INTRAMOLECULAR CATALYSIS IN SOME ALIPHATIC KETO-ACIDS

A thesis submitted to the University of Stirling
for the degree of Doctor of Philosophy

A. D. Covington, A.R.I.C.

Department of Chemistry
December 1973

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

63

ABSTRACT

INTRAMOLECULAR CATALYSIS IN SOME ALIPHATIC KETO-ACIDS

An abstract of a thesis submitted to the University of Stirling for the degree of Doctor of Philosophy

A. D. Covington, A.R.I.C.

Department of Chemistry
December 1973

ABSTRACT

Ring-chain tautomerism and the kinetics of halogenation have been investigated in the following keto-acids:

$CH_3CO(CH_2)_nCO_2H$, where n = 2,3,4.

$PhCO(CH_2)_nCO_2H$, where n = 2,3,4.

2-methyl levulinic acid.

2,2-dimethyl levulinic acid.

3-methyl levulinic acid.

3,3-dimethyl levulinic acid.

2,2,3-trimethyl levulinic acid.

5,5-dimethyl-4-oxo hexanoic acid.

The percentage of ring-lactol present in dilute aqueous solution at 25.0°C has been estimated by the comparison of two measured dissociation constants: firstly, the 'mixed' dissociation constant i.e. the equilibrium mixture of both straight chain and ring-lactol tautomers, by the measurement of pH and secondly, the 'true' dissociation constant i.e. the straight chain tautomer alone, by the measurement of the kinetics of the general base-catalysed decomposition of nitramide. The results are discussed with reference to the structure of the keto-acids. Bredt's work on the tautomeric equilibrium in levulinic acid has been repeated and his conclusion concerning the structure of the acetyl derivative has been confirmed.

Rates of halogenation of both self-buffered and acetate-buffered substrates have been measured spectrophotometrically at 25.0°C. Rate constants have been obtained for the intra- and inter-molecular processes contributing to the observed rate. For four of the keto-acids, in which two sites are available for reaction, the relative rates of deuterium exchange at the two sites have been estimated by N.M.R. spectroscopy. An attempt has been made to rationalise the observed correlations between rate of reaction, site of reaction and the structure of the keto-acids.

Activation parameters have been measured for the halogenation of levulinic acid and 6-oxo heptanoic acid. The results have been rationalised in terms of the effect of substrate chain length on the transition states postulated for the intra-molecular and the inter-molecular processes considered.

Acetyl levulinic acid has been used as a model to evaluate the role played by the ring acid tautomer in the kinetics.

December 1973

ACKNOWLEDGEMENTS

I wish to thank my supervisor, Professor R. P. Bell, F.R.S., for his invaluable teaching and help during the research.

I thank the Science Research Council for the award of a maintenance grant.

I would also like to record the gratitude due to the following:-
past and present members of Professor Bell's research group for their interest and willingness to discuss my work. In particular, I thank Dr. B. G. Cox and Dr. R. L. Tranter.
Professor W. Parker, for his generosity and Dr. R. W. Hay, for acting as temporary supervisor during the absence of Professor Bell.
Mrs. J. Weber, for all her help and for typing this thesis.
my parents, for their patience.
Peter and Joan Armstrong and Dave and Doreen Waterston, to whom I owe so much.
Arthur and Kathleen Keeler, whose uncomplaining payment of income tax made this research possible.
Steve and Gwen Grainger, for their kindness and, of course, Jan.

I dedicate this thesis to

Janet, Geoffrey, Simon, Samantha and Alexander

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Enzymes are molecules, invariably containing protein, which catalyse metabolic reactions in living tissue. They are characterised by two outstanding properties:

(1) reaction specificity, with respect to the substrate as a whole or to a centre in the substrate, e.g. succinate dehydrogenase catalyses the conversion of succinic acid to fumaric acid. The presence of any other dibasic acid inhibits its action and the cis-product, maleic acid, is not formed.

The reduction of pyruvate by the lactate dehydrogenase of muscle gives only L-lactate. The organism Bacillus delbrückii catalyses the same reaction, but only yields the D-isomer.[1]

(2) large rate enhancement compared with the analogous non-enzymic reaction, e.g. the hydrolysis of urea takes place with a pH-independent first-order rate constant of 4.15×10^{-5} s^{-1} at 100°C and an energy of activation of 113.7 kJ mol^{-1}.[2] The hydrolysis of urea, bound to urease (assuming a molecular weight of 438,000 and the presence of only one active site in the enzyme molecule) in an enzyme-substrate complex, takes place at 20.8°C and pH 8.0 with a first-order rate constant of 3×10^{4} s^{-1} and an activation energy of the order of 46 kJ mol^{-1}.[3] Extrapolating the non-enzymic rate to 20.8°C gives a rate constant of 3×10^{-10} s^{-1}. Thus the enzyme increases the rate by a factor of 10^{14}. This corresponds to a lowering of the free energy of activation by 80 kJ mol^{-1}.[4]

In comparing an enzyme-catalysed reaction and a non-enzymic reaction, it is certain that the mechanisms, rate laws and properties of the solvent around the reactants and the transition states will be different. Thus it is uncertain whether a decrease in the free energy of activation, of which an example is quoted above, is caused by a change in the enthalpy or the entropy of activation or both.

The 'lock and key' model of an enzyme-substrate complex postulates that a specific substrate fits into a reaction site in the enzyme molecule, where it is in the right orientation for reaction with catalysing groups in the enzyme. Since the reactants are brought together from dilute solution, changes made in solvation, and then aligned for reaction, it would be expected that such processes be reflected in the entropy of activation. The 'strain or distortion' theory[4] says that if the active site of the enzyme is rigid, then the substrate is subjected to distortion in such a way that its structure must approach the transition state of the reaction in order to undergo binding; the binding energy provides the driving force which allows the substrate to bind in the distorted configuration. Similarly, the 'induced-fit' theory[5] suggests that the binding energy is utilised to bring catalytic groups into their proper position relative to a substrate to provide specificity. The two latter views both incorporate the necessity of molecular distortions, which are enthalpic processes. In general, all that can be said of activation parameters in enzyme-catalysed and non-enzymic reactions is that formation of an enzyme-substrate complex

results in a decrease in the free energy of activation.

In order to shed some light on the complicated processes involved in enzyme-catalysed reactions, it is necessary to simplify the system. This may be done by studying 'models' of enzymes and there are two main lines of approach:

(i) by modelling the whole enzyme, e.g. the enzyme carbonic anhydrase catalyses the hydration of carbonyl groups; it is found in animals, where its main function is to facilitate the excretion of carbon dioxide. It is known that metal ions, such as zinc, are necessary for it to be active and a model for the reaction is the zinc ion-catalysed hydration of pyridine-2-aldehyde: this reaction is 10^7 times faster than the spontaneous hydration by water. This is only a factor of ten slower than the enzyme-catalysed reaction. The kinetics indicate that the zinc ion and the aldehyde stoichiometry is 1:1 in the activated complex, which may be represented by figure 1.1.[6]

(ii) by bringing the reaction site of the substrate and the catalysing group together in the same molecule. The effected decrease in the free energy of activation may be interpreted here, as a movement of the reactants part-way along the reaction co-ordinate towards the transition state. This is a more general method than (i), since the concern is to gather information about the energy requirements and the effect of substituents on reactants in close proximity and to compare these intra-molecular rates with those obtained from corresponding inter-molecular processes, e.g. the di-anion of salicyl phosphate undergoes hydrolysis at a very great rate

FIGURE 1.1.

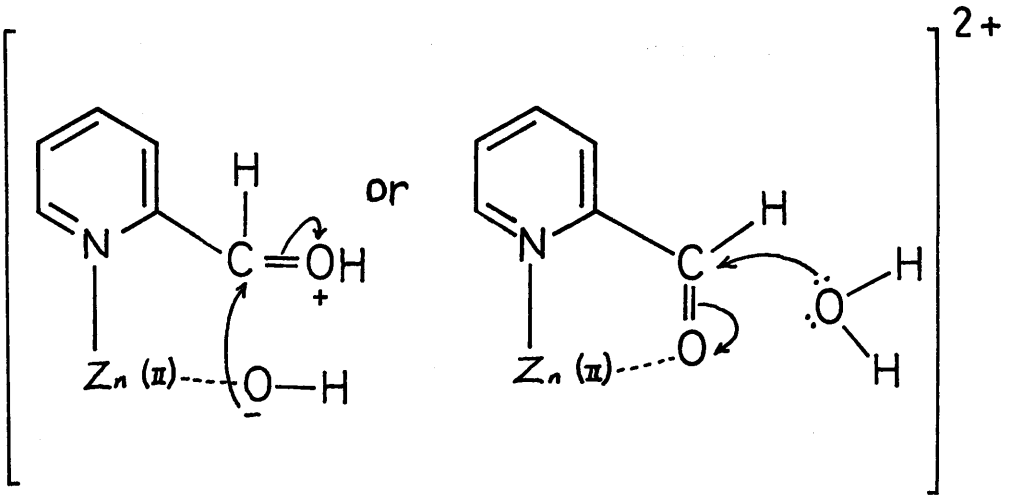
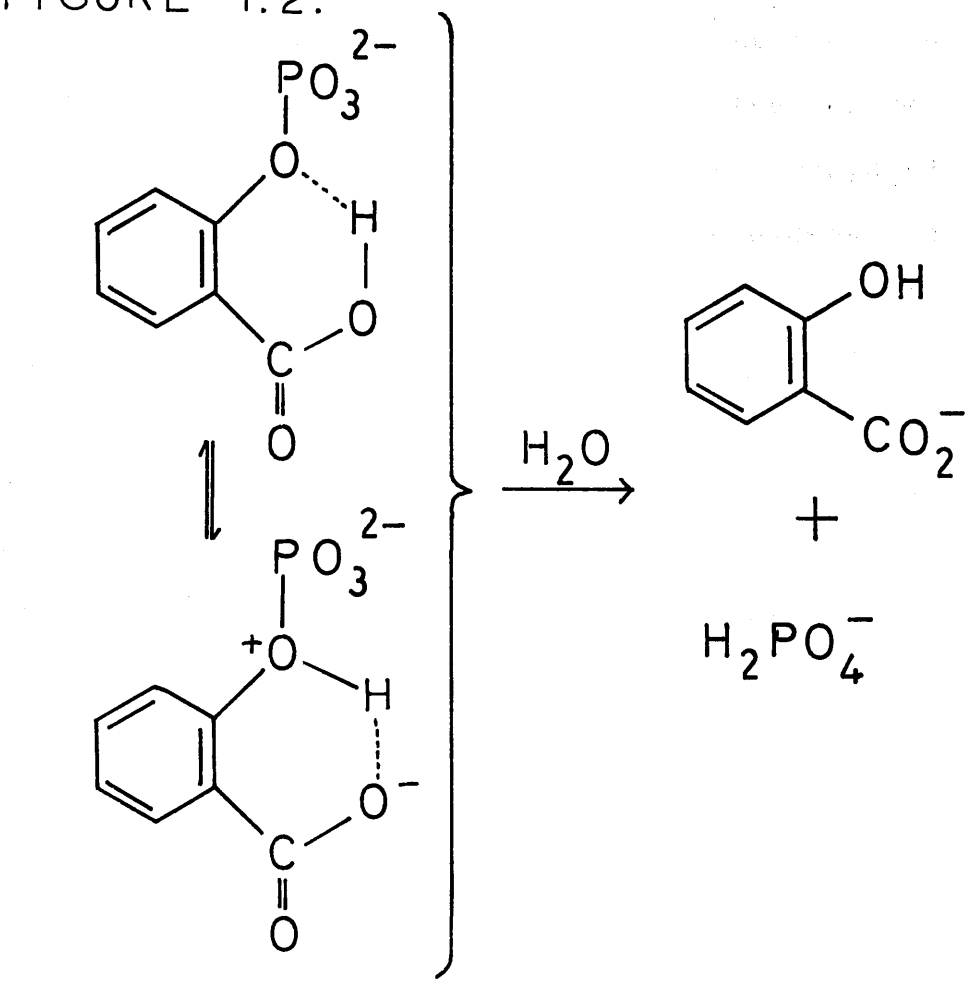


FIGURE 1.2.



relative to its para-substituted isomer. It has been shown[7] that the greater rate is due to general acid-base catalysis by the ortho-carboxylic acid group. The reaction mechanism is represented in figure 1.2.

Many systems have been studied in recent years[4] in an attempt to emulate enzymic rate enhancement. It is believed that most enzyme catalysed processes involve proton-transfer and much effort has been put into examining those reactions in which the rate-determining step is the transfer of a proton to or from the reactive site of a substrate. Such a case is the enolisation of carbonyl compounds.

Enolisation of the carbonyl-methylene group plays an important role in metabolism; in living tissue there are enzymes whose function it is to catalyse reactions involving keto-enol tautomerism, in order that further reaction may occur: e.g. during anaerobic muscular contraction the hexose chains of glycogen are broken down to produce D-glyceraldehyde-3-phosphate and di-hydroxy acetone phosphate. Only the aldehyde can react further in the pathway to lactic acid and the inter-conversion of the two products is catalysed by triosephosphate isomerase.[1,8] It has been shown by Rieder and Rose[9] that the reaction does not take place by a direct intra-molecular hydrogen transfer, since a tritium atom is incorporated when the reaction is carried out in tritiated water. Topper[10] postulated a bound enolate ion as an intermediate. Rose and Connell[11] showed by tritium labelling of D-fructose-6-phosphate on c_1 that reaction with triosephosphate isomerase produced D-glucose-6-phosphate with tritium incorporated at c_2. This

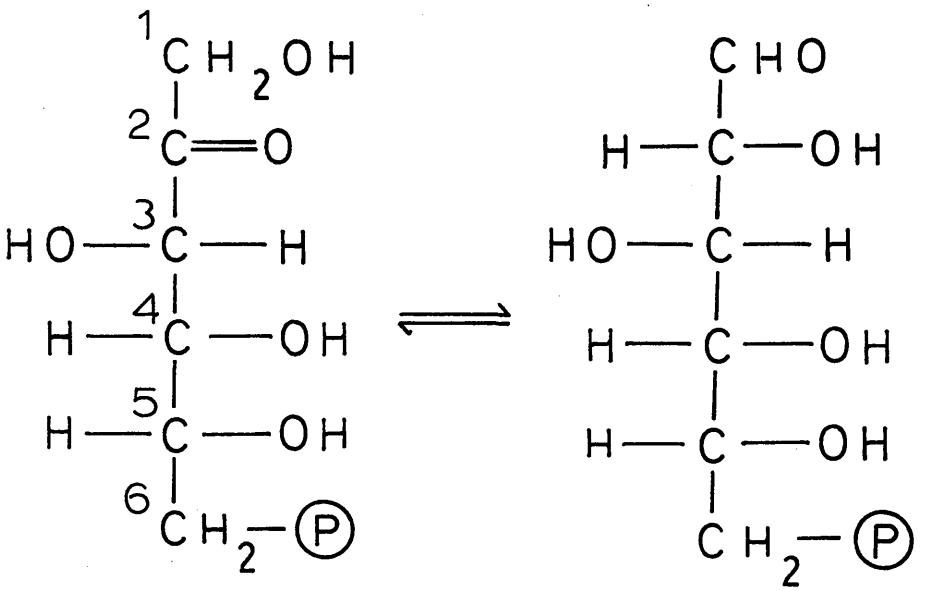
confirmed a di-enol intermediate with proton-transfer from carbon. See figure 1.3.

Enolase catalyses the removal of a water molecule from 2-phosphoglyceric acid to give phosphoenolpyruvate.[12] Pyruvate kinase catalyses the transfer of phosphate from phosphoenolpyruvate to ADP (adenosine di-phosphate) to give pyruvic acid and ATP (adenosine tri-phosphate), which serves as an energy storage unit for metabolic reactions.[13,14] See figure 1.4.

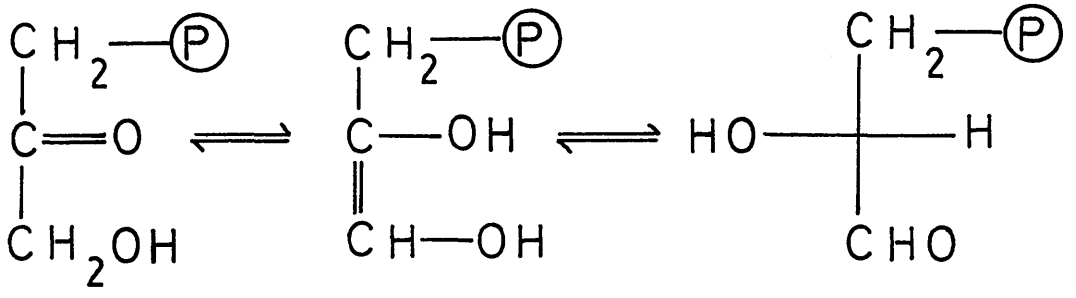
The amino-acid valine may be converted, through several stages, to methylmalonyl co-enzyme A[1], an intermediate in the synthesis of fatty acids. The asymmetric centre of the molecule can be modified by the action of methylmalonyl-CoA racemase. It has been shown[15] that racemisation does not occur by the transfer of the co-enzyme A from one carboxylic acid group to the other. Overath[16] showed that the hydrogen atom on the asymmetric centre exchanges with tritium when the reaction is carried out in tritiated water. This result was interpreted as evidence for the mechanism shown in figure 1.5. The enol produced has a planar conformation and the enzyme can add a proton to either side of the plane to give both the D- and the L-isomer.

Lowry suggested[17] that the catalytic activity of enzymes might be the result of concerted action by two or more general acid or general base catalysts at the active site, acting on different parts of the substrate. Swain and Brown[18] investigated this possibility by studying the mutarotation of tetramethyl glucose in benzene, catalysed by pyridine and phenol mixtures. It was found that the reaction followed a third-order

FIGURE 1.3.



D-FRUCTOSE-6-PHOSPHATE ⇌ D-GLUCOSE-6-PHOSPHATE



DI-HYDROXY-ACETONE PHOSPHATE ⇌ DI-ENOL ⇌ D-GLYCER-ALDEHYDE-3-PHOSPHATE

$-\text{Ⓟ} = -OPO_3^{2-}$

FIGURE 1.4.

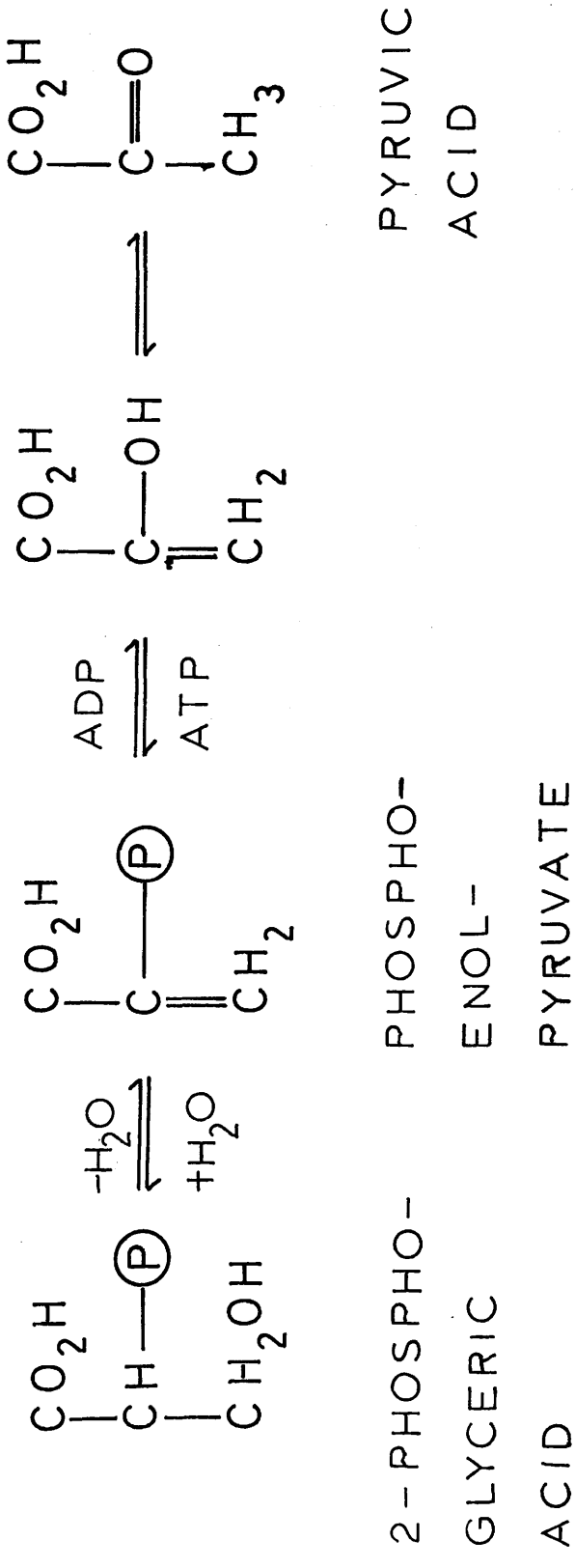

2-PHOSPHO-
GLYCERIC
ACID
PHOSPHO-
ENOL-
PYRUVATE
PYRUVIC
ACID
-H2O
+H2O
ADP
ATP

FIGURE 1.5.

OH
HO2C.C=C—CoA
CH3
O
HO2C.CH.C—CoA
CH3
(CH3)2CH.CH.CO2H
NH2
VALINE
METHYLMALONYL
CO-ENZYME A

rate law:

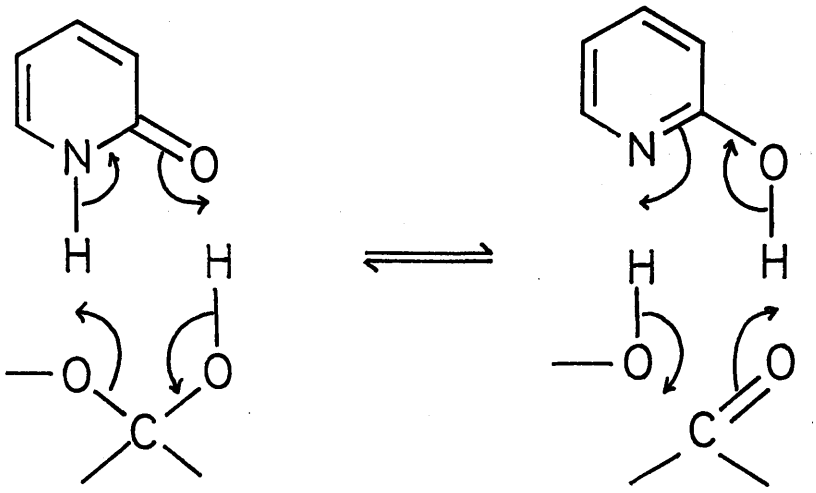
$$v = k[\text{glucose}][\text{phenol}][\text{pyridine}].$$

This indicates that both phenol and pyridine (or their conjugate ions) are required in the transition state, presumably acting as acid and base catalysts. It was further found that, in equivalent concentrations, there was a 50-fold increase in rate when the mutarotation was catalysed by 2-pyridone (figure 1.6(i)) or 2-hydroxy pyridine (figure 1.6(ii)). The mechanism of that reaction, which is schematically represented by figure 1.6(iii), is unlikely in water where there is a very high concentration of effective proton donors and acceptors. However, such a term has been detected in the kinetics of the enolisation of acetone, catalysed by acetic acid buffers;[19,20] but it is possible that this represents catalysis by the hydrogen-bonded acid-base pair $[A\text{-}H\text{---}A]^-$, rather than concerted acid-base catalysis.[19,21]

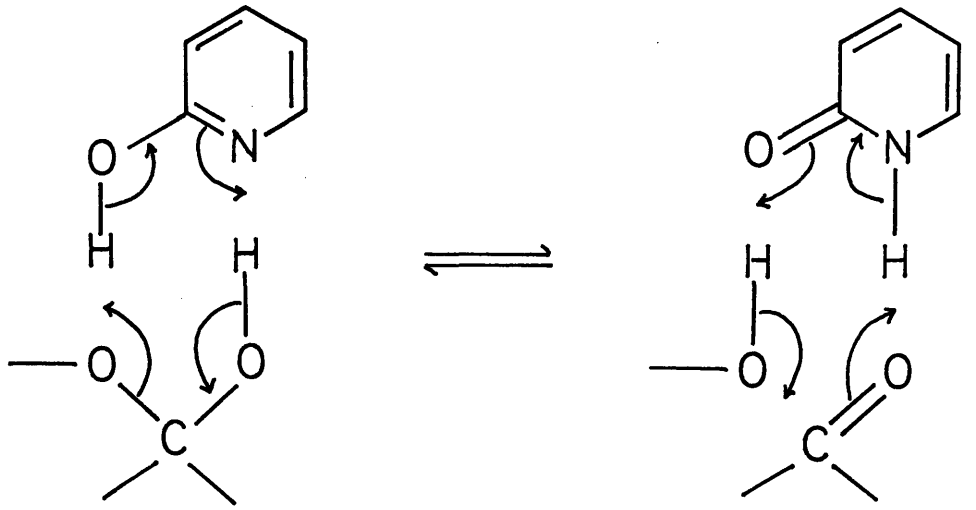
A model system for enzyme-catalysed enolisation requires the catalysing group to be linked to the carbonyl group in such a way as to facilitate the protonation of the carbonyl oxygen (acid catalysis) or the abstraction of an α-proton (base catalysis). An example of this type of system is found with keto-acids. Aromatic keto-acids have been studied by, amongst others, Harper and Bender[22] and Bell and his co-workers.[23,24] In these compounds the carbon skeleton is rigid, fixing the reacting groups in a favourable orientation for reaction. Bell and Fluendy[25] have reported intra-molecular-catalysed rates of enolisation for the aliphatic series $CH_3CO(CH_2)_nCO_2H$, where the molecule is much more flexible

FIGURE 1.6.

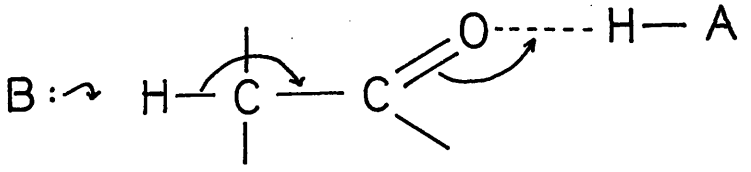
(i)



(ii)



(iii)



and reaction is correspondingly less favoured.

The substitution of bulky groups around the reaction sites in aliphatic keto-acids will alter the chemical properties and the rates of enolisation. It is the purpose of the present research to provide a quantitative assessment of those changes.

CHAPTER 2

PREPARATION OF KETO-ACIDS

In describing the preparation of the keto-acids, it will be the practice to quote references and the broad scheme of the synthesis. Purification of the compounds was carried out with no regard for maximum recovery from impure material and hence quantities of reagents and yields provide no useful information. All materials used were of normal reagent quality, but for final crystallisations, de-ionised water distilled from potassium permanganate or solvents of AnalaR grade were used.

In determining the purity of the substrates used for kinetics, several criteria had to be met. The results and any deviations from acceptability are given with each compound:

(a) melting point or boiling point in agreement with published values.

(b) NMR spectrum (obtained with a Perkin-Elmer R10 spectrometer) consistent with the structure of the compound.

(c) determined equivalent weight in agreement with the calculated value. Equivalent weights were measured by titration with BDH Concentrated Volumetric Solutions sodium hydroxide, using phenolphthalein as indicator. The results are accurate to $\pm$ 0.2%.

(i) Levulinic acid, $CH_3CO(CH_2)_2CO_2H$

The commercially available material (BDH Ltd.) was redistilled through a fractionating column.
b.pt.: 112-5°C at 0.7 torr. (lit. 124-5°C at 2.1 torr.[26])
equiv.wt.: 116.3 (calc.: 116.1)

(ii) 5-oxo hexanoic acid, $CH_3CO(CH_2)_3CO_2H$

The commercially available material (Aldrich Chemical Co.) was redistilled through a fractionating column.
b.pt.: 109-111°C at 0.6 torr. (lit. 180°C at 20 torr.[27])
equiv.wt.: 129.9 (calc.: 130.1)

(iii) 6-oxo heptanoic acid, $CH_3CO(CH_2)_4CO_2H$

The preparation used was that of Ruzicka, Seidel, Schinz and Pfeiffer.[28]
2-methyl cyclohexanone was oxidised by chromium trioxide in dilute sulphuric acid. The final product was crystallised four times from dry diethyl ether.
m.pt.: 36-8°C (lit. 30-42°C - several sources[29])
equiv.wt.: 144.6 (calc.: 144.1)

(iv) 2-methyl levulinic acid, $CH_3COCH_2CH(CH_3)CO_2H$.

The acid was prepared by a standard acetoacetic ester synthesis with ethyl 2-bromopropionate and subsequent hydrolysis with dilute aqueous caustic soda.[26] The final product was distilled three times.
b.pt.: 94-6°C at 0.5 torr. (lit.: 106-8°C at 0.7 torr.)
equiv.wt.: 129.2 (calc.: 130.1)

(v) 2,2-dimethyl levulinic acid (mesitonic acid), $CH_3COCH_2C(CH_3)_2CO_2H$

The preparation used was that of Lapworth,[30] but with a modification.

One mole of mesityl oxide in six times its weight of boiling alcohol was added to a solution of two moles of potassium cyanide in three times its weight of hot water. The solution was heated for 15 minutes on a water bath and then cooled. One third of a mole of ferrous sulphate was added and the solution brought back to the boil, being kept alkaline by the addition of caustic soda. The precipitated potassium ferrocyanide was filtered off and the filtrate diluted with water. The solution was extracted with ether to remove the mesitononitrile reaction product. Evaporation of the ether yielded a very small quantity of brown oil. Lapworth's method was to treat this nitrile residue with concentrated hydrochloric acid to hydrolyse it to the corresponding acid. Since the quantity of nitrile obtained was so small it was discarded.

However, it had been noticed that the filtrate from the precipitated potassium ferrocyanide smelled of ammonia. This could only have arisen from the hydrolysis products of mesitononitrile. The solution was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal solution was dried and evaporated to give a brown oil. The residue was crystallised six times from ethyl bromide/hexane, to give colourless crystals.

m.pt.: 74-6°C. (lit.: 75.5-76.5°C)

equiv.wt.: 143.9 (calc.: 144.1)

(vi) 3-methyl levulinic acid, $CH_3COCH(CH_3)CH_2CO_2H$

Methyl 2-bromoethyl ketone was prepared by the method of Catch, Elliot, Hey and Jones.[31]

3-methyl levulinic acid was then prepared by the method of Adams and Long.[32]

The bromo-ketone was condensed with diethyl sodio-malonate. The di-ester product was hydrolysed with alcoholic caustic potash and the di-acid decarboxylated by heating to 140°C. The residue was distilled twice, crystallised twice from ethyl bromide/hexane and redistilled to give colourless crystals on condensing.

b.pt.: 82-4°C at 0.1 torr. (lit.: 95-7°C at 0.3 torr.)

m.pt.: 30-32°C (lit.: 28-31°C)

equiv.wt.: 130.2 (calc.: 130.1)

(vii) 3,3-dimethyl levulinic acid, $CH_3COC(CH_3)_2CH_2CO_2H$

Ethyl 3,3-dimethyl succinate was prepared by the method of Baumgarten and Gleason.[33]

Zinc-copper couple was prepared by the method of Simmons and Smith.[34]

Zinc methyl iodide was prepared by the method of Birch, Kon and Norrish.[35]

Zinc methyl iodide was added to the acyl chloride derivative of the half-ester, prepared by the action of thionyl chloride and the resulting ester was hydrolysed with dilute caustic soda. The product was distilled twice and

crystallised three times from methylene dichloride/hexane.
m.pt.: 42-4°C. (lit.: 44°C[26])
equiv.wt.: 130.0 (calc.: 130.1)

(viii) 2,2,3-trimethyl levulinic acid, $CH_3COCH(CH_3)C(CH_3)_2CO_2H$

The preparation used was that of Bardhan.[36]

Ethyl 3-hydroxy-2,2,3-trimethyl n-valerate was prepared by the Reformatsky reaction with methyl ethyl ketone and ethyl 2-bromo iso-butyrate. The hydroxy-ester was dehydrated by distillation from phosphorus pentoxide and the resultant unsaturated ester hydrolysed with 10% methyl-alcoholic caustic potash. The unsaturated acid was treated with excess bromine and distilled to give the lactone of 4-hydroxy-2,2,3-trimethyl pent-3-enoic acid. The unsaturated lactone was hydrolysed with caustic potash and acidified to yield the 2,2,3-trimethyl levulinic acid as a green oil. The oil was crystallised four times from ethyl bromide/40-60 petroleum ether to give large, colourless crystals.
m.pt.: 77-8°C. (lit. 77-8°C)
equiv.wt.: 158.0 (calc.: 158.1)

(ix) 5,5-dimethyl 4-oxo hexanoic acid, $(CH_3)_3CCO(CH_2)_2CO_2H$

ω-bromopinacolone was prepared by the method of Jackman, Klenk, Fishburn, Tullar and Archer.[37]

5,5-dimethyl-4-oxo-2-carbethoxy hexanoate ester was prepared by the action of the bromoketone on diethyl sodio-malonate. The di-ester was refluxed with concentrated

hydrochloric acid to give 5,5-dimethyl-4-oxo hexanoic acid. The product was crystallised four times from 60-80 petroleum ether and twice from diethyl ether.

m.pt.: 64-6°C (lit.: 65-6°C.[38])

equiv.wt.: 157.1 (calc.: 158.1)

(x) 3-benzoyl propionic acid, $PhCO(CH_2)_2CO_2H$

The preparation used was that of Somerville and Allen.[39]

Succinic anhydride and aluminium chloride were warmed in benzene to yield a brown solid. The solid was extracted with sodium hydroxide and the crude 3-benzoyl propionic acid was precipitated from aqueous solution on acidification. The resultant white solid was crystallised three times from water to give colourless needles.

m.pt.: 115-6°C. (lit.: 116°C)

equiv.wt.: 178. 3 (calc.: 178.1)

(xi) 4-benzoyl butyric acid, $PhCO(CH_2)_3CO_2H$

The method of preparation was that used for 3-benzoyl propionic acid, except for the substitution of glutaric for succinic anhydride. The product was crystallised four times from water to give colourless needles.

m.pt.: 127-8°C (lit.: 132°C.[40])

equiv.wt.: 192.0 (calc.: 192.1)

(xii) 5-benzoyl pentanoic acid, $PhCO(CH_2)_4CO_2H$

The preparation used was that of Hill.[41]

Adipic acid was refluxed with acetic anhydride to give the poly-anhydride of adipic acid, which was added as a benzene solution to aluminium chloride in benzene. The procedure then followed that described for 3-benzoyl propionic acid. The product was crystallised three times from water and once from benzene/hexane to yield a white, crystalline solid.

m.pt.: 77-8°C. (lit.: 70-71°C)

equiv.wt.: 207.0 (calc.: 206.1)

CHAPTER 3

PART (i): INTRODUCTION TO RING-CHAIN TAUTOMERISM

The word tautomerism was proposed by Laar[42] to describe the mobile equilibrium between two compounds containing weakly bonded hydrogen atoms.

Jones[43] has recently published a comprehensive review of the subject and was able to draw some general conclusions from the data available. The structural requirements for ring-chain tautomerism can be stated in general terms with regard to the chain tautomer: it must possess at least two functional groups, one containing a multiple bond and the other capable of effecting an addition reaction at the multiple bond. Jones distinguishes between 'electrophilic' and 'nucleophilic' tautomerism, shown in figure 3(i).1. The tautomeric equilibrium of the type exhibited by the compounds presently under consideration is also shown; it is an example of electrophilic tautomerism. Three generalisations may be made concerning ring-chain tautomerism which are applicable to this system:

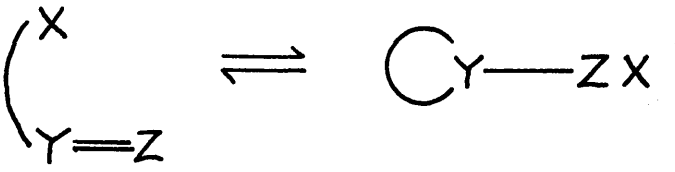
(a) in the case of acids and acid derivatives, the acid salts are always acyclic.

(b) 5- or 6-membered rings are formed preferentially; when either may arise from a chain structure, the 5-membered ring is usually favoured.

(c) ring stability increases with increasing substitution by alkyl groups.

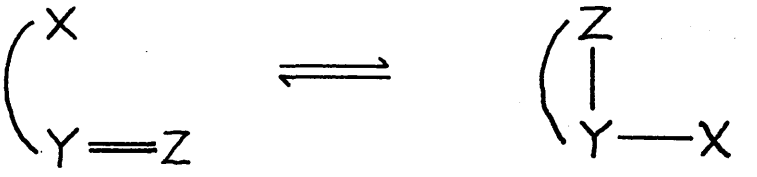
FIGURE 3(i).1.

ELECTROPHILIC TAUTOMERISM:

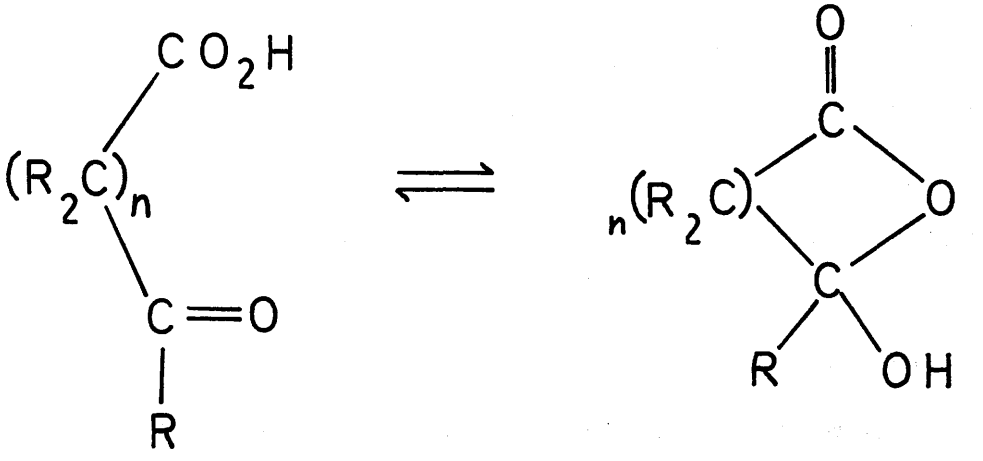


X = ELECTROPHILE

NUCLEOPHILIC TAUTOMERISM:



X = NUCLEOPHILE



R = H, ALKYL, ARYL.

In the present research, ring-chain tautomerism in alkyl-substituted aliphatic keto-acids was investigated. The effect of gem-dialkyl groups in favouring cyclic rather than acyclic species is well known and is generally termed the 'gem-dimethyl' effect. Some of the examples of this effect will be presented, followed by some of the explanations offered to account for it.

Glutaric anhydride is easily decomposed with water, 3,3-dimethyl glutaric anhydride may be boiled in water for hours with little change and 2,2,3-trimethyl glutaric anhydride crystallises from hot water with water of crystallisation.[44]

In the nineteen twenties, great interest was shown in the properties of a compound called Balbiano's acid, which is the major product from the oxidation of camphoric acid with hydrogen iodide and red phosphorus.[45] Thorpe showed the presence, in this compound, of the cyclic tautomer of 3,3,4-trimethyl-2-oxo glutaric acid.[46] Qudrat-I-Khuda summarised the effect of methyl groups on the ring-chain equilibrium in 3,3-dimethyl-2-oxo glutaric acid[47] (see figure 3(i).2).

Rothstein and Shoppee[49] compared the stability of the hydroxy-lactone ring of Balbiano's acid and its methyl derivative (compounds (b) and (c) in figure 3(i).2) by boiling for several hours with baryta solution and measuring the extent of ring-opening:

FIGURE 3 (i). 2.

CHAIN ONLY 48.
CHAIN AND RING 46.
RING ONLY 49.
(CH3)2 C.CO.CO2H
CH2.CO2H
(a)
(CH3)2 C.CO.CO2H
CH3.CH.CO2H
BALBIANO'S ACID
(b)
(CH3)2 C.CO.CO2H
(CH3)2 C.CO2H
(c)
CO2H
HO
O
C
C=O
(CH3)2 C
R2 C

COMPOUND	BARYTA CONC.	% FISSION
Balbiano's acid (b)	N/100	100
	N/10	100
methyl deriv. (c)	N/100	40
	N/10	95

Dutt[50] investigated the effect of methyl substitution and chain-length on ring-tautomer formation, by examining derivatives of phenolsuccinein and phenolglutarein, shown in figure 3(i).3. In dilute solution, when R=R'=H, it was found that the 5-membered ring is more stable than the 6-membered ring. In the phenolglutarein series, it was shown that, by following the disappearance of the red-coloured chain-form, III, in dilute alkali, the formation of species II was first order in III and the rate increased in the series:

$$R,R' = H,H < H,Me < Me,Me.$$

In figure 3(i).4, the equilibrium for the tetramethyl compound I lies far to the right i.e. in favour of the ring,[51] but the unsubstituted compound, II, does not react in the ring-form, showing only a tendency to pass into a 5-membered ring by the elimination of water.[52]

All attempts to prepare the anilic acid and acid chloride of tetramethyl succinic acid have failed; the ring anil and anhydride being invariably formed.[53]

Linstead and Rydon[54] estimated the stability of substituted 4-butyrolactones by boiling for 48 hours with soda-lime, then analysing for unchanged lactone:

FIGURE 3(i).3.

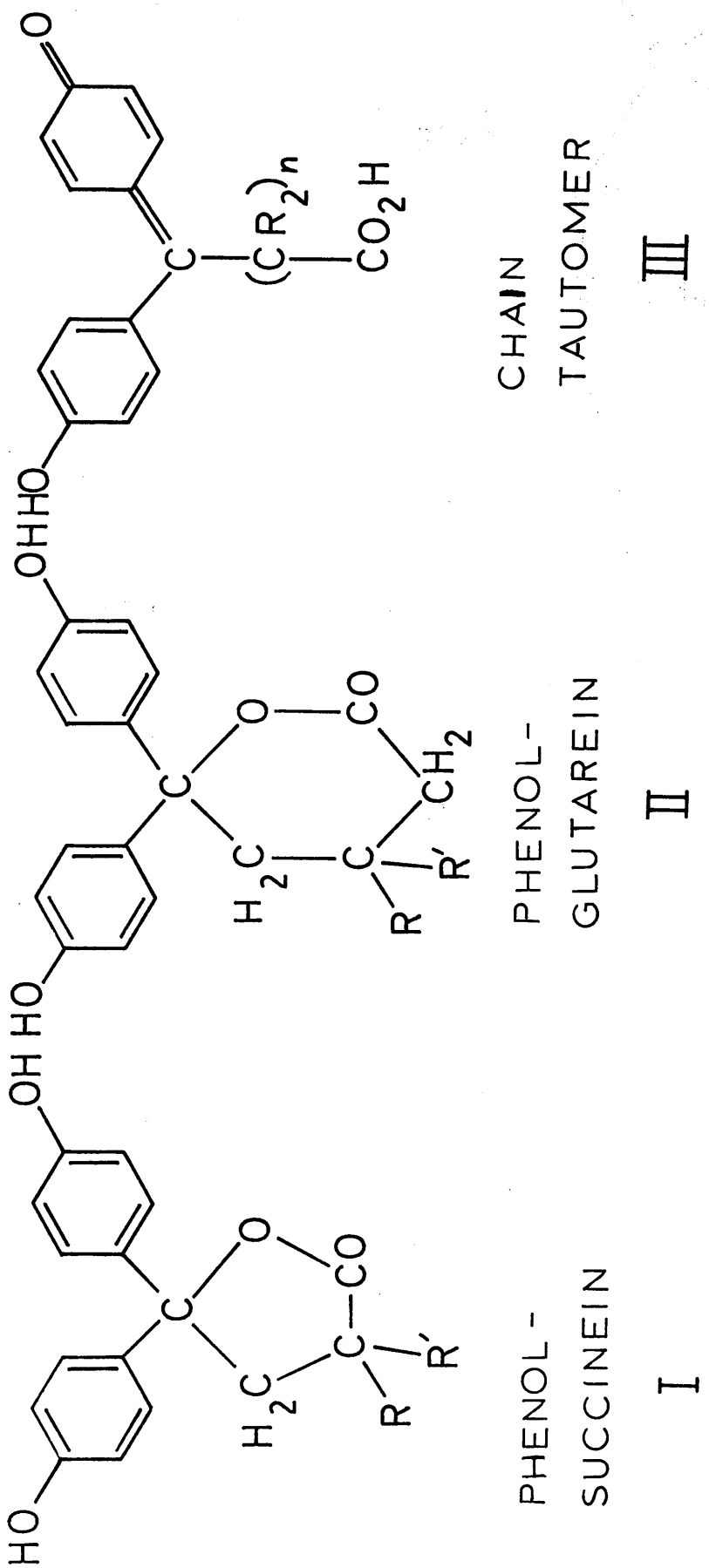
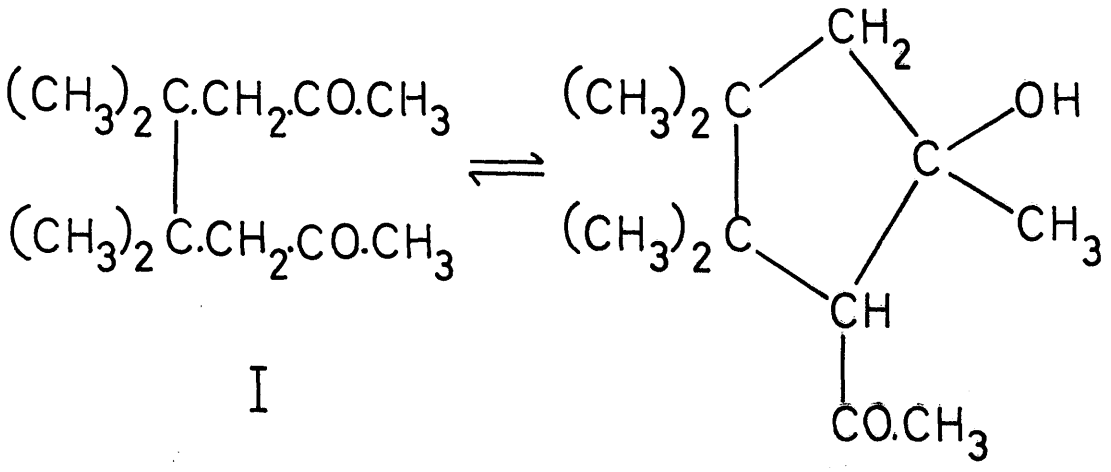
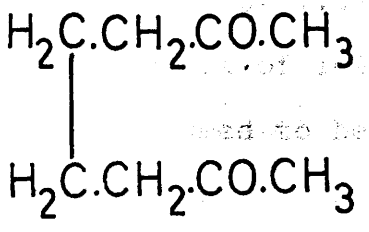

O
$(CR_2)_n$
CO_2H
OH HO
O
CO
CH_2
H_2C
C
R
R'
HO
CHAIN TAUTOMER
III
PHENOL-GLUTAREIN
II
PHENOL-SUCCINEIN
I

FIGURE 3(i).4.



I



II

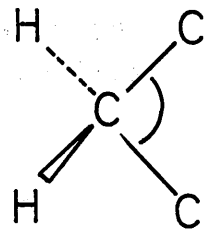
LACTONE	% UNCHANGED
unsubstituted	75.1
4-methyl	92.7
4,4-dimethyl	95.1

Thorpe and his co-workers claimed to have proved conclusively that geminal-dialkyl substitution on a carbon atom affected the remaining two valencies by reducing the angle between them, which favoured ring-closure by reducing angle-strain in the cyclic species. Ingold[55] calculated values for the modified valence angles by assuming that the groups exerted a spherical domain proportional to their atomic volumes (figure 3(i).5). The values may be compared with his calculated value of 109.5° for the normal tetrahedral angle, which was assumed to be normal only when the carbon was quaternary. Ingold pointed out that these effects are not due to the repulsion between electrically similar methyl groups, but are essentially connected with volume relations. This is demonstrated by cases in which electrically dissimilar groups, such as methyl and carbethoxyl can take the place of the gem-dimethyl grouping e.g. dimethyl diacetyl-succinic ester is converted, under exceedingly mild conditions, to a 5-carbon ring ketone, but the analogous reaction of the unmethylated derivative cannot be brought about.[56]

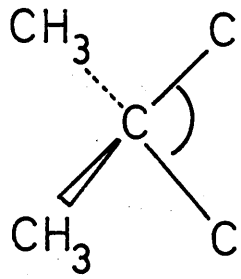
Brown and van Gulick[57] investigated the gem-dialkyl effect on the rate of ring-closure of 4-bromobutylamines.

FIGURE 3(i).5.

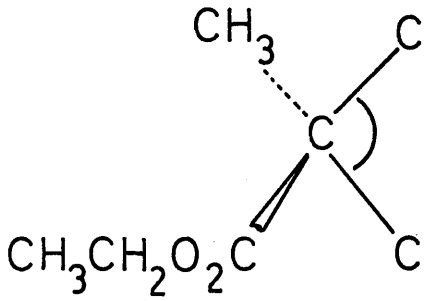
CALCULATED ANGLE



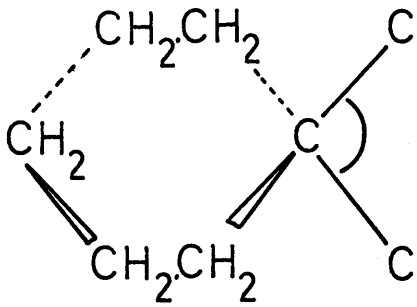
115·3°



109·5°



109·5°



107·2°

	COMPOUND	RELATIVE RATE
(i)	4-bromobutylamine	1.0
(ii)	1,1-dimethyl	2.2
(iii)	2,2-dimethyl	158
(iv)	3,3-dimethyl	0.16
(v)	2,2-diphenyl	5250
(vi)	2,2-di-iso-propyl	9190

The series (i) - (iii) shows the common trend of increasing rate when a gem-dimethyl group is present and an enhanced increase when that gem-dimethyl carbon is quaternary. The decrease in rate on going from (i) to (iv) is an example of the unreactivity of neo-pentyl halides to Sn2 reaction, which, it is generally agreed, is due entirely to steric factors, since the methyl substituents are too far from the centre of reaction to exert an appreciable polar effect.[58,59] The series (i), (iii), (vi) verifies the observations of Thorpe and his co-workers that increasing the size of the alkyl groups increases the tendency to ring-closure. Moreover, the results, quoted above, would seem to exclude electronic effects of the substituents as exerting anything other than a minor influence on the rate, as phenyl and iso-propyl groups have opposite electronic effects, but similar steric requirements. In the discussion the authors suggested that substitution profoundly affects the distribution of rotational configurations by reason of non-bonded interactions with the chain, favouring coiled configurations over what would be the energetically preferred extended configuration of the parent molecule. This implies

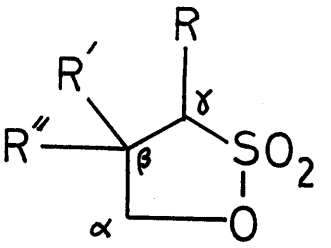
that the decrease in entropy for a rotationally-restricted, coiled molecule, upon going into the transition state, would be less than that for the parent molecule and thus would increase the cyclisation probability.

Bordwell, Osborne and Chapman,[60] using their own results and those of Nilsson,[61] attempted to rationalise the effect of methyl substitution on the ring-opening solvolysis of 5-membered ring sultones (see figure 3(i).6):

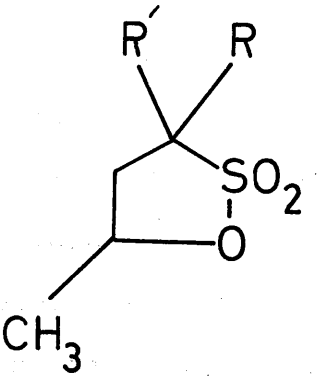
COMPOUND I		R	R'	R"	RELATIVE RATE (40°C)
	(a)	H	H	H	1.0
	(b)	H	Me	H	0.21
	(c)	H	Me	Me	0.0035
	(d)	Me	H	H	1.4
COMPOUND II		R	R'		
	(e)	H	H		1.3
	(f)	Me	Me		0.7
COMPOUND III		R	R'	R"	
	(g)	H	H	H	3100
	(h)	H	H	Me	170
	(i)	H	Me	Me	18
	(j)	Me	H	Me	3.7

	E_a (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} deg^{-1} at 40°C)
(a)	85	-58
(b)	-	-
(c)	94	-78
(d)	81	-69
(e)	89	-44
(f)	77	-86
(g)	85	+9.6
(h)	80	-31
(i)	85	-36
(j)	82	-58

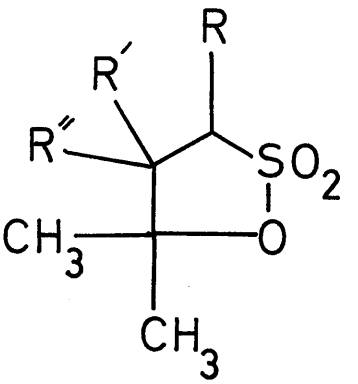
FIGURE 3(i).6.



I



II



III

The three series: (a) to (c)
(e) to (f)
(g) to (i)

show the expected stabilisation due to increased alkyl substitution. The authors examined at length the series (g) to (j) to exemplify their thesis that the general effect in operation is steric hindrance to rotation during the ring-opening process. This theory becomes clearer on examination of Fischer projections of the reaction sequence, shown in figure 3(i).7. If it is assumed there is a staggered conformation in the ground state, the hydrolysis may be pictured as involving ion-pair formation and rotation about c_α-c_β and c_β-c_γ to allow separation of the ions. It is apparent that both rotations are required for complete separation. This view of the reaction is supported by the series (a), (e) and (g) i.e. going from a primary to a tertiary sultone, where a rate increase is observed due to stabilisation of the carbonium ion. It was pointed out that the larger decrease in entropy of activation from (h) to (j) than from (h) to (i) is consistent with steric hindrance and the requirement of both rotations.

Bordwell thus regards the solvolysis rate differences as arising from steric considerations which are manifested in the entropy of activation and he disregards the Thorpe-Ingold valence angle effect insofar as there was no experimental measurement of bond-angle modification available. However Kuhn,[62] in an examination of hydrogen-bonding in glycols by infra-red spectroscopy, obtained results, interpreted in terms of a decrease in hydrogen-bond length in the series given in figure 3(i).8. He attributes the difference between

FIGURE 3(i).7.

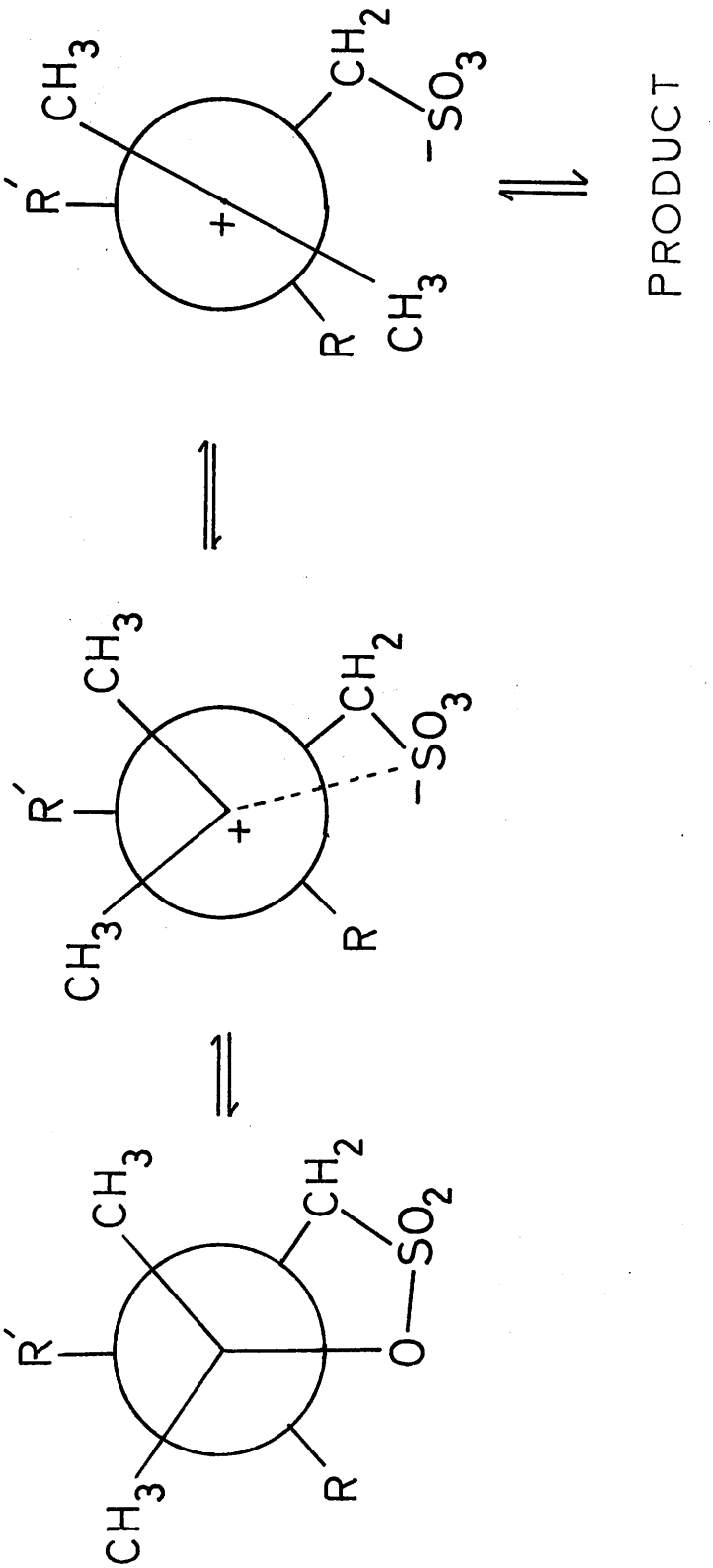

CH3
R'
CH2
-SO3
+
R
CH3
PRODUCT
CH3
R'
CH2
-SO3
+
CH3
R
CH3
R'
CH2
SO2
O
CH3
R

FIGURE 3(i).8.

OH
OH
H
H
CH3
CH3
dl-BUTANE
23-DIOL
III
OH
OH
H
H
CH3
CH3
meso-BUTANE
2,3-DIOL
II
OH
OH
H
H
H
H
ETHYLENE
GLYCOL
I

the substituted diols and the unsubstituted diol as due to Thorpe-Ingold deformation and the difference between II and III as due to steric interactions, which may be appreciated from the Fischer projections, since intra-molecular hydrogen-bonding is facilitated by the approach of the hydrogen groups, which must involve a decrease in the dihedral angle, ϕ. Similarly, Eberson[63] reports an increase in intra-molecular hydrogen-bonding (detected by I.R.) in alkyl succinic acids with increasing substitution and increasing size of substituents. Schleyer[64] has studied hydrogen-bonding in substituted propane-diols by I.R. and has calculated the carbon chain bond angle for the compounds $RR'C(CH_2OH)_2$:

R	R'	angle C-C-C
H	H	112.2°
H	1° alkyl	110.5°
1° alkyl	1° alkyl	109.5°

He also quotes accurately measured values for angles in hydrocarbons:

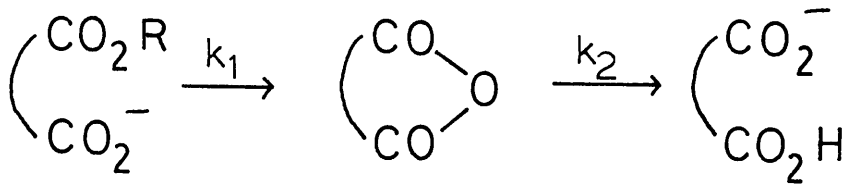
COMPOUND	angle C-C-C	METHOD
propane	112.4°	micro-wave[65]
iso-butane	111.1°	micro-wave[66]
neo-pentane	109.5°	electron diffraction[67]

Schleyer estimates the benefit, due to the Thorpe-Ingold effect, of one gem-dimethyl group in the cyclisation of n-hexane, to be only 0.8 kJ mol^{-1}. From the work of Allinger and Zalkow,[68] that contribution is small compared to other conformational and thermodynamic influences. The authors compared experimental

values of energy terms found for ring-closure of substituted hexanes with theoretical values. In short, the enthalpy change was calculated from a basis of minimum enthalpy in the chain and the ring and then consideration of the number of gauche interactions. The entropy change was calculated from the number of isomers, the symmetry of the species and the branching in the molecule. Reasonable agreement was found between the calculated and experimental values and in all cases of substitution, there was a shift in the equilibrium towards the cyclic compound. Neither the enthalpy nor the entropy could be credited with providing exclusively the driving force for the reaction. If the closure of the ring is a rate-determining step, then the argument may be applied to values of $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$, since activation energies are determined by an equilibrium between the open-chain species and the transition state, which may be considered to have a modified cyclic geometry. The authors also claim that the data available for ring-closure to 5-membered species shows a qualitative parallelism, but theoretical values are not readily accessible because of the indefinite ring conformations.

Bruice and Pandit[69] measured the rate of hydrolysis of monophenyl esters of alkyl-substituted dibasic acids. The reaction under consideration is shown in figure 3(i).9. In all cases the variation of reaction rate follows the expected sequence. The difference between the rates for glutaric and succinic compounds will be discussed later in chapter 4. In their view, the observation of the gem-dimethyl effect in the solvolysis of the anhydride cannot be explained by employing

FIGURE 3(i).9.



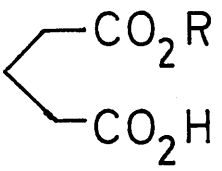
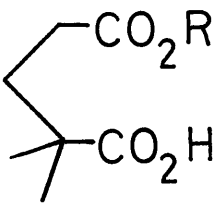
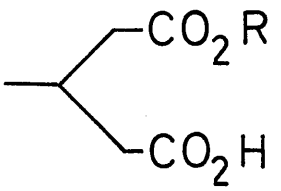
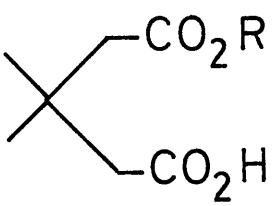
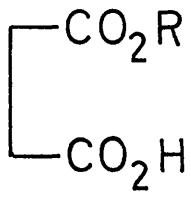
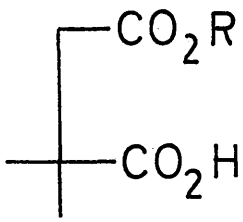
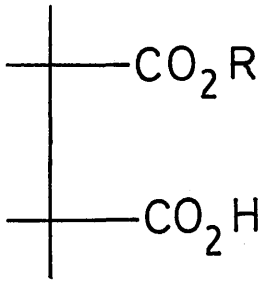
ESTER	$k_1 \times 10^3$ min.$^{-1}$ *	$k_2 \times 10^3$ min.$^{-1}$ **
	4·44	230
	16	76
	19·4	140
	85	17

FIGURE 3(i).9. cont.

ESTER	$k_1 \times 10^3 min^{-1}$ *	$k_2 \times 10^3 min^{-1}$ **
	102	340
	320	210
	10	

** pH 6·5
35°c.
28·5% v/v EtOH/H_2O

* 30°c.
50% v/v DIOXAN/H_2O

R = p-BROMOPHENYL
p-METHOXYPHENYL

Bordwell's concept of steric hindrance to ring-opening, since only the rate of nucleophilic attack, k_1, can be kinetically important. For the same reason the Thorpe-Ingold hypothesis is dismissed. The authors propose two contributions as being most logical:

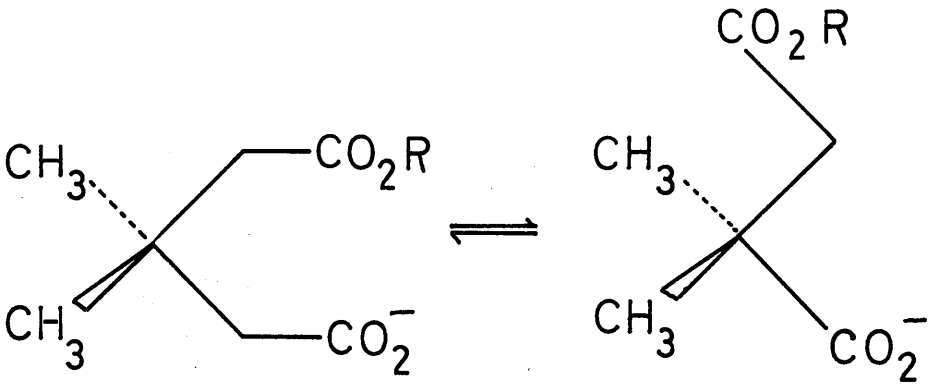
(a) the ring-closure reaction proceeds at a greater rate with alkyl-substitution because of the resultant decrease in unprofitable rotamer distribution,

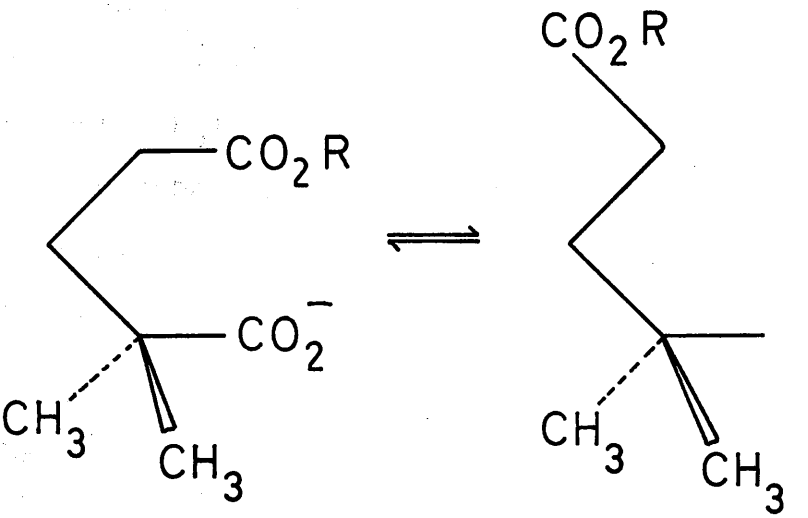
(b) the negative gem-dimethyl effect on ring-opening is due to steric hindrance to the approach of lyate species to the anhydride carbonyl group.

Thus, in succinic acid, steric hindrance and charge repulsion make the trans-configuration of the carboxyl groups the more stable conformation. The introduction of alkyl groups decreases the stability of the trans-configuration relative to the cis, because of non-bonded repulsion between the alkyl and carboxyl groups. It was proposed that the increase in rate of anhydride formation, accompanying gem-disubstitution is due to a decrease in the probability of the unprofitable rotamer distributions, in which the reacting groups have rotated away from each other. A similar argument may be applied to the glutaric acid derivatives.

The greater enhancement of rate due to 3,3- over 2,2-disubstitution in the formation of glutaric anhydride is accounted for by the 3,3-configuration affording maximum steric repulsion to the rotation of the carboxyl and ester groups away from each other i.e. the groups are more constrained to occupy a close juxtaposition, as shown in figure 3(i).10.

FIGURE 3(i).10.





For anhydrides with the same steric demands, it was postulated that the rate of solvolysis should be related to the apparent dissociation constant, K_a', of the mono-ester by the linear free energy equation:[70]

$$\log \frac{k_2}{k_o} = E \log \frac{K_a'}{K_o'}$$

Steric hindrance to the approach of lyate ions and molecules will decrease the $\log(k_2/k_o)$ values by an amount, designated S, leading to the expression:

$$\log \frac{k_2}{k_o} = E \log \frac{K_a'}{K_o} - S$$

Plotting $\log(k_2/k_o)$ against $\log(K_a'/K_o')$, using succinic anhydride and p-bromophenyl and p-methoxyphenyl succinate as references, it was found that a straight line could be drawn through the points for unsubstituted species; deviations from this line are regarded as steric parameters:

ANHYDRIDE	S
glutaric	0
succinic	0
maleic	0
exo-3,6-endoxo-Δ^4-tetrahydrophthalic	0
3-methyl glutaric	0.1
3,3-dimethyl glutaric	1.13
2,2-dimethyl glutaric	0.45
2,2-dimethyl succinic	0.21
tetramethyl succinic	1.40

Inspection of the table reveals that the differences in the rates of solvolysis of the first four anhydrides are attributable to electronic effects only. Thus, Bruice and Pandit are proposing that the gem-dimethyl effect is due both to an enthalpic contribution (steric interactions) and an entropic contribution (rotamer distribution).

Storm and Koshland[71] have measured the equilibrium constants and rates of lactonisation of some hydroxy-acids. A rough, but not exact, parallel was found between the forward rates and the equilibrium constants i.e. the transition state is product-like. It is suggested that the rates are caused by a selection of ground states, in the open-chain analogues, for those geometries which react most readily and that the confined geometry of the intra-molecular compounds has selected those ground states which are already in a highly favourable geometry or those which can readily assume a highly favoured transition state geometry.

It is now possible to summarise the current views of the factors which go to make up the gem-dimethyl effect:

(a) Thorpe-Ingold valence bond deformation contributes little,

(b) inductive effects contribute little. In fact, it may be difficult to assign the direction of this effect, e.g. the commonly held view that methyl groups exert a +I effect is exemplified by the studies of Rydon and Linstead[72] on the effect of methyl groups on lacto-enoic tautomerism, but Jackman and Kelly,[73] in an NMR study of aliphatic ketones, have obtained results which they rationalised in terms of a -I effect,

(c) although it might appear that entropy considerations provide the driving force for ring-formation, it is certain that enthalpic considerations cannot be disregarded.

In 1886, Bredt published his much quoted research on the keto-lactol tautomeric equilibrium of levulinic acid.[74] By treating levulinic acid with acetic anhydride, an acetyl derivative of the acid was prepared. All possible structures were considered and from the observations that the new compound had no acidic properties and distillation yielded α- and β-angelica-lactones (cyclic lactones), it was concluded that it was the acyl derivative of the ring tautomer. Hence, it was deduced that levulinic acid exists predominantly in the ring-form. This work will be discussed further later.

Qudrat-I-Khuda[75] showed that 3,3-diethyl-4-oxo hexanoic acid exists in its lactol form and quoting Bredt, suggested that alkyl-substituted levulinic acids should exhibit a lactol modification, the extent of which would depend on the amount of substitution. He proposed, in the paper, to determine the effect of structure on the equilibrium, but a search of the literature failed to reveal any published results.

More recently, Pascual and his co-workers[26] have estimated the keto-lactol equilibrium constants for several methyl-substituted levulinic acids. Consider the equilibria:

$$\underset{\text{LACTOL}}{AX} + \underset{\text{SOLVENT}}{LH} \overset{K_x}{\rightleftharpoons} \underset{\text{KETO-ACID}}{AH} + \underset{\text{SOLVENT}}{LH} \overset{K_o}{\rightleftharpoons} \underset{\text{CHAIN ANION}}{A^-} + LH_2^+$$

$$K_x = \frac{a_{AX}}{a_{AH}} \quad \text{and} \quad K_o = \frac{a_{A^-} \cdot a_{LH_2^+}}{a_{AH}}$$

Hence, it can be shown:

$$\log(K_x + 1) = pK - pK_o$$

where: pK_o is the pK of the chain acid

pK is the pK of the equilibrium mixture of the ring and chain acids.

Experiments were carried out in 80/20 v/v methylcellusolve/water at 25°C, using approx. 4×10^{-3}M total acid concentration. pK was determined by titrating the acid. The assumption was then made that levulinic acid exists solely as the chain tautomer, an α-methyl increases pK_o by 0.22[76] and β-methyls do not significantly affect pK_o.[70] The following results were obtained:

compound	pK_o	pK	K_x	% ring
levulinic acid	6.9	6.87	0	0
2-methyl	7.1	7.00	0	0
2,2-dimethyl	7.3	7.52	0.7	41
3-methyl	7.1	6.84	0	0
3,3-dimethyl	7.1	6.92	0	0
2,2,3-trimethyl	7.3	8.24	7.7	88

The results were verified qualitatively by I.R. and N.M.R. spectroscopy.

Jones[43] has pointed out the dangers of estimating tautomeric equilibria by chemical methods, in that there is the implicit assumption that the relative amounts of ring and chain species are the same in the presence of reagents as in the pure form, formation of derivatives is faster than equilibration and that chain tautomers react to form only acyclic derivatives, while ring tautomers react to form only cyclic derivatives. These points may be illustrated by the following figures:

COMPOUND	% RING		
	method (a)[77,78]	method (b)[78]	method (c)[79,23,24]
2-formyl benzoic acid	31		94
2-acetyl benzoic acid	0		81
3,4,5,6-tetrachloro-2-acetyl benzoic acid		17	92

where: method (a) utilised the well known fact that organo-cadmium reagents do not ordinarily attack carbonyl or acid functions. It was argued that reaction must only occur with the hydroxyl of the ring tautomer and yields of methyl derivatives obtained by reaction with methyl cadmium chloride would be an estimate of the ring tautomer. The reaction was carried out in organic solvent.

method (b) involved the analysis, by I.R., U.V. and N.M.R. spectroscopy, the mixture of normal and pseudo-methyl esters obtained by Fischer-Speier esterification.

method (c) is an extension of the method of Pascual[26] in which pK_o was determined from kinetic measurements of the general base-catalysed decomposition of nitramide. The results quoted above refer to dilute aqueous solution. (This method is

discussed fully below.)

Results which depend upon a chemical step in their derivation must be scrutinised closely, even when supplemented by a physical technique. Having obtained a mixture of normal and pseudo-esters of 2-formyl and 2-acetyl esterification, subsequent qualitative I.R. examination by Jones[77,78] was reported to confirm open-chain structures. However, Grove and Willis,[80] using the same procedure, claimed a preponderance of ring tautomers.

It is apparent that full reliance can be placed only on purely physical techniques for measuring tautomeric equilibria and it is necessary to state the conditions to which the figures refer.

$r = [HL]/[L^-]$, the buffer ratio,

$-pH = [H_3O^+] f_{H_3O^+}$

$pK_a = pH + \log r - \log f_{\pm}$

The observed dissociation constant, K', is obtained [illegible] pH and the spectrometric values of [illegible]

PART (ii): DETERMINATION OF DISSOCIATION CONSTANTS BY THE MEASUREMENT OF pH

For the dissociation of an acid:

$$HL + H_2O \rightleftharpoons H_3O^+ + L^- \qquad \text{equation (i)}$$

$$K_a = \frac{a_{H_3O^+} \times a_{L^-}}{a_{HL}}$$

$$= \frac{[H_3O^+][L^-]}{[HL]} \cdot \frac{f_{H_3O^+} \times f_{L^-}}{f_{HL}}$$

where: K_a = thermodynamic dissociation constant

f = activity coefficient.

Let $f_{H_3O^+} \times f_{L^-} = f_{\pm}^2$ and assuming $f_{HL} = 1$, then

$$K_a = \frac{[H_3O^+][L^-]}{[HL]} \cdot f_{\pm}^2$$

$$pK_a = -\log[H_3O^+] + \log r - 2 \log f_{\pm}$$

where: $r = [HL] / [L^-]$, the buffer ratio,

But, $10^{-pH} = [H_3O^+] f_{H_3O^+}$

$$pK_a = pH + \log r - \log f_{\pm}$$

The observed dissociation constant, K', is obtained from the measured pH and the stoichiometric values of $[HL]$ and $[L^-]$ i.e.

$$pK' = pH. + \log r.$$

To obtain the true buffer ratio, r', a correction must be applied to the stoichiometric value because of the reaction represented by equation (i):

$$[HL]_{corrected} = [HL]_{stoich.} - [H^+]$$

$$[L^-]_{corrected} = [L^-]_{stoich.} + [H^+].$$

No correction need be applied for the hydrolysis:

$$H_2O + L^- \rightleftharpoons HL + OH^-$$

since, in solutions of the acids studied,
$[H^+] \approx 10^{-5}M$ and $[OH^-] \simeq 10^{-9}M$.

$$pK'' = pH + \log r'.$$

$$pK_a = pK'' - \log f_{\pm}$$

The activity coefficient term may be calculated from the empirical Davies equation[81]:

$$-\log f_{\pm} = \frac{0.5\ I^{\frac{1}{2}}}{(1 + I^{\frac{1}{2}})} - 0.2I$$

where: I = ionic strength of the solution, which may be calculated from the equation:

$$I = \tfrac{1}{2}\sum c_i Z_i^{\,2}$$

where: c = concentration of the i'th ion.

Z = charge on that ion.

EXPERIMENTAL

Keto-acid buffers were prepared from stock acid solutions and B.D.H. C.V.S. sodium hydroxide. The ionic strength was adjusted by the addition of AnalaR potassium chloride solution. The water used was first de-ionised, then distilled from potassium permanganate.

pH measurements were made with a Radiometer pH meter, using a type G202C glass electrode and reference calomel electrode. The pH meter was standardised between pairs of readings at pH 4.008 (0.05M potassium hydrogen phthalate) and at pH 6.48 (Radiometer phosphate buffer). The temperature was maintained at 25.0 $\pm$ 0.05°C. All solutions were prepared in duplicate and every result is quoted.

[illegible]	[illegible]	[illegible]
0.999	4.604	2.49
0.999	4.608	2.47
0.668	4.607	2.47
[illegible]	4.612	2.44
[illegible]	4.613	2.44

$pK_a = 4.610 \pm 0.01$

$K_a = 2.45 \pm 0.05 \times 10^{-5}$

PART (iii): RESULTS

LEVULINIC ACID

I = 0.02M

pH	r'	pK_a	$K_a \times 10^5$
3.961	3.861	4.606	2.48
3.961	3.861	4.606	2.48
4.190	2.302	4.610	2.45
4.196	2.302	4.616	2.42
4.383	1.492	4.615	2.43
4.388	1.492	4.620	2.40
4.546	0.999	4.604	2.49
4.550	0.999	4.608	2.47
4.724	0.668	4.607	2.47
4.919	0.431	4.612	2.44
4.920	0.431	4.613	2.44

$$pK_a = 4.610 \pm 0.01$$

$$K_a = 2.45 \pm 0.05 \times 10^{-5}$$

5-OXO HEXANOIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
3.737	7.398	4.650	2.24
3.731	7.378	4.642	2.28
4.028	3.879	4.660	2.19
4.032	3.882	4.665	2.17
4.245	2.300	4.650	2.24
4.248	2.301	4.653	2.22
4.434	1.502	4.654	2.22
4.445	1.502	4.665	2.16
4.607	1.011	4.655	2.21
4.610	1.011	4.658	2.20
4.773	0.680	4.649	2.24
4.776	0.680	4.652	2.23
4.976	0.442	4.665	2.16
4.981	0.442	4.670	2.14
5.216	0.263	4.680	2.09
5.217	0.263	4.680	2.09

$$pK_a = 4.659 \pm 0.02$$

$$K_a = 2.19 \pm 0.10 \times 10^{-5}$$

6-OXO HEPTANOIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
4.088	3.998	4.733	1.85
4.093	4.000	4.739	1.82
4.312	2.420	4.739	1.82
4.302	2.419	4.729	1.87
4.480	1.587	4.724	1.89
4.488	1.588	4.732	1.85
4.652	1.078	4.728	1.87
4.650	1.078	4.726	1.88
4.823	0.736	4.733	1.85
4.828	0.736	4.738	1.83
5.000	0.490	4.734	1.85
5.006	0.490	4.740	1.82
5.199	0.304	4.726	1.88
5.206	0.304	4.731	1.86

$$pK_a = 4.732 \pm 0.01$$

$$K_a = 1.85 \pm 0.04 \times 10^{-5}$$

3-BENZOYL PROPIONIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
3.926	5.609	4.718	1.91
3.921	5.588	4.712	1.94
4.194	2.894	4.699	2.00
4.191	2.894	4.696	2.01
4.413	1.703	4.688	2.05
4.420	1.704	4.695	2.02
4.629	1.058	4.697	2.01
4.629	1.058	4.697	2.01
4.830	0.657	4.691	2.04
4.834	0.657	4.704	1.98
5.068	0.385	4.697	2.01
5.073	0.386	4.703	1.98
5.410	0.190	4.732	1.85
5.397	0.190	4.719	1.91

$$pK_a = 4.703 \pm 0.03$$

$$K_a = 1.98 \pm 0.13 \times 10^{-5}$$

4-BENZOYL BUTYRIC ACID

I = 0.002M

pH	r'	pK_a	$K_a \times 10^5$
4.170	4.183	4.812	1.54
4.428	2.197	4.791	1.62
4.408	2.184	4.768	1.71
4.660	1.254	4.779	1.66
4.647	1.251	4.765	1.72
4.890	0.726	4.772	1.69
4.876	0.725	4.757	1.75
5.147	0.394	4.763	1.73
5.144	0.394	4.760	1.74
5.550	0.167	4.794	1.61

$$pK_a = 4.776 \pm 0.04$$

$$K_a = 1.68 \pm 0.14 \times 10^{-5}$$

5-BENZOYL PENTANOIC ACID

I = 0.004M

pH	r'	pK_a	$K_a \times 10^5$
4.072	5.842	4.866	1.36
4.073	5.845	4.869	1.35
4.322	2.944	4.820	1.51
4.544	1.727	4.810	1.55
4.743	1.072	4.802	1.58
4.737	1.072	4.796	1.60
4.940	0.668	4.794	1.61
5.180	0.394	4.804	1.57
5.523	0.197	4.846	1.43
5.540	0.197	4.863	1.37

$$pK_a = 4.827 \pm 0.04$$

$$K_a = 1.49 \pm 0.13 \times 10^{-5}$$

2-METHYL LEVULINIC ACID

I = 0.02M

pH	r'	pK_a	$K_a \times 10^5$
3.906	3.832	4.547	2.83
3.902	3.830	4.543	2.86
4.134	2.290	4.552	2.81
4.136	2.290	4.554	2.79
4.327	1.486	4.557	2.77
4.332	1.486	4.562	2.74
4.500	0.995	4.556	2.78
4.498	0.995	4.554	2.79
4.680	0.665	4.561	2.75
4.685	0.665	4.566	2.72
4.880	0.428	4.569	2.69
4.878	0.428	4.567	2.71
5.127	0.251	4.585	2.60
5.126	0.251	4.584	2.61
5.489	0.112	4.596	2.53

$$pK_a = 4.564 \pm 0.02$$

$$K_a = 2.73 \pm 0.13 \times 10^{-5}$$

2,2-DIMETHYL LEVULINIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
4.018	8.286	4.980	1.05
4.333	4.007	4.979	1.05
4.341	4.007	4.987	1.03
4.558	2.388	4.980	1.05
4.562	2.389	4.984	1.04
4.747	1.555	4.982	1.04
4.752	1.555	4.987	1.03
4.909	1.048	4.973	1.06
4.918	1.049	4.982	1.04
5.095	0.709	4.989	1.03
5.098	0.709	4.989	1.03
5.277	0.466	4.989	1.03
5.277	0.466	4.989	1.03
5.503	0.283	4.998	1.00
5.497	0.283	4.992	1.02
5.798	0.141	4.991	1.02

$$pK_a = 4.986 \pm 0.01$$

$$K_a = 1.03 \pm 0.03 \times 10^{-5}$$

3-METHYL LEVULINIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
3.577	7.348	4.501	3.15
3.580	7.355	4.505	3.13
3.877	3.630	4.495	3.20
3.887	3.634	4.505	3.12
4.102	2.157	4.494	3.21
4.123	2.159	4.515	3.05
4.308	1.386	4.508	3.11
4.316	1.387	4.516	3.05
4.483	0.915	4.502	3.14
4.492	0.915	4.511	3.08
4.678	0.599	4.513	3.07
4.686	0.599	4.521	3.01
4.894	0.372	4.522	3.00
4.893	0.372	4.522	3.01
5.173	0.201	4.534	2.92
5.172	0.201	4.533	2.93

$$pK_a = 4.512 \pm 0.02$$

$$K_a = 3.07 \pm 0.15 \times 10^{-5}$$

3,3-DIMETHYL LEVULINIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
3.733	7.455	4.649	2.24
3.736	7.462	4.652	2.23
4.027	3.838	4.655	2.22
4.026	3.838	4.654	2.22
4.237	2.322	4.646	2.26
4.234	2.322	4.643	2.27
4.429	1.519	4.654	2.22
4.432	1.519	4.657	2.20
4.590	1.025	4.644	2.27
4.597	1.025	4.651	2.23
4.769	0.691	4.652	2.23
4.763	0.691	4.646	2.26
4.951	0.452	4.650	2.24
4.953	0.452	4.652	2.23
5.183	0.271	4.659	2.19
5.176	0.271	4.652	2.23

$$pK_a = 4.651 \pm 0.01$$

$$K_a = 2.23 \pm 0.04 \times 10^{-5}$$

2,2,3-TRIMETHYL LEVULINIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^6$
4.744	8.920	5.738	1.83
4.742	8.920	5.736	1.84
5.086	4.036	5.735	1.84
5.088	4.036	5.737	1.83
5.315	2.367	5.733	1.85
5.316	2.367	5.734	1.85
5.511	1.528	5.738	1.83
5.510	1.528	5.737	1.83
5.686	1.023	5.739	1.82
5.681	1.023	5.734	1.84
5.857	0.686	5.737	1.83
5.854	0.686	5.734	1.85
6.046	0.445	5.738	1.83
6.043	0.445	5.735	1.84

$$pK_a = 5.736 \pm 0.01$$

$$K_a = 1.84 \pm 0.02 \times 10^{-6}$$

5,5-DIMETHYL-4-OXO-HEXANOIC ACID

I = 0.01M

pH	r'	pK_a	$K_a \times 10^5$
3.862	7.845	4.800	1.58
3.857	7.830	4.794	1.61
4.169	3.911	4.805	1.57
4.167	3.911	4.803	1.57
4.393	2.346	4.807	1.56
4.388	2.346	4.802	1.58
4.576	1.529	4.804	1.57
4.572	1.529	4.800	1.59
4.740	1.030	4.796	1.60
4.745	1.030	4.801	1.58
4.913	0.695	4.798	1.59
4.916	0.695	4.801	1.58
5.111	0.454	4.812	1.54
5.111	0.454	4.812	1.54
5.337	0.273	4.816	1.53
5.335	0.273	4.815	1.53

$$pK_a = 4.804 \pm 0.02$$

$$K_a = 1.57 \pm 0.05 \times 10^{-5}$$

PART (iv): DETERMINATION OF DISSOCIATION CONSTANTS BY THE GENERAL BASE-CATALYSED DECOMPOSITION OF NITRAMIDE

The decomposition of nitramide:

$$NH_2NO_2 \rightarrow N_2O + H_2O$$

has been shown, by Brönsted and Pedersen,[82] to be unimolecular with respect to nitramide and in solutions of weak acids, the rate is given by:

$$k = k_o + \Sigma k_B[A^-]$$

where: $[A^-]$ = concentration of any anion

k_B = catalytic constant of that anion

k_o = 'spontaneous' rate. In strong acids the rate is independent of the acid used and hence k_o is attributed to catalysis by water.

The weaker the acid the stronger is the anion as a base and the values of k_B were found to obey the general expression:

$$\log k_B = \log G + \beta pK_a$$

where: G and β are empirical constants.
The expression is known as a Brönsted equation. The relationship holds for non-aqueous solvents; the values of G and β varying with solvent and charge-type of the catalyst.

Baughan and Bell[83] determined the catalytic constants of eight carboxylic acids over a range of temperatures and hence obtained values for G, β and k_o.

If it is assumed that the anion of a keto-acid, exhibiting ring-chain tautomerism, does not exist in the ring

form, then the pK_a determined by the measurement of the rate of nitramide decomposition, is a true dissociation constant for the chain tautomer. However, if the assumption is not valid, then it is possible for even a very low concentration of ring anion to contribute appreciably to the observed rate, due to the high basic strength such a species would have. Consider the case in which there is a low concentration of ring anion present:

$$\begin{array}{ccc} [HL]_c & \rightleftharpoons & H^+ + [L^-]_c \\ \uparrow\downarrow & & \uparrow\downarrow \\ [HL]_R & \rightleftharpoons & H^+ + [L^-]_R \end{array}$$

where: subscripts c and R refer to chain and ring species respectively.

$$[L^-]_R \ll [L^-]_c$$

The observed catalytic constant, k_B, may be expressed as the sum of contributions from the ring and chain tautomers:

$$k_B[L^-]_T = k_c[L^-]_c + k_R[L^-]_R$$

where: $[L^-]_T$ = total anion concentration.

$$k_B = k_c + k_R \frac{[L^-]_R}{[L^-]_c}$$

since $[L^-]_c \simeq [L^-]_T$.

$$K_c = \frac{[H^+][L^-]_c}{[HL]_c} \quad \text{and} \quad K_R = \frac{[H^+][L^-]_R}{[HL]_R}$$

$$\frac{[L^-]_R}{[L^-]_c} = \frac{[HL]_R}{[HL]_c} \cdot \frac{K_R}{K_c}$$

Let $$K = \frac{[HL]_R}{[HL]_c}$$

$$k_B = k_c + k_R \cdot \frac{K_R}{K_c} \cdot K$$

$$= k_c \left[1 + \frac{K_R}{K_c} \cdot \frac{k_R}{k_c} \cdot K \right]$$

From the Brönsted equation:

$$\frac{k_R}{k_c} = \left(\frac{K_R}{K_c} \right)^{-\beta}$$

$$k_B = k_c \left[1 + K \left(\frac{K_R}{K_c} \right)^{(1-\beta)} \right]$$

If the following values are substituted into the expression:

$\beta = 0.8$

$K_c = 10^{-5}$, for derivatives of levulinic acid.

$K_R = 10^{-13}$ - a reasonable model for the cyclic tautomer is methylene glycol, $CH_2(OH)_2$, which has $pK_a = 13.3$,[84] then the expression reduces to:

$$k_B = k_c.$$

The existence of ring anion was investigated in the case of 2-formyl benzoic acid, which is 94% ring tautomer.[79] The pK_a was measured by the decomposition of nitramide ($\beta = 0.8$) and by the mutarotation of glucose, which is another general-base catalysed reaction with $\beta = 0.4$. The values obtained were identical within experimental error and this is taken to indicate a negligible contribution from the term in K_R.

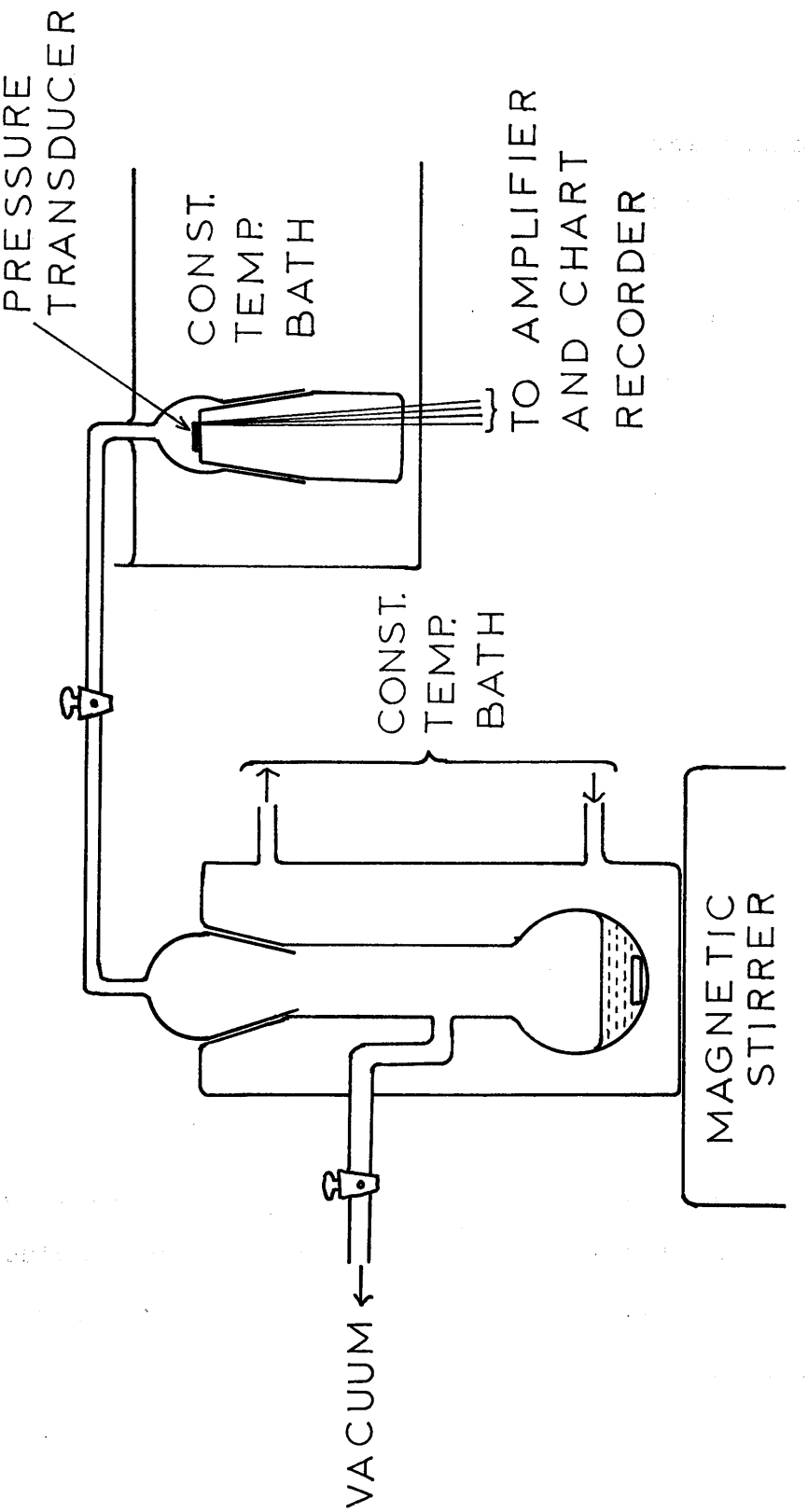
EXPERIMENTAL

Buffer solutions of the keto-acids were prepared as described in chapter 3 part (ii). Nitramide was prepared by a standard procedure[85] and all kinetic measurements were taken at 25.0 ± 0.1°C. The reaction was followed using the apparatus described by Bell and Trotman-Dickenson,[86] in which the pressure of the evolved nitrous oxide was indicated by the height of a mercury column. Using 5 ml of buffer solution and about 15 mg of nitramide, the pressure change was approximately 200 mm Hg.

The pH of all solutions was about 5, at which it is possible to neglect catalysis by hydroxyl ion[130] and hence substitute into the rate equation the value for k_o reported by Bell and Baughan.[83] In line with their results, rate constants have been quoted with units of min^{-1} and decadic logarithms were used throughout.

Because of the ease with which nitrous oxide supersaturates water, gas evolution had to be stimulated by tapping the reaction vessel continuously by hand. In an attempt to eliminate the need for constant attention during the reaction, an automatic apparatus was designed by Dr. R. L. Tranter of Stirling University, shown in figure 3(iv) 1. The rate of evolution of nitrous oxide was followed by monitoring the output, to a chart recorder, from a sub-miniature pressure transducer (series PS-A, Kyowa Electronic Instruments Co. Ltd.). The transducer has a capacity of 2 kg cm^{-2} and using 2 ml of solution and about 15 mg of

FIGURE 3 (iv). 1.


PRESSURE TRANSDUCER
CONST. TEMP. BATH
TO AMPLIFIER AND CHART RECORDER
CONST. TEMP. BATH
MAGNETIC STIRRER
VACUUM

nitramide, the pressure change was approximately 100 mm Hg. The tap between the pressure transducer and the reaction vessel is necessary to maintain the working pressure at the pressure transducer, in order to reduce the response time which increases if the apparatus is opened regularly to the atmosphere.

Unfortunately, however, preliminary experiments with acetate buffers gave results which yielded pK_a values that were too high. The apparatus was thoroughly tested: there was no fault in the amplifier, the pressure transducer gave a linear response over the working pressure range, the chart recorder responded linearly and the ground-glass joints accurately maintained the low pressure. Closer examination of the traces obtained revealed that, during reaction, the half-life appeared to decrease. Since it has been well-established that the reaction is first-order, it is apparent that the problem lies with the evolution of gas out of the aqueous medium. Using the apparatus described by Bell and Trotman-Dickenson, it was known that violent tapping was required to obtain accurate, consistent results and this is emphasised by the observation that even vigorous agitation by magnetic stirrer is not efficient. The new apparatus is undoubtedly an improvement on the older method, but further research is needed to optimise the performance.

In the results, quoted below, the value of the pK_a is the mean of the values calculated for each kinetic result and the error is the maximum deviation from the mean.

PART (v): RESULTS

LEVULINIC ACID

r = 1.00

I = 0.10

$[L^-] \times 10^3 M$	$k \times 10^3$ min^{-1}	k_B M^{-1} min^{-1}	pK_a	$K_a \times 10^5$
10.0	13.01	1.176	4.622	2.39
10.0	12.57	1.132	4.600	2.51
10.0	11.98	1.073	4.569	2.69
8.0	9.60	1.044	4.554	2.79
8.0	10.31	1.132	4.600	2.51
6.0	7.85	1.101	4.584	2.61
6.0	8.29	1.174	4.621	2.39
4.0	5.75	1.124	4.596	2.54
4.0	5.97	1.179	4.623	2.38
2.0	3.57	1.159	4.614	2.43
2.0	3.39	1.071	4.568	2.70

$$pK_a = 4.60 \pm 0.05$$

$$K_a = 2.51 \pm 0.28 \times 10^{-5}$$

5-OXO HEXANOIC ACID

r = 1.01
I = 0.10

$[L^-]$ x 10^3M	k x 10^3 min^{-1}	k_B M^{-1} min^{-1}	pK_a	K_a x 10^5
10.0	15.75	1.453	4.743	1.81
10.0	14.44	1.322	4.689	2.05
10.0	14.96	1.374	4.711	1.95
8.0	12.77	1.444	4.740	1.82
8.0	12.01	1.349	4.701	1.99
6.0	9.83	1.435	4.736	1.85
6.0	9.87	1.442	4.739	1.82
4.0	7.01	1.448	4.741	1.82
2.0	4.11	1.445	4.740	1.82

$$pK_a = 4.73 \pm 0.04$$

$$K_a = 1.87 \pm 0.18 \times 10^{-5}$$

2-METHYL LEVULINIC ACID

r = 1.00

I = 0.10

$[L^-]$ x 10^3M	k x 10^3 min^{-1}	k_B M^{-1} min^{-1}	pK_a	K_a x 10^5
10.07	11.93	1.061	4.563	2.74
10.07	12.35	1.102	4.585	2.60
10.07	12.39	1.106	4.587	2.59
8.06	9.89	1.073	4.569	2.69
8.06	9.21	0.988	4.522	3.00
6.04	7.57	1.045	4.554	2.79
6.04	7.79	1.082	4.574	2.67
4.03	5.99	1.176	4.622	2.39
4.03	5.63	1.086	4.576	2.65
2.01	3.44	1.085	4.576	2.66
2.01	3.38	1.056	4.560	2.75

$$pK_a = 4.57 \pm 0.05$$

$$K_a = 2.68 \pm 0.29 \times 10^{-5}$$

2,2,3-TRIMETHYL LEVULINIC ACID

r = 5.41

I = 0.10

$[L^-] \times 10^3 M$	$k \times 10^3$ min^{-1}	k_B M^{-1} min^{-1}	pK_a	$K_a \times 10^5$
6.60	12.97	1.780	4.859	1.38
6.60	12.48	1.706	4.835	1.46
5.28	10.13	1.688	4.829	1.48
5.28	10.13	1.688	4.829	1.48
5.28	11.47	1.941	4.909	1.23
3.96	7.65	1.624	4.807	1.56
3.96	7.53	1.593	4.776	1.67
2.64	5.42	1.591	4.795	1.60
1.32	3.69	1.871	4.888	1.29
0.66	2.33	1.682	4.827	1.49

$$pK_a = 4.84 \pm 0.07$$

$$K_a = 1.46 \pm 0.23 \times 10^{-5}$$

The following pK_a values are not as well defined as previous values, since lack of time prevented a full investigation of the nitramide kinetics.

2,2-DIMETHYL LEVULINIC ACID

r = 1.00

I = 0.10

$[L^-] \times 10^2 M$	$k \times 10^3$ min^{-1}	k_B M^{-1} min^{-1}	pK_a	$K_a \times 10^5$
10.0	14.38	1.313	4.685	2.07
5.0	9.11	1.573	4.789	1.63
4.0	5.25	1.314	4.685	2.07
2.0	3.56	1.154	4.611	2.45

$pK_a = 4.69 \pm 0.10$

$K_a = 2.06 \pm 0.43 \times 10^{-5}$

3,3-DIMETHYL LEVULINIC ACID

r = 1.00

I = 0.10

$[L^-] \times 10^2 M$	$k \times 10^3$ min^{-1}	k_B M^{-1} min^{-1}	pK_a	$K_a \times 10^5$
10.0	11.95	1.070	4.568	2.70
10.0	12.10	1.082	4.574	2.67
10.0	12.44	1.119	4.593	2.55

$pK_a = 4.58 \pm 0.02$

$K_a = 2.64 \pm 0.09 \times 10^{-5}$

5,5-DIMETHYL-4-OXO HEXANOIC ACID

r = 1.00

I = 0.10

$[L^-]$ x 10^2M	k x 10^3 min^{-1}	k_B M^{-1} min^{-1}	pK_a	K_a x 10^5
10.0	13.93	1.268	4.665	2.16
10.0	16.22	1.497	4.760	1.74
10.0	15.59	1.434	4.736	1.84

$pK_a = 4.72 \pm 0.05$

$K_a = 1.91 \pm 0.17 \times 10^{-5}$

3-BENZOYL PROPIONIC ACID

r = 1.00

I = 0.10

$[L^-]$ x 10^2M	k x 10^3 min^{-1}	k_B M^{-1} min^{-1}	pK_a	K_a x 10^5
10.0	12.97	1.172	4.620	2.40
10.0	13.87	1.262	4.662	2.18
10.0	15.21	1.396	4.720	1.91

$pK_a = 4.67 \pm 0.05$

$K_a = 2.16 \pm 0.25 \times 10^{-5}$

PART (vi): DISCUSSION OF RING-CHAIN TAUTOMERIC EQUILIBRIUM RESULTS

Using a modification of the method of Pascual et al.[26], described in chapter 3 part (i), the amount of ring tautomer present in a dilute aqueous solution of the keto-acid at 25.0°C may be estimated from the measured values of the dissociation constants.

TABLE 3(vi).1:

compound		10^5K_a(pH)	10^5K_a(nitramide)	% ring
(i)	$CH_3CO(CH_2)_2CO_2H$	2.45±0.05	2.51±0.28	2 ± 12
(ii)	$CH_3CO(CH_2)_3CO_2H$	2.19±0.10	1.87±0.18	0
(iii)	$CH_3CO(CH_2)_4CO_2H$	1.85±0.04		
(iv)	$PhCO(CH_2)_2CO_2H$	1.98±0.13	2.16±0.25	8 ± 15
(v)	$PhCO(CH_2)_3CO_2H$	1.68±0.14		
(vi)	$PhCO(CH_2)_4CO_2H$	1.49±0.13		
(vii)	$CH_3COCH_2CH(Me)CO_2H$	2.73±0.13	2.68±0.29	0 ± 12
(viii)	$CH_3COCH_2CMe_2CO_2H$	1.03±0.03	2.05±0.34	50 ± 18
(ix)	$CH_3COCH(Me)CH_2CO_2H$	3.07±0.15		
(x)	$CH_3COCMe_2CH_2CO_2H$	2.23±0.04	2.64±0.08	15 ± 5
(xi)	$CH_3COCH(Me)CMe_2CO_2H$	0.184±0.002	1.46±0.23	87 ± 2
(xii)	$(CH_3)_3CCO(CH_2)_2CO_2H$	1.57±0.05	1.91±0.22	18 ± 22

The errors quoted in table 3(v).1 are standard deviations. The results given for the percentage of ring tautomer demonstrate the inherent problem of the analytical technique: extreme accuracy in the determination of the dissociation constants is required for precise measurement of the tautomeric equilibrium and the smaller the quantity of ring tautomer present, the greater that precision must be. The measurement of the kinetics of nitramide decomposition is subject to much larger errors than the measurement of pH and small, significant differences between the two dissociation constants are not easily defined.

The results for levulinic acid (compound (i)) exemplify the problem. The percentage of ring tautomer is calculated to be 2 ± 12. This indicates the presence of a small proportion of ring tautomer in the acid, but the error forces the conclusion that the acid exists, to all intents and purposes, only in the chain form.

The results quoted for compounds (i) and (ii), two members of a homologous series, suggests that the tautomeric equilibrium is unaffected by chain length, although it might be inferred that ring formation is favoured more for 5-membered than for 6-membered rings. Such an inference would not be strictly justified, as the ring content must be considered to be zero in both compounds.

3-benzoyl propionic acid shows some evidence of the presence of some ring tautomer, but the error means it must be assumed to exist only as the chain tautomer. This might be expected on consideration of the nature of the terminal group, which will stabilise the carbonyl group by conjugation and hence favour the chain tautomer (see

chapter 4 part (v)). Thus it is unlikely that this compound would exist to the same or to a greater extent in the ring form as levulinic acid.

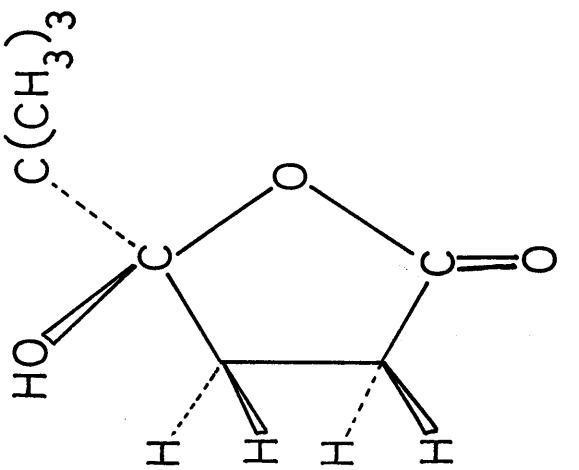
2-methyl levulinic acid (compound (vii)) shows no evidence of ring tautomer formation. It would not be expected that a single methyl substituent would affect the equilibrium, but such is not the case for a gem-dimethyl derivative. Even allowing for the large error, 2,2-dimethyl levulinic acid (compound (viii)) exists to a large extent as the ring tautomer. However, the other gem-dimethyl derivative, 3,3-dimethyl levulinic acid (compound (x)) also exists in the ring form, but to a lesser extent than the 2,2-dimethyl derivative. This, presumably, is due to the fact that formation of the 3,3-dimethyl lactol introduces steric interactions not present in the 2,2-dimethyl lactol (see figure 3(vi).1(i)).

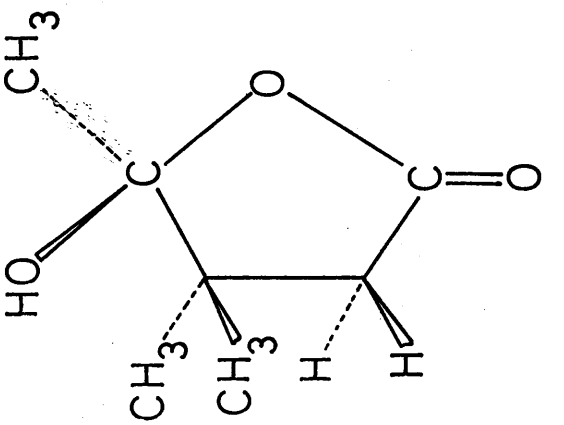
2,2,3-trimethyl levulinic acid (compound (xi)) exists predominantly as the ring tautomer. The small error in the result shows that when the difference between the dissociation constants is large, the large error in pK_a(nitramide) does not greatly affect the accuracy of the final result. Comparison of the figures quoted for ring content in compounds (i), (vii), (viii), (x) and (xi) clearly demonstrates the influence of substitution in the chain in favouring the formation of the ring tautomer.

The error quoted in the result given for 5,5-dimethyl-4-oxo hexanoic acid (compound (xii)) means that there is no real evidence to support the existence of a ring tautomer. This might be expected because, although the hyperconjugative effect of the t-butyl group will increase the basic strength of the carbonyl oxygen, the size of the

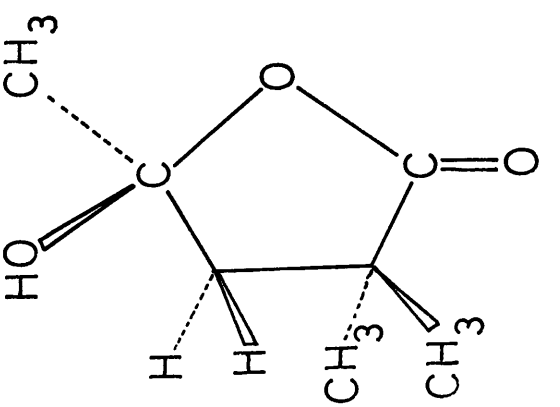
FIGURE 3 (*vi*).1.

(ii)





(i)



terminal group introduces steric hindrance to the formation of a ring (see figure 3(vi).1(ii)). There is evidence that, in organic solvents, 2-pivaloyl benzoic acid exists to a slightly greater extent as the ring tautomer than 2-acetyl benzoic acid,[142] but this has been attributed to the relief of steric strain which is a consequence of the necessary proximity of the two reactive groups.

DISCUSSION OF BREDT'S WORK ON LEVULINIC ACID.[74]

Acetyl levulinic acid was prepared by the method quoted by Bredt i.e. levulinic acid and an equivalent quantity of acetic anhydride were refluxed for two hours and then left overnight at room temperature. The resultant yellow solid was crystallised four times from methylene dichloride/40-60 pet.ether, to yield white crystals.

m.pt.: 75-6°C (Bredt quotes no m.pt.)

The white solid was examined by N.M.R. spectroscopy. Spectra were obtained for carbon tetrachloride solutions, using T.M.S. as the standard.

compound	signal	chemical shift (tau)	integral
levulinic acid	multiplet	7.35	4
	singlet	7.85	3
acetyl derivative	multiplet	7.4	4
	singlet	7.95	3
	singlet	8.25	3

The values of the proton signal integrals for the acetyl derivative immediately rule out the possibility that the compound is the enol acetate. Taking into account the results of the chemical tests performed by Bredt, the values

of the integrals lead to no other conclusion but that the compound is the acyl derivative of the ring tautomer, as concluded by Bredt. On the basis of his investigation, Bredt proposed that levulinic acid exists predominantly as the ring tautomer. It has already been shown that, in aqueous solution, this is not the case, but the conditions under which the derivative was prepared were not those of dilute, aqueous solution. It is possible that the ring-chain equilibrium varies with solvent, but it is unlikely to be a large effect, as may be seen from the following results obtained for 2-acetyl benzoic acid.

solvent	method	% ring
water	nitramide decomposition	81[23]
dioxan	I.R.	84[142]
dioxan	N.M.R.	81[142]
80% w/w 2-methoxy-ethanol-water	N.M.R.	71[142]

It is entirely possible that there is a very small proportion of ring tautomer in levulinic acid and if equilibration is faster than the rate of reaction with acetic anhydride, then the acid would appear to react completely as the ring tautomer.

CHAPTER 4

PART (i): GENERAL INTRODUCTION TO INTRA-MOLECULAR CATALYSED ENOLISATION

The phenomenon of keto-enol tautomerism:

$$\underset{\text{KETO}}{=CH-CO-} \rightleftharpoons \underset{\text{ENOL}}{=C=C(OH)-}$$

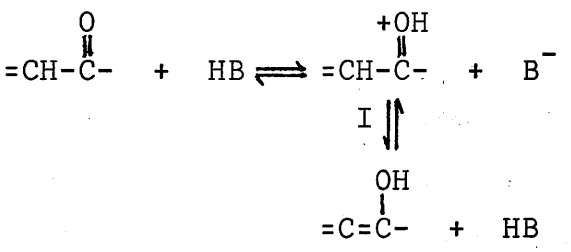
is well known in organic chemistry. Since the discovery of ethyl acetoacetate[87] and the subsequent recognition of its property of reacting both as a ketone and as an unsaturated alcohol,[88] many compounds have been found to exhibit this type of equilibrium and the field has been extended to include non-carbonyl compounds, e.g.[89]

$$\underset{\text{NITRO}}{=CH-NO_2} \rightleftharpoons \underset{\text{ACI}}{=C=NO.OH}$$

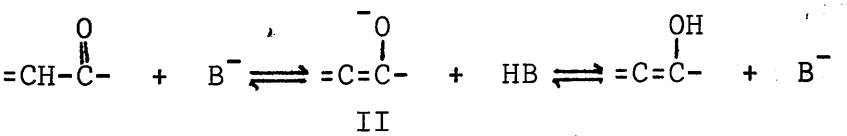
Lapworth was the first to show that the halogenation of acetone proceeded via the enol tautomer.[90] He found that the rate of reaction with iodine in dilute aqueous solution was independent of iodine concentration, the rate was the same for iodine and bromine under the same conditions and the rate was accelerated by the presence of strong acid or alkali (although further reactions often take place under alkaline conditions e.g. the iodoform reaction with acetone and similar substances). These facts led him to suggest that the rate-determining process was the enolisation of the ketone, since it was known that enols react rapidly with halogens and the interconversion of keto and enol isomers is catalysed by both acids and bases.

Dawson,[91] in an extensive study of the iodination of acetone, found that the reaction was catalysed, not only by hydrogen or hydroxyl ions, but also by undissociated acid molecules and by the anions of weak acids. Similar results were obtained for the halogenation of other carbonyl compounds.[92,93] In view of this additional information, the enolisation may now be reconsidered in terms of general acid-base catalysis:

acid catalysis



base catalysis



Each mechanism involves a two-stage reaction and there is no direct transfer of a hydrogen atom from the carbon to the oxygen. In fact, the hydroxyl hydrogen will probably not be the same atom as that on the methine carbon. Each mechanism also requires the participation of both an acid and a base, though the order of attack is different. It is not, however, necessary deliberately to add both an acid and a base in order to bring about the change; in water,

or similar protic medium, the solvent molecules themselves can act either as acids or bases. The acid-catalysed mechanism, above, is in accord with Lapworth's interpretation of halogenation, but for basic catalysis some modification is necessary. The proposed mechanism involves the anion, II, as an intermediate in the formation of the enol and it would be anticipated that this anion will react very rapidly with halogens. This is found to be the case for ketones which are sufficiently acidic to be converted completely to the enolate ion.[94] This means that, in the presence of halogen, no enol will be formed and the measured rate of halogenation, under conditions of basic catalysis, is therefore the rate of ionisation of the ketone, rather than its rate of enolisation. The enol is, however, involved in the mechanism of acid catalysis, since the cation, I, will not be reactive towards halogens.

The most widely investigated substituent effects on the reactions of organic molecules are electronic effects transmitted through the carbon skeleton and steric effects. In addition, some substituents may influence a reaction by stabilising a transition state or intermediate, by becoming bonded or partially bonded to the reaction centre. This behaviour has been termed 'neighbouring group participation'[95] or, if an increased reaction rate results, 'intra-molecular catalysis'.[96] In recent years, a great deal of work has been done on intra-molecular catalysis and the rate-enhancement which results over the corresponding inter-molecular catalysed reaction. Bender and Neveu[97] published a comparison of inter- and intra-molecular catalysis, using data available

before 1958 and Capon[98] has, more recently, produced a rather more rigorous review of neighbouring group participation.

It has been seen that the halogenation of ketones is subject to inter-molecular catalysis by acids and bases. Prior to 1962, when Bell and Fluendy[25] published results for the rates of iodination of aliphatic keto-carboxylic acids, it had not been recognised that enolisation or ionisation of ketones could be catalysed by an intra-molecular process. The bromination and racemisation of 2-O-carboxy-benzylindan-1-one was studied under acid[99] and acetate-buffered[100] conditions. The bromination of levulinic and pyruvic acids has been studied under acid conditions[101,102] and with glycine catalysis between pH4 and pH9.[103] None of these results were interpreted in terms of an intra-molecular mechanism, which undoubtedly contributed significantly to the observed rate c.f. the values of inter- and intra-molecular catalysed rates quoted by Bell and Fluendy.

Figures 4(i), 1(a) and (b) show the probable transition states for the intra-molecular catalysed processes. In the acid-catalysed mechanism, apart from the purely intra-molecular process represented, it is possible that there is solvent participation, but that would be kinetically equivalent. The possibility of attack at the terminal methyl is represented in the base-catalysed mechanism only, but a similar situation applies equally to acid catalysis. Bell and Fluendy, by the use of a radio-active iodine tracer technique, estimated in excess of 80% reaction at the 3-position (methylene group). In the comparison of intra-molecular catalysed reaction in an homologous series, it is necessary to know the proportions of the measured rate due to reaction at the two available sites.

FIGURE 4(i).1(a).

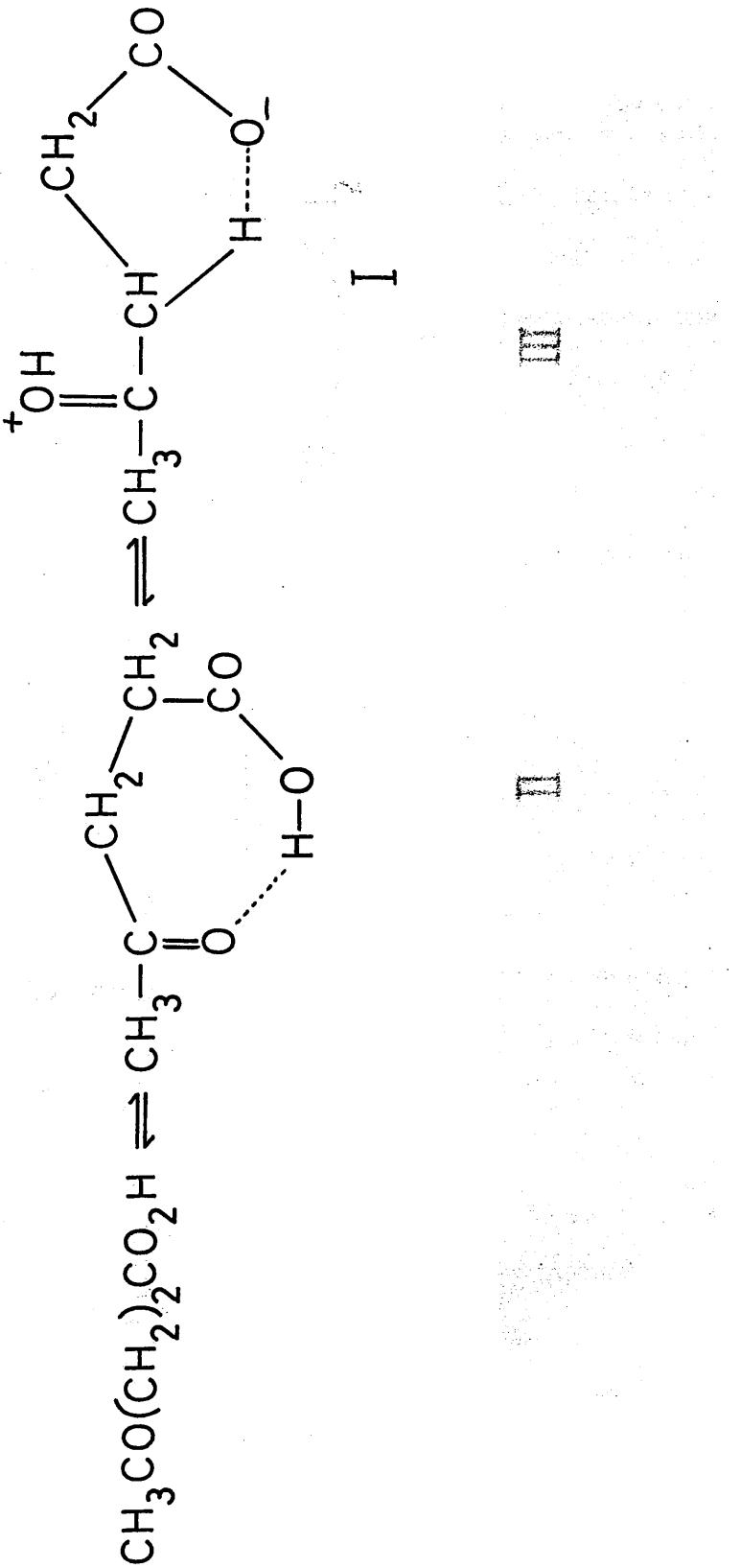
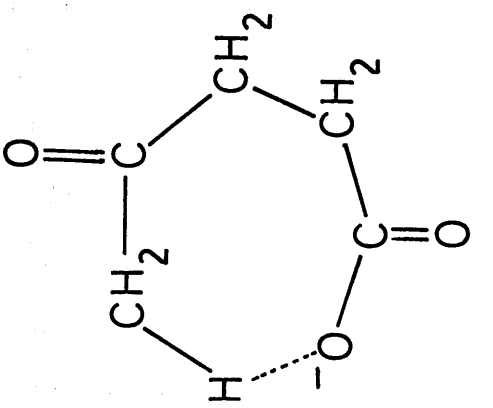
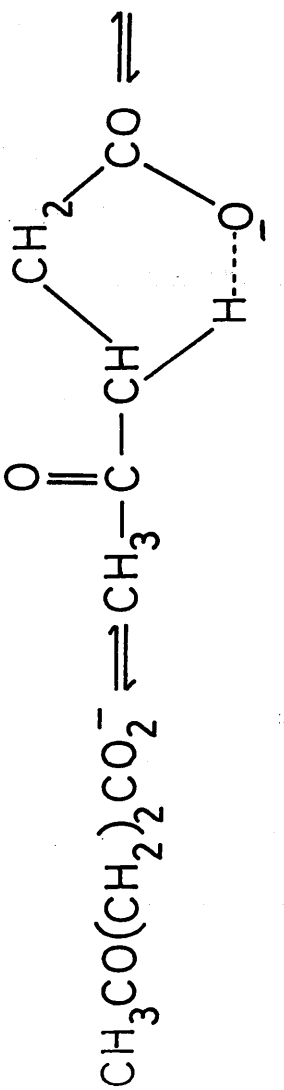


FIGURE 4(i).1(b).



III

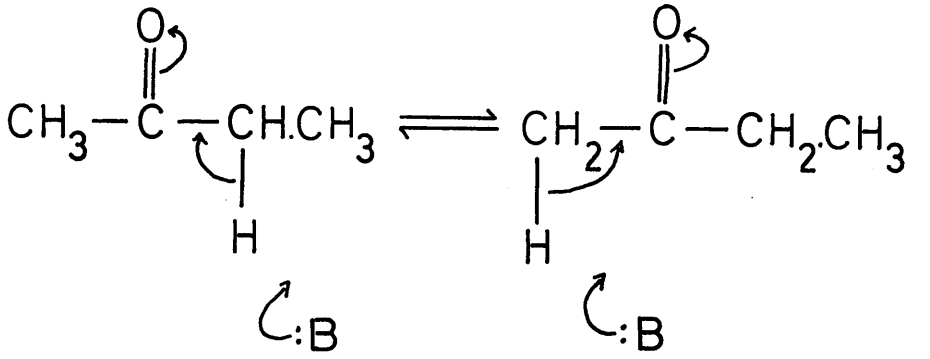


II

In the homologous series, $CH_3CO(CH_2)_nCO_2H$, the terminal site is a methyl group i.e. a primary carbon, whilst the alternative site involves a secondary carbon. A similar situation occurs in butan-2-one. Cardwell[104,105] proposed that the effect of methyl groups on the rate of competing enolisation in asymmetric ketones could be rationalised in terms of the two distinct mechanisms of enolisation. If we consider the rate-determining steps in butan-2-one, as shown in figure 4(i) 2., it may be seen that, although the products may be the same, the processes are rather different and the charged atom must affect, in some way, the nature of the reaction. In summarising the results of many investigations of enolisation and tautomeric equilibrium in ketones and nitro-compounds, Cardwell suggested that base-catalysed enolisation was controlled by a Hoffman-type rule (i.e. the least substituted enol is favoured) and acid-catalysed enolisation was controlled by a Saytzeff-type rule (i.e. the most substituted enol is favoured).

Hughes[196] has suggested that, in base-catalysed enolisation, alkyl groups act in an inductive manner to hinder the loss of a proton to a base. Hauser and Adams[107] have suggested that, in acid-catalysed enolisation, alkyl groups exert an hyperconjugative effect, since the reaction is analogous to the well-known reaction of dehydrohalogenation, as shown in figure 4(i) 3. Examples of the effect of alkyl groups on enolisation are given below:

FIGURE 4(i).2.


O
CH3—C—CH.CH3
CH2—C—CH2.CH3
H
H
:B
:B

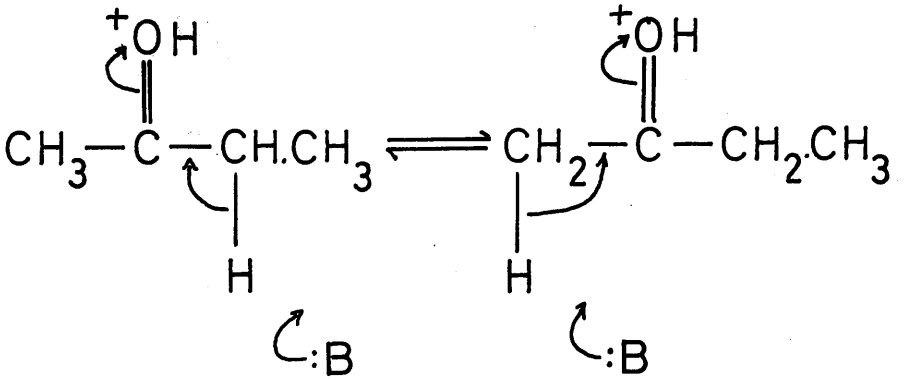
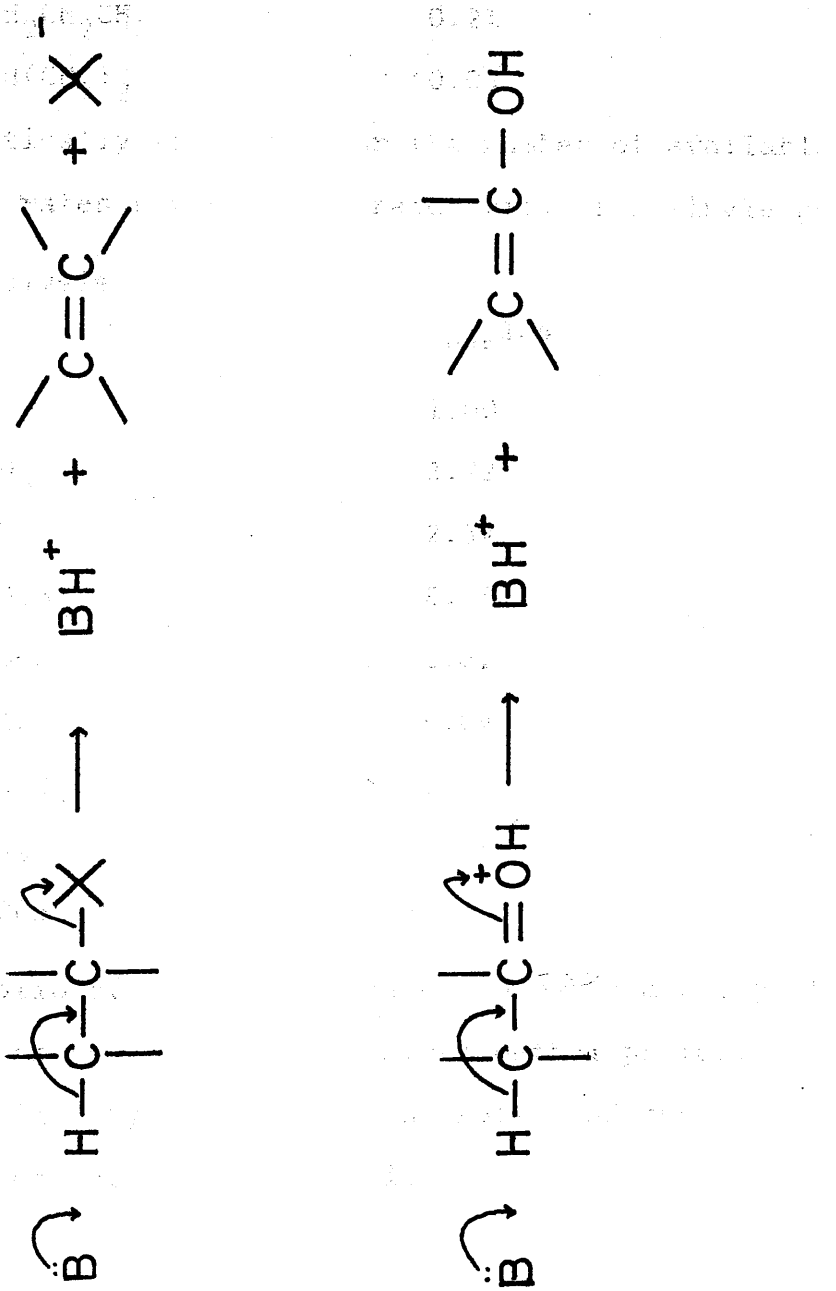

+OH
+OH
CH3—C—CH.CH3
CH2—C—CH2.CH3
H
H
:B
:B

FIGURE 4(i). 3.



base catalysis

compound	relative rate*[108]
$PhCOCH_3$	1.00
$PhCOCH_2CH_3$	0.23
$PhCOCH(CH_3)_2$	0.09
$PhCOCH_2CH_2CH_3$	0.18
$PhCOCH_2CH_2CH_2CH_3$	0.21
$PhCOCH_2CH(CH_3)_2$	0.09

* statistically corrected for the number of available protons, i.e. the rates refer to the reactivity of a single proton.

acid catalysis

compound	r**[104]
CH_3COCH_3	1.00
$MeCH_2COCH_3$	3.72
$EtCH_2COCH_3$	2.54
$n\text{-}PrCH_2COCH_3$	5.08
$n\text{-}BuCH_2COCH_3$	2.32
$n\text{-}AmCH_2COCH_3$	6.04
$i\text{-}PrCH_2COCH_3$	1.67
$Me_2CHCOCH_3$	9.18
$Me.EtCHCOCH_3$	11.4

** r = ratio of the rate of reaction of an alkyl proton to the rate of reaction of a terminal methyl proton. The values were obtained by measuring total rates and then examining the products of mono-bromination.

Several workers[109-113] have followed the enolisation of butan-2-one in deuterium oxide by N.M.R. spectroscopy and showed that, in acid solution, the methylene proton is more readily exchanged, as predicted and, in base-catalysed reaction, the ratio of reactivity of the protons is 1.0 $\pm$ 0.1. Rappe[114] has reported anomalous results from his studies on the halogenation of butan-2-one, which were said to be best explained by considering mechanisms which did not involve an enol intermediate. However, Swain and Dunlap[115] demonstrated the invalidity of the results as arising from unjustified initial assumptions and their findings have been confirmed by Cox and Knipe[116] by kinetic measurements of all the processes involved in the total reaction.

Bell and his co-workers[117] have measured the rate of enolisation of some symmetrical ketones

ketone	$k_{H^+}(M^{-1}\ s^{-1})$	$k_{OH^-}(M^{-1}\ s^{-1})$
CH_3COCH_3	2.7×10^{-6}	2.5×10^{-1}
$CH_3CH_2COCH_2CH_3$	2.7×10^{-6}	3.8×10^{-2}
$(CH_3)_2CHCOCH(CH_3)_2$	1.8×10^{-6}	2.1×10^{-3}

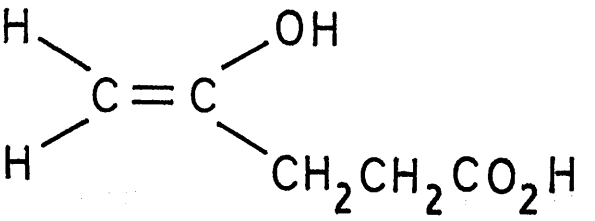
The values quoted are not corrected for the statistical difference, but it is apparent that the substituent hypothesis is supported and that base-catalysed ionisation is much more sensitive to methyl substitution. The authors suggested that, in the case of base catalysis, the differences in rate indicate a considerable steric effect.

The foregoing results may be applied to levulinic acid and its alkyl derivatives in terms of acid catalysis favouring reaction at the 3-position and base catalysis

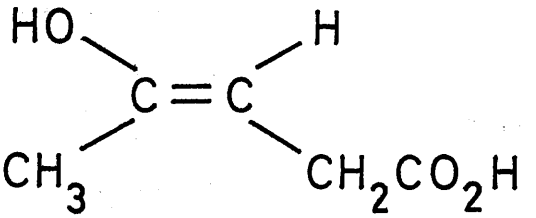
favouring neither site. However, further factors must be considered. There are three possible enols of levulinic acid, as shown in figure 4(i) 4. Since the volume of a methyl group is similar to that of an hydroxyl group, II and III, will not be distinguished and will be favoured over I, because of steric interaction between the hydroxyl and the propionic acid chain, in view of the fact that Rappe[118] has reported extended Hückel calculations on butan-2-one, which indicate that the trans-enol is favoured by about 6 $kJ.mol^{-1}$ over the cis-enol. In addition, the inductive effect of the carboxylic acid group will act to a greater extent on the 3-position and therefore favour ionisation at that position. The argument, above, applies to both inter- and intra-molecular processes, but for the intra-molecular catalysis there is an over-riding effect of the size of the ring in the transition state.

In levulinic acid, there may be two intra-molecular transition state rings; one five-membered and one seven-membered ring. Many results are available, in the literature, from which the effect of ring-size on rate of reaction may be seen. In general, the trend is: 5-membered > 6-membered > 7-membered. The results of Bell and Fluendy may appear to violate this trend, insofar as they found 5-oxo hexanoic acid reacted faster than levulinic acid. This contrasts, for example, with the observation of Gaetjens and Morawetz[119] that the hydrolysis of acid phenyl succinates is much more rapid than that of the corresponding glutarates, i.e. a 5-membered ring is formed more readily than a 6-membered ring. However, the transition state of the keto-acids contains a proton

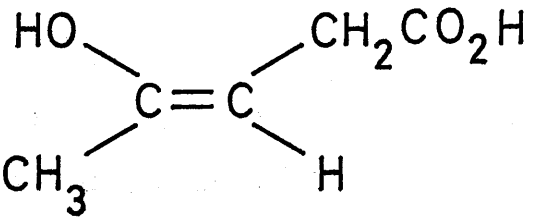
FIGURE 4(i).4.



I



II



III

and hence the transition states have sometimes been designated $4\frac{1}{2}$- and $5\frac{1}{2}$-membered rings. The slightly higher frequency factor for 5-membered ring formation has been taken to indicate that the five-atom chain has a greater tendency to exist in a coiled (as distinct from a zig-zag) conformation than a 4- or 6-atom chain. Although cases exist in which the order of 5- and 6-membered rings is reversed, it is found that the 7-membered ring is formed most slowly. This means that, in levulinic acid, intra-molecular catalysis favours the 3-position.

It has been mentioned above that Bell and Fluendy estimated in excess of 80% of the total reaction occurred at the 3-position. It is possible to estimate the relative rates of the two sites by considering their results of the intra-molecular base-catalysed rates in terms of the composition of the total rate.

compound		rate x 10^8 s^{-1}	composition of rate
(i)	$CH_3CO(CH_2)_2CO_2^-$	29.8	3 x H(7) + 2 x H(5)
(ii)	$CH_3CO(CH_2)_4CO_2^-$	7.2	3 x H(9) + 2 x H(7)
(iii)	$CH_3CO(CH_2)_5CO_2^-$	3.4	3 x H(10) + 2 x H(8)
(iv)	$CH_3CO(CH_2)_{11}CO_2^-$	3.2	3 x H(16) + 2 x H(14)

where: the figures in brackets refer to the size of the ring transition state.

We may then write:

$$\text{rate (i)} = 3\,\nu_7 + 2\,\nu_5$$

$$\text{rate (ii)} = 3\,\nu_9 + 2\,\nu_7$$

where the subscripts refer to ring-size.

If it is assumed that in (iii) there is no difference between the reactivities of the two sites, which seems probable on comparison of (iii) and (iv), then is possible to assign a value to the rate of ionisation of a proton by a 9-membered ring:

$$\text{rate (iii)} = 5\ \nu_9$$

Solving the equations:

$$\frac{\nu_5}{\nu_7} = 4.4$$

i.e. $\frac{\text{rate at 3-position}}{\text{rate at 5-position}}$ = approx. **3**.

There is little available data for reactions analogous to the reaction under consideration. Harper and Bender,[22] in comparing the intra-molecular base-catalysed enolisation of 2-acetyl and 2-iso-butyryl benzoic acids, showed a $2\frac{1}{2}$-fold rate-enhancement in the more substituted compound. This was explained in terms of steric hindrance to rotation about the spine of the iso-butyryl group, where the preferred conformation directs the proton towards the carboxylate group and hence formation of the transition state results in little loss of rotational entropy. Assuming 21 J deg^{-1} mol^{-1} for rotation about a single band[120] and allowing for the retarding inductive effect, obtained from kinetic studies on acetophenone and iso-butyrophenone, calculation predicts a rate-enhancement in agreement with experiment. But, in this system the molecule is rigid, with the reacting groups locked in position ready for reaction, unlike the aliphatic case, where rotation is possible about all the bonds between the reacting groups and

it is necessary, initially, to bring the molecule, from whatever ground-state conformation it may adopt, to an analogous cyclic conformation.

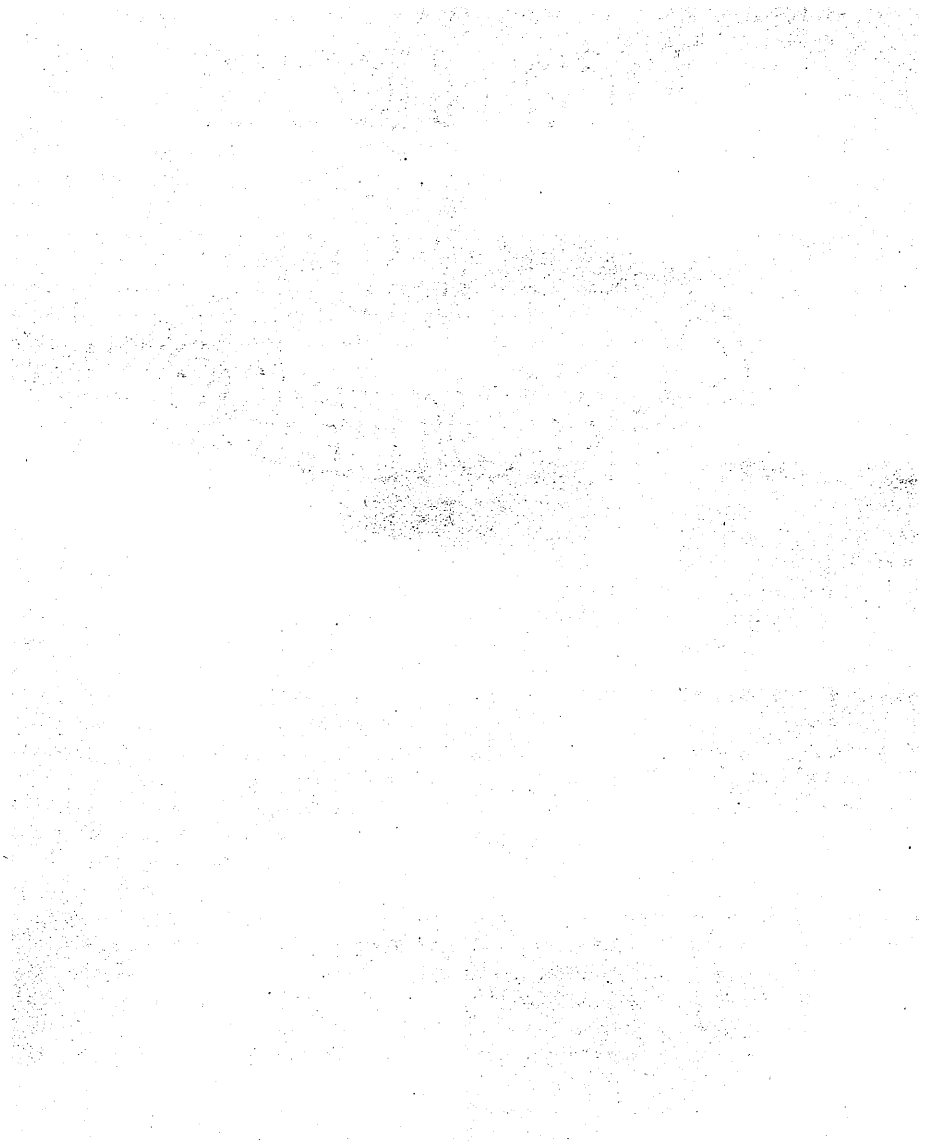
Wilson and Lewis[121] measured the rates of iodination of aliphatic nitro-carboxylic acids. They found the major contributor to the observed rate to be the intra-molecular base-catalysed process and that rate to be a maximum for 4-nitropentanoic acid i.e. corresponding to a 6-membered transition state, consistent with the findings of Bell and Fluendy. It was further found that 4-nitro-3-methyl pentanoic acid reacted twice as fast as the unsubstituted compound.

Bell and Fluendy reported the following values for the activation energies of the intra-molecular base-catalysed rates in their aliphatic keto-acids.

compound	E_a(kJ mol^{-1})
$CH_3CO(CH_2)_2CO_2^-$	92
$CH_3CO(CH_2)_3CO_2^-$	83
$CH_3CO(CH_2)_4CO_2^-$	92

The rate measurements were not sufficiently accurate to warrant apportionment between enthalpy and entropy terms and although the results have been rounded off, the closeness of the figures to that of 95 kJ mol^{-1}, reported by Smith[122] for the acetate-catalysed iodination of acetone, was regarded as evidence that the formation of a cyclic transition state does not greatly modify the activation energy. It is, therefore, of interest to repeat this work in order to determine the effect

of ring-size in the transition state on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, since, as has been pointed out in Chapter I, it is not always predictable.



PART (ii): KINETICS - THEORETICAL

The accepted mechanism for acid-catalysed halogenation is given in figure 4(ii) 1:[123]

A_i = i'th species of acid

B_i = its conjugate base

X_2 = halogen.

The reaction scheme may be written in the form:

$$HS + \Sigma A_i \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [HSH]^+ + \Sigma B_i \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SH + \Sigma A_i$$

$$SH + X_2 \xrightarrow{k_3} SX + H^+ + X^-$$

where: HS = ketone

$[HSH]^+$ = conjugate acid of the ketone

SH = enol

k(subscript) = pseudo first order rate constant, assuming that the concentration of ΣA_i and ΣB_i remain effectively constant during the reaction.

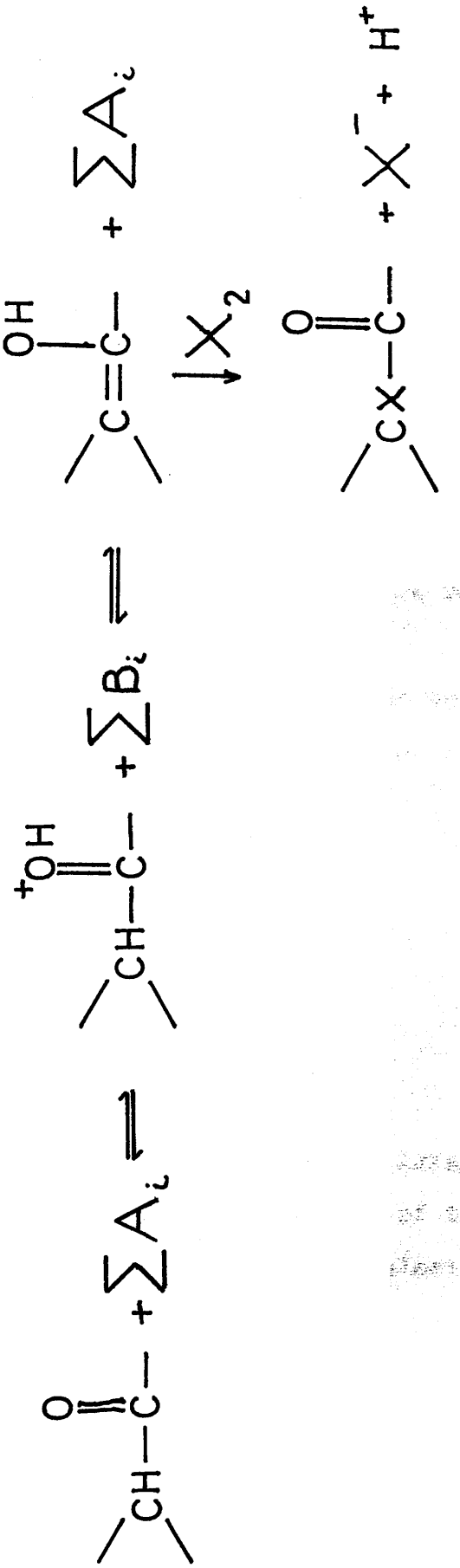
For ketones, k_1, k_{-1} and k_3 are all large. The equilibrium concentration of protonated ketone is rapidly reached, ionisation, catalysed by base, occurs slowly and the enol produced reacts rapidly with the halogen in an irreversible process. The observed velocity is represented by:

$$\nu_{obs} = [HSH^+] \Sigma \pi_i [B_i]$$

where: π = catalytic rate constant for the base B.

$$\nu_{obs} = [HSH^+] . \frac{[HS]}{[HS]} \Sigma \pi_i [B_i]$$

FIGURE 4 (ii).1.



Since $K_{HSH^+} = \frac{[H^+][HS]}{[HSH^+]}$ and $K_i = \frac{[H^+][B_i]}{[A_i]}$

then $$\nu_{obs} = \frac{[HS]}{K_{HSH^+}} \cdot [H^+] \Sigma \pi_i [B_i]$$

$$= \frac{[HS]}{K_{HSH^+}} \cdot \Sigma_i \pi_i [A_i]$$

and the observed first-order rate constant may be written as:

$$k_{obs} = \frac{1}{K_{HSH^+}} \cdot \Sigma K_i \pi_i [B_i]$$

General acid catalysis is observed and the reaction is zero-order in halogen.

The accepted mechanism for base-catalysed halogenation is given in figure 4(ii) 2.[123] The reaction scheme may be written in the form:

$$HS + \Sigma B_i \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^- + \Sigma A_i$$

$$S^- + X_2 \xrightarrow{k_3} SX + X^-$$

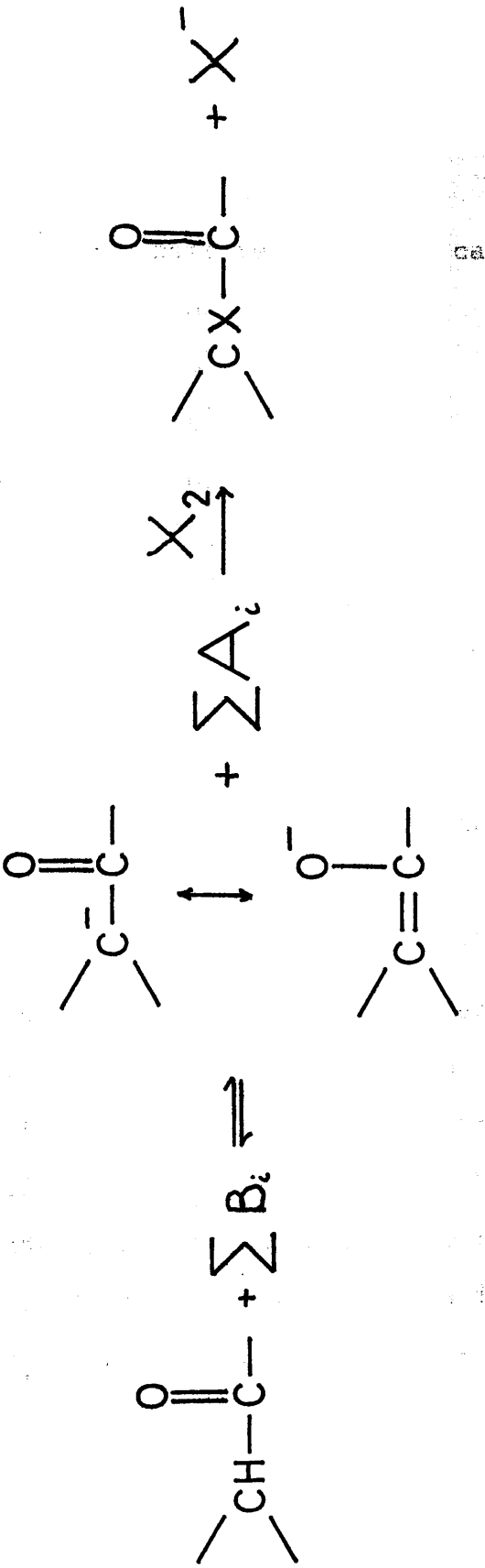
As in the case of acid catalysis, k_3 is large. The rate-determining step is the ionisation of the ketone to give the enolate anion. The observed velocity is given by

$$\nu_{obs} = [HS] \Sigma \pi_i [B_i]$$

and the observed first-order rate constant is given by:

$$k_{obs} = \Sigma \pi_i [B_i]$$

FIGURE 4 (ii). 2.



General base catalysis is observed and the reaction is zero-order in halogen.

There are several possible mechanisms by which a keto-acid can enolise. In the absence of added buffer systems:

reaction	substrate	catalyst
1	HL	H^+
2	L^-	H^+
3	L^-	OH^-
4	HL	OH^-
5	HL	HL
6	L^-	L^-
7	HL	L^-
8	L^-	HL
9	L^-	H_2O
10	L^-	intra-molecular
11	HL	H_2O
12	HL	intra-molecular

Interest is centred on the intra-molecular terms and the reaction conditions may be adjusted to minimise the contribution of many of the terms to the total rate. In buffered solutions, k_2, k_3 and k_4 can be neglected. Bell and Fluendy[25] have shown that under those conditions, it is also possible to neglect the terms in k_1, k_5 and k_6. The terms in k_{10} and k_{12} are indistinguishable from the terms in k_9 and k_{11}, because of kinetic equivalence, but it can be concluded from the observed rates that the intra-molecular

processes will be much faster than the corresponding processes involving water as an inter-molecular catalyst. Reactions 7 and 8 are also kinetically equivalent.

The rate expression is now given by

$$v = k_7[HL][L^-] + k_8[HL][L^-] + k_{10}[L^-] + k_{12}[HL].$$

Putting $r = [HL]/[L^-]$, the buffer ratio, the expression can be simplified:

$$v = [L^-]\left(k_{10} + rk_{12}\right) + [L^-]^2 r(k_7 + k_8)$$

At constant buffer ratio, a plot of $v/[L^-]$ against $[L^-]$ gives a straight line, of slope $r(k_7 + k_8)$ and intercept $\left(k_{10} + rk_{12}\right)$.

Let $v - [L^-]^2 r(k_7 + k_8) = k_e$

then $k_e = k_{10}[L^-] + rk_{12}[L^-]$

$[HL]_T = [HL] + [L^-]$, total substrate concentration.

$R = 1/r$

By algebraic manipulation, the expression in k_e becomes:

$$(1 + R)k_e = Rk_{10}[HL]_T + k_{12}[HL]_T$$

With solutions of differing buffer ratio, a plot of $(1 + R)k_e$ against R gives a straight line, of slope $k_{10}[HL]_T$ and intercept $k_{12}[HL]_T$.

In the presence of an added buffer system, such as acetic acid/acetate, the following processes will contribute to the total rate:

reaction	substrate	catalyst
1	HL	intra-molecular
2	L^-	intra-molecular
3	HL	L^-
	L^-	HL
4	HL	OAc^-
5	L^-	HOAc
6	L^-	OAc^-
7	HL	HOAc

Reactions 1, 2 and 3 are the reactions designated 12, 10 and (7 + 8), respectively, in the previous list.

The rate expression is given by:

$$v = k_1[HL] + k_2[L^-] + k_3[HL][L^-] + k_4[HL][OAc^-]$$

$$+ k_5[L^-][HOAc] + k_6[L^-][OAc^-] + k_7[HL][HOAc]$$

Let $a = [HL] + [L^-]$, total substrate concentration.

K_1 = dissociation constant of the substrate.

K_2 = dissociation constant of acetic acid.

r = acetate buffer ratio, $[HOAc]/[OAc^-]$.

Although r has been used for a different buffer ratio here, the kinetic results, below, have been set out to allow for no ambiguity.

$$\frac{[HL]}{[L^-]} = r\frac{K_2}{K_1}$$

$$\frac{[HL]}{a} = \frac{K_2 r}{(K_1 + K_2 r)} \text{ and } \frac{[L^-]}{a} = \frac{K_1}{(K_1 + K_2 r)}$$

Substituting into the rate expression:

$$\frac{v(K_1 + K_2 r)}{a} = k_1 K_2 r + k_2 K_1 + \frac{k_3 a K_1 K_2 r}{(K_1 + K_2 r)}$$

$$+ [OAc^-]\left\{r(k_4 K_2 + k_5 K_1) + k_6 K_1 + k_7 K_2 r^2\right\}$$

To obtain the rate constants, which are the only unknowns in the rate expression, series of solutions were made up containing acetate buffer at four different buffer ratios. Thus, at each buffer ratio, $v(K_1 + K_2r)/a$ was plotted against acetate concentration and straight lines were obtained, with intercepts comprising terms only in [HL] and [L^-] and slopes comprising terms involving also [HOAc] and [OAc^-].

Taking the intercepts of the graphs, there are four equations in three unknowns. As each unknown is part of a different coefficient of r, solving the simultaneous equations yields values for k_1, k_2 and k_3. In the case of the slopes, there are four equations in four unknowns, but only three coefficients of r. k_4 and k_5 cannot be separated because the processes are kinetically equivalent and it may be that the processes are also physically equivalent, since the transition states are very similar (see figure 4(ii) 3). In the equilibrium suggested, neither side will be greatly favoured, as the dissociation constants of the two acids are very similar (see chapter 3, above). From other work, it is generally true that base catalysis is the faster process and hence the results here may be simplified, with little error, by quoting that coefficient of r as arising from acetate attack on the acid substrate. Similarly, the inter-molecular process, involving substrate acid and substrate anion, is most probably only anion attack on acid substrate.

In both the self-buffered and acetate-buffered kinetics, the best straight lines through the experimental points were determined by the method of least mean squares.

FIGURE 4(ii).3.

ACID SUBSTRATE
BASE CATALYST
ANION SUBSTRATE
ACID CATALYST
i.e.
HL + OAc⁻ ⇌ L⁻ + HOAc
TRANSITION STATE

To analyse the acetate-catalysed kinetics, the equations arising from the slopes and intercepts were treated, as four sets of three simultaneous equations; the quoted rate constants being obtained from the mean and the error from the maximum deviation from the mean. When a rate constant came out as negative, that term was set to zero and will be quoted as "indeterminate".

Activation parameters were calculated from the standard Arrhenius and transition state theory equations:

$$\ln k = \ln A - \frac{E_a}{RT}$$

$$\ln \frac{k}{T} = \ln \frac{k}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R}$$

where all the symbols have the usual meaning. The best straight lines were obtained by the method of least mean squares and the errors quoted are standard deviations.

The rate component interpreted as intra-molecular base-catalysis could alternatively be attributed to an inter-molecular hydroxyl ion-catalysed reaction, due to the equilibrium:

$$L^- + H_2O \rightleftharpoons HL + OH^-$$

It is possible to estimate a value for this catalytic constant, k_{OH^-}, in the following way. The rate of disappearance of iodine for intra-molecular catalysis is represented by the expression:

$$v = k_2[L^-]$$

and the rate for inter-molecular catalysis by:

$$v = k_{OH^-}[HL][OH^-]$$

Equating the expressions and rearranging in terms of the ionic product of water and the dissociation constant of

the substrate:

$$k_{OH^-} = k_2 \cdot \frac{K_a}{K_w}$$

Substituting with known values:

$$K_{OH^-} = \sim 400\ M^{-1}\ s^{-1}$$

Bell[117] has reported a value of $4 \times 10^{-2}\ M^{-1}\ s^{-1}$ for the rate of hydroxyl ion-catalysed halogenation of diethyl ketone. Thus the inter-molecular mechanism is unlikely and the measured rate is, in fact, for an intra-molecular process.

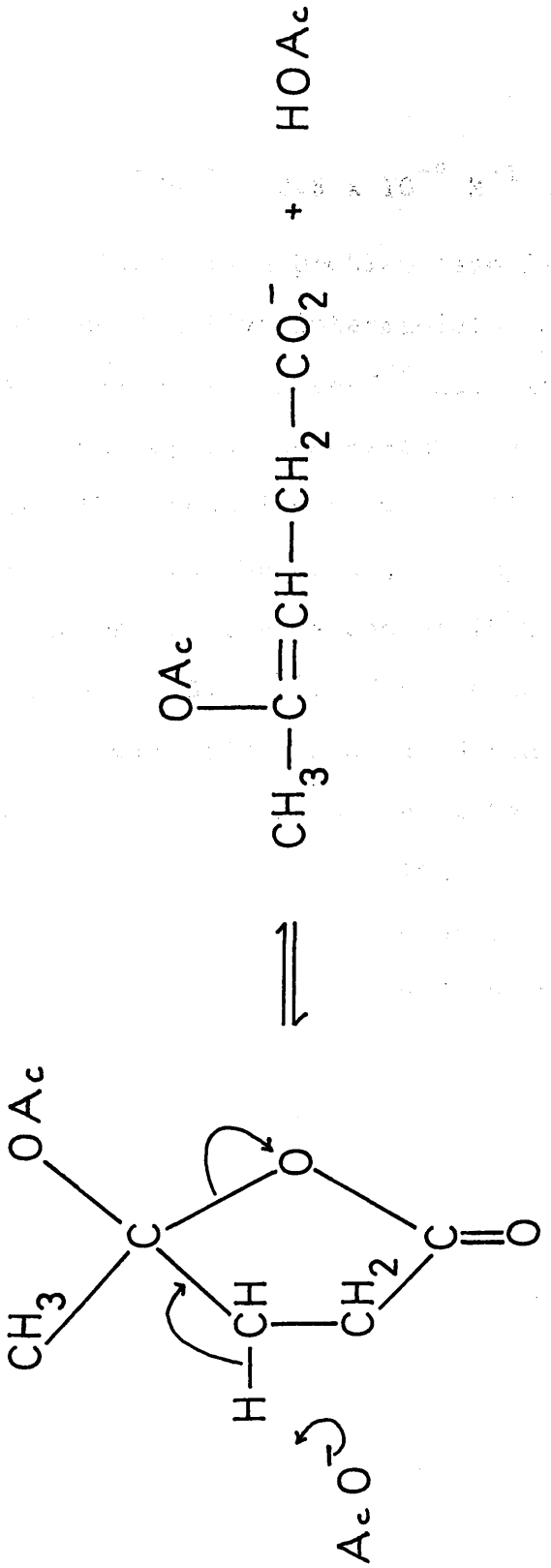
Some of the keto-acids studied have been shown to exist, to a greater or lesser extent, in the ring form. In substituting experimental values into the rate equation, it is important to know what part the ring acid plays in the kinetics. Having already established (see chapter 3, part (iv)) that acetyl levulinic acid is a derivative of the ring tautomer of levulinic acid, it could be used as a model for the ring tautomer of levulinic acid. Consequently the rates of its acetate-catalysed iodination were measured. The envisaged mechanism is shown in figure 4(ii) 4. Under zero-order conditions the rate expression is:

$$v = k_{H_2O}[S][H_2O] + k_{OAc^-}[S][OAc^-]$$

The following results were obtained:

$10^{11} v/MS^{-1}$	$10^2[OAc^-]$
4.04	10.0
3.75	7.5
3.61	5.0
3.18	2.5

FIGURE 4(ii). 4.



[s] = substrate, 3.8×10^{-2}M in 4% v/v dioxan/water.

acetate buffer ratio = 1.00

$[H_2O]$ = 55.51M.

$$k_{H_2O} = 1.4 \times 10^{-11}\ M^{-1}\ s^{-1}$$

$$k_{OAc^-} = 2.6 \times 10^{-9}\ M^{-1}\ s^{-1}$$

There is a problem associated with this mechanism, in that the reactive intermediate is not an enol, but an enol acetate. Kirby and Meyer[124] have investigated the ketonisation of 2-acetoxy-cyclohexene-1-carboxylate, for which they proposed the mechanism shown in figure 4(ii) 5. They estimated the half-life of the ester, decomposing to the anhydride, to be of the order of a second at 25°C and k_2 to have a minimum value of about 0.2 s^{-1}. The subsequent hydrolysis of the ketene derivative will also be a rapid reaction. An analogous sequence may be applied to the enol acetate of levulinate anion, as shown in figure 4(ii) 6. Although the two mechanisms are not exactly the same, the important point is that the formation of the anhydride will be rapid and whatever the hydrolysis products may be, for it is certain that a ketene will not be formed, the substrate derivative will react with tri-iodide ion.

A second possibility in the iodination of acetyl levulinic acid is that hydrolysis of the ester group is a rapid reaction and then the observed rate is due to the rate-determining step of attack by lyate species and not to proton abstraction. The rate expression may be written:

$$v = k_{H^+}[H^+][S] + k_{OAc^-}[OAc^-][S] + k_{HOAc}[HOAc][S]$$

FIGURE 4(ii).5.

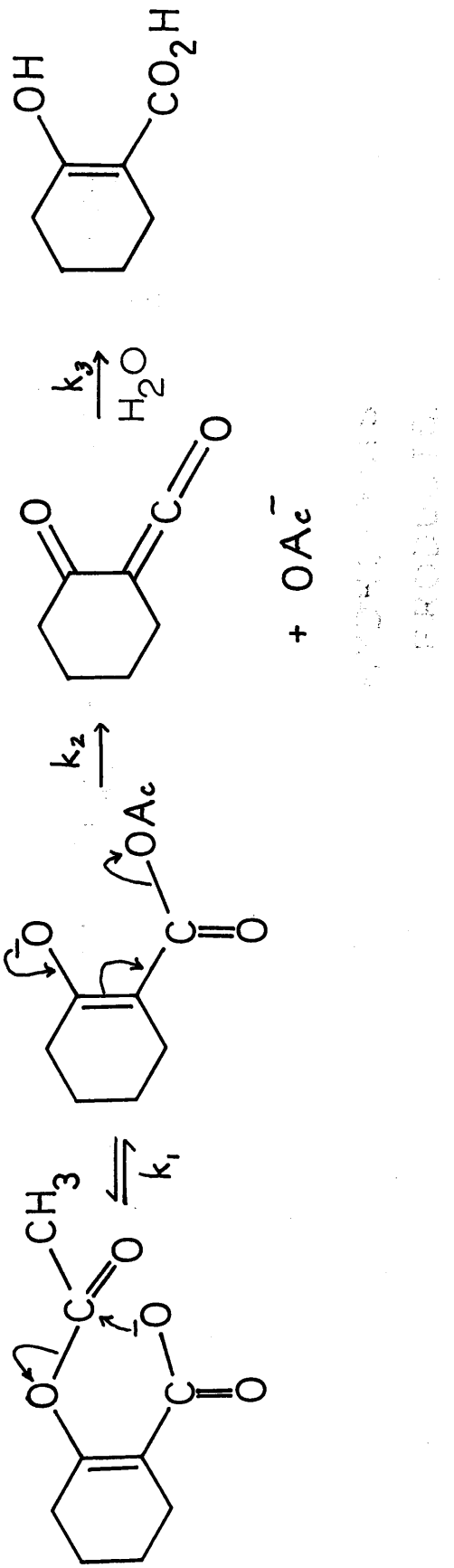
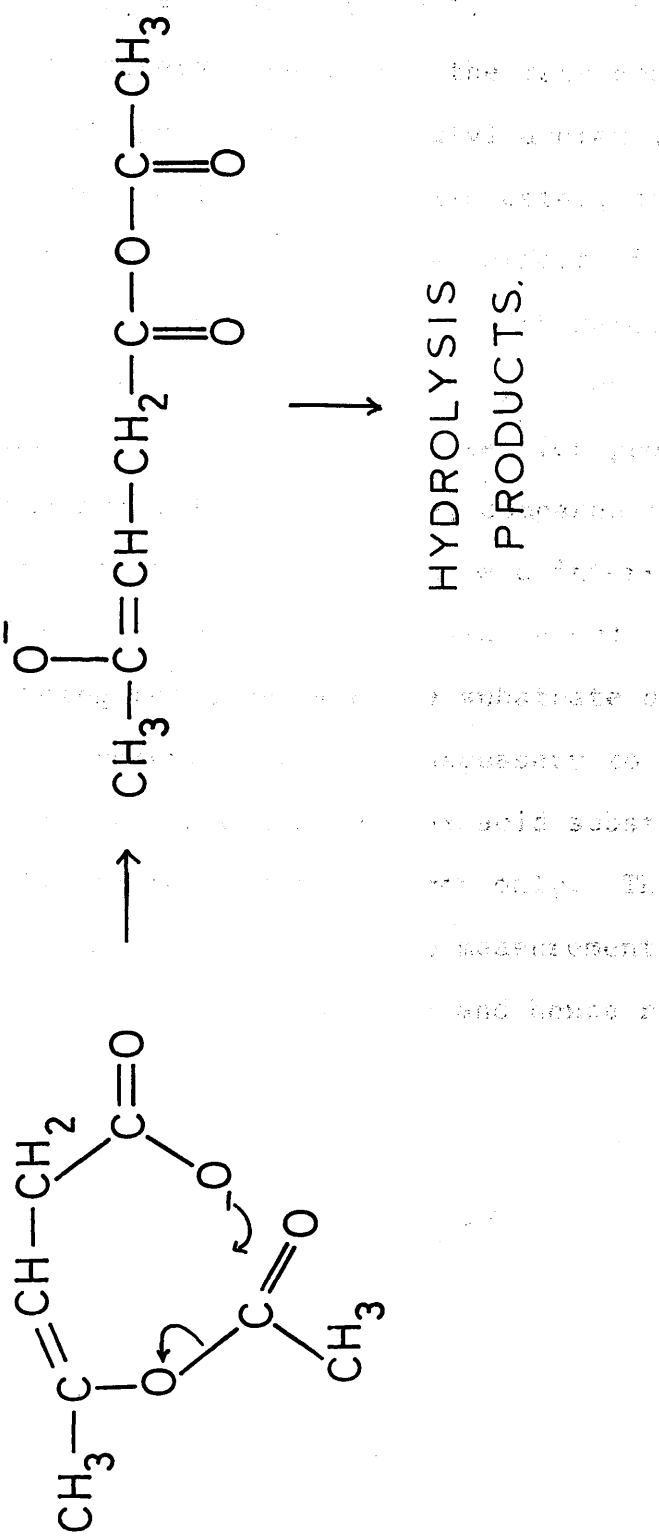


FIGURE 4 (ii). 6.



At the experimental pH of 5, hydrolysis by hydroxyl ion may be neglected. Substituting the experimental values for zero buffer concentration:

$$k_{H^+} = \sim 10^{-4}\ M^{-1}\ s^{-1}.$$

This is close to the observed value for the rate constant of the acid-catalysed hydrolysis of t-butyl acetate,[125] which is a reasonable model for the cyclic ester, since steric factors are more important than inductive effects in the hydrolysis of esters.[58] It seems probable, therefore, that the measured rates refer to ester hydrolysis. Nonetheless it may be inferred that the rates calculated for proton abstraction are maximum values and hence, compared to the contributions to the total rate by intra- and inter-molecular processes involving the chain tautomer (see below), may be neglected. This being the case, where a substrate can exist as the ring tautomer, it will be necessary to apply a correction to those rates which involve acid substrate, so that the rates refer to the chain tautomer only. The rate constants, quoted below with the kinetic measurements, are not corrected for ring-chain tautomerism and hence refer to total acid substrate.

PART (iii): KINETICS - EXPERIMENTAL

The enolisation of most of the keto-acids studied was followed by observing the rate of change of tri-iodide ion concentration. Both iodine and tri-iodide ion react with enols,[126] but the large extinction coefficient of tri-iodide enables concentrations of the order of 10^{-5}M to be used, which is more convenient for following reactions under zero-order conditions.

Autrey and Connick[127] reported the extinction coefficient of tri-iodide to be 2.640×10^4 M^{-1} cm^{-1} at 353 nm. Bell and Fluendy[25] obtained a value of 2.528×10^4 $M^{-1}cm^{-1}$, which is in close agreement with that obtained by Barnes[128] of 2.55×10^4 M^{-1} cm^{-1}. Throughout this study, the extinction coefficient of tri-iodide was taken to be 2.528×10^4 M^{-1} cm^{-1} and all iodination reactions were followed at 353 nm. Molecular iodine and tri-iodide ion are in equilibrium in aqueous solution:

$$I_2 + I^- \rightleftharpoons I_3^-$$

$$K = \frac{[I_3^-]}{[I_2][I^-]}$$

It is necessary to take account of this equilibrium and the concentration of iodide ion in order to calculate the effective extinction coefficient, ε_{eff}. In all the iodination experiments, 0.1M potassium iodide was present in solution. Taking the values for K, obtained by Autrey and Connick,[127] the following figures were calculated:

$t^{o}C$	K	$\varepsilon_{eff} \times 10^{-4}$
25.0	714	2.492
35.0	544	2.481
45.0	417	2.467
55.0	328	2.450

In some cases, the kinetics were followed by the rate of disappearance of molecular bromine. As for iodination, bromination was followed spectrophotometrically, using an extinction coefficient of 187 at 400 nm, measured by Bell and Pring.[129] Because the stability constants of Br_3^- and Br_2Cl^- are low, it is no advantage to have halide present in solution.

INSTRUMENTATION.

Two spectrophotometers were used: a Gilford 2400 and a Gilford 2400-S. These instruments have a four-cell automatic cuvette and chart recorder. The temperature in the cuvette is monitored by a thermosensor with output to the chart recorder, so that the temperature is continuously recorded throughout a reaction. The thermosensor was calibrated, in a mercury bath, against a standard N.P.L. mercury-in-glass thermometer. Both instruments were thermostatted to 25.0 $\pm$ 0.1^{o}C by circulation from a water bath. For higher temperatures, the error must be considered to be commensurately greater, since initiation of the reaction required opening the cuvette for a short time.

APPARATUS.

Glass volumetric apparatus of grade B accuracy was used throughout. Pipettes were standardised by weighing the

volume of distilled water delivered and were found to be accurate to < ± 0.2%. For spectrophotometric measurements, silica cells of 1 cm. pathlength, fitted with Teflon stoppers, were used.

SOLUTIONS AND MATERIALS.

Stock solutions of the keto-acids were prepared by dissolving known weights in water, which had been de-ionised and then distilled from potassium permanganate. The concentration was checked by titration with standard BDH CVS sodium hydroxide. Titration was necessary for the liquid acids, which tended to be hygroscopic; in other cases it served to check the equivalent weight. Keto-acid buffers were prepared by partial neutralisation of stock acid solution with standard sodium hydroxide solution.

Acetate buffers were prepared from BDH CVS acetic acid and sodium hydroxide. In making up acetate-buffered solutions of the keto-acids, the pH of the keto-acid buffer was made the same as that of the acetate buffer by using the relationship:

$$r_{HL} = \frac{K_{aHOAc}}{K_{aHL}} \times r_{HOAc}$$

The acetate-buffered solutions were obtained by making up one solution of keto-acid with a high concentration of acetate-buffer and one solution of keto-acid containing no acetate-buffer. The solutions were then mixed in varying proportions and their pH values were checked for consistency with a Radiometer pH meter.

In all the kinetic measurements, an ionic strength of 0.2M was maintained by the addition of a solution of AnalaR potassium chloride or sodium perchlorate, for iodination and bromination respectively.

MEASUREMENT OF RATES OF REACTION.

Since the experimental technique was essentially the same for all the compounds studied, a general method is described here and any modifications to the general method will be presented with the results obtained for that particular keto-acid.

The rate of enolisation was followed spectrophotometrically, by following the rate of decrease of tri-iodide ion concentration with time at 353 nm. At this wavelength, all components of the solutions have a negligible absorption. Initially, the concentration of tri-iodide was of the order of 10^{-5}M and the concentration of the substrate was such that the ratio of substrate to tri-iodide was never less than 100:1 and was usually 1000:1. Thus, the concentration of substrate remained effectively constant and zero-order conditions were indicated by the observation that optical density decreased linearly with time.

The observed rate of disappearance of tri-iodide was calculated from the expression:

$$v_{obs} = \frac{\Delta d}{t \times \varepsilon_{eff}} \cdot M\ s^{-1}$$

where Δd = change in optical density in time t secs.

All solutions were prepared in duplicate and samples were brought to thermal equilibrium by standing in the thermostatted cuvette. Each cell held approximately 2.5 ml

of solution and the addition of 2×10^{-6}l of 5×10^{-2}M iodine (BDH CVS) solution, by Hamilton syringe, gave an optical density of about 0.8. When all the iodine had reacted, a second addition was made and hence each kinetic result is the mean of four runs, which usually agreed to within $\pm$ 2%.

In nearly all the experiments, the optical density decreased with time in a strictly linear manner. Since the substrate was always in very great excess, it may be concluded that only mono-iodination was taking place. In no case could the presence of reactive impurity be detected, which would take the form of an initial curvature to the trace, corresponding to a much more rapid decrease of iodine concentration, according to a first-order rate law. However, it was common to observe curvature at the end of a run. This amounted to only a few percent of the reaction and indicates that iodination is not completely irreversible in all cases or that scavenging is not effective at very low iodine concentrations.

$k_{12} = 1.5 \pm 0.2 \times 10^{-9}$ s^{-1}

PART (iv): KINETICS RESULTS

LEVULINIC ACID: self-buffered kinetics (25.0°C)

r = 2.078

$[L^-] \times 10^2$ M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.997	35.6	34.3
1.99	75.0	74.8
2.99	122	122
3.99	175	175
4.99	231	234
5.98	303	300
6.98	366	372
7.98	453	450

a = 0.1228 M

r	$[L^-] \times 10^2$ M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.230	9.98	316	319
0.366	8.99	302	303
0.537	7.99	288	284
0.757	6.99	260	261
1.050	5.99	239	235
1.461	4.99	207	207
2.078	3.99	170	175

$$(k_7 + k_8) = 1.51 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$$

$$k_{10} = 28.2 \pm 0.2 \times 10^{-8}\ s^{-1}$$

$$k_{12} = 1.5 \pm 0.2 \times 10^{-8}\ s^{-1}$$

LEVULINIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 2.816 \times 10^{-2}$M

r	$[OAc^-] = 10^2$M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.60	0	59.1	58.6
	2.67	63.0	63.8
	5.33	68.5	68.9
	8.00	74.3	74.1
1.00	0	50.7	50.3
	2.67	56.0	56.7
	5.33	62.5	63.1
	8.00	69.9	69.5
2.75	0	32.4	31.7
	2.67	40.0	40.9
	5.33	49.1	50.0
	8.00	59.6	59.2
5.67	0	21.0	20.6
	2.80	31.6	32.2
	5.60	44.1	43.7
	8.40	55.6	55.3

$k_1 = 1.5 \pm 0.1 \times 10^{-8}$ s^{-1}

$k_2 = 28.0 \pm 0.2 \times 10^{-8}$ s^{-1}

$k_3 = 1.3 \pm 0.2 \times 10^{-6}$ M^{-1} s^{-1}

$k_4 = 1.65 \pm 0.09 \times 10^{-6}$ M^{-1} s^{-1}

$k_6 = 0.27 \pm 0.05 \times 10^{-6}$ M^{-1} s^{-1}

$k_7 = 0.02 \pm 0.02 \times 10^{-6}$ M^{-1} s^{-1}

LEVULINIC ACID: acetate-catalysed kinetics (35.5°C)

$a = 2.808 \times 10^{-2}$M

r	$[OAc^-] \times 10^{-2}$M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.60	0	241	235
	2.67	242	250
	5.33	263	265
	8.00	284	281
1.00	0	205	202
	2.67	219	222
	5.33	241	242
	8.00	262	262
2.75	0	129	128
	2.67	159	158
	5.33	190	189
	8.00	222	219
5.67	0	85.6	85.0
	2.80	124	123
	5.60	167	161
	8.40	199	199

$k_1 = 7.5 \pm 4.4 \times 10^{-8}$ s^{-1}

$k_2 = 113 \pm 6 \times 10^{-8}$ s^{-1}

$k_3 = 4.2 \pm 3.2 \times 10^{-6}$ M^{-1} s^{-1}

$k_4 = 5.96 \pm 0.53 \times 10^{-6}$ M^{-1} s^{-1}

$k_6 = 0.35 \pm 0.20 \times 10^{-6}$ M^{-1} s^{-1}

k_7 = indeterminate

LEVULINIC ACID: acetate-catalysed kinetics (44.5°C)

$a = 2.796 \times 10^{-2}$ M

r	$[OAc^-] \times 10^2$ M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.60	0	772	768
	2.67	821	821
	5.33	880	873
	8.00	928	926
1.00	0	649	653
	2.67	704	717
	5.33	768	780
	8.00	843	844
2.75	0	419	409
	2.67	503	498
	5.33	598	587
	8.00	684	677
5.67	0	275	271
	2.80	393	386
	5.60	511	501
	8.40	628	616

$k_1 = 27 \pm 8 \times 10^{-8}$ s^{-1}

$k_2 = 381 \pm 13 \times 10^{-8}$ s^{-1}

k_3 = indeterminate

$k_4 = 15.3 \pm 1.4 \times 10^{-6}$ M^{-1} s^{-1}

$k_6 = 3.5 \pm 0.9 \times 10^{-6}$ M^{-1} s^{-1}

$k_7 = 0.4 \pm 0.2 \times 10^{-6}$ M^{-1} s^{-1}

LEVULINIC ACID: acetate-catalysed kinetics (53.0°C)

$a = 2.785 \times 10^{-2}$M

r	$[OAc^-] \times 10^2$M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.60	0	2066	2046
	2.67	2138	2158
	5.33	2265	2269
	8.00	2396	2381
1.00	0	1759	1752
	2.67	1852	1894
	5.33	2027	2036
	8.00	2159	2178
2.75	0	1128	1131
	2.67	1350	1337
	5.33	1600	1543
	8.00	1763	1749
5.67	0	752	780
	2.80	1069	1034
	5.60	1354	1289
	8.40	1525	1543

$k_1 = 101 \pm 7 \times 10^{-8}$ s^{-1}

$k_2 = 1006 \pm 12 \times 10^{-8}$ s^{-1}

k_3 = indeterminate

$k_4 = 40.0 \pm 4.5 \times 10^{-6}$ M^{-1} s^{-1}

$k_6 = 4.6 \pm 1.9 \times 10^{-6}$ M^{-1} s^{-1}

k_7 = indeterminate

5-OXO HEXANOIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 1.444 \times 10^{-2}$M

r	$[OAc^-] \times 10^2$M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	197	194
	2.67	197	196
	5.33	201	198
	8.00	201	200
1.00	0	153	157
	2.67	155	160
	5.33	161	163
	8.00	163	166
2.50	0	106	106
	2.67	109	110
	5.33	113	115
	8.00	115	119
5.14	0	75.2	74.2
	2.67	79.4	79.4
	5.33	84.7	84.7
	8.00	90.2	89.9

$k_1 = 20.1 \pm 7.2 \times 10^{-8}$ s^{-1}

$k_2 = 180 \pm 11 \times 10^{-8}$ s^{-1}

k_3 = indeterminate

$k_4 = 1.69 \pm 0.42 \times 10^{-6}$ M^{-1} s^{-1}

k_6 = indeterminate

k_7 = indeterminate

6-OXO HEPTANOIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 2.987 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	22.4	22.6
	2.67	25.3	25.2
	5.33	28.1	27.9
	8.00	30.3	30.5
1.00	0	21.3	21.5
	2.67	25.2	25.0
	5.33	28.7	28.5
	8.00	32.0	32.1
2.75	0	19.5	19.8
	2.67	25.0	25.3
	5.33	30.6	30.8
	8.00	36.2	36.4
5.67	0	19.5	19.0
	2.80	27.4	27.4
	5.60	36.3	35.8
	8.40	45.1	44.2

$k_1 = 6.0 \pm 0.2 \times 10^{-8}\ s^{-1}$

$k_2 = 8.3 \pm 0.3 \times 10^{-8}\ s^{-1}$

k_3 = indeterminate

$k_4 = 0.65 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_6 = 0.16 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_7 = 0.09 \pm 0.01 \times 10^{-6}\ M^{-1}\ s^{-1}$

6-OXO HEPTANOIC ACID: acetate-catalysed kinetics (35.7°C)

$a = 2.978 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	76.1	77.0
	2.67	87.0	86.1
	5.33	94.9	95.1
	8.00	104	104
1.00	0	72.1	71.8
	2.67	84.0	83.8
	5.33	95.9	95.8
	8.00	108	108
2.75	0	64.2	64.2
	2.67	81.7	82.7
	5.33	99.8	101
	8.00	120	120
5.67	0	62.3	60.4
	2.80	87.5	87.8
	5.60	115	115
	8.40	145	143

$k_1 = 18.6 \pm 0.3 \times 10^{-8}\ s^{-1}$ $\quad k_4 = 2.28 \pm 0.05 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 29.3 \pm 0.7 \times 10^{-8}\ s^{-1}$ $\quad k_6 = 0.54 \pm 0.04 \times 10^{-6}\ M^{-1}\ s^{-1}$

k_3 = indeterminate $\quad k_7 = 0.27 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$

6-OXO HEPTANOIC ACID: acetate-catalysed kinetics (45.7°C)

$a = 2.966 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	230	228
	2.67	257	252
	5.33	281	276
	8.00	310	300
1.00	0	204	207
	2.67	235	240
	5.33	266	272
	8.00	302	305
2.75	0	178	177
	2.67	225	228
	5.33	274	278
	8.00	333	328
5.67	0	169	162
	2.80	235	237
	5.60	309	312
	8.40	393	387

$k_1 = 47.9 \pm 2.3 \times 10^{-8}\ s^{-1}$ $\quad k_4 = 6.38 \pm 0.50 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 90.5 \pm 4.7 \times 10^{-8}\ s^{-1}$ $\quad k_6 = 1.33 \pm 0.42 \times 10^{-6}\ M^{-1}\ s^{-1}$

k_3 = indeterminate $\quad k_7 = 0.73 \pm 0.14 \times 10^{-6}\ M^{-1}\ s^{-1}$

6-OXO HEPTANOIC ACID: acetate-catalysed kinetics (55.1°C)

$a = 2.954 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	610	599
	2.67	677	669
	5.33	725	739
	8.00	818	810
1.00	0	544	549
	2.67	626	636
	5.33	714	724
	8.00	814	811
2.75	0	478	477
	2.67	597	601
	5.33	709	725
	8.00	852	849
5.67	0	450	441
	2.80	614	610
	5.60	781	780
	8.40	989	949

$k_1 = 133 \pm 8 \times 10^{-8}\ s^{-1}$

$k_2 = 236 \pm 13 \times 10^{-8}\ s^{-1}$

k_3 = indeterminate

$k_4 = 16.9 \pm 3.2 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_6 = 4.7 \pm 2.7 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_7 = 1.2 \pm 1.0 \times 10^{-6}\ M^{-1}\ s^{-1}$

3-BENZOYL PROPIONIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 4.154 \times 10^{-3} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.05	0	33.8	33.3
	2.67	34.1	34.0
	5.33	34.0	34.7
	8.00	34.2	35.5
0.10	0	32.2	32.0
	2.67	32.6	32.3
	5.33	32.9	32.6
	8.00	33.4	33.0
0.20	0	29.7	29.6
	2.67	30.6	30.4
	5.33	31.7	31.2
	8.00	32.7	32.1
0.30	0	26.8	27.5
	2.67	28.3	29.1
	5.33	29.8	30.7
	8.00	31.3	32.2

k_1 = indeterminate

$k_2 = 83.8 \pm 2.2 \times 10^{-8}$ s^{-1}

k_3 = indeterminate

$k_4 = 0.36 \pm 0.13 \times 10^{-6}$ M^{-1} s^{-1}

k_6 = indeterminate

k_7 = indeterminate

4-BENZOYL BUTYRIC ACID: self-buffered kinetics (25.0°C)

Due to the insolubility of this compound and higher homologues, it was necessary to measure the rates of reaction under conditions of very low buffer ratio. At the relatively high pH of these solutions, the possibility of hydroxyl ion-catalysis contributing to the observed rate must be taken into account. At high pH, the rate expression may be written:

$$v = k_{10}[L^-] + k_{OH^-}[L^-][OH^-]$$

$$[L^-] = \frac{[HL]_T}{(r+1)}$$

By algebraic manipulation, it can be shown that:

$$v(1 + r) = k_{10}[HL]_T + k_{OH^-}[HL]_T \cdot K_w \cdot \frac{1}{r}$$

The contribution due to hydroxyl ion-catalysis can be assessed by comparing the mean value of $v/[L^-]$ with the value of k_{10}, obtained by plotting $v/[L^-]$ against $[OH^-]$. The hydroxyl ion concentration may be estimated from the measured value of the pK_a (see above). If the two values of k_{10} are significantly different, then hydroxyl ion-catalysis must be taken into account and the true value of k_{10} may be obtained by plotting $v(1 + r)$ against $1/r$.

$a = 1.117 \times 10^{-2} M$

$r \times 10^2$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
5.38	1360	1378
4.20	1395	1394
3.04	1408	1409
1.92	1440	1425
0.81	1437	1440
0.45	1467	1446

Mean value of $v/[L^-] = 1300 \times 10^{-8}\ s^{-1}$

Plotting $v/[L^-]$ against $[OH^-]$ gives $k_{10} = 1294 \times 10^{-8}\ s^{-1}$

$$k_{10} = 1.30 \pm 0.01 \times 10^{-5}\ s^{-1}$$

5-BENZOYL PENTANOIC ACID: self-buffered kinetics (25.0°C)

$a = 1.268 \times 10^{-2}$ M

$r = 10^2$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
5.63	108	109
4.59	110	110
3.56	111	111
2.56	113	112
1.57	113	114
0.60	116	116

Mean value of $v/[L^-] = 90.9 \times 10^{-8}$ s^{-1}

Plotting $v/[L^-]$ against $[OH^-]$, gives $k_{10} = 90.3 \times 10^{-8}$ s^{-1}

Plotting $v/(1 + r)$ against $1/r$, gives $k_{10} = 89.9 \times 10^{-8}$ s^{-1}

$$k_{10} = 9.00 \pm 0.01 \times 10^{-7} \text{ s}^{-1}$$

2-METHYL LEVULINIC ACID: self-buffered kinetics (25.0°C)

r = 2.038:

$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.498	19.6	19.4
0.996	41.1	41.6
1.495	67.3	66.7
1.993	95.3	94.4
2.491	126	125
2.989	159	158
3.488	198	194
3.986	231	233

r	$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.215	4.982	158	168
0.350	4.484	160	159
0.519	3.986	146	149
0.736	3.488	141	137
1.025	2.989	123	124
1.430	2.491	112	110
2.038	1.993	91.7	94.4
3.050	1.495	77.9	77.4

$(k_7 + k_8) = 2.75 \pm 0.05 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 30.1 \pm 0.3 \times 10^{-8}\ s^{-1}$

$k_{12} = 3.0 \pm 0.5 \times 10^{-8}\ s^{-1}$

2-METHYL LEVULINIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 3.067 \times 10^{-2}$M

r	$[OAc^-] \times 10^2$M	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
1.00	0	67.0	67.6
	1.667	72.7	72.8
	3.333	78.5	78.1
	5.000	83.8	83.1
	6.667	88.7	88.6
	8.333	93.3	93.8
2.53	0	45.7	46.5
	1.70	54.4	54.4
	3.40	62.8	62.3
	5.10	71.5	70.2
	6.80	78.8	78.1
	8.50	85.2	86.0
5.00	0	32.5	31.7
	1.428	40.2	40.3
	2.856	48.2	49.0
	4.284	57.8	57.6
	5.712	66.7	66.3
	7.140	75.9	74.9
	8.568	84.6	83.6

$k_1 = 1.5 \pm 0.5 \times 10^{-8}$ s^{-1}

$k_2 = 31.6 \pm 0.4 \times 10^{-8}$ s^{-1}

$k_3 = 3.0 \pm 0.5 \times 10^{-6}$ M^{-1} s^{-1}

$k_4 = 1.98 \pm 0.04 \times 10^{-6}$ M^{-1} s^{-1}

$k_6 = 0.35 \pm 0.05 \times 10^{-6}$ M^{-1} s^{-1}

$k_7 = 0.10 \pm 0.05 \times 10^{-6}$ M^{-1} s^{-1}

2,2-DIMETHYL LEVULINIC ACID: self-buffered kinetics (25.0°C)

r = 1.503

$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.25	4.4	4.2
0.50	10.0	9.8
1.00	25.1	25.2
1.25	34.9	35.0
1.75	59.2	58.7
2.00	73.9	72.7

r	$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
4.005	0.50	17.6	17.0
2.337	0.75	22.2	21.6
1.503	1.00	25.0	25.2
1.002	1.25	28.2	28.0
0.668	1.50	29.1	29.8
0.430	1.75	30.6	30.7
0.251	2.00	30.6	30.6
0.112	2.25	29.8	29.7

$(k_7 + k_8) = 7.4 \pm 0.2 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 11.1 \pm 0.3 \times 10^{-8}\ s^{-1}$

$k_{12} = 2.0 \pm 0.3 \times 10^{-8}\ s^{-1}$

2,2-DIMETHYL LEVULINIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 2.503 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	28.2	28.1
	2.67	40.0	39.8
	5.33	51.4	51.4
	8.00	62.2	63.1
1.00	0	23.5	23.6
	2.67	39.4	39.0
	5.33	54.9	54.3
	8.00	71.0	69.6
2.50	0	16.7	17.0
	2.67	36.8	36.3
	5.33	55.0	55.5
	8.00	74.6	74.7
4.67	0	12.9	13.5
	2.50	33.6	33.1
	5.00	51.7	52.8
	7.50	71.2	72.4

$k_1 = 3.2 \pm 0.3 \times 10^{-8}\ s^{-1}$ $\quad k_4 = 3.50 \pm 0.32 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 12.9 \pm 2.0 \times 10^{-8}\ s^{-1}$ $\quad k_6 = 0.26 \pm 0.18 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_3 = 4.5 \pm 1.4 \times 10^{-6}\ M^{-1}\ s^{-1}$ $\quad k_7$ = indeterminate

3-METHYL LEVULINIC ACID: self-buffered kinetics (25.0°C)

During this research, 3-methyl levulinic acid was prepared on four occasions by three different methods and every specimen exhibited a decelerating curve when scavenged with iodine. In each case the compound was assumed to be pure, since the criteria set out in chapter 2 had been met and so it was concluded that the curvature was due to poor scavenging by tri-iodide ion.

An attempt was then made to measure the rates using bromine, which is known to be a more efficient scavenger, but those traces accelerated. It seemed probable that the observed effect was due to multiple bromination. To test the idea a trace was obtained for the reaction of approximately 1% of the total dissolved substrate with bromine. The initial and final rates were measured. Knowing the initial rate and the time of measurement of the second rate, assuming, for simplicity, that only dibromination takes place, it should be possible to predict an intermediate rate and obtain a value for the rate constant of the reaction in which a second bromine is incorporated.

Under zero-order conditions, the rate of disappearance of bromine is given by:

$$v = k_1[SH_2] + k_2[SHBr]$$

where: $[SH_2]$ = substrate

$[SHBr]$ = mono-brominated substrate.

$$\frac{d[SHBr]}{dt} = k_1[SH_2] - k_2[SHBr]$$

and it is easily shown that the rate expression is:

$$v = k_1[SH_2](2 - e^{-k_2 t}) \quad 93$$

It can be seen from the equation, at t = 0, the rate is reduced to the usual zero-order, mono-halogenation situation.

Substituting the experimental values:

$$k_2 = 3 \times 10^{-5}\ s^{-1}$$

Measured intermediate rate = 560×10^{-10} M s^{-1}

Predicted intermediate rate = 520×10^{-10} M s^{-1}

Allowing for errors in the measurements, the agreement within 7% is acceptable as confirmation of the only possible explanation for the curvature of the kinetic traces. The observation is not is not unprecedented, since Bell and Prue[131] reported accelerating kinetics in the hydroxyl ion-catalysed iodination of acetone, using a heterogeneous buffer of zinc hydroxide and zinc sulphate, and this was also attributed to multiple halogenation.

For 3-methyl levulinic acid, the kinetics were followed by the disappearance of molecular bromine and measurement of initial rates.

[illegible] are subject to considerable errors, due to the inaccuracy in measuring initial rates, arising from the small optical density change when using bromine.

a = 0.1166M

r = 1.665

$[L^-]$ x 10^2M	observed rate x 10^{10} M s^{-1}	calculated rate x 10^{10} M s^{-1}
2.50	62	62
3.13	89	84
3.75	110	108
4.38	137	134
5.00	153	162
5.63	206	194

r	$[L^-]$ x 10^2M	observed rate x 10^{10} M s^{-1}	calculated rate x 10^{10} M s^{-1}
4.83	2.00	67	79
2.89	3.00	96	105
1.92	4.00	118	127
1.33	5.00	148	145
0.944	6.00	145	160
0.666	7.00	169	171

$(k_7 + k_8) = 1.8 \pm 0.5 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 15 \pm 1 \times 10^{-8}\ s^{-1}$

$k_{12} = 1.5 \pm 0.5 \times 10^{-8}\ s^{-1}$

The rate constants are subject to considerable errors, due to the inaccuracy in measuring initial rates, arising from the small optical density change when using bromine.

3,3-DIMETHYL LEVULINIC ACID: self-buffered kinetics (25.0°C)

r = 0.970:

$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.70	15.2	15.0
1.39	30.4	30.3
2.09	49.6	46.5
2.78	66.8	63.2
3.48	81.8	80.4
4.17	98.7	98.1

r	$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
4.253	1.00	30.1	30.6
1.627	2.00	48.6	48.8
0.751	3.00	67.6	65.8
0.501	3.50	73.9	73.8
0.313	4.00	79.2	81.4
0.167	4.50	89.3	88.8

$(k_7 + k_8) = 0.64 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 18.9 \pm 0.2 \times 10^{-8}\ s^{-1}$

$k_{12} = 2.1 \pm 0.2 \times 10^{-8}\ s^{-1}$

3,3-DIMETHYL LEVULINIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 2.627 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	36.4	36.9
	2.67	38.8	39.1
	5.33	41.8	41.3
	8.00	42.8	43.6
1.00	0	29.2	30.1
	2.67	32.8	32.9
	5.33	35.9	35.7
	8.00	38.0	38.5
2.50	0	20.6	20.7
	2.67	24.3	24.3
	5.33	28.3	27.9
	8.00	31.6	31.5
5.14	0	14.7	14.8
	2.80	19.5	19.1
	5.60	23.8	23.4
	8.40	27.2	27.7

$k_1 = 2.4 \pm 0.4 \times 10^{-8}\ s^{-1}$ $\quad k_4 = 0.69 \pm 0.05 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 18.6 \pm 0.4 \times 10^{-8}\ s^{-1}$ $\quad k_6 = 0.17 \pm 0.04 \times 10^{-6}\ M^{-1}\ s^{-1}$

k_3 = indeterminate $\quad k_7$ = indeterminate

2,2,3-TRIMETHYL LEVULINIC ACID

It was observed that the kinetic traces of the iodination of this compound accelerated. The values of the rates, quoted below, are measured initial rates. As in the case of 3-methyl levulinic acid, it was thought that the curvature could only be due to multiple halogenation. The kinetics were repeated, using molecular bromine as scavenger, but these traces also accelerated. The initial rates were measured, but because the reactions were slow and the optical density change was very small, the values were subject to considerable error. However, it was shown that there was no inconsistency between the two sets of results. For one trace, where the zero-order reaction was allowed to go to completion, it was found that the initial and final rates were in the ratio of approximately 1:3, which also supports the likelihood of multiple halogenation.

2,2,3-TRIMETHYL LEVULINIC ACID: self-buffered kinetics (25.0°C)

r = 0.894

$[L^-]$ x 10^2M	observed rate x 10^{10} M s^{-1}	calculated rate x 10^{10} M s^{-1}
0.46	2.5	2.3
0.91	5.7	5.4
1.37	9.8	9.6
1.83	14.7	14.6
2.29	20.7	20.5

r	$[L^-]$ x 10^2M	observed rate x 10^{10} M s^{-1}	calculated rate x 10^{10} M s^{-1}
2.788	0.80	8.7	8.6
1.525	1.20	10.4	10.6
0.894	1.60	12.0	11.9
0.515	2.00	12.7	12.5
0.377	2.20	12.1	12.4
0.263	2.40	12.4	12.2

$(k_7 + k_8) = 2.4 \pm 0.2 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 3.4 \pm 0.2 \times 10^{-8}\ s^{-1}$

$k_{12} = 0.7 \pm 0.2 \times 10^{-8}\ s^{-1}$

2,2,3-TRIMETHYL LEVULINIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 3.054 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	7.4	6.9
	2.67	15.4	16.5
	5.33	23.9	26.0
	8.00	32.3	35.6
1.00	0	5.1	4.9
	2.67	16.0	15.4
	5.33	27.2	25.8
	8.00	38.2	36.3
2.50	0	3.1	3.4
	2.67	15.3	14.5
	5.33	26.2	25.6
	8.00	38.3	36.7
4.67	0	2.8	2.5
	2.50	13.6	13.1
	5.00	24.4	23.6
	7.50	35.0	34.3

$k_1 = 0.69 \pm 0.05 \times 10^{-8}\ s^{-1}$ $k_4 = 1.42 \pm 0.10 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 3.7 \pm 1.2 \times 10^{-8}\ s^{-1}$ k_6 = indeterminate

$k_3 = 2.4 \pm 0.2 \times 10^{-6}\ M^{-1}\ s^{-1}$ k_7 = indeterminate

5,5-DIMETHYL-4-OXO-HEXANOIC ACID: self-buffered kinetics (25.0°C)

r = 1.165

$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	5.5	5.8
1.00	11.3	12.3
1.50	19.4	19.6
2.00	27.1	27.5
2.50	35.3	36.1
3.00	44.3	45.4
3.50	52.9	55.4
4.00	63.2	66.0

r	$[L^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.299	5.00	62.1	62.4
0.443	4.50	59.0	59.1
0.624	4.00	54.4	55.1
0.855	3.50	51.1	50.6
1.165	3.00	45.8	45.4
1.598	2.50	38.7	39.7
2.247	2.00	32.7	33.3

$(k_7 + k_8) = 1.20 \pm 0.05 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_{10} = 10.6 \pm 0.3 \times 10^{-8}\ s^{-1}$

$k_{12} = 0.3 \pm 0.1 \times 10^{-8}\ s^{-1}$

5,5-DIMETHYL-4-OXO-HEXANOIC ACID: acetate-catalysed kinetics (25.0°C)

$a = 1.855 \times 10^{-2} M$

r	$[OAc^-] \times 10^2 M$	observed rate $\times 10^{10}$ M s^{-1}	calculated rate $\times 10^{10}$ M s^{-1}
0.50	0	14.0	14.0
	2.67	15.3	15.2
	5.33	16.4	16.5
	8.00	17.6	17.7
1.00	0	10.8	11.0
	2.67	12.7	12.8
	5.33	14.2	14.5
	8.00	16.0	16.3
2.75	0	6.4	6.4
	2.67	9.0	8.9
	5.33	11.5	11.4
	8.00	13.9	13.9
5.67	0	4.0	4.0
	2.67	6.7	6.8
	5.33	9.5	9.7
	8.00	12.4	12.5

$k_1 = 0.38 \pm 0.19 \times 10^{-8}\ s^{-1}$ $\quad k_4 = 0.66 \pm 0.02 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_2 = 10.3 \pm 0.7 \times 10^{-8}\ s^{-1}$ $\quad k_6 = 0.02 \pm 0.01 \times 10^{-6}\ M^{-1}\ s^{-1}$

$k_3 = 1.82 \pm 0.69 \times 10^{-6}\ M^{-1}\ s^{-1}$ $\quad k_7$ = indeterminate

PART (V): DISCUSSION OF KINETIC RESULTS

DETERMINATION OF ACTIVATION PARAMETERS

To obtain the rate constants from the kinetic expressions, the first procedure adopted was to use the thermodynamic dissociation constants measured at 25.0°C and those results are quoted above. As a possible refinement, the dissociation constants of both acetic and levulinic acids were measured at different temperatures. In this instance, 'apparent' pK's were measured at I = 0.2M, using the expression:

$$pK = pH + \log r$$

The experimental method was the same as that used for the thermodynamic pK_a determination. The total concentration of the acids was almost exactly the same, the stoichiometric values of the buffer ratio were uncorrected and the temperatures were accurate to ± 0.1°C.

Levulinic acid:

temperature (°C)	apparent pK	apparent K x 10^5
25.0	4.483 ± 0.01	3.29 ± 0.10
35.0	4.481 ± 0.01	3.30 ± 0.06
45.0	4.480 ± 0.01	3.31 ± 0.07
55.0	4.480 ± 0.01	3.31 ± 0.12

Acetic acid:

temperature (°C)	apparent pK	apparent K x 10^5	10^5K_a*
25.0	4.615 ± 0.02	2.43 ± 0.09	1.753
35.0	4.615 ± 0.01	2.43 ± 0.05	1.728
45.0	4.625 ± 0.01	2.37 ± 0.09	1.670
55.0	4.634 ± 0.02	2.32 ± 0.06	1.589

* presented for comparison.[137]

The results for the two acids are each the mean of sixteen measurements.

Substituting these values into the kinetic expressions yields rate constants identical with those obtained using thermodynamic dissociation constants, which might be expected since the variation of K with temperature is slight and it is the ratio of the dissociation constants that is required for the kinetic analysis.

In the determination of activation parameters the greatest possible accuracy is needed and for this reason only those rates which are major contributors to the total rate are worth investigating. In this research, only the base-catalysed intra-molecular rate, k_2, and the inter-molecular acetate catalyst-acid substrate rate, k_4, will be considered.

Levulinic acid:

rate	E_a	$\Delta H^{\ddagger}$	$-\Delta S^{\ddagger}$
k_2	105 ± 2	101 ± 2	31 ± 5
k_4	91 ± 1	89 ± 1	58 ± 2

6-oxo heptanoic acid:

rate	E_a	$\Delta H^{\ddagger}$	$-\Delta S^{\ddagger}$
k_2	91 ± 1	88 ± 1	85 ± 1
k_4	88 ± 1	85 ± 1	78 ± 2

where: E_a and $\Delta H^{\ddagger}$ have units kJ mol^{-1}

$\Delta S^{\ddagger}$ has units J deg^{-1} mol^{-1}, quoted for 298°K

It should be pointed out, initially, that it was recognised that these results would be made more complete by the inclusion of activation parameters for 5-oxo hexanoic acid. However, it may be seen from the kinetic results, quoted in chapter 4 part (iv), that the intra-molecular base-catalysed rate is responsible for almost all the observed rate and the inter-molecular acetate-catalysed rate is subject to considerable error.

Since the values for the entropy of activation are dependent upon the concentration scale used, it is not possible to compare $\Delta S^{\ddagger}$ for k_2 and k_4 within a single compound, but $\Delta S^{\ddagger}$ for each process may be compared between the compounds. $\Delta H^{\ddagger}$ represents the height of an energy barrier and comparisons may be made between processes within a single compound. The differences and similarities between the activation energies are reflected in the enthalpies of activation, differing by the theoretical term of RT.
For the inter-molecular process, $\Delta H^{\ddagger}$ differs little between the two compounds. This is to be expected since little difference would be predicted between processes involving attack of acetate ion on substrates which have ionisable protons in very similar chemical environments. $\Delta H^{\ddagger}$ for k_2 of 6-oxo heptanoic acid is similar to the values obtained for the inter-molecular process, indicating that the formation of a 7-membered ring transition state does not greatly modify the activation energy and the enthalpy of activation. However, $\Delta H^{\ddagger}$ for k_2 of levulinic acid is significantly greater than the other values of $\Delta H^{\ddagger}$.
If the transition states for the intra-molecular base-catalysed processes are examined, it can be seen that, to allow approach

of the carboxylate group to the 3-proton in levulinate anion, the molecule must adopt a planar conformation. For close approach, there must be bond angle strain and steric interaction between vicinal protons. The 6-oxo heptanoate anion is able to minimise these unfavourable, enthalpic effects by adopting a puckered conformation, in which each carbon-carbon valence angle is tetrahedral and all proton-proton interactions are gauche.

Formation of the cyclic transition state for k_2 results in a loss of rotational entropy and the longer the carbon chain the greater this loss will be. Page and Jencks,[132] in considering the influence of entropic contributions to reaction rates, examined data for the entropy of reaction in the cyclisation of paraffins to give the corresponding saturated, alicyclic species. The loss of entropy per internal rotation was calculated, then corrected for bending and stretching modes present in a loose transition state, of which that for k_2 must be an example, especially due to the inclusion of a proton in the ring. The figures are quoted for gas-phase reaction at 298°K:

reaction product	$-\Delta S$ per int.rot. (J deg^{-1} mol^{-1})
cyclopentane	20.0
cycloheptane	15.5

If it is assumed that the rate-determining step of these reactions involves a cyclic transition state, the results may be applied to the entropy of activation of the keto-acid system:

compound	No. of lost rotations	$-\Delta S^{\ddagger}_{calc.}$	$-\Delta S^{\ddagger}_{obs.}$
$CH_3CO(CH_2)_2CO_2^-$	2	40.0	31
$CH_3CO(CH_2)_4CO_2^-$	4	62.0	85

In going from the ground state to the transition state, rotations in CH_2-CH_2 and CH_2-CO_2^- are lost and these account for the figures quoted above. In those transition states there will be partial double bond character between the carbonyl and methylene groups and if this is regarded as loss of, say, half a rotation, then $-\Delta S^{\ddagger}_{calc.}$ should be about 50 and 70 J deg^{-1} mol^{-1} for levulinate and 6-oxo heptanoate, respectively.

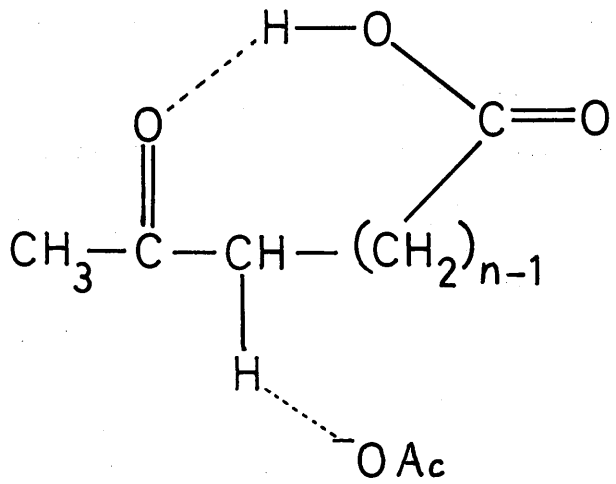
The results given for the entropy of activation for the inter-molecular processes also show a difference similar to that found for k_2. It is possible that the inter-molecular reaction is assisted by intra-molecular protonation, or stabilisation of the protonated carbonyl group, by the carboxylic acid group (see figure 4(v).1(a)). Formation of such a species would result in loss of rotational entropy, which would be greater in the larger transition state ring. Bell and Page[138] have proposed a similar structure to account for the observation that the acid-catalysed iodination of 2-oxo-bicyclo[2,2,2]octane-1-carboxylic acid is about 200 times faster than that of the ester (see figure 4(v).1(b)).

The relative values of $\Delta S^{\ddagger}$ for the two compounds may be predicted in terms of the loss of rotational entropy, but it would not be expected that $\Delta S^{\ddagger}_{calc.}$, obtained in this way, would agree with experiment, since other entropic effects are present, e.g.

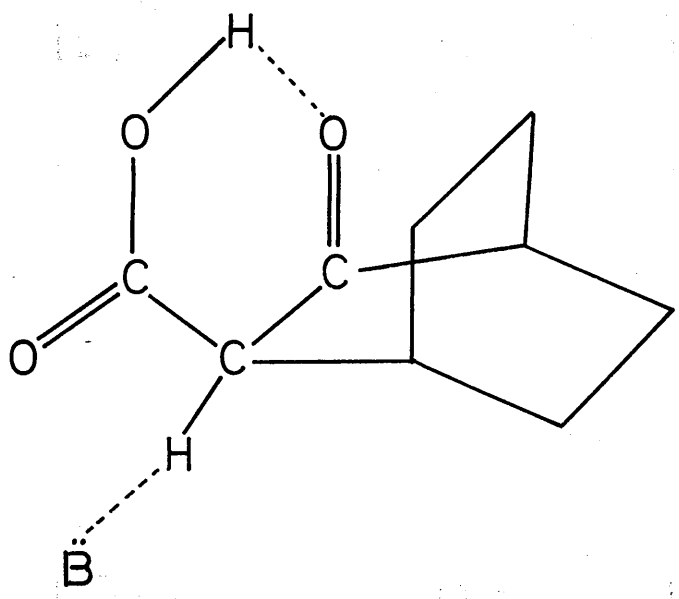
(i) contributions to the ground state of intra-molecularly hydrogen-bonded structures; either between the carbonyl

FIGURE 4 (v). 1.

(a)



(b)



oxygen and the carboxylic acid group or between the carbonyl oxygen and the carboxylate group, through an intervening solvent molecule.

(ii) the relative contributions to the total rate of reaction at the alternative sites.

(iii) solvent reorientation on going from the ground state to the transition state.

KINETICS AT 25°C

The effect of chain length on rate of reaction has been studied in two homologous series:

TABLE 4(v).1: $CH_3CO(CH_2)_nCO_2H$

rate	process	n = 2	3	4
$10^8k_1(s^{-1})$	$[HL]_{intra}$	1.5	20.1	6.0
$10^8k_2(s^{-1})$	$[L^-]_{intra}$	28.2	180	8.3
$10^6k_3(M^{-1}s^{-1})$	$[HL] + [L^-]$	1.51		
$10^6k_4(M^{-1}s^{-1})$	$[HL] + [OAc^-]$	1.65	1.69	0.65
$10^6k_6(M^{-1}s^{-1})$	$[L^-] + [OAc^-]$	0.27		0.16
$10^6k_7(M^{-1}s^{-1})$	[HL] + [HOAc]	0.02		0.09
10^6				

TABLE 4(v).2: $PhCO(CH_2)_nCO_2H$

rate	process	n = 2	3	4
$10^8k_2(s^{-1})$	$[L^-]_{intra}$	83.8	1300	90.0

The intra-molecular base-catalysed rates for the phenyl keto-acids show a maximum when n = 3, corresponding to a 6-membered ring transition state, as do the values in table 4(v).1, in agreement with the observations of Bell and

Fluendy. In all cases, these rates are the largest contributors to the total rates and will be considered first.

It has already been pointed out that there are two possible reaction sites in the methyl keto-acids and a simple derivation for the relative rates was presented in part (i) of this chapter. The result, although indicating the preferred site on the basis of transition state ring size, did not agree quantitatively with the experimental observation of Bell and Fluendy, who used an iodine tracer technique, or the estimate of an order of magnitude difference, found in this research, by an NMR technique, (see below). It was hoped that a comparison of the two homologous series would provide a more accurate measurement of the rate of reaction at the terminal methyl group.

TABLE 4(v).3:

	n = 2	3	4
$k_2(Ph)/k_2(Me)$	3.0	7.2	10.8

where $k_2(Ph)/k_2(Me)$ = ratio of the observed values of k_2 in the two series.

If, in any of the methyl keto-acids, reaction occurs exclusively at the methylene site, then the ratio of the observed rates for that value of n could be considered to be the intrinsic ratio, arising from the relative influence of the terminal groups. Using that ratio, a value may then be calculated for the rate at the methylene site in the other compounds which would give this ratio and hence the rates at each site may be obtained:

intrinsic ratio*	$10^8 k_{n=2}(s^{-1})$	$10^8 k_{n=3}(s^{-1})$
7.2	12	
10.8	8	150

* from table 4(v).3.

k = calculated rate (k_2) at the methylene position.

Comparison of these figures for levulinic acid ($k_{n=2}$) with the observed rate of 28 x $10^{-8} s^{-1}$ suggests that reaction at the terminal carbon is favoured more than reaction at the methylene carbon. This does not fit the known facts and it may be inferred that some effect, dependent upon the nature of the terminal group and the chain length, is operating. The nature of the effect is not clear, but a possible contribution invokes intra-molecular hydrogen-bonding between the carboxylate group and the carbonyl oxygen, through an intervening water molecule. The presence of such species in the ground state will favour reaction, from the argument given above for $\Delta S^{\ddagger}$ and will become less probable with increasing chain length. Such species will be most favoured by a highly polarised carbonyl group and hence will be more favoured in the methyl keto-acids (see below). Consider the following results, obtained by Knipe[133]:

compound	$10^6 k_2(s^{-1})$	$-\Delta S^{\ddagger}$(J deg^{-1} mol^{-1})
$PhCO(CH_2)_2CO_2H$	2.3	44
$PhCO(CH_2)_3CO_2H$	33	

* reaction in 12% v/v methanol/water.

There is a greater loss of entropy in the reaction of 3-benzoyl propionic acid than for levulinic acid. Comparison of these kinetic results and those given in table 4(v).2 reveals that the ratio of $k_2(n=2)$ to $k_2(n=3)$ is lower in the mixed solvent than in pure water by 7%. Since the addition of methanol to water will reduce the hydrogen-bonding throughout the solvent and hence reduce any intra-molecular, solvent-dependent hydrogen-bonding, this change is in the right direction. The argument is not powerful, as it is based upon differences which may not be significant. But it can be said that the experimental results are not inconsistent with the notion of the variation of anionic, intra-molecular hydrogen-bonding with chain length.

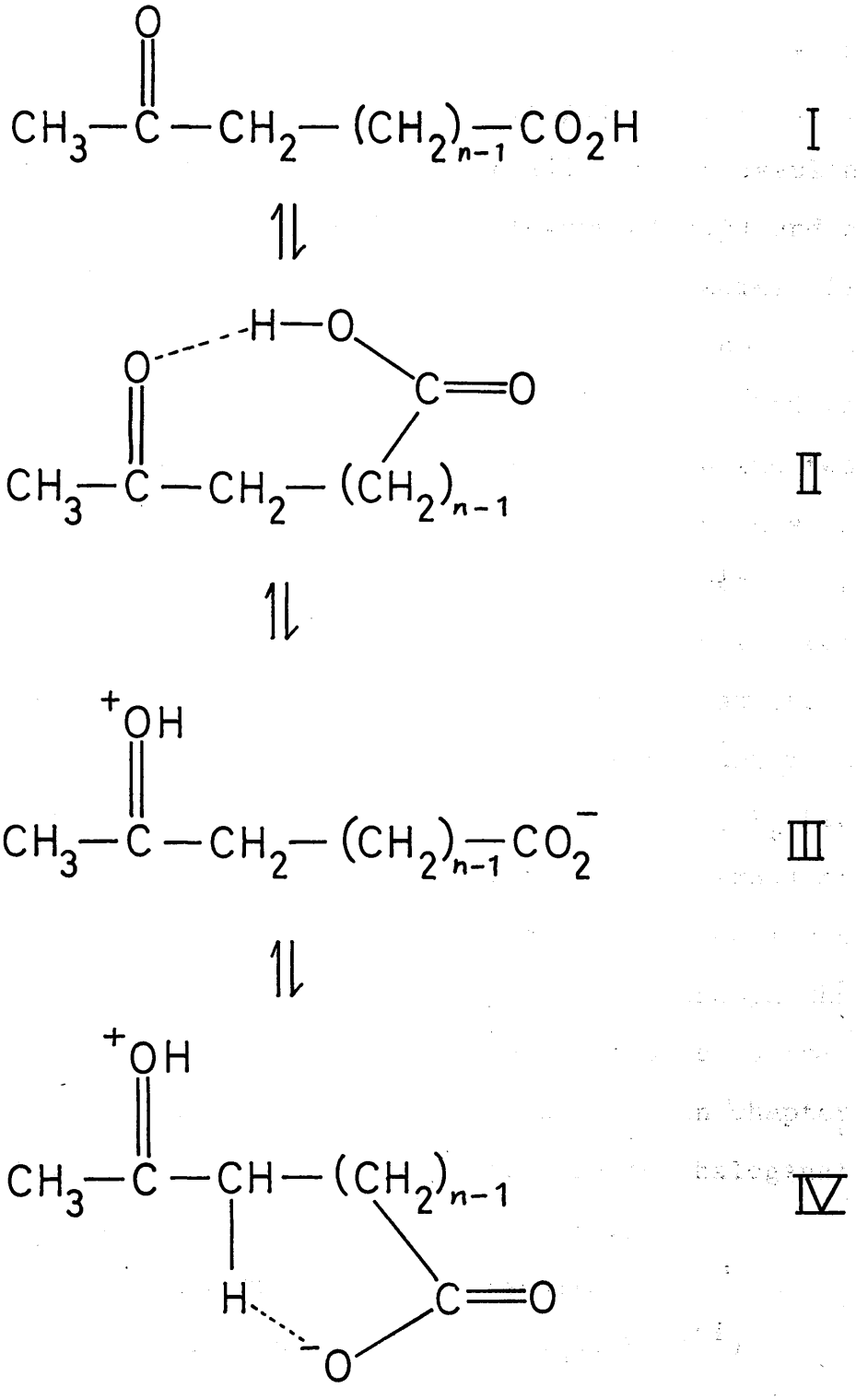
The ratio of k_1 to k_2 (see table 4(v).1) increases across the series by a factor of about 20. Possible equilibria, involving the acid substrate, are represented in figure 4(v).2. The lower value of n will favour structure II, whilst the higher value of n will favour structures III and IV. Thus the effect of the pre-equilibria is to favour the ratio k_1/k_2 as the chain length increases.

Consider the rates of the inter-molecular reaction between acetate ion and the acid substrate:

compound	n = 2*	3*	4*
$CH_3CO(CH_2)_nCO_2H$	1.65	1.69	0.65
$PhCO(CH_2)_nCO_2H$	0.36		

* $10^6 k_4 (M^{-1}s^{-1})$

FIGURE 4 (v). 2.



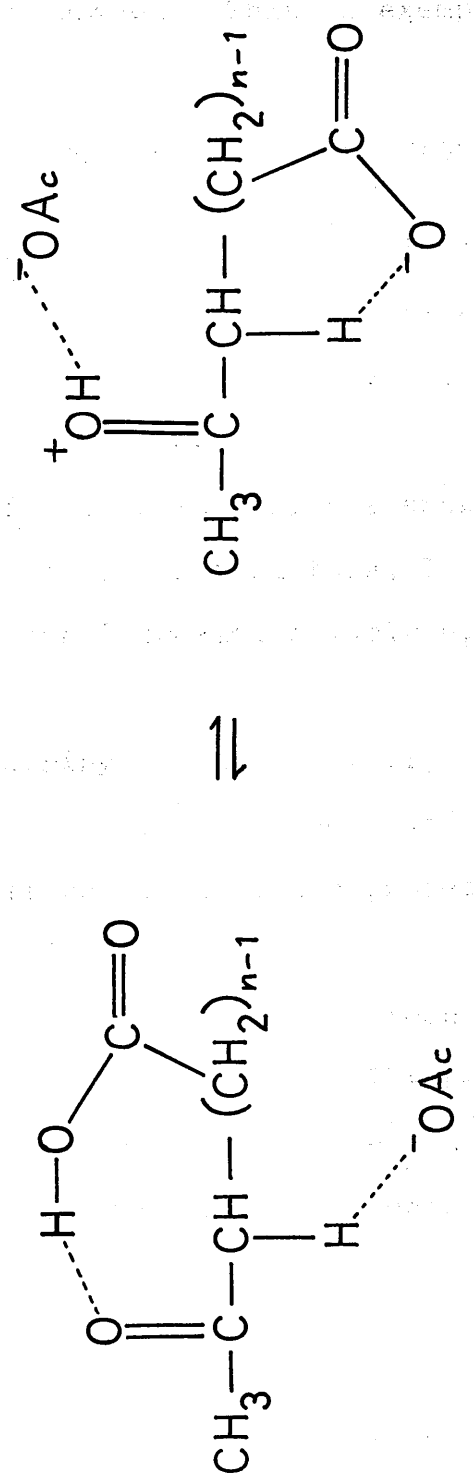
Even though there are quite large errors associated with these rates, the series does not exhibit a uniform trend. If the argument proposed for k_1 is correct, then, in this process, acetate ion will attack levulinic acid with the structure of species II (figure 4(v).2) and attack 6-oxo heptanoic acid with the structure of species III (figure 4(v).2). Although the system here is not being rigorously defined, the pre-equilibria suggest that the probability of electrostatic repulsion between the two carboxylate groups is greater in the longer chain substrate and hence an overall rate decrease may be expected across the series. However, the non-uniform trend in the rate indicates that some other effect is operating at the same time. It has been assumed that this observed inter-molecular contribution to the rate is k_4 and in doing so, k_5 has been neglected (see figure 4(v).3). If there is a small contribution to this rate by the concerted process, then some indication of a maximum rate at n = 3 would be expected. Although the evidence is not conclusive, influence of a concerted mechanism remains a possibility. It has already been mentioned in chapter 1 that concerted catalysis has been detected in the halogenation of acetone in the presence of acetate buffer.

Consider the following results:

compound	$k_{OH^-}(M^{-1}s^{-1})$
CH_3COCH_3	0.15 [134]
$PhCOCH_3$	0.24 [135]

Correcting for the statistical difference, the effect of the phenyl group is to increase the reactivity

FIGURE 4(v). 3.



of the methyl group, to base-catalysis, by a factor of about 3. The phenyl group is conjugated with the adjacent carbonyl group and the double bond of the enolate anion, which increases the acidity of the protons and decreases the basic strength of the carbonyl oxygen. This is exemplified by the equilibrium constant for the reaction:

$$CH_3CHO + H_2O \rightleftharpoons CH_3CH(OH)_2$$

which is about unity, while there is no detectable hydration of benzaldehyde, showing stabilisation of the carbonyl group in the latter.[139] Thus the low value of k_4 for 3-benzoyl propionic acid, compared to that for levulinic acid, is a consequence of the pre-equilibria shown in figure 4(v).2, in which the open-chain structure, I, will be relatively more favoured than the intra-molecularly hydrogen-bonded structure, II.

Referring to table 4(v).1, the rates quoted for k_6 and k_7 are not very well known and would not be expected to be very different, since the processes involve attack of catalyst at similar sites.

Consider the following results for methyl-substituted derivatives of levulinic acid. The rates are quoted at 25°C and are observed rates, not corrected for ring-chain tautomerism or statistical differences.

TABLE 4(v).4.

compound		10^8k_1	10^8k_2	10^6k_3	10^6k_4	10^6k_5	10^6k_7
(i)	levulinic acid	1.5	28.2	1.51	1.65	0.27	0.02
(ii)	2-methyl	3.0	30.1	2.75	1.98	0.35	0.10
(iii)	2,2-dimethyl	2.0	11.1	7.4	3.5	0.26	
(iv)	3-methyl	1.5	15	1.8			
(v)	3,3-dimethyl	2.1	18.9	0.64	0.69	0.17	
(vi)	2,2,3-trimethyl	0.7	3.4	2.4	1.42	0.17	
(vii)	5,5,5-trimethyl*	0.3	10.6	1.20	0.66	0.02	

* more correctly called 5,5-dimethyl-4-oxo hexanoic acid.

At the outset, before attempting to analyse the large quantity of data presented in this table, it may be pointed out that a statistical correction to the rates obtained for 3-methyl levulinic acid indicates that the reactivity is not substantially different from that of levulinic acid or 2-methyl levulinic acid. Hence, any arguments proposed for the effect of methyl substitution will apply to this singly-substituted compound and no more mention of this compound will be made at this stage.

The relative rates of reaction at the two available sites may be estimated by following the rate of decrease of the integrated proton N.M.R. signal. This was done for four of the above compounds. By the addition of sodium deuteroxide, solutions of the keto-acids with buffer ratios of about unity were prepared with deuterium oxide as solvent. For the substituted acids, the unreactive methyl substituents acted as an internal reference, but in the case of levulinic acid, a low concentration of 1,4-dioxan acted as an external reference.

The results, not obtained with great precision, are the mean of duplicate experiments. The exchange of protons for deuterons was followed by a Perkin-Elmer R10 NMR spectrometer:

TABLE 4(v).5:

compound	r_g	r_H
levulinic acid	0.11 ± 0.03	0.07 ± 0.02
2-methyl	0.20 ± 0.03	0.13 ± 0.02
2,2-dimethyl	1.6 ± 0.1	1.0 ± 0.1
2,2,3-trimethyl	32 ± 13	10 ± 4

where: r_g = ratio of the rate of reaction at the terminal methyl to the rate of reaction at the methylene site.

r_H = ratio of the relative rates of reaction of a single proton in the methyl and methylene positions.

These figures may be verified qualitatively by inspecting the NMR spectra before and after exchange has occurred. In levulinic acid, the multiplet at 7.5 tau (two coupled methylene groups) shrinks to a small, broad singlet, whilst the singlet at 8 tau (methyl group) appears relatively unaffected. In 2,2,3-trimethyl levulinic acid, the singlet at 8.5 tau (terminal methyl group) is reduced to a small, broad singlet, whilst the quartet at 8 tau (single proton in the 3-position coupled with a methyl group in the 3-position) and the multiplet at 9 tau (three substituted and unreactive methyl groups) appear relatively unaffected.

In a solution of buffer ratio about unity the largest contributor to the total rate is the intra-molecular

base-catalysed rate, k_2 and the results given in table 4(v).5 will certainly apply to that rate. The intra-molecular acid-catalysed rate, k_1, also involves intra-molecular proton abstraction and hence the results in table 4(v).5 will be applied to that rate, with probably little error.

Consider first the corrected rates for the intra-molecular base-catalysed rate, k_2.

TABLE 4(v).6:

compound	$10^8 k_2(CH_2)$	$10^8 k_2(CH_3)$
levulinic acid	25	3
2-methyl	25	5
2,2-dimethyl	4	7
3,3-dimethyl*	-	18.9
2,2,3-trimethyl†	0.1(0.2)	3.3

* included for completeness, but reaction is only possible at the terminal methyl.

† result in parenthesis allows for the statistical difference.

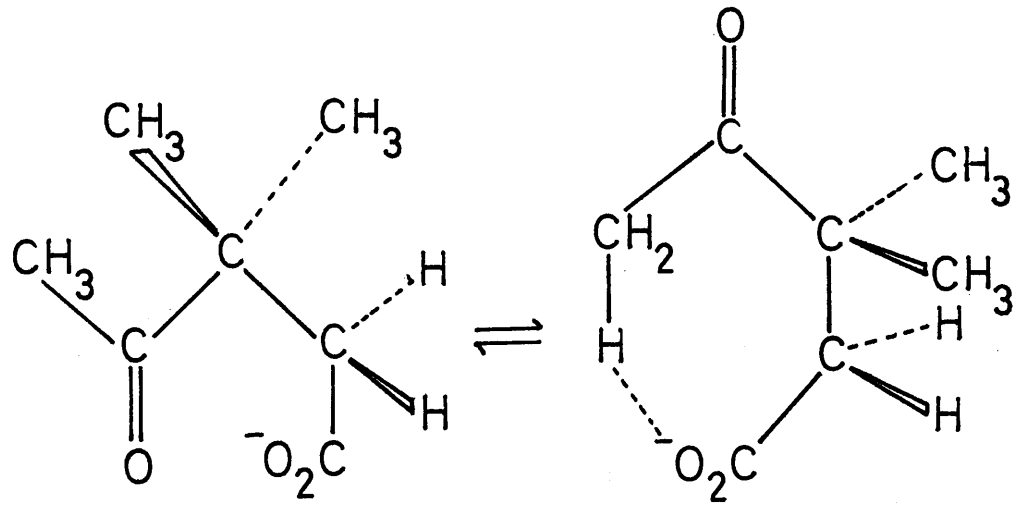
The trend of reaction rate at the methylene site shows that increasing substitution leads to a decrease in rate of reaction. From table 4(v).6, it follows that increasing substitution leads to an increasing proportion of the observed rate arising from reaction at the alternative site, but not necessarily an increase in rate at that site. These rate differences may be rationalised in terms of the influence of both entropic and enthalpic factors.

Increased substitution means less loss of rotational entropy, on formation of the transition state, but it also means an increase in enthalpically unfavourable steric interactions, which are maximised in the 5-membered transition state ring and can be relieved by the formation of a puckered 7-membered transition state ring. There is no uniform trend of reactivity at the terminal methyl position and this might be expected, since the conformation of the ring is not definite. Examination of some possible conformations of ground states and transition states, represented in figure 4(v).4, may help to clarify the situation. Comparison of the equilibria shown for the 2,2- and 3,3-dimethyl derivatives indicates that the 3,3-dimethyl transition state is relatively more favoured than that of the 2,2-dimethyl derivative, with respect to the more open chain conformation, due to restriction of free rotation of the acetyl group. The conformations of possible transition states shown for the 2,2,3-trimethyl derivative indicate that the asymmetry of the molecule introduces the effect of rotamer distribution, as structure II will be favoured over I and the decreased number of possible conformations with minimised steric interactions will serve to reduce the observed rate of reaction.

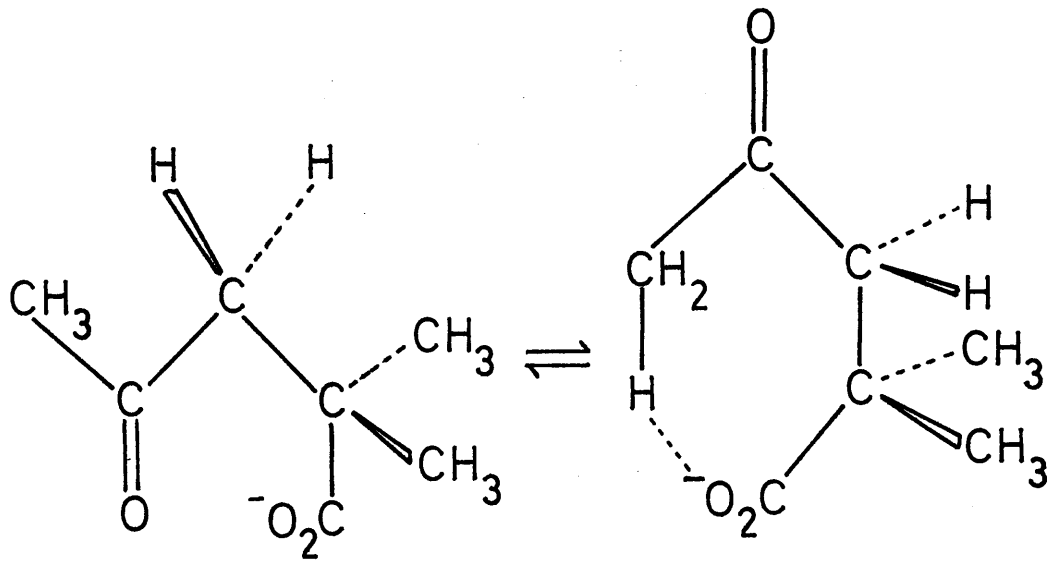
Consider the rates of reaction of the intra-molecular acid-catalysed process, k_1. Where necessary, these rates have been corrected for ring-chain tautomeric equilibrium.

Bearing in mind that these rates are not known as accurately as those for the corresponding values of k_2, it is apparent that the results given in table 4(v).7 follow the trends observed in table 4(v).5, for presumably the same reasons.

FIGURE 4(v).4.



3,3-DIMETHYL



2,2-DIMETHYL

FIGURE 4(v). 4. cont.

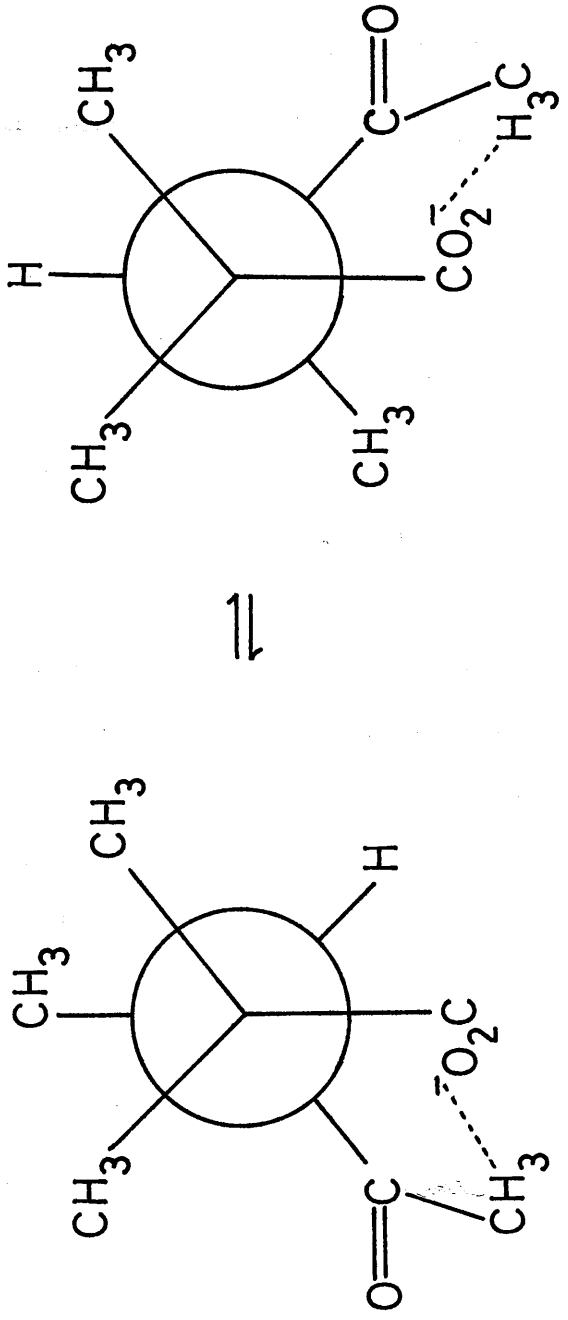


TABLE 4(v).7:

compound	$10^8 k_1$(obs.)	$10^8 k_1(CH_2)$	$10^8 k_1(CH_3)$
levulinic acid	1.5	1.35	0.15
2-methyl	3.0	2.5	0.5
2,2-dimethyl	4.0	1.5	2.5
3,3-dimethyl	2.5	-	2.5
2,2,3-trimethyl*	5.8	0.2(0.4)	5.6

* the figure in parentheses allows for the statistical difference.

The more regular nature of the variation of rate with structure may be a reflection of the influence of intra-molecular protonation to assist reaction.

The inter-molecular rates are rather less straightforward to analyse, since proton-abstraction occurs by attack of a separate catalysing species and the site of reaction is not easily predicted. It was established in part (i) of this chapter that acid-catalysis favours reaction at the methylene site and base-catalysis favours reaction at neither site. It is probable that little error will be incurred by assuming an equal probability of reaction at each ionisable proton.

The relative values for k_3 are reflected in those for k_4, which is to be expected, since the difference between the two processes lies only in the nature of the inter-molecular catalyst. However, why the relative values of k_3 and k_4 should vary between the compounds is not clear, as the basic strength of the attacking anions is similar. (See Table 4(v).8).

Considering first compounds (i), (ii), (iii) and (v), there is a well defined trend of increased rate of reaction with

TABLE 4(v).8:

compound		10^6k_3(obs)	10^6k_4(obs)	10^6k_3(corr)	10^6k_4(corr)
(i)	levulinic acid	1.51	1.65	1.51	1.65
(ii)	2-methyl	2.75	1.98	2.75	1.98
(iii)	2,2-dimethyl	14.8	7.0	14.8	7.0
(iv)	3,3-dimethyl	0.76	0.82	1.3	1.4
(v)	2,2,3-trimethyl	20.0	11.8	25.0	14.8
(vi)	5,5,5-trimethyl	1.2	0.66	3.0	1.65

where: k(obs) has been corrected for ring-chain tautomerism

k(corr) is k(obs), corrected for reaction of five protons.

increased substitution. This presumably is a consequence of the increasing assistance to the rate by intra-molecular hydrogen-bonding or protonation. By applying all the corrections that have been discussed so far, it is possible to make a true comparison between the rates of reaction of levulinic acid and those compounds in which only one site is available for reaction.

TABLE 4(v).9:

compound	10^8k_1	10^8k_2	10^6k_3	10^6k_4	10^6k_6
levulinic acid	0.15	3	1.51	1.65	0.27
3,3-dimethyl	2.5	18.9	1.3	1.4	0.28

TABLE 4(v).10:

compound	10^8k_1	10^8k_2	10^6k_3	10^6k_4	10^6k_6
levulinic acid	1.35	25	1.51	1.65	0.27
5,5,5-trimethyl	0.3	10.6	3.0	1.65	0.05

Taking first the results for 3,3-dimethyl levulinic acid, given in table 4(v).9, the enhanced intra-molecular rates arise from the gem-dimethyl effect, as has been discussed already. The inter-molecular rates are similar to those of levulinic acid, but even allowing for the lack of precision, there is an indication that those rates are smaller than those for levulinic acid. The relative rates may arise from the combination of two influences: assistance from intra-molecular protonation and steric hindrance to inter-molecular attack due to the 3-gem-dimethyl group (see figure 4(v).5(i).)

The rationalisation of the results given for 5,5-dimethyl-4-oxo hexanoic acid, given in table 4(v).10, may be helped by considering the following rates of reaction:

TABLE 4(v).11:

compound	base catalysis*	acid catalysis†
CH_3COCH_3	2.5	1.1
$CH_3COC(CH_3)_3$	1.0	1.0

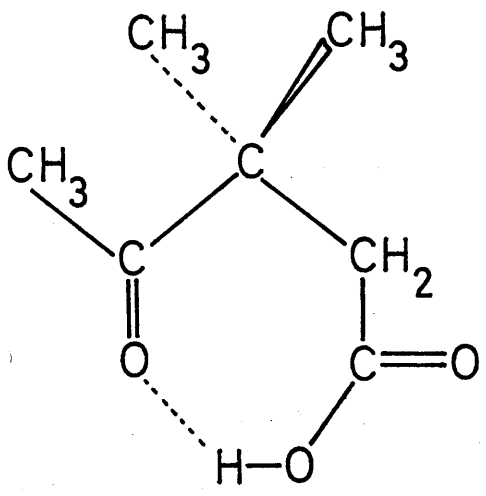
The figures refer to relative rates of iodination and are corrected for the statistical difference.

* hydroxyl ion-catalysis.[136] The authors attribute the relative rates to steric hindrance by the t-butyl group.

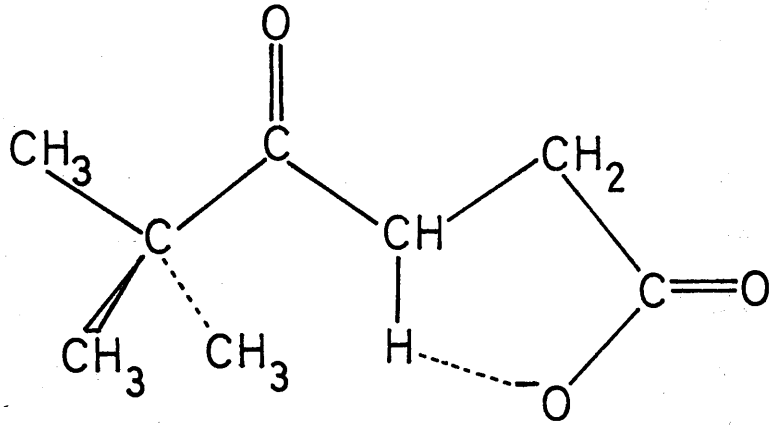
† reaction in 75% HoAc.[140] The authors suggest hyperconjugation to be a contributing influence, but comparison with the base-catalysed rates suggests that steric hindrance must be an important factor c.f. chapter 4 part (i).

FIGURE 4(v).5.

(i)



(ii)



In table 4(v).10, the values given for k_2 closely follow the relative rates for base-catalysis, given above, which may be appreciated by inspection of figure 4(v).5(ii) Similarly, k_1 is lower in the t-butyl keto-acid. The greater rate observed in the t-butyl keto-acid for the inter-molecular acid-catalysed processes, k_3 and k_4, must be due in part to the effect of hyperconjugation to increase the basic strength of the carbonyl oxygen.

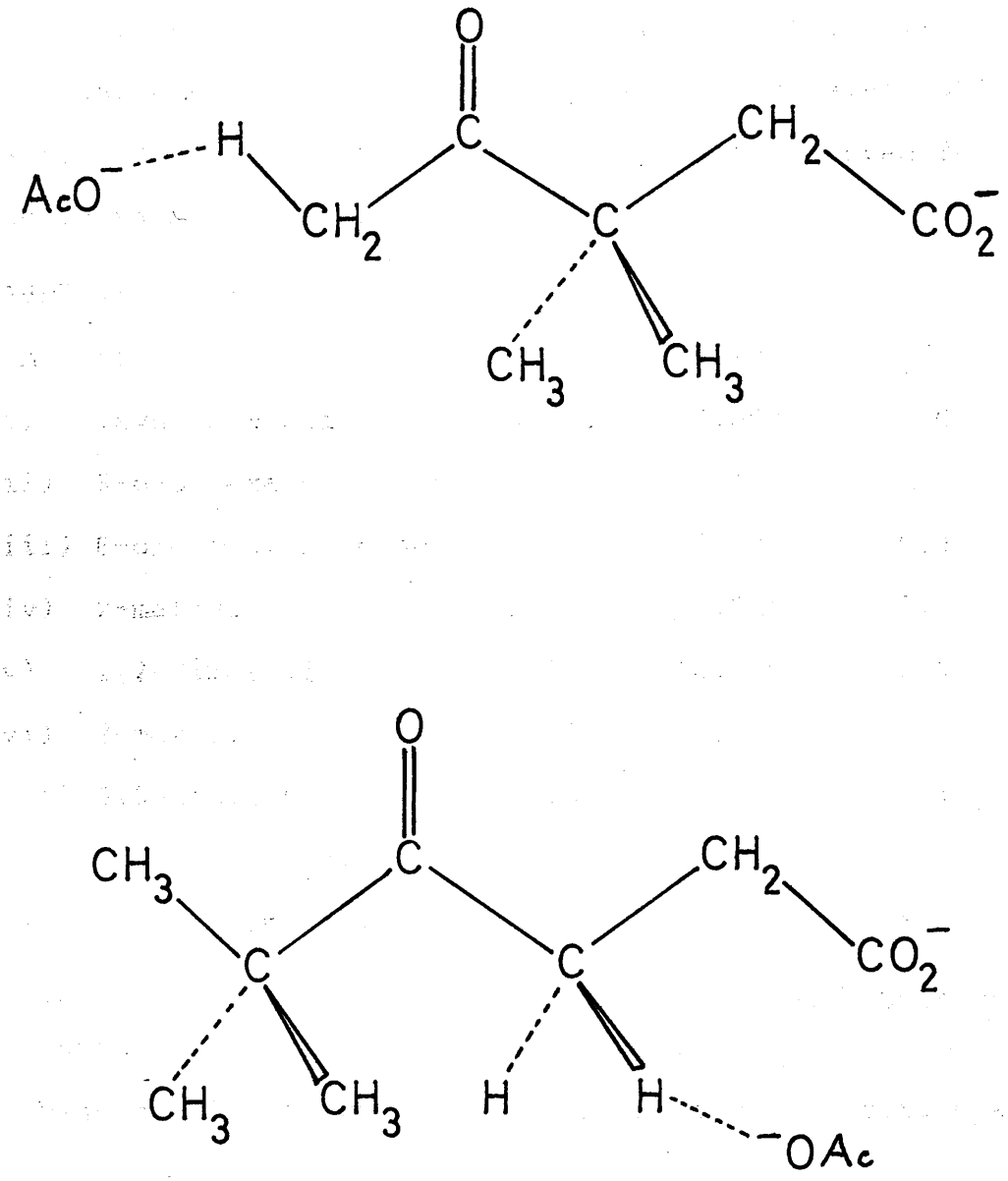
The observed rates of base-catalysed inter-molecular reaction, k_6, may be treated in the same way as k_3 and k_4, by assuming equal reactivity for all available protons:

TABLE 4(v).12:

compound		$10^6 k_6$(obs.)	$10^6 k_6$(corr.)
(i)	levulinic acid	0.27	0.27
(ii)	2-methyl	0.35	0.35
(iii)	2,2-dimethyl	0.26	0.26
(iv)	3,3-dimethyl	0.17	0.28
(v)	2,2,3-trimethyl	0.17	0.21
(vi)	5,5,5-trimethyl	0.02	0.05

Allowing for the fact that these observed rate constants are not accurately known, there is great similarity between all the compounds except (vi). This would be expected for reactions involving anion attack on protons in very similar chemical environments. It is likely that the substrates will adopt a straight-chain conformation in the transition state and inspection of possible transition states suggests that, for compounds (i) - (v), steric effects will not differ greatly and will only exert an exceptional influence in compound (vi) (see figure 4(v).6.)

FIGURE 4(v).6.



The efficiency of intra-molecular processes may be compared by calculating the effective concentration of the intra-molecular catalyst at the reaction site, i.e. the concentration of inter-molecular catalyst which is required to give the same rate as that observed for the intra-molecular process.

TABLE 4(v).13:

compound		k_1/k_3*	k_1/k_4*	k_2/k_6†
(i)	levulinic acid	0.010	0.009	1.0
(ii)	5-oxo hexanoic acid		0.12	
(iii)	6-oxo heptanoic acid		0.09	0.4
(iv)	2-methyl	0.011	0.015	0.9
(v)	2,2-dimethyl	0.003	0.006	0.4
(vi)	3-methyl	0.008		
(vii)	3,3-dimethyl	0.033	0.030	1.1
(viii)	2,2,3-trimethyl	0.003	0.005	
(ix)	5,5,5-trimethyl	0.003	0.004	5

* acid-catalysis, with proton abstraction by substrate anion and acetate anion, respectively.

† base-catalysis, with proton abstraction by acetate anion.

The effective concentrations quoted in table 4(v).13 are molarities.

It must be noted that these effective concentrations are subject to considerable error, as their calculation involves the inclusion of at least one rate constant which is not accurately known.

The results for compounds (i) - (iii), the homologous series, clearly demonstrate the maximum efficiency of the 6-membered ring transition state.

The figures in table 4(v).13 refer to the observed rates and hence those effective concentrations quoted for compounds (iv) - (ix) should be corrected for reaction at each site and for the number of available protons.

TABLE 4(v).14:

compound	$10^2k_1/k_3(CH_3)$	$10^2k_1/k_4(CH_3)$	$10^2k_1/k_3(CH_2)$	$10^2k_1/k_4(CH_2)$
levulinic acid	0.2	0.2	2.2	2.0
2-methyl	0.3	0.4	2.3	3.1
2,2-dimethyl	0.4	0.9	0.2	0.4
3,3-dimethyl	3.3	3.1		
2,2,3-trimethyl	0.4	0.6	0	0
5,5,5-trimethyl			0.2	0.4

TABLE 4(v).15:

compound	$k_2/k_6(CH_3)$	$k_2/k_6(CH_2)$
levulinic acid	0.2	2.3
2-methyl	0.2	1.8
2,2-dimethyl	0.5	0.4
3,3-dimethyl	1.1	
2,2,3-trimethyl	0.3	0
5,5,5-trimethyl		5

From tables 4(v).14 and 15, the factor of two orders of magnitude clearly shows the efficiency of base-catalysis compared with acid-catalysis.

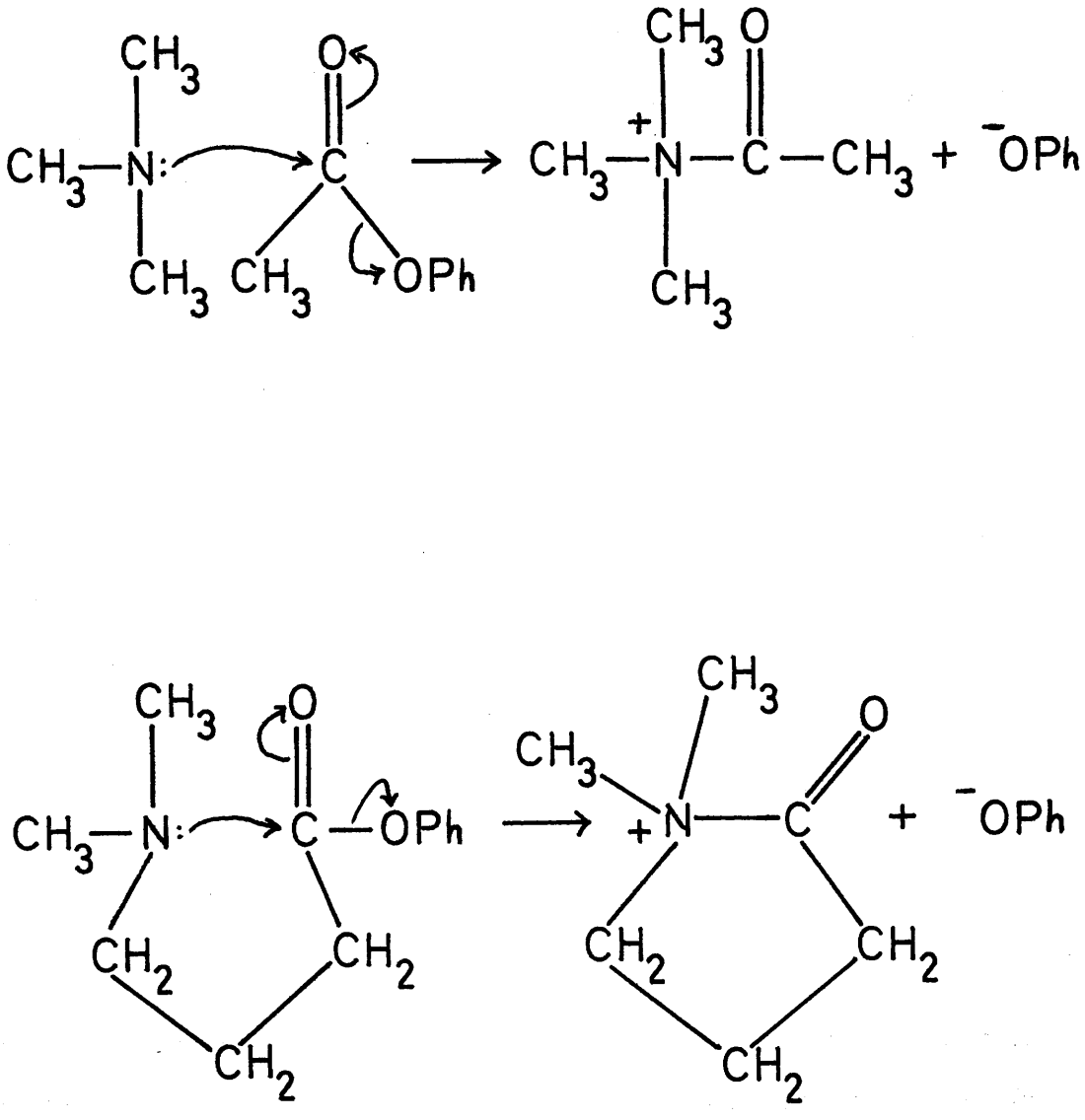
Bell and his co-workers[23] have investigated the intra-molecular base-catalysed and the inter-molecular acetate-catalysed iodination of 2-acetyl benzoic acid. Comparison of the two rates reveals an effective concentration

of 5M. To make a true comparison between that substrate and the more flexible aliphatic keto-acid, levulinic acid, one must use the value of $k_2/k_6(CH_3)$, given in table 4(v).15, since that also refers to a 7-membered ring transition state for reaction at the terminal methyl group. It can be seen that the constraint of proximity of the reacting groups has the effect of making the aromatic intra-molecular reaction about 25 times more efficient than that of the aliphatic reaction.

Because these effective concentrations are attainable in solution, the rapid rates of the intra-molecular processes may be ascribed largely to the effect of local concentration. Such is not the case for, for example, the comparison between the inter-molecular aminolysis of phenyl acetate by trimethylamine and the intra-molecular reaction of phenyl 4-(N,N-dimethylamino) butyrate (see figure 4(v).7), where the ratio of these rates is 1250M.[141] This implies that the concentration of the trialkylamine in the neighbourhood of the acyl group is 1250M. Since this is unattainable, the efficiency of the intra-molecular process must arise from other factors and in this case the entropy is responsible.

So far in the analysis of the kinetic data, no mention has been made of the role played by the basicity of the substrate anion in contributing to the observed rate differences. Inspection of table 3(vi).1. shows that differences in dissociation constant between the various substrates are fairly small and hence would not be expected to exert a significant influence upon the relative rates of reaction.

FIGURE 4(v).7.


CH3
O
CH3—N:
C
CH3
CH3
OPh
CH3
O
+
CH3—N—C—CH3
CH3
+ ⁻OPh
CH3
O
CH3—N:
C—OPh
CH2
CH2
CH2
CH3
CH3
O
+
CH3—N
C
CH2
CH2
CH2
+ ⁻OPh

In part (iv) of this chapter, it was mentioned that of all the compounds studied, only the 3-methyl and 2,2,3-trimethyl levulinic acids gave rise to anomalous kinetic traces. It is possible that the arguments presented above may provide reasons why these compounds behaved in a different manner.

It is clear that the observed rates of reaction (albeit initial rates) for 3-methyl levulinic acid are not anomalous. Allowing for the statistical difference at the 3-position, the intra-molecular rates are comparable with those for levulinic and 2-methyl levulinic acids. However, the rates were obtained by bromination, because iodination gave decelerating curves. The theory of poor scavenging was proposed to explain the deceleration and this may be justified on the basis that, since the large tri-iodide anion must react with a planar enol or enolate anion, which is fully substituted at the site of reaction, steric hindrance is present for all lines of approach. (This may explain, in part, the preference for iodine reaction at the terminal methyl of 2,2,3-trimethyl levulinic acid, as approach to the Δ^3-2,2,3-trimethyl levulinic acid enol or enolate anion is even more sterically hindered.) It would not be expected that the observed rates of intra-molecular reaction of 3-methyl levulinic acid would be distributed between the two possible sites of reaction very differently from that shown for levulinic acid and hence it is the Δ^3-enol that must be considered to be the reactive intermediate. On this basis, the relative ease of reaction of molecular

bromine, a smaller species, is explained. However, bromination traces were observed to accelerate. After the incorporation of one bromine atom, the molecule could be considered to be a substrate very like 3,3-dimethyl levulinic acid, where both 3-positions are blocked to reaction. It has been shown that reaction at the terminal methyl of 3,3-dimethyl levulinic acid is fast and it is possible that the 3-methyl-3-bromo substrate facilitates the reaction of a second bromine at the 5-position. This would mean that, in a single reaction, the final observed rate of reaction would be about twice the initial rate of reaction. In one instance, a bromination (under zero-order conditions) was allowed to go to completion and it was found that the final rate was about 1.7 times the initial rate.

In the accelerating traces obtained for the iodination of 2,2,3-trimethyl levulinic acid, it has already been pointed out that the final observed rate was about three times the initial rate. This is entirely consistent with the proposed explanation of multiple-halogenation, particularly as it has been shown that essentially all the rate is due to reaction at the terminal methyl group. However, why only this compound should exhibit multiple-iodination is not clear.

CHAPTER 5

GENERAL CONCLUSIONS

The results obtained for the ring-chain tautomeric equilibria and the kinetics of halogenation can be brought together and conclusions drawn concerning ring formation, with particular reference to the 'gem-dimethyl' effect.

The activation parameters measured for the halogenation of levulinic acid and 6-oxo heptanoic acid show that there are different entropy and enthalpy contributions to the formation of 5- and 7-membered ring transition states. These differences have been explained in terms of the loss of internal rotational entropy and enthalpic steric interactions between vicinal protons, which, in combination, favour the formation of the smaller ring transition state.

The argument was extended to the methyl-substituted derivatives of levulinic acid. It has been shown that increasing substitution of methyl groups between the reacting groups of the intra-molecular processes increases the preference for reaction involving a 7-membered ring transition state with respect to a 5-membered ring transition state. From the point of view of loss of internal rotational entropy, such a shift in the site of reaction is not favoured, but it may be rationalised in terms of the minimisation of vicinal steric interactions, which would occur on going from a planar to a puckered ring transition state.

It has been shown that increased substitution favours the formation of the lactol tautomer, which is consistent with the rotational entropy argument, but the relative values of

the equilibrium constants in 2,2-dimethyl and 3,3-dimethyl levulinic acids also indicates the presence of enthalpic factors.

The experimental observations in this research do not allow a detailed analysis of the nature of the 'gem-dimethyl' effect, but it can be said that the results are consistent with the view that both entropic and enthalpic factors are involved in the phenomenon.

REFERENCES

1. E. Baldwin, Dynamic Aspects of Biochemistry. C.U.P. 5th ed. (1967).

2. W.H.R. Shaw and D. G. Walker, J.Amer.Chem.Soc. 80 5337 (1958).

3. M. C. Wall and K. J. Laidler, Arch.Biochem.Biophys. 43 299 (1953).

4. W. P. Jencks, Catalysis in Chemistry and Enzymology. McGraw-Hill (1969).

5. D. E. Koshland, Proc.Natl.Acad.Sci.U.S. 44 98 (1958).

6. Y. Pocker and J. E. Meany, J.Amer.Chem.Soc. 89 631 (1967).

7. M. L. Bender and J. M. Lawlor, J.Amer.Chem.Soc. 85 3010 (1963).

8. M. Dixon and E. C. Webb, Enzymes. Longmans (1967).

9. S. V. Rieder and I. A. Rose, J.Biol.Chem. 234 1007 (1959).

10. Y. J. Topper, J.Biol.Chem. 225 419 (1957).

11. I. A. Rose and E. L. O'Connell, J.Biol.Chem. 236 3086 (1961).

12. F. Wold and C. E. Ballou, J.Biol.Chem. 227 313 (1957).

13. J. F. Kachmar and P. D. Boyer, J.Biol.Chem. 200 669 (1953).

14. B. Axelrod, Metabolic Pathways. Vol.I. Academic Press (1960).

15. R. Mazumder, T. Sasakawa, Y. Kaziro and S. Ochoa, J.Biol.Chem. 237 3065 (1962).

16. P. Overath, G. M. Kellerman and F. Lynen, Biochem.Z. 335 500 (1962).

17. T. M. Lowry, J.Chem.Soc. 2883 (1925).
J.Chem.Soc. 2557 (1927).

18. C. G. Swain and J. F. Brown, J.Amer.Chem.Soc. 74 2534, 2538 (1958).

19. H. M. Dawson and E. Spivey, J.Chem.Soc. 2180 (1930).

20. R. P. Bell and P. Jones, J.Chem.Soc. 88 (1953).

21. H. S. Rossotti, Nature 188 936 (1960).

22. E. T. Harper and M. L. Bender, J.Amer.Chem.Soc. 87 5625 (1965).

23. R. P. Bell, B. G. Cox and J. B. Henshall, J.Chem.Soc. Perkin II 1232 (1972).

24. J. B. Henshall, Ph.D. thesis, University of Stirling (1972).

25. R. P. Bell and M.A.D. Fluendy, Trans.Faraday Soc. 59 1623 (1963).

26. C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P. F. Sommer and W. Simon, Helv.Chim.Acta. 47 213 (1964).

27. Dictionary of Organic Compounds. Eyre and Spottiswoode Ltd. (1965).

28. L. Ruzicka, C. F. Seidel, H. Schinz and H. Pfeiffer, Helv.Chim.Acta. 31 422 (1948).

29. Dictionary of Organic Compounds and Beilstein.

30. A. Lapworth, J.Chem.Soc. 85 1218 (1904).

31. J. R. Catch, D. F. Elliot, D. H. Hey and E.R.H. Jones, J.Chem.Soc. 272 (1948).

32. R. Adams and R. S. Long, J.Amer.Chem.Soc. 62 2292 (1940).

33. H. E. Baumgarten and D. C. Gleason, J.Org.Chem. 16 1658 (1951).

34. H. E. Simmons and R. D. Smith, Org.Synth. 41 72 (1961).

35. J. F. Birch, G.A.R. Kon and W.S.A.P. Norrish, J.Chem.Soc. 123 1370 (1923).

36. J. C. Bardhan, J.Chem.Soc. 2604 (1928).

37. M. Jackman, M. Klenk, B. Fishburn, B. F. Tullar and J. Archer, J.Amer.Chem.Soc. 70 2886 (1948).

38. N. Hellström and J. Gronowitz, Kgl.Lantbruks-Högskol.Ann. 25 363 (1959), from C.A. 54:9751.

39. L. F. Somerville and C.F.H. Allen, Org.Synth.Coll. Vol.II 81 (1966).

40. A. Ali, R. D. Desai, R. F. Hunter and S.M.M. Muhammad, J.Chem.Soc. 1013 (1937).

41. J. W. Hill, J.Amer.Chem.Soc. 54 4105 (1932).

42. C. Laar, Ber. 19 730 (1886).

43. P. R. Jones, Chem.Revs. 63 461 (1963).

44. W. H. Perkin and J. F. Thorpe, J.Chem.Soc. 75 65 (1899).

45. L. Balbiano, Ber. 27 2136 (1894).

46. G.A.R. Kon, A. Stevenson and J. F. Thorpe, J.Chem.Soc. 650 (1922).

47. M. Qudrat-I-Khuda, J.Chem.Soc. 201 (1929).

48. W. H. Perkin and J. F. Thorpe, J.Chem.Soc. 79 757 (1901).

49. E. Rothstein and C. W. Shoppee, J.Chem.Soc. 532 (1927).

50. S. Dutt, J.Chem.Soc. 1132 (1926).

51. I. Vogel, J.Chem.Soc. 594 (1927).

52. W. H. Perkin and Marshall, J.Chem.Soc. 57 241 (1890).

53. K. von Auwers and Gardner, Ber. 23 3622 (1890).

54. R. P. Linstead and H. N. Rydon, J.Chem.Soc. 580 (1933).

55. C. K. Ingold, J.Chem.Soc. 119 308 (1921).

56. R. Willstätter and C. H. Clark, Ber. 47 298 (1914).

57. R. F. Brown and N. M. von Gulick, J.Org.Chem. 21 1046 (1956).

58. C. K. Ingold, Structure and Mechanism in Organic Chemistry. G. Bell and Sons Ltd. (1953).

59. M. S. Newman, Steric Effects in Organic Chemistry, Wiley (1956).

60. F. G. Bordwell, C. E. Osborne and R. D. Chapman, J.Amer.Chem.Soc. 81 2698 (1958).

61. H. Nilsson, Ph.D. thesis, University of Lund, Sweden (1946).

62. C. P. Kuhn, J.Amer.Chem.Soc. 74 2492 (1952).

63. L. Eberson, Acta Chem.Scand. 13 224 (1959).

64. P. von R. Schleyer, J.Amer.Chem.Soc. 83 1368 (1961).

65. D. R. Lide, J.Chem.Phys. 33 1514 (1960).

66. D. R. Lide and D. E. Mann, J.Chem.Phys. 29 914 (1958).

67. R. L. Livingston, C. Lurie and C.N.R. Rao, Nature 185 458 (1960).

68. N. L. Allinger and V. Zalkow, J.Org.Chem. 25 701 (1960).

69. T. C. Bruice and U. K. Pandit, J.Amer.Chem.Soc. 82 5858 (1960).

70. R. W. Taft, Steric Effects in Organic Chemistry, Wiley (1956).

71. D. E. Koshland and D. R. Storm, J.Amer.Chem.Soc. 94 5805 (1972).

72. R. P. Linstead and H. N. Rydon, J.Chem.Soc. 577 (1933).

73. L. M. Jackman and D. P. Kelly, J.Chem.Soc. (B) 102 (1970).

74. J. Bredt, Ann. 236 225 (1886).

75. M. Qudrat-I-Khuda, J.Chem.Soc. 1913 (1929).

76. P. F. Sommer, C. Pascual, V. P. Arya and W. Simon, Helv.Chim.Acta. 46 1734 (1963).

77. P. R. Jones and S. L. Congdon, J.Amer.Chem.Soc. 81 4291 (1959).

78. P. R. Jones and A. A. Lavigne, J.Org.Chem. 25 2020 (1960).

79. R. P. Bell, B. G. Cox and B. A. Timimi, J.Chem.Soc. (B) 2247 (1971).

80. J. F. Grove and H. A. Willis, J.Chem.Soc. 877 (1951).

81. C. W. Davies, J.Chem.Soc. 2093 (1938).

82. J. N. Brönsted and K. J. Pedersen, Z.Phys.Chem. 108 185 (1924).

83. E. C. Baughan and R. P. Bell, Proc.Roy.Soc.(London) 158 464 (1937).

84. R. P. Bell and D. P. Onwood, Trans.Faraday Soc. 58 1557 (1962).

85. C. A. Marlies, V. K. LaMer and J. Greenspan, Inorg.Synth. Vol.I (1939).

86. R. P. Bell and A. F. Trotman-Dickenson, J.Chem.Soc. 1288 (1949).

87. A. Geuther, Göttinger Anzeigen 281 (1863).

88. J. Wislicenus, Ann. 186 161 (1877).

89. A. Hantzsch and O. W. Schultze, Ber. 29 699,2251 (1896).

90. A. Lapworth, J.Chem.Soc. 85 30 (1904).

91. H. M. Dawson and F. Powis, J.Chem.Soc. 2135 (1913) and later papers.

92. K. J. Pedersen, J.Phys.Chem. 37 751 (1933).
J.Phys.Chem. 38 601 (1934).

93. R. P. Bell and O. M. Lidwell, Proc.Roy.Soc.(London), A 176 88 (1940).

94. R. P. Bell, Advances in Catalysis. Academic Press. Inc. Vol.IV 165 (1952).

95. S. Winstein and R. E. Buckles, J.Amer.Chem.Soc. 64 2780 (1942).

96. M. L. Bender, J.Amer.Chem.Soc. 79 1258 (1957).

97. M. L. Bender and M. C. Neveu, J.Amer.Chem.Soc. 80 5388 (1958).

98. B. Capon, Quart.Revs. 18 45 (1964).

99. C. K. Ingold and C. L. Wilson, J.Chem.Soc. 773 (1934).

100. S. K. Hsü and C. L. Wilson, J.Chem.Soc. 623 (1936).

101. E. D. Hughes and H. B. Watson, J.Chem.Soc. 1945 (1929).

102. E. D. Hughes, H. B. Watson and E. D. Yates, J.Chem.Soc. 3318 (1932).

103. A. A. Yasnikov, E. A. Shilov and K. I. Matkovskii, Ukrain.Khim.Zhur. 23 333 (1957) from C.A. 52:4500.

104. H.M.E. Cardwell and A.E.H. Kilner, J.Chem.Soc. 2430 (1951).

105. H.M.E. Cardwell, J.Chem.Soc. 2442 (1951).

106. E. D. Hughes, Nature 147 813 (1941).

107. C. R. Hauser and J. T. Adams, J.Amer.Chem.Soc. 66 345 (1944).

108. D. P. Evans and J. J. Gordon, J.Chem.Soc. 1414 (1938).

109. C. Rappe, Acta.Chem.Scand. 20 2305 (1966).

110. A. A. Bothner-By and C. Sun, J.Org.Chem. 32 492 (1967).

111. J. Warkentin and O. J. Tee, J.Amer.Chem.Soc. 88 5540 (1966).

112. J. Warkentin and C. Barnett, J.Amer.Chem.Soc. 90 4629 (1968).

113. C. Rappe and W. H. Sachs, J.Org.Chem. 32 4127 (1967).

114. C. Rappe, Acta.Chem.Scand. 19 276 (1965).
20 376 (1966).
20 1721 (1966).
21 857 (1967).
21 1823 (1967).

115. C. G. Swain and R. P. Dunlap, J.Amer.Chem.Soc. 94 7204 (1972).

116. B. G. Cox and A. C. Knipe, J.Chem.Soc. Perkin II 1391 (1973).

117. R. P. Bell, G. R. Hillier, J. W. Mansfield and D. G. Street, J.Chem.Soc.(B) 379 (1967).

118. C. Rappe, Acta.Chem.Scand. 20 2236 (1966).

119. E. Gaetjens and H. Morawetz, J.Amer.Chem.Soc. 82 5328 (1960).

120. P. D. Bartlett and R. R. Hiatt, J.Amer.Chem.Soc. 80 1402 (1958).

121. H. Wilson and E. S. Lewis, J.Amer.Chem.Soc. 94 2283 (1972).

122. G. F. Smith, J.Chem.Soc. 1744 (1934).

123. R. P. Bell, The Proton in Chemistry, Methuen (1959).

124. A. J. Kirby and G. Meyer, J.Chem.Soc. Perkin II 1446 (1972).

125. T. C. Bruice and S. J. Benkovic, Bio-organic Mechanisms Vol.I. W. A. Benjamin Inc. (1966).

126. R. P. Bell and K. Yates, J.Chem.Soc. 1927, 2285 (1962).

127. A. D. Autrey and R. E. Connick, J.Amer.Chem.Soc. 73 1842 (1951).

128. D. J. Barnes, D.Phil. thesis, University of Oxford (1969).

129. R. P. Bell and M. Pring, J.Chem.Soc.(A) 1607 (1966).

130. L.K.J. Tong and A. R. Olsen, J.Amer.Chem.Soc. 63 3406 (1941).

131. R. P. Bell and J. E. Prue, Trans.Faraday Soc. 46 5 (1950).

132. M. I. Page and W. P. Jencks, Proc.Natl.Acad.Sci.U.S. 68 1678 (1971).

133. A. C. Knipe, unpublished results.

134. J. R. Jones, Trans.Faraday Soc. 61 95 (1965). 65 2138 (1969).

135. J. R. Jones, R. E. Marks and S. C. Subba Rao, Trans.Faraday Soc. 63 111, 993 (1967).

136. C. F. Cullis and M. H. Hashmi, J.Chem.Soc. 2512 (1956).

137. H. S. Harned and R. W. Ehlers, J.Amer.Chem.Soc. 55 2379 (1933).

138. R. P. Bell and M. I. Page, J.Chem.Soc. Perkin II 1681 (1973).

139. R. P. Bell, Adv.Phys.Org.Chem. 4 1 (1966).

140. D. P. Evans and J. R. Young, J.Chem.Soc. 1314 (1954).

141. T. C. Bruice and S. J. Benkovic, J.Amer.Chem.Soc. 85 1 (1963).

142. K. Bowden and G. R. Taylor, J.Chem.Soc.(B) 1390 (1971).