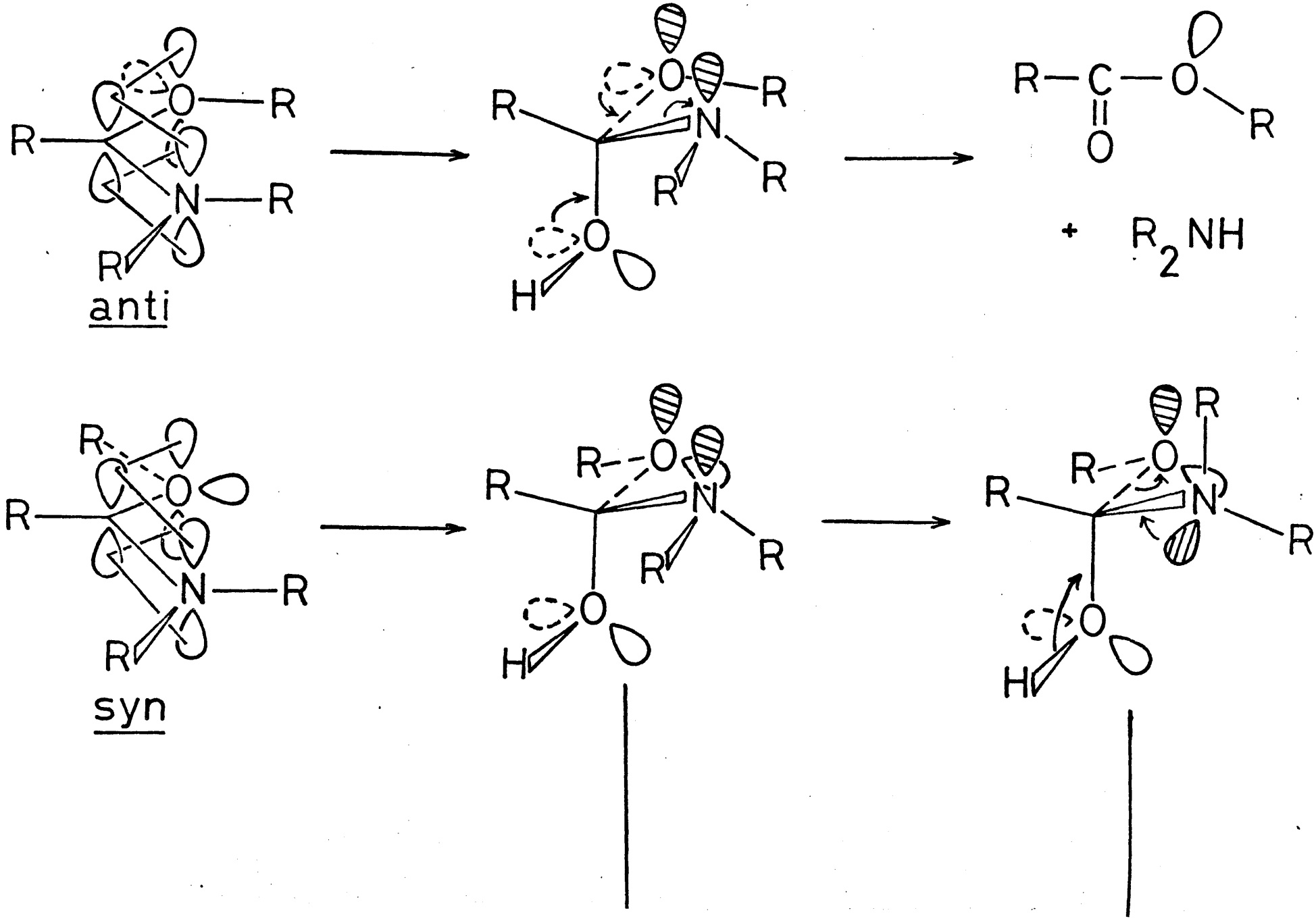


Fig. 81 (cont'd)

lactone. The mechanism can be viewed as producing hydroxy-ester directly and lactone only after partial rearrangement and does not necessarily have to be neglected especially if, as Deslongchamps, one assumes breakdown occurs faster than rearrangement).

The breakdown of hemiorthoamides, obtained either from the aminolysis of esters or hydrolysis of imidate salts, can similarly be shown to be dependent on structure. Imidate salts can either have syn or anti conformations and by considering the structures of the intermediates in basic media (see fig. 82) it can be shown that the anti form is likely to give only ester and amine. The syn form, due initially to its lack of breakdown potential, must rearrange first before decomposition of the tetrahedral intermediate resulting in the possible product of both ester and amide. The amide and alcohol products are generally accepted as being the thermodynamically controlled species since under equilibrating conditions ester/amine products undergo equilibration to predominantly amide/alcohol. No information about any orbital assisted breakdown of the tetrahedral intermediate can therefore be obtained from a reaction giving amide/alcohol products.

In the first examples studied by Deslongchamps of the basic hydrolysis of anti imidate salts the observed products,


anti
+ R2NH
syn

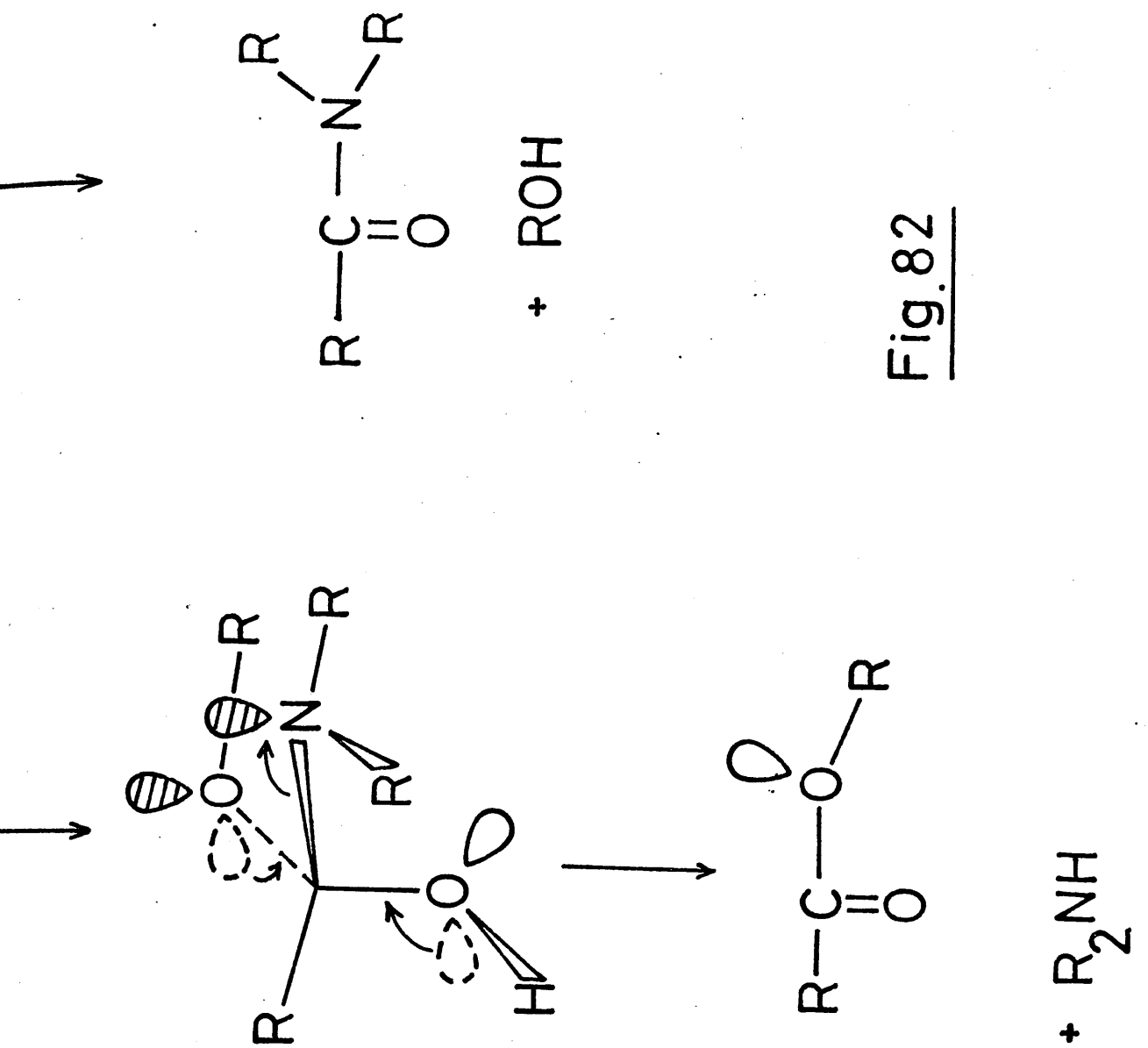


Fig.82

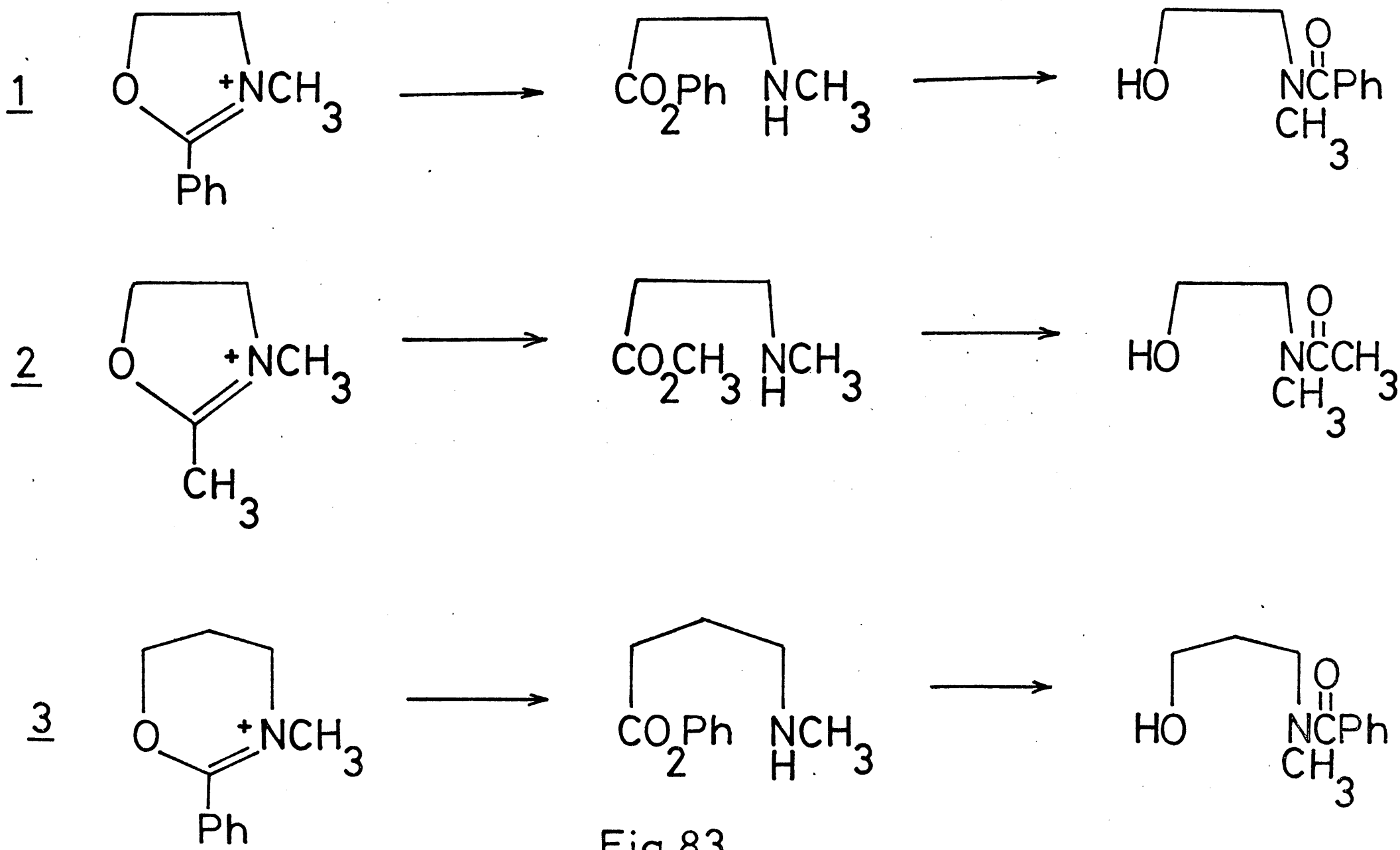
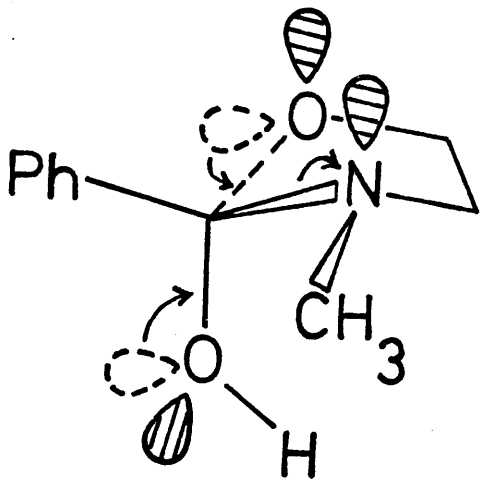
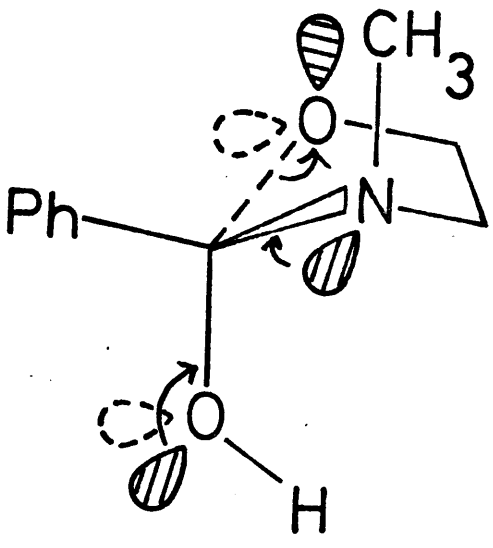

1
O
+NCH3
Ph
CO2Ph
NCH3
H
HO
O
NCPh
CH3
2
O
+NCH3
CH3
CO2CH3
NCH3
H
HO
O
NCCH3
CH3
3
O
+NCH3
Ph
CO2Ph
NCH3
H
HO
O
NCPh
CH3

Fig.83



4

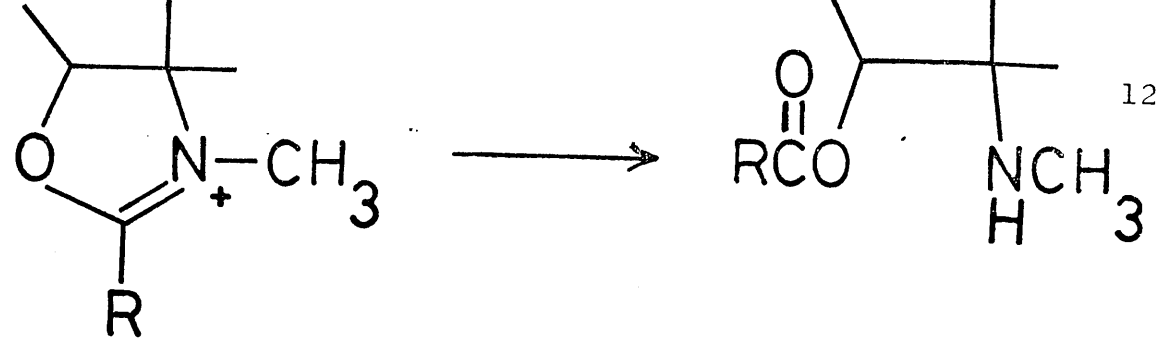


5

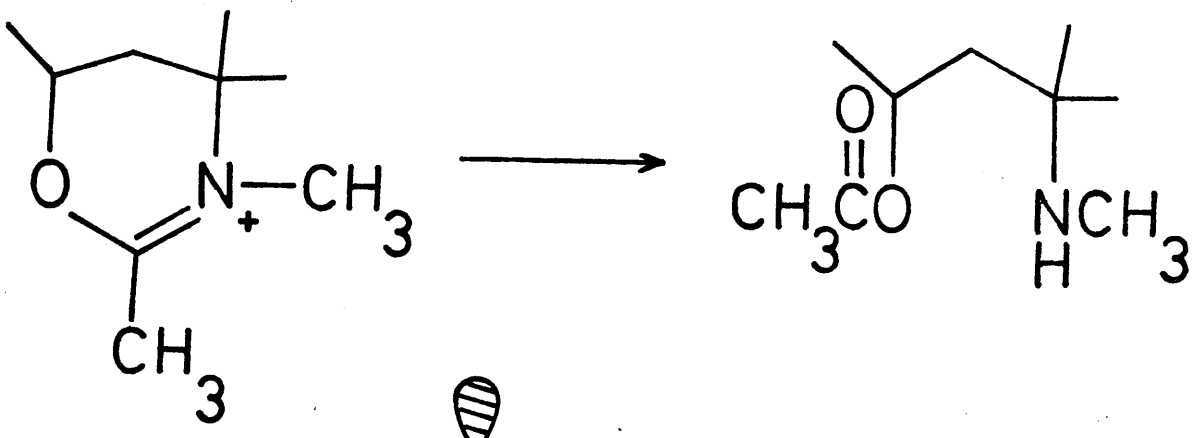
Fig. 84

TABLE 7

Substrate	Product	Comments
1	1B only	1C after 24 hours
2	2B mainly	2C after $1\frac{1}{2}$ hours
3	3B only	No trace of 3C after 5 hours in Na_2SO_3
3	3B mainly	3C after 30 minutes



R = CH_3, C_2H_5, $C(CH_3)_3$



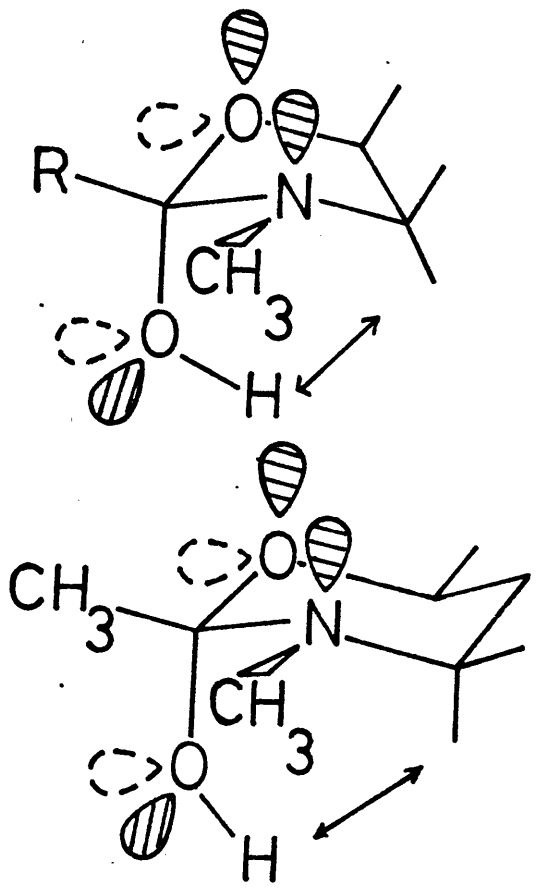


Fig.85

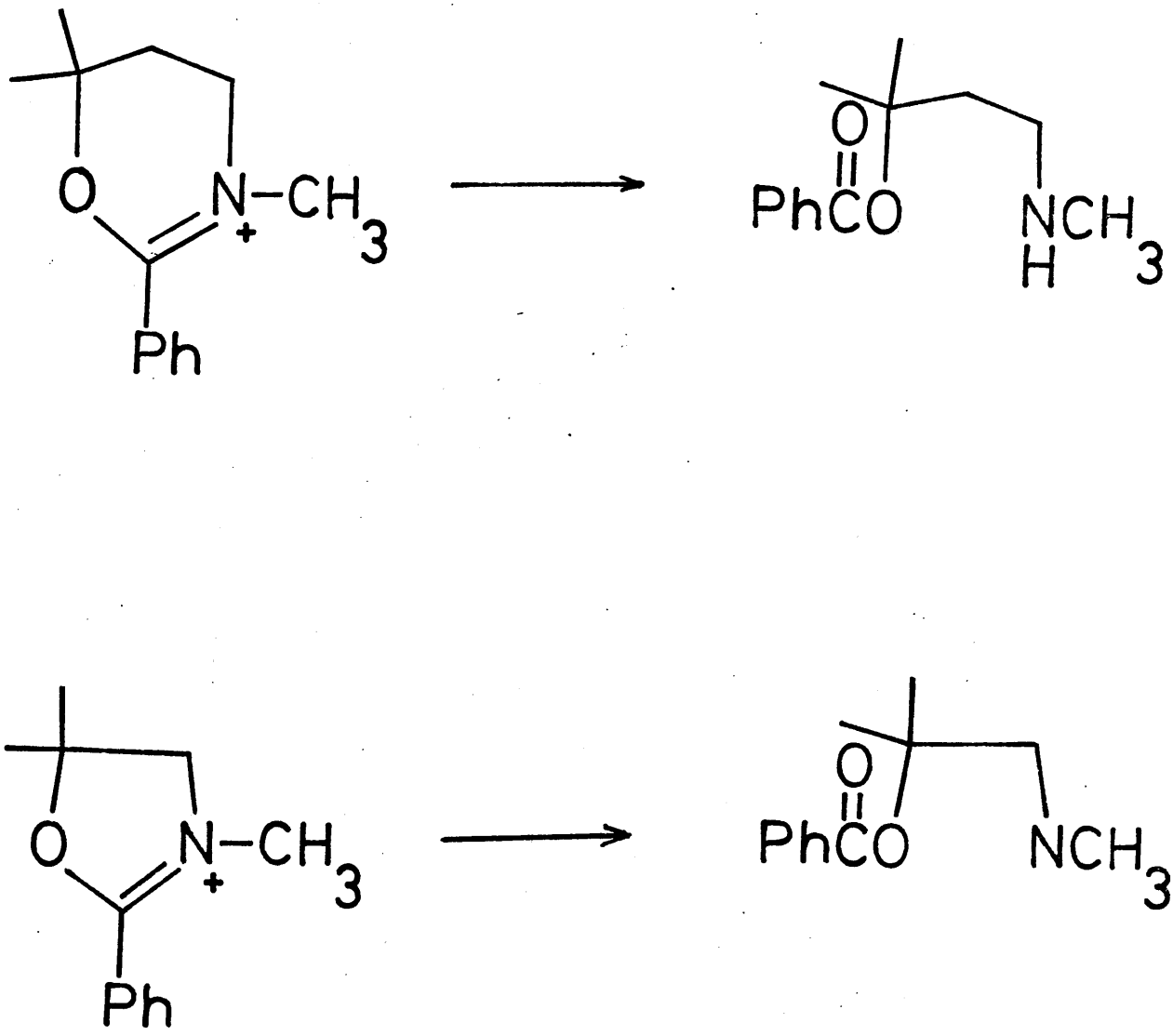


Fig. 86

considering the most likely breakdown (see fig.83 and table 7) was the formation of ester/amine products with in some cases increasing quantities of amide/alcohol with time. The latter observation was explained as being due to the equilibration conditions possible. The equilibration of the ester/amine to amide/alcohol can be rationalised by considering reformation of the tetrahedral intermediate from the ester/amine (cyclic system). Two intermediates can occur, (fig. 84) the original species 4 and a more stable tetrahedral intermediate 5. Breakdown of 4 gives no effective change whereas breakdown of 5 can either give ester/amine or the more stable amide/alcohol. The hydrolysis of several sterically hindered cyclic imidates has led to the conclusion that steric hindrance when adjacent to the nitrogen tends to assist cleavage of the C-N bond (fig. 85); in systems where sterically hindered groups are adjacent to the oxygen in the ring (see fig. 86) competitive effects of orbital orientation and steric effects resulted in the deduction that the former was the stronger since the products obtained were still the esters. The value of ~5k cal/mole ascribed to this stabilisation by Deslongchamps however would appear rather high since cleavage of the C-N bond also serves to reduce steric strain; the methyl groups moving away decreasing any interactions.

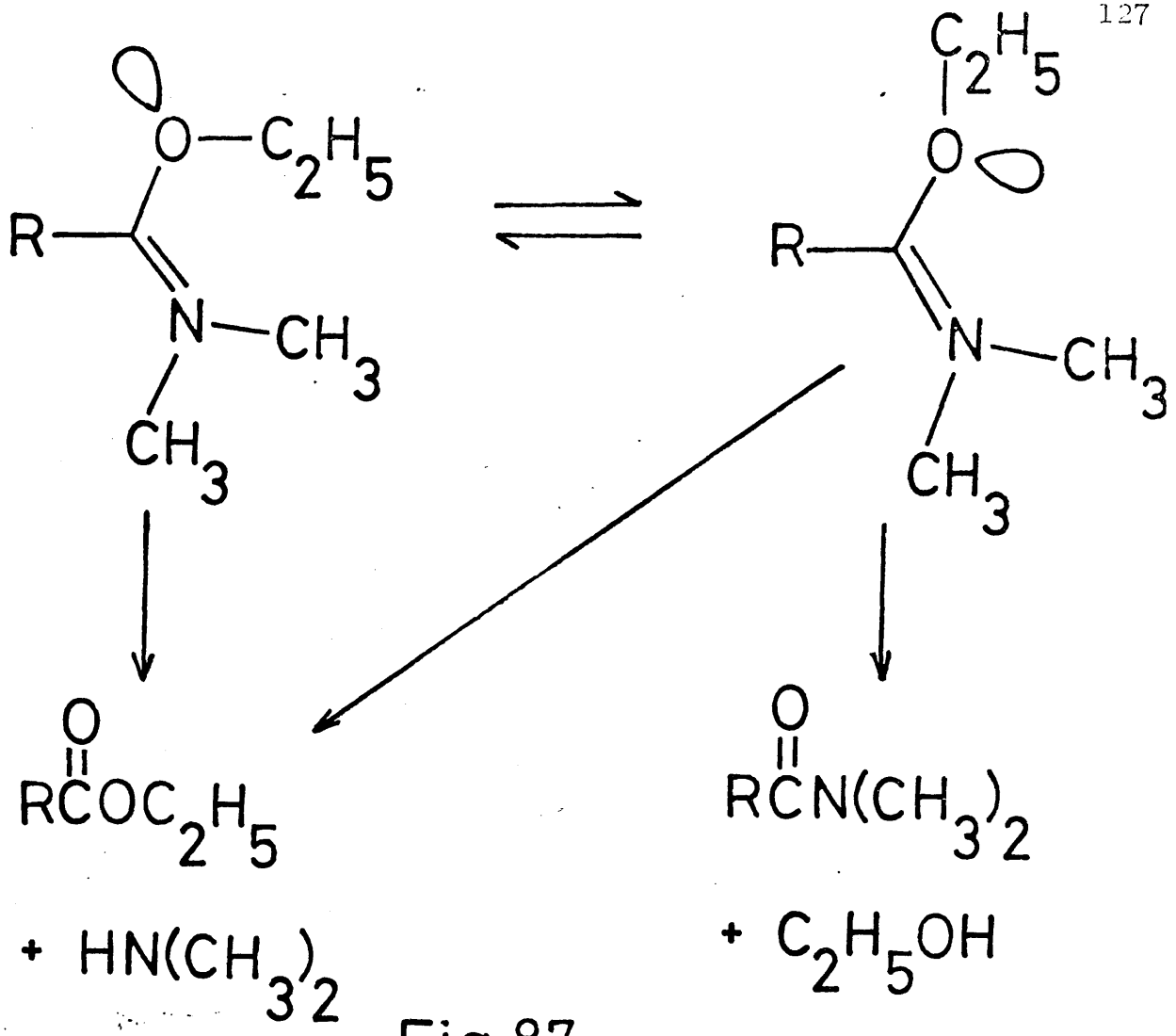
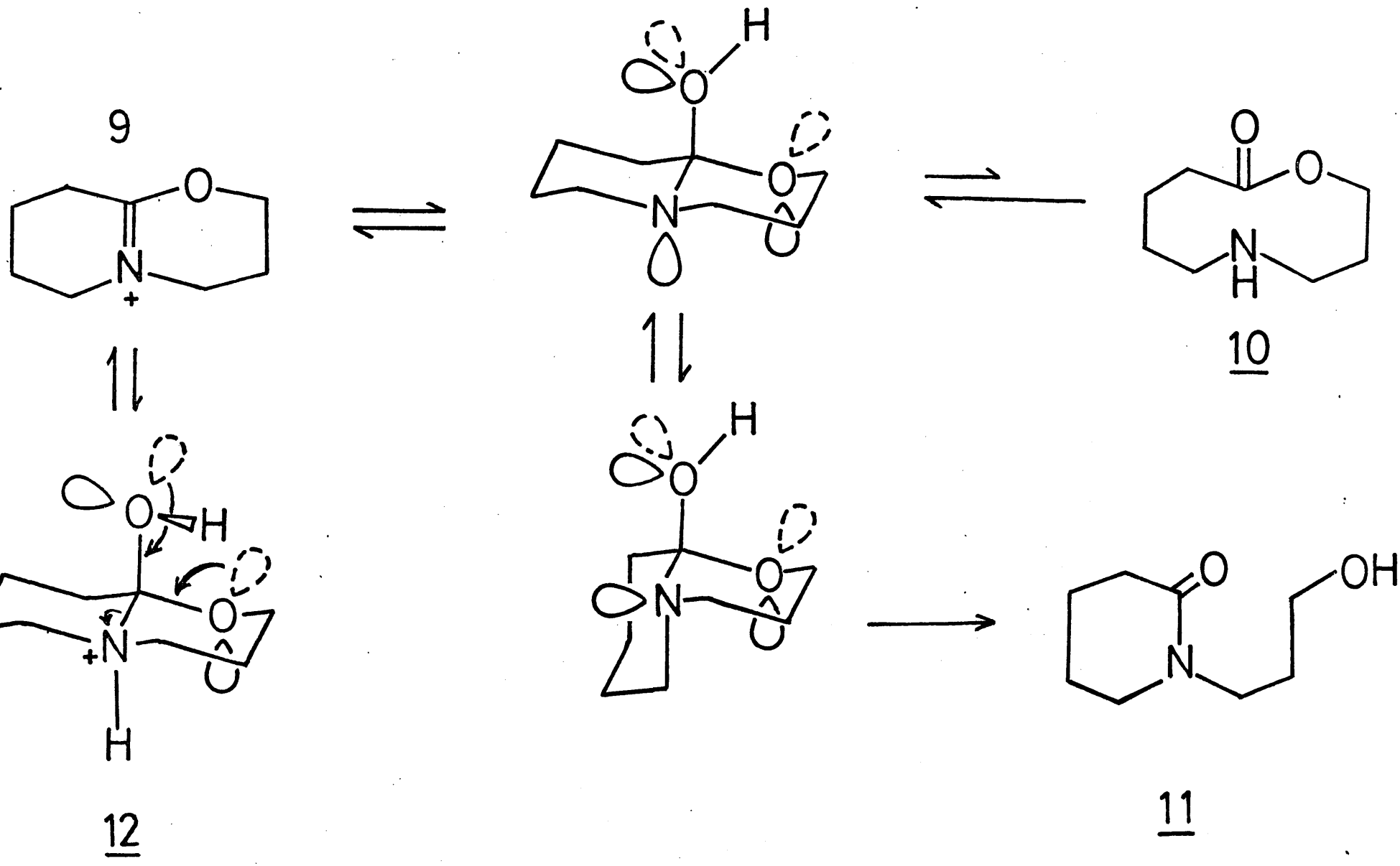


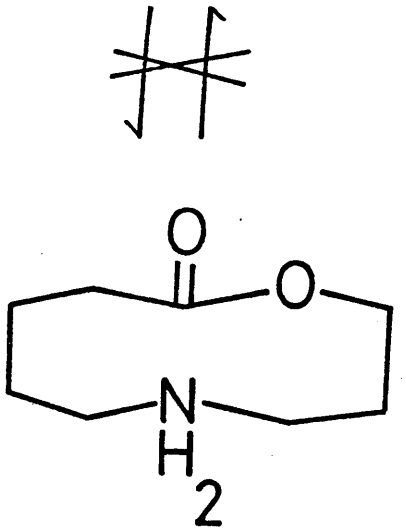
Fig.87

TABLE 8

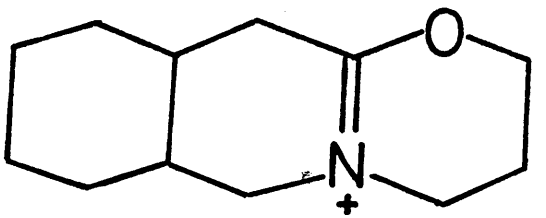
Basic Hydrolysis of imidate salts

R	% Ester	% Amide
H	50	50
CH_3	81	19
C_6H_{11}	50	50
$(CH_3)_3C$	>98	-
C_6H_5	>98	-


9
10
11
12

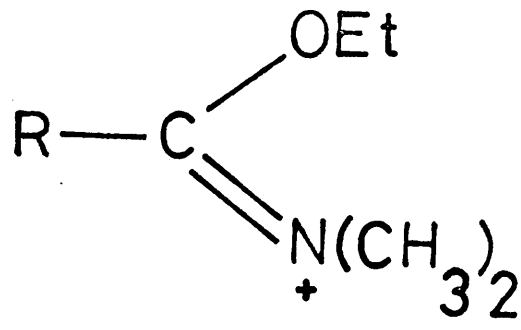


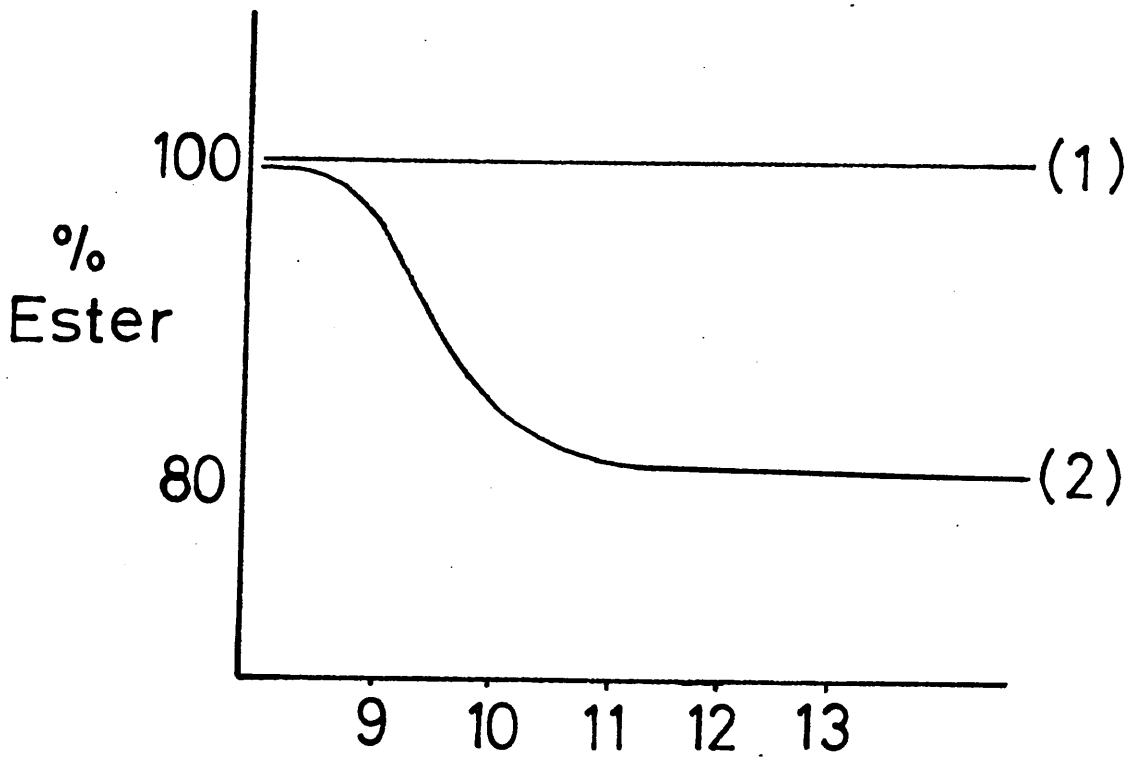
13



14

Fig.88





(1) is followed by

$R = Ph, C(CH_3)_3$

(2) by

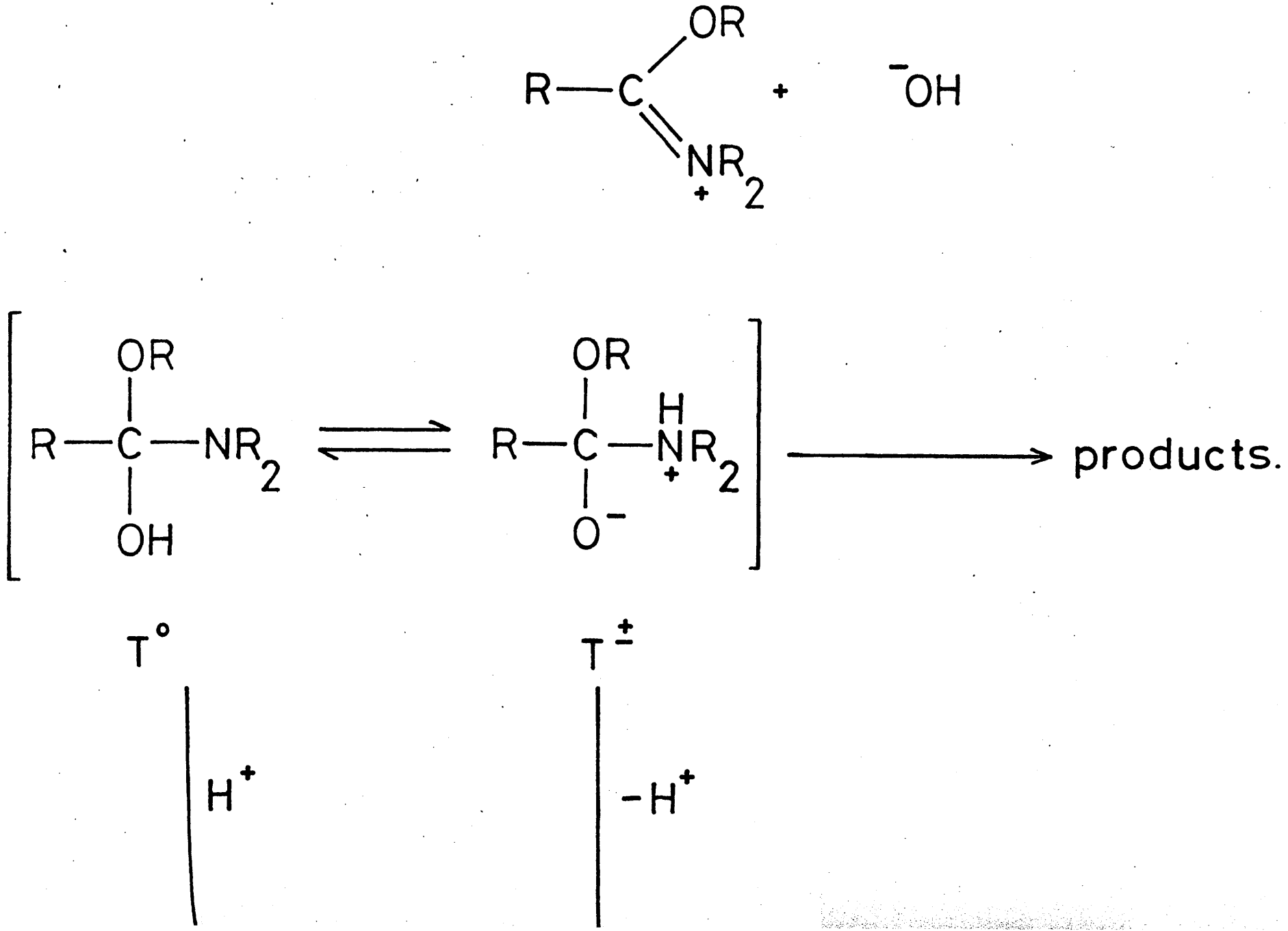
$R = CH_3, C_6H_{11}$

Fig. 89

Since syn and anti conformations of imidates give rise to different products the study of the hydrolysis of several acyclic imidates where R increases in size (see fig. 87) should result in less amide formation as the quantity of syn imidate decreases. This has been studied by Deslongchamps and is shown to be the case (see table 8). Results on similar imidate salts where syn and anti configurations which could be considered as being in equilibrium gave similar results.

A study of the imidate salts 9 in basic solution was shown to result in the product 11 presumably via the mechanism fig.88. However acid hydrolysis of 9 which should produce intermediate 12 was not observed to react and breakdown to product 13. While tetrahedral intermediate 12 should breakdown by orbital assistance this was not observed and no fitting explanation could be given since most imidate salts studied, except 14, undergo acid hydrolysis.

While the previous discussion of Deslongchamps' work has been about the hydrolysis of imidates in highly basic media the products usually vary with pH (see fig. 89). By observing that predominantly anti conformers give ester/amine products over the whole pH range and predominantly syn conformers change from ester/amine to amide/ester products Deslongchamps postulated, considering the reaction mechanism


OR
R—C
NR2
+
OH
products.
T°
H+
T±
-H+

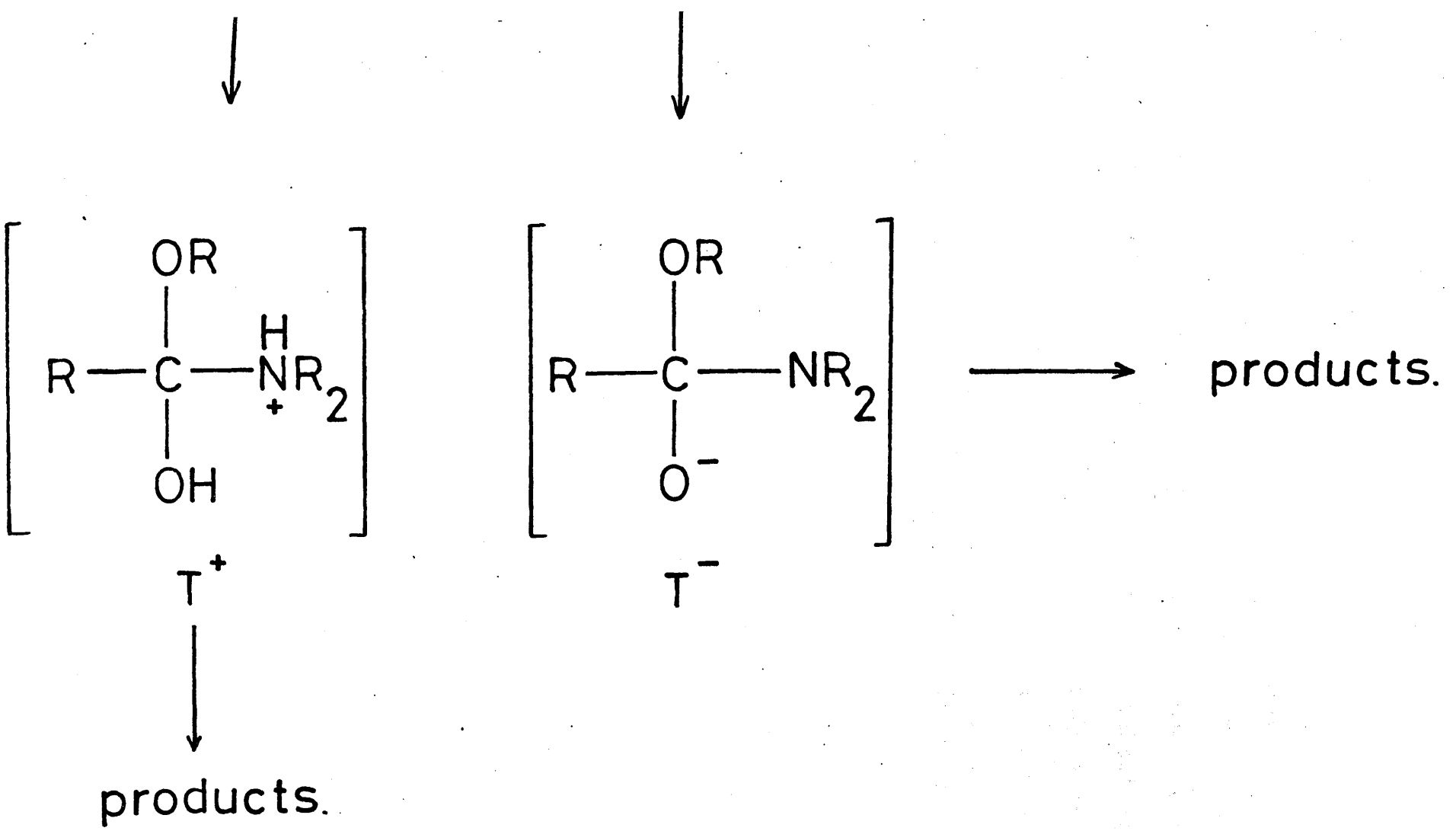


Fig. 90

(fig. 90) that in acid solution the tetrahedral intermediate would exist as T^{+}, in base as $T^{\ominus}$ and in neutral solution $T^{\pm}$. All these forms of tetrahedral intermediate in a post-anti tetrahedral intermediate result in the same products, ester/amine. In a post-syn tetrahedral intermediate breakdown of the initial tetrahedral intermediate cannot occur, a rotation being necessary (fig. 82) to produce tetrahedral intermediates A and B. While conformer A can be cleaved in any of the ionised forms conformer B can cleave only in the T^{-} form (since nitrogen is protonated in $T^{\pm}$ and T^{+}). It can easily be seen, therefore, how the products of syn imidates arise as pH changes.

While the stereoelectronic theory as proposed by Deslongchamps does, to a certain extent, explain the effective products of all the reactions studied it is seen that, especially, in the case of ozonolysis other deductions can be made as to why selective product production occurs. In all cases the tetrahedral intermediates formed were assumed to "breakdown of their own accord" and no account is taken of buffer or base catalysis of any kind (suggested from kinetics). It should be borne in mind that the products and mechanistic pathways of hydrolysis of imidate, amides, esters, etc. can also be explained by assuming proton transfer as slow steps in the reactions. This would lend itself to suggest then that O-H

bonds were not interchangeable with oxygen lone pairs as was suggested by Deslongchamps and that $T^{\ominus}$ is in fact a differently powered donor than T^{o} etc. with assistance in certain cases from base catalysis. If in the case of T^{o} that the O-H bond had to be antiperiplanar to the leaving group fewer examples of conformers would in fact breakdown to products without rotation initially.

Thermodynamical Calculations of Tetrahedral Intermediates

Estimates of the relative stabilities of simple tetrahedral intermediates have been carried out by Guthrie[155] who used the fact, originally calculated by Hine,[168] that the free energy change associated with the reaction of a hydroxy compound with methanol to form the methoxy compound and water was approximately dependent only on the number of substituents on the hydroxy compound (see table 9). Making the assumption that the ΔG° values, for a given number of substituents, will be the same if the hydroxy compound was an ortho acid derivative the standard free energies for the reactions

$$RC(OH)_2OCH_3 + 2CH_3OH \rightleftharpoons RC(OCH_3)_3 + 2H_2O$$

$$RC(OH)_3 + 3CH_3OH \rightleftharpoons RC(OCH_3)_3 + 3H_3O$$

could be calculated and hence give the free energies of formation of the orthoacids and hydrated methyl esters. A further extension of this argument resulted in the calculation of the free energies of the following reactions which could be used

$$RCO_2H + H_2O \rightleftharpoons RC(OH)_3$$

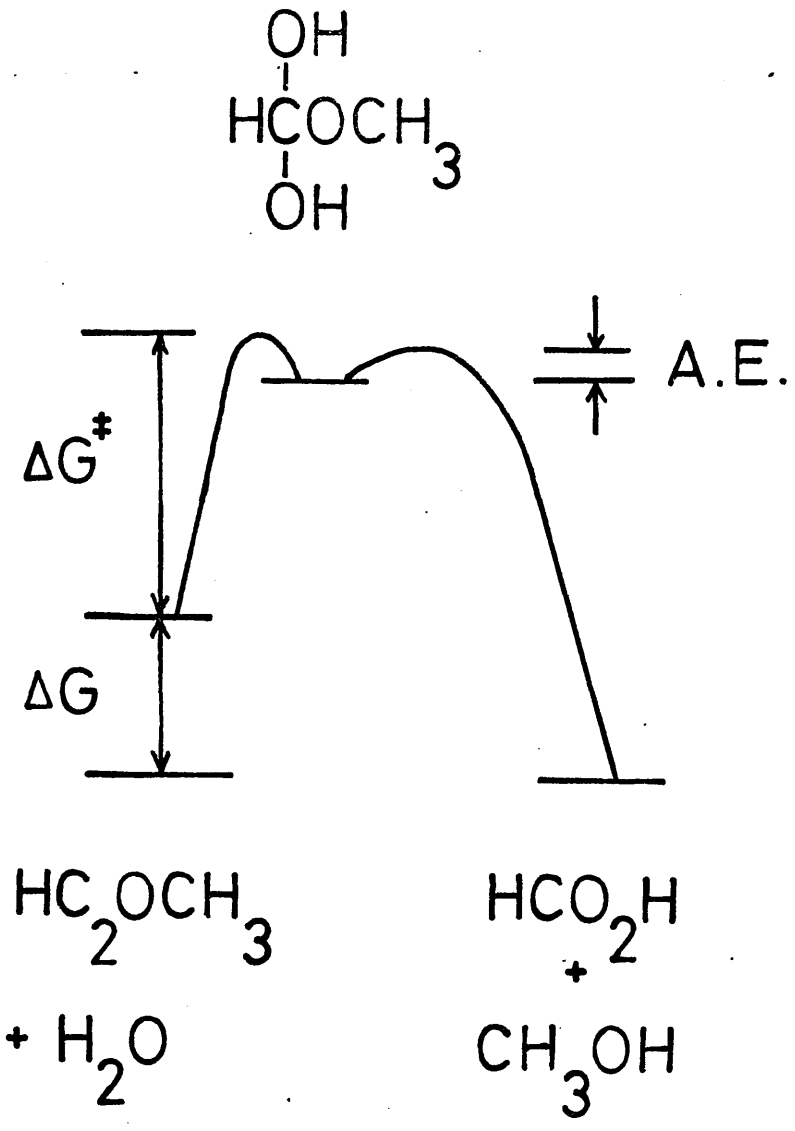
$$RCO_2CH_3 + H_2O \rightleftharpoons RC(OH)_2CH_3$$

for the effective hydration of esters and acids in water. It was estimated that the error, arising from the scatter in the

TABLE 9

No. of Substituents	ROH	ΔG° k cal/mol	Average tending to
0	CH_3OH	- 0.75	~ - 0.6
1	CH_3CH_2OH	- 0.07	~ 0.0
	$HOCH_2OH$	+ 0.32	
2	$(CH_3)_2CHOH$	+ 0.39	+ 0.6
	$(CH_3)(OH)CHOH$	+ 0.25	
	$(CH_3)(OCH_3)CHOH$	+ 1.07	
3	$(CH_3)_2(OH)COH$	+ 1.11	+ 1.2
	$(CH_3)_2(OCH_3)COH$	+ 1.19	

$$R_1R_2R_3\,COH + CH_3OH \rightleftharpoons R_1R_2R_3\,COMe + H_2O$$



$\Delta G^{\ddagger}$ represents the activation energy.

ΔG represents the free energy difference of starting materials and products.

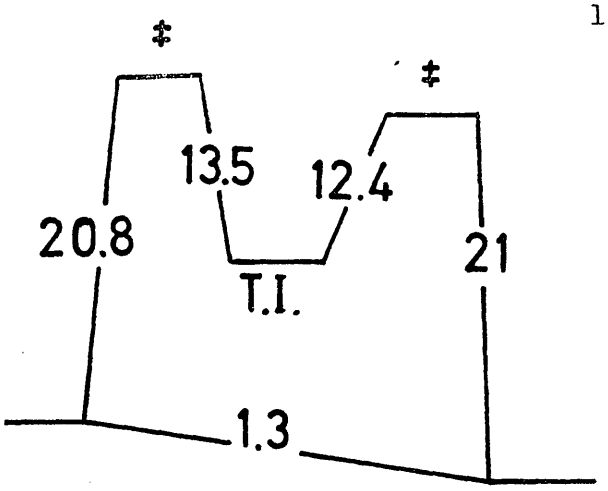
A.E. represents activation energy of the decomposition of the tetrahedral intermediate.

Fig. 91

(a)

$HCO_2Me + H_2O + 1M\ H^{\oplus}$

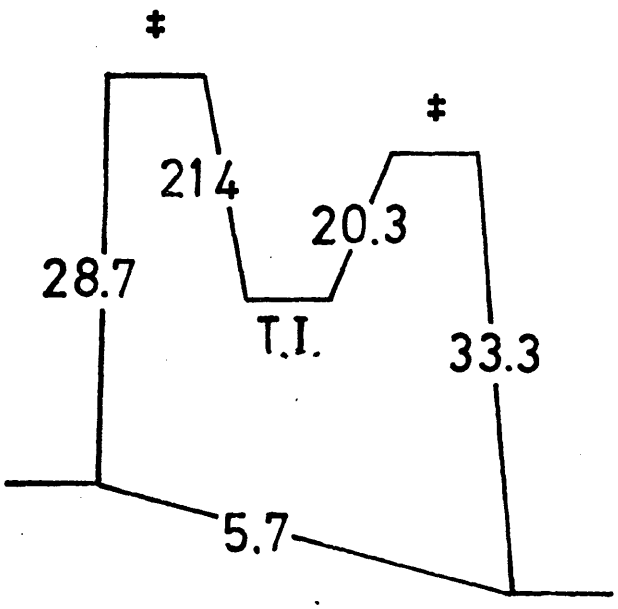
$\rightarrow\ HCO_2H + MeOH + H^{\oplus}$



(b)

pH7

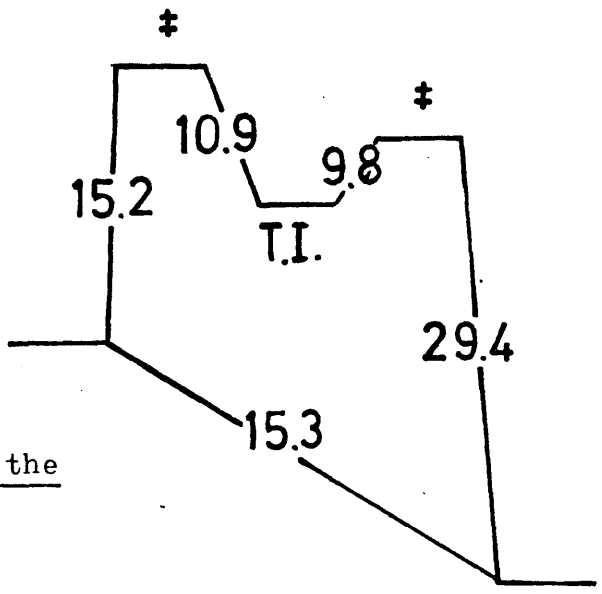
$HCO_2Me + H_2O \rightarrow HCO_2^{\ominus} + MeOH$



(c)

$HCO_2Me + 1M\ NaOH \rightarrow$

$HCO_2^{\ominus} + MeOH$



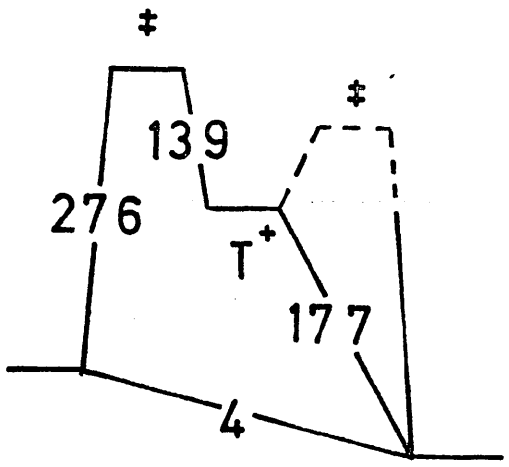
Reaction Co-ordinate Diagrams for the Hydrolysis of Methyl Formate.

Fig 92

pH 1

$HCONMe_2 + H^{\oplus} \rightarrow$

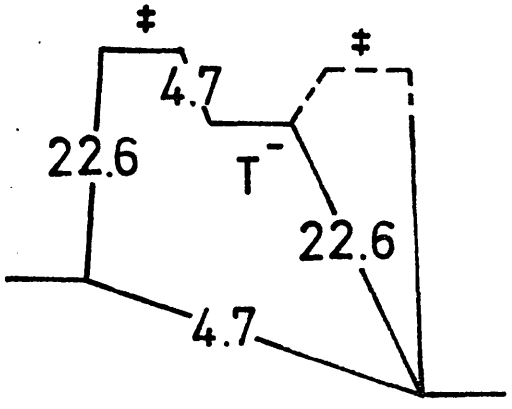
$HCO_2H + {}^{+}NH_2Me$



pH 14

$HCONMe_2 + {}^{\ominus}OH \rightarrow$

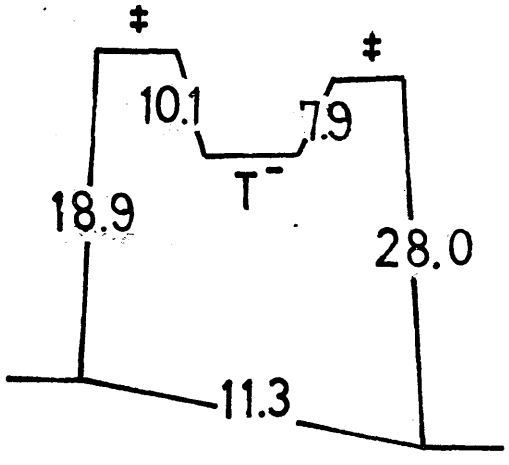
$HCO_2^{-} + HNMe_2$



pH 10

$HCO_2Me + HNMe_2 + {}^{\ominus}OH$

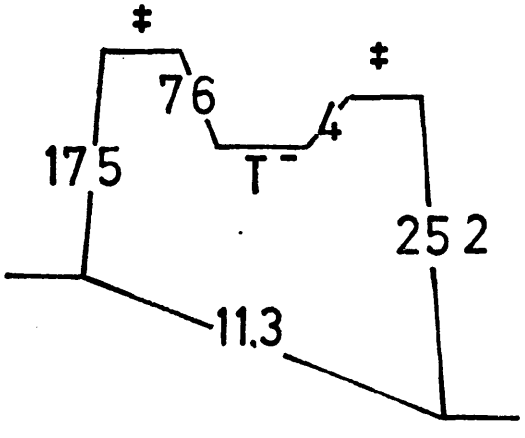
$\rightarrow HCONMe_2 + MeOH$



pH 12

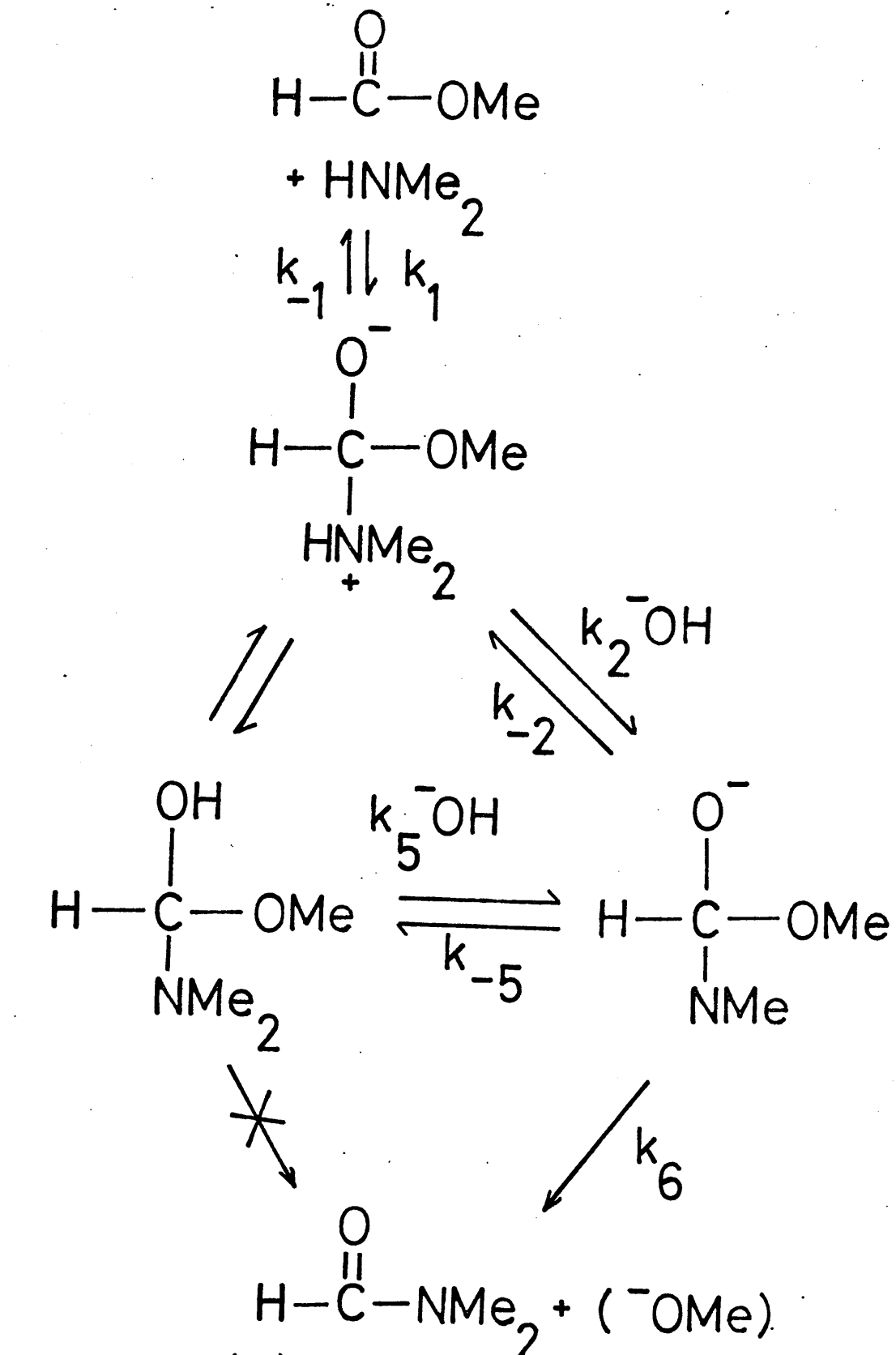
$HCO_2Me + HNMe + {}^{\ominus}OH$

$\rightarrow HCONMe + MeOH$



Reaction Co-ordinate Diagrams for Simple hydrolyses and aminolysis reactions.

Fig.93

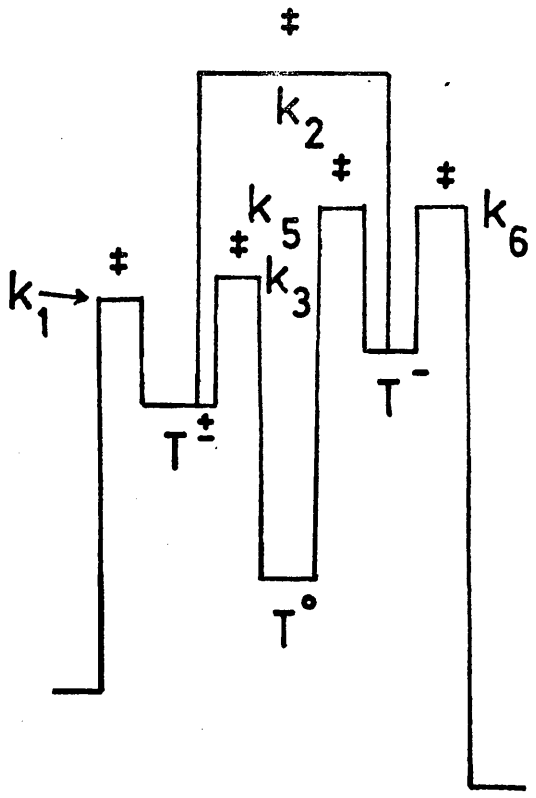


proposed by Jencks.

Fig. 94

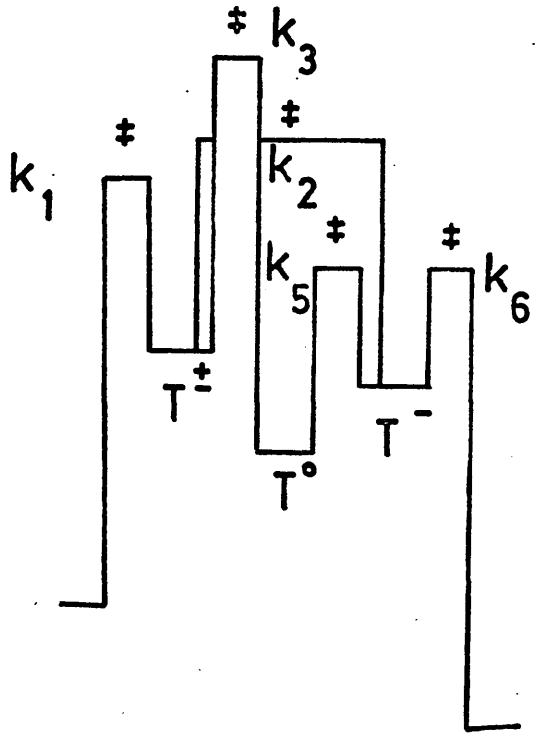
pH 8

$HCO_2Me + NHMe_2$
$\rightarrow HCONMe + MeOH$



pH 12

$HCO_2Me + NHMe_2$
$\rightarrow HCONNMe_2 + MeOH$



Reaction Co-ordinate Diagrams calculated by Guthrie for the aminolysis of methyl formate.

Fig.95

first calculation about the average, would give ~2kcal/mole error in the final values. Knowing the rates of hydrolysis of the esters studied the initial activation energy could be calculated (fig. 91). The final unknown, that of the activation energy of the decomposition of the tetrahedral intermediate could be calculated if the rate of oxygen exchange and rate of hydrolysis was known. This was estimated from data of k_H/k_e from several other esters and the free energy calculated from it. While a great many assumptions and estimations were made the general picture of the relative stability of the tetrahedral intermediate could be obtained (see fig. 92) over a large pH range. While fig. 92(b) represents the water catalysed reaction this is only a minor path, even at the minimum of the pH rate profile (ca pH5).

Similar calculations have been carried out for the hydrolysis of simple amides and the aminolysis of esters (see fig. 93). More detailed analysis of the aminolysis of methyl formate have been shown to be in accord with the pathway proposed by Jencks[172] with similar changes in the rate determining steps (see figs. 94 & 95). A recent addition, via this kind of study, has been the evaluation of the Free Energy changes associated with the addition of water to this time, thioesters.[156]

The estimation of the free energy difference for the addition of nucleophiles to carbonyl compounds has also been

estimated by Fastrez by the use of linear free energy relationships.[169] Despite a number of assumptions, which limit the accuracy of the work, reasonably good correlations have been obtained with localisation energies of the order 15-22 kcals/mole for amides, 14-18 kcals/mole for esters and acids and 11 kcal/mole for ethylthioacetate in reasonable agreement with Guthrie's work.

Ab Initio Studies of Tetrahedral Intermediates

In view of all the studies of tetrahedral intermediates and the subsequent postulation of the interaction of anti-periplanar orbitals, in not only controlling products as suggested by Deslongchamps[136] but as far afield as effects on ^{35}Cl nuclear quadrupole resonance frequencies of α-chloro-ethers,[157] as an interpretation of the anomeric effect,[158] and from X-ray studies[163] it is not surprising that theoretical calculations should have been carried out.

Studies, via ab initio calculations, on a number of simple systems, hydroxymethanes[159,160] (protonated and un-protonated) the tetrahedral intermediate (expected from base catalysed hydrolysis of methyl formate[161]) and aminodihydroxy-methanes,[162] have all produced similar results which can effectively be summarised as agreeing, at least theoretically, with the view that antiperiplanar orbitals stabilise the immediate C-O bond while weakening the C-O bond antiperiplanar to the lone pair.

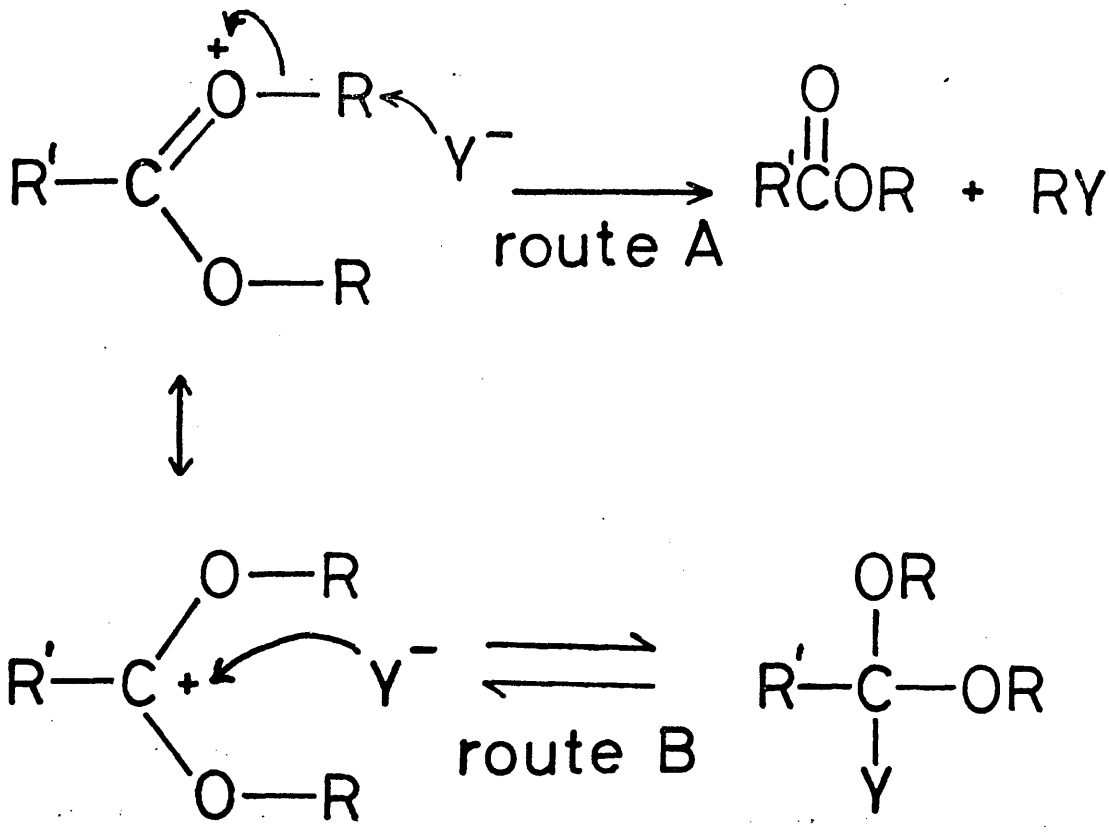
While these calculations help to confirm previous views their value in the direct study of tetrahedral intermediates can be considered rather debateable.

DISCUSSION

PREPARATIVE EXPERIMENTAL

Synthesis of Acetoxy-dimethoxy-methane

Initial attempts to synthesise this compound were based on the premise that no synthesis could be found in the literature. The first method, therefore, would appear rather crude in light of later knowledge. The reaction of dimethoxycarbenium bromide, which was formed at low temperature, and acetic acid can, according to Perst,[164] occur in two different ways (fig. 96). The nucleophile (acetic acid) can either attack the carbenium ion centre (route B) or the alkyl function (route A). The reaction by route B is a reversible process, the addition product only being isolated when the energy of formation of the bond is large enough. This can be best explained by considering again fig. 96 where addition of the nucleophile to the carbenium centre is the kinetically controlled step of the reaction. When an equilibrium system can be established the nucleophile can react to form the thermodynamically controlled final products via route A. According to Perst[164] the reaction depends not only on the nucleophile and the energy of the ambient cation but also on the solvent used, the reaction time and the temperature. The information can be summarised generally, however as the kinetically controlled product will be obtained if (a) a strong nucleophile is used



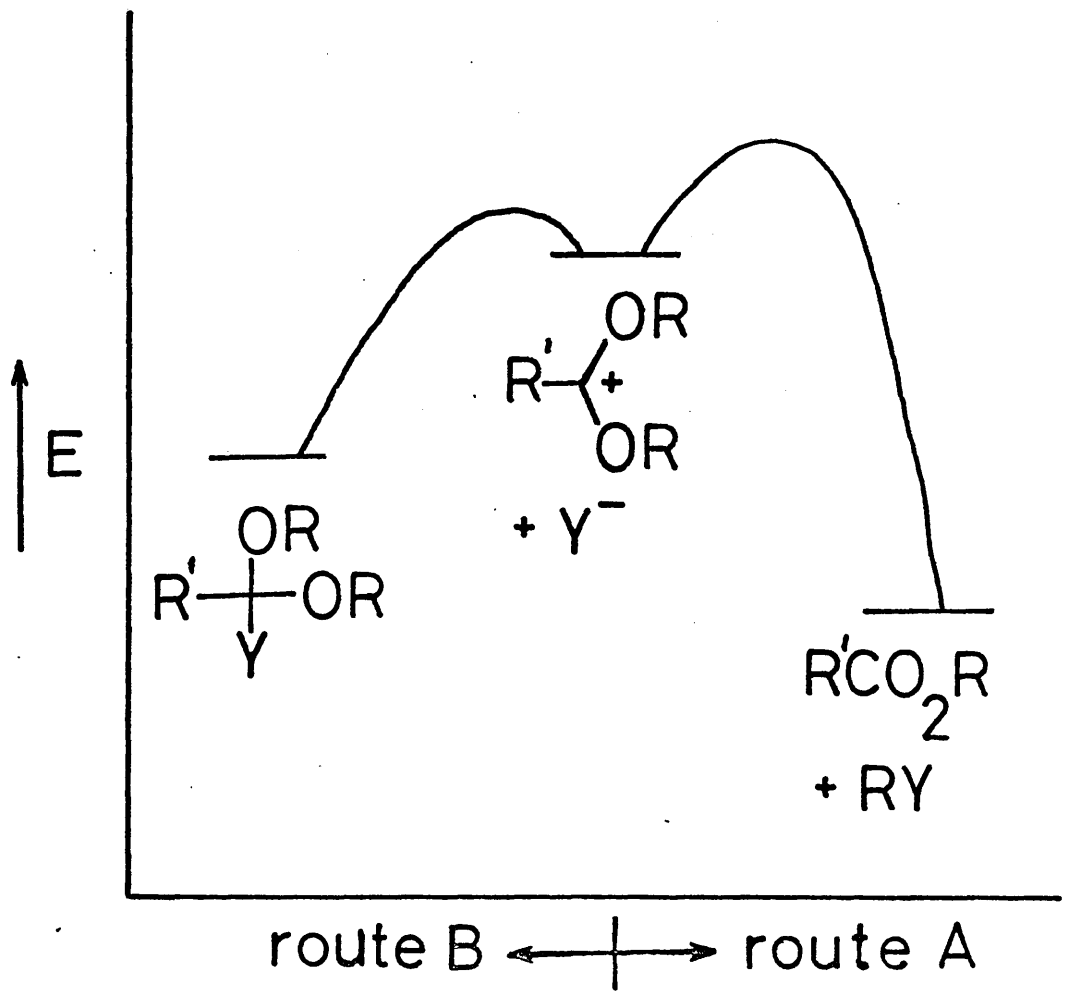


Fig. 96

(b) the energy of the ambient cation is high. The thermodynamically controlled reaction however requires (a) a weak nucleophile and (b) a low energy cation. A summary of the effective outcome on various reactions can be seen in Perst[164] (page 90).

The reaction, therefore, of dimethoxycarbenium bromide and acetic acid can be considered as the reaction of a weak nucleophile so that this may tend to favour the thermodynamic products. A further problem arose in this reaction of the formation of one equivalent of hydrobromic acid which could easily have promoted the breakdown of any product formed by route B and the lack of this product when finally checked by N.M.R. A similar rationalisation can be used to explain the lack of product obtained by Method 3, the reaction of dimethoxycarbenium fluoroborate with dry acetic acid, i.e. the reaction of a weak nucleophile and the formation of fluoroboric acid. Method 4 constitutes the first attempt to increase the nucleophilicity of the acetic acid to that of the acetate ion. However this increase in nucleophilic character did not appear to be enough. No acid was formed in this reaction in the hope that any acid catalysed breakdown could be stopped.

Method 2, the reaction of trimethyl orthoformate with acetic anhydride is basically that of an exchange reaction. It was noted that both routes A and B occurred but the kinetically controlled reaction predominated during the first

50% of the reaction. A problem, however, arose as to the separation of the acetoxy-dimethoxy-methane and the acetic anhydride and this could only be resolved by the very slow use of a spinning band column distillation apparatus. The study of the synthesis of acetoxy-dimethoxy-methane had been prompted by the similar reaction of acetoxy exchange[12] observed in acetals where no problem of separation occurred. While this method constituted a synthesis of the required product the problems encountered in the separation suggested that this method was a rather poor route. At this time the synthesis of acetoxy-dimethoxy-methane was found in the literature,[14] method 5; the reaction of the mixed anhydride with trimethyl orthoformate. While this method also required the use of the spinning band column, the separation was much more easily attained and also resulted in a much faster reaction using the more reactive formic/acetic anhydride system.

Synthesis of acetoxy- and chloroacetoxy-derivatives

While any attempts to synthesise 2-acetoxy- and 2-chloro-acetoxy-dioxolan derivatives directly from the reaction of the orthoesters and the corresponding acid did not result in the required products, the reaction of acetoxy-dimethoxy-methane, with the orthoesters, gave the corresponding exchange reaction, to give the acetoxy product. Similarly the reaction of these acetoxy compounds with chloroacetic acid was the only route to the chloroacetoxy compounds.

The attempted synthesis of 2-acetoxy-2-methoxy-tetrahydropyran by method 1 (reacting 2,2-dimethoxytetrahydropyran, acetoxy-dimethoxy-methane and acetic acid) similar to that used for the synthesis of 2-acetoxy-1,3-dioxolan has also added evidence to the discussion by Perst[164] of the attack of the nucleophile at other centres of the "postulated" oxonium salt intermediate. The resultant products obtained were δ-valerolactone and methyl δ-acetoxyvalerate, i.e. attack had occurred on the alkyl function via thermodynamic control of the products. All attempts to increase the reactivity of the nucleophile using crown ether/potassium acetate, etc. resulted in the same products.

Similar attempted preparations of α-acetoxy-α,α-dimethoxy--toluene, initially using different ratios of substrates and catalysts, different solvents and attempts to activate the nucleophile, have so far resulted in negative results. One route, however, (method 8) would appear to be reasonably promising. The reaction of α,α-dimethoxy-α-phenoxy-toluene and acetic anhydride at 35°C showed in its N.M.R. a peak for an acetoxy group not previously observed in any of the other reactions. No attempts at the isolation of this species have been tried, however, to date.

Attempted synthesis of phenoxy and p-nitrophenoxy derivatives

The synthesis of α,α-dimethoxy-α-phenoxy-toluene was, in itself, quite a difficult process requiring several methods

before the isolation of this compound could be carried out in reasonably good yield. By varying the quantity of nucleophile to substrate (orthoester) it was possible to show the formation of a small quantity of the required product although the main product at this stage was methyl benzoate. Simply by changing the acid catalyst (a last ditch effort) from toluene-p-sulphonic acid to methane-sulphonic acid, the yield of product was increased dramatically. The acidity functions[165] of both methane-sulphonic acid and toluene-p-sulphonic acid, in aqueous solution, indicate the former would be more effective at catalysing the ionisation of the neutral substrate; however, the exact acidities in benzene solution may be dramatically different. The difference in yields cannot conclusively be explained, therefore, in terms of the different acidities of the acids. The only other possibility, that of the presence of water of crystallisation in toluene-p-sulphonic acid and not in the dried redistilled methane-sulphonic acid, seems highly dubious in view of the small quantity of acid added.

Phenol is generally thought to be a rather poor nucleophile compared to phenoxide and it seems, therefore, rather strange that the attempted synthesis of 2-phenoxy-2-phenyl-1,3-dioxolan from 2-phenyl-1,3-dioxolenium fluoroborate and tetramethylammonium phenoxide, did not give the required product. Time did not allow the synthesis to be attempted

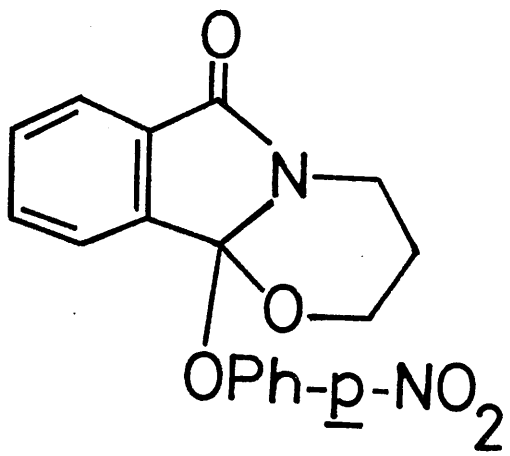


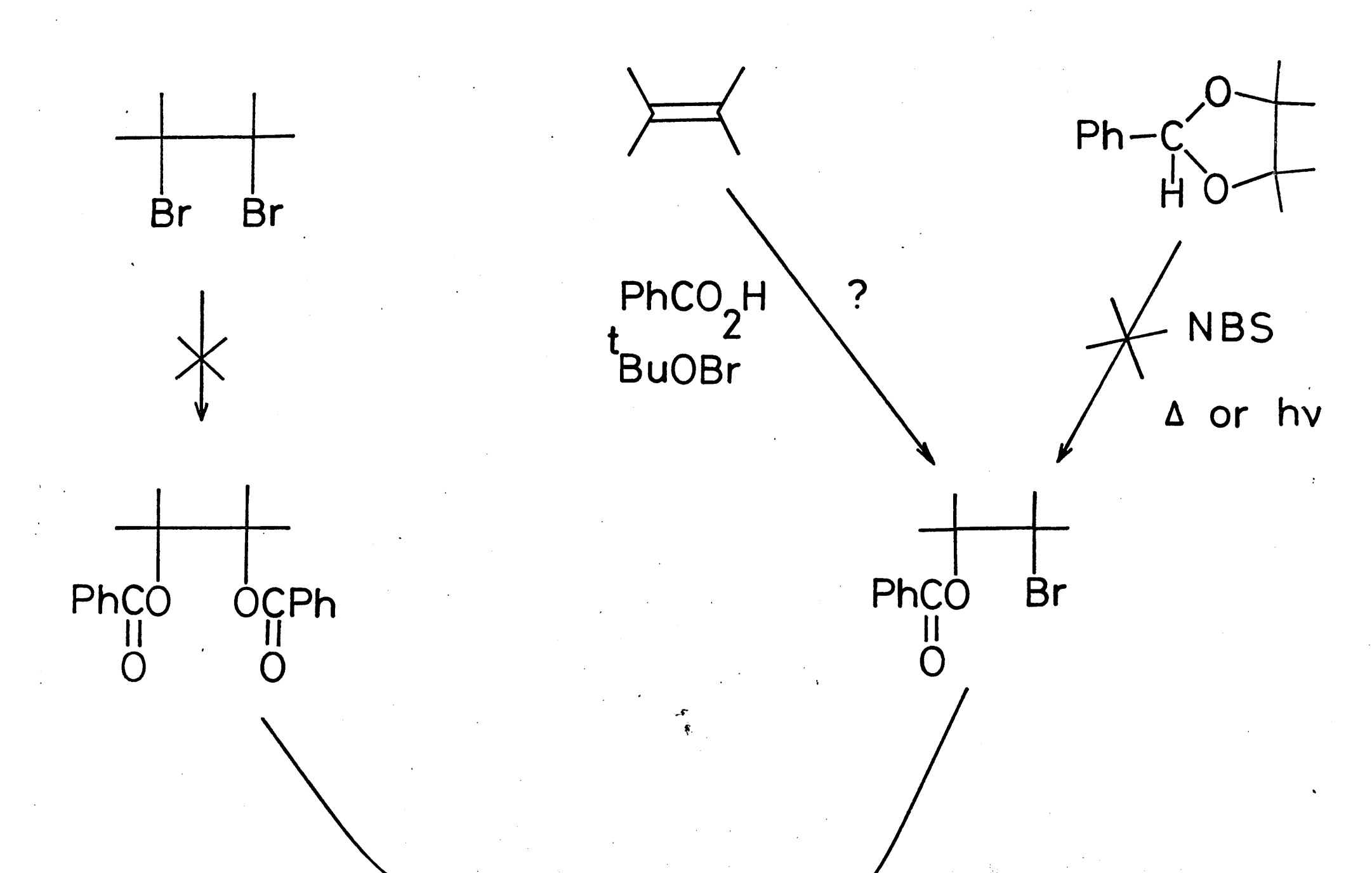
Fig. 97

by the reaction of phenol and 2-methoxy-2-phenyl-1,3-dioxolan in the hope of getting the "poorer" nucleophile to work.

The synthesis of 2-methoxy-2-phenoxy-tetrahydropyran parallels that of the synthesis of α,α-dimethoxy-α-phenoxy--toluene with the observation that methane-sulphonic acid produces a small quantity of required product whereas toluene--p-sulphonic acid produced more. The reaction time and the flask temperature during the reaction were found to be very critical in this case. Reaction times over 24-28 hours produced increasing quantities of methyl-5-phenoxy-valerate.

All attempts at preparing α,α-dimethoxy-α-p-nitrophenoxy--toluene, using methane-sulphonic acid as catalyst, by progressively reducing the molar equivalents of p-nitrophenol resulted, only, in the formation of p-nitroanisole and methyl-5-p-nitrophenoxy-valerate. While none of the required product was obtained further reduction in the molar equivalents of p-nitrophenol and careful study at various temperatures may result in success.

Several methods were tried to synthesise 2-methoxy-2-p--nitrophenoxy-tetrahydropyran from the O-methyl valerolactonium fluoroborate salt and from 2,2-dimethoxytetrahydropyran without success. To date only one p-nitrophenoxy- derivative, of an ortho-amide, is known to the authors. This is shown in fig. 97 and can be seen to also contain a carbonyl adjacent to the nitrogen atom.


Br
Br
PhCO2H
tBuOBr
?
Ph
C
O
H
O
NBS
Δ or hv
PhCO
OCPh
O
O
PhCO
Br
O

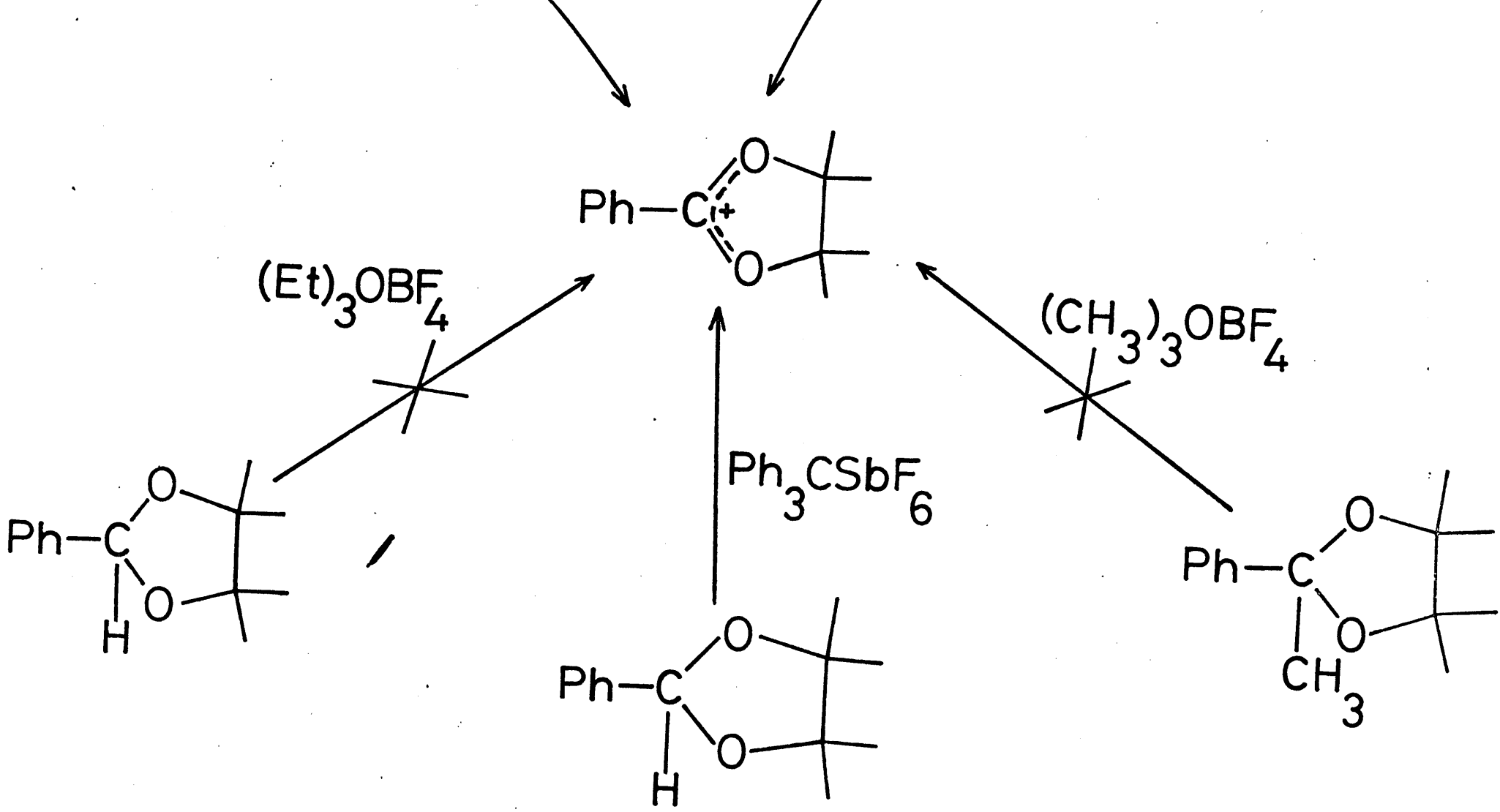


Fig. 98

Attempted Synthesis of 2-methoxy-2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan

Since direct methods of the synthesis of the above compound from trimethyl orthobenzoate and pinacol proved unsuccessful it was noted that a possible route to this compound could be obtained by the synthesis of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolenium fluoroborate followed by methanolysis.

The synthesis of the fluoroborate salt was observed to be similar to that of a cyclobutane system (see fig. 98) either via the dibenzoate ester and subsequent reaction with boron trifluoride or via the halogenated monobenzoate and subsequent reaction with silver fluoroborate. While attempts were carried out on the former reaction the precursor, 2,3-dimethyl--but-2-ene, was ordered for the second reaction. After 10 months this precursor still has not arrived!

All attempts to synthesise the dibenzoate ester from both ordinary esterification reactions and replacement reactions have proved unsuccessful. The latter reaction that of silver benzoate and 2,3-dibromo-2,3-dimethyl-butane resulted in the monoester elimination product.

Similarly attempts to synthesise the brominated monoester by the reaction of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan in the presence of N-bromosuccinimide (N.B.S.) with both photochemical and thermal routes have proved negative.

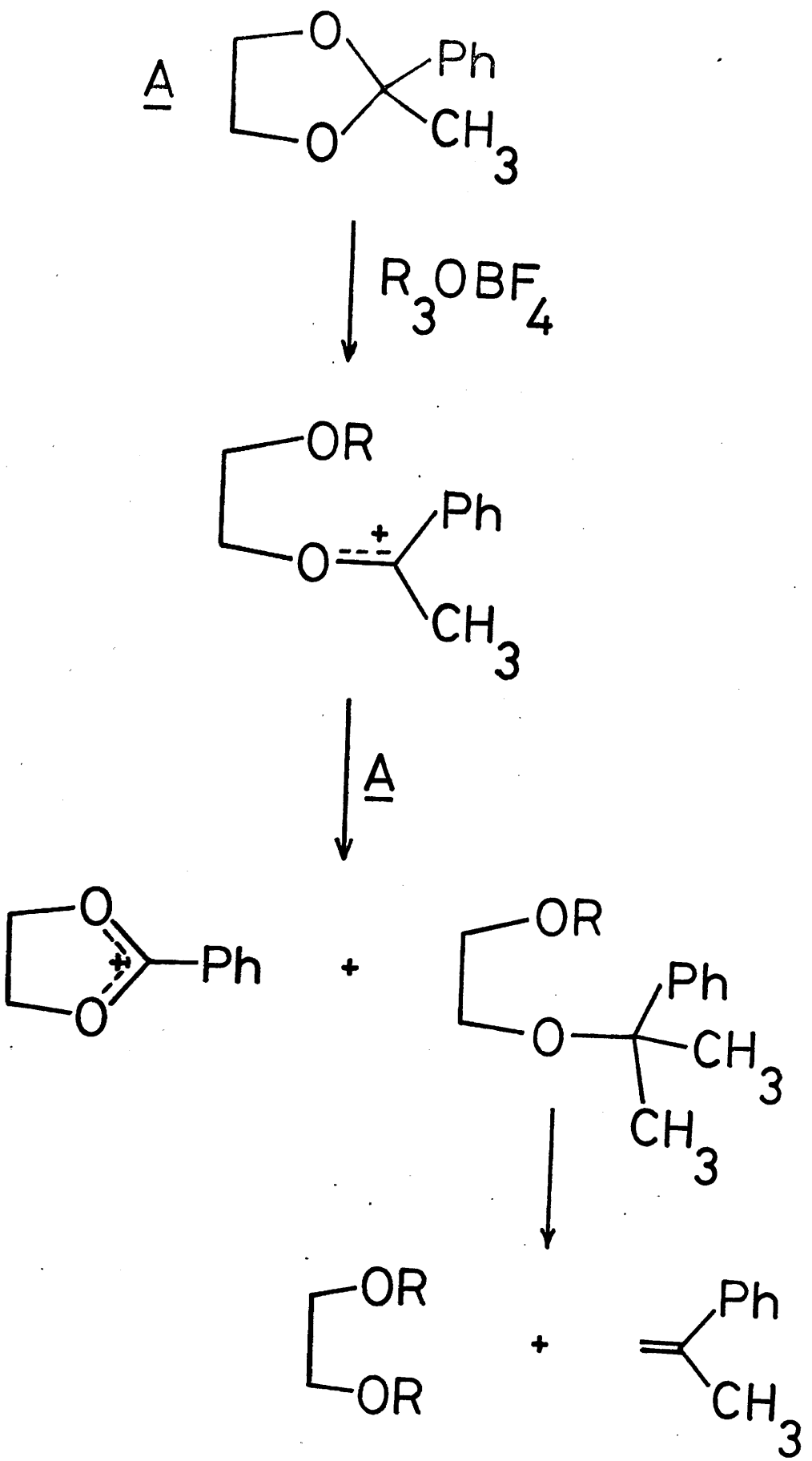


Fig. 99

Attempts were also made to remove methyl and hydrogen groups by oxonium salts by the methods of Kabuss[A] (see fig. 99) and Meerwein[B] but without success (see also Perst,[164] page 43). Whereas both references had studied the unsubstituted dioxolans it was hoped that this could be extended to the tetramethyl derivative. This of course was found not to be true. In Meerwein's paper a further possible reaction was seen which could be extended to the phenyl derivative of the substituted dioxolans. It was tried and found to be successful (method 3).

Preliminary studies on the methanolysis of the carbenium salt obtained has shown the formation of the 2-methoxy derivative and the open chain form. The first attempt to distill this material resulted in its decomposition, possibly because a high enough vacuum was not used

A. See Preparative Experimental Ref. 23.
B. " " " Ref. 24.

DISCUSSION - U.V. Spectroscopy Kinetics)

Hydrolysis of di-t-butoxy benzal and α-acetoxy-α-t-butoxy-toluene.

The background introduction to acetal hydrolysis has been discussed in several reviews and also by several previous Ph.D. students.[128]

It is sufficient to say that acetal hydrolysis is understood to be a multistep reaction, being, either specific acid catalysed involving protonated substrate, carboxonium ion and hemiacetal as consecutive discrete intermediates along the reaction pathway to formation of the aldehyde product, or general acid catalysed involving concurrent protonation and bond breaking in the initial step with no discrete species being formed in that first step (see figure 100).

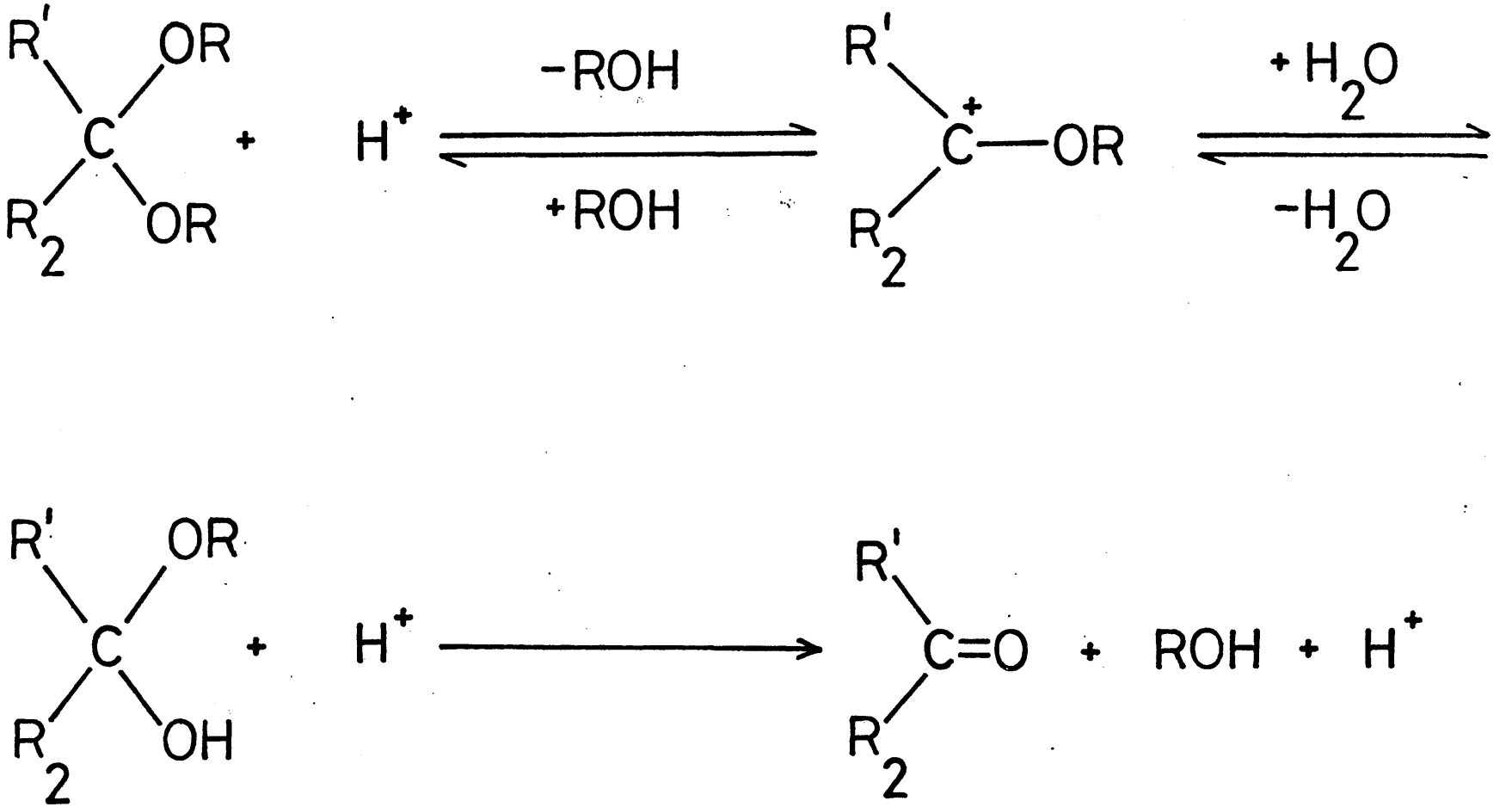
Buffer Catalysis

Throughout the experimental work the technique of Bell[173] was used, the pseudo-first order rate constants being determined at various buffer concentrations while the ionic strength, buffer ratio and pH were held constant. For all the buffer concentrations used the concentration of the undissociated acid was taken as the stoichiometric concentration.

The results are given in the Kinetic Experimental (U.V. Spectroscopy) Section in Tables 16-22.

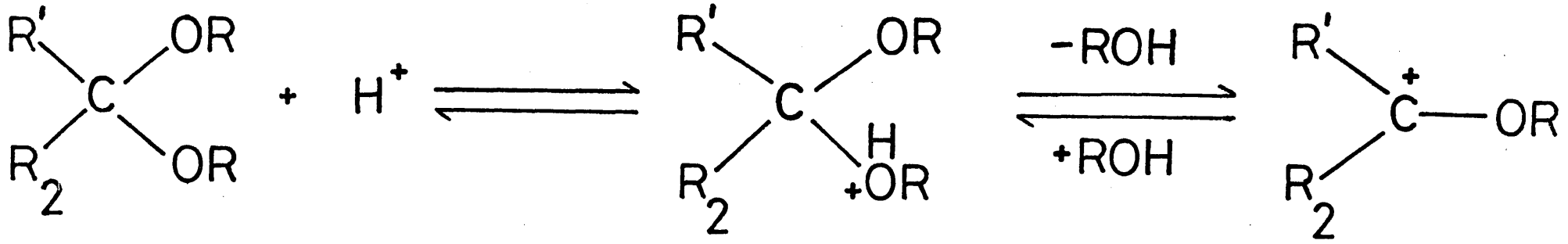
Kinetic Rate Law

While the general rate equation for the hydrolysis of acetals as found in the review by Cordes and Bull[129] is repre-


R'
OR
C
R2
OR
+
H+
-ROH
+ROH
R'
C+
OR
R2
+H2O
-H2O
R'
OR
C
R2
OH
+
H+
R'
C=O
R2
+
ROH
+
H+

1st step—Catalysis

Specific Acid.



General Acid.

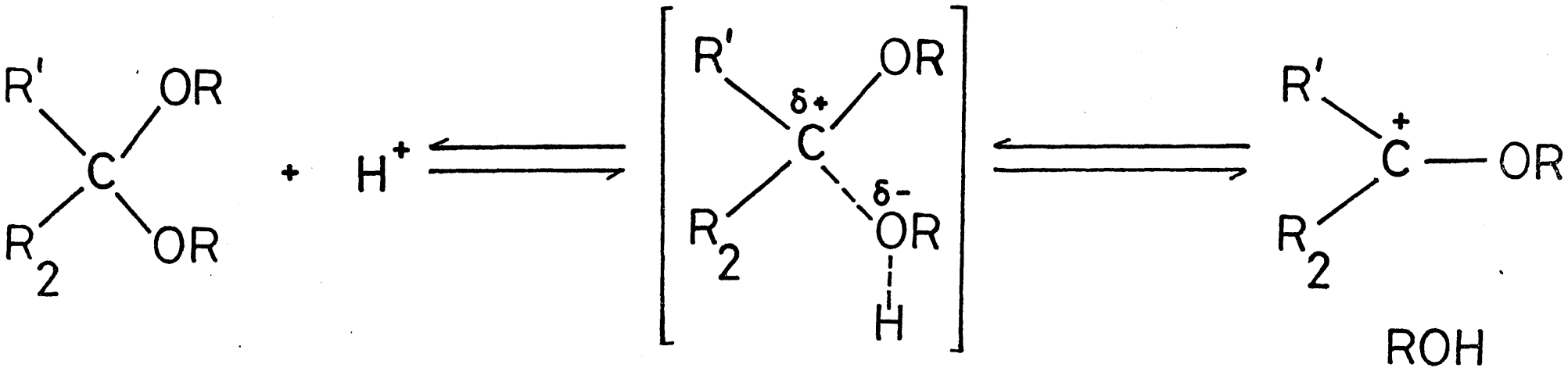


Fig.100

sented as

$$k_{obs} = k_{H^{\oplus}}[H^+] + \sum_i k_{HA}[HA]_i + k_o$$

This equation is not representative, however, where the rate determining step is decomposition of the hemiacetal. Later it will be shown that with di-t-butyl benzal rate determining decomposition of the acetal occurs at high pH and rate determining decomposition of the hemiacetal occurs at low pH. Similarly the hydrolysis of the acylal, α-acetoxy-α-t-butoxy--toluene, in the pH range studied was always rate determining decomposition of the hemiacetal.

Further terms are required to be added to the rate equation above in view of the possibility of catalysis of the breakdown of the hemiacetal species by base catalysis and, at least in theory, the possibility of general base catalysis.

$$k_{obs} = k_o + k_{H^{\oplus}}[H^{\oplus}] + \sum_i k_{HA}[HA] + \sum_j k_{A^{\ominus}}[A^-] + k_{^{\ominus}OH}[^{\ominus}OH]$$

A plot of k_{obs} as buffer concentration results, therefore, in different assignments to the slope in the case of acetal hydrolysis depending on the rate determining step of the reaction. At high pH where rate determining breakdown of the acetal is observed the equations are represented as;

$k_{obs} = k_{slope}[HA] + k_{int}$ where only one acid buffer is present

$k_{int} = k_{H^+}[H^+] + k_o$

$k_{slope} = k_{HA}$

At low pH for acetal hydrolysis and for the complete range of acylal hydrolysis studied;

$$k_{obs} = k_o + k_H + [H^+] + k_{-OH}[^-OH] + k_{HA}[HA] + \frac{k_A - Ka[HA]}{[H^+]}$$

since

$$Ka = \frac{[A^-][H^+]}{[HA]}$$

A plot of k_{obs} as [HA] gives

$$k_{int} = k_o + k_H + [H^+] + k_{-OH}[^-OH]$$

$$K_\omega = [H^+][^-OH]$$

$$\text{i.e. } k_{int} = k_o + k_H + [H^+] + \frac{k_{OH}K\omega}{[H^+]}$$

$$k_{slope} = k_{HA} + \frac{k_A - Ka}{[H^+]}$$

Site of Bond Fission

Isotopic and related studies of acetals have shown that the cleavage of the pro-acyl/oxygen bond occurred rather than alkyl/oxygen bond cleavage.

In the case of α-acetoxy-α-t-butoxy-toluene the position of initial bond cleavage of the acetoxy or t-butyl group is a point of consideration. Many studies on related acylals have been interpreted in terms of reaction at the acetoxy-carbon or rate determining fission between the pro-acyl carbon and the

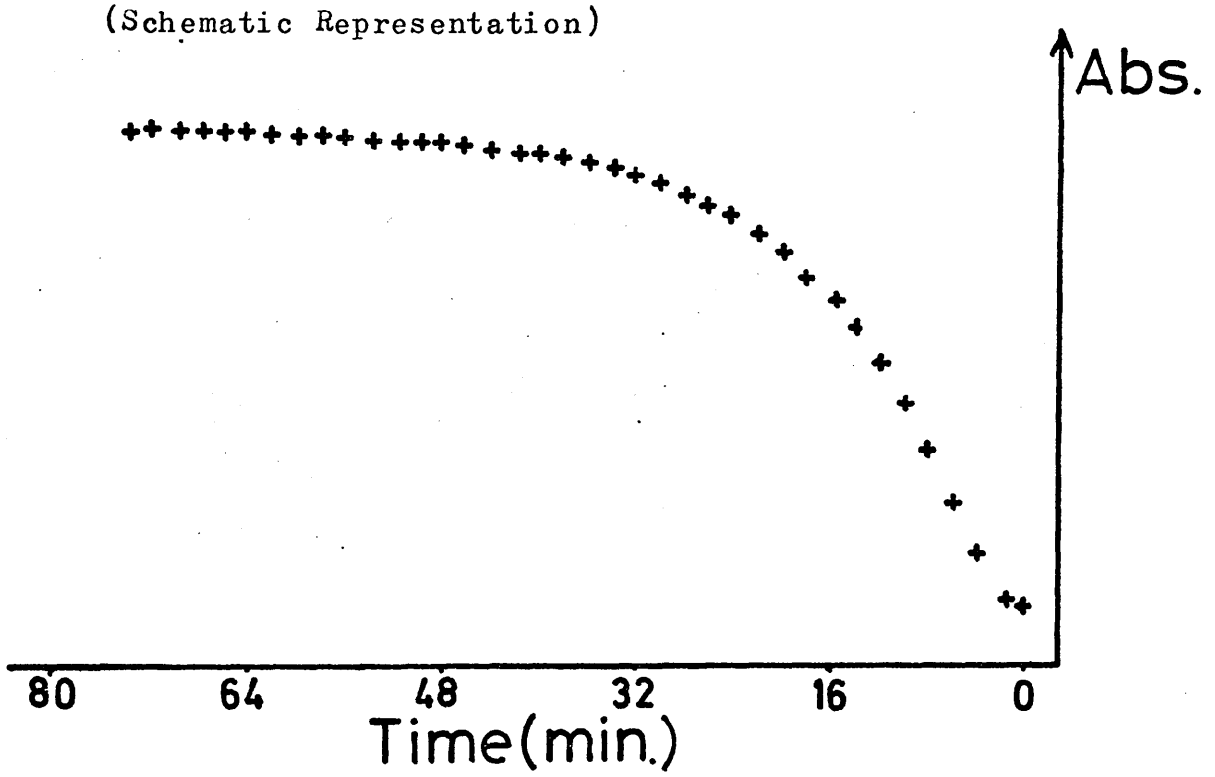
acetoxy or alkoxy groups. Summarily, therefore, reactions of acylals can be regarded as either a simple ester hydrolysis or the loss of a good leaving group, acetate, with subsequent reaction of the carboxonium ion.

An approximate value for the rate of hydrolysis of α-acetoxy-α-methoxy-toluene, with acyl oxygen fission, can be estimated from the rate of hydrolysis of α-acetoxy-α-p-nitrophenoxy-toluene. This compound was shown by Fife and De to react by this pathway, the alternative pathway via a carboxonium ion being unfavourable because of the electron-withdrawing properties of the nitro-phenol group. Since replacement of the p-nitrophenoxy group by the methoxy group would not be expected to have a large effect on the rate of reaction which involves attack at the acyl group the observation that α-acetoxy-α-p-nitrophenoxy-toluene reacts 10^3 to 10^5 times slower than α-acetoxy-α-methoxy-toluene suggests that any reaction of the latter involving acyl-oxygen fission is negligible. It was also shown that α-chloracetoxy-α-methoxy-toluene hydrolyses at an identical rate to that of α-acetoxy-α-methoxy--toluene which was explained by Capon et al[174] as being due to initial loss of the acetoxy or chloroacetoxy function followed by rate determining decomposition of the hemiacetal formed.

While steric effects could play an important part in changing the reaction mechanism in going from α-acetoxy-α--methoxy-toluene to α-acetoxy-α-t-butoxy-toluene, a brief comparison of the rates of hydrolysis extrapolated to zero

GRAPHS OF Absorbance versus time for the Hydrolysis of Di-t-butyl Benzal

1. Phosphate Buffer pH 6.77 I = 0.05M
(Schematic Representation)



2. Imidazole Buffer pH 7.05 I = 0.05M
(Schematic Representation)

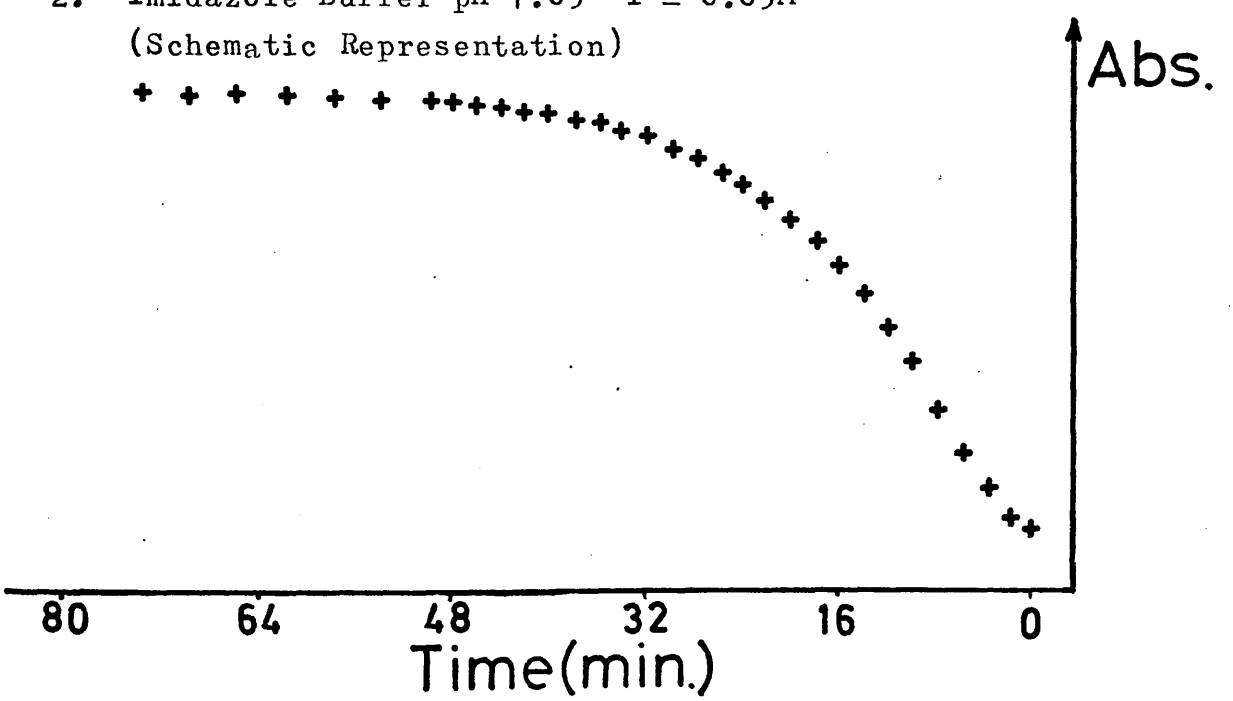


Fig. 101

buffer concentration show very similar results (table 10). Both rates are much greater than the rate obtained for the hydrolysis of α-acetoxy-α-p-nitrophenoxy-toluene. Further comparisons will be given later in the discussion.

Table 10

pH	Buffer	$10^2 k_o (sec^{-1})$	15°C
4.64	Acetate	1.62[a]	α-acetoxy-α-methoxy-toluene
4.63	Acetate	1.84[b]	α-acetoxy-α-t-butoxy-toluene
1.0	(HCℓ 0.1M)	0.76[c]	α-acetoxy-α-p-nitrophenoxy-toluene

a. Ref. 174 c. Ref. 176 (I = 0.05M)

b. This work

Change in the Rate Determining Step with pH

Buffer catalysis was observed in the hydrolysis of di-t-butoxy-benzal in acetate buffer at pH 3.99 (table 16). Unfortunately the separate k_{H_2O}, k_{H^+}, etc. values cannot be calculated from one intercept value.

At pH 4.63 and up to approximately pH 7 varying magnitudes of an induction period (see fig. 101) could be observed. As a consequence of this while rate constants could be obtained which "fitted" a 1st order plot the standard deviations showed very large errors (table 19).

Similar observations in the hydrolysis of other acetals have also shown this two step nature in their rate plots.

At pH 7.03 there was a return to 1st order kinetics (within experimental error with a possible slight induction period ~ 1 min) with a very much reduced rate constant (table 20) but in this case no buffer catalysis in imidazole was seen.

A comparison of the rates of hydrolysis k_{obs} and the plots of k_{obs} versus acid concentration for di-t-butoxy benzal and α-acetoxy-α-methoxy-toluene, at pH 3.99 show almost identical values for the rate constants and slopes of the lines (see tables 16 and 17).

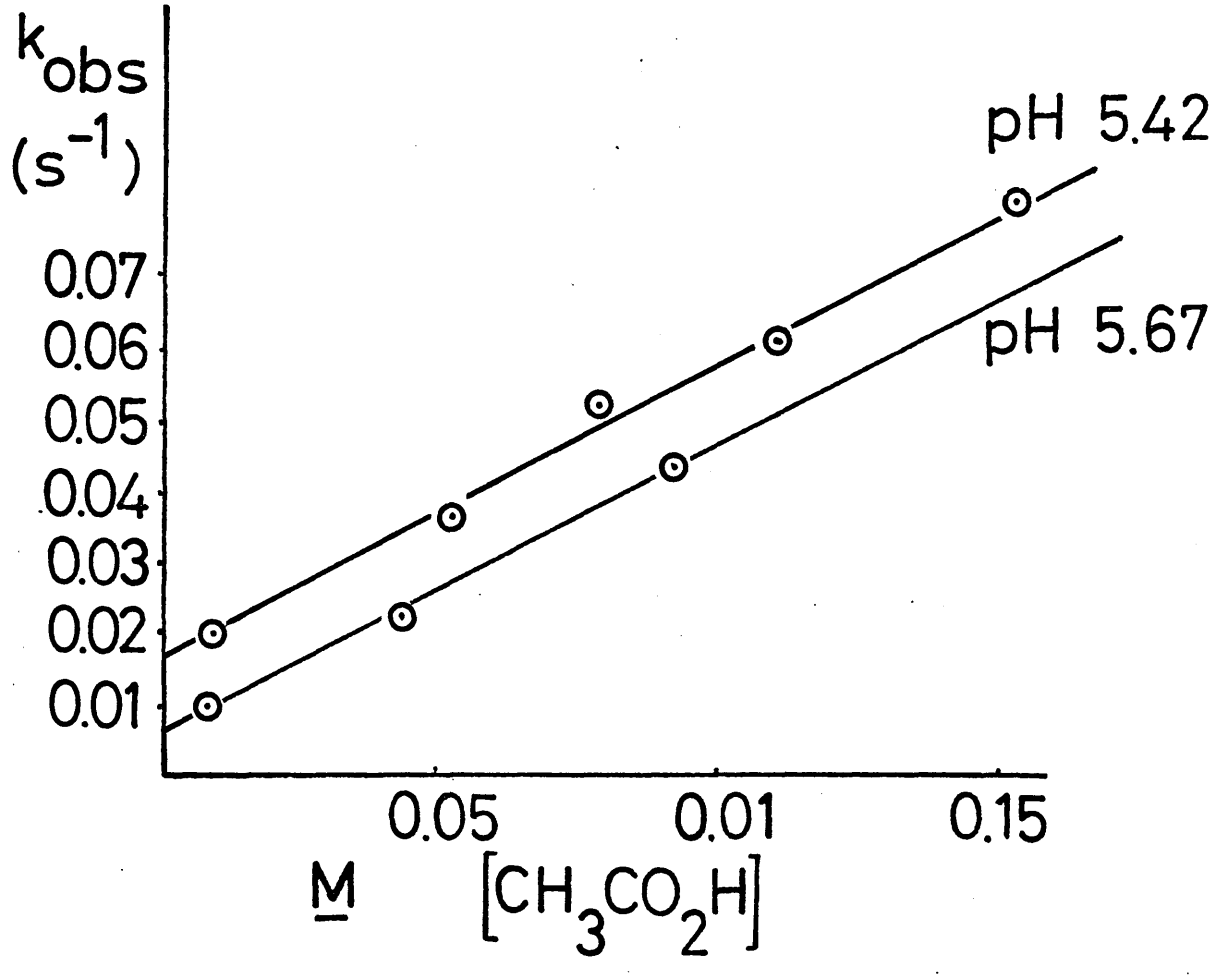
A similar comparison at pH 7.03 (tables 20 and 21) shows a dramatic difference in the type of catalysis, α-acetoxy-α-t--butoxy-toluene having pronounced buffer catalysis and approximately 10 times faster at zero acid concentration.

The intervening pH range, at pH 4.63 in acetate buffer, 1st order rate constants can still be obtained for α-acetoxy-α--t-butoxy-toluene hydrolysis with buffer (table 18).

The above considerations have resulted in the suggestion that a change in the rate determining step for the hydrolysis of di-t-butoxy benzal has taken place over the central pH region with rate determining breakdown of the hemiacetal at low pH and rate determining breakdown of the acetal at high pH.

In the original studies of the hydrolysis of di-t-butoxy benzal by Anderson and Fife[177] no comment was given on any induction period in the kinetic traces. Their studies were carried out at 25°C in aqueous solution containing a final concentration of 1% acetonitrile (derived from the stock solution of the

Plot of k_{obs} versus acetic acid concentration for the Hydrolysis of di-t-butoxy benzal.



Ref. 177

Fig. 102

acetal). The ionic strength was maintained at 1.0M by potassium chloride.

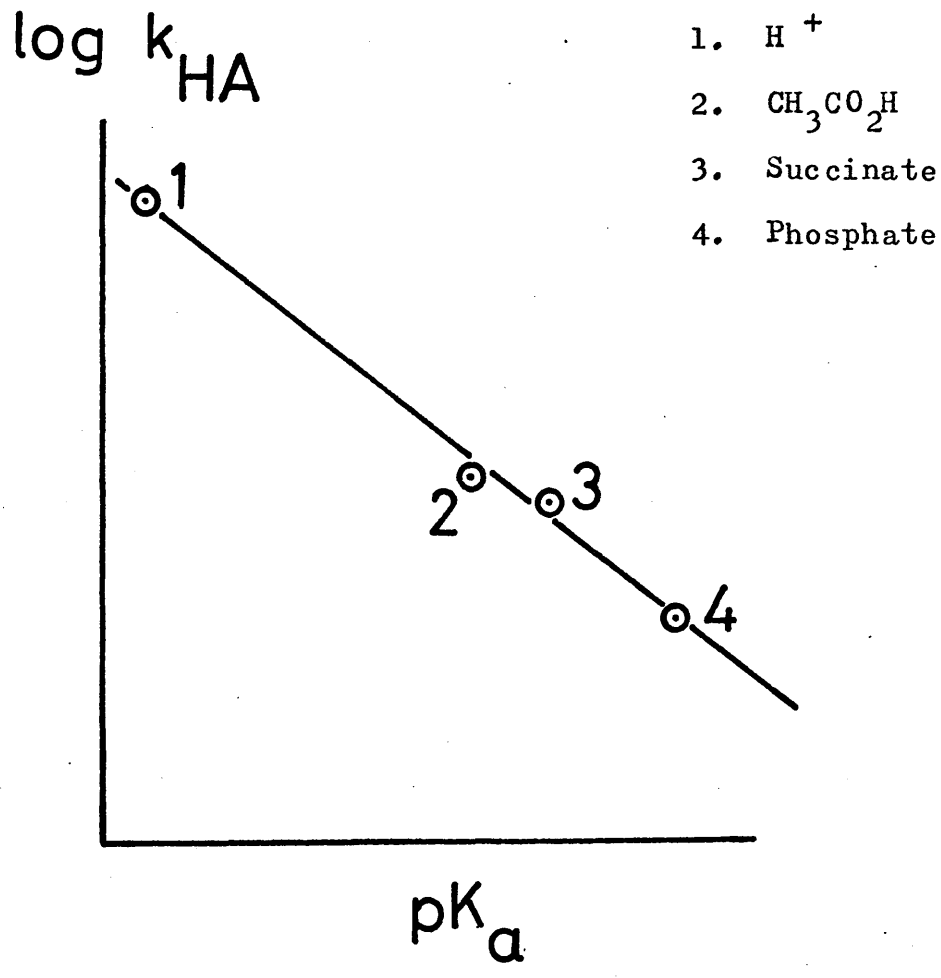
General acid catalysis was observed with a high hydrolysis rate (see fig. 102) and was explained as being due to "facilitation of bond breaking by release of steric strain produced by the bulky t-butyl groups in the ground state".

Several questions, however, arise as to whether the results are in fact correct but problems arise in the direct comparison of these to present results in this thesis.

The problems are that the ionic strength of the solutions are different and hence the acid concentration is effectively higher in Anderson and Fife's study. The temperature is 25°C rather than 15°C for present studies. These factors may have resulted in a change in the position of changeover in the rate determining step to much higher pH values.

In their study Anderson and Fife showed only the pH's at which acetate buffer hydrolysis occurred (see fig. 102) but in the case of phosphate buffer no pH was given and one can only assume it was quite near to pH 6 if no induction period was observed. The observation of general acid catalysis suggests that breakdown of the hemiacetal was being observed, since under conditions where the breakdown of the acetal is rate-determining the reaction in imidazole buffer, at least, would appear to be specific acid catalysed or very weakly general acid catalysed as stated earlier.

Plot of k_{HA} for General Acid Catalysis of the Hydrolysis versus pKa of catalysing acid.



Ref. 177

Fig 103

The values of k_{obs} extrapolated to zero buffer concentration are of the order $1.4 \times 10^{-2} sec^{-1}$ and $0.7 \times 10^{-3} sec^{-1}$ in acetate buffers at pH 5.42 and 5.67 at 25°C. These values are of the same magnitude to that obtained at pH 3.99 in acetate buffer in the present study of di-t-butyl benzal of $7.7 \times 10^{-2} sec^{-1}$ at 15°C.

The graph of the plot of k_{HA} for the general acid catalysed hydrolysis of di-t-butyl benzal versus the pKa of the catalysing acid is shown in fig. 103. (Copied from the diagram in the paper by Anderson and Fife). It is interesting to note that the points taken for this plot correspond to the acids hydronium, acetic, succinic and phosphoric. These acids, as with other acids of different general structures, should not necessarily lie on the same linear plot as shown. In fact taking acetic and succinic acids which have a similar structure, a completely different slope can be obtained. The value of this slope calculated through all the points by Anderson and Fife may not in fact be correct.

Analysis of Results

Whereas the individual rate constants cannot be obtained for the hydrolysis of di-t-butoxy benzal due to insufficient data, values of k_{H^+}, k_{H_2O} and k_{-OH} can be obtained for the breakdown of benzaldehyde t-butyl hemiacetal from the results of α-acetoxy-α-t-butoxy-toluene (table 11). For comparison the corresponding values for benzaldehyde methyl hemiacetal

from the hydrolysis of α-acetoxy-α-methoxy-toluene are also included.

Table 11 Buffer Independent Rate Constants for the Breakdown of Benzaldehyde Hemiacetals at 15°C.[a] PhCH(OR)OH

R	$k_{H_2O}(M^{-1}s^{-1})$	$k_{-OH}(M^{-1}s^{-1})$	$k_{H^+}(M^{-1}s^{-1})$
CH_3	9.33×10^{-5}	6.87×10^{5}	261
$C(CH_3)_3$[b]	8.29×10^{-6}	4.526×10^{5}	766.53

a. Ionic Strength = 0.05 M.

b. Errors in values of k_{H_2O} S.D = 33%; k_{-OH} S.D = 6.48% k_{H^+} S.D = 0.7% estimated by the method in ref.

It can easily be seen that within experimental error k_{H_2O} and k_{-OH} decrease with the increased number of methyl groups. k_{H^+}, however, increases with the increase in the methyl groups. Similar observations by Jencks et al[175] are seen for the hydrolysis of formaldehyde hemiacetals (see table 12).

Table 12 Buffer Independent Rate Constants for the Breakdown of Formaldehyde hemiacetals at 25°C[a] $CH_2(OR)OH$

R	$k_{H_2O}(M^{-1}s^{-1})$	$k_{-OH}(M^{-1}s^{-1})$	$k_{H^+}(M^{-1}s^{-1})$
CH_3	3.27×10^{-5}	2.34×10^{3}	0.58
CH_2CH_3	2.93×10^{-5}	1.3×10^{3}	0.74

a. Ionic Strength = 1.0 M.

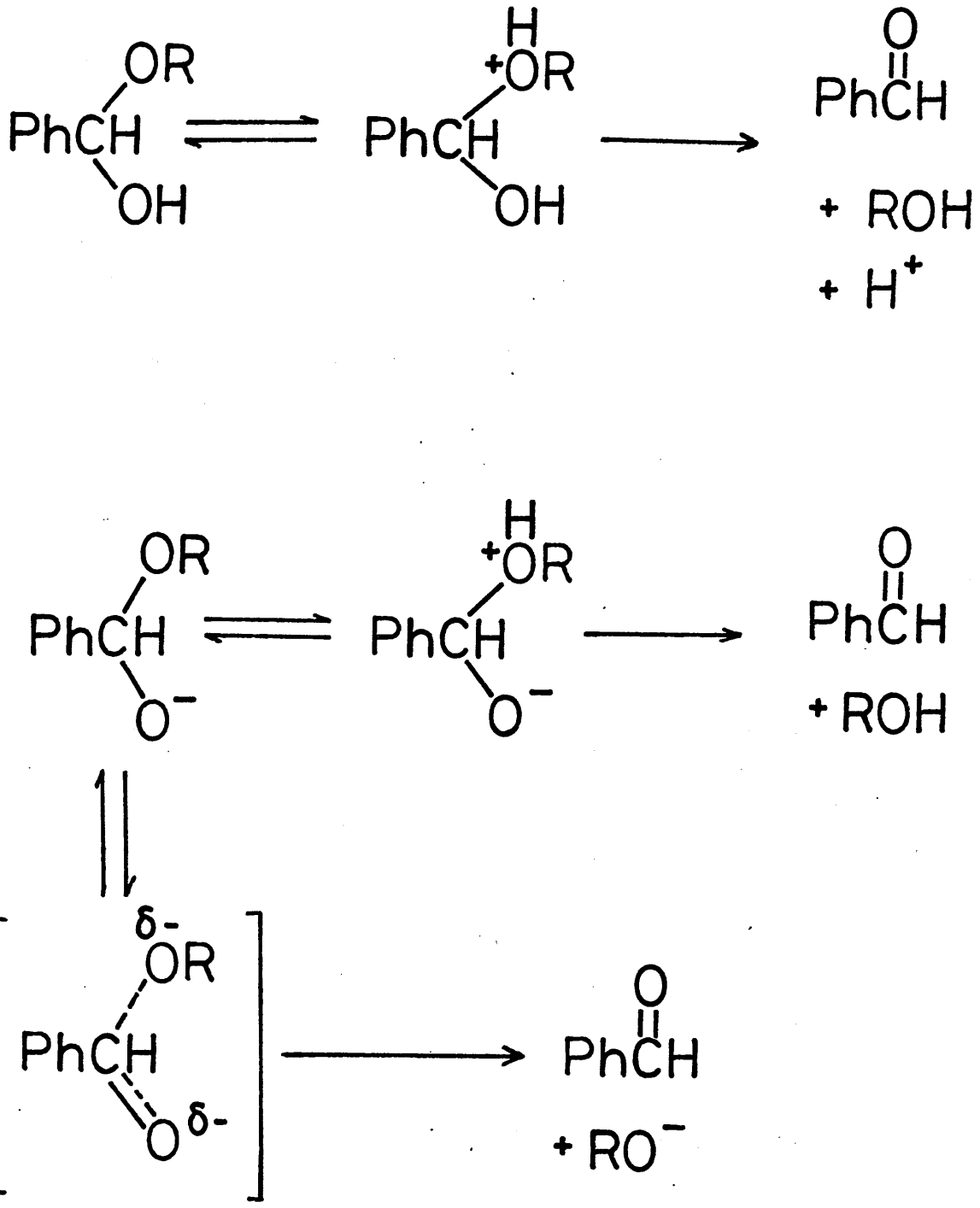

OR
PhCH
OH
H
+OR
PhCH
OH
O
PhCH
+ ROH
+ H+
OR
PhCH
O−
H
+OR
PhCH
O−
O
PhCH
+ ROH
δ-
OR
PhCH
O δ-
O
PhCH
+ RO−

Fig. 104

It can be argued that a more electron-releasing function acts to donate more electrons towards the oxygen of the O-alkyl group resulting in easier protonation and hence loss of the alkyl function in acid solution (fig. 104). However steric interactions must also contribute to this rate enhancement. In the case of alkaline hydrolysis this electron donation would tend to destabilise the transition state where an alkoxy function would tend to be formed since a partial negative charge would already be located on the oxygen of the O-alkyl function (fig. 104).

The intervening pH, where k_{H_2O} would tend to contribute much more, is more difficult to define since both ease of protonation and release of steric strain should play important parts (fig. 104)

A comparison of the results in tables 11 and 12 for R = methyl show the differences in the rate constants between benzaldehyde and formaldehyde hemiacetals. Quantitatively in the case of the formaldehyde hemiacetal the k_{H_2O} contributes much more to the rate of hydrolysis since both k_{H^+} and k_{-OH} are very much smaller, by a factor of 10^2-10^3 than for the corresponding benzaldehyde hemiacetal. On the other hand the introduction of a phenyl group has only a small effect on k_{H_2O}. This is reflected in the pH rate profiles where a much broader "U" shaped curve is apparent for the formaldehyde hemiacetals than for the benzaldehyde hemiacetals.

DISCUSSION - Nuclear Magnetic Resonance Spectroscopy Kinetics

Two sets of representative spectra for the hydrolysis of acetoxy-dimethoxy-methane are shown in figs. 105 and 106; differing only in the D_2O/acetone-D_6 ratio.

Precooling the substrate in acetone-D_6 to a much lower temperature than -35°C, usually -50°C, followed by the rapid addition of the required quantity of D_2O usually resulted in the observation of a much greater proportion of starting material in the initial N.M.R. spectrum. Then by warming up the N.M.R. instrument to -35°C the spectra shown in figs. 105 and 106 could be obtained. As the reaction progressed the loss of starting material, characterised by the loss of peaks at 6.17, 3.38 and 2.12δ, could be observed with concurrent increase in peaks at 5.27, 3.26 and 2.02δ. A much slower increase in the expected product peaks at 8.22 and 3.73δ was also observed over the whole reaction time. At the completion of the reaction, on warming to room temperature no change in the peak positions of the final products could be seen over the time interval studied i.e. several hours. The peak assigned to water varied with temperature.

It should be expected that the N.M.R. spectrum of the tetrahedral intermediate in this reaction should be very similar to that of trimethyl orthoformate considering the very great similarity in structure. The chemical shifts of

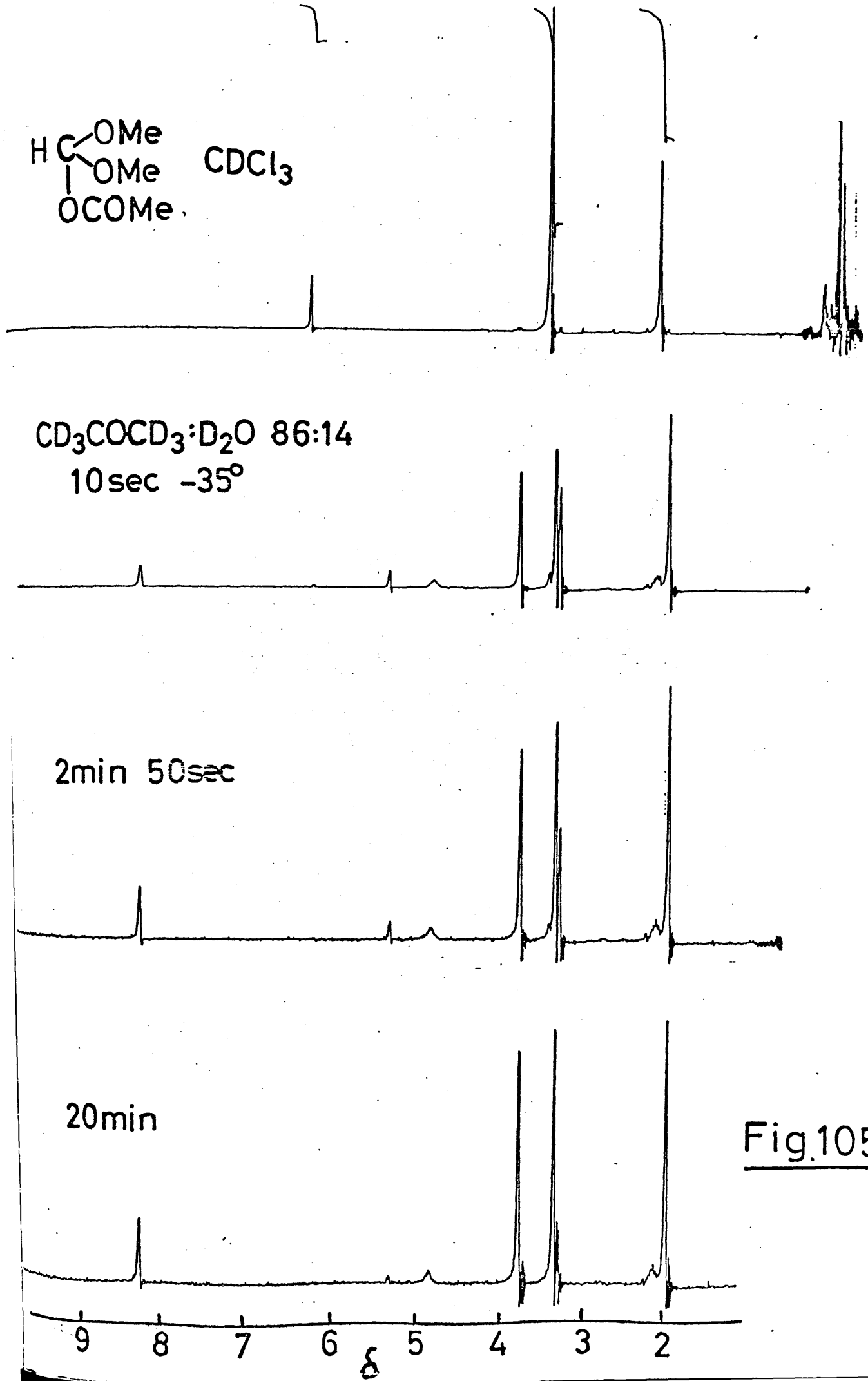

H C OMe
OMe
OCOMe
CDCl3
CD3COCD3:D2O 86:14
10sec -35°
2min 50sec
20min
9
8
7
6
5
4
3
2
δ

Fig.105

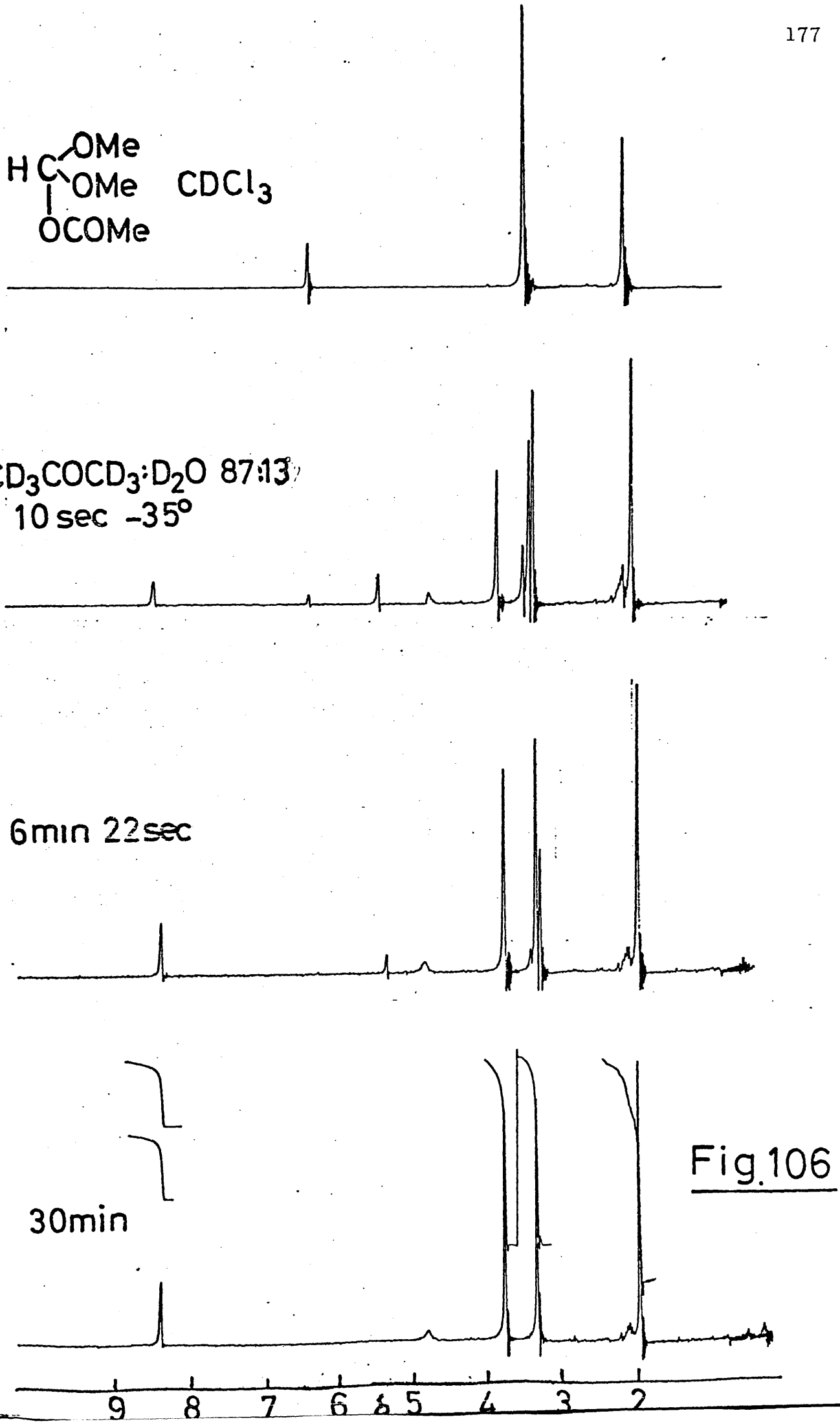
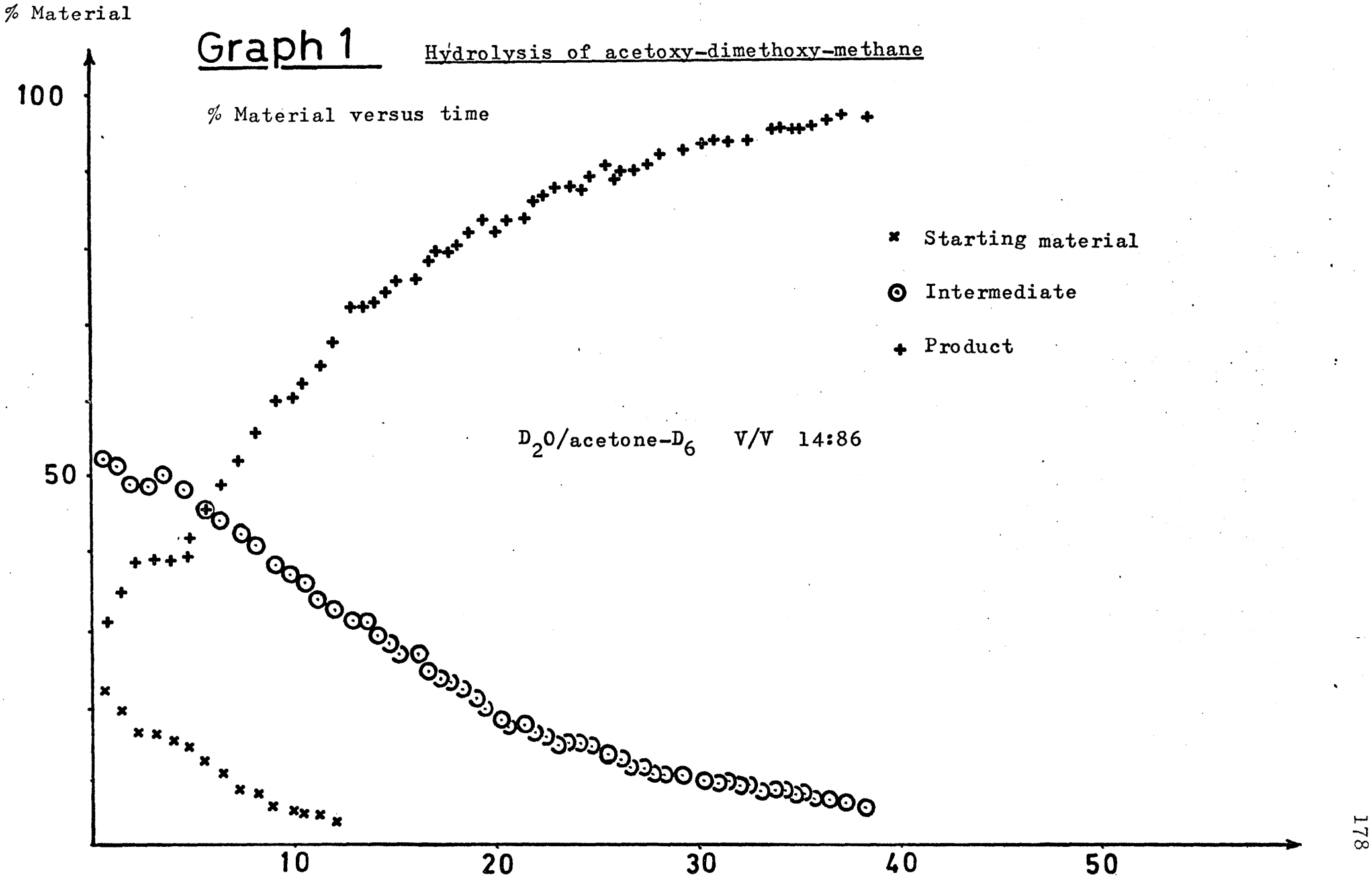

H C OMe
OMe
OCOMe
CDCl3
CD3COCD3:D2O 87:13
10 sec -35°
6min 22sec
30min
9
8
7
6
δ
5
4
3
2

Fig.106


% Material
Graph 1
Hydrolysis of acetoxy-dimethoxy-methane
% Material versus time
100
50
10
20
30
40
50
Starting material
Intermediate
Product
D2O/acetone-D6 V/V 14:86

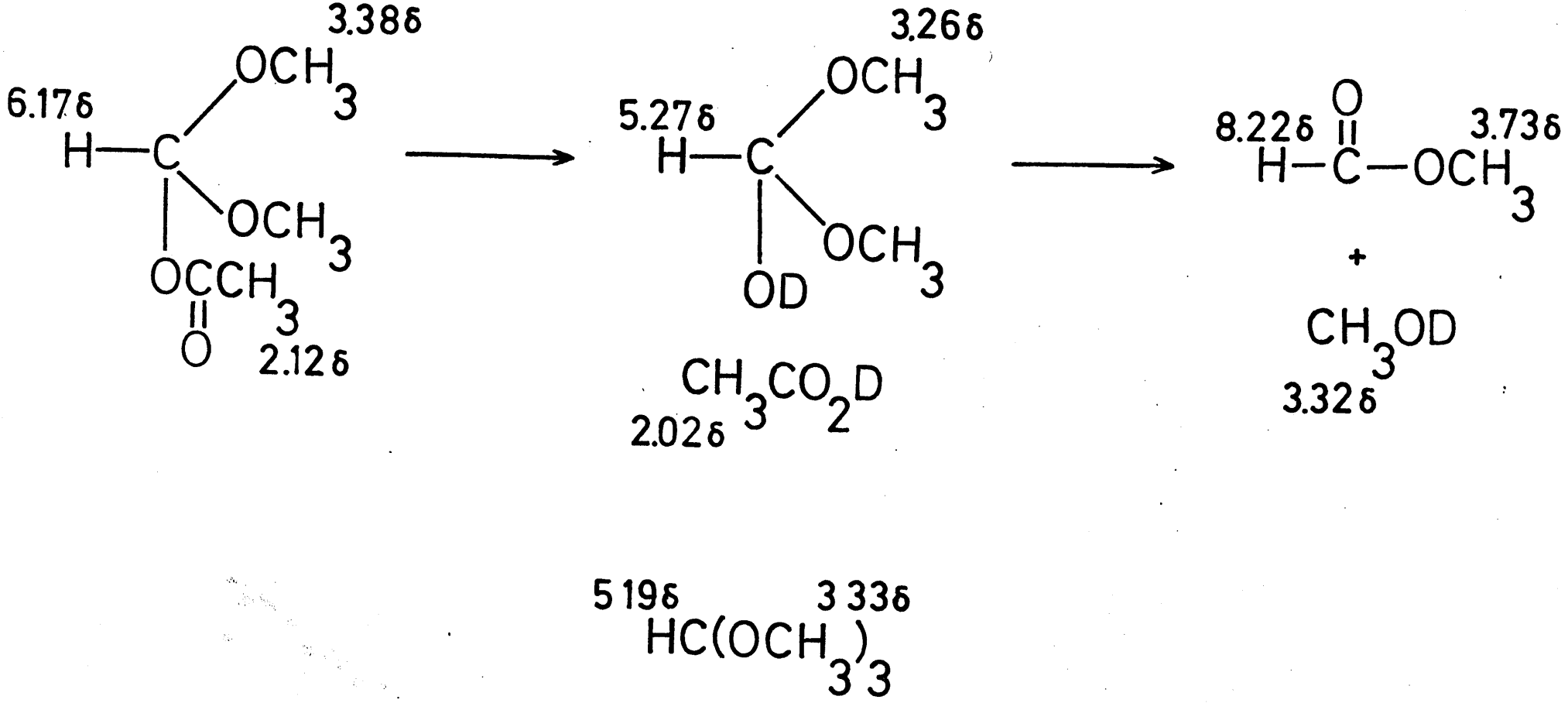
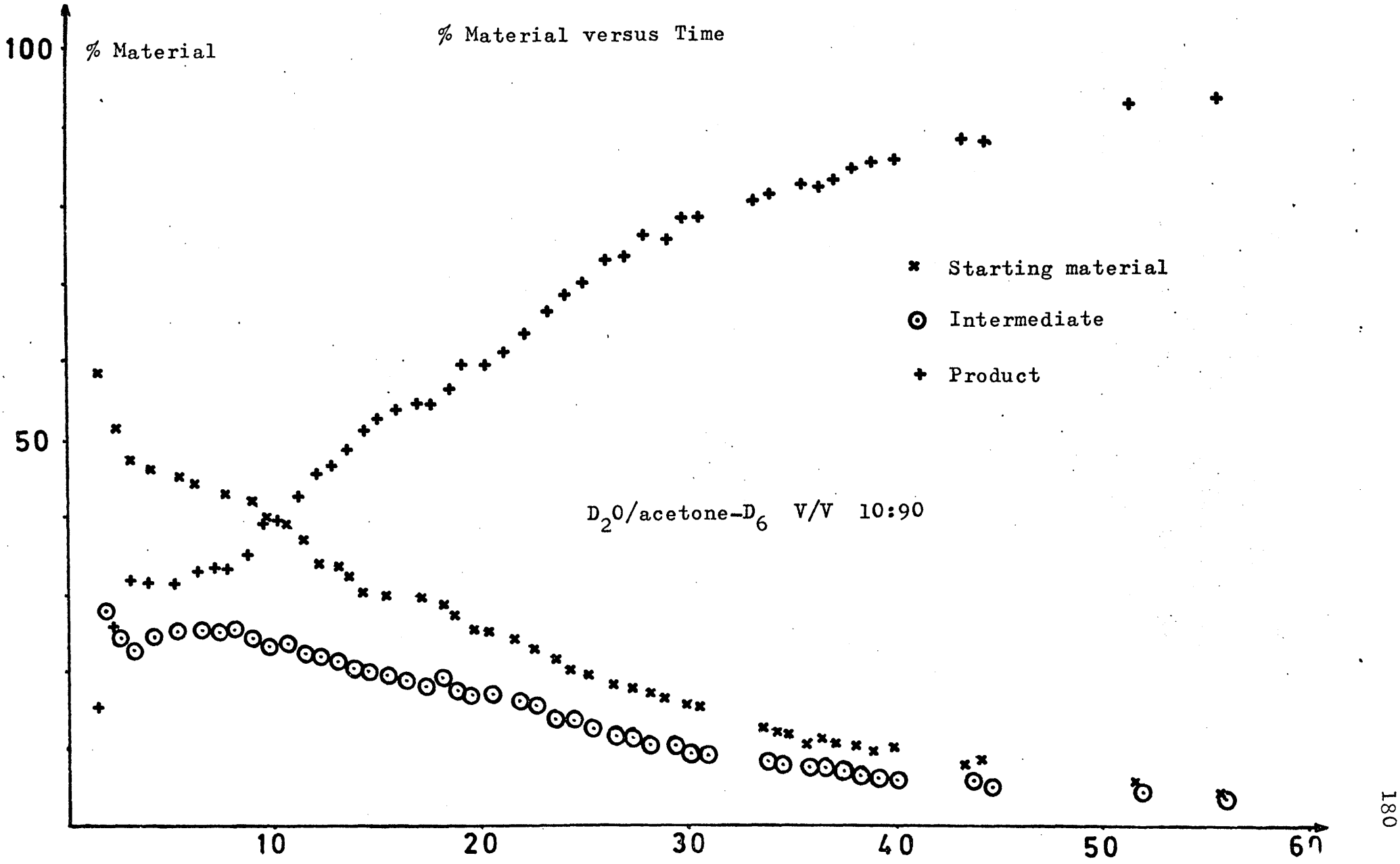

3.38δ
OCH3
6.17δ
H—C
OCH3
OCCH3
O
2.12δ
3.26δ
OCH3
5.27δ
H—C
OCH3
OD
CH3CO2D
2.02δ
8.22δ
O
H—C—OCH3
3.73δ
+
CH3OD
3.32δ
5.19δ
3.33δ
HC(OCH3)3

Fig. 107

Graph 2

Hydrolysis of acetoxy-dimethoxy-methane



trimethyl orthoformate are given, therefore, in fig. 107

Two plots of loss of starting material, formation of product and change in concentration of tetrahedral intermediate versus time are given in graphs 1 and 2. It can be seen that initially, over a period of ca 2.5 minutes, temperature equilibrium has not been attained resulting in an initial fast reaction (graphs 1 and 2). It can be seen that a 4% change in the D_2O concentration has resulted in an approximate 10-fold increase in the rate constant for the hydrolysis of the starting material (see graphs 1 and 2 ; and tables 27 and 28 for rate constants). The rate of hydrolysis of intermediate, however, does not seem to have changed to any extent. The complex kinetics in the second example (graph 2) has so far not allowed the calculation of the rate of formation of product.

The rate constants given in tables 24 to 26 for the hydrolysis of acetoxy-dimethoxy-methane and its resulting intermediate are those initially obtained. The later values recorded in tables 27 and 28 are further studies which first showed the inconsistency of the data being obtained when the composition of the mixed solvent D_2O/acetone-D_6 was only approximate. This data is presented only for completeness and should not be taken for any later comparisons.

Tables 27 and 28 represent the summary of the work carried on the hydrolysis of acetoxy-dimethoxy-methane where

the D_2O/acetone-D_6 ratio is known accurately.

During the hydrolysis of any of the acetoxy-compounds it is possible that the acetic acid, and hydronium ion, formed initially would catalyse further hydrolysis of the remaining starting material and tetrahedral intermediate. Unfortunately the experimental data is not good enough to distinguish this autocatalysis by the fitting to more accurate equations of the type,

$$-\frac{d[SM]}{dt} = k_o[SM] + k_{AcOH}[SM][AcOH] + k_H + [SM][H^+]$$

$$\frac{d[I]}{dt} = k_o'[I] + k_{AcOH}'[I][AcOH] + k_H' + [I][H^+] - \Big(k_o[SM] + k_{AcOH}[SM][AcOH] + k_H + [SM][H^+] \Big)$$

where [SM] is the concentration of starting material and [I] is the concentration of intermediate.

Within experimental error the results fitted the first order rate equation. Attempts to detect the catalysis by the liberated acetic acid by varying the concentration of starting material has led to random scatter (see tables Acid catalysis of the decomposition of starting material and tetrahedral intermediate has been observed under other conditions (see below).

The hydrolysis of 1-acetoxy-4,4,5,5-tetramethyl-1,3--dioxolan in D_2O/acetone-D_6 represents the observation of the

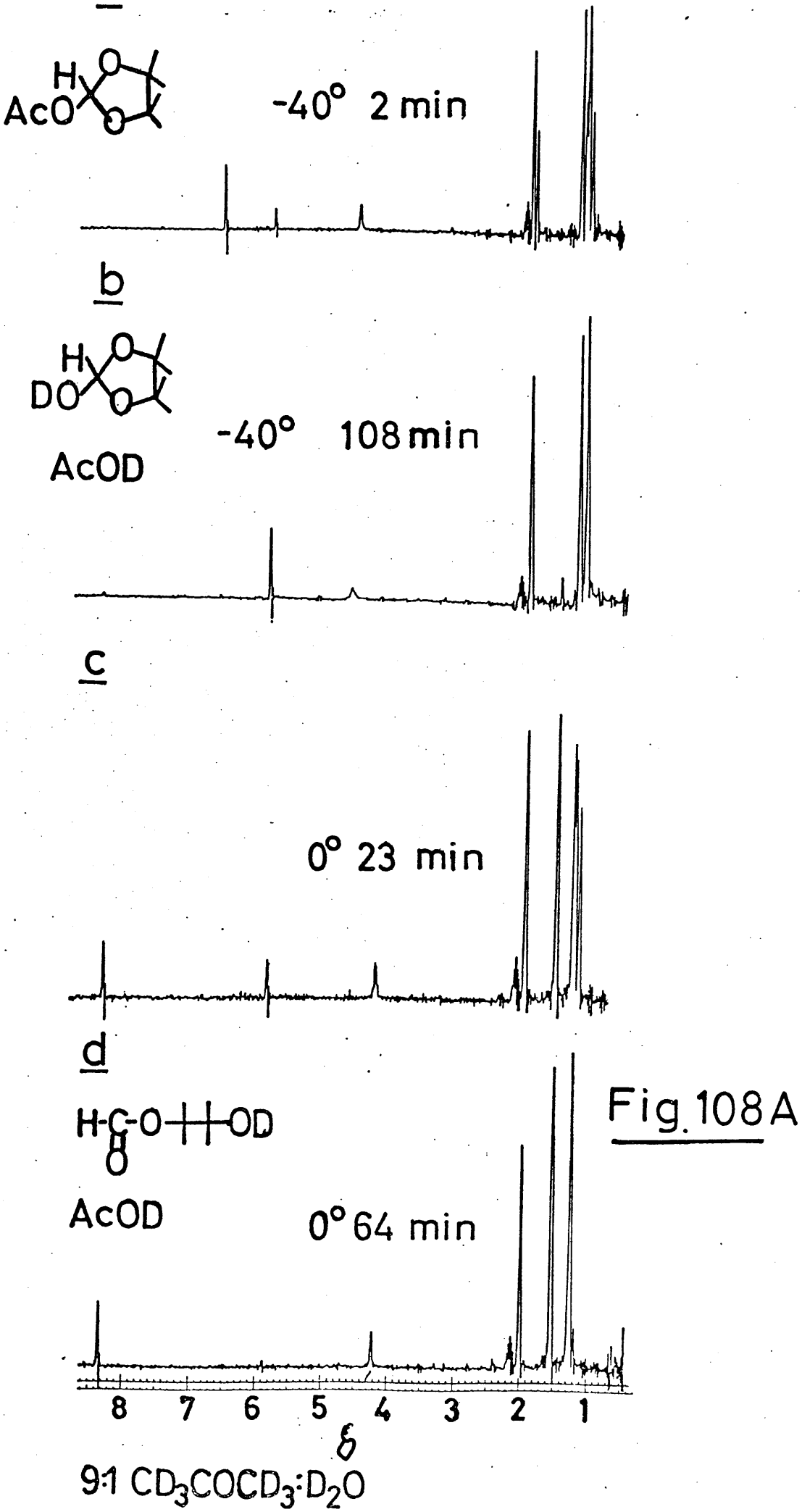

a
AcO
H
-40° 2 min
b
DO
H
AcOD
-40° 108 min
c
0° 23 min
d
H-C-O-OD
O
AcOD
0° 64 min
8
7
6
5
4
3
2
1
δ
9:1 CD3COCD3:D2O

Fig. 108A

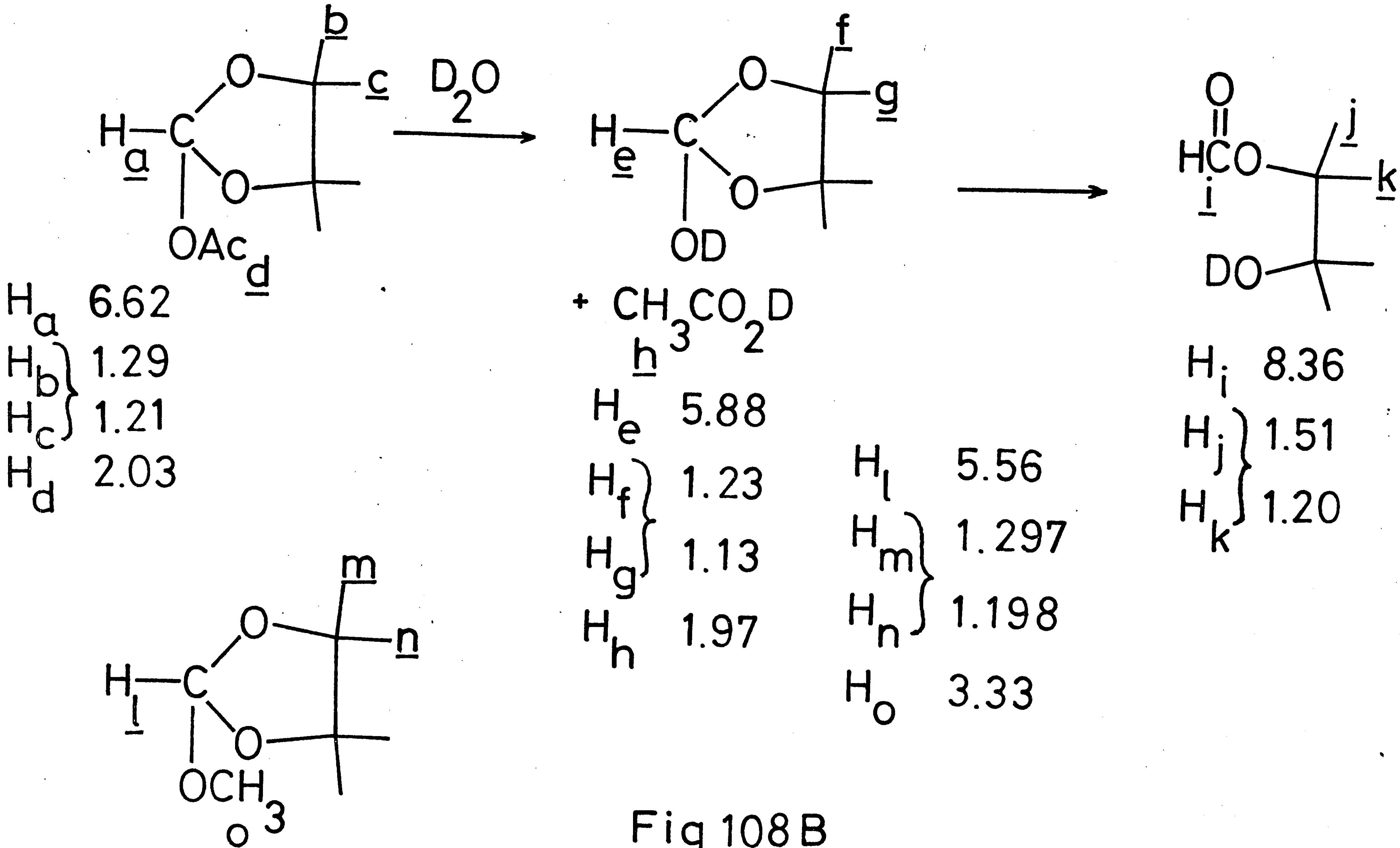
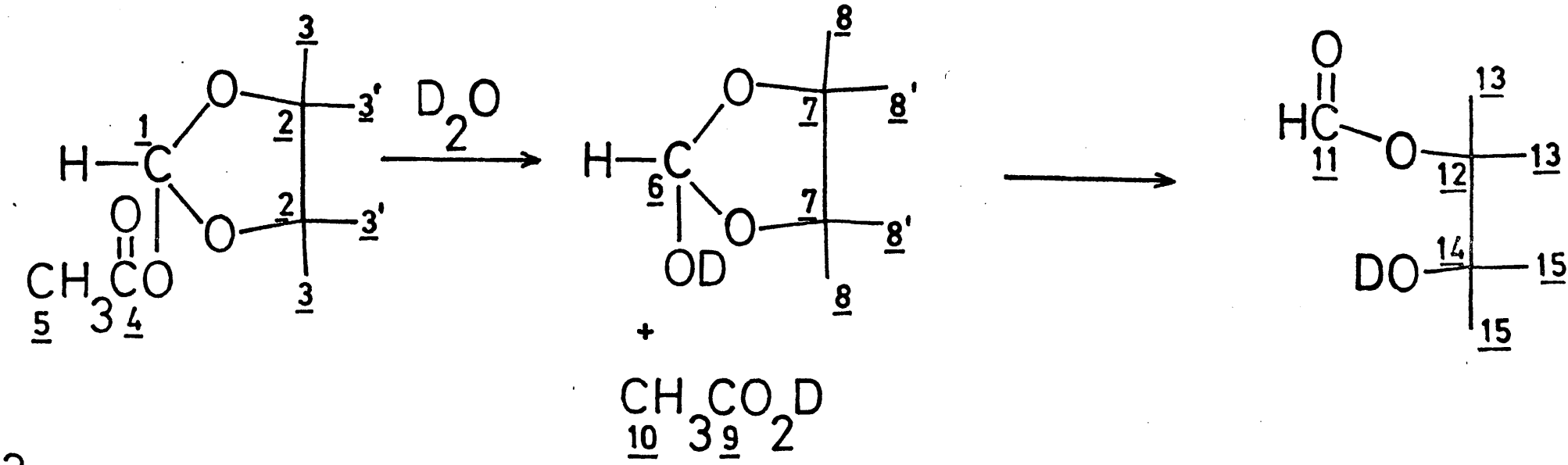

H a — C — OAc d
b
c
D2O
H e — C — OD
f
g
+ CH3CO2D
h
HCO
i
j
k
DO
Ha 6.62
Hb 1.29
Hc 1.21
Hd 2.03
He 5.88
Hf 1.23
Hg 1.13
Hh 1.97
Hi 8.36
Hj 1.51
Hk 1.20
H l — C — OCH3
m
n
o
Hl 5.56
Hm 1.297
Hn 1.198
Ho 3.33

Fig.108B

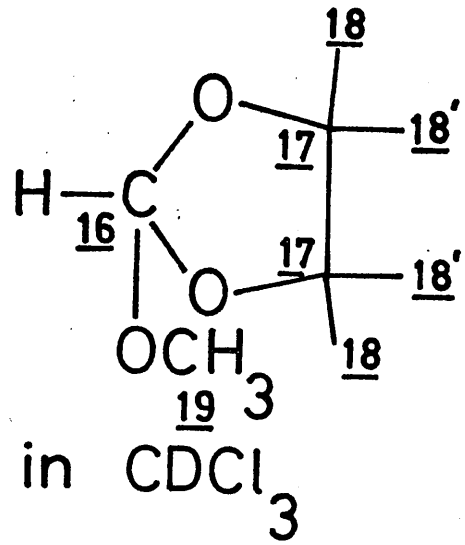
most stable tetrahedral intermediate studied in the investigation. Fig. 108A shows representative N.M.R. spectra at varying stages of the hydrolysis beginning initially at -40°C. Table 29 gives the calculated first order rate constants derived from this study. The loss of starting material can easily be observed by the loss of the acetoxy peak at 2.03δ and concurrent formation of acetic acid at 1.97δ. Similar replacement of the proton on the C_2 position of the dioxolan at 6.62δ by a new peak at 5.88δ and of the two peaks corresponding to the methyl groups of the starting material (at 1.29 and 1.21δ) by two new peaks at 1.23 and 1.13δ can easily be seen. The final spectrum obtained of this intermediate species is extremely similar to that observed for 1-methoxy-4,4,5,5-tetramethyl-1,3-dioxolan having the chemical shift shown in fig. 108B. The multiplet centred at 2.13δ is acetone while the broad peak at 4.12δ is water.

The formation of product is observed at a much slower rate than the loss of starting material and only becomes reasonably fast at -10 → 0°C. Therefore on warming to 0°C the intermediate spectrum (fig. 108A(b)) changes continuously with the loss of the peaks which had formed at -40°C and the formation of new peaks representative of the hydrolysed product (see fig. 108B for values). The complete loss of the intermediate species occurred after approximately 70 minutes. The rate constants are given in table 29(a) - (c).



C^{13} peaks (p.p.m.) in D_2O/D_6–Acetone

C_1	109.6	C_4	?	C_8 }	22.92	C_{11}	162.9
C_2	84.48	C_5	21.34	$C_{8'}$ }	22.87	C_{12}	87.55
C_3 }	23.55	C_6	109.92	C_9	?	C_{13}	25.09
$C_{3'}$ }	23.37	C_7	82.13	C_{10}	20.98	C_{14}	22.25



C_{15}	74.38
C_{16}	114.87
C_{17}	82.6
C_{18}	23.6
$C_{18'}$	23.15
C_{19}	52.6

Fig. 109

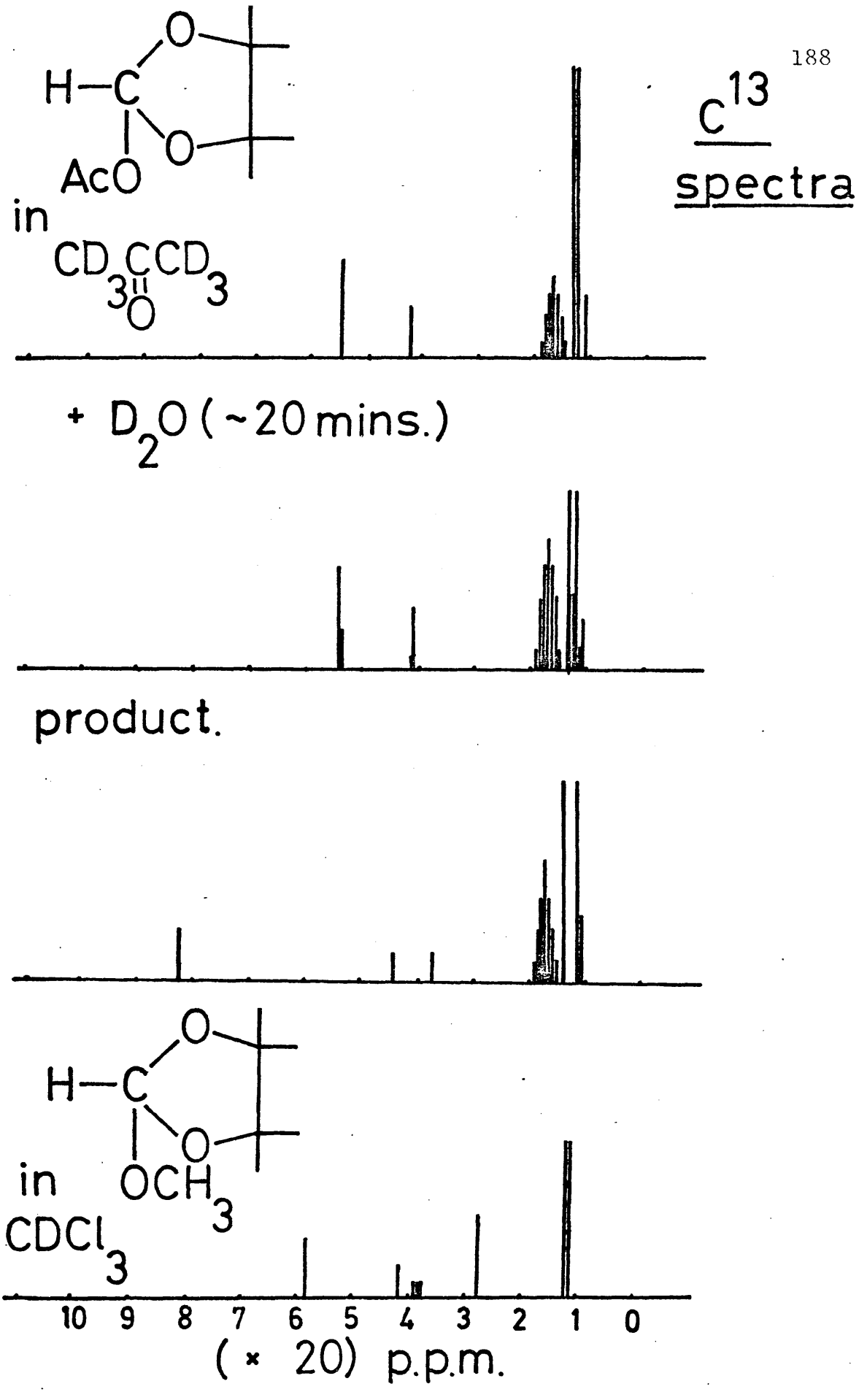

H
O
O
AcO
in
CD3CCD3
O
C13
spectra
+ D2O (~20 mins.)
product.
H
O
O
in OCH3
CDCl3
10 9 8 7 6 5 4 3 2 1 0
(× 20) p.p.m.

Fig.110

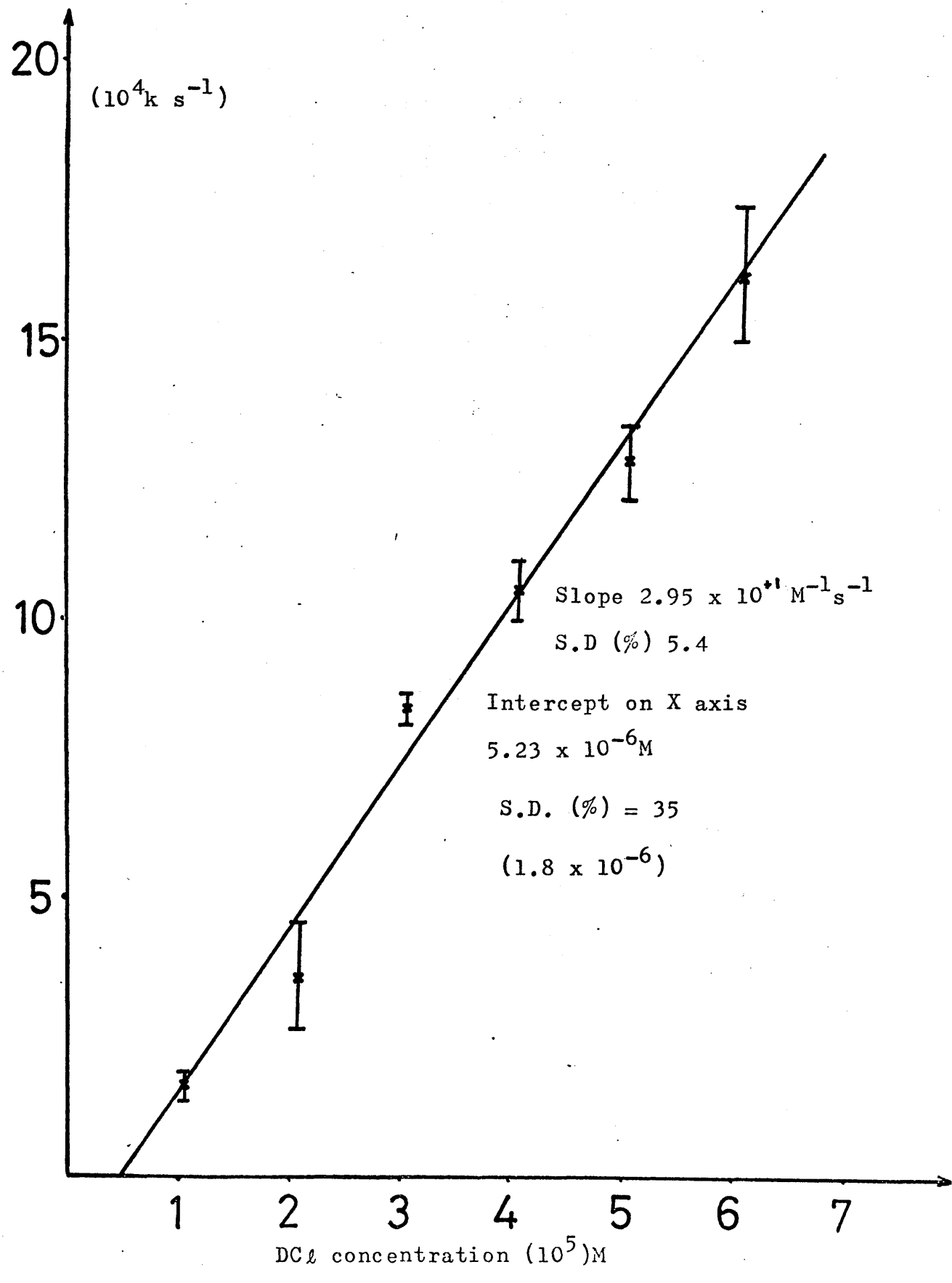
Under certain circumstances, as in the above study, the percentage of intermediate present at any one time could be as great as 95% as seen by proton N.M.R. It was thought, therefore, that studies of these tetrahedral intermediates could also be carried out by ^{13}C N.M.R. The limitations of this method, however, required that the lifetime of any intermediate had to be quite long to enable the Fourier Transform spectrum to be obtained clearly. These considerations therefore, limited the study to the hydrolysis of 1-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan and the resulting tetrahedral intermediate generated from it. The results of the assignment of peaks to functional groups in the starting material, intermediate and product are shown in fig. 109 together with the chemical shifts observed for 1-methoxy-4,4,5,5-tetramethyl-1,3-dioxolan.

The rapid loss of starting material, at -35°C, could clearly be seen by obtaining time averaged spectra at approximately 30 minute intervals. A much slower increase in product could be observed during this period. The final spectrum of the products of the reaction was obtained by warming the sample to ambient temperature and re-running the sample. Fig. 110 a - d are line drawings showing the observed spectra obtained during this study.

Graph 3

Hydrolysis of 1-hydroxy-4,4,5,5-tetramethyl-1,3-dioxolan

DCℓ/acetone-D_6 V/V 10:90 at -40°C



The study of the hydrolysis of 1-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan in deuterated hydrochloric acid/acetone-D_6 (V/V 1:9) (which was freshly made up before use) showed very pronounced acid catalysis, in fact, at no time was the starting material observed in these reactions. Graph 3 shows the change in the rate of hydrolysis of the tetrahedral intermediate versus acid concentration at -40°C derived from the calculated rates in table 31. While it could be deduced that the starting material and intermediates were both acid catalysed time did not allow the return to a study of the varying of substrate concentration at constant temperature in D_2O/acetone-D_6.

It can be seen that while a least squares calculation can be carried out on the results on graph 3 the line of best fit through the points has a negative intercept for zero acid concentration. The standard deviation of the intercept on the x-axis, is reasonably large ca 35%. An even greater standard deviation would be expected if consideration of the errors in each of the points had been taken into account. It seems reasonable to assume that the graph should in fact extrapolate through or very near to the origin within the errors of the experiment.

The study of the hydrolysis of 1-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan in sodium deuteroxide of 1.69×10^{-2}M in acetone-D_6 (V/V 1:9) at 20°C showed decreased quantities

of tetrahedral intermediate in this reaction (table 30). The starting material was present, in this case, for the whole reaction time.

At the end of the reaction the ratio of acid/acetate, for (15 μlitres) 8.1×10^{-5} moles of substrate used, and sodium deuteroxide concentration present from the beginning of the reaction, gave an acid/acetate ratio of 8.6. Throughout the reaction, however, the buffer ratio should be expected to change continuously from an alkaline solution to an acidic buffered solution. The rates of hydrolysis of the starting material are given in table 30 but are calculated on the basis of first order kinetics with no account being taken of the change in solution pH.

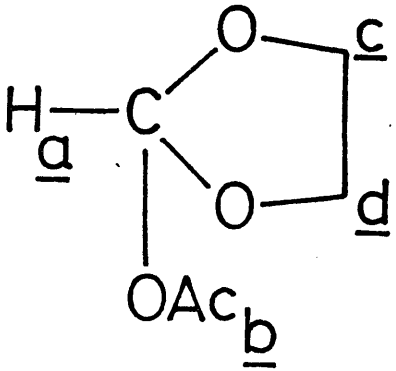
The hydrolysis of 1-chloroacetoxy-4,4,5,5-tetramethyl-1,3-dioxolan in D_2O/acetone-D_6 (1:9) showed no sign of starting material at -40°C when studying the C-H region (5-9δ) of the N.M.R. spectrum. The measurements of the rate constants for the hydrolysis of the tetrahedral intermediate, observed as having the same chemical shift of C_2-H (5.89δ), are given in table 32. These initial studies did not, however, allow the study so far of the complete N.M.R. spectrum due to lack of time. The value of the rate constant at 0°C would appear to be approximately 2-3 times faster than the rate of loss of the tetrahedral intermediate derived from 1-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan, however, care is taken in inter-

preting this large change from one value where only 10-15% of the reaction was studied and not so far repeated.

The study of the hydrolysis of acetoxy-diethoxy-methane by monitoring the C-H region (5-9δ) of the spectrum also showed the presence of a tetrahedral intermediate (C-H=5.21δ). Again lack of time did not allow the study of the whole spectrum as well as the calculation of reasonably accurate rate constants. However it was noted that the starting material, measured by the C-H peak (6.30δ) decayed very fast over a period of 4-8 minutes (in D_2O/acetone-D_6 V/V 1:9) giving a new peak (5.21δ) corresponding to the tetrahedral intermediate. This peak decayed at a slower measurable rate to product (C-H 8.0δ). The results of this study are given in table 33 where there is possibly a gradation of rate evidence as the substrate concentration is changed.

The study of acetoxy-diethoxy-methane in very weakly acidic solutions, (DCl/acetone-D_6) the acid concentration being 2×10^{-5}M and 5×10^{-5}M before dilution with acetone, showed very little difference in the rate constant for decomposition of the tetrahedral intermediate in D_2O/acetone-D_6 at the same temperature and concentration of substrate (table 34).

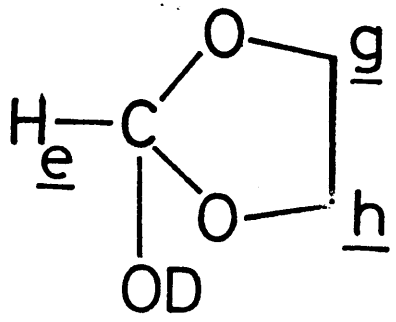
It should be noted at this stage that the temperature of solvent and rate of mixing greatly affected the length of time over which the starting material was observed in all these reactions.



H_a 6 77

H_b 2 01

H_c, H_d 4 1(m)



+

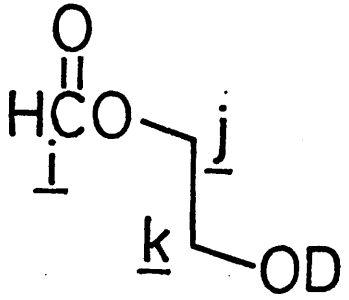
CH_3CO_2D

f

H_e 5 97

H_f 1 96

H_g, H_h 6 05(m)



H_i 8.17

H_j 4.21(t) 3.6 Hz.

H_k 3 75(t)

H_l 5 59

H_m 3 24

H_n, H_o 3 94(m)

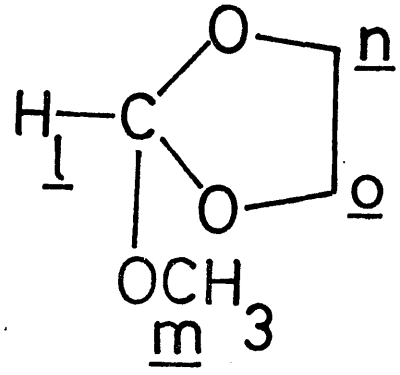


Fig. 111

Preliminary studies in acetate buffer/acetone-D_6 at -40°C, (see table 35), showed the loss of acetoxy-diethoxy--methane over the whole reaction interval. At no time did the starting material disappear completely while the tetrahedral intermediate was being observed. Although first order rate constants have been calculated the effect on the rate of changing buffer ratio is not known. The final buffer ratio, at the end of the reaction, would be expected to be 14.3:1. A direct, comparison of this ratio to the previous study of the different precursor, 1-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan in NaOD/acetone, is difficult in view of the different intermediates likely to be obtained.

Limited time did not allow the study and calculation of rate constants for the hydrolysis of chloroacetoxy-diethoxy--methane.

As already stated in the experimental section initial studies on the hydrolysis of 2-acetoxy-1,3-dioxolan in D_2O/acetone-D_6 (V/V 1:9) showed no evidence for the existence of a tetrahedral intermediate (table 36). However later studies showed that by changing the D_2O/acetone-D_6 ratio the tetrahedral intermediate could be seen with loss of the starting material being fast enough to obtain the rate of hydrolysis of the tetrahedral intermediate (table 37).

The hydrolysis study in D_2O/acetone-D_6 at -35°C showed in the first spectrum measured both starting material and intermediate with a small trace of product. The loss of starting material could be seen by the decrease in both the C-H peak (C_2 of dioxolan) and the increase in the corresponding C-H peak (C_2) of the tetrahedral intermediate. The peak corresponding to the acetoxy group of the starting material could also be seen to decrease concurrently an increase in another peak corresponding to acetic acid could be observed. Approximately 27% product had been formed when all the starting material had disappeared. It should be expected that by increasing the water concentration even further the rate of loss of starting material should be speeded up to a much greater extent than the loss of tetrahedral intermediate. The loss of intermediate could be seen quite clearly by observing the C-H peak (C_2 of dioxolan and formate peak of product) region of the spectrum. No change was observed in the acetate region during this period. In the $-CH_2-$ region (C_4 and C_5 of dioxolan etc.) it was much more difficult to observe and separate the multiplets since starting material and intermediate overlapped considerably. The $-CH_2-$ region of the product was slightly clearer in that two separated multiplets could be observed at the end of the reaction, one of which had partly overlapped with the $-CH_2-$ region of the intermediate. (See fig. 111 for values).

Direct comparisons of the rates of hydrolysis of the different acetoxy compounds and their tetrahedral intermediates is difficult in view of the various temperatures and D_2O/acetone-D_6 ratios in which the reactions were studied, only qualitative comparisons are, therefore, really possible under these circumstances.

Table 13 shows the values of the rate constants for the different acetoxy compounds. Similarly table 14 shows the values of the rate constants for hydrolysis of the tetrahedral intermediates obtained from these compounds.

Variation in the rates of hydrolysis of the starting acetoxy compounds would appear to be rather small, increasing by a factor of 2 to 3 where the steric effects may likely act to assist the expulsion of the acetoxy group. A very similar picture is seen for the hydrolysis of the corresponding ortho esters[167] with a slight decrease in rate with the 2-methoxy-1,3-dioxolan (table 15). The hydrolysis of the hemiorthoformates shows a slightly different picture with the hydrolysis of 1-hydroxy-4,4,5,5-tetramethyl-1,3-dioxolan being very much slower. In both dioxolan systems, slower than the acyclic reactions, the cleavage in this case is that of an endocyclic bond whereas for both the orthoesters and the acetoxy compounds cleavage of an exocyclic bond was rate determining. (See also table 38 for comparison of hydrolysis of an orthoester under conditions used).

Table 13 — The hydrolysis of the acetoxy-compounds

Concentration of starting material ($\times 10^2$)M	Compound	Rate Constant $10^4 k(s^{-1})$	Temperature	Solvent Ratio[a]
2.0 (15 µlitres)	acetoxy-dimethoxy-methane	3.33	-35°C	50:450
-	acetoxy-diethoxy-methane	-	-	-
2.0 (15 µlitres)	1-acetoxy-1,3-dioxolan	1.24	-35°C	50:450
1.6 (15 µlitres)	1-acetoxy-4,4,5,5-tetra-methyl-1,3-dioxolan	4.24	-40°C	50:450

a. Solvent D_2O/acetone-D_6

Table 14 The hydrolysis of the hemiorthoformates

Concentration of starting material ($\times 10^2$)M	Compound	Rate Constant $10^3 k(s^{-1})$	Temperature	Solvent Ratio[a]
2.0 (15 µlitres)	hydroxy-dimethoxy-methane	1.15	-35°C	70:430
1.8 (15 µlitres)	hydroxy-diethoxy-methane	1.0	-40°C	50:450
2.0 (15 µlitres)	1-hydroxy-1,3-dioxolan	0.358	-35°C	70:430
1.6 (15 µlitres)	1-hydroxy-4,4,5,5-tetra-methyl-1,3-dioxolan	0.40	-10°C	50:450

a. Solvent D_2O/acetone-D_6.

Table 15 The hydrolysis of orthoesters [a]

Compound	Rate Constant $10^3 k(s^{-1})$	HA [b]	10^2[HA] M
Trimethylorthoformate	1.70	$H_2PO_4^-$	6.67
Triethylorthoformate	6.02	$H_2PO_4^-$	6.67
1-methoxy-1,3-dioxolan	0.675 [c]	$H_2PO_4^-$	6.67
1-methoxy-4,4,5,5-tetra-methyl-1,3-dioxolan	1.90	$H_2PO_4^-$	6.67

a. Temperature + 25°C.

b. solvent-water. buffer ratio.

c. Value obtained by multiplying the value for 2-(2-methoxyethoxy)-1,3-dioxolan given in table 1 by the ratio of the values of 2-methoxy-1,3-dioxolan to that of 2-(2-methoxy-ethoxy)-1,3-dioxolan in table 2.

DISCUSSION

Hydrolysis of orthoesters

The study of the hydrolysis of cyclic orthoesters, by Deslongchamps,[136] as has been described in the introduction, showed the absence of lactone in the products. In order to explain his results it was necessary to assume that the tetrahedral intermediate formed broke down to products faster than any change in its conformation could occur.

Two points became prominent from the present work in this thesis, the first being that tetrahedral intermediates did exist and were observable over quite long time intervals, and second, that preliminary work on the hydrolysis of 1-methoxy-1-phenoxy-tetrahydropyran (in an attempt to generate a further tetrahedral intermediate) strongly suggested that both hydroxy-methyl -ester and methanol were being produced. If the reaction proceeded as reported by Deslongchamps equal signals for the alcohol and alkyl ester should be observed. If however any lactone were formed this should lead to the signal for the alcohol becoming much greater than the ester signal. Also the integrals of the protons ($-CH_2-$) adjacent to the oxygen in the lactone ring should be equally noticeable. This led, as shown in the Experimental Section, to the study of the much more easily available orthoesters, dimethoxytetrahydropyran and diethoxytetrahydropyran under Deslongchamps' conditions (slightly modified)* and in mixed solvents. The results of

* See Experimental Section page 263

this work are summarised in tables 39 to 44.

What the results in fact show is that both δ-valerolactone and hydroxy-alkoxy-ester are formed in the hydrolysis. Similar observations are obtained with the diethoxy compound.

The results have been communicated to Professor Deslongchamps,** who has since confirmed them and obtained a similar result for the hydrolysis of dimethoxytetrahydrofuran. On the other hand he has stated that only the hydroxy-ester was found in the bicyclic system shown in fig. 114. The main problem arising in Deslongchamps' original study was that of the acetylation of the hydroxyester by the reaction with pyridine/acetic anhydride followed by vapour phase chromatography. Two possible sources of error in the results could have occurred from firstly the possible polymerisation of the lactone under these conditions or alternatively the loss of the lactone when the excess pyridine/acetic anhydride was removed under high vacuum.

Studies of the hydrolysis of dimethoxytetrahydropyran in DCl/acetone-D_6 solutions have shown the stability of the products (lactone and hydroxy-esters) even up to quite high acid concentrations where only slow acid hydrolysis was observed (table

Studies by ^{13}C N.M.R. of the hydrolysis of diethoxy-tetrahydropyran in D_2O (with 10^{-3} M toluene-p-sulphonic acid)/acetone-D_6 mixture has also shown the presence of lactone. A comparison of the peak heights of the products suggests

** Personal Communication

that δ-valerolactone is present as 25% of the hydroxy-ester. It should be noted, however, that comparison of the peak heights in ^{13}C N.M.R. spectra is not necessarily very accurate due to a difference in the Nuclear Overhauser Effects for the different molecules. The ^{13}C N.M.R. results are given together with a schematic representation of the spectrum shown in fig. 112.

The lack of specificity in the cleavage of these cyclic orthoesters together with the result that hydrolysis of the bicyclic ring structure (see above **) gave only one product is initially a little disconcerting. Two possible explanations can be forwarded to explain these results. The first is, obviously, in view of the existence as stated earlier of tetrahedral intermediates having possible long lifetimes, the rate of conformational inversion is faster than that of breakdown of the tetrahedral intermediate. The second is that conformational motion on going to the initial transition state, on loss of the alcohol function, is greatly affected by whether the axial or equatorial group leaves.

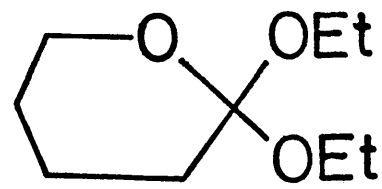
The breaking of the axial bond in dimethoxytetrahydropyran may result in a carbenium ion in a half chair conformation as shown in fig. 113. Breaking of the equatorial bond, however, may result in the generation of the ion in the boat conformation via route b since a conformational change in the orthoester into the twist boat conformation would be required if any assistance of the loss of the leaving group was invoked by antiperiplanar orbitals.

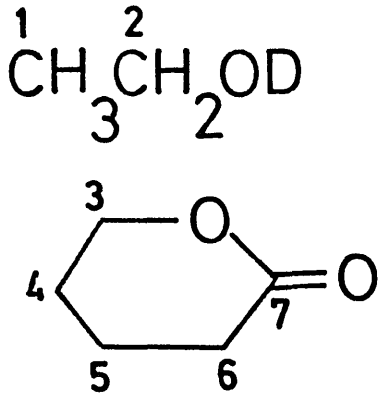
C_1	18.46 Hz.	C_6	30.13 Hz.	C_{11}	34.37 Hz.
C_2	57.47 ··	C_7	172.20 ··	C_{12}	174.11 ··
C_3	69.80 ··	C_8	61.65 ··	C_{13}	60.52 ··
C_4	22.77 ··	C_9	32.58 ··	C_{14}	14.45 ··
C_5	19.46 ··	C_{10}	22.04 ··		

Key for ^{13}C values.

C^{13} spectrum of the products of

D_2O / D_6–Acetone V/V 1/9





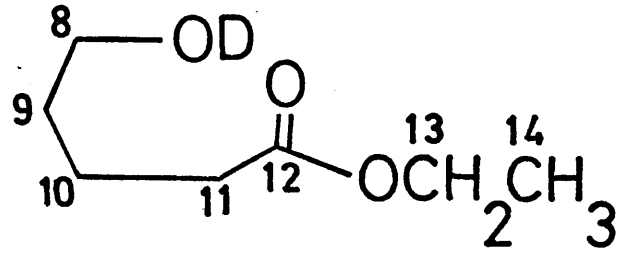


Fig. 112

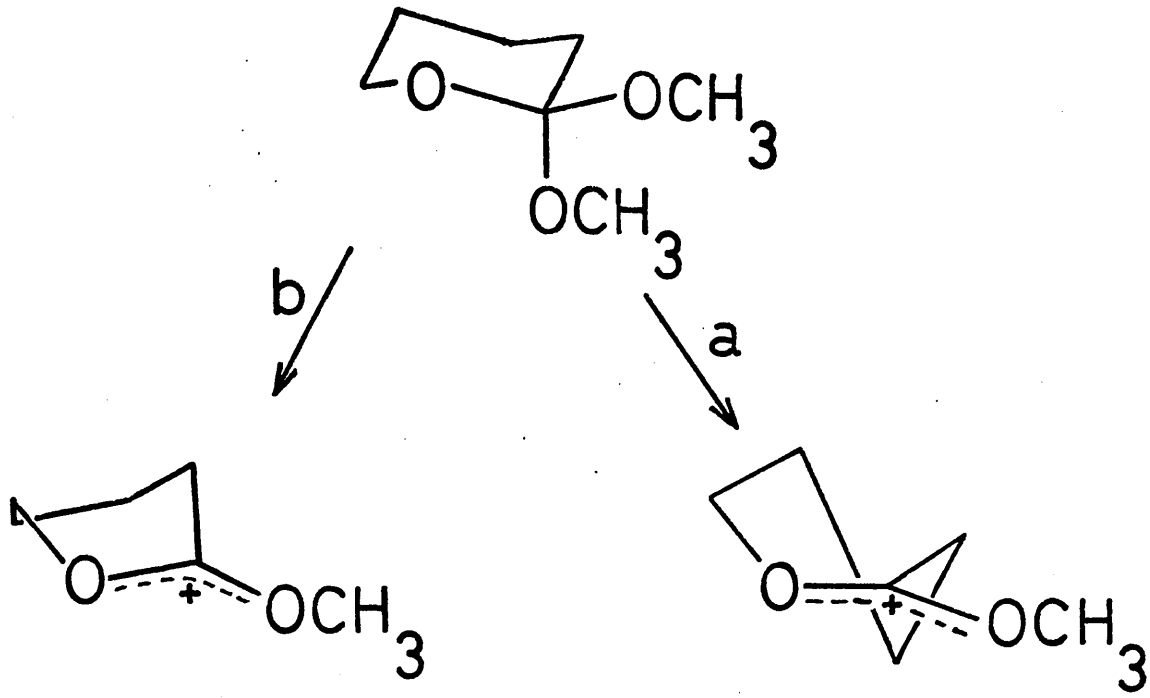


Fig.113

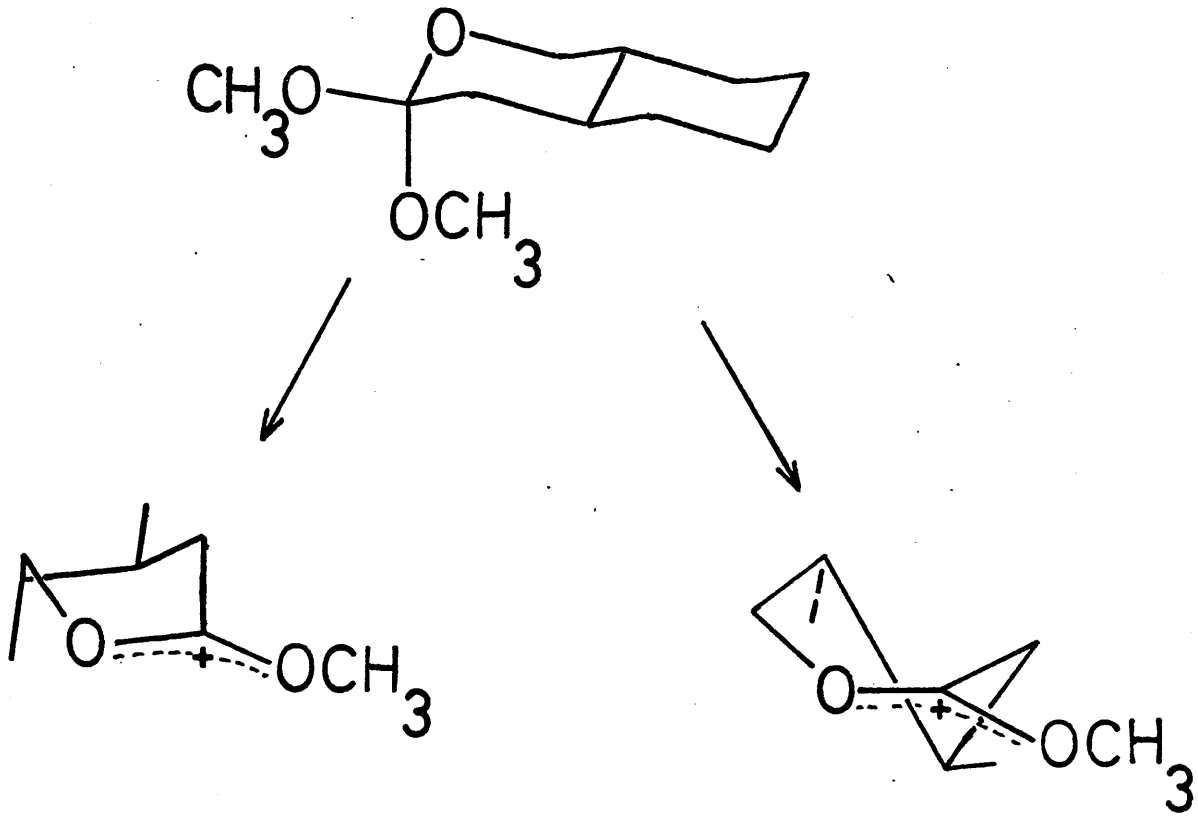


Fig.114

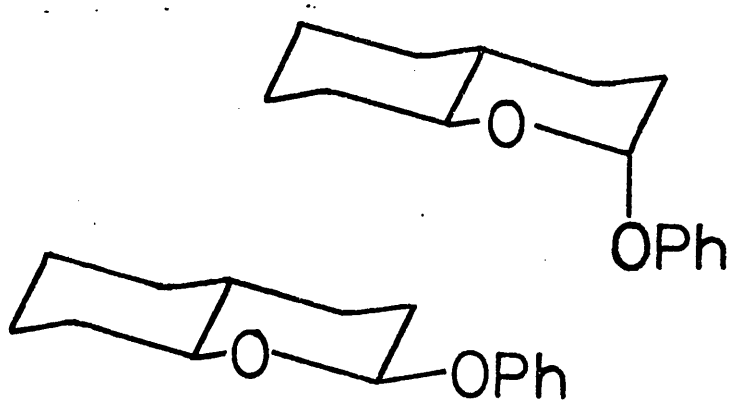


Fig.115

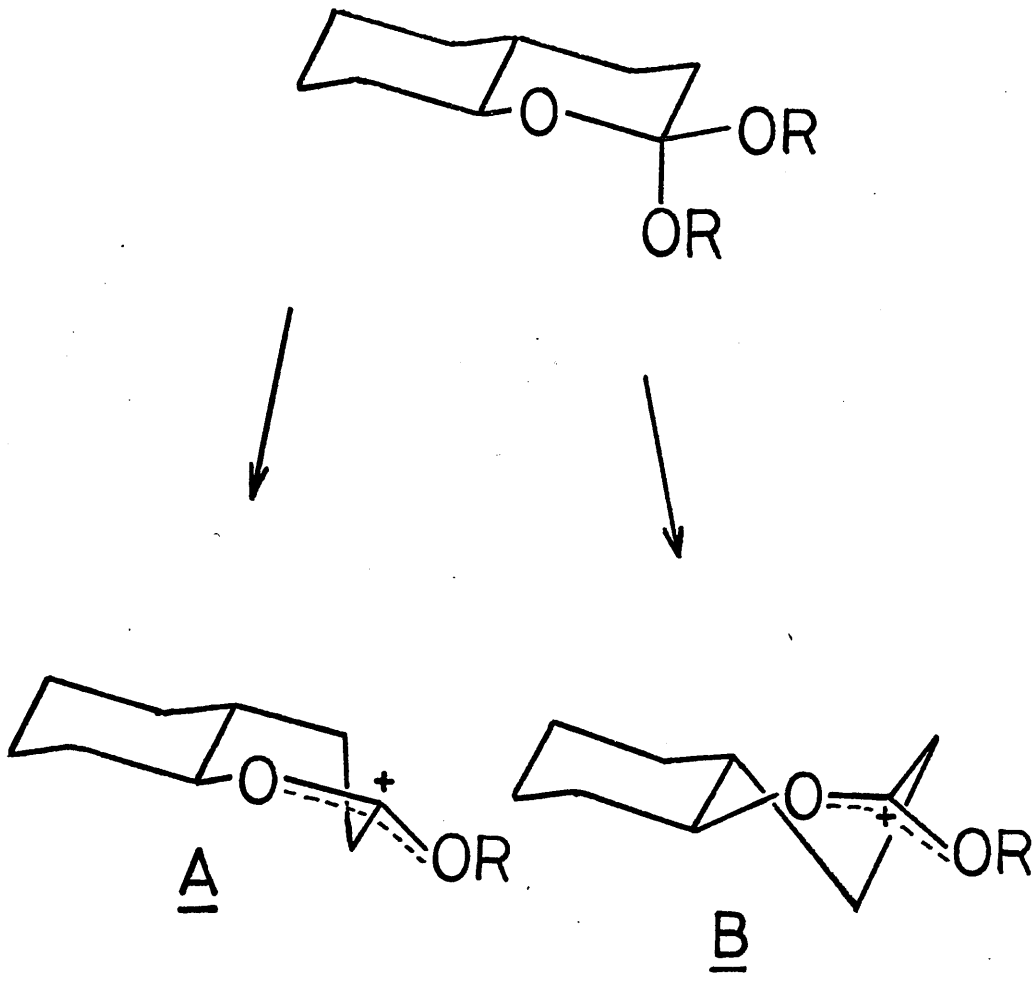


Fig.116

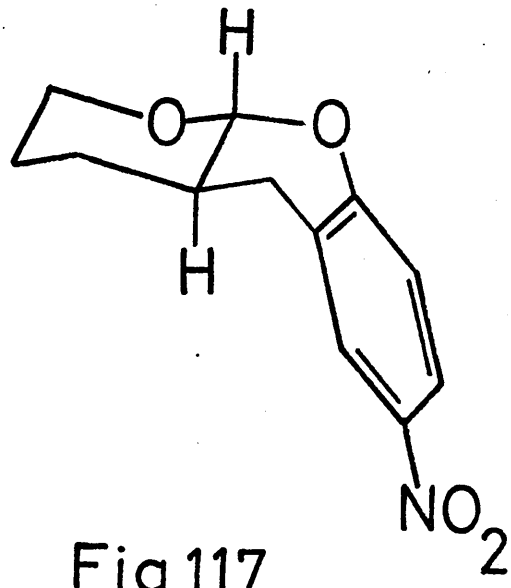


Fig.117

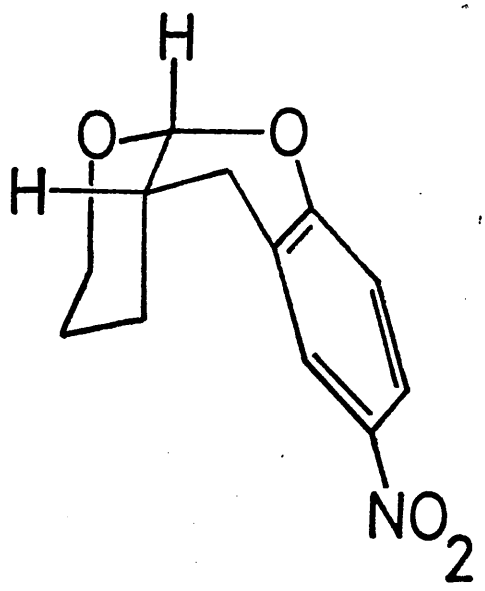


Fig.118

Competitive cleavage, therefore, of axial or equatorial carbon-oxygen bonds of the alkoxy groups (assuming little or no cleavage of the ring carbon-oxygen bond) if the two conformations, half-chair and boat, were of equal or similar stability. The little information that exists on the relative stabilities of the conformations of valerolactones tends to suggest that both conformations are relatively similar in energy. The implication in the case of the ions 1 and 2 would seem quite evident.

Fission in the hydrolysis of the bicyclic orthoester where the second ring is fused trans would favour axial carbon-oxygen bond cleavage (see figure 114), equatorial bond fission resulting in much greater strain in the formation of a boat conformation.

Hydrolysis of the cyclic acetal (fig. 115) by Chandrasekhar and Kirby[170] showed no rate increase of the axial anomer over the equatorial anomer in contrast to what would have been expected via stereoelectronic control as is proposed by Deslongchamps. The difference in rates of hydrolysis has been explained purely in terms of the different ground state energies suggesting that the difference in transition state energies is very little. The small difference in transition state energies can easily be explained by invoking the arguments of the previous discussion of dialkoxytetrahydropyrans since

the transition state carboxonium ions of the Type A and B should not differ greatly in energy (fig. 116).

An extension and possible speculation from this work is the likely observation that the products of hydrolysis of orthoester should consist of both lactone and hydroxyester since cleavage of the axial and equatorial carbon-oxygen bonds should not differ in transition state energy.

As a continuing study on acetal hydrolysis Kirby and Martin[171] have studied the tricyclic acetals (see figs. 117 and 118). These differ in lone pair orbital alignment, in that, acetal (fig. 117) has no lone pair orbital antiperiplanar to the (p-nitrophenyl oxygen) leaving group (the molecule being locked in one conformation due to the trans ring junction). Comparisons of the rates of hydrolysis have shown stereoelectronic control (antiperiplanar orbitals assisting the expulsion of the leaving group in the second acetal (see fig. 118) is quite prominent. Acetal (fig. 118) hydrolyses at least 3000 times faster than acetal (fig. 117). It was further shown that both acetals differ also in their rate determining step; C-O bond cleavage in the former and hydration in the latter. These results are in stark contrast to Kirby et al[170] previous study (fig. 115) where no stereoelectronic control effects had been observed between the two semi-rigid isomers.

DISCUSSION - Negative Results.

The Hydrolysis of N,N-Dimethylformamide Dimethyl Acetal and O-Methyl-N,N-Dimethylformidenium Methylsulphate.

The lack of observation of hydrolysis intermediates, by N.M.R., with N,N-dimethylformamide dimethyl acetal does not necessarily rule out the participation of tetrahedral intermediates. The possibility of the formation of two different intermediates is shown in fig. 119. The rate of hydrolysis of the tetrahedral intermediate dimethoxy-hydroxy-methane is very much faster than that of N,N-dimethyl-formamide dimethyl acetal. The rate measurements were carried out at -35°C for the former and 0°C for the latter. The other possible intermediate, N,N-dimethylformamide methyl hemiacetal would also be expected to hydrolyse at least as rapidly as that of dimethoxy-hydroxy-methane. The rate determining step of the hydrolysis of N,N-dimethylformamide dimethyl acetal is, therefore, likely not to be the decomposition of any intermediate.

This conclusion is supported by attempts to generate N,N-dimethylformamide methyl hemiacetal directly from the hydrolysis of O-methyl-N,N-dimethylformamidenium methylsulphate.

Although it was possible to find hydrolysis conditions where the starting material could be observed, no intermediates were ever detected presumably because the ion is so stable. It reacts more slowly with water than the intermediate undergoes breakdown.

The Hydrolysis of 1-N,N-diethyl-Prop-1-yne

The hydrolysis of 1-N,N-diethyl-prop-1-yne also did not show any presence of any tetrahedral intermediate. Previous studies[178] on related compounds have shown that the rate determining step is the reaction with water, subsequent reactions being much faster. It is highly unlikely that any observation of tetrahedral intermediates will or would be obtained by this route.

The Hydrolysis of Carboxonium Salts

Hydrolysis of the carboxonium salts showed immediate hydrolysis with no sign of starting materials or intermediates but only products were observed. The question arises as to the reason of this extremely fast hydrolysis. Assuming, for the present, the formation of tetrahedral intermediates the possibility and probability of acid catalysis producing extremely fast hydrolysis is apparent. The observation of a sudden increase in temperature also suggests the possibility of the hydrolysis via solution "hot spots" and hence hydrolysis at a much higher temperature than would be expected under the conditions studied. The probability/possibility that all carboxonium salts would give similar results suggests that no observation of tetrahedral intermediates should be possible. A rather important point, however, is the observation of a tetrahedral intermediate by Kresge et al[90] from 2-phenyl-1,3-

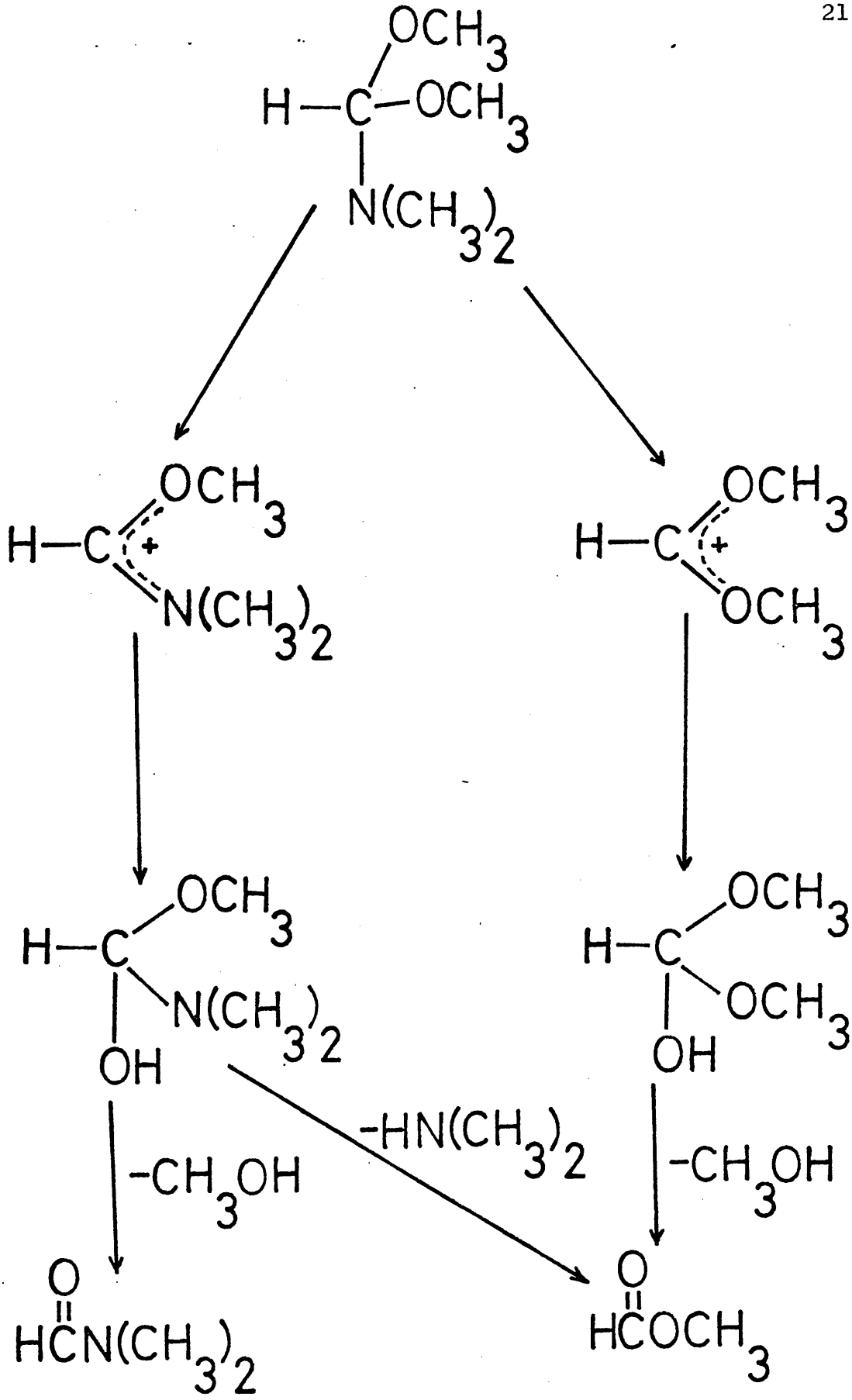

OCH3
H—C—OCH3
N(CH3)2
OCH3
H—C
N(CH3)2
OCH3
H—C
OCH3
OCH3
H—C
N(CH3)2
OH
OCH3
H—C
OCH3
OH
-HN(CH3)2
-CH3OH
-CH3OH
O
HCN(CH3)2
O
HCOCH3

Fig. 119

dioxolenium fluoroborate by stopped flow spectroscopy. The possibility of "mixing problems" may, therefore, be an explanation for the lack of any tetrahedral intermediates. The observation of similar "mixing problems" in the hydrolysis of acylated compounds where formation of orthoesters could be observed under certain hydrolysis conditions also adds thought to this possible explanation.

Acyl Migration

Attempts to show possible recyclisation of two esters, ethylene glycol monoformate and pinacol monobenzoate, in various acid solutions and temperatures, failed under the initial conditions studied. It would seem that studies of pinacol monoformate may be a better substrate for observation of this equilibria in view of the restricted rotation in the pinacol residue and little steric repulsion being present with a simple hydrogen rather than aromatic function.

PREPARATIVE EXPERIMENTAL

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

I.R. spectra were determined using either a Perkin Elmer 225, Perkin Elmer 257 or a Perkin Elmer 580 spectrometer. The following abbreviations were used: sh = sharp, b = broad, m = medium.

N.M.R. (nuclear magnetic resonance spectroscopy) spectra were determined for routine work on a Varian T60 (60 MHz) or a Perkin Elmer R32 (90 MHz) N.M.R. spectrometer. Low and high temperature work was carried out on either a Perkin Elmer R32, Varian HA100 (100 MHz) or Varian XL100 spectrometer. Chemical shifts were measured downfield from internal tetramethyl silane and are quoted in both Hertz (Hz) and delta values. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, the chemical shift of d, t and q are quoted for the centre of the signal. The value of the integration for a particular peak is quoted as e.g. 4H i.e. the integration is equivalent to 4 hydrogens relative to other signals. Coupling constants are given, after the integration, in Hertz.

Elemental analyses were carried out in the University of Glasgow and are quoted as percentages.

All compounds obtained commercially were checked by N.M.R. for purity and usually purified before use.

PREPARATION OF 2 METHOXY-1,3-DIOXOLANS.

The methoxy-1,3-dioxolans were prepared by the method of Kankaanpera[1] by the transorthoesterification of equimolar amounts of trimethyl orthoformate and the 1,2-alkanediols using toluene-p-sulphonic acid as catalyst. The methanol liberated was azeotroped with benzene.

PREPARATION OF 2-METHOXY-2-PHENYL-1,3-DIOXOLAN.

2-methoxy-2-phenyl-1,3-dioxolan was prepared by the method of Rieche, Schmitz and Beyer[2] by the reaction of equimolar quantities of trimethyl orthobenzoate and dry ethylene glycol, with toluene-p-sulphonic acid as catalyst. The reaction time was limited to reduce the possibility of the side reaction of dimerisation.

PREPARATION OF OXONIUM FLUOROBORATE SALTS.

Both trimethyl and triethyl oxonium fluoroborates were obtained from Lancaster Synthesis. In addition the latter was sometimes synthesised by the method of Meerwein[7] by the reaction of epichlorohydrin and boron trifluoride etherate.

PREPARATION OF TETRAMETHYLAMMONIUM ACETATE.

The preparation of tetramethylammonium acetate was carried out by the method described by Fieser and Fieser.[4]

Tetramethylammonium hydroxide and acetic acid were allowed to react at room temperature and the solid obtained, on

evaporation, was crystallised from acetone, dried in a vacuum desiccator, recrystallised from dry acetonitrile and redried in the vacuum desiccator before use.

PREPARATION OF SODIUM PHENOXIDES.

The phenol, in dried N,N-dimethylformamide (DMF), was added to a cooled suspension of sodium hydride in DMF. The sodium phenoxide was obtained by evaporation and drying in a vacuum desiccator.

PREPARATION OF TETRAMETHYLAMMONIUM PHENOXIDE.

Equimolar quantities of tetramethylammonium hydroxide and phenol were shaken until all the phenol dissolved. This solution was then left for 3 hours and the solvent removed under vacuum. The solid material was recrystallised twice from dry acetonitrile and dried under vacuum for several days.

PREPARATION OF SILVER BENZOATE.

This material was prepared as described by Fieser and Fieser[5] and dried under vacuum for several days.

PREPARATION OF DIMETHOXYCARBENIUM FLUOROBORATE.

The preparation of the fluoroborate salt was carried out, in a dry box, by the method of Borch.[6]

To 5.5 mls (50 m moles) of trimethyl orthoformate at -30°C was added a solution of 7.3 mls (56 m moles) of boron trifluoride etherate in 6 mls of dry methylene chloride, dropwise with

stirring, over 5 minutes. The mixture was brought to 0°C stirred for 15 minutes, cooled to -30°C and filtered. The solid product was suspended in 5 mls of methylene chloride at -70°C, the lumps broken up, and refiltered. Traces of solvent were removed under vacuum.

PREPARATION OF DIMETHOXY, PHENYLCARBENIUM FLUOROBORATE.

The method of preparation by Meerwein et al[7] was followed by the reaction of trimethyl orthobenzoate, in o-dichlorobenzene, with boron trifluoride etherate in a dry box. It should be noted that this fluoroborate salt reacted quite quickly with diethyl ether and acetonitrile to give their corresponding fluoroborate salts; filtering of the ethereal solution had, therefore, to be quite fast and complete to stop major decomposition of the material.

PREPARATION OF 2-PHENYL-1,3-DIOXOLENIUM FLUOROBORATE.

Similarly the preparation of this salt was carried out by the method of Meerwein[7] in a dry box. The reaction of this salt with acetonitrile was much slower.

PREPARATION OF METHYL δ-VALEROLACTONIUM FLUOROBORATE.

The preparation of this compound is given in the preliminary section of the synthesis of 2,2-dimethoxytetrahydropyran.

PREPARATION OF O-METHYL-N,N-DIMETHYLFORMIDENIUM METHYLSULPHATE.

The preparation of this compound was carried out by the method Bredereck, Effenberger and Simchen[8] by the reaction of equimolar quantities of N,N-dimethylformamide and dimethyl sulphate, at 70°C, the resulting liquid being checked for purity by (N.M.R.) nuclear magnetic resonance spectroscopy.

PREPARATION OF 2,3-DIBROMO-2,3-DIMETHYL-BUTANE.

2,3-dibromo-2,3-dimethyl-butane was prepared by the method of Johnson[9] by the reaction of pinacol and phosphorous tribromide in benzene solution. The yield obtained was approximately 80% on recrystallisation from benzene.

m.p. 74.5 - 75.5°C white solid.

N.M.R. ($CDCl_3$) 90 MHz. 180 Hz, 1.997δ(s)

I.R. (CCl_4) ν cm^{-1}. 3000, 2985, 2940, 2872 sh (C-H aliphatic)
535 sh (C-Br stretch).

microanalysis. Found: C, 29.5; H, 4.97;
Calc. for $C_6H_{12}Br_2$: C, 29.53; H, 4.92%.

PREPARATION OF 2-PHENYL-4,4,5,5-TETRAMETHYL-1,3-DIOXOLAN.

Equimolar quantities of benzaldehyde, pinacol and trimethyl orthoformate, with toluene-p-sulphonic acid as catalyst, were heated and the methanol formed collected by distillation. The residual liquid was treated with K_2CO_3, filtered, and distilled under reduced pressure.

b.p. 78 - 79°C at 0.65 mm Hg. f.p. 24°C.

lit. value[9] 82 - 83°C at 1.4 mm Hg.

N.M.R. ($CDCl_3$) 90 MHz. 110 Hz, 1.22δ(s, 6H); 115 Hz, 1.28δ(s, 6H); 536 Hz, 5.96δ(s, 1H); 648 - 682 Hz, 7.2 - 7.58δ(m, 5H).

microanalysis. Found: C, 75.7; H, 8.84;

Calc. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.74%.

PREPARATION OF 2-PHENYL-2,4,4,5,5-PENTAMETHYL-1,3-DIOXOLAN.

Equimolar quantities of acetophenone, pinacol and trimethyl orthoformate, with toluene-p-sulphonic acid as catalyst, were heated and the methanol formed collected by distillation. The residual liquid was treated with K_2CO_3, filtered and distilled under reduced pressure.

b.p. 63 - 64°C at 0.8 mm Hg.

lit. value[10] 77 - 78°C at 1.2 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 61 Hz, 1.01δ(s, 6H); 68 Hz, 1.133δ (s, 6H); 97 Hz, 1.63δ(s, 3H); 131 - 162 Hz, 2.18 - 2.75δ(m, 5H).

I.R. (CCl_4) ν cm^{-1}. 3095, 3065, 3015 (C-H aromatic) 3000, 2980, 2940 (C-H aliphatic).

PREPARATION OF BENZALDEHYDE Di-t-BUTYL ACETAL.

The procedure of Cawley and Westheimer[12] was followed by the reaction of benzal chloride with excess potassium t-butoxide under reflux. The benzal chloride and t-butanol were dried and

distilled immediately before use.

b.p. 47 - 48°C at 0.6 mm Hg. clear liquid

58 - 60°C at 1 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 73 Hz, 1.2 δ(s, 18H); 342 Hz, 5.7 δ(s, 1H); 404 - 456 Hz, 6.73 - 7.6 δ(m, 5H).

90 MHz. 109.8Hz, 1.22 δ(s, 18H); 515 Hz, 5.72 δ(s, 1H); 646 - 675 Hz, 7.18 - 7.50 δ(m, 5H).

I.R. (neat) ν cm^{-1} 2975, 2930 b (CH_3 stretch).

3025, 3060 m (C-H aromatics).

2860 (C-H acetal).

1450, 1456 m (CH_3 deformation, asymmetric).

1390, 1363 m (CH_3 deformation, symmetric).

1095, 1064, 1043, 1004 (acetal, C-O-C-O-C stretch).

PREPARATION OF α-ACETOXY-α-t-BUTOXY-TOLUENE.[13]

Equimolar quantities of benzaldehyde di-t-butyl acetal and dry acetic anhydride were heated gently under a nitrogen atmosphere, the reaction being monitored by N.M.R. until completion. Low pressure distillation yielded the product (~80% yield).

b.p. 51°C at 0.08 mm Hg. clear liquid.

N.M.R. ($CDCl_3$) 60 MHz. 80 Hz, 1.33 δ(s, 9H); 124 Hz. 2.06 δ(s, 3H); 421 Hz, 7.0 δ(s, 1H); 434 - 460 Hz, 7.22 - 7.67 δ(m, 5H).

90 MHz. 116 Hz, 1.29δ(s, 9H); 181 Hz, 2.01δ(s, 3H); 627 Hz, 6.97δ(s, 1H); 651 - 677 Hz, 7.23 - 7.52δ(m, 5H).

I.R. (neat) ν cm^{-1} 3015, 3030 (C-H stretch, aromatics). 2970, 2930 (CH_3 stretch). 2865 (C-H acylal). 1730 b (carbonyl stretch). 1450, 1472 sh (CH_3 deformation asymmetric) 1365 b, 1389 sh (CH_3 deformation symmetric). 1240 b (carbonyl C-O stretch). 1115, 1070, 1025, 1004 (C-O-C-O-C stretch).

microanalysis. Found: C, 70.20; H, 8.27;

$C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%.

PREPARATION OF α-t-BUTOXY-α-CHLOROACETOXY-TOLUENE.

Benzaldehyde di-t-butyl acetal (0.2 moles) and chloroacetic anhydride (0.1 moles) were allowed to react at room temperature until completion of the reaction. The mixture was then distilled under high vacuum (0.01 mm Hg) leaving the α-t-butoxy-α-chloroacetoxy-toluene. At no time was the temperature allowed above 60°C.

Yield ~ 70% clear liquid.

N.M.R. ($CDCl_3$) 90 MHz. 115.0 Hz, 1.28δ(s, 9H); 352 Hz, 3.91δ(s, 2H); 631 Hz, 7.01δ(s, 1H); 646 - 677 Hz, 7.18 - 7.52δ(m, 5H).

(neat liquid unlocked) 90 MHz. 109.0 Hz, 1.21δ(s, 9H); 348 Hz, 3.87δ(s, 2H); 638 Hz, 7.09δ(s, 1H); 648 - 662 Hz, 7.2 - 7.36δ(m, 3H); 666 - 686 Hz, 7.4 - 7.62δ(m, 2H).

I.R. (CCl_4) ν cm^{-1} 3075, 3042 sh (C-H aromatics). 2980, 2940, 2910 b (C-H aliphatics). 1760 b (carbonyl stretch).

Microanalysis. Microanalysis of the compound could not be obtained due to continuous decomposition.

PREPARATION OF ACETOXY-DIMETHOXY-METHANE(DIMETHOXY-METHYL ACETATE.

Method 1.[14] Trimethyl orthoformate was dissolved in liquid SO_2 at -80°C and bromine added. The resulting salt was then reacted with acetic acid and the solution allowed to warm up to room temperature. No sign of acetoxy-dimethoxy-methane was found; the resulting N.M.R. spectrum consisted of only the hydrolysed product. No further experiments were carried out.

Method 2. Equimolar quantities of trimethyl orthoformate and acetic anhydride were refluxed under nitrogen and the reaction monitored by N.M.R. spectroscopy. After approximately 50-60% reaction (before too much decomposed material had formed) the resulting solution was initially distilled under water vacuum from

normal distillation apparatus to yield the crude acetate/ anhydride mixture. This was then purified by very slow distillation through a spinning band column to yield pure acetoxy-dimethoxy-methane.

b.p. 67 - 68°C at 35 mm Hg. clear liquid.

lit. value.[14] 69°C at 35 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 205 Hz, 3.42δ(s, 6H); 126 Hz, 2.1δ(s, 3H); 371 Hz, 6.18δ(s, 1H).

I.R. (CCl_4) ν cm^{-1}. 3004 sh, 2951 b, 2910 m (CH_3 stretch).
2845 sh (methoxy stretch).
1755 b (carbonyl stretch).
1452-1393 b (CH_3 deformation).

microanalysis. Found: C, 44.51; H, 7.6;

Calc. for $C_5H_{10}O_4$: C, 44.77; H, 7.51%.

Method 3. To a solution of dimethoxycarbenium fluoroborate in dry methylene chloride, at -78°C under dry nitrogen, was added a slight excess of dry acetic acid. The mixture was stirred for 1 hour at this temperature and then allowed to warm up to room temperature. No product was obtained.

Method 4. Equimolar quantities of the fluoroborate salt and tetramethylammonium acetate were mixed, in a dry box, at room temperature (the former was in methylene chloride solution, the latter in nitromethane). The reaction was exothermic

but the desired product was not observed by N.M.R.

The reaction was repeated, in a sealed system under nitrogen, by the addition of the nitromethane solution to a cooled solution of the fluoroborate, at -78°C, but the desired product was not obtained.

Method 5. The preparation of acetoxy-dimethoxy-methane was carried out by the method of Scheeren and Stevens[15] using the mixed formic acid/acetic anhydride with trimethyl orthoformate at room temperature. The reaction was monitored by N.M.R. and distilled before a build-up of the decomposition material occurred. Yield ~ 55%.

b.p. 48°C at 20 mm Hg. clear liquid.

lit. value[14] 69°C at 35 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 205 Hz. 3.42δ(s, 6H); 126 Hz, 2.10δ(s, 3H); 372 Hz, 6.20δ(s, 1H).

90 MHz. 310 Hz, 3.45δ(s, 6H); 186 Hz, 2.07δ(s, 3H); 554 Hz, 6.15δ(s, 1H).

100 MHz. 324 Hz, 3.42δ(s, 6H); 208 Hz, 2.08δ(s, 3H); 617 Hz, 6.17δ(s, 1H).

I.R. (CCl_4) ν cm^{-1}. 3004, 2951, 2910 (CH_3 stretch).

2845 sh (methoxy stretch).

1755 b (carbonyl stretch).

1452, 1394 (CH_3 deformation).

PREPARATION OF 2-ACETOXY-1,3-DIOXOLAN.

The preparation of 2-acetoxy-1,3-dioxolan was carried out by the method of Scheeren, Van der Veek and Stevens[16] by allowing a mixture of 2-methoxy-1,3-dioxolan (0.2 moles), acetoxy-dimethoxy-methane (0.2 moles) and dry acetic acid (0.4 moles) to react under reduced pressure (15-20 mm) for approximately 10 hours followed by fractionation through a spinning band column.

b.p. 41-43°C at 0.4 mm Hg. clear liquid.
55-56°C at 0.8 mm Hg.

lit. value[15] 42-43°C at 0.4 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 118.8 Hz, 1.98 δ(s, 3H); 245 Hz. 4.08 δ(m, 4H); 410 Hz, 6.83 δ(s, 1H).
90 MHz. 182 Hz, 2.02 δ(s, 3H); 369 Hz, 4.10 δ(m, 4H); 615.5 Hz, 6.84 δ(s, 1H).
100 MHz. 202 Hz, 2.02 δ(s, 3H); 411 Hz, 4.11 δ(m, 4H); 680 Hz, 6.80 δ(s, 1H).

I.R. (CCl_4) ν cm^{-1}. 2990, 2975 b (C-H aliphatic)
2908 (CH_2-O stretch)
1750 b (carbonyl C=O)

PREPARATION OF 2-ACETOXY-4,4,5,5-TETRAMETHYL-1,3-DIOXOLAN.

The product was obtained by a method similar to that used for the synthesis of 2-acetoxy-1,3-dioxolan.

b.p. 58-59°C at 0.8 mm Hg.

lit. value[15] 50-51°C at 0.4 mm Hg.

N.M.R. ($CDCl_3$) 60 MHz. 123 Hz, 2.05δ(s, 3H); 74 Hz, 1.23δ(s, 6H); 80 Hz, 1.33δ(s, 6H); 404 Hz, 6.73δ(s, 1H).

90 MHz. 182 Hz, 2.02δ(s, 3H); 109 Hz, 1.21δ(s, 6H); 118 Hz, 1.31δ(s, 6H); 602 Hz, 6.69δ(s, 1H).

100 MHz. 204 Hz, 2.04δ(s, 3H); 111 Hz, 1.11δ(s, 6H); 116 Hz, 1.16δ(s, 6H); 670 Hz, 6.70δ(s, 1H).

I.R. (CCl_4)ν cm^{-1} 2998, 2980 b (C-H aliphatic).

2935 b (C-H aliphatic).

1750 (carbonyl stretch).

PREPARATION OF ACETOXY-DIETHOXY-METHANE(DIETHOXYMETHYL ACETATE).

This compound could be obtained by the reaction of triethyl orthoformate with acetic anhydride or the mixed formic acid/acetic anhydride[15] but was obtained commercially from the Aldrich Chemical Company. This material was distilled before use.

b.p. 64-65°C at 20 mm Hg.

lit. value[14] 60°C at 11 mm Hg.

N.M.R. ($CDCl_3$) 90 MHz. 567 Hz, 6.30δ(s, 1H); 333 Hz, 3.70δ(q, 4H, 7.65 Hz); 185.5 Hz, 2.06δ(s, 3H); 109 Hz, 1.21δ(t, 6H, 7.65 Hz).

I.R. (CCl_4) ν cm^{-1} 2980 b (C-H aliphatics).
2903, 2938 (C-H aliphatics).
1751 (carbonyl stretch).

PREPARATION OF CHLOROACETOXY DERIVATIVES.

Method 1. All attempts to synthesise the chloroacetoxy compounds directly from the orthoesters were unsuccessful.

Method 2. The preparation of these chloroacetoxy derivatives was carried out by a method similar to that of Scheeren et al[16] by reacting equimolar quantities of the acetoxy compound and chloroacetic acid with heating under reduced pressure in a spinning band column. The acetic acid was distilled off slowly (bottom temperature being kept below 50°C). The remaining liquid was then distilled under high vacuum.

CHLOROACETOXY-DIETHOXY-METHANE Yield ~ 80%

b.p. 61-63°C at 0.07 mm Hg. clear liquid.

N.M.R. ($CDCl_3$) 60 MHz. 386 Hz, 6.43δ(s, 1H); 249 Hz, 4.15δ(s, 2H); 235 Hz, 3.92δ(q, 4H, 7Hz); 83 Hz, 1.38δ(t, 6H, 7Hz).

microanalysis: Found: C, 42.98; H, 6.35; Cl, 18.19;
$C_7H_{13}O_4Cl$ requires C, 42.76; H, 6.65; Cl, 18.1%.

2-CHLOROACETOXY-4,4,5,5-TETRAMETHYL-1,3-DIOXOLAN.

b.p. 108-110°C at 0.03 mm Hg. clear liquid. Yield ~ 80%.

N.M.R. ($CDCl_3$) 60 MHz. 409 Hz, 6.82δ(s, 1H); 243 Hz, 4.05δ(s, 3H); 79 Hz, 1.32δ(s, 12H).
90 MHz. 608.5 Hz, 6.76δ(s, 1H); 365.5 Hz, 4.06δ(s, 3H); 113.5 Hz, 1.26δ(s, 12H).

microanalysis: No satisfactory microanalysis could be obtained due to continuous decomposition while samples were being made up for analysis.

2-CHLOROACETOXY-1,3-DIOXOLAN.

Although 2-chloroacetoxy-1,3-dioxolan was observed by N.M.R. during the reaction, isolation of the pure material could not be carried out by distillation under the conditions used due to decomposition of the material.

PREPARATION OF 2,2-DIALKOXY-TETRAHYDROPYRANS.

The preparation of these compounds was carried out by the method of Deslongchamps.[17]

δ-Valerolactone (10 m moles) and trialkyloxonium fluoroborate (10 m moles) were dissolved in anhydrous dichloromethane under dry nitrogen. The solution was magnetically stirred at room temperature for the period of the reaction (in the case of triethyloxonium fluoroborate approximately 3-4 hours; trimethyloxonium fluoroborate was stirred overnight).

When the fluoroborate salt was required it was isolated by the addition of dry ether until the solution became turbid. The solution was kept at 0°C overnight and the resulting crystals filtered in a dry box.

For the synthesis of the dialkoxy compound the fluoroborate salt in solution was added dropwise, to a precooled solution (-78°C) of sodium alkoxide (30 m moles) in 35 mls of alcohol,

under a nitrogen atmosphere. The reaction was then magnetically stirred at -78°C for approximately 1 hour. The mixture was allowed to warm up to room temperature and ether was added. The organic phase was washed with aqueous sodium bicarbonate, dried over potassium carbonate and evaporated to dryness yielding crude orthoester. Purification was by vacuum distillation.

2,2-DIMETHOXY-TETRAHYDROPYRAN.

b.p. 27-28°C at 0.7 mm Hg. Clear liquid
58-60°C under water vacuum.

N.M.R. ($CDCl_3$) 60 MHz. 84-108 Hz, 1.4-1.8 δ(m, 6H); 194 Hz, 3.25 δ(s, 6H); 225 Hz, 3.78 δ(t, 2H, 6Hz).
90 MHz. 121.5-157.5 Hz, 1.35-1.75 δ(m, 6H); 290 Hz, 3.22 δ(s, 6H); 335.5 Hz, 3.73 δ(t, 2H, 5.4 Hz).

d_6-acetone 90 MHz. 112.5-153 Hz, 1.25-1.70 δ(m, 6H); 282 Hz, 3.13 δ(s, 6H); 329.4 Hz, 3.66 δ(t, 2H, 4.95 Hz).

I.R. (CCl_4)ν cm^{-1} 2965, 2920 sh (C-H stretch)
2880 sh (CH_2-O stretch)
2840 sh (CH_3-O stretch)
1340, 1350, 1358, 1362 (CH_3 deformation, symmetric)
1440, 1455, 1470 (CH_3 deformation, asymmetric)

1105, 1113, 1140, 1154, 1171, 1193
1040, 1048, 1052, 1085 (C-O stretch).

2,2-DIETHOXY-TETRAHYDROPYRAN.

b.p. 32-34°C at 0.5 mm Hg. Clear liquid

lit. value[17] 72-74° at 20 mm Hg.

N.M.R. ($CDCl_3$) 90 MHz. 105.7 Hz, 1.17δ(6, 6H, 7.29 Hz); 117-162 Hz, 1.3-1.8δ(m, 6H); 318 Hz, 3.54δ(q, 4H, 7.29 Hz); 337 Hz, 3.74δ(t, 2H, 4.0 Hz).

I.R. (CCl_4) ν cm^{-1} 2975, 2943, 2935 b (C-H aliphatics). 2890 b (C-H aliphatics). 1040, 1055, 1080 (C-O-C stretch).

ATTEMPTED PREPARATION OF 2-ACETOXY-2-METHOXY-TETRAHYDROPYRAN.

Method 1. The attempted method of preparation was similar to the preparation of 2-acetoxy-1,3-dioxolan by allowing 2,2-dimethoxy-tetrahydropyran (0.02 moles), acetoxy-dimethoxy-methane (0.02 moles) and acetic acid (0.04 moles) to react with heating under reduced pressure. The reaction was continually monitored by N.M.R. for completion of the reaction. The products obtained were δ-valerolactone (observed by N.M.R.) and by low pressure distillation methyl 5-acetoxyvalerate.

b.p. 54-55°C at 0.2 mm Hg. Clear liquid.

N.M.R. ($CDCl_3$) 90 MHz. 139-161 Hz, 1.55-1.79δ(m, 4H); 180 Hz, 2.0δ(s, 3H); 210 Hz, 2.33δ(5, 2H, 6.3 Hz); 329 Hz, 3.66δ(s, 3H); 3.66 Hz, 4.07δ(t, 2H, 5.76 Hz).

I.R. (CCl_4) ν cm^{-1}. 2960 b (C-H aliphatics).
2880, 2850 (C-H aliphatics).
1745 (carbonyl C=O).

microanalysis: Found: C, 55.26; H, 8.28;
Calcd. for $C_8H_{18}O_4$ C, 55.16; H, 8.10%

Method 2. Method 1 was repeated but no heating was carried out. The reaction time was limited to 25 minutes then low boiling components were removed under high vacuum. The resulting liquid contained only methyl 5-acetoxyvalerate and starting material.

Method 3. O-Methyl-δ-valerolactonium fluoroborate (0.05 moles) was dissolved in dry dichloromethane and 18-crown-6-ether (0.003 moles) was added. Dry potassium acetate (0.05 moles), pulverised, was added to the above solution, cooled to -78°C, with continuous stirring, the whole system being kept under a dry nitrogen atmosphere. The reaction mixture was stirred at -78°C for 1 hour but on warming to room temperature and working up, as method 1, the N.M.R. spectrum showed only methyl 5-acetoxy-valerate and methyl acetate.

Method 4. Method 3 was repeated using the hexafluoroantimonate salt (obtained from the reaction of δ-valerolactone and trimethyloxonium hexafluoroantimonate). The N.M.R. spectrum of the resulting solution showed the presence of methyl 5-acetoxy-valerate and methyl acetate as before.

Method 5. Method 4 was repeated using tetramethylammonium acetate, instead of 18-crown-6/potassium acetate. The same products as those of the other methods were obtained.

ATTEMPTED PREPARATION OF α-ACETOXY-α,α-DIMETHOXY-TOLUENE.

Method 1. Equimolar quantities of trimethyl orthobenzoate and dry acetic anhydride were heated gently under nitrogen with constant monitoring by N.M.R. The only products observed were methyl benzoate and methyl acetate.

Method 2. The mixed formic acid/acetic anhydride system was reacted with trimethyl orthobenzoate at room temperature and monitored by N.M.R. The same products, as those in method 1, were obtained.

Method 3. All the following reactions were carried out at ambient temperature in sealed N.M.R. tubes.

(a) Equimolar quantities of trimethyl orthobenzoate, acetoxy-dimethoxy-methane and acetic acid were monitored by N.M.R. The products noted were methyl benzoate, etc. with no sign of the required material.

(b) Trimethyl orthobenzoate and acetoxy-dimethoxy-methane were mixed in equimolar amounts. The products obtained were as before.

(c) Trimethyl orthobenzoate and acetoxy-dimethoxy-methane were mixed in volumetric ratio 3:1 respectively. The products obtained were as before.

(d) Equimolar quantities of trimethyl orthobenzoate and acetoxy-dimethoxy-methane were mixed with a trace of toluene-p-sulphonic acid as catalyst but the same products were obtained.

Method 4. Dimethoxy phenyl carbenium fluoroborate (0.038 moles) was dissolved in dry ethylene chloride (1,2 dichloro-ethane) and added dropwise under nitrogen to a solution containing acetic acid (0.038 moles) and 2,6-lutidine (0.076 moles) at -78°C. The reaction was stirred, at this temperature for 1 hour before warming to room temperature. The products were as before.

Method 5. Dimethoxy phenyl carbenium fluoroborate was dissolved in dry methylene chloride and 18-crown-6 ether added (see previous reaction to synthesise 2-acetoxy-2-methoxy-tetrahydropyran). Potassium acetate was added to this cooled solution at -78°C but on warming after 1 hour the products were as before.

Method 6. Equimolar quantities of the fluoroborate salt and acetoxy-dimethoxy-methane were dissolved in o-dichloro-benzene at room temperature. No acetoxy compound was observed by N.M.R. Problems would have arisen in the isolation of the product if it had been formed.

Method 7. Equimolar quantities of trimethyl orthobenzoate and dry acetic acid were heated gently in benzene under nitrogen and monitored by N.M.R. The products obtained were methyl benzoate, methanol and methyl acetate.

Method 8. 1,1-dimethoxy-1-phenoxy-toluene (0.02 moles) and acetic anhydride (0.01 moles) were allowed to react at 35°C in benzene solution. As yet no product has been isolated.

ATTEMPTED PREPARATION OF 2-ACETOXY-2-PHENYL-1,3-DIOXOLAN.

Method 1. 2-methoxy-2-phenoxy-1,3-dioxolan (0.01 moles) acetoxy-dimethoxy-methane (0.01 moles) and acetic acid (0.02 moles) were heated under reduced pressure and the reaction monitored by N.M.R. The product obtained, as seen by N.M.R. was 2-acetoxy ethyl benzoate; no sign of the 2-acetoxy-2-phenyl-1,3-dioxolan was observed.

Method 2. The procedure was identical with method 1 but no acetic acid was used. The results were as before.

Method 3.

(a) 2-phenyl-1,3-dioxolenium fluoroborate (0.00375 moles) was dissolved in dry acetonitrile. This was then added to a solution of 18-crown-6 ether (0.1 molar) and potassium acetate (0.00375 moles) in acetonitrile. The N.M.R. spectrum showed the only product to be 2-acetoxy ethyl benzoate.

(b) The above method was repeated in benzene solution but the products obtained were the same.

Method 4.

(a) Equimolar quantities of tetramethylammonium acetate and 2-phenyl-1,3-dioxolenium fluoroborate were allowed to react in methylene chloride at room temperature; only 2-acetoxy ethyl benzoate was obtained.

(b) The above reaction was repeated by cooling the tetramethylammonium acetate solution to -78°C followed by dropwise addition of the fluoroborate salt to this solution at that temperature. On warming to room temperature (after approximately 1 hour) the products were observed to be the same as previously.

ATTEMPTED PREPARATION OF 2-PHENOXY-2-PHENYL-1,3-DIOXOLAN.

2-Phenyl-1,3-dioxolenium fluoroborate (0.01 moles) in methylene chloride was added dropwise under nitrogen, to a cooled solution (-78°C) of tetramethylammonium phenoxide in methylene chloride/acetonitrile (4:1). The reaction mixture was kept at this temperature for 1 hour. On warming to room temperature and removal of the solvent only 2-phenoxy ethyl benzoate was obtained.

PREPARATION OF α,α-DIMETHOXY-α-PHENOXY-TOLUENE.

Method 1. Equimolar quantities of phenol and trimethyl orthobenzoate were refluxed in benzene, under nitrogen, with a trace of toluene-p-sulphonic acid as catalyst. The reaction was monitored by N.M.R. but only methyl benzoate (δ Me=3.89) and anisole (δ Me=3.77) could be observed.

Method 2. Trimethyl orthobenzoate (0.1 moles) and phenol (0.05 moles) were refluxed in benzene,[18] under nitrogen, with toluene-p-sulphonic acid as catalyst. The reaction was monitored by N.M.R. until the theoretical amount of product had formed. The yield obtained was approximately 2 drops of prcduct after removal of low boiling components by high vacuum distillation.

Method 3. Method 2 was repeated using redistilled methane-sulphonic acid as catalyst giving approximately 60-70% yield of a clear liquid which crystallised to give a white solid.

b.p. 92-93°C at 0.018 mm Hg.

m.p. 46-46.5°C

N.M.R. ($CDCl_3$) 90 MHz. 291 Hz, 3.23δ(s, 6H); 607-648 Hz, 6.75-7.2δ(m, 5H); 648-666 Hz, 7.2-7.4δ (m, 3H); 675-702 Hz, 7.5-7.8δ(m, 2H)

I.R. (CCl_4) ν cm^{-1} 3000, 3018, 3022, 3070 sh (C-H aromatics). 2946, 2905 (C-H aliphatics). 2840 (CH_3 stretch) 1270 (C-O-C stretch).

microanalysis: Found: C, 73.55; H, 6.68;

$C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%.

ATTEMPTED PREPARATION OF α,α-DIMETHOXY-α-pNO_2-PHENOXY-TOLUENE.

Method 1. Method 1 of the preparation of 1,1-dimethoxy-1-phenoxy-toluene was repeated, this time using recrystallised

p-nitrophenol. p-nitroanisole ($\delta MeO = 3.91$) was obtained in good yield.

Method 2. Similarly method 3 of the preparation of 1,1-dimethoxy--1-phenoxy-toluene was repeated using p-nitrophenol. The product obtained was again the p-nitroanisole.

Method 3. Trimethyl orthobenzoate (0.15 moles) and p-nitrophenol (0.05 moles) were refluxed in benzene with methanesulphonic acid as catalyst. The products obtained were as before.

ATTEMPTED PREPARATION OF α-BENZOXY-α,α-DIMETHOXY-TOLUENE.

Benzoic acid (0.05 moles) and trimethyl orthobenzoate (0.1 moles) were refluxed, under nitrogen, in benzene. Continuous monitoring by N.M.R. showed formation of methyl benzoate and methanol.

ATTEMPTED PREPARATION OF α,α-DIMETHOXY-α-TRIFLUOROACETOXY-TOLUENE.

Method 1. Trifluoroacetic acid (0.05 moles) and trimethyl orthobenzoate (0.1 moles) were allowed to react in benzene at room temperature. The N.M.R. spectrum showed immediate formation of methyl benzoate.

Method 2.

(a) Equimolar quantities of the trifluoroacetic mixed anhydride (trifluoroacetic acid and acetic anhydride) and trimethyl orthobenzoate were allowed to react at room temperature. The

reaction was monitored by N.M.R. The product obtained was again methyl benzoate.

(b) The above reaction was carried out using methylene chloride as solvent but the same products were obtained.

PREPARATION OF 2-METHOXY-2-PHENOXY-TETRAHYDROPYRAN.

Method 1. 2,2-Dimethoxy-tetrahydropyran (0.1 moles) was refluxed with phenol (0.05 moles) in benzene, under nitrogen, with a trace of toluene-p-sulphonic acid as catalyst. The reaction was monitored by N.M.R. but only the methyl-5-phenoxy valerate was observed with a slight trace of other material.

Method 2. Method 1 was repeated using methane sulphonic acid as catalyst.

b.p. 72-74°C at 0.08 mm Hg.

N.M.R. ($CDCl_3$) 90 MHz. 140-174 Hz, 1.56-1.93 δ(m, 6H); 312 Hz, 3.47 δ(s, 3H); 356 Hz, 3.96 δ(t, 2H, 4.5 Hz); 627-664Hz, 6.97-7.38 δ(m, 5H).

I.R. (CCl_4) ν cm^{-1} 2978 b (C-H aliphatics).
3005, 3015 (C-H aromatics).
1742 (carbonyl C=O).
1523 (NO_2 stretch, symmetric).
1345 (NO_2 stretch, asymmetric).

microanalysis:

No analysis could be obtained as the small quantity of material obtained was used for kinetic studies and time did not allow further preparation of material.

ATTEMPTED PREPARATION OF 2-METHOXY-2-p-NITROPHENOXY-TETRAHYDRO-PYRAN.

2,2-Dimethoxy-tetrahydropyran (0.15 moles) and p-nitrophenol (0.05 moles) were refluxed in benzene, under nitrogen with a trace of methane sulphonic acid as catalyst. The products obtained were p-nitroanisole (minor product) and methyl 5-p-nitrophenoxyvalerate, a crystalline solid which was recrystallised from acetonitrile.

m.p. 78.5-79.5°C.

N.M.R. ($CDCl_3$) 90 MHz. 329 Hz, 3.66 δ(s, 3H); 156-176 Hz, 1.74-1.95 δ(m, 4H); 215 Hz, 2.39 δ(t, 2H, 1HZ); 407 δ(t, 2H, 0.9 Hz); 623 Hz, 6.92 δ(d, 2H, 0.9Hz 8.15 δ(d, 2H, 0.9 Hz).

I.R. (CCl_4) ν cm^{-1} 3004, 3080, 3110 (C-H aromatics).
2880 sh (CH_3 stretch).
2960 b (C-H aliphatic).
1738 (carbonyl stretch).

microanalysis: Found: C, 56.7; H, 5.83; N, 5.54;
$C_{12}H_{15}O_5N$ requires C, 56.9; H, 5.93; N, 5.53%

Method 2.

(a) O-Methyl δ-valerolactonium fluoroborate (0.1 moles) was dissolved in methylene chloride, sodium p-nitrophenoxide in tetrahydrofuran (THF) was added dropwise with vigorous stirring to this solution at -78°C. On warming after 3 hours at -78°C the N.M.R. spectrum of the material showed only p-nitroanisole and the methyl 5-p-nitrophenoxyvalerate.

(b) The above method was repeated with sodium p-nitrophenoxide in methylene chloride as a finely ground slurry, under nitrogen. The products observed were as before.

ATTEMPTED PREPARATION OF 2-PHENYL-2-p-NITROPHENOXY-1,3-DIOXOLAN.

To a solution of 2-phenyl-1,3-dioxolenium fluoroborate in methylene chloride at -78°C under nitrogen was added a slurry of sodium p-nitrophenoxide in methylene chloride. On warming to room temperature, after approximately 3 hours, no product was observed by N.M.R.

ATTEMPTED PREPARATION OF 2-PHENYL-2-METHOXY-4,4,5,5-TETRAMETHYL--1,3-DIOXOLAN.

Equimolar quantities of trimethyl orthobenzoate and pinacol with a trace of toluene-p-sulphonic acid as catalyst were heated under nitrogen with continuous monitoring by N.M.R. The products obtained showed only the benzoate ester.

ATTEMPTED PREPARATION OF THE DIBENZOATE ESTER OF PINACOL.

Method 1. All attempts to synthesise the dibenzoate ester[19] by a variety of normal esterification reactions via the acid/alcohol, acid halide/alcohol combinations were unsuccessful.

Method 2. To a stirred suspension of silver benzoate (0.2 moles) in 150 mls dry acetonitrile was added slowly a solution of 2,3 dibromo 2,3 dimethyl butane in 30 mls benzene

while the temperature was maintained at 70-75°C. The mixture was stirred at this temperature for 24 hours and then cooled and filtered. The solid was washed with 400 mls of 80% pentane/20% ether and the combined filtrates were extracted several times with water, twice with 5% aqueous Na_2CO_3 solution and finally dried with $MgSO_4$. On evaporation of the solvent the resulting liquid was T.L.C. on silica with ether 10%/pentane 100% as solvent. The resulting T.L.C. consisted of one major and two minor products. The major material accounted for approximately 80% product.

N.M.R. ($CDCl_3$) 90 MHz 147.6 Hz, 1.64δ(s, 6H); 160 Hz, 1.78δ(broadened s, 3H); 465 Hz, 5.17δ(m, 1H); 475 Hz, 5.28δ(broadened s, 1H); 675-702 Hz, 7.5-7.8δ(m, 3H); 736-752 Hz, 8.18-8.35δ(m, 2H).

I.R. (thin film) ν cm^{-1} 3070, 3095 (C-H aromatics).
2993, 2915, 2950 (C-H aliphatic).
1720 (C=O stretch).
1699 (olefinic stretch).
1605, 1595 (aromatic double bond).
1280 (C-O stretch).

microanalysis. Found: C, 75.58; H, 7.56;

$C_{13}H_{16}O_2$ requires C, 75.47; H, 7.84%.

ATTEMPTED SYNTHESES OF 3-BROMO-2,3-DIMETHYL BUT-2-YL BENZOATE.

Method 1. The reaction of equimolar quantities of 2-phenyl--4,4,5,5-tetramethyl-1,3-dioxolan and N-bromosuccinimide with 1% Azo-iso-butonitrile as radical initiator in CCl_4, photolysed with light,[20] gave a minimum of five products by T.L.C. Quantities of material likely to be obtained by this method would have been rather small and therefore this method was abandoned.

Method 2. The thermal bromination[21] with N-bromosuccinimide and barium carbonate in carbon tetrachloride gave a similar mixture of products.

Method 3. Method 2 in acetonitrile[22] gave no better results and so was also abandoned.

ATTEMPTED SYNTHESES OF 2-PHENYL-4,4,5,5-TETRAMETHYL-1,3-DIOXOLENIUM SALTS.

Method 1.[23] The reaction of equimolar quantities of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolan and triethyl oxonium fluoroborate in dry methylene chloride, with gentle warming, resulted in initial attempts being unsuccessful.

Method 2.[24] Equimolar quantities of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan and triethyl oxonium fluoroborate were heated in a sealed system and the diethyl ether collected in a methanol/dry-cold trap. The resultant semicrystalline salt,

which was left in the flask, was dissolved in methylene chloride but initial attempts at crystallisation were unsuccessful. Both methods 1 and 2 were abandoned in favour of method 3.

Method 3.[24] Equimolar quantities of 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolan and triphenylcarbenium hexachloroantimonate, in dry methylene chloride under nitrogen, was stirred overnight at room temperature. Dry diethyl ether was then added until turbid and solution allowed to crystallise. The crystals obtained were filtered under nitrogen and any solvent remaining was evaporated off under vacuum.

(m.p.) 130°C decomp. white crystalline solid.

N.M.R. (d_6-acetone) 90 MHz 184.2 Hz, 2.046δ(s, 12H);
693.0_764.0 Hz, 7.7-8.49δ(m, 5H).

Microanalysis. So far all attempts to obtain a microanalysis have failed due to the rapid decomposition of the material in the presence of moisture.

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KINETIC EXPERIMENTAL (U.V. SPECTROSCOPY)

Buffer Solutions. "Analar" grade chemicals were used in the preparation of all buffered solutions. These were made up with degassed, deionised water and the stock solutions were diluted, where appropriate, by stock potassium chloride solution which was at the same ionic strength. Stock solutions of the acetal and the acylal were prepared with Merck "spectro-grade" dioxan immediately prior to use.

The pHs of all the buffered solutions were measured with a Radiometer Model 26 pH meter with an external temperature compensator. A Radiometer type G202C glass electrode and a calomel electrode type K401 were used. The pH meter was standardised against commercial standard buffers as near as possible to the pH being measured.

Spectroscopic Rate Determinations

All rate constants were determined on a Cary 16 spectrometer fitted with an automatic five cell compartment and temperature thermostatting bath which kept the temperature within $\pm$ 0.05°C. The temperature inside the cell compartment was monitored immediately before and after the kinetic runs using a calibrated thermometer.

Data for the change in the absorption signal obtained by the spectrophotometer was fed as a voltage signal, being proportional to the absorption, via the recorder interface

and the analogue/digital converter directly to the computer. Control of the sampling rate, automatic sample changing and calculation of results was carried out by the computer using a modified Mathchat computer language system.

10 mm Spectrosil quartz U.V. cells were used. 2.5 ml of the buffer was added to each cell approximately 30 minutes prior to starting the runs to allow temperature equilibration. 25µlitres of stock dioxan solution of substrate was injected into the buffer so that all rate constants for aqueous solutions relate to 1% dioxan.

RESULTS PART 1

The hydrolysis of the compound was followed by measuring the release of the aldelydic product at 280 nm at a temperature of 15°C.

While α-chloroacetoxy-α-t-butoxy-toluene is shown as having been synthesised no kinetics were carried out on this compound.

Table 16 The acetic acid catalysed hydrolysis of benzaldehyde di-t-butyl acetal (di-t-butoxy-benzal).

$[CH_3CO_2H]/_4 = [CH_3CO_2^-]$ pH 3.99 I = 0.05M

$[A^-]$ M	Weighted Average $10k(s^{-1})$	S.D(%)
0.025	0.905	6.86
0.020	0.881	4.65
0.015	0.846	2.20
0.010	0.830	1.4
0.005	0.800	1.68

Plot of weighted averages $k_{slope} = 0.524\ M^{-1}s^{-1}$ S.D(%) = 5.56

$k_{int} = 7.74 \times 10^{-2}\ s^{-1}$ S.D(%) = 0.62

Table 17 The acetic acid catalysed hydrolysis of α-acetoxy--α-t-butoxy-toluene

$[CH_3CO_2H]/_4 = [CH_3CO_3^-]$ pH 3.99 I = 0.05M

$[A^-]$ M	Weighted Average $10k(s^{-1})$	S.D(%)
0.025	0.936	1.37
0.020	0.898	2.17
0.015	0.874	1.76
0.010	0.848	1.49
0.005	0.818	3.15

Plot of weighted averages $k_{slope} = 0.573\ M^{-1}s^{-1}$ S.D(%) = 4.37

$k_{int} = 7.89 \times 10^{-2} s^{-1}$ S.D(%) = 0.53

Table 18 The acetic acid catalysed hydrolysis of α-acetoxy--α-t-butoxy-toluene

$[CH_3CO_2H]$ = $[CH_3CO_2^-]$ pH 4.63 I = 0.05M

[AH] M	Weighted Average $10^2k(s^{-1})$	S.D(%)
0.025	2.036	1.64
0.020	1.995	0.97
0.015	1.953	0.50
0.010	1.911	0.95
0.005	1.889	0.41

Plot of weighted averages $k_{slope} = 7.57 \times 10^{-2} M^{-1} s^{-1}$ S.D(%) = 5.8

$k_{int} = 1.84 \times 10^{-2} s^{-1}$ S.D(%) = 0.39

Table 19 The acetic acid catalysed hydrolysis of benzaldehyde-di-t-butyl acetal (di-t-butoxy-benzal)

$[CH_3CO_2H] = [CH_3CO_2^-]$ pH 4.63 I = 0.05M

[AH] M	Weighted Average $10^2k(s^{-1})$	S.D(%)
0.025	1.842	17.9

Table 20 The imidazole catalysed hydrolysis of benzaldehyde--di-t-butyl acetal (di-t-butoxy-benzal)

$[Im] = [ImH^+]$ pH 7.03 I = 0.05M

[Im] M	Weighted Average $10^4 k(s^{-1})$	S.D(%)
0.025	4.706	1.92
0.020	4.671	3.34
0.015	4.633	2.07
0.010	4.744	1.84
0.005	4.657	2.52

Plot of weighted averages $k_{slope} = 5.12 \times 10^{-5} M^{-1} s^{-1} \approx 0.$ S.D(%) = 108

$k_{int} = 4.674 \times 10^{-4} s^{-1}$ S.D(%) = 1.12

Table 21 The imidazole catalysed hydrolysis of α-acetoxy--α-t-butoxy-toluene

[Im] = [ImH^+] pH 7.03 I = 0.05M

[Im] M	Weighted Average $10^2k(s^{-1})$	S.D(%)
0.025	1.558	4.96
0.020	1.309	1.98
0.015	1.056	1.95
0.010	0.827	3.64
0.005	0.563	1.83

Plot of weighted averages $k_{slope} = 0.494\ M^{-1}s^{-1}$ S.D(%) = 1.06

$k_{int} = 3.21 \times 10^{-3}s^{-1}$ S.D(%) = 2.71

Table 22 The phosphate catalysed hydrolysis of α-acetoxy-α--t-butoxy-toluene

$[KH_2PO_4] = [K_2HPO_4]$ pH 6.79 I = 0.1 M

[Phos] M	Weighted Average $10^2k(s^{-1})$	S.D(%)
0.1	1.074	4.75
0.08	0.919	2.69
0.06	0.751	1.64
0.04	0.563	3.49
0.02	0.386	2.70

Plot of weighted averages $k_{slope} = 8.67 \times 10^{-2} M^{-1} s^{-1}$ S.D(%) = 2.0

$k_{int} = 2.18 \times 10^{-3} s^{-1}$ S.D(%) = 5.4

KINETIC EXPERIMENTAL (NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY)

All solvents used in the nuclear magnetic resonance spectroscopy (N.M.R.) kinetic studies were commercially available deuterated solvents and were used immediately on opening to reduce the likelihood of moisture absorption.

Analysis of Results

An inherent defect in the method of analysis of the results in this thesis was that during the recording of the N.M.R. spectra the pen required a finite time to travel between peaks in order to obtain a complete and accurate spectrum. In order to reduce this possible source of error on the faster runs limited areas of the N.M.R. spectrum were monitored.

The percentage of each material present was calculated from the height of one of its signals. This required calibration factors since all the signals did not have the same width. These were obtained by weighing 25 µlitres of the formate ester and the corresponding orthoester, running the N.M.R. spectrum and measuring the peak heights of the formate and $HC(OR)_3$ protons. From this data and the concentration of each species the calibration factors for the formate peaks were obtained. It was assumed that any peak widening observed for the orthoesters would be applicable to the tetra-

hedral intermediate and acetoxy compound. The correction for the formate ester derived from 2-acetoxy-1,3-dioxolan was assumed to be identical to that for ethyl formate. These correction factors are given in table 23.

The calculation of the relative percentages of each species, starting material, intermediate or product could then be obtained from the data by assuming the relative heights multiplied by the calibration factors for starting material, intermediate and product added up to 100%.

Experimental Method

All N.M.R. samples were made up to 0.5 mls of solution by the required quantities of solvents. Tetramethylsilane (TMS) was normally added to all mixed solvent systems, with the exception of solutions where the aqueous fraction was great enough to cause the TMS to form a separate layer. The TMS, when used, was an internal standard and the locking signal for the N.M.R. spectrometer.

Hydrolysis of Acetoxy-dimethoxy-methane

Initial studies on the hydrolysis of acetoxy-dimethoxy--methane were carried out on a Varian T60 N.M.R. spectrometer at ambient temperature (~ +35°C) by dissolving 15 µlitres of the substrate in deuterium oxide at +2°C followed by rapid shaking and monitoring in the N.M.R. probe. Being a rather crude method it is not surprising that the resulting spectrum

Table 23

Compound	Calibration Factor
methyl formate	1.54
ethyl formate	1.33
pinacol monoformate	1.0

showed only products with no sign of starting material or intermediate. Similar attempts by this method using sodium acetate buffer (0.1 M NaOAc/0.1 M AcOH) gave only the spectrum of the product.

A preliminary study, at +25°C, with the substrate dissolved in a mixture of buffer and dimethyl sulphoxide (0.1 M NaOAc/0.1 M AcOH in D_2O (2 vols) + D_3CSOCD_3 (1 vol)) showed similar negative results.

A systematic study by variable temperature N.M.R., with varying concentrations of deuterated water and deuterated acetone; progressively more acetone at progressively lower temperatures; resulted in the observation in D_2O/Acetone (1:9 V/V) at -60°C of starting material (the solvent being initially cooled and the substrate added by syringe with shaking). It had been noted that the D_2O/Acetone mixture when initially removed from the probe was partly frozen and liquified as the solution warmed up slightly at room temperature during addition of substrate and shaking. The initial spectrum obtained showed predominantly starting material but also showed a small peak at 5.27δ. However, problems with slow freezing of the solution at such a low temperature required that higher temperatures had to be utilized. Slow freezing occurred at temperatures up to ~ -45 to -50°C.

Studies were therefore initiated at -35°C and showed that the starting material decayed to intermediate, dimethyl-

hemiorthoformate faster than the intermediate hydrolysed to products (table 24 for rate constants). A similar study in buffer/acetone mixture at V/V ca 1:9 gave a slower decrease in starting material resulting in a situation where at no time was there complete loss of starting material with tetrahedral intermediate present (table). While this observation was originally thought to be significant, attempts to repeat the initial observations of loss of starting material, in D_2O/Acetone-D_6, followed by loss of tetrahedral intermediate to product resulted, using both 15 and 20 μℓ. substrate at -35°C, in a much slower rate of loss of starting material than had previously been observed. It had been thought that the quantity of starting material, and hence produced acid, greatly affected the rate of reaction but little change in the rates of 15 μℓ and 20 μlitres of sample could be found. A second consideration, that of change in temperature, was considered since temperature calibration and a slight drift (~ 1°C) could be observed over the period of the reaction but monitoring the temperature accurately in later experiments ruled out this possibility.

The final solution to the "unrepeatable" results was obtained by varying the ratio of D_2O to acetone-D_6 since the initial step in the reaction was found to be very susceptible to the water concentration (see table 28); a few percent variation resulted in a large change in rate.

Hydrolysis of related acetoxy-compounds

Studies on other acetoxy-derivatives, acetoxy-diethoxy--methane, 2-acetoxy-1,3-dioxolan, 2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan and the chloroacetoxy derivative, 2-chloroacetoxy-4,4,5,5-tetramethyl-1,3-dioxolan were carried out, the results of which are summarised in the Results and Discussion Sections. Initially in the case of 2-acetoxy-1,3--dioxolan it was not possible to observe any tetrahedral intermediate in D_2O/acetone-D_6 (V/V 1:9) but on changing the D_2O/acetone-D_6 ratio to greater water concentration the tetrahedral intermediate could be observed.

The possibility of studying the tetrahedral intermediate by C^{13}(carbon-13) N.M.R. (nuclear magnetic resonance spectroscopy) was applied to the most stable tetrahedral intermediate observed; the tetrahedral intermediate derived from 2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan. The results are shown in the Results Section.

Hydrolysis of Orthoesters

Studies in the hydrolysis of 2-methoxy-1,3-dioxolan in D_2O/acetone-D_6 were carried out at varying low temperatures from -45°C up to 0°C but no change in the substrate spectrum could be observed. Studies, therefore, in varying concentrations of DCℓ in DCℓ/acetone-D_6 (V/V 1:9) mixtures resulted in slow hydrolysis of the orthoester at -20°C, in 0.01 M DCℓ

(before dilution by acetone-D_6), but no observation of any transient peaks was observed. A similar study of the hydrolysis of trimethyl orthoformate showed a similar slow hydrolysis. The corresponding substrate, acetoxy-dimethoxy--methane, appeared to hydrolyse instantaneously at this acid concentration and temperature (-20°C). N.M.R. Studies of the hydrolysis of 2-methoxy-4,4,5,5-tetramethyl-1,3-dioxolan in various acid concentration solutions (DCℓ/acetone-D_6) also showed no sign of any intermediate species. The hydrolysis in 0.2 M DCℓ/acetone-D_6 (V/V 1:9; 0.2 M DCℓ before dilution by acetone) at -40°C showed a reasonably fast reaction time of ~ 4 minutes for complete hydrolysis but not however as fast as the corresponding acetoxy-compound under the same conditions.

Attempts to generate tetrahedral intermediates from α,α-dimethoxy-α-phenoxy-toluene and 2-methoxy-2-phenoxy--tetrahydropyran in DCℓ/acetone-D_6 showed negative results with the rates of hydrolysis being very slow. Contrary to expectation, however, the preliminary study of the hydrolysis of 2-methoxy-2-phenoxy-tetrahydropyran showed the unusual formation of both methanol and methyl ester.

Studies, therefore, were carried out on the hydrolysis of dimethoxy-tetrahydropyran and diethoxytetrahydropyran to check if there was formation of both alcohol and methyl and ethyl esters. Since Deslongchamps' study resulted in the

conclusion that only ethyl ester and not lactone was formed in the hydrolysis of diethoxy-tetrahydropyran.

Initial studies involved the general procedure of Deslongchamps' where orthoester (0.5 mmoles) was dissolved in deuterated methylene chloride (0.05 mls), cooled then poured onto cold water (0.5 mls) containing a small amount of toluene-p-sulphonic acid (10^{-3}M) at 0°C. Rigorous agitation for 20 minutes was followed by the quenching of the reaction mixture by acetone-D_6 (3 mls) precooled to 0°C to form a single phase. Deslongchamps procedure did not involve quenching with acetone but the reaction of the products to form stable ester adducts (see Discussion). In this investigation the single phase solution was then immediately run in an N.M.R. spectrometer thermostatted at 0°C to obtain the relative concentrations of methanol and methyl ester and hence ratio of lactone to methyl ester products.

A further variation of this hydrolysis was carried out in the attempt to remove the initial problem arising from a two phase system. The hydrolyses of both the dimethoxy and diethoxy tetrahydropyrans were therefore carried out in acetone-D_6D_2O (containing 10^{-3}M toluene-p-sulphonic acid) at various ratios (V/V) and room temperature and the relative intensities of the peaks calculated. Similar studies using various concentrations of DCℓ showed the methyl ester to be

quite stable up to fairly high acid concentrations. Similar work using deuterated acetonitrile/D_2O containing 10^{-3}M acid was also carried out (see results).

Hydrolysis of N,N-Dimethylformamide Dimethyl Acetal

Initial studies of the hydrolysis of N,N-dimethylformamide dimethyl acetal (20 μℓ) in 0.01M DCℓ/acetone-D_6 at 40°C showed little change in the spectrum of the substrate the temperature having to be increased to -30°C before a very slow reaction took place. Observations at this temperature showed a slow formation of dimethylformamide and methanol. It was not possible to assign any peaks to methyl formate product until approximately 2 hours after the start of the reaction since the rate of formation seemed much slower. A further increase in the temperature to 0°C was required to produce complete hydrolysis over a period of 1 hour.

A similar study in 0.1M DCℓ/Acetone-D_6 of the hydrolysis of N,N-dimethylformamide dimethyl acetal, at -45°C, showed a slightly faster initial reaction (approximately 5% of the reaction) followed by an effective stopping of the reaction. The temperature had to be increased to -35°C then to 0°C to produce a reasonably fast rate of hydrolysis and complete hydrolysis respectively. The similar observation of dimethylformamide and methanol as main products was observed. From considerations of the respective heights of the methanol and

dimethylformamide peaks methanol formation did not appear to lead to formation of the dimethylformamide. No other peaks were observed which could be assigned to the other possible tetrahedral intermediate postulated during the reaction (see scheme

Hydrolysis of O-methyl-N,N-Dimethylformidenium Methylsulphate

Hydrolysis of the imidate salt, O-methyl-N,N-dimethyl--formidenium methylsulphate in both D_2O/Acetone-D_6 and 0.1M sodium acetate/Acetone-D_6 showed a similar lack of any intermediate species from their N.M.R. studies at low temperature. Hydrolysis in D_2O/Acetone-D_6 (V/V, 1:9) from the N.M.R. spectra showed initial formation of N,N-dimethylformamide (DMF), the methanol peak being hidden by the methylsulphate peak. At low temperature -40°C - 20°C the substrate could be observed to slowly decay while a similar slow increase in the DMF was observed. At a later stage in the reaction (~ 40-45% reaction), at -20°C, the formation of methyl formate and protonated dimethylamine was observed and by the end of the reaction gave ~50-55% methyl formate, 45-50% DMF. Similar spectra were observed for the sodium acetate/Acetone-D_6 hydrolysis but with methyl formate observable from the start of the reaction; finally resulting in ~60-70% methyl formate.

Hydrolysis of 1-N,N-diethylamino-Prop-1-yne

The study of the hydrolysis, in 1M HCℓ/Acetone-D_6, of 1-N,N-diethylamino-propyne at -50°C was hampered by poor resolution. However on increasing the temperature stepwise the slow hydrolysis could be monitored up to 0°C - no intermediate was observed.

Hydrolysis of carbenium salts

Hydrolysis of dimethoxycarbenium fluoroborate in D_2O/Acetone-D_6 (V/V 1:9) by the addition of deuterium oxide to a precooled solution of the salt in acetone (-60°C) resulted in immediate formation of methyl formate and methanol. Care had to be exercised by cooling the acetone before addition of the fluoroborate salt since at room temperature the salt reacted with the acetone to give methyl formate by a non-hydrolysis route. Hydrolysis by a similar method (precooling the acetone, etc.) using varying concentrations of sodium acetate solution/Acetone-D_6 (V/V 1:9) mixtures, until the sodium acetate concentration was the fluorate salt, was tried in the hope of reducing the rate of hydrolysis by auto-catalysis by fluoroboric acid proved equally unsuccessful; the substrate hydrolysing apparently instantaneously.

Similar studies on each of the carbenium salts described in the preparative experimental section produced similar negative results of any observation of intermediates, each salt hydrolysing instantly.

It was observed that the heat of reaction of the hydrolysis of the carbenium salts was very dramatic, producing an immediate increase in temperature, when some of the dimethoxycarbenium fluoroborate was added to an aqueous solution of acetone (1:9 V/V). No quantitative calculations were, however, carried out.

A solution of dimethoxycarbenium fluoroborate (15 µlitres) in precooled acetone was made up and kept at low temperature. Addition of a similar quantity of dimethoxy-acetoxy-methane (15 µlitres) to this cooled solution at -50°C gave two partially broadened peaks corresponding to each of the substrates. The broadening of the peaks might possibly have been due to an exchange reaction equilibrium or machine resolution. However no studies on this phenomenon were carried out. Addition of 50 µlitres of D_2O to the 450 µlitre acetone solution resulted in immediate formation of product with no sign of any intermediate for either substrate.

Acyl Migration

Preliminary studies on the possible equilibration and recyclisation of two esters ethylene glycol monoformate and pinacol monobenzoate in DCℓ/Acetone-D_6 (V/V 1:9) at varying acid concentrations up to 0.01M DCℓ and up to 100°C in sealed N.M.R. tubes resulted in little change in the N.M.R. spectra with no observed coalescence of any peaks. Notably no hydrolysis of these esters to the acid and alcohol was seen during the

period of study (~2 hours). The only change noted in the spectra on returning the sample to room temperature was the notable exchange of the acetone and water peak heights and integrations.

RESULTS PART 2.

1. The Hydrolysis of Acetoxy-dimethoxy-methane

TABLE 24 (A) Rate of hydrolysis of starting material.

Substrate Concentration = 1.4×10^{-1} M (10 µlitres)

Temperature; -35°C

Solution; D_2O/acetone-D_6 V/V ca 1:9

Rate constant 10^3k (s^{-1})	S.D (%)
1.70	3.89

(B) Rate of hydrolysis of intermediate.

Rate constant 10^4k (s^{-1})	S.D (%)
3.73	2.74

Weighted Average

TABLE 25 Rate of hydrolysis of starting material.

Substrate Concentration = 2.6×10^{-1} M (20 µlitres)

Temperature; -35°C

Solution; D_2O/acetone-D_6 V/V ca 1:9

Rate constant 10^4k (s^{-1})	S.D (%)
2.41	2.50
2.28	2.03

Weighted Average $2.33 \times 10^{-4} s^{-1}$ S.D (%) 3.95

TABLE 26 Rate of hydrolysis of starting material.

Substrate concentration = 2.0×10^{-1} M (15 µlitres)

Temperature; -35°C

Solution; Buffer/acetone-D_6 V/V ca 1:9

Buffer 0.1M NaOAc/0.1M AcOD

Rate constant 10^4k (s^{-1})	S.D (%)
1.795	2.65

TABLE 27 Rate of hydrolysis of starting material.

Temperature; -35°C

Solution; D_2O/acetone-D_6 V/V 1:9 (50:450)

Quantity of starting material		Rate constant 10^4k (s^{-1})	S.D (%)
3.4×10^{-1} M	(25 µlitres)	4.90	1.1
2.6×10^{-1} M	(20 µlitres)	3.49	1.15
2.0×10^{-1} M	(15 µlitres)	3.33	1.37

TABLE 28 (A) Rate of hydrolysis of starting material.

Temperature; -35°C

Solution; D_2O/acetone-D_6 V/V (70:430)

Quantity of starting material		Rate constant 10^3k (s^{-1})	S.D (%)
1.4×10^{-1} M	(10 µlitres)	3.30	7.1
2.0×10^{-1} M	(15 µlitres)	-	-
2.6×10^{-1} M	(20 µlitres)	2.04	7.9
3.2×10^{-1} M	(25 µlitres)	2.91	4.5

(B) Rate of hydrolysis of intermediate.

Quantity of starting material		Rate constant 10^4k (s^{-1})	S.D (%)
1.4×10^{-1} M	(10 µlitres)	6.78	1.15
2.0×10^{-1} M	(15 µlitres)	11.53	1.16
2.6×10^{-1} M	(20 µlitres)	11.32	2.94
3.2×10^{-1} M	(25 µlitres)	12.34	1.06

2. <u>The Hydrolysis of 2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan</u>

TABLE 29 (A) Rate of hydrolysis of starting material.

Substrate Concentration = 1.6×10^{-1} M (15 µlitres)

Temperature; -40°C

Solution; D_2O/acetone-D_6 V/V 1:9

Rate constant 10^4k (s^{-1})	S.D (%)	monitored by;
4.16	2.32	acetate peaks
4.55	4.23	H-C peaks

Weighted Average $4.24 \times 10^{-4} s^{-1}$ S.D (%) = 7.44

(B) Rate of hydrolysis of intermediate

Temperature; -10°C Concentration as above

Rate constant 10^4k (s^{-1})	S.D (%)	monitored by;
3.91	2.3	methyl peaks
4.11	3.65	H-C peaks

Weighted Average $3.97 \times 10^{-4} s^{-1}$ S.D (%) = 3.98

(C) Rate of hydrolysis of intermediate

Temperature; 0°C

Rate constant 10^4k (s^{-1})	S.D (%)	monitored by;
5.48	1.67	methyl peaks
6.31	3.29	H–C peaks

Weighted Average $5.62 \times 10^{-4} s^{-1}$ S.D (%) = 12.6

TABLE 30 Rate of hydrolysis of starting material.

Substrate Concentration = 1.6×10^{-1} M (15 µlitres)

Temperature; -20°C

Solution; 1.69×10^{-2}M NaOD/acetone-D_6 V/V 1:9

Rate constant 10^4k (s^{-1})	S.D (%)
6.23	4.46

TABLE 31 Rate of hydrolysis of intermediate.

Substrate Concentration = 1.6×10^{-1} M (15 µlitres)

Temperature; -40°C

Solution; DCl/acetone-D_6 V/V 1:9

Final Concentration of acid (after addition of acetone)	Rate constant 10^4k (s^{-1})	S.D (%)
10^{-5}M	1.72	1.98
	1.29	2.38
	1.60	1.32

Weighted Average $1.65 \times 10^{-4} s^{-1}$ S.D (%) 14.5

Final Concentration of acid (after addition of acetone)	Rate constant $10^4 k$ (s^{-1})	S.D (%)
2×10^{-5}M	3.47	1.98
	2.97	1.54
	4.82	3.50
	3.36	1.36
Weighted Average	$3.58 \times 10^{-4} s^{-1}$	S.D (%) 28.9
3×10^{-5}M	8.62	2.17
	8.26	1.31
Weighted Average	$8.35 \times 10^{-4} s^{-1}$	S.D (%) 3.0
4×10^{-5}M	10.92	4.33
	10.41	2.19
Weighted Average	$10.51 \times 10^{-4} s^{-1}$	S.D (%) 4.0
5×10^{-5}M	13.4	4.5
	12.3	5.4
	13.5	4.2
	12.9	2.3
	13.4	2.3
	11.7	6.1
Weighted Average	$1.30 \times 10^{-3} s^{-1}$	S.D (%) 5.74
6×10^{-5}M	15.8	5.7
	15.5	4.2
	17.8	4.8
Weighted Average	$1.62 \times 10^{-3} s^{-1}$	S.D (%) 7.77

3. The Hydrolysis of 1-chloroacetoxy-4,4,5,5-tetramethyl-1,3-dioxolan

TABLE 32 Rate of hydrolysis of intermediate.

Substrate Concentration = 2.0×10^{-1} M (15 µlitres)

Solution: D_2O/acetone-D_6 V/V 1:9

Temperature	Rate constant 10^4k (s^{-1})	S.D (%)
-20°C	6.41	2.57
0°C	16.39	3.55

4. The Hydrolysis of acetoxy-diethoxy-methane

TABLE 33 Rate of hydrolysis of intermediate.

Temperature; -40°C

Solution; D_2O/acetone-D_6 V/V 1:9

Substrate Concentration	Rate constant 10^3k (s^{-1})	S.D (%)
3.0×10^{-1} M (25 µlitres)	1.42	4.0
	2.58	3.4
	1.38	2.1
	1.65	3.9
	1.21	4.3
	1.36	9.2
	1.16	3.4
Weighted Average	$1.39 \times 10^{-3} s^{-1}$	S.D (%) 36.8

Substrate Concentration		Rate constant $10^3 k$ (s^{-1})	S.D (%)
2.4×10^{-1} M	(20 µlitres)	1.01	2.0
		0.96	1.6
		3.29	1.8
		2.11	2.6
		1.20	2.4
		1.21	4.1
		1.04	5.7
		1.10	3.4
		1.44	2.0
Weighted Average		$1.16 \times 10^{-3} s^{-1}$	S.D (%) 72
Substrate Concentration			
1.8×10^{-1} M	(15 µlitres)	1.22	2.7
		0.68	2.6
		1.24	4.1
		1.13	7.3
		0.96	3.4
		1.25	6.0
		0.83	5.0
		0.61	12.4
Weighted Average		$0.87 \times 10^{-3} s^{-1}$	S.D (%) 33

Substrate Concentration	Rate constant 10^3k (s^{-1})	S.D. (%)
1.2×10^{-1}M (10 µlitres)	1.55	3.5
	0.56	1.5
	0.69	2.8
	0.46	1.4
	0.66	8.8
	0.62	10.6
	0.58	11.7
	0.68	4.1
	0.92	6.9
Weighted Average	$0.53 \times 10^{-3}s^{-1}$	S.D (%) 75

TABLE 34 Rate of hydrolysis of intermediate.

Substrate Concentration = 1.2×10^{-1} M (10 µlitres)

Temperature;

Solution; DCl/acetone-D_6

Final concentration of acid (after addition of acetone)	Rate constant 10^3k (s^{-1})	S.D (%)
5×10^{-6}M	0.69	3.5
2×10^{-6}M	0.66	4.2

TABLE 35 Rate of hydrolysis of starting material.

Substrate Concentration = 1.2×10^{-1} M (10 µlitres)

Temperature;

Solution; Buffer/acetone-D_6

Buffer 0.1M NaOAc/0.1M AcOD

Rate constant 10^3k (s^{-1})	S.D (%)
1.06	6.23

5. <u>The Hydrolysis of 2-Acetoxy-1,3-dioxolan</u>

TABLE 36 Rate of hydrolysis of starting material.

Substrate Concentration = 2.0×10^{-1} M (15 µlitres)

Temperature; -30°C

Solution; D_2O/acetone-D_6 V/V 1:9

Rate constant 10^4k (s^{-1})	S.D (%)	monitored by;
2.31	3.4	H-C peaks
2.36	2.4	H-C peaks
1.73	2.3	acetoxy peaks

TABLE 37 (A) Rate of hydrolysis of starting material.

Substrate Concentration = 2.0×10^{-1} M (15 µlitres)

Temperature; -35°C

D_2O/acetone-D_6 ratio	Rate constant 10^4k (s^{-1})	S.D (%)
1:9 (50:450)	1.24	0.8
(60:440)	1.35	0.6
(70:430)	9.87	2.6

(B) Rate of hydrolysis of intermediate.

Solution; D_2O/acetone-D_6 V/V (70:430)

Rate constant 10^4k (s^{-1})	S.D (%)
3.60	1.1
3.56	2.6

6. The Hydrolysis of 2-methoxy-4,4,5,5-tetramethyl-1,3-dioxolan

TABLE 38 (A) Concentration of substrate and chloroacetic acid (added as catalyst) equivalent to X µlitres of 2-chloroacetoxy-4,4,5,5-tetramethyl-1,3-dioxolan.

Temperature + 35°C

Solution; D_2O/acetone-D_6 V/V 1:9

Concentration of substrate	X	Rate constant 10^4k (s^{-1})	S.D (%)
3.2×10^{-1} M	25	1.51	3.2
2.6×10^{-1} M	20	1.34	2.7
2.0×10^{-1} M	15	0.60	2.2
1.4×10^{-1} M	10	0.41	1.3

(B) Concentration of substrate and acetic acid (added as catalyst) equivalent to X µlitres of 2-acetoxy-4,4,5,5-tetramethyl-1,3-dioxolan.

Temperature + 35°C

Solution; D_2O/acetone-D_6 V/V 1:9

Concentration of substrate	X	Rate constant 10^4k (s^{-1})	S.D (%)
2.65×10^{-1}M	25	1.43	2.4
		1.41	0.7
1.07×10^{-1}M	10	0.84	1.4

NOTE. Rates have, normally, been given to two points after the decimal. The accuracy of these values are only normally within 2-10% by N.M.R. studies. The standard deviations are those obtained for the quality of fit of that particular run.

RESULTS PART 3.

Hydrolysis of 2,2-dimethoxytetrahydropyran

Method of Analysis

The peak integrations corresponding to methanol and hydroxy-methoxy ester were measured. A representative spectrum is shown in fig. 120. The general overall reaction can be represented as in fig. 121. The ratio of methanol to hydroxy-methoxy ester can then be calculated.

Let a be the concentration of methanol,

b be the concentration of hydroxy-methoxy ester,

then $a = 3y$

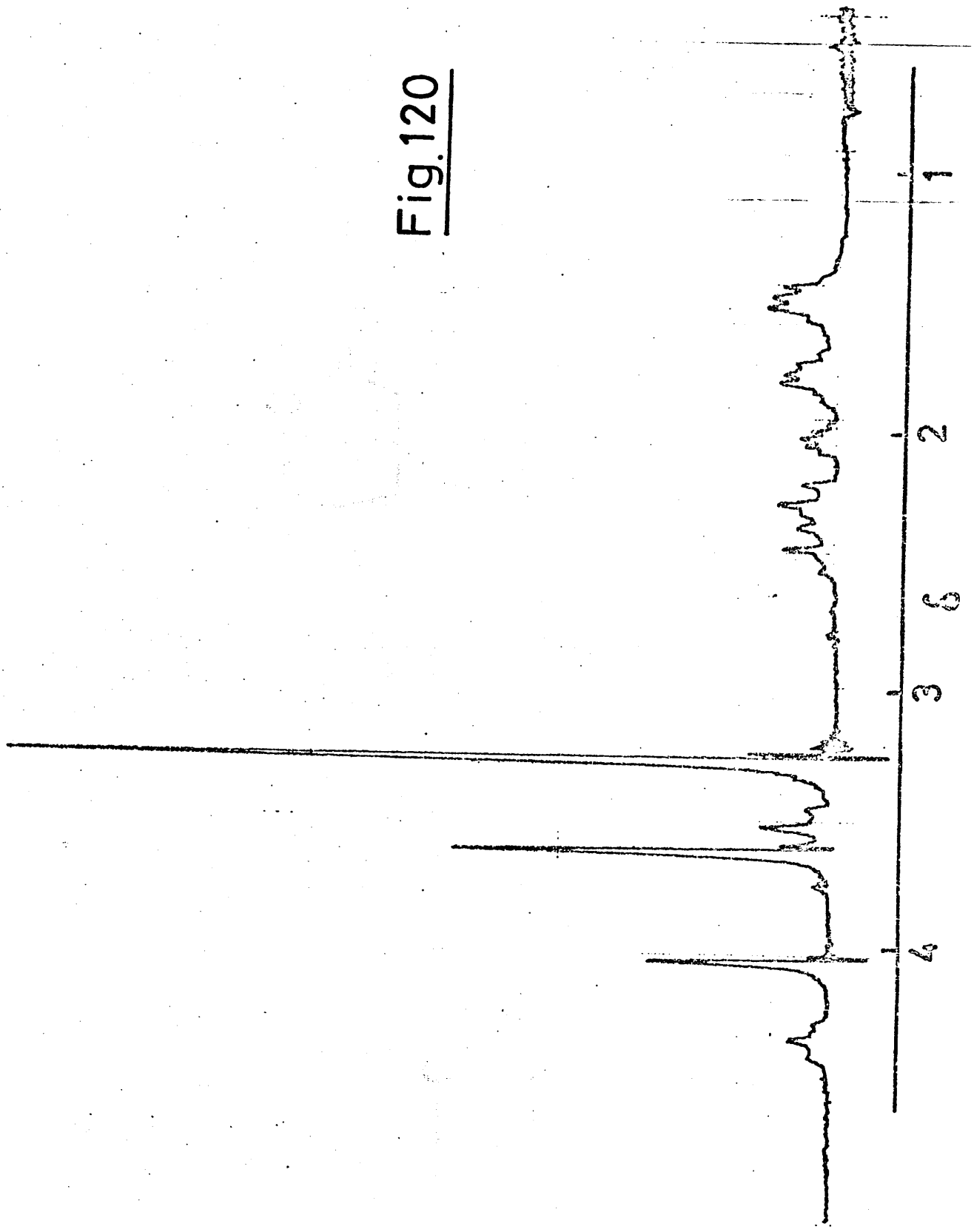
$b = 6x + 3y$

where x is the quantity of reaction producing lactone and y is the quantity of reaction producing hydroxy-methoxy ester.

$$\text{i.e. } \frac{b}{a} = \frac{2x + y}{y}$$

$$\text{then } \% \text{ lactone} = \frac{b - a}{b + a}$$

Fig.120



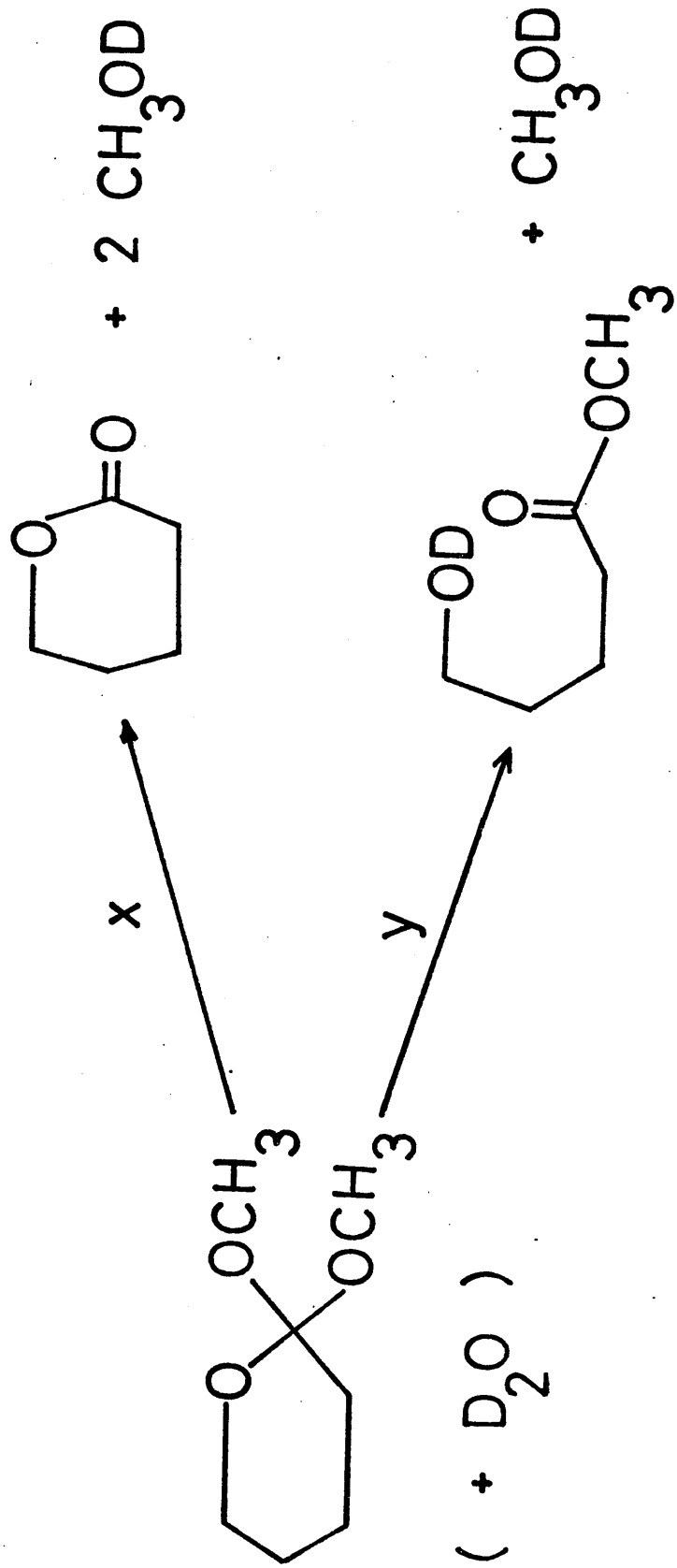


Fig. 121

Table 39

Deslongchamps' Method

Percentage Lactone 35% (average of 8 values).

(See experimental section for summary of method).

Table 40

Hydrolysis in D_2O/acetone-D_6.[a] Temperature 35°C

D_2O/acetone-D_6 ratio	% lactone
10:90	33
20:80	33
30:70	33
40:60	30
50:50	29
60:40	32
70:30	32
80:20	34
90:10	33
100: 0	35

a. All D_2O/acetone-D_6 solutions used D_2O containing 10^{-3}M toluene-p-sulphonic acid before dilution.

Table 41

Hydrolysis in deuterated hydrochloric acid

Concentration of Acid	Time (minutes)	% lactone
0.2M	3.75	23
	6.67	25
	11.5	27
	17.8	29
0.1M	7.5	25
	13.0	22
5×10^{-2}M	1.5	22
	6.67	23
	15.9	24.5
10^{-2}M	7.8	27
	35.0	23
2×10^{-3}M	6.33	24.5
	15.0	27

Table 42

Hydrolysis in D_2O/deuterated acetonitrile (CD_3CN)[a]

D_2O/CD_3CN ratio	% lactone
90:10	40
80:20	39
70:30	39
60:40	38
50:50	40
40:60	40
30:70	42
20:80	44
10:90	44

a. All D_2O/CD_3CN solutions contained D_2O with 10^{-3}M toluene-p-sulphonic acid before dilution.

Table 43

Hydrolysis in D_2O/deuterated dimethylsulphoxide (DMSO).[a]

D_2O/DMSO ratio	% lactone
10:90	43
20:80	38
30:70	39
40:60	40
50:50	41
60:40	41
70:30	41
80:20	40
90:10	44
100: 0	41

a. All D_2O/DMSO solutions used D_2O containing 10^{-3}M toluene-p-sulphonic acid before dilution.

Hydrolysis of 2,2-diethoxytetrahydropyran

Method of Analysis

The peak integrations corresponding to ethanol ($-CH_2-$) and ethoxy ester ($-CH_2-$) were measured. The temperature of reaction was adjusted so as to allow the facilitation of these measurements where overlap with water occurred. The general overall reaction is represented as in fig. 122.

Let a be the concentration of ethyl ester

b be the concentration of ethanol,

then $a = 2y$

$b = 4x + 4y$

i.e. $\frac{x}{x + y} = \frac{b - 2a}{b}$

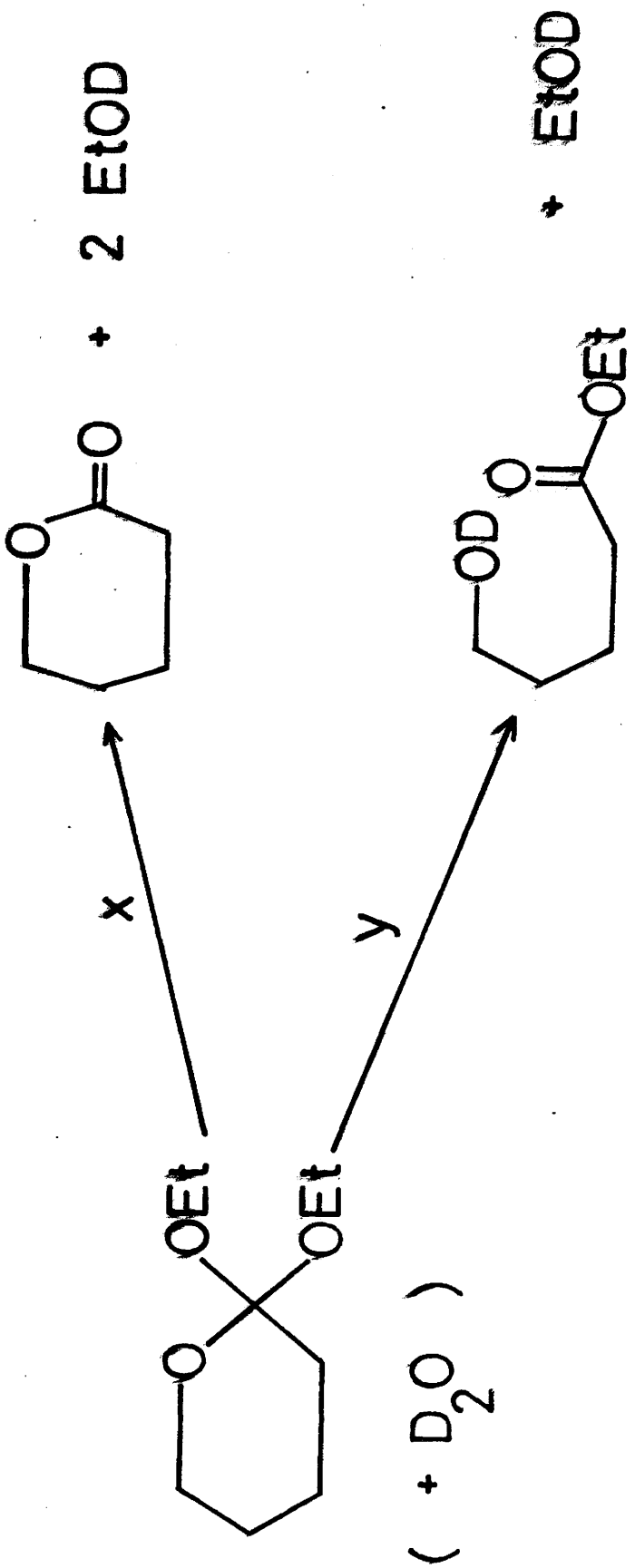


Fig.122

Table 44

Hydrolysis in D_2O/acetone-D_6.[a]

D_2O/acetone-D_6 ratio	% lactone
10:90	22
20:80	25
30:70	28
40:60	29
50:50	26
60:40	31
70:30	30
80:20	31
90:10	30
100: 0	31

a. All D_2O/acetone-D_6 solutions used D_2O containing 10^{-3}M toluene-p-sulphonic acid before dilution.

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