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KINETICS OF INTRAMOLECULAR CATALYSIS

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

J. B. Henshall

Department of Chemistry
December 1972

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ABSTRACT

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The 'mixed' acid dissociation constant values for a series of substituted aromatic ortho-acetyl carboxylic acids and one alicyclic ortho-acetylcarboxylic acid have been measured in water at 25°C. The 'true' acid dissociation constant values have been found by first determining the catalytic constant for the decomposition of nitramide by the keto-acid anion in water at 25°C and then comparing these results with those already obtained for some simple carboxylic acids whose acid dissociation constants are known. The values obtained were checked in a few cases by determining the catalytic constants for the mutarotation of glucose in water at 18°C and comparing these with values already obtained for some simple carboxylic acids. Comparison of the 'mixed' and 'true' acid dissociation constants have been made and the percentage of ring-chain tautomerism for each keto-acid determined. Infra red data for each keto-acid are also provided.

Rate constants for the intramolecular base catalysed enolization have been determined in water at 25°C and rate constants have also been obtained for intermolecular catalysis by acetate ions and pyridine. The reactions have been followed by recording spectrophotometrically the disappearance of tri-iodide at 353 nm. Some attempt has been made to relate the structure of the keto-acid to the rate of enolization.

The rate for the bimolecular reaction involving two keto-acid anions has been estimated for each keto-acid and this value compared with that observed for the intramolecular base catalysed reaction. From these data the effectiveness of the intramolecular process compared to that of the intermolecular process has been estimated and is discussed in terms of effective molarity, c_i.

The intermolecular processes involving pyridine and acetate ions have been compared in an attempt to estimate qualitatively steric effects associated with the acetyl group. Possible alternative mechanisms to explain apparent intramolecular catalysis are also suggested.

ACKNOWLEDGEMENTS

I wish to thank everyone who has assisted in the preparation of this thesis. In particular I thank Professor R. P. Bell, F.R.S., for his guidance, help and teaching. I am grateful to numerous members of the chemistry department for helpful advice and interesting discussions. I wish to thank the S.R.C. and the Clayton Aniline Co. Ltd. for financial support. I am grateful to Mrs. J. Weber for the typing of this thesis.

CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

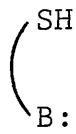
The ionization of a ketone, SH, by a base, B, can be represented by the equation

$$SH + B \rightleftharpoons S^- + BH^+$$

If, instead of the base, B, an enzyme, E, is substituted which brings about the same ionization then the process might be represented by the equation

$$SH + E \rightleftharpoons SH\text{---}E \rightleftharpoons S^- + H\text{---}E^+$$

The removal of the proton would be a unimolecular process involving the enzyme-substrate complex SH---E. A suitable model to simulate the enzyme-substrate complex would consist of a basic group attached by a co-valent bond to the ketone. This could be represented schematically as



In this case intramolecular catalysis by the base, B, would be involved in the proton transfer. The intramolecular models and the enzymatic reactions share in common the bringing together of reactant species within a single molecule or complex respectively.

In fact many workers have studied the mechanism of a model nonenzymatic reaction in order to aid understanding of the mechanism of catalysis of an enzymatic reaction (1,2). It is generally considered that for an enzymatic process to occur the enzyme requires the specific binding of one or more substrate molecules to the catalytic site to form an enzyme-substrate complex. As complex formation enables direct utilization of the binding forces to decrease the free energy of activation of the catalysed reaction, an enzymatic reaction may proceed via an entirely different mechanism than that of a related nonenzymatic reaction.

A system which enables intramolecular participation of a basic group in a proton transfer can be used to represent the isomerase enzymes (3,4). The isomerases

bring about molecular rearrangements in their substrates and it is believed that for a number of these enzymatic reactions only proton transfer is involved. For example the enzyme D-glucose-6-phosphate isomerase brings about the interconversion of aldoses and ketoses (Fig. 1).

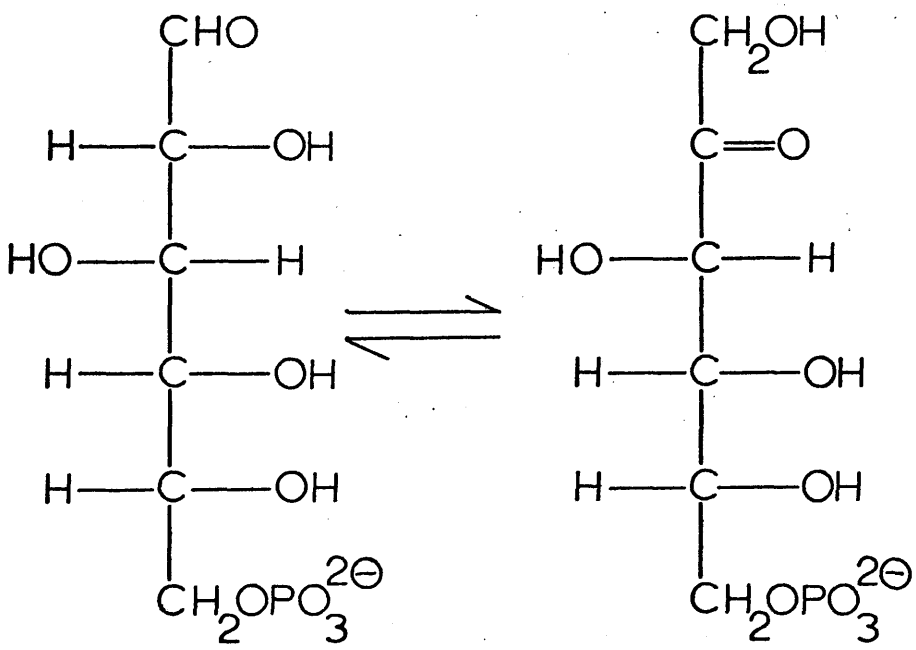
Rose and O'Connell (5) have shown by tritium experiments that when fructose-6-phosphate is labelled with tritium in the C-1 position and is isomerized by the enzyme, the glucose derivative produced was partially tritiated in the C-2 position, partial tritiation of the solvent also occurring. A proton transfer mechanism with an enediol intermediate was postulated with the same basic group, B, involved in the proton loss from C-1 and the proton uptake by C-2 (Fig. 2).

Hines and Wolfe (6) showed by kinetic and pH-dependence studies that the reaction requires an unprotonated group, B, with a pK_a 6-7 and a protonated group, AH^+, with a pK_a 9-10. It is thought that B may be a histidine residue and AH^+ may be the ε-ammonium group of a lysine residue which can donate a proton to the carbonyl. Later studies have shown that a histidine residue may be essential for the catalytic activity (7). The pK_a value of histidine is approximately 6 which means that at the pH values at which most enzymes function, this residue can act as a donor or an acceptor of protons.

A model system to function, in part, in a similar manner to that of the isomerase enzymes would need to contain a group with easily removable protons and a basic group to abstract these protons. Such a condition is achieved with aliphatic and aromatic keto-acids. The basic group is the carboxylate ion and the acidic protons are attached to the carbon atom adjacent to the carbonyl group. Kinetic studies illustrating the intramolecular base catalysed ionization of some aliphatic keto-acids have already been made by Bell and Fluendy (8) and their results are discussed later.

FIG. 1

INTERCONVERSION OF ALDOSES AND KETOSES BY D-GLUCOSE-6-PHOSPHATE ISOMERASE

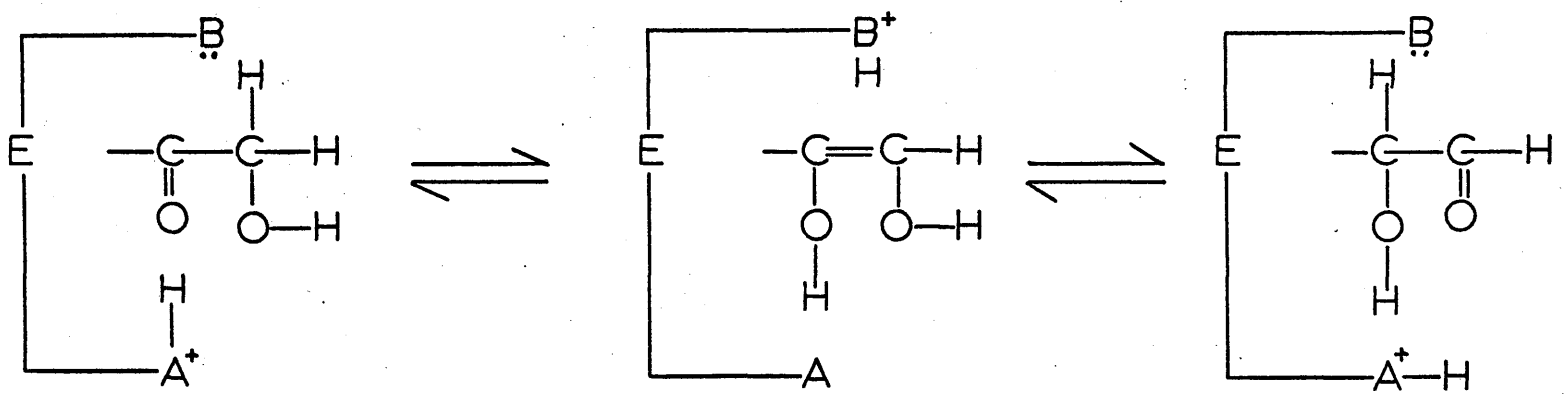


D-GLUCOSE-6-PHOSPHATE.

D-FRUCTOSE-6-PHOSPHATE.

FIG. 2

SUGGESTED MECHANISM FOR THE INTERCONVERSION OF ALDOSES AND KETOSES BY D-GLUCOSE-6-PHOSPHATE ISOMERASE



An aromatic model system where the two reactants are adjacent to each other is of more interest than the aliphatic system because of the specific orientation of the two groups. Comparison of the probable pK_a of an aromatic keto-acid ($pK_a \sim 4$) with that of the histidine residue ($pK_a \sim 6$) indicates that the carboxylate ion is a relatively weaker base and therefore a relatively slower rate of proton abstraction can be expected for this model system. However despite this disadvantage aromatic keto-acids were studied in an attempt to determine the magnitude of the intramolecular proton transfer process as compared to the intermolecular proton transfer process and therefore to illustrate the advantage of bringing the two reactants into close proximity.

CHAPTER 2

RING-CHAIN TAUTOMERISM

INTRODUCTION

It is well known that nearly all ortho-substituted benzoic acids are stronger than the parent acid, regardless of the electron type of the substituent, while their influence as meta- and para-substituents may be either acid-strengthening or acid-weakening, depending upon the electronic character of the individual group. The ortho-isomer is also generally the strongest of the three isomers (9). This increase in acidity for ortho-substituted benzoic acids can be explained in a number of ways.

(a) The strength of the ortho-substituted acids is sometimes considerable because of direct interaction between the adjacent groups. For example, intramolecular hydrogen bonding stabilizes the anion (II) from salicyclic acid (I) by delocalizing its charge. This cannot occur for meta- and para-hydroxybenzoic acids. The effect is even more pronounced when hydrogen bonding can occur with a hydroxyl group in both ortho-positions. 2,6-Dihydroxybenzoic acid has a pK_a of 1.3 compared to the pK_a of benzoic acid of 4.2.

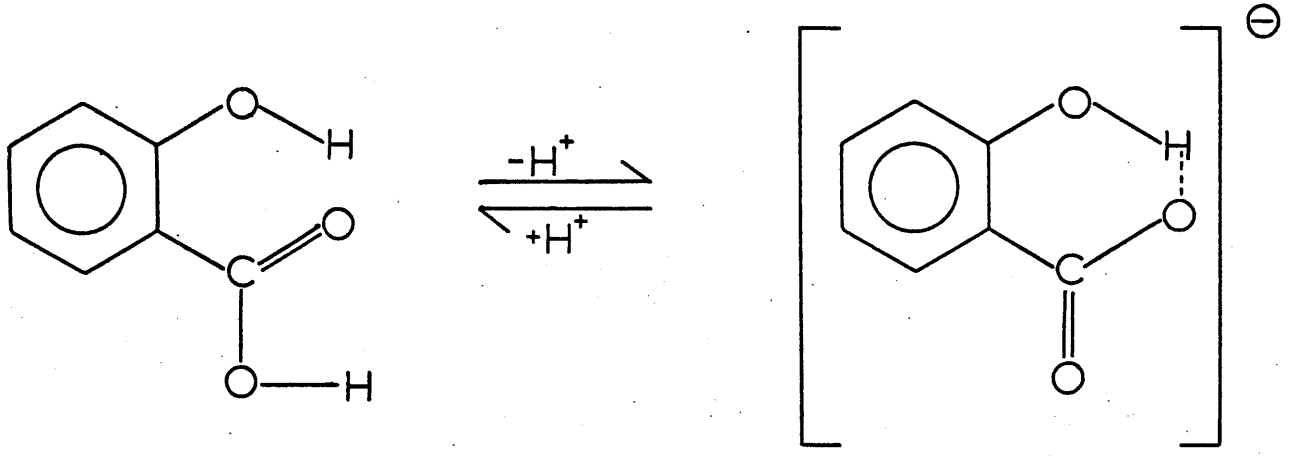
(b) Steric effects may prevent stabilization of the anion by special interactions, such as hydrogen bonding, with orientated solvent molecules.

(c) It is believed that a steric effect is exerted by the ortho-substituent causing the carboxyl group to twist about the C-COOH bond, therefore preventing coplanar arrangement of the system. This would have the effect of decreasing the resonance energy of the system. The data supports the view that this steric inhibition of resonance is an acid-strengthening influence.

These three effects make analysis of ionization reactions highly complicated.

Although ortho-substituted benzoic acids are in general stronger acids than the corresponding meta- and para-isomers there appear to be exceptions. One such anomaly

INTRAMOLECULAR HYDROGEN BONDING IN THE SALICYLIC ACID ANION



I II

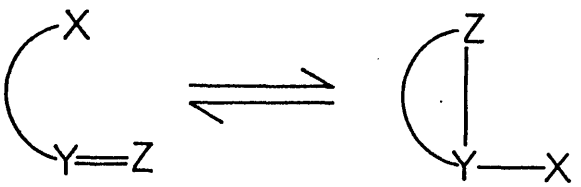
is in the series of monosubstituted acetylbenzoic acids. Bray, Dippy and Hughes (10) measured the dissociation constants for ortho-, meta- and para-acetylbenzoic acids at 25°C by the conductivity method and their results are listed below.

	$10^5 K_a$	pK_a
ortho-acetylbenzoic acid	7.49	4.13
meta-acetylbenzoic acid	14.9	3.83
para-acetylbenzoic acid	19.9	3.70

If the carboxyl group was twisted out of the plane of the ring then it would be expected that the acid would be considerably stronger than the parent acid (pK_a 4.2). The fact that the ortho-isomer is only a little stronger than benzoic acid was interpreted in terms of the acetyl group being preferentially twisted out of the plane of the ring resulting in inhibition of its mesomeric effect. This implies that the conjugative capacity of the acetyl group is substantially weaker than that of the carboxyl group. However these workers did not take into consideration the possibility of ring-chain tautomerism.

A review of the literature concerning ring-chain tautomerism up to 1962 has been made by Jones (11). Only work concerned with keto-acids and some related systems, published up to the present time, will be considered here.

Jones suggested that there are two types of ring-chain tautomerism, either nucleophilic or electrophilic, depending upon the electronic nature of X in the generalized equilibrium (III). When X is electron-deficient, the tautomerism is described as electrophilic and when X is electron-rich, the tautomerism is described as nucleophilic. An example of electrophilic tautomerism is given by ortho-acetylbenzoic acid, where (IV) is the chain tautomer and (V) the ring tautomer. A similar case exists for ortho-formylbenzoic acid. An example of nucleophilic tautomerism exists in the closely related esters of ortho-acetylbenzoic acid, where (VI) is the 'normal' or chain ester



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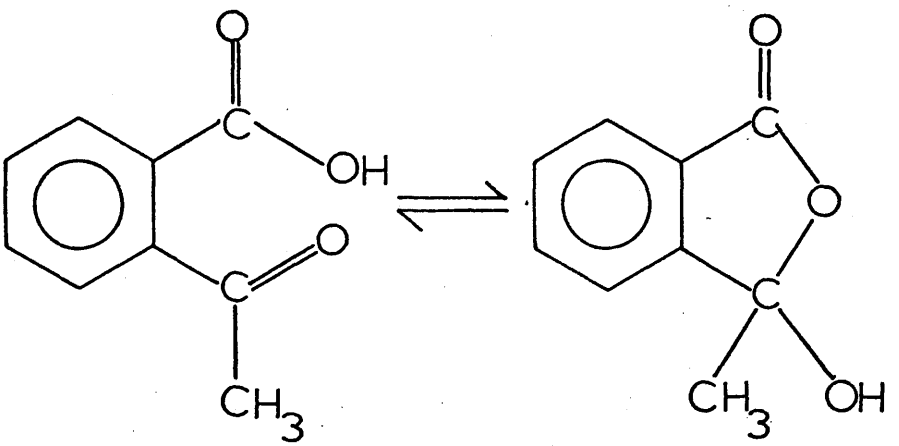
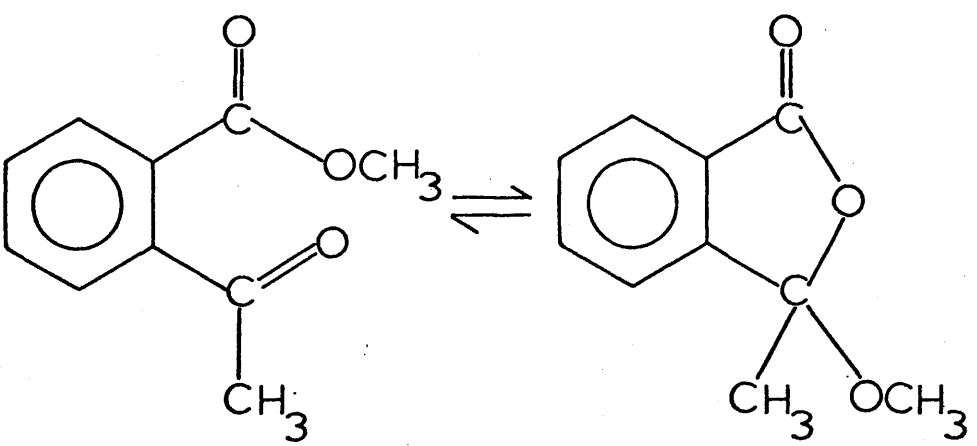
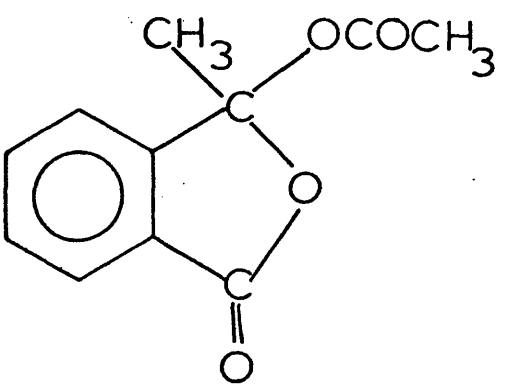


IV V



VI VII



VIII

and (VII) the 'pseudo' or ring ester. Again a similar case exists for the methyl esters of ortho-formylbenzoic acid.

A wide variety of chemical and physical methods are available for the assignment of a ring and chain structure. However, great care is required when assigning structures by relying solely on chemical methods, especially when the two tautomers are easily interconvertible. Spectrophotometric techniques are therefore to be preferred.

Grove and Willis (12), using infra-red spectroscopy, concluded that ortho-acetylbenzoic acid exists, in the solid state, as the ring tautomer (V), because of the existence of bands at 3205 cm^{-1} due to 'alcoholic' - OH and 1732 cm^{-1} due to C=O associated with a 5-membered lactone ring. However Jones and Congdon (13), in a similar investigation, concluded from their data that the chain tautomer (IV) exists in the solid state. They argued that a value of 1732 cm^{-1} was too low to be attributed to the carbonyl group of a 5-membered lactone ring and compared this figure with the corresponding band in the spectrum of 3-acetoxy-3-methyl-phthalide (VIII) which is found at 1780 cm^{-1} in the same medium. Jones and Congdon assigned a value of 3280 cm^{-1} to the -OH band, 75 cm^{-1} higher than that reported by Grove and Willis, and this band, together with the higher of two carbonyl bands (1735 cm^{-1} and 1725 cm^{-1}), they attributed to monomeric -COOH on the basis of values previously reported for this functional group (14). The lower carbonyl band was ascribed to the ketone function on the assumption that an acyl or carboxyl group in the ortho-position exerts an hypsochromic shift on the absorption of its neighbouring substituent.

It is interesting to note that at this time ortho-formylbenzoic acid was suggested by Wheeler, Young and Erley (15), from infra-red evidence, to exist as the cyclic tautomer in the solid state. A band at 1738 cm^{-1} was considered to be due to the carbonyl group of a 5-membered lactone ring. The predominance of the cyclic tautomer in aqueous solution has recently been found by Bell, Cox and Timimi (16) using chemical techniques.

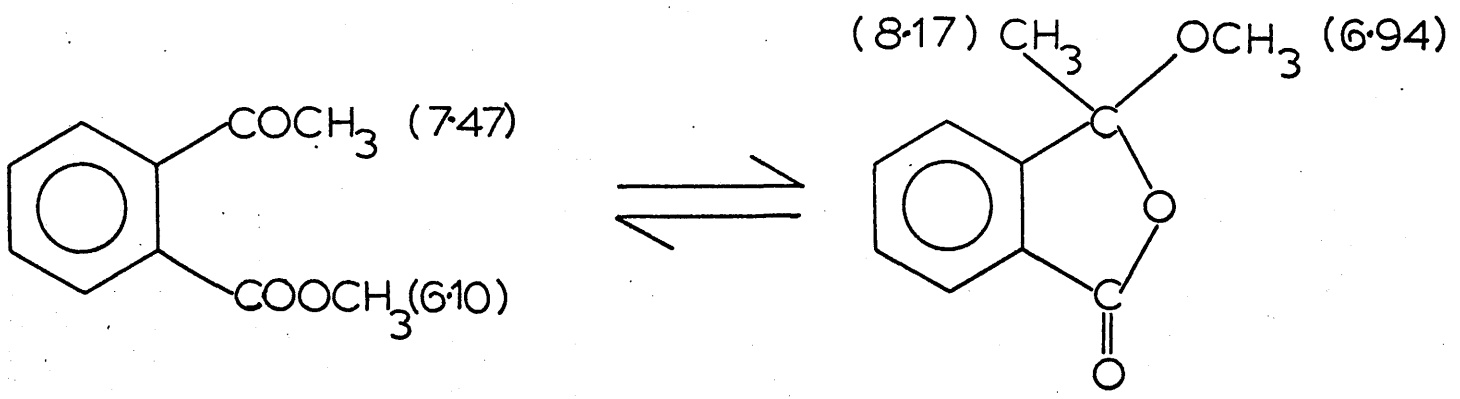
Wheeler (17), using ultra-violet spectroscopy, suggested that in ethanol solution ortho-acetylbenzoic acid probably existed as the lactol (V). This was supported by infra-red data, in methylene chloride solution, obtained by Erley, Potts, Jones and Desio (18) which gave bands which could be explained by structure (V). The same workers, using nuclear magnetic resonance spectroscopy, studied the 'pseudo' and 'normal' methyl esters of ortho-acetylbenzoic acid in chloroform solution and a quantitative estimate of each was made, the ratio of ring to chain being found to be 3:1. The chemical shift values for the various methyl groups are listed (IX), ortho-acetylbenzoic acid itself having a τ value of 8.02. This value is the time-averaged value from the ring and chain tautomers of the keto-acid. If it is assumed that the pure acid tautomers would exhibit τ values for the methyl groups identical with those in the model esters then calculation indicates 63% ring tautomer and 37% chain tautomer for ortho-acetylbenzoic acid itself.

A more complete study by Jones and Desio (19) using ultra-violet (methanol solution), infra-red (nujol mull) and nuclear magnetic resonance spectroscopy (chloroform solution) showed the presence of a ring-chain tautomeric mixture in fast equilibrium. From the nuclear magnetic resonance data a slightly larger value of 80% for the ring-tautomer was calculated, again making use of the 'normal' and 'pseudo' methyl esters.

Later work by Finkelstein and co-workers (20) using a dimethyl sulphoxide-d_6 solution of ortho-acetylbenzoic acid showed by nuclear magnetic resonance spectroscopy the presence of both ring and chain tautomers, the relative intensities of the bands indicating a ratio of 1:2. On the addition of a trace of hydrochloric acid the two peaks coalesced indicating a fast interconversion of tautomers.

Studies of other compounds relevant to this work have also been made. Jones and Desio (19) in a study similar to that for ortho-acetylbenzoic acid showed that the 3,4,5,6-tetrachloro and 6-methyl-derivatives of ortho-acetylbenzoic acid exist mainly as the ring tautomer and that the 3-nitro-derivative exists as approximately a 1:1

THE CHEMICAL SHIFT VALUES FOR THE VARIOUS METHYL GROUPS OF METHYL ORTHO-ACETYLBENZOATE



IX

mixture of the ring and chain tautomers. Lansbury and Bieron (21) have shown by nuclear magnetic resonance spectroscopy that 8-acetyl-1-naphthoic acid exists as the cyclic tautomer in chloroform solution. This is supported by evidence from infra-red spectroscopy in the solid state (22). Evidence to suggest that ortho-isobutyryl-benzoic acid exists as the cyclic tautomer in the solid state has been published by Letsinger and Vullo (23) using infra-red spectroscopy and this has been supported by infra-red studies in dioxan solution carried out recently by Bowden and Taylor (24).

The apparent acidity of these acids will involve the values of their tautomeric equilibrium constants. In aqueous solution it can be considered that the chain and ring tautomers of ortho-acetylbenzoic acid are in rapid equilibrium. Most methods of determining acid dissociation constants involve measurement of both these species together with the anion by spectrophotometric, potentiometric or conductometric techniques. The pK_a value obtained by Bray, Dippy and Hughes for ortho-acetylbenzoic acid can be considered to be a 'mixed' pK_a. It has been shown (25) that the 'true' pK_a value, pK_a^T, (i.e. for the acid as 100% chain tautomer) is related to the value observed by the relationship

$$pK_a^T = pK_a - \log(K_e + 1)$$

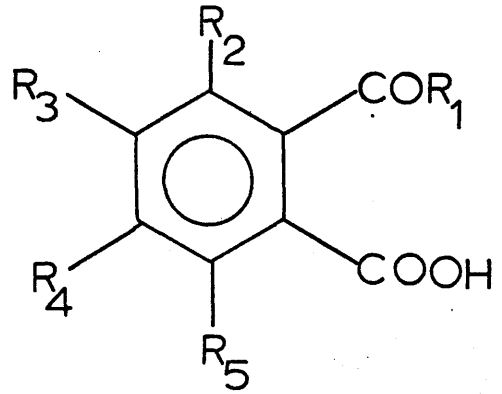
where $K_e = [AH]\text{ring}/[AH]\text{chain}$

From this relationship it can be seen that the value of pK_a^T always indicates a stronger acid than the value of the pK_a. K_e has been measured directly using infra-red spectroscopy (24) and nuclear magnetic resonance spectroscopy (19,24) for a number of keto-acids including ortho-acetylbenzoic acid. From knowledge of this value and the observed dissociation constant the 'true' dissociation constant has been calculated. However it is possible to measure the 'true' dissociation constant without prior knowledge of the tautomeric equilibrium constant K_e, by using data obtained from the decomposition of nitramide or the mutarotation of glucose catalysed by carboxylate

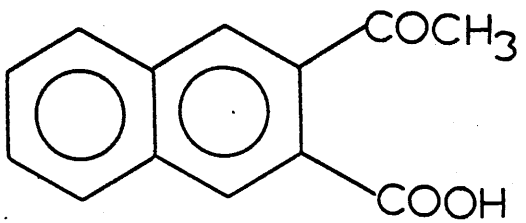
ions in aqueous solution. In these methods for determining the 'true' acid dissociation constant K_a^T, which will be discussed in detail later, it is assumed that with acids and acid derivatives exhibiting ring-chain tautomerism, the anions are always acyclic. Gore, Barnes and Petersen (26) and Wexler (27) using infra-red techniques on aqueous solutions of the sodium and potassium salts demonstrated that they are always acyclic. The 'true' acid dissociation constants for ortho-formylbenzoic acid (16) and later for ortho-acetylbenzoic acid (28) have been determined in this manner. Experimental work shows that (IV) is a stronger acid (pK_a^T 3.5) than either the meta- or para-isomers, this being in agreement with the results discussed earlier for other monosubstituted benzoic acids.

In the present work infra-red spectroscopy has been used to determine which tautomer is present in the solid state. The 'true' acid dissociation constants have been determined by nitramide decomposition reactions and in some cases the values obtained were verified by catalysis of the mutarotation of glucose. The 'mixed' acid dissociation constants have been measured when values were not available in the literature. From the knowledge of both acid dissociation constants the tautomeric equilibrium constant, K_e, has been determined for each keto-acid enabling the percentage of ring and chain tautomers to be determined.

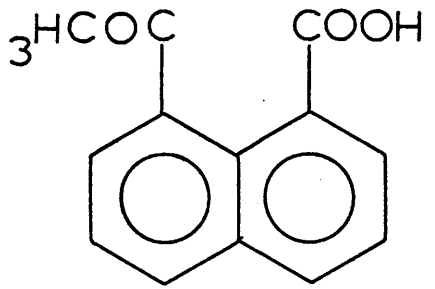
NAME AND FORMULA (CHAIN TAUTOMER) OF KETO-ACIDS STUDIED



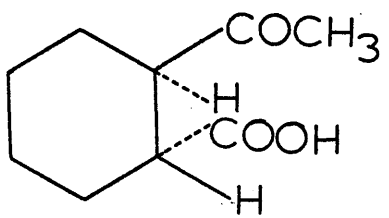
	R_1	R_2	R_3	R_4	R_5
ORTHO-ACETYLBENZOIC ACID (X)	CH_3	H	H	H	H
ORTHO-ISOBUTYRYLBENZOIC ACID (XI)	$CH(CH_3)_2$	H	H	H	H
2-ACETYL-3-NITROBENZOIC ACID (XII)	CH_3	NO_2	H	H	H
2-ACETYL-3,4,5,6-TETRACHLOROBENZOIC ACID (XIII)	CH_3	Cl	Cl	Cl	Cl
2-ACETYL-4,5-DIMETHYLBENZOIC ACID (XIV)	CH_3	H	CH_3	CH_3	H
2-ACETYL-4,5-DIMETHOXYBENZOIC ACID (XV)	CH_3	H	OCH_3	OCH_3	H
2-ACETYL-6-METHYLBENZOIC ACID (XVI)	CH_3	H	H	H	CH_3



2-ACETYL-3-NAPHTHOIC ACID (XVII)



8-ACETYL-1-NAPHTHOIC ACID (XVIII)



TRANS-2-ACETYLCYCLOHEXANE-
CARBOXYLIC ACID (XIX)

EXPERIMENTAL

(i) Preparation of the keto-acids

All materials used were of normal reagent quality unless otherwise stated. For final recrystallizations deionized water distilled over alkaline potassium permanganate was used and solvents were of AnalaR quality.

ortho-Acetylbenzoic Acid (X)

The procedure used was one previously described by Yale (29). The crude acid was recrystallized twice from benzene and twice from water.

Yield 24g. (42% based on phthalic anhydride)
m.p. 117-118.5°C (lit. m.p. 114-5°C (13), 115-7°C (30), 117.5-119.5°C (31)).

ortho-Isobutyrylbenzoic Acid (XI)

The preparation of the acid was based on the method by de Benneville (32). All apparatus was dried overnight at 80°C and the usual precautions taken in the preparation of Grignard reagents. The Grignard was prepared using magnesium (9.25g; 0.38 mol.), dried overnight at 80°C, sodium dried ether (300 ml) and isopropyl bromide (47g; 0.38 mol.). The mixture was cooled to 0°C externally with ice and the cadmium alkyl prepared using anhydrous cadmium chloride (30.25g; 0.165 mol.), dried overnight at 150°C, addition taking 30 minutes. The mixture was stirred for 2 hours at 0°C and then finely ground phthalic anhydride (44.5g; 0.3 mol.) added over a period of 30 minutes. The stirring was continued, the temperature being kept at 0°C, until a gummy precipitate was formed which prevented further stirring. The outside of the vessel was packed with ice and left overnight. Next morning the reaction was again cooled to 0°C and hydrolysed with sulphuric acid (10% v/v). The solution was filtered and the two layers separated. The aqueous layer was washed with ether and the combined ether extracts washed with sodium carbonate solution (5% w/v) to remove acidic material. The alkaline solution was then acidified with hydrochloric acid (S.G. 1.180) and the white precipitate obtained filtered off, washed with water and dried at 60°C. The crude material

was recrystallized from benzene to give a solid melting at 90 - 97°C. The solid was dissolved with sodium hydroxide solution (10% w/v) and gradually reprecipitated with hydrochloric acid solution (10% v/v). At pH 6.3 the insoluble material was filtered off, washed with water and dried (m.p. 121 - 124°C). The filtrate was further acidified to pH 4.8 and after filtration and washing, the dried product had a melting range of 90 - 97°C. This material was redissolved in sodium hydroxide solution (10% w/v) and then acidified, as before, to pH 5.8, filtered, washed with water and dried (m.p. 124 - 127°C). The two portions of high melting material were recrystallized three times from water.

Yield 5.4g (9.4% based on phthalic anhydride)
m.p. 122.5-123.5°C (lit. m.p. 121.8-122.5°C (31) 121.5-122.5°C (23), 120-1°C (33)).

2-Acetyl-3-Nitrobenzoic Acid (XII)

3-Nitrophthalic acid (34) was converted to the corresponding anhydride (35) which was then used without further purification. The acid was prepared by a procedure similar to that described by Yale (29). All apparatus was dried overnight at 120°C.

A finely ground mixture of 3-nitrophthalic anhydride (33g; 0.174 mol.) and malonic acid (20.1g; 0.195 mol.), both dried overnight at 80°C, was placed in a single-necked 500 ml round-bottom flask and pyridine (21 ml), dried over potassium hydroxide pellets and then distilled, added. The flask was fitted with a condenser and drying tube and the mixture heated on a boiling water bath until no more carbon dioxide was evolved (4 hours). The brown viscous solution was poured into cold water (150 ml), the flask being washed out with a further 50 ml water. The mixture was stirred for five minutes and then filtered. The filtrate was acidified with hydrochloric acid (S.G. 1.180) to congo red papers, and a brown oil formed (Note 1). The solution was left to stand in an ice-bath for 1 hour and then left overnight to attain room temperature. An orange precipitate was obtained which was filtered off, washed with water and dried at 60°C.

Recrystallization twice from benzene gave a light orange solid with m.p. 159 - 160°C. Recrystallization from water, with charcoal treatment, gave almost colourless crystals.

Yield 7.3g (23.7% based on 3-nitrophthalic anhydride)
m.p. 163-164°C (lit.m.p. 159-160°C (36)
159-161°C (19), 164-165° (37)).

Note 1. After acidification the mixture can be extracted with ether and the extracts dried over anhydrous calcium sulphate. Removal of the ether on a rotary evaporator gives a pink-orange solid which can be digested with benzene to give the impure product. Recrystallization gives a material of equal quality.

2-Acetyl-3,4,5,6-Tetrachlorobenzoic Acid (XIII)

The acid was prepared by the method given by Jones and Desio (19). The crude pale yellow material (22.1g m.p. 174-178°C) was recrystallized from benzene to give a white solid and a pink filtrate.

Yield 12g (31.4% based on the anhydride)
m.p. 179-185°C.

Recrystallization 3 times from 50-50 dioxan-water gave a white amorphous solid.

Yield 6.6g
m.p. 185-187°C (lit.m.p. 184-186°C (19))
Calculated for $C_9H_4Cl_4O_3$ C.35.80, H.1.34, Cl.46.95
Found C.36.00, H.1.57, Cl.46.49

2-Acetyl-4,5-Dimethylbenzoic Acid (XIV)

2,3-Dimethyl-1,3-butadiene was prepared from pinacol (38) and a Diels-Alder reaction with maleic anhydride (39) gave 4,5-dimethyl-cis Δ^4-tetrahydrophthalic anhydride which was then dehydrogenated with sulphur to give 4,5-dimethyl-phthalic anhydride.

The Diels-Alder adduct (117g; 0.65 mol.) and powdered sulphur (45.5g; 1.42 mol.) were added as an intimate mixture to a 500 ml flask. The mixture was heated to 250-260°C for 30 minutes during which time a copious amount of hydrogen sulphide was evolved. The reaction was allowed to cool

and the solid recrystallized from benzene, activated charcoal being added to decolourize the solution. The product was finally sublimed to give 4,5-dimethylphthalic anhydride.

Yield 72g (66.4% based on the adduct).

The keto-acid was prepared by adapting the method used to prepare 2-acetyl-3,4,5,6-tetrachlorobenzoic acid. The Grignard was prepared in the usual manner with magnesium (5.1g; 0.21 mol.) and methyl iodide (29.7g; 0.21 mol.). The reaction mixture was cooled to 0°C and anhydrous cadmium chloride (38.4g; 0.21 mol.), dried overnight at 150°C, added over a period of 15 minutes. The reaction mixture was stirred for 90 minutes and allowed to rise to room temperature. The mixture was again cooled to 0°C and 4,5-dimethylphthalic anhydride (37g; 0.21 mol.) added over 1 hour. Sodium dried benzene (200 ml) was added and the reaction refluxed for 6 hours. The reaction mixture was cooled to 0°C and decomposed with hydrochloric acid (10% v/v) followed by filtration and separation of the two layers. The aqueous layer was washed with ether and the combined ether extracts washed with sodium carbonate solution (5% w/v). The alkaline solution was then acidified with hydrochloric acid (S.G. 1.180) and allowed to stand overnight. Filtration, drying at 60°C and recrystallization twice from benzene, once from ethanol-water and once from benzene gave a white crystalline solid.

Yield 15g (37.2% based on anhydride)

m.p. 148-148.5°C

Calculated for $C_{11}H_{12}O_3$	C.68.75, H.6.25
Found	C.68.93, H.6.42

2-Acetyl-4,5-Dimethoxybenzoic Acid (XV)

4,5-Dimethoxyphthalic anhydride was prepared by combining the methods given by G. A. Edwards et al. (40) and Tetsulara Ikeda et al. (41). This anhydride (m.p. 181-185°C lit.m.p. 175-177°C (41)) was used without further purification. Preparation of the keto-acid was the same as that given for 2-acetyl-4,5-dimethylbenzoic acid the material used being magnesium (1.7g; 0.07 mol.), methyl iodide (10g; 0.07 mol.), anhydrous cadmium chloride (12.8g; 0.07 mol.) and 4,5-dimethoxyphthalic anhydride (15g; 0.07 mol.). The mixture was decomposed

and worked up in the usual manner. However, final acidification failed to give a precipitate. The acidic solution was extracted with ether and the ethereal solution dried over anhydrous sodium sulphate. Removal of the ether on a rotary evaporator produced a pale yellow oil which could not be induced to crystallize. The oil was placed under vacuum in a desiccator to remove the last traces of solvent and a white fluffy solid was obtained.

Yield 5g m.p. 110-130°C.

Purification was achieved by refluxing the solid for 3 hours in methanol with a trace of concentrated sulphuric acid. Most of the methanol was then removed, ether added, and the mixture extracted with sodium carbonate solution (5% w/v) to remove acidic material. The ether was removed and the resulting oil refluxed for 1 hour with sodium hydroxide solution (10% w/v). The solution was cooled, acidified and extracted with ether. The ether solution was dried over anhydrous sodium sulphate and then removed to leave a white solid.

Yield 2g (12.4% based on anhydride)

m.p. 139-140°C.

Equivalent weight. Calculated 224

Found 225

2-Acetyl-6-Methylbenzoic Acid (XVI)

3-Methyl-1,2,3,6-tetrahydrophthalic anhydride was prepared as described by Newman and McCleary (42). They also give a method for dehydrogenation using bromine but skin-irritating products were obtained when this was tried. Instead of attempting purification it was decided to dehydrogenate a further sample using sulphur as in the case for the preparation of the 4,5-dimethyl keto-acid.

An intimate mixture of the adduct (38.4g; 0.23 mol.) and sulphur (15g; 0.47 mol.) was heated to 250-260°C for 2 hours. A brown-black solid was obtained on cooling. The mixture was vacuum distilled, the distillate solidifying on cooling. Recrystallization from benzene/60 - 80° petroleum ether gave 3-methylphthalic anhydride as clusters of small needles.

Yield 11.5g (30.7% based on the adduct)

m.p. 115-116°C (lit.m.p. 114.5-117°C (42)).

The keto-acid was prepared as described by Jones and Desio (19). The pale yellow oil that separated out at the final stage of the process solidified overnight. This was recovered by filtration, dried, and recrystallized twice from benzene-pentane. It was finally recrystallized twice from water.

Yield 4.5g (16.8% based on anhydride)

m.p. 127.5-128.5°C (lit.m.p. 122-124°C (19), 126-127°C (43)).

Equivalent weight	Calculated	178
	Found	177

2-Acetyl-3-Naphthoic Acid (XVII)

A finely ground mixture of 2,3-naphthalene dicarboxylic anhydride (35.64g; 0.18 mol.) and dry malonic acid (21.84g; 0.21 mol.) was heated with dry pyridine (35 ml) on a boiling water bath for 4 hours. The yellow solution and unreacted anhydride was poured into 300 ml cold water and the white precipitate formed filtered off. The filtrate was treated with hydrochloric acid (40 ml S.G. 1.180) and allowed to stand for 3 days at room temperature. The precipitated material was filtered off and washed with a little water. It was dried at 80 - 90°C and recrystallized three times from benzene.

Yield 1.74g (4.5% based on anhydride)

m.p. 169 - 170°C.

It was also prepared using the same method as that for the tetrachloro keto-acid. In this case magnesium (2.6g; 0.107 mol.), methyl iodide (16g; 0.108 mol.), anhydrous cadmium chloride (19. 2g; 0.105 mol.) and 2,3-naphthalene dicarboxylic anhydride (20.8g; 0.105 mol.) was used. The reaction mixture was then worked up in the usual way.

Yield 2.4g (6.2% based on anhydride)

m.p. 169.5-170.5°C (lit.m.p. 170-171°C (30))

8-Acetyl-1-Naphthoic Acid (XVIII)

The keto-acid was prepared by the method described by Jones and Lavigne (22). After three recrystallizations from

aqueous ethanol colourless crystals were obtained.

Yield 1.0g (10.9% based on anhydride)

m.p. 170.5-171.5°C (lit.m.p. 173-174°C (22))

Trans-2-Acetylcyclohexanecarboxylic Acid (XIX)

Cis-hexahydrophthalic anhydride was prepared from the di-acid (84g; 0.49 mol.) and acetic anhydride (100 ml.), the mixture being refluxed for 90 minutes. The solvent was distilled off and the remaining liquid vacuum distilled, the fraction boiling at 100°C at 0.8 mm being collected. The liquid solidified on cooling.

Yield 63.9g (85% on acid)

The keto-acid was prepared via a Grignard type reaction (32). The methyl cadmium was prepared in the usual manner with magnesium (7.3g; 0.3 mol.), methyl iodide (45g; 0.3 mol.) and anhydrous cadmium chloride (55g; 0.3 mol.). The anhydride (47g; 0.3 mol.), dissolved in dry ether (150 ml), was added during 30 minutes and the mixture heated to reflux. After 30 minutes a gummy material was deposited that made stirring impossible. Refluxing was continued for a further 3 hours and the mixture then cooled to 0°C and worked up in the normal way. No product was deposited after acidification and so the solution was extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate, filtered, and the ether removed leaving a brown oil. The oil was dissolved in benzene, heated to boiling, and 80-100° petroleum ether added until a solid just started to precipitate. After cooling, filtering and drying the solid was recrystallized from water to give clusters of white needles.

Analysis by titration with standard sodium hydroxide solution indicated a mixture of the desired product and the dibasic acid. Purification was achieved by converting the acids to their corresponding methyl esters (c.f. 2-acetyl-4,5-dimethoxybenzoic acid). The esters were dissolved in ether and the mono-ester of the dibasic acid was removed with sodium carbonate solution (10% w/v). The keto-acid was recovered as previously described. Recrystallization three times from water

gave the desired product.

Yield 5.1g (9.8% based on anhydride)

m.p. 137-138°C.

Equivalent weight	Calculated	170
	Found	170.5

(ii) Infra-red spectroscopy

The spectra of the keto-acids were obtained with samples as mulls in nujol or hexachloro-1,3-butadiene using a Perkin Elmer 457 infra-red spectrophotometer and sodium chloride plates. The spectra were scanned from 4000-250 cm^{-1} and were calibrated by superimposing the polystyrene film absorption band at ν_{max} 1602 cm^{-1}. Table 1 shows the infra-red absorption frequencies in the -OH region and C=O region only.

(iii) Measurement of the 'mixed' acid dissociation constant, K_a.

Required acid dissociation constants not recorded in the literature have been determined spectrophotometrically either by adding a small quantity of the keto-acid to a known buffer solution or by adding a small quantity of indicator to buffer solutions prepared from the keto-acid (44). Table 2 lists the keto-acids whose acid dissociation constants have been determined in this way, the buffer system and indicator used and the wavelengths at which the measurements were taken. 2-Acetyl-4,5-dimethylbenzoic acid has been chosen to illustrate the determination of K_a using known buffer solutions and the keto-acid as indicator and 2-acetyl-3-naphthoic acid to illustrate the method using an indicator and buffer solutions of the keto-acid. The data and calculation for both these acids is given in full. For all the other keto-acids only the final measured acid dissociation constants are listed; table 5.

(a) 2-Acetyl-4,5-dimethylbenzoic acid

A stock solution of the keto-acid was prepared by dissolving the acid in sodium hydroxide solution so that the final concentration of both the acid and sodium hydroxide was 10^{-3}M. From this stock solution 1 ml was diluted to 10 ml

with 0.1M hydrochloric acid solution and the optical density measured at 25°C over the range 200 - 450 nm using a Unicam SP800 spectrophotometer and 1 cm silica cells. The procedure was repeated, replacing 0.1M hydrochloric acid solution by 0.1M sodium hydroxide solution and it was assumed that the spectra obtained corresponded to the completely unionized and completely ionized species respectively. From these spectra 265 nm was chosen as the wavelength at which the optical density of the solutions of the keto-acid in buffer solution should be determined. The optical densities of the two solutions were then measured accurately at 265 nm using a Unicam SP500 spectrophotometer thermostated at 25°C. The pK_a of the keto-acid was estimated from knowledge of the pK_a value of ortho-acetylbenzoic acid and the effect of various substituents in the benzene ring. A buffer whose pK_a value approximates to this estimated pK_a value was selected and solutions of varying buffer ratio, [acid]/[base], not far from 1:1, were used to dilute the stock solution of the keto-acid to 10^{-4}M. The extent of ionization was determined by measuring the optical density with the SP800 spectrophotometer. This procedure was repeated with solutions of various buffers, at a buffer ratio between 0.5 and 2, until a solution was obtained in which approximately half the keto-acid was ionized. In this case a formic acid - sodium formate buffer was found to be suitable. Eight solutions were then prepared with buffer ratios varying from 0.166 to 2.18 $[HCOOH]/[HCOO^-]$. The buffer solutions were prepared by partial neutralization of 0.106M formic acid solution with 0.1M sodium hydroxide solution. A final total volume of 100 ml was found to be adequate for each reading. The optical densities of the solutions were then measured accurately at 265 nm, as before. The total concentration of the keto-acid was 10^{-4}M and the ionic strength was kept constant at I = 0.01M. The reference cell always contained a blank of the appropriate buffer. The results are given in table 3.

By definition

$$pK_a = pH + \log[\text{acid}]/[\text{base}]$$

$$= pH + \log(\varepsilon_i - \varepsilon)/(\varepsilon - \varepsilon_m) \qquad (1) \text{ (for } \varepsilon_i > \varepsilon_m)$$

where

ε_i = Extinction coefficient of the ionized species

ε_m = Extinction coefficient of the neutral molecule

ε = Extinction coefficient of the keto-acid in buffer solution.

Also

$$K_{HCOOH} = ([H^+][HCOO^-])/[HCOOH] \qquad (2)$$

Combining equations (1) and (2) gives

$$K_{HCOOH}[HCOOH]/[HCOO^-] = K_a(\varepsilon_i - \varepsilon)/(\varepsilon - \varepsilon_m)$$

The same total concentration of keto-acid is used for all measurements and so the extinction coefficient, ε, can be replaced by the optical density, d, so that

$$K_{HCOOH}[HCOOH]/[HCOO^-] = K_a(d_i - d)/(d - d_m) \quad (\text{for } d_i > d_m)$$

where

d_i = optical density of the ionized species

d_m = optical density of the neutral molecule

d = optical density of the keto-acid in buffer solution.

A plot of $K_{HCOOH}[HCOOH]/[HCOO^-]$ against $(d_i - d)/(d - d_m)$ will give a slope corresponding to the dissociation constant, K_a, of the keto-acid. No correction for activity coefficients is necessary, since the two acids are of the same charge type. No trend, dependent upon the buffer ratio, was observed. The dissociation constant for formic acid was taken as 1.77×10^{-4} at 25°C.

For some of the other keto-acids acetic acid-sodium acetate buffers were used. The dissociation constant of acetic acid was taken as 1.758×10^{-5} at 25°C, otherwise the procedure was identical.

From the results in table 3 a plot of $1.77 \times 10^{-4}[HCOOH]/[HCOO^-]$ against $(d_i - d)/(d - d_m)$ (Fig.3) gives a slope of 5.78×10^{-5} which corresponds to the acid dissociation constant for 2-acetyl-4,5-dimethylbenzoic acid. This corresponds to a pK_a value of 4.24.

(b) 2-Acetyl-3-naphthoic acid

This method was used for two of the keto-acids because the similarity between the absorption spectra of the anion and the neutral molecule made it difficult to use the method just described.

Seven separate solutions of the keto-acid were prepared by partially neutralizing about 0.0214g of the acid with sodium hydroxide solution so that the stoicheiometric buffer ratio $[HA]/[A^-]$ varied between 0.25 and 4 with a final total concentration of the keto-acid of 10^{-3}M. Various indicators were added to samples of each buffer and an indicator found which changed colour in about half of these solutions. Bromophenol blue was found to be a suitable indicator for 2-acetyl-3-naphthoic acid. A 10^{-5}M stock solution of this indicator was then prepared and equal amounts (10 ml) were added to fresh buffer solutions of the keto-acid prepared as described above. The ionic strength of the solutions was adjusted to I = 0.001M with potassium chloride solution. A final total volume of 100 ml was found to be adequate for each experiment. The optical densities of the solutions were then measured at 590 nm and 435 nm, these wavelengths corresponding to the maximum absorption of the ionized and neutral species of the indicator respectively. A Unicam SP500 spectrophotometer was used, thermostated at 25°C.

From the optical density measurements the relative concentrations of ion (I^-) and molecule (HI) of the indicator can be found. Using these values and the pK_{ind} of the indicator at an ionic strength of 0.001M (45) the pH of each

solution can be determined from the expression

$$pK_{ind} = pH + \log(O.D._{435}/O.D._{590})$$

where

$$\log(O.D._{435}/O.D._{590}) = \log([HI]/[I^-])$$

The true buffer ratio of the keto-acid can now be calculated and hence its pK_a from the expression

$$pK_a = pH + \log([HA] - [H^+])/([A^-] + [H^+])$$

The data is given in table 4 and a value of 4.47 $\pm$ 0.06 was obtained for the pK_a of 2-acetyl-3-naphthoic acid. The thermodynamic dissociation constant values used for all the keto-acids studied are listed in table 5 together with the corresponding pK_a values.

(iv) Measurement of the 'true' acid dissociation constant, K_a^T

(a) Decomposition of nitramide

Brönsted and Pedersen (47) first demonstrated the general catalysed decomposition of nitramide by basic anions. Baughan and Bell (48) have reported catalytic constants, k_B, for eight carboxylate ions over a range of temperatures in aqueous solution. A linear plot of log k_B against the pK_a of the corresponding acids, Fig.4, can be represented by the general expression

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

where G and β are constants describing the system. Interpolation on this linear plot when the catalytic constants of other carboxylate anions have been determined enables the pK_a of the corresponding acid to be found. This technique has been used in the present work for the determination of the 'true' acid dissociation constants.

The apparatus used was the same as that described by Bell and Trotman-Dickenson (49), nitramide was prepared as previously described (50) and the experiments were carried out at 25°C for consistency with the method of Baughan and Bell. The rate of decomposition of nitramide was followed by measuring the pressure of

evolved nitrous oxide at suitable time intervals. For each experiment about 12 mg of nitramide in 5 ml of a solution of the keto-acid anion was used, this giving a total pressure change of approximately 200 mm Hg. From the pressure and time data the observed first-order velocity constant was calculated for each of about five concentrations of anion using the 'end-point' method, the estimated accuracy of these constants being $\pm$ 3%. The buffer ratio [acid]/[base] used was 0.1 for ortho-acetylbenzoic acid and solutions of the other keto-acids had a pH value of approximately 6. The ionic strength was kept constant at I = 0.1M.

From the catalytic constant, k_B, obtained by plotting observed first-order velocity constants against concentrations of anion and measuring the gradient of the resulting straight line the pK_a^T value of the keto-acid was determined by reference to the calibration graph obtained from the results of Baughan and Bell.

The calculated first-order velocity constants, k_{calc}, for the decomposition of nitramide have been obtained from the general expression

$$k_{calc} = k_o + k_B[A^-]$$

where k_o = the catalytic constant for water molecules and hydroxide ions

k_B = the catalytic constant for the keto-acid anion, A^-.

2-Acetyl-3-naphthoic acid has been chosen to illustrate this technique and the data necessary for the calculation of k_B is given in table 6. Fig.5 shows a typical plot for the determination of the observed first-order velocity constant and Fig.6 shows a plot of the observed first-order velocity constant for the decomposition of nitramide against the concentration of anion. Table 7 contains the results obtained for all the other keto-acids studied. k_o varies slightly for each keto-acid due to catalysis by hydroxide ions, the pH varying slightly for each stock solution. The accepted value for the spontaneous rate is 4.7×10^{-5} sec^{-1} (Ref. 48). Because of the lower acidity

of 8-acetyl-1-naphthoic acid and hence the high pH needed for solution (pH7) it was found impossible to determine pK_a^T for this keto-acid. At this pH the rate of decomposition of nitramide would be complicated by catalysis by hydroxide ions and by the nitramide anion.

(b) Mutarotation of glucose

Brönsted and Guggenheim (51) measured the catalytic constants, k_B, for the mutarotation of glucose catalysed by the anions of eleven carboxylic acids with pK_a values ranging from 2.8 to 5.1. A plot of log k_B for the anions against the pK_a of the conjugate acids gave a straight line, Fig.7. The catalytic constants for the mutarotation of glucose catalysed by keto-acid anions were therefore determined to enable evaluation of pK_a^T for the conjugate acids by reference to this plot. This method for the evaluation of pK_a^T parallels that using the anion catalysed decomposition of nitramide and provides confirmation of the data obtained by the latter method.

The change in rotation of glucose at 436 nm was measured using a Perkin Elmer digital polarimeter, reading to 0.001^o, enabling the use of low concentrations of glucose (< 1%) which minimized the dilution effect of addition of solid glucose to the solutions of the keto-acid anion. Therefore correction to the concentration value of these solutions was considered unnecessary. The experiments were carried out at 18^oC for consistency with the work of Brönsted and Guggenheim. For each keto-acid the observed first-order velocity constants were calculated either by Guggenheim's method or by the 'end point' method from kinetic data obtained for each of five-concentrations of anion. This enabled the catalytic constant for each anion to be calculated by the same method described in the section dealing with the decomposition of nitramide experiments. The catalytic solutions had a buffer ratio [acid]/[base] of 0.1 for ortho-acetylbenzoic acid and solutions of the other keto-acids had a pH value of approximately 6. The ionic strength of the

solutions was kept constant at I = 0.2M and 5 ml of solution was adequate for each experiment. Catalysis by hydrogen ions, hydroxide ions or undissociated keto-acid were not corrected for in the final results.

The kinetic data for 2-acetyl-4,5-dimethylbenzoic acid is given in table 8, Fig.8 shows a typical plot for the determination of the observed first-order velocity constant and a plot of the first-order velocity constants against concentration is given in Fig.9, the value of the gradient being equal to the catalytic constant, k_B. These results are typical of those obtained for the determination of pK_a^T by this method. The calculated first-order velocity constants have been obtained from the expression

$$k_{calc} = k_o + k_B[A^-]$$

described in the section on the decomposition of nitramide. The observed and calculated first-order velocity constants and the values of K_a^T and pK_a^T for the keto-acids studied are listed in table 9. The value of k_o varies slightly for each keto-acid and this can be attributed to catalysis by hydroxide ions due to slight differences in the pH value of the stock solutions.

TABLE 1

The name and formula of the keto-acids are listed at the beginning of the experimental section.

Keto-acid	Mull	-OH region (cm^{-1})	carbonyl region (cm^{-1})	Tautomer
X	nujol	3265	1735,1725	Ring
	halocarbon	3265	1730	Ring
XI	nujol	3315	1738,1722	Ring
	halocarbon	3315	1737,1722	Ring
XII	nujol	(Broad between	1710,1690	Chain
	halocarbon	∿3200-2400)	1710,1690	Chain
XIII	nujol	(Broad between	1770,1750	Ring
	halocarbon	3600-3100 Max	1770,1750	Ring
		at 3400-3300)		
XIV	nujol	3385,3350	1740,1720	Ring
	halocarbon	3385,3350	1740,1720	Ring
XV	nujol	3280	1708	Ring
	halocarbon	3280	1708	Ring
XVI	nujol	3375	1737,1710	Ring
	halocarbon	3375	1738,1715	Ring
XVII	nujol	(Broad between	1700,1685	Chain
	halocarbon	3200-2300)	1700,1685	Chain
XVIII	nujol	3400	1685	Ring
	halocarbon	3400	1685	Ring
XIX	nujol	(Broad between	1705,1690	Chain
	halocarbon	3400-2300)	1705,1690	Chain

TABLE 2

The name and formula of the keto-acids are listed at the beginning of the experimental section.

Keto-acid	Buffer	Indicator	Wavelength (nm)
XIII	Formic Acid	Keto-Acid	255
XIV	Formic Acid	Keto-Acid	265
XV	Acetic Acid	Keto-Acid	277.5
XVI	Acetic Acid	Keto-Acid	252
XVII	Keto-Acid	Bromophenol Blue	435,590
XVIII	Acetic Acid	Keto-Acid	328
XIX	Keto-Acid	Bromocresol Green	442,614

TABLE 3

Data for the Determination of the Dissociation Constant of 2-Acetyl-4,5-dimethylbenzoic Acid at 25°C

Analytical wavelength 265 nm

dm = 0.315 Ionic strength I = 0.01M

di = 0.751 Final concentration of keto-acid = 10^{-4}M

Final total volume 100 ml.

0.1M NaOH (ml)	0.106M HCOOH (ml)	O.D.	$\frac{[HCOOH]}{[HCOO^-]}$	$1.77 \times 10^{-4} \frac{[HCOOH]}{[HCOO^-]}$	$d_i - d$	$d - d_m$	$\frac{d_i - d}{d - d_m}$
10	11	0.602	0.166	0.294	0.149	0.287	0.52
10	12	0.555	0.272	0.481	0.196	0.240	0.82
10	15	0.474	0.590	1.044	0.277	0.159	1.74
10	17	0.442	0.802	1.419	0.309	0.127	2.43
10	20	0.416	1.120	1.982	0.335	0.101	3.38
10	23	0.395	1.438	2.545	0.356	0.080	4.45
10	25	0.387	1.650	2.920	0.364	0.072	5.05
10	30	0.373	2.180	3.858	0.378	0.058	6.52

DETERMINATION OF K_a FOR 2-ACETYL-4,5-DIMETHYLBENZOIC ACID AT 25°C.

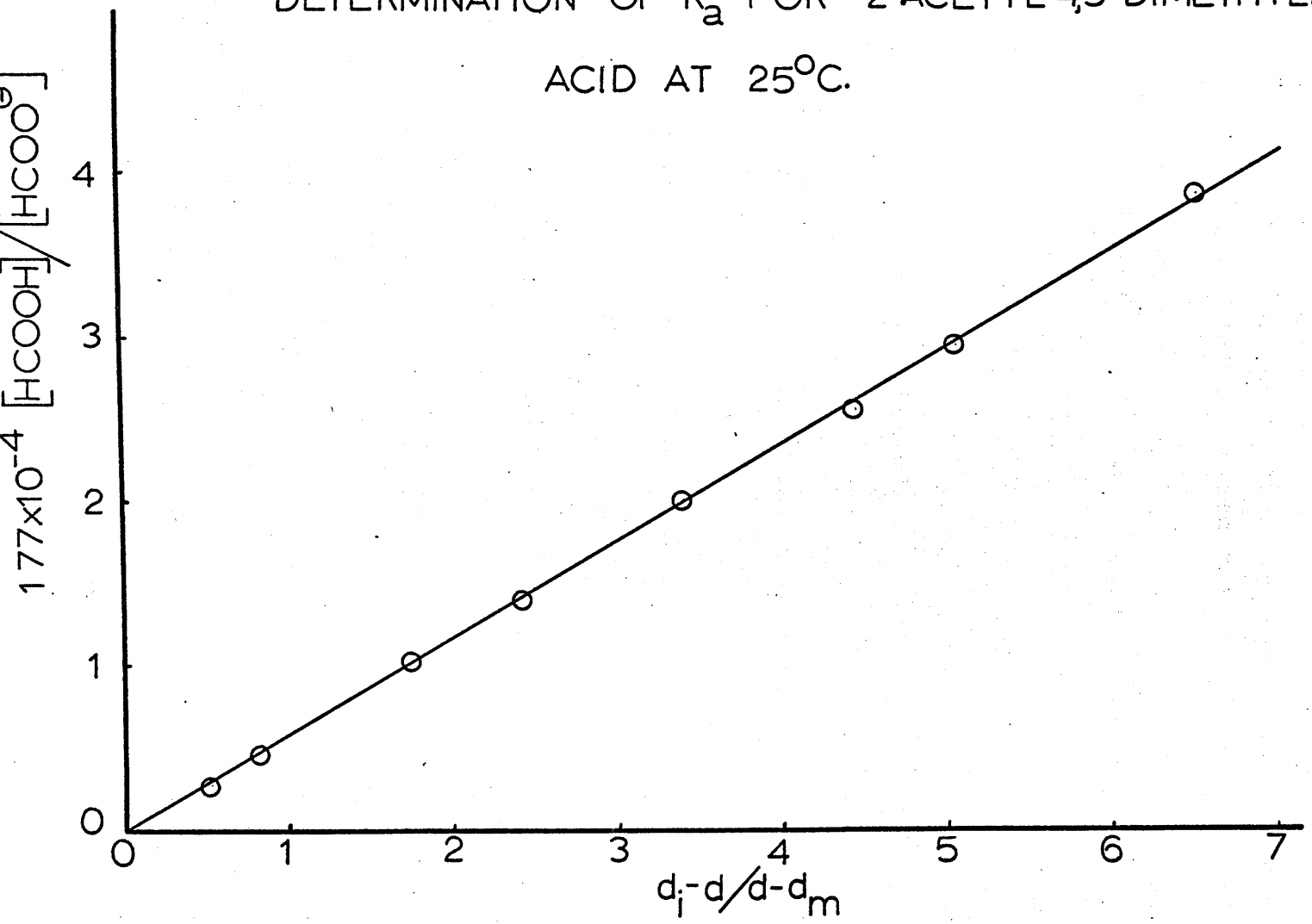


FIG. 3

TABLE 4

Data for the Determination of the Dissociation Constant of 2-Acetyl-3-naphthoic Acid at 25°C

Analytical wavelengths 435nm and 590nm

Ionic strength I = 0.001M

Final total volume 100 ml

Final concentration of keto-acid = $\sim 10^{-3}$M

Final concentration of indicator = $\sim 10^{-5}$M

d_{435} = optical density of the neutral species of the indicator

d_{590} = optical density of the ionized species of the indicator

Keto-acid (g)	0.01M NaOH (ml)	$\frac{[HA]}{[A^-]}$	d_{590}	d_{435}	$pK_{ind} - \log \frac{d_{435}}{d_{590}}$	$\log \frac{[HA]-[H^+]}{[A^-]+[H^+]}$	pK_a
0.02154	2	4.03	0.075	0.092	4.10	0.41	4.51
0.02140	3	2.33	0.101	0.085	4.26	0.26	4.52
0.02147	4	1.51	0.123	0.077	4.39	0.11	4.50
0.02156	5	1.01	0.147	0.070	4.51	- 0.05	4.46
0.02143	6	0.67	0.174	0.060	4.66	- 0.22	4.44
0.02163	7	0.44	0.213	0.050	4.83	- 0.40	4.43
0.02161	8	0.26	0.257	0.039	5.01	- 0.60	4.41

$$pK_a = 4.47 \pm 0.06$$

TABLE 5

Thermodynamic Dissociation Constants and pK_a Values at 25°C*

* Data for XII at 20°C

Keto-Acid	$10^6 K$	pK_a
X (Ref.10)	74.10	4.13
XI (Ref.31)	28.20	4.55
XII (Ref.46)	549.0	3.26
XIII	78.75	4.10
XIV	57.83	4.24
XV	37.50	4.43
XVI	20.70	4.68
XVII	33.88	4.47
XVIII	3.05	5.52
XIX	24.55	4.61

NITRAMIDE DECOMPOSITION BY THE CARBOXYLATE ION AT 25°C (Ref 48)

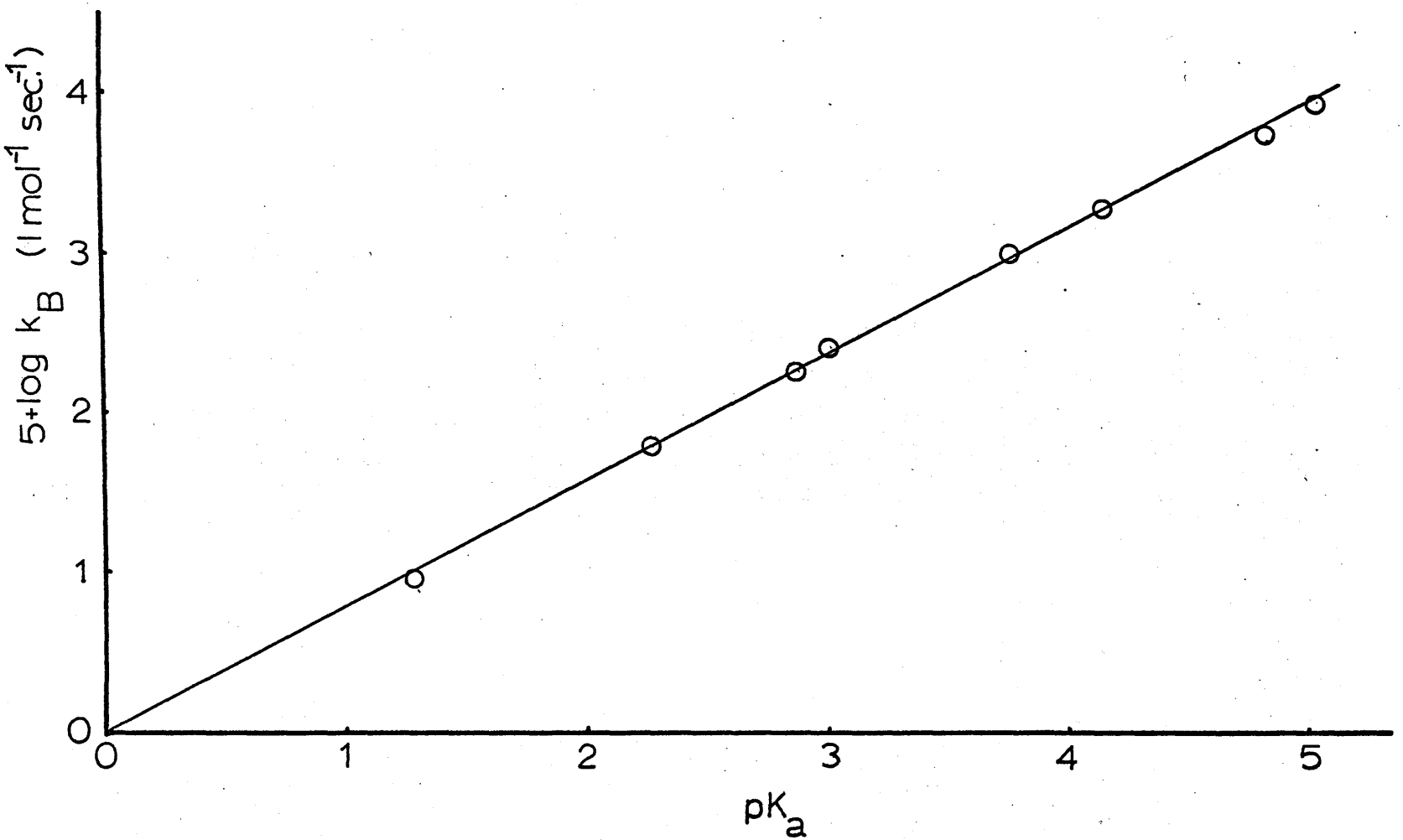


FIG 4

TABLE 6

Data obtained for the Catalysis of Nitramide Decomposition at 25°C by 2-Acetyl-3-naphthoic Acid

Concentration of anion (mol l^{-1})	0.01		0.02		0.03		0.04		0.05	
	time (min)	reading (cm)	time (min)	reading (cm)	time (min)	reading (cm)	time (min)	reading (cm)	time (min)	reading (cm)
	0	6.70	0	7.90	0	6.70	0	8.00	0	7.10
	5	7.55	2	8.52	3	7.65	2	8.85	2	7.90
	10	8.20	4	9.00	6	8.50	4	9.60	4	8.75
	15	8.80	6	9.32	10	9.50	6	10.25	7	9.80
	25	9.80	11	10.30	15	10.55	10	11.45	10	10.75
	35	10.75	15	11.10	20	11.50	16.5	13.50	15	11.90
	45	11.62	22	12.10	25	12.40	23.5	15.49	20	13.00
	55	12.48	30	13.50	30	13.20	29	16.58	25	13.98
	70	13.65	40	14.81	40	14.82	37	18.10	30	14.80
	80	14.30	50	16.11	50	16.25	45	19.25	35	15.50
	90	14.85	62	17.30	60	17.30	50	19.70	40	16.02
	105	15.60	70	18.00	71	18.20	60	20.80	50	16.89
	120	16.30	80	18.52	80	18.89	71	21.72	60	17.80
	135	16.90	90	18.95	90	19.40	80	22.40	75	18.60
	150	17.40	105	19.65	107	20.05	90	23.00	90	19.15
	180	18.30	120	20.20	129	20.70	105	23.80	120	19.70
	225	19.30	150	20.95	150	21.45	120	24.35	150	20.00
	270	20.05	180	21.35	∞	22.10	∞	25.30	∞	20.30
	∞	20.80	∞	22.60						

FIG 5

log(l_∞-l) v's time FOR THE DECOMPOSITION OF NITRAMIDE BY AN AQUEOUS SOLUTION OF 0·04M 2-ACETYL-3-NAPHTHOIC ACID AT 25°C.

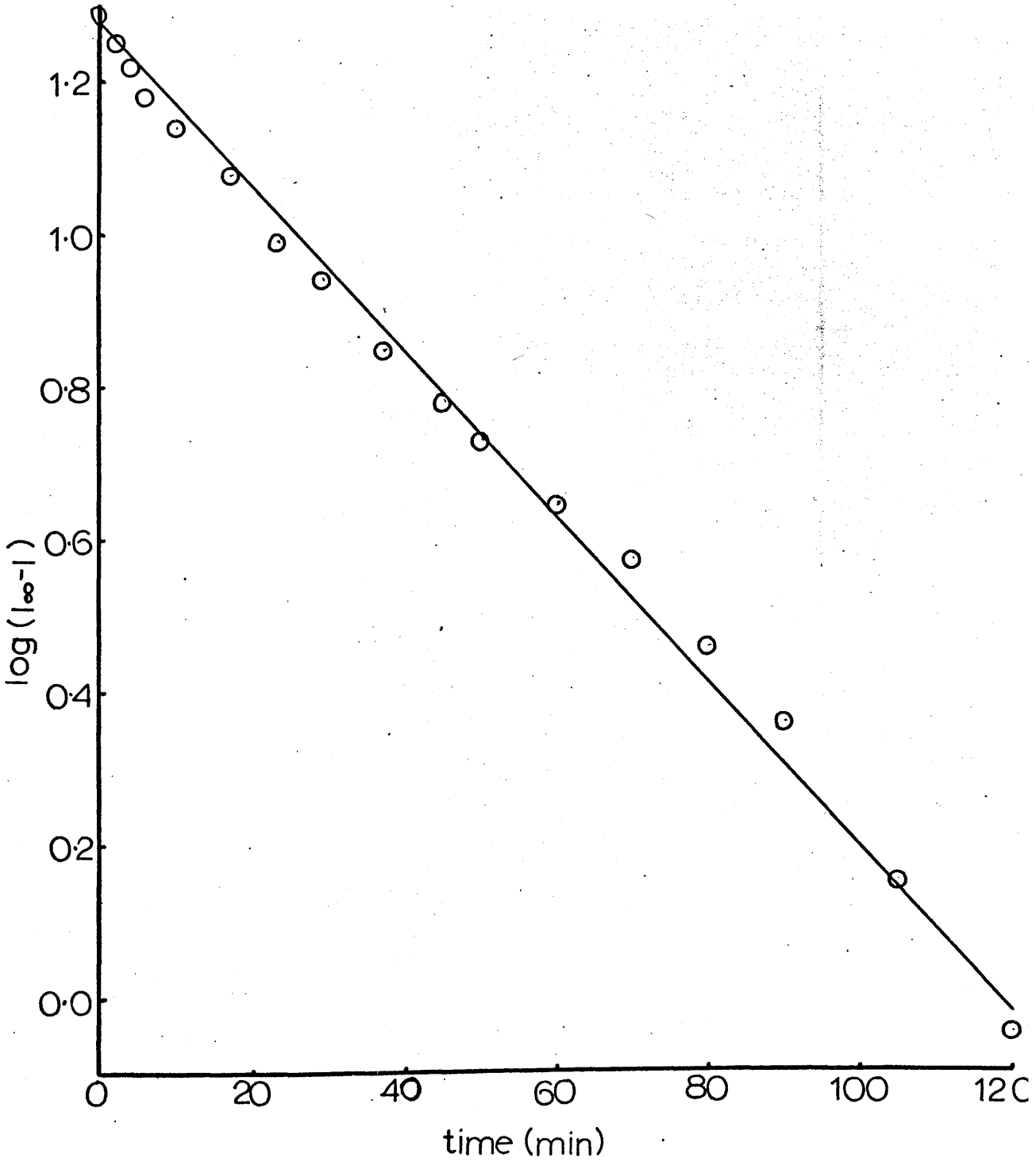


FIG 6

CATALYSIS OF NITRAMIDE DECOMPOSITION BY 2-ACETYL-3-NAPHTHOIC ACID AT 25°C

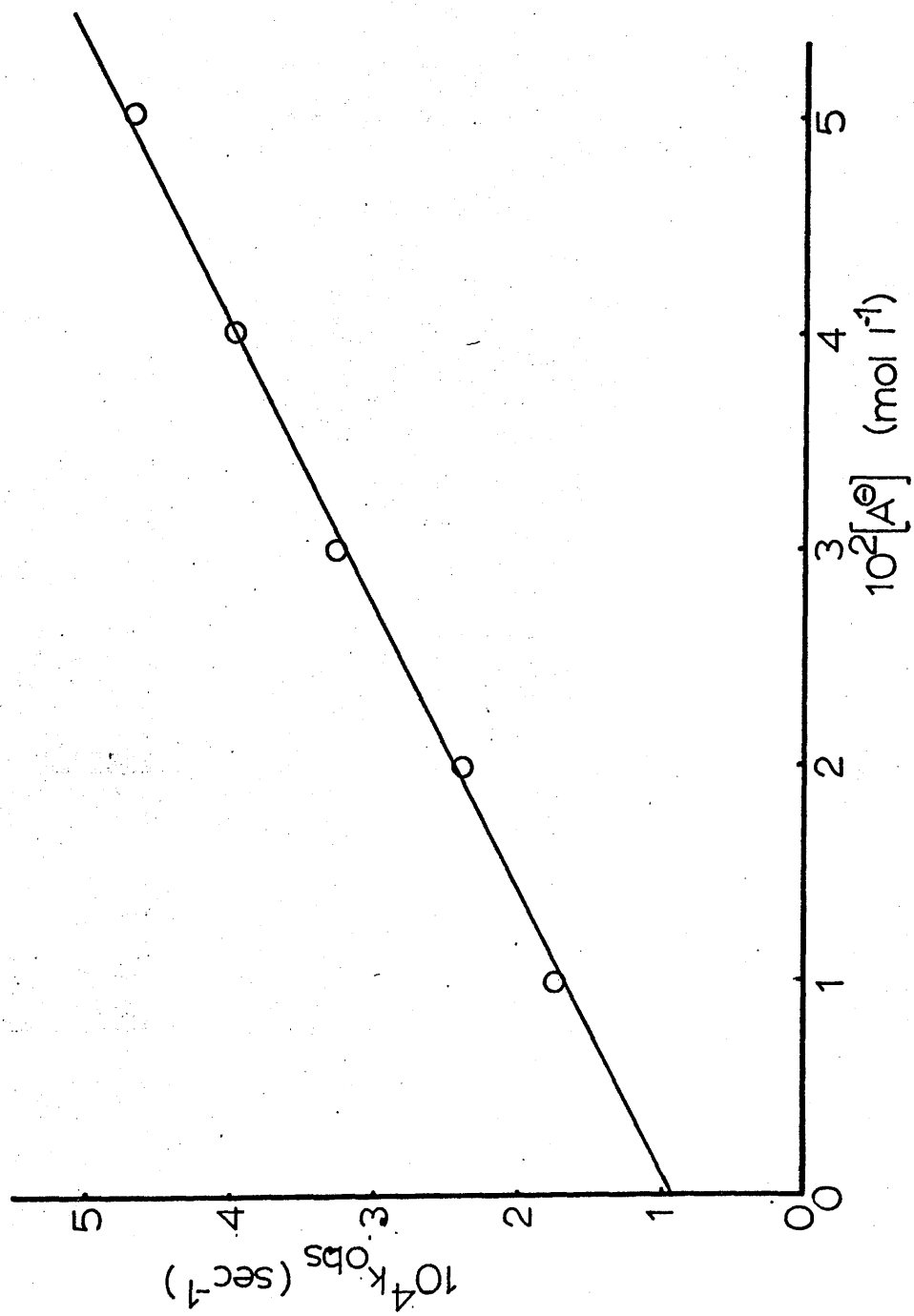


TABLE 7

Catalysis of Nitramide Decomposition at 25°C

k = first-order velocity constant in s^{-1}

$[A^-]$ = concentration of keto-acid anion, mol l^{-1}

* Results by B. G. Cox.

Ortho-acetylbenzoic acid (X)*

$$k_{calc} = 4.7 \times 10^{-5} + 6.27 \times 10^{-3}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
$10^6 k$	obs	175	309	431	538	667
	calc	172	298	423	549	674

$$K_a^T = 3.09 \times 10^{-4}, \quad pK_a^T = 3.51$$

Ortho-isobutyrylbenzoic acid (XI)

$$k_{calc} = 12.2 \times 10^{-5} + 6.16 \times 10^{-3}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
$10^6 k$	obs	248	370	496	592	753
	calc	245	368	492	615	738

$$K_a^T = 2.10 \times 10^{-4}, \quad pK_a^T = 3.68$$

2-Acetyl-3-nitrobenzoic acid (XII)

$$k_{calc} = 6.2 \times 10^{-5} + 2.71 \times 10^{-3}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
$10^6 k$	obs	123	168	228	251	352
	calc	116	170	224	279	333

$$K_a^T = 8.32 \times 10^{-4}, \quad pK_a^T = 3.08$$

(TABLE 7 continued)

2-Acetyl-3,4,5,6-tetrachlorobenzoic acid (XIII)

$$k_{calc} = 8.9 \times 10^{-5} + 2.33 \times 10^{-3}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	284	308	344	419	461
	calc	270	317	364	410	457

$$K_a^T = 1.00 \times 10^{-3},\ pK_a^T = 3.00$$

2-Acetyl-4,5-dimethylbenzoic acid (XIV)

$$k_{calc} = 11.2 \times 10^{-5} + 7.61 \times 10^{-3}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	262	449	548	673	911
	calc	264	416	569	721	873

$$K_a^T = 2.24 \times 10^{-4},\ pK_a^T = 3.65$$

2-Acetyl-4,5-dimethoxybenzoic acid (XV)

$$k_{calc} = 5.9 \times 10^{-5} + 7.3 \times 10^{-3}[A^-]$$

$10^3[A^-]$		10	20	30	40	50
10^6k	obs	120	214	288	352	416
	calc	132	205	278	351	424

$$K_a^T = 2.34 \times 10^{-4},\ pK_a^T = 3.63$$

(TABLE 7 continued)

2-Acetyl-6-methylbenzoic acid (XVI)

$$k_{calc} = 12.8 \times 10^{-5} + 5.25 \times 10^{-3}[A^-]$$

$10^3[A^-]$		16	32	48	64	78.4
10^6k	obs	198	311	381	480	524
	calc	213	297	381	465	540

$$K_a^T = 3.55 \times 10^{-4},\ pK_a^T = 3.45$$

2-Acetyl-3-naphthoic acid (XVII)

$$k_{calc} = 9.8 \times 10^{-5} + 7.52 \times 10^{-3}[A^-]$$

$10^3[A^-]$		10	20	30	40	50
10^6k	obs	175	239	331	401	470
	calc	173	248	323	398	474

$$K_a^T = 2.29 \times 10^{-4},\ pK_a^T = 3.64$$

Trans-2-acetylcyclohexanecarboxylic acid (XIX)

$$k_{calc} = 12.1 \times 10^{-5} + 26.03 \times 10^{-3}[A^-]$$

$10^3[A^-]$		4	8	12	16	20
10^6k	obs	138	226	355	447	548
	calc	135	239	343	447	551

$$K_a^T = 4.68 \times 10^{-5},\ pK_a^T = 4.33$$

FIG 7

MUTAROTATION OF GLUCOSE BY THE CARBOXYLATE ION AT 18°C (Ref 51)

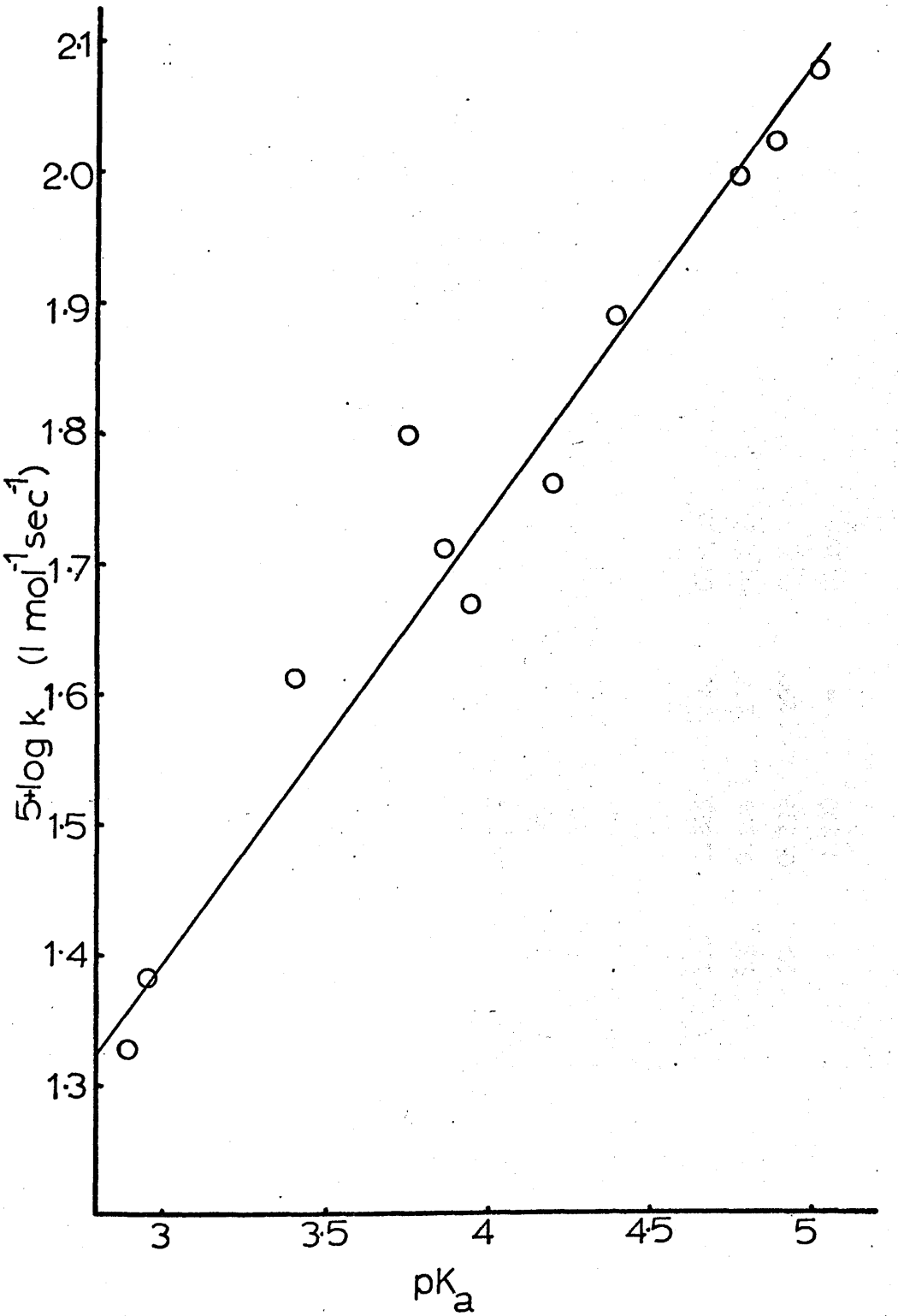


TABLE 8

Data obtained for Catalysis of Glucose Mutarotation at 18°C by 2-Acetyl-4,5-dimethylbenzoic Acid

Concentration of anion (mol l^{-1})	0.02		0.04		0.06		0.08		0.1	
	time (min)	reading °	time (min)	reading °	time (min)	reading °	time (min)	reading °	time (min)	reading °
	0	0.435	0	0.388	0	0.385	0	0.428	0	0.408
	10	0.418	10	0.365	10	0.360	10	0.404	10	0.378
	20	0.400	20	0.343	20	0.338	20	0.383	20	0.350
	30	0.386	30	0.327	30	0.320	30	0.368	30	0.328
	40	0.373	40	0.308	40	0.305	40	0.353	40	0.313
	50	0.363	50	0.294	50	0.288	50	0.340	50	0.295
	60	0.353	60	0.283	60	0.275	60	0.328	60	0.283
	70	0.344	70	0.273	70	0.265	70	0.318	70	0.273
	80	0.336	80	0.265	80	0.255	80	0.310	80	0.259
	90	0.330	90	0.255	100	0.242	90	0.303	100	0.245
	110	0.318	110	0.241	120	0.230	100	0.298	120	0.233
	120	0.315	120	0. 231	140	0.222	120	0.287	140	0.225
	150	0.304	150	0.225	160	0.215	150	0.275	160	0.218
	200	0.293	200	0.210	190	0.208	180	0.270	220	0.208
	∞	0.280	∞	0.195	∞	0.193	∞	0.255	∞	0.204

FIG 8

log(l_∞-l) vs time FOR THE MUTAROTATION OF GLUCOSE BY AN AQUEOUS SOLUTION OF 0·02M 2-ACETYL-4,5-DIMETHYLBENZOIC ACID AT 18°C

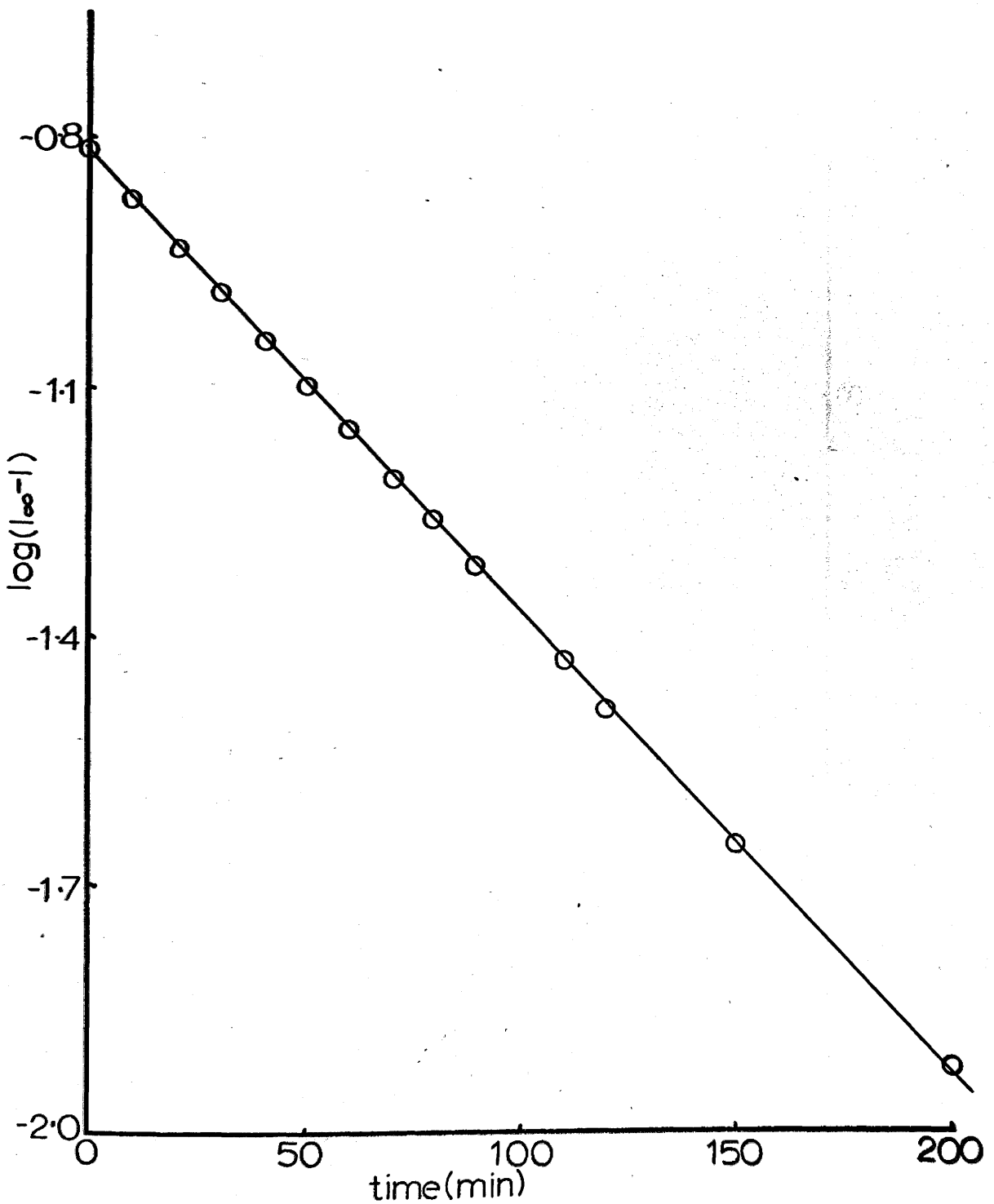


FIG 9

CATALYSIS OF GLUCOSE MUTAROTATION BY 2-ACETYL-4,5-DIMETHYLBENZOIC ACID AT 18°C

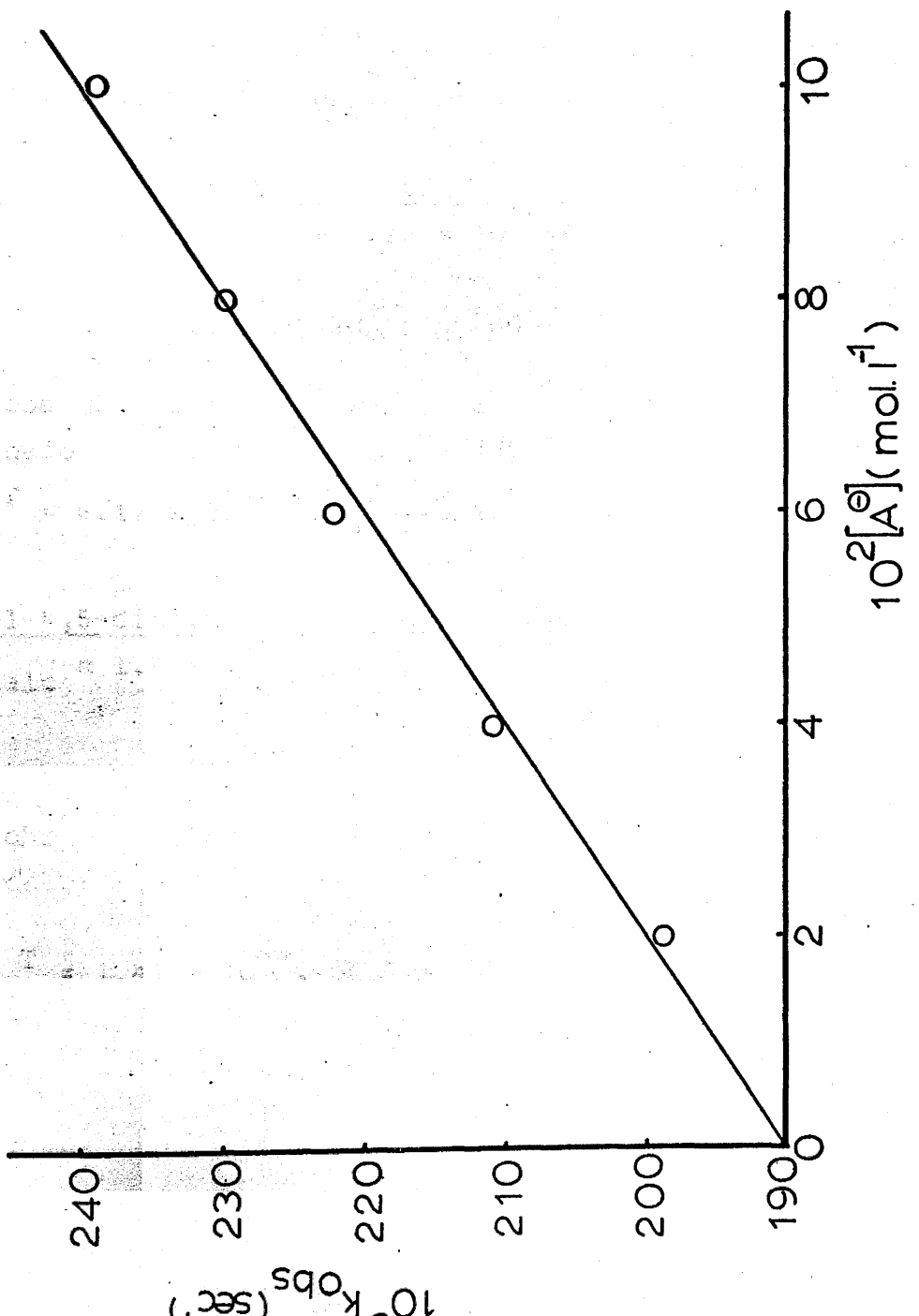


TABLE 9

Catalysis of Glucose Mutarotation at 18°C

k = first-order velocity constant in s^{-1}

* B. G. Cox.

$[A^-]$ = concentration of keto-acid anion, mol l^{-1}

Ortho-acetylbenzoic acid (X)*

$$k_{calc} = 1.9 \times 10^{-4} + 4.6 \times 10^{-4}[A^-]$$

$10^3[A^-]$		40	80	120	160	200
10^6k	obs	208	225	246	259	276
	calc	208	227	245	254	282

$$K_a^T = 1.82 \times 10^{-4}, \quad pK_a^T = 3.74$$

2-Acetyl-3-nitrobenzoic acid (XII)

$$k_{calc} = 1.8 \times 10^{-4} + 3.15 \times 10^{-4}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	187	192	200	205	212
	calc	186	193	199	205	212

$$K_a^T = 6.17 \times 10^{-4}, \quad pK_a^T = 3.21$$

2-Acetyl-4,5-dimethylbenzoic acid (XIV)

$$k_{calc} = 1.9 \times 10^{-4} + 4.95 \times 10^{-4}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	199	211	222	230	239
	calc	200	210	220	230	240

$$K_a^T = 1.41 \times 10^{-4}, \quad pK_a^T = 3.85$$

(TABLE 9 continued)

2-Acetyl-4,5-dimethoxybenzoic acid (XV)

$$k_{calc} = 3.1 \times 10^{-4} + 3.9 \times 10^{-4}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	315	323	332	337	347
	calc	315	323	330	338	346

$$K_a^T = 3.16 \times 10^{-4},\ pK_a^T = 3.49$$

Trans-2-acetylcyclohexanecarboxylic acid (XIX)

$$k_{calc} = 2.8 \times 10^{-4} + 8.9 \times 10^{-4}[A^-]$$

$10^3[A^-]$		20	40	60	80	100
10^6k	obs	298	312	335	350	368
	calc	297	315	332	350	368

$$K_a^T = 2.69 \times 10^{-4},\ pK_a^T = 4.57$$

DISCUSSION

Analysis of Infra-red Data

Ideally the ring and chain structures should exhibit characteristically different spectra. The ring structure should show a typical -OH stretching frequency while the carbonyl bands for the ring and chain tautomers would differ in position and number. In practice this situation is not realized and it is only possible to obtain qualitative results.

In this work it has been assumed that the absence of a normal -OH absorption band indicates the chain structure in the solid state. The infra-red spectra of 2-acetyl-3-naphthoic acid, 2-acetyl-3-nitrobenzoic acid and trans-2-acetyl-cyclohexanecarboxylic acid each show a broad absorption band between ~3300 cm^{-1} to ~2350 cm^{-1} which was attributed to the keto-acid dimer. Therefore it was deduced from the spectra of these three keto-acids that they exist as the chain tautomer in the solid state. In all the other cases studied the results indicated that the keto-acids exist in the cyclic form as the typical -OH stretching absorption was observed in the frequency range 3400 cm^{-1} to 3265 cm^{-1}. The carbonyl stretching frequencies were observed in the expected range for all the keto-acids. In the majority of cases two bands were observed, the higher being attributed to the lactone carbonyl stretching frequency and the lower to the stretching of the carbonyl associated with the carboxyl and/or acetyl groups. The results are not in complete agreement with those obtained by other workers.

-OH Stretching Frequency. For 2-acetyl-3,4,5,6-tetrachlorobenzoic acid a band at 3180 cm^{-1} has been reported for the solid state (19). However, in the present work, a band was observed between 3600 cm^{-1} and 3100 cm^{-1} with a maximum at 3400 cm^{-1} to 3300 cm^{-1}. A broad band between 3200 cm^{-1} and 2400 cm^{-1}, attributed to dimerization, was observed for the 3-nitro derivative but no definite maximum could be assigned unlike the reported value (19) for this keto-acid of 2950 cm^{-1} for the solid. A band at 3375 cm^{-1}, 25 cm^{-1} higher than that previously recorded, as a liquid film, (19) was observed for the 6-methyl derivative.

C=O Stretching Frequency. For the keto-acids listed below two bands were observed where only one has been previously reported (19). This has been interpreted as the separation of the lactone carbonyl band from the other carbonyl stretching frequencies.

Keto-acid	reported C=O frequency	observed C=O frequency
X	1725 cm^{-1} (solid)	1735, 1725 cm^{-1}
XIII	1755 cm^{-1} (solid)	1770, 1750 cm^{-1}
XVI	1750 cm^{-1} (liquid film)	1737, 1710 cm^{-1}

Analysis of K_a Data

Correlation of these 'mixed' acid dissociation constant values with substituent effects is impossible because of the existence of a ring tautomer.

Analysis of K_a^T Data

The values of the 'true' acid dissociation constants have been obtained from kinetic studies of the decomposition of nitramide and the mutarotation of glucose catalysed by the keto-acid anion in aqueous solution. It has been assumed that the anion of the keto-acid is always acyclic (11) which means that these dissociation constants refer to the keto-acid as if it existed entirely as the chain tautomer.

The values obtained from catalysis of the decomposition of nitramide are considered to be more accurate. Catalysis of the mutarotation of glucose suffers from three disadvantages.

(a) the points on the plot of log k_B against pK_a are more scattered than is the case for nitramide. This could be due to steric hindrance resulting from the relatively large bulk of the glucose molecule.

(b) the catalytic constant is rather insensitive to the basic strength of the catalyst (β in the Brönsted equation is 0.40 compared with 0.80 for the nitramide decomposition).

(c) the water catalysed reaction makes a considerable contribution to the observed velocity.

The acid dissociation constants have only been determined in a few cases by catalysis of the mutarotation of glucose, purely as a check on the values obtained by the catalysis of the decomposition of nitramide. Despite the above disadvantages there is favourable agreement between the values obtained by both methods.

It might be suggested that the ion of the ring tautomer may be present at a very low concentration and contribute appreciably to the observed catalysis because of its high basic strength.

Let HX and HY represent the chain and ring tautomers respectively, X^- and Y^- represent the corresponding anions and k_x and k_y the catalytic constants for these species. The rate of decomposition of nitramide or mutarotation of glucose is represented by the equation

$$k = k_o + k_x[X^-] + k_y[Y^-] \qquad (3)$$

where k_o is the spontaneous rate of decomposition or mutarotation.

If we assume that

$$k_y/k_x = (K_{HX}/K_{HY})^{\beta}$$

where K_{HX} and K_{HY} are the acid dissociation constants for the chain and ring tautomers respectively then substituting for k_y in equation (3) gives

$$k = k_o + k_x[X^-] + k_x(K_{HX}/K_{HY})^{\beta}[Y^-] \qquad (4)$$

By definition

$$K_{HX} = [H^+][X^-]/[HX]$$

and

$$K_{HY} = [H^+][Y^-]/[HY]$$

which gives

$$[Y^-] = (K_{HY}[HY][X^-])/(K_{HX}[HX])$$

Substituting for $[Y^-]$ in equation (4) gives

$$k = k_o + k_x[X^-] + k_x(K_{HX}/K_{HY})^{\beta}[X^-](K_{HY}/K_{HX})[HY]/[HX])$$

As $K_e = [HY]/[HX]$

we obtain

$$k = k_o + k_x[X^-]\left[1 + K_e(K_{HY}/K_{HX})^{1-\beta}\right] \qquad (5)$$

The β values for the two catalytic reactions studied are very different (0.40 and 0.80) and the fact there is agreement between the two methods is evidence that the third term in equation (5) is small, so that

$$k \simeq k_o + k_x[X^-]$$

This conclusion is supported by considering the probable value of K_{HY}. A reasonable model for the cyclic tautomer is methylene glycol which has a reported pK_a value of 13.3 (52). Substituting this value into equation (5) together with the known values of K_e and K_{HX} gives a value of approximately 10^{-10}. This means that $k_y[Y^-]$ contributes a negligible quantity to the value of k.

Equilibrium Constant, K_e, for Ring-Chain Tautomerism

From the values of the 'mixed' acid dissociation constants, K_a, and the 'true' acid dissociation constants, K_a^T, the equilibrium constant, K_e, for each keto-acid can be determined.

If it is assumed that

$$K_a = [H^+][A^-]/([AH]_c + [AH]_r)$$

where $[AH]_c$ = concentration of the acid in the chain form

$[AH]_r$ = concentration of the acid in the ring form

and $K_a^T = [H^+][A^-]/[AH]_c$

then combining these two expressions gives

$$K_a([AH]_c + [AH]_r) = K_a^T[AH]_c$$

$$\therefore \quad K_a^T/K_a = ([AH]_r/[AH]_c) + 1$$

$$\therefore \quad pK_a^T = pK_a - \log(K_e + 1)$$

where $[AH]_r/[AH]_c = K_e$.

From the values of K_e the percentage of the keto-acid in the ring and chain forms can be calculated. The equilibrium constant and percentage ring tautomer, for each keto-acid in aqueous solution, are listed in table 10.

Jones and Desio (19) have obtained, by N.M.R. techniques, quantitative data for four of the keto-acids studied here. For 2-acetyl-3-nitrobenzoic acid a value of 34% ring tautomer is obtained from K_a and K_a^T data. This figure is lower than that obtained by Jones and Desio who report that 57% is in the ring form. The same workers have reported that the tetrachloro- and 6-methyl-derivatives are predominantly in the ring form and this is in agreement with the present work where values of 92% and 94% respectively have been obtained. Again there is reasonable agreement for ortho-acetylbenzoic acid, 80% ring being reported and 76% being calculated from the present work. It must be remembered, however, that the present results were determined in aqueous solution while those of Jones and Desio were determined in chloroform solution. The tautomeric equilibrium for each keto-acid need not be the same in the two solutions although it has been reported (24) that K_e appears to be relatively insensitive to changes in the medium.

If ortho-acetylbenzoic acid is taken as reference then it is interesting to note that those keto-acids whose added substituents do not interfere sterically with the acetyl and carboxyl groups already present have similar percentages of ring tautomer present at equilibrium. Ortho-isobutyryl-benzoic acid may also be added to this list as it seems likely that the methyls of the isopropyl group do not interfere with the carboxyl group. For these five keto-acids the

TABLE 10

Equilibrium constant and percentage ring tautomer in aqueous solution

Keto-acid	K_e	% ring tautomer
X	3.2	76
XI	5.6	85
XII	0.52	34
XIII	12.0	92
XIV	2.9	74
XV	5.1	84
XVI	16.0	94
XVII	6.3	86
XIX	0.91	47

percentage of ring tautomer ranges from 74 - 86%. As soon as groups are substituted in the ring that interfere sterically with either the acetyl or carboxyl groups then the percentage in the ring form at equilibrium falls outside this range. Substitution of a methyl group adjacent to the carboxyl group seems to be very effective in forcing the molecule into the cyclic structure. This suggests that the steric strain between the methyl and carboxyl groups is partially relieved by cyclization rather than by twisting of the carboxyl group out of the plane of the benzene ring. This indicates that the loss of resonance stabilization is less in forming the cyclic tautomer than in twisting of the carboxyl group.

Substitution in the 3-position appears to have the reverse effect. The presence of a nitro group in the 3-position results in the preferential twisting of the acetyl group out of the plane of the benzene ring (10). This would be expected to inhibit the formation of the cyclic tautomer and so result in a high percentage of the chain tautomer as was observed (66%). This suggests that the keto-acid remains in the chain conformation rather than taking up the cyclic conformation because this will result in the minimum loss in resonance stabilization.

The tetrachloro derivative also has a large proportion of the acid in the cyclic form at equilibrium. In this case there is the possibility of steric effects from chlorine atoms in both the 3- and 6-positions. A chlorine in the 6-position will have the same steric influence as a methyl group in this position because of the similar van der Waals radii for the two substituents (values of 1.80 and 2.0Å for the van der Waals radii of the chlorine atom and the methyl group respectively). This would result in preferential cyclization. Opposing this will be steric interaction between a chlorine atom in the 3-position and the methyl of the acetyl group. If the molecule were to remain totally as the chain tautomer then there would be loss of resonance stabilization from both the acetyl and carboxyl groups. However this is not

the case and it is suggested that cyclization is preferred because the resulting planar cyclic conformation will still possess some resonance stabilization through the carbonyl of the lactone ring.

Calculation from the values obtained for the 'mixed' and 'true' acid dissociation constant of trans-2-acetylcyclohexanecarboxylic acid show that this keto-acid exists approximately in the ratio 1:1 ring to chain tautomer. No examples could be found in the literature for values of K_e for similar compounds although it is known that trans-2-para-bromo-benzoylcyclohexanecarboxylic acid can form a pseudo cyclic acetate (53).

CHAPTER 3

INTER- AND INTRAMOLECULAR CATALYSIS

INTRODUCTION

Catalysis of ionization or enolization of ketones has been thoroughly studied and ample information concerning intermolecular general acid-base catalysis is available (54,55). In the present system, for self buffered solutions and acetic acid-sodium acetate buffered solutions, we have both intra- and intermolecular catalysis effected either by a carboxylic acid group (acid catalysis) or by the corresponding anion (base catalysis) the rate determining step being the formation of the enol or enolate ion either of which reacts rapidly with halogen. In the case of pyridine buffered solutions intermolecular base catalysis can be effected by the pyridine molecule and acid catalysis by the corresponding cation.

Intermolecularly Catalysed Halogenation of Ketones

Acid Catalysis. The accepted mechanism for acid catalysed halogenation is

$$>CH - \overset{O}{\overset{\|}{C}} - + \Sigma A_i \rightleftharpoons >CH - \overset{OH^+}{\overset{\|}{C}} - + \Sigma B_i \rightleftharpoons >C = \overset{OH}{\overset{|}{C}} - + \Sigma A_i$$

$$>C = \overset{OH}{\overset{|}{C}} - + X_2 \rightarrow >CX - \overset{O}{\overset{\|}{C}} - + X^- + H^+$$

where A_i is the acid labelled i, B_i is the conjugate base and X is a halogen. This reaction can be written in an abbreviated form, as follows:-

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

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

where SH and HS are the ketone and enol respectively, HSH^+ the conjugate acid of the ketone and k(subscript) the first-order constant for the particular process, provided that the concentration of ΣA_i and ΣB_i remain effectively constant.

For ketones, k_1, k_{-1} and k_3 are all fast so that an equilibrium quantity of HSH^+ is rapidly achieved. The HSH^+ reacts slowly with ΣB_i to form the reactive enol which is very rapidly removed by the irreversible halogenation step k_3. The observed velocity is represented by

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

$$= [SH]\Sigma\pi_i'[B_i][HSH^+]/[SH]$$

The observed first-order velocity constant is therefore

$$k_{obs} = \Sigma\pi_i'[B_i][HSH^+]/[SH]$$

Since $K_{HSH^+} = [H^+][SH]/[HSH^+]$

and for an acid A_i

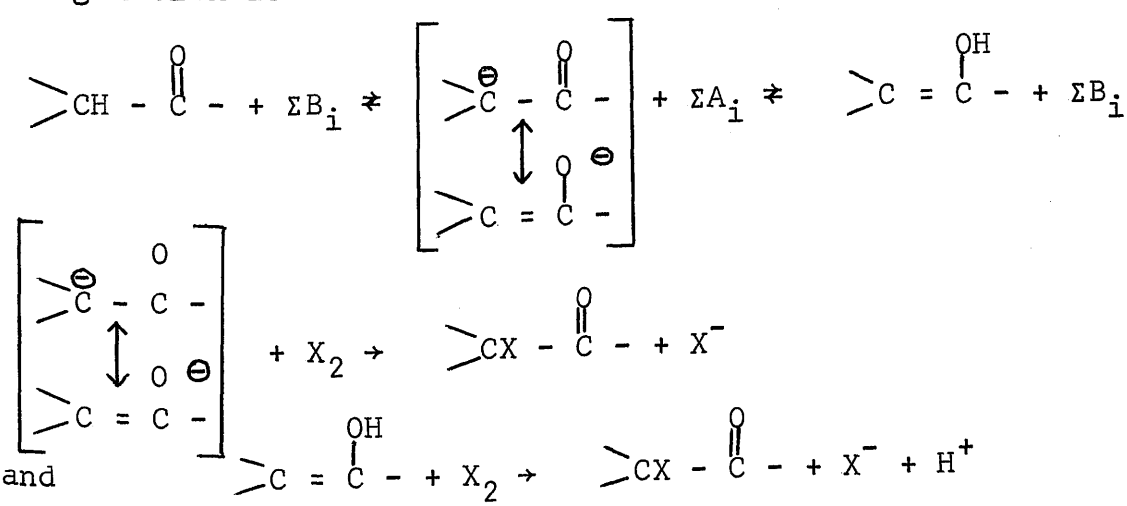
$$[H^+] = K_i[A_i]/[B_i]$$

then the observed first-order velocity constant becomes

$$k_{obs} = \Sigma\pi_i'[A_i]K_i/K_{HSH^+}$$

where π_i' is the catalytic rate constant for the base B_i. General acid catalysis is observed and the reaction is zero-order in halogen.

Base Catalysis. The accepted mechanism for the base catalysed halogenation is



and

which can be abbreviated, as before, giving

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

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

$$HS + X_2 \xrightarrow{k_4} SX + X^- + H^+$$

The rate determining step, except for the case of very low halogen concentrations (56), is the proton transfer from carbon to form the enolate ion (step 1). Therefore the observed velocity is given by

$$v_{obs} = \Sigma k_1 [B_i] [SH]$$

and the observed first-order velocity constant is

$$k_{obs} = \Sigma k_1 [B_i]$$

which is zero-order in halogen.

Intramolecularly Catalysed Halogenation of Ketones

Very little has been published on intramolecular acid-base catalysis of ketones. The bromination and racemization of 2(o-carboxybenzyl)-indanone (57,58), the bromination of levulinic acid (59) and the iodination of levulinic acid in the presence of glycine catalyst (60) have been studied but the results were not interpreted in terms of intramolecular catalysis. However, intramolecular base catalysis in the ionization of a series of aliphatic keto-acids using iodine as a scavenger, was reported by Bell and Fluendy (8) and their results will now be considered.

The aliphatic keto-acids studied can be represented by the general formula $CH_3CO(CH_2)_nCOOH$ where n = 2,3,4 and 5.

TABLE 11

n = number of methylene groups

k = first-order velocity constant

n	$10^8 k$ (sec^{-1})
2	29.8
3	179.0
4	7.2
5	3.4

It can be seen from table 11 that the velocity constant for the base catalysed ionization is at a maximum for 5-keto hexanoic acid. It is believed that a proton from the methylene group adjacent to the carbonyl is removed in preference to a methyl proton (8,61) and recent evidence by Covington (62) tends to support this fact. This means that a 6-membered cyclic transition state (including the proton being transferred) is involved. In the ionization of 6-keto heptanoic acid there is a 7-membered cyclic transition state and as might be expected the observed rate is much slower.

It has been shown by Harper and Bender in their study of ortho-isobutyrylbenzoic acid (31) that in a more rigid system, in which the acetyl and carboxyl groups have a favourable orientation, there is a marked increase in the rate of intramolecular base catalysis when compared to the more flexible aliphatic system. A velocity constant for the intramolecular base catalysed process of 5×10^{-6} sec^{-1} was observed, a 7-membered cyclic transition state being involved. This represents a rate enhancement of about 70 when compared to 6-keto heptanoic acid. This rate enhancement can be explained in terms of the loss of internal rotational motions in going from the aliphatic to the aromatic system which results in a lowering of the free energy of activation (63) or different acidities of the ketones involved.

If the results for the general base catalysed iodination of acetophenone and isobutyrophenone are compared it is found that the methyl ketone is iodinated faster than the isopropyl ketone (64). However Harper and Bender noted that ortho-acetylbenzoic acid iodinated at a slower rate than ortho-isobutyrylbenzoic acid. This they explained in terms of a reduction in the entropy of activation for ortho-isobutyrylbenzoic acid due to steric assistance of the isopropyl group, the lone α-hydrogen being directly adjacent to the ortho-carboxylate ion. Opposing this is a retarding influence of the α-alkyl groups of the ortho-isobutyrylbenzoic acid which is explained as an inductive effect although the effect of the alkyl groups on the stability of the intermediate enolate ion should also be considered. Calculation indicates that the steric assistance overrides the inductive effect. This is in accordance with the observed results, the ortho-isobutyrylbenzoate ionization being faster by a factor of about 2.5.

A detailed kinetic study of ortho-acetylbenzoic acid has not been reported. It is the purpose of this thesis to rectify this and to extend the work to other closely related systems.

General Rate Expressions for the Ionization of Keto-Acids

A number of intramolecular and intermolecular processes can be considered for self buffered solutions of keto-acids.

Reaction	Substrate	Catalyst
1	A^-	intramolecular
2	HA	intramolecular
3	A^-	A^-
4	HA	HA
5	HA	A^-
6	A^-	HA
7	HA	H_3O^+
8	A^-	H_3O^+
9	HA	OH^-
10	A^-	OH^-
11	HA	H_2O
12	A^-	H_2O

where HA and A^- represent the keto-acid and the corresponding anion respectively.

A rate expression of the form

$$v = k_1[A^-] + k_2[HA] + k_3[A^-]^2 + k_4[HA]^2 + (k_5+k_6)[HA][A^-]$$
$$+ [H_3O^+](k_7[HA] + k_8[A^-]) + [OH^-](k_9[HA] + k_{10}[A^-])$$
$$+ [H_2O](k_{11}[HA] + k_{12}[A^-])$$

can be written where v represents the observed velocity of iodination and k(subscript) the first-order and second-order velocity constants for the particular process. Comparison with work on related systems suggest that many of the catalytic processes contribute little to the observed rate and that a simplified rate expression may be written in which only intramolecular catalysis due to the carboxylate anion is considered

$$\text{i.e.} \quad v = k_1[A^-]$$

The calculated rate constants have been obtained using this simplified expression which will be justified in detail when discussing the results obtained for ortho-acetylbenzoic acid. Hence the first-order velocity constants have been obtained by dividing the rate of disappearance of iodine (v in mol l^{-1} sec^{-1}) by the concentration of the anion.

When the pH of the solution is less than 6 the stoicheiometric concentration of the anion must be corrected by adding $[H^+]$. The hydrogen ion concentration was calculated from the thermodynamic dissociation constant and activity coefficients calculated from the Davies Equation:

$$-\log f_{\pm} = (0.5\sqrt{I}/(1 + \sqrt{I})) - 0.2I$$

where I is the ionic strength and $f_{\pm}$ the activity coefficient.

By definition

$$K_c = K_a/f_{\pm}^2$$

where K_a is the thermodynamic dissociation constant and

K_c is the dissociation constant at a given ionic strength.

Let α and β denote the stoicheiometric concentrations of HA and A^- respectively, a and b the true concentrations of HA and A^- respectively and h the hydrogen ion concentration.

$$a = \alpha - h \quad \text{and} \quad b = \beta + h$$

Hence $$K_c = hb/a = h(\beta + h)/(\alpha - h)$$

which gives

$$h = -[(\beta + K_c) + \sqrt{(\beta + K_c)^2 + 4K_c\alpha}]/2$$

Knowledge of the hydrogen ion concentration enables calculation of the true concentrations of the acid and anion in the reaction system and therefore the effective buffer ratio.

Harper and Bender in their study of ortho-isobutyryl-benzoic acid failed to detect any intermolecular catalysis in the presence of acetate buffers. They considered this to be due to steric interference between the isopropyl and carboxylate groups resulting from the lone α-hydrogen being directly adjacent to the ortho-carboxylate ion. Such interference would effectively shield the α-hydrogen from approaching catalytic species. There is no steric interference with the ortho-acetylbenzoate ion and therefore intermolecular catalysis is observed.

For solutions of ortho-acetylbenzoic acid buffered by acetic acid-sodium acetate four intermolecular processes can be written as given below:

Reaction	Substrate	Catalyst
13	A^-	AcO^-
14	HA	AcO^-
15	A^-	AcOH
16	HA	AcOH

This gives a rate expression of the form

$$v = k_1[A^-] + k_{13}[AcO^-][A^-] + k_{14}[AcO^-][HA] + k_{15}[AcOH][A^-] + k_{16}[AcOH][HA]$$

where AcOH and AcO^- refer to acetic acid and acetate ion respectively. The other symbols have been described earlier

in this section. The above rate expression is an extension of the simplified rate expression obtained for self buffered solutions.

By definition

$$AcOH \overset{K_1}{\rightleftharpoons} H^+ + AcO^-$$

$$HA \overset{K_2}{\rightleftharpoons} H^+ + A^-$$

and therefore

$$H^+ = K_1[AcOH]/[AcO^-]$$
$$= K_1 r$$

where K_1 and K_2 represent the dissociation constants for acetic acid and the keto-acid respectively at an ionic strength of 0.3M and r represents the buffer ratio [acetic acid]/[sodium acetate].

Hence

$$[HA]/[A^-] = [H^+]/K_2 = K_1 r/K_2$$

Let a represent $HA + A^-$, then

$$[A^-]/a = K_2/(K_2 + K_1 r)$$

and

$$[HA]/a = K_1 r/(K_2 + K_1 r)$$

The rate expression can now be written as

$$v/a = (k_1 K_2 + k_{13} K_2 [AcO^-] + k_{14} K_1 r [AcO^-] + k_{15} K_2 r [AcO^-]$$
$$+ k_{16} K_1 r [AcOH])/(K_2 + K_1 r)$$

which simplifies to

$$v(K_2 + K_1 r)/a = k_1 K_2 + [AcO^-](k_{13} K_2 + k_{14} K_1 r + k_{15} K_2 r + k_{16} K_1 r^2)$$

A graph of $v(K_2 + K_1 r)/a$ against $[AcO^-]$ gives an intercept with a value of $k_1 K_2$ and a slope of value $(k_{13} K_2 + k_{14} K_1 r + k_{15} K_2 r + k_{16} K_1 r^2)$. With a series of experiments,

for each of a number of buffer ratios, k_{13}, $(k_{14}K_1+k_{15}K_2)$ and k_{16} may be estimated. This treatment assumes that r is constant within each series of experiments. This procedure is valid for the less acid acetate buffers, where $r < 0.5$. With the more acid acetate buffers, where $r = 0.5$, 1.0 and 10.0, the hydrogen ion concentration is no longer negligible compared with the concentration of the other acidic and basic species thus causing the true buffer ratio to vary within each series of experiments.

Representing the stoicheiometric concentrations of acetic acid, acetate ion and keto-acid anion by α_1, β_1 and β_2 respectively; the true concentrations of acetic acid, keto-acid, acetate ion and keto-acid anion by a_1, a_2, b_1, b_2 respectively and the hydrogen ion concentration by h it follows that

$$a_1 \rightleftharpoons b_1 + h; \quad a_1 + b_1 = \alpha_1 + \beta_1 \tag{6}$$

and

$$a_2 \rightleftharpoons b_2 + h; \quad a_2 + b_2 = \beta_2 \tag{7}$$

A further three equations can be written,

$$K_1 = b_1 h / a_1 \tag{8}$$

$$K_2 = b_2 h / a_2 \tag{9}$$

$$b_1 + b_2 = h + \beta_1 + \beta_2 \tag{10}$$

Rearrangement gives the true concentration in terms of the stoicheiometric concentrations and the hydrogen ion concentration

$$a_1 = \alpha_1 - h - a_2 \tag{11}$$

$$b_1 = \alpha_1 + h + a_2 \tag{12}$$

$$b_2 = \beta_2 - a_2 \tag{13}$$

$$a_2 = \beta_2 h / (K_2 + h) \tag{14}$$

Substituting equations (11) to (14) into equation (8) gives, after rearrangement, the cubic equation

$$h^3 + h^2(K_1 + K_2 + \beta_1 + \beta_2) + h(K_1K_2 + K_2\beta_1 + K_1\beta_2 - K_1\alpha_1) - \alpha_1K_1K_2 = 0$$

Solving this equation for the hydrogen ion concentration enables the true concentrations of acetate and keto-acid anion to be calculated from the equations

$$b_1 = \beta_1 + h + \beta_2h/(K_2 + h) \qquad \text{for acetate ions}$$

and $$b_2 = \beta_2 - \beta_2h/(K_2 + h) \qquad \text{for the keto-acid anion}$$

In the case of $r = 0.1$, the correction for hydrogen ion concentration is small and h^3 was neglected. In experiments using more acid acetate buffers ($r > 0.1$) the full cubic equation was solved.

The dissociation constants K_1 and K_2 were calculated from the thermodynamic dissociation constants and the activity coefficient. The activity coefficient was obtained from the Davies Equation as before. However in all experiments, the ionic strength of the solutions containing acetate buffers was 0.3M which is outside the range of application of the Davies Equation. However this value does agree reasonably well with empirical activity coefficient values for sodium acetate, potassium iodide, potassium chloride and sodium perchlorate (65).

The approximate values of the activity coefficients obtained from the Davies Equation for ionic strengths of 0.2M and 0.3M are given in Appendix 1 as are the acid dissociation constants of the keto-acids calculated from these values. No attempt was made to determine any of these activity coefficients or dissociation constants experimentally.

A full analysis for acetate buffered solutions was only attempted for ortho-acetylbenzoic acid. The results indicate that the contributions of processes 14, 15 and 16 are negligible and therefore the rate expression may be simplified to

give

$$v = k_1[A^-] + k_{13}[AcO^-][A^-]$$

A detailed analysis is given in the discussion section. The observed first-order velocity constant, k_{obs}, is defined as $v/[A^-]$. The calculated first-order velocity constants, k_{calc}, were obtained from the expression

$$k_{calc} = k_1 + k_{13}[AcO^-]$$

and were found to compare favourably with the values of k_{obs}.

Such a rigorous analysis was not attempted for pyridine buffered solutions. Calculated first-order velocity constants obtained from the expression

$$k_{calc} = k_1 + k_{py}[\text{pyridine}]$$

are in agreement with the observed first-order velocity constants. This indicates that intermolecular catalysed ionization can be observed only between the keto-acid anion and pyridine.

Hence for all the other keto-acids, the catalytic constants for the acetate ion and pyridine molecule have been obtained by plotting the observed first-order velocity constant against the true concentration of acetate ion or pyridine, the slope giving the required catalytic constant k_{13} or k_{py} respectively. The intercept corresponds to the observed velocity in the absence of catalyst, k_1.

EXPERIMENTAL

Very low concentrations of iodine, about 10^{-5}M, can be measured spectrophotometrically by observing the absorption due to the triiodide ion. Both iodine and the triiodide ion are capable of halogenating enols (66). By observing the change in the triiodide concentration with respect to time, the rate of proton transfer may be conveniently followed. As the product from the halogenation of 2-acetyl-3-nitrobenzoic acid was found to absorb at approximately the same wavelength as the triiodide ion it was impossible to use the spectrophotometric technique for this compound. In this case the 'Dead Stop' method (67) was used. The kinetics of all the other compounds were determined spectrophotometrically.

(i) Instrumentation

Three different spectrophotometers were used in this work.

(a) Unicam SP 700A - A standard production model was used fitted with a constant temperature cell housing (SP 770).

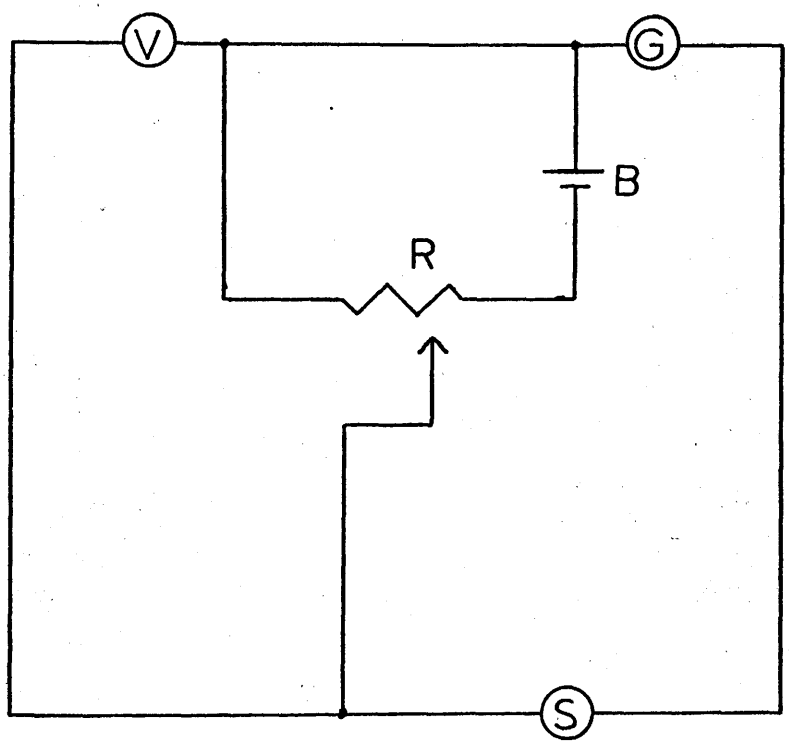
(b) Unicam SP 500 Series 2 - This instrument was fitted with an automatic cell changer (SP 506), a constant temperature cell holder (SP 507) and a programmer controller (SP 505). Output to a Unicam SP 22 recorder enabled the optical density readings to be kept as a permanent record.

(c) Gilford 2400 - This instrument has a thermostated, four cell automatic cell holder and a chart recorder. The cell holder is fitted with a thermosensor with output to the recorder which enables any temperature drift to be detected.

All instruments were thermostated at $25^{\circ} \pm <0.1^{\circ}C$ using a water bath fitted with a Grant S.B.2 Type heater and pump. Temperature control was provided by a mercury contact thermometer. All pipes between the thermostat baths and the instruments were well lagged. The temperature of the cell compartment was measured (for the SP 700A and SP 500) using a standardized mercury thermometer when lagging was used to prevent heat transference between the cell holder and the atmosphere.

FIG 11

CIRCUIT DIAGRAM



S= "DEAD STOP" APPARATUS.

V=VOLTMETER.

G=GALVANOMETER.

R=RHEOSTAT.

B=MERCURY BATTERY.

When monitoring the disappearance of triiodide ions it is necessary to ensure that the ratio of triiodide concentration to free iodine concentration is constant. This is achieved by the presence of an excess of iodide ions. Therefore all experiments were conducted with 0.1M iodide ions (added as potassium iodide) and an analytical concentration of about 10^{-5}M iodine. This gives an excess of iodide ions by a factor of about 10^{4}. Assuming a value of $1.5 \pm 0.2 \times 10^{-3}$M for the triiodide ion dissociation constant (31) the effective extinction coefficient, ε_{eff}, can be calculated. Rearrangement of equation (16) gives

$$[I_3^-]/[I_2] = [I^-]/K_{I_3^-} = 66.67$$

and therefore

$$\varepsilon_{eff} = (25{,}280 \times 66.67)/67.67$$

$$= 24{,}910.$$

(b) Measurement of the Rates of Ionization

Since the experimental method was essentially the same for all the keto-acids studied (except 2-acetyl-3-nitrobenzoic acid) a general method is described here and any modifications to the method will be described with the results obtained for the appropriate keto-acid.

The rate of proton transfer was followed by observing the rate of iodination spectrophotometrically. The concentration of iodine during each experiment was determined by measuring the optical density of the triiodide ion at 353 nm. With the exception of 2-acetyl-3-naphthoic acid and 8-acetyl-1-naphthoic acid all other constituents of the reaction mixture were found to have a negligible absorption at this wavelength. The ratio of the keto-acid to iodine was usually of the order of 1000:1. Complete disappearance of iodine represents about 0.1% reaction of the keto-acid, the concentration of which therefore remained effectively constant throughout the iodination. In all spectrophotometric experiments the optical density decreased linearly with time for at least 80% of the reaction indicating a zero-order reaction with respect to iodine.

For iodination experiments without an added buffer ortho-acetylbenzoic acid was the only keto-acid studied which was sufficiently soluble in water to enable solutions of varying buffer ratio to be prepared by adding varying amounts of sodium hydroxide solution to the aqueous keto-acid. Therefore it was possible to study the kinetics of this keto-acid from about pH2 up to about pH6. Self buffered solutions of all the other keto-acids, except 8-acetyl-1-naphthoic acid, could only be prepared by dissolving the keto-acid in sufficient sodium hydroxide solution to bring the pH to about 6 (glass electrode). A pH of 6 was the lowest pH at which complete solution was easily obtained. Self buffered solutions of 8-acetyl-1-naphthoic acid could only be studied at pH7 because it was extremely insoluble in solutions of lower pH. In this case a blank solution at the same pH was simultaneously monitored during the kinetic runs to evaluate any corrections necessitated by iodine oxidation reactions. It was assumed that these side reactions were insignificant at pH6 and below.

The true concentration of the keto-acid anion, $[A^-]$, was obtained by correcting the stoicheiometric concentration by adding $[H^+]$, as shown previously. Sufficient potassium iodide was added to give a final concentration of 0.1M iodide ions and potassium chloride or sodium perchlorate solution was added to give a final ionic strength of 0.2M. Usually 10 ml of this reaction mixture, containing about 10^{-2}M keto-acid, was sufficient for each experiment.

The buffer solutions used were made by mixing solutions of acetic acid and sodium hydroxide or of pyridine and hydrochloric acid. The keto-acids were added to the buffer solutions as a solution of the sodium salt, prepared by neutralizing the acid with sodium hydroxide solution. In acetate buffers an ionic strength of 0.3M was used and in pyridine buffers an ionic strength of 0.2M. The concentration of $[A^-]$ in the presence of acetate buffers was calculated as described previously but the keto-acids were considered to be completely ionized in the presence of pyridine buffers (pH > 6).

The prepared reaction mixtures were first brought to 25°C in a water bath and then a sample transferred to a cuvette

which had also been brought to 25°C by standing in the thermostated cell holder of the spectrophotometer. About 2.2 μl of 0.1N iodine solution was then added to the cuvette using a syringe. The cuvette was stoppered and shaken before being placed in the cell holder. The optical density, d, measurements were compared to those of a water blank for all keto-acids except 8-acetyl-1-naphthoic acid. The sample cuvette was removed at the end of the reaction, a further 2.2 μl of iodine solution was added and the run repeated. A typical trace is shown in Fig.12.

The observed rate of disappearance of iodine is calculated from the expression

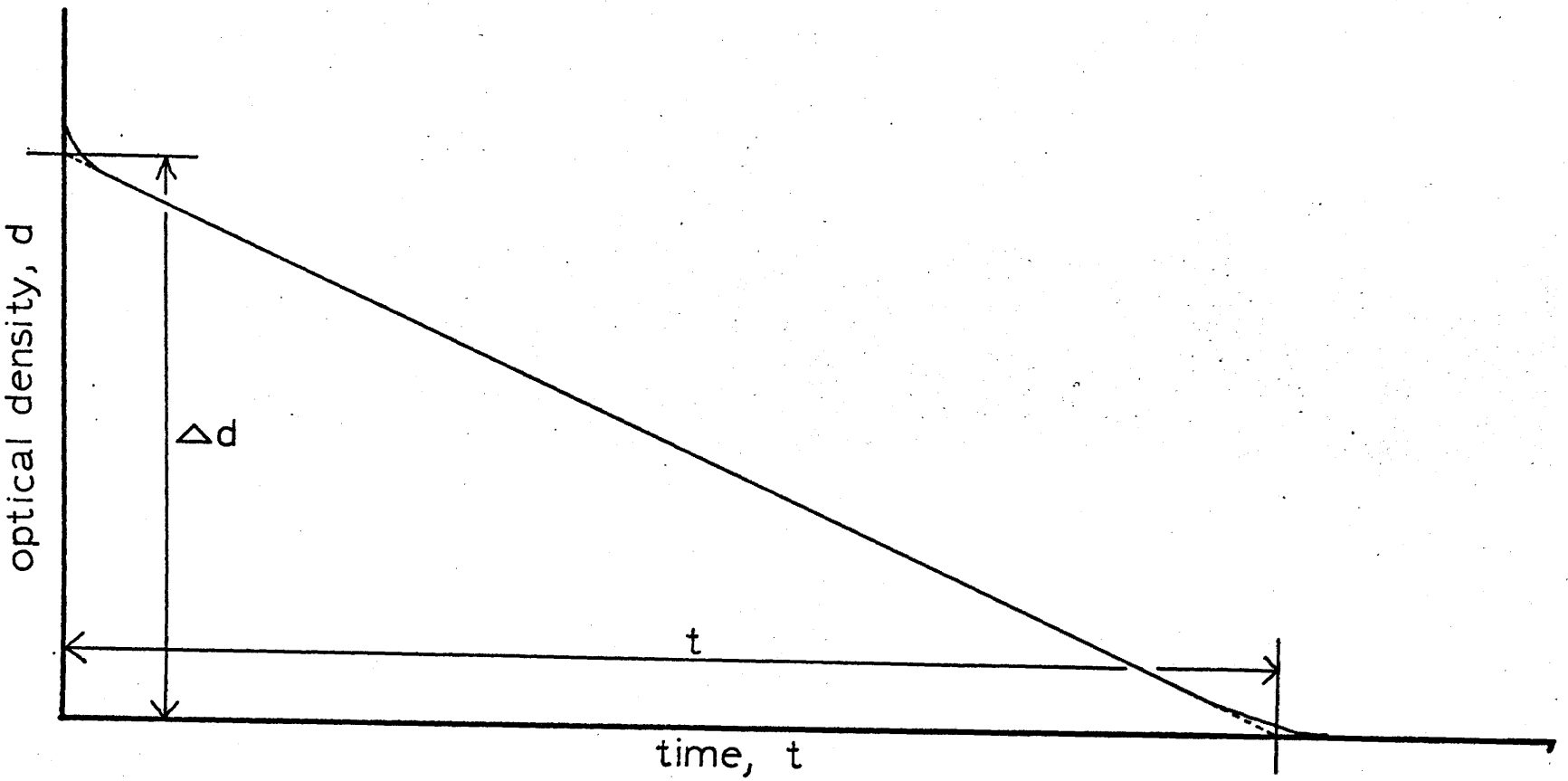
$$v_{obs} = \Delta d/t \times \varepsilon_{eff} \text{ mol } l^{-1} \text{ sec}^{-1}$$

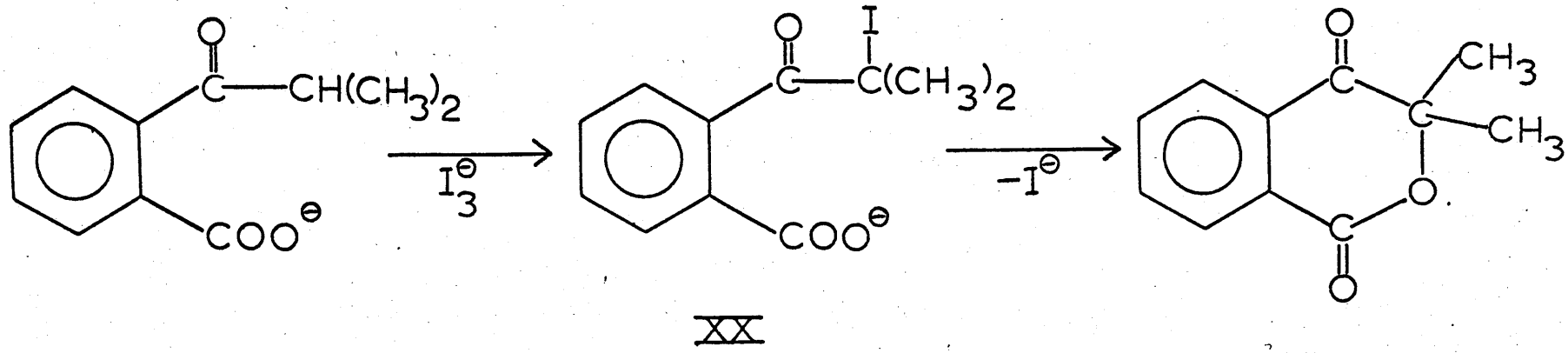
As mentioned in the introduction, and will be justified in the discussion of the results for ortho-acetylbenzoic acid, the first-order velocity constant was calculated by dividing the observed rate of disappearance of iodine by the concentration of the anion. The initial fast reaction shown in Fig.12 was only apparent with the first addition of iodine. The second addition of iodine gave a rate a few percent slower than the first, further additions of iodine giving no change in the rate and no initial fast reaction. The slightly faster overall run and the initial fast reaction was attributed to a small amount of a more reactive impurity in the keto-acid. Therefore the results obtained from the first addition of iodine were ignored. A decrease in reaction velocity at the end of each experiment was attributed to ineffective scavenging at very low concentrations of iodine ($< 10^{-6}$M) rather than to slight reversibility of the iodination reaction, since the optical density eventually falls to zero.

Harper and Bender (31) have shown that iodinated ortho-isobutyrylbenzoic acid rapidly forms a lactone (XX). Under basic conditions the mono-iodinated ortho-acetylbenzoic acid would be expected to iodinate at a faster rate than the parent compound because of the increased acidity of the remaining α-hydrogens. At no time was an enhancement in the rate of disappearance of iodine observed and it has therefore been assumed that the lactone rapidly formed as shown in (XXI), is analogous to (XX).

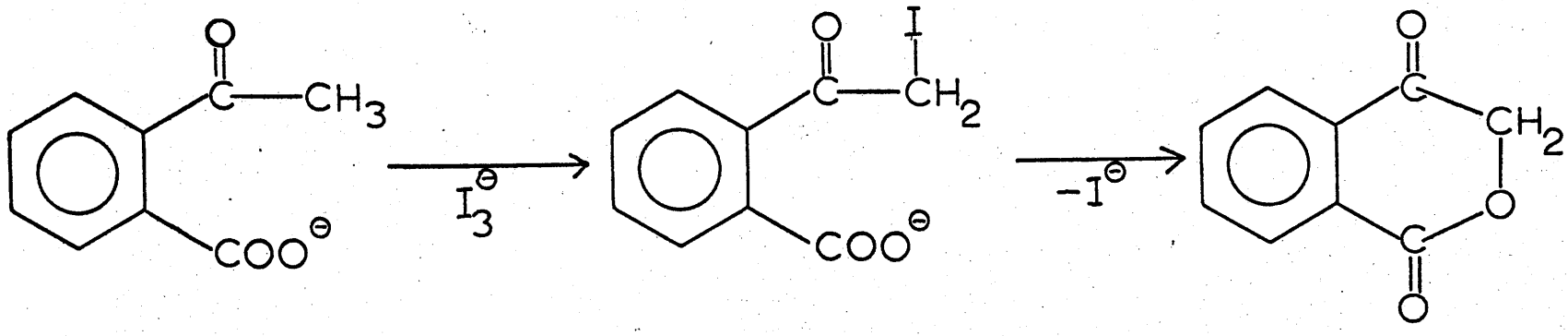
FIG 12

A TYPICAL PLOT OBTAINED FOR THE RATE OF DISAPPEARANCE OF IODINE





XX



XXI

Intramolecular catalysis is impossible for this lactone and its iodination in the presence of acetate ions or pyridine should be relatively slow. The expected acceleration in rate was noted during the iodination of para-acetylbenzoic acid (28) in acetate and pyridine buffers.

The apparatus and circuitry used for the 'Dead Stop' method (67) has already been described. A stock solution of 2-acetyl-3-nitrobenzoic acid adjusted to pH6 was made as previously described. Potassium iodide and sodium perchlorate solutions were added to a portion of the stock solution to give a reaction mixture of 2×10^{-2}M keto-acid, 0.1M iodide ions and an ionic strength of 0.2M for self buffered and pyridine buffered solutions and of 0.3M for acetate buffered solutions. The reaction was initiated by the addition of 20 µl 0.1N iodine solution to 10 ml of the reaction mixture which was immersed in a thermostated bath at 25°C. After five minutes 1 ml of sample was transferred to the titration vessel, this being sufficient to completely cover the platinum electrodes. The solution was stirred magnetically and titrated with 10^{-3}M sodium thiosulphate solution contained in a micrometer syringe, the tip of the needle being immersed in the sample solution. One division on the syringe scale corresponded to 10^{-7} mol l^{-1} iodine. The end-point of the titration was indicated by zero deflection on the galvanometer.

Fresh 1 ml samples were titrated at convenient time intervals and a plot of 10^{7}N against time constructed, where N corresponds to the concentration of iodine titrated. The slope of this graph corresponds to the rate of disappearance of iodine.

The analysis of all the kinetic results is given in the discussion section.

EXPERIMENTAL RESULTS

Ortho-acetylbenzoic acid (X)

Kinetic method - Spectrophotometric

Apparatus and materials - as described

Since this acid was the first to be studied* the observations were extended over a wider range of self buffered solutions (Table 12) than in subsequent work. The true concentration of ortho-acetylbenzoic acid was calculated by applying a correction for hydrogen ion concentration. A mean first-order velocity constant, $k_1 = 1.98 \times 10^{-6}$ sec^{-1}, was obtained from a series of seventeen experiments. If the results of experiments conducted at pH < 4 are ignored because of the magnitude of the corrections applied then a slightly higher value, $k_1 = 2.05 \times 10^{-6}$ sec^{-1}, was obtained.

Table 13 contains the results obtained for the rates of ionization in acetate buffered solutions. The values for k_{13}, $(K_1k_{14} + K_2k_{15})$ and k_{16} have been estimated from data given in Table 14 and from the slope of the plots of $v(K_2 + K_1r)/a$ against $[AcO^-]$, the concentration of acetate ions. These plots are shown in Fig.13, 14 and 15. It was concluded that intermolecular catalysis by acetate ions on ortho-acetylbenzoate is important and the calculated first-order velocity constants have therefore been obtained from the expression

$$k_{calc} = 2.05 \times 10^{-6} + k_{13}[AcO^-] \text{ sec}^{-1}$$

where the catalytic constant for acetate ions, k_{13}, equals 4.0×10^{-6} l mol^{-1} sec^{-1}.

Such a rigorous analysis was not attempted for pyridine buffered solutions. The main purpose in these experiments was to demonstrate intermolecular catalysis by pyridine molecules. The results are given in Table 15.

* in conjunction with B. G. Cox.

A plot of the first-order velocity constant against pyridine concentration has a slope corresponding to the catalytic constant for pyridine, k_{py}. The first-order velocity constants were calculated from the expression

$$k_{calc} = 2.15 \times 10^{-6} + k_{py}[\text{pyridine}] \text{ sec}^{-1}$$

where $k_{py} = 2.33 \times 10^{-5}$ l mol^{-1} sec^{-1}.

TABLE 12

Rate of ionization of ortho-acetylbenzoic acid in self buffered solutions at 25°C

$[A^-]$ = true concentration of substrate anion, (mol l^{-1})

r = stoicheiometric buffer ratio, [acid]/[base]

k = first-order velocity constant (sec^{-1})

I = ionic strength (mol l^{-1})

v = rate of disappearance of iodine (mol l^{-1} sec^{-1})

* = solution brought to pH6 by adding sodium hydroxide solution

† = results obtained by B. G. Cox

I	r	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.20	*	0.01	100	20.3	203
0.20	*	0.01	200	40.8	204
0.20	*	0.01	250	50.8	203
0.20	*	0.01	300	61.5	205
0.20	*	0.01	400	82.0	205
0.13†	0.0265	0.033	300	63.4	211
0.13†	0.110	0.14	300	63.6	212
0.13†	0.133	0.17	300	63.0	210
0.13†	0.204	0.28	300	64.2	214
0.125†	0.224	0.30	250	46.5	186
0.12†	0.525	0.65	201	41.0	204
0.115†	1.08	1.36	151	29.8	197
0.11†	2.12	2.56	103	18.4	179
0.11†	5.16	5.69	55.7	9.69	174
0.20†	20.6	13.2	28.2	5.25	186
0.20	31.0	14.6	24.6	4.70	191
0.20	40.5	16.3	23.8	4.25	179

Mean k = 1.98×10^{-6} sec^{-1}

Mean k (excluding last 5 results) = 2.05×10^{-6} sec^{-1}

TABLE 13

Rate of ionization of ortho-acetylbenzoic acid in acetate buffers at 25°C

I = 0.3M throughout

r' = true buffer ratio

$[AcO^-]$ = true concentration of acetate ions (mol l^{-1})

† = results obtained by B. G. Cox

$k_{calc} = 2.05 \times 10^{-6} + 4.0 \times 10^{-6}[AcO^-]$ sec^{-1}

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10}v$	10^8k_{obs}	10^8k_{calc}
	r = 0.1					
0.1	98	40	3.0	231	237	221
0.1†	293	40	3.0	690	235	221
0.1	98	80	3.0	248	254	238
0.1†	305	80	3.0	786	258	238
0.1	98	120	3.0	260	266	253
0.1†	293	120	3.0	804	274	253
0.1	98	160	3.0	277	284	269
0.1†	317	160	3.0	865	273	269
0.1	98	200	3.0	289	296	285
0.1†	285	200	3.0	812	285	285
	r = 0.2					
0.2	96	200	5.9	285	298	285
	r = 0.25					
0.25	94	201	7.4	286	303	285
	r = 0.5					
0.49	90	201	14.8	265	296	286
	r = 1.0					
0.91	82	42	27.4	172	209	222
0.95	82	82	28.7	185	227	238
0.97	81	122	29.1	198	243	254
0.98	81	162	29.3	209	257	271
0.98	81	202	29.5	220	271	286

(TABLE 13 continued)

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10}v$	10^8k_{obs}	10^8k_{calc}
	r = 10.0					
8.38	33.6	47	252	65.2	194	221
9.10	31.8	87	274	70.2	221	240
9.38	31.1	127	282	75.6	243	256
9.53	30.8	167	286	80.0	260	272
9.62	30.6	207	289	84.6	276	288

TABLE 14

Relation of $v(K_2 + K_1r)/a$ to $[AcO^-]$

r = stoicheiometric buffer ratio

v = rate of disappearance of iodine (mol l^{-1} sec^{-1})

a = stoicheiometric concentration of $[HA] + [A^-]$

K_1 = dissociation constant of acetic acid at ionic strength 0.3M

K_2 = dissociation constant of ortho-acetylbenzoic acid at ionic strength 0.3M

$[AcO^-]$ = true concentration of acetate ions (mol l^{-1})

r' = true buffer ratio

For r = 0.1

10^8 v/a	r'	$10^{10}v(K_2 + K_1r)/a$	$[AcO^-]$
231	0.1	2.96	0.04
248	0.1	3.18	0.08
260	0.1	3.33	0.12
277	0.1	3.56	0.16
289	0.1	3.71	0.20

Slope of plot $10^{10}v(K_2 + K_1r)/a$ vs $[AcO^-]$ = 4.7×10^{-10} l mol^{-1} sec^{-1}

Average true buffer ratio = 0.1

For r = 1.0

10^8 v/a	r'	$10^{10}v(K_2 + K_1r)/a$	$[AcO^-]$
172	0.91	2.66	0.042
185	0.95	2.88	0.082
198	0.97	3.09	0.122
209	0.98	3.27	0.162
220	0.98	3.44	0.202

Slope of plot $10^{10}v(K_2 + K_1r)/a$ vs $[AcO^-]$ = 4.9×10^{-10} l mol^{-1} sec^{-1}

Average true buffer ratio = 0.96

For r = 10.0

10^8 v/a	r'	$10^{10}v(K_2 + K_1r)/a$	$[AcO^-]$
65.2	8.38	2.47	0.047
70.2	9.10	2.81	0.087
75.6	9.38	3.09	0.127
80.0	9.53	3.30	0.167
84.6	9.62	3.52	0.207

Slope of plot $10^{10}v(K_2 + K_1r)/a$ vs $[AcO^-]$ = 6.5×10^{-10} l mol^{-1} sec^{-1}

Average true buffer ratio = 9.2

FIG 13

$10^{10} v(K_2+K_1 r)/a$ v's $[AcO^{\ominus}]$ for $r = 0{\cdot}1$

slope = $4{\cdot}7 \times 10^{10}$ l.mol.$^{-1}$ sec.$^{-1}$

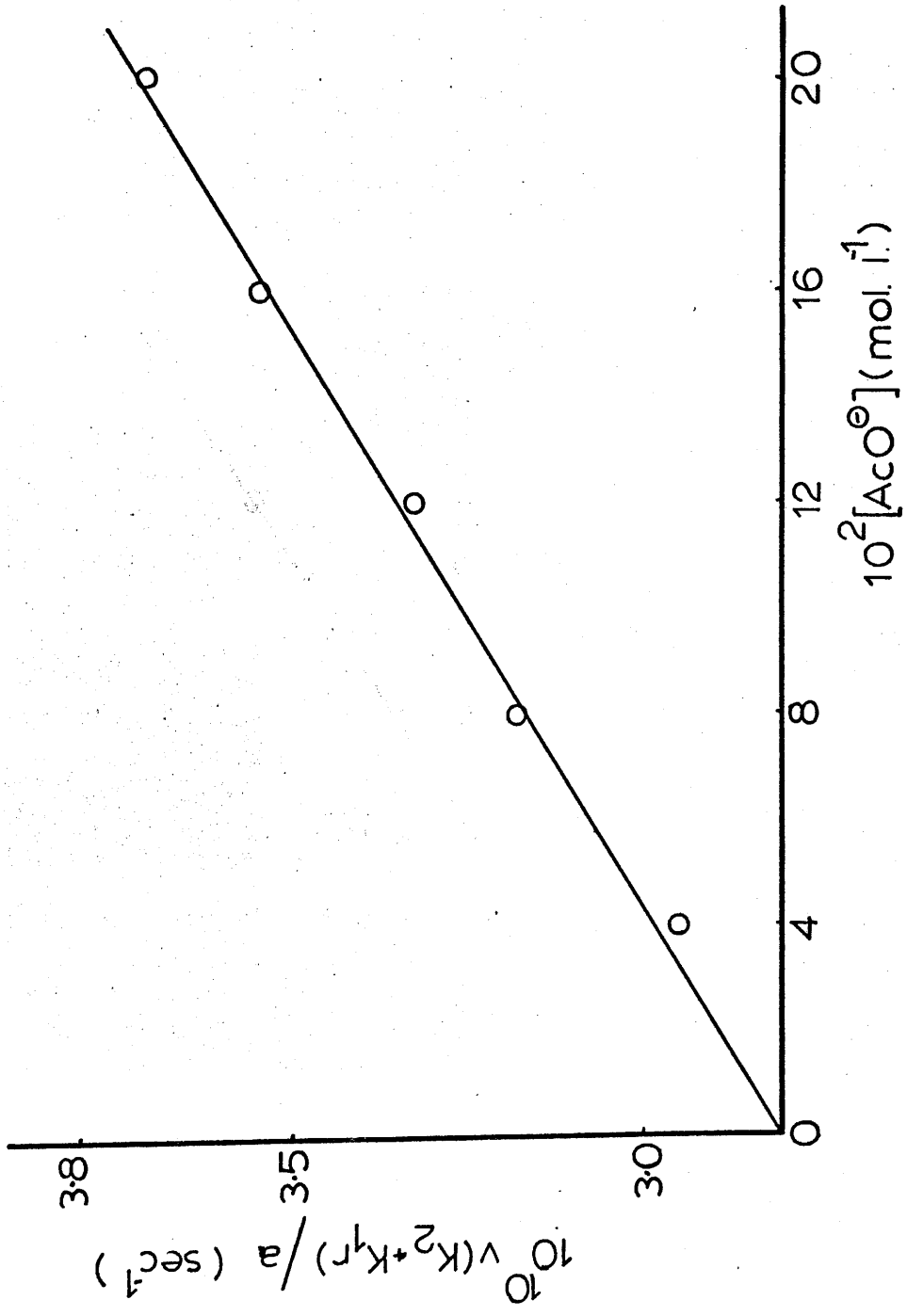


FIG 15

$10^{10} v(K_2 + K_1 r)/a$ v's $[AcO^{\ominus}]$ for r = 10·0

slope = $6{\cdot}5 \times 10^{-10}$ $l mol^{-1} sec^{-1}$

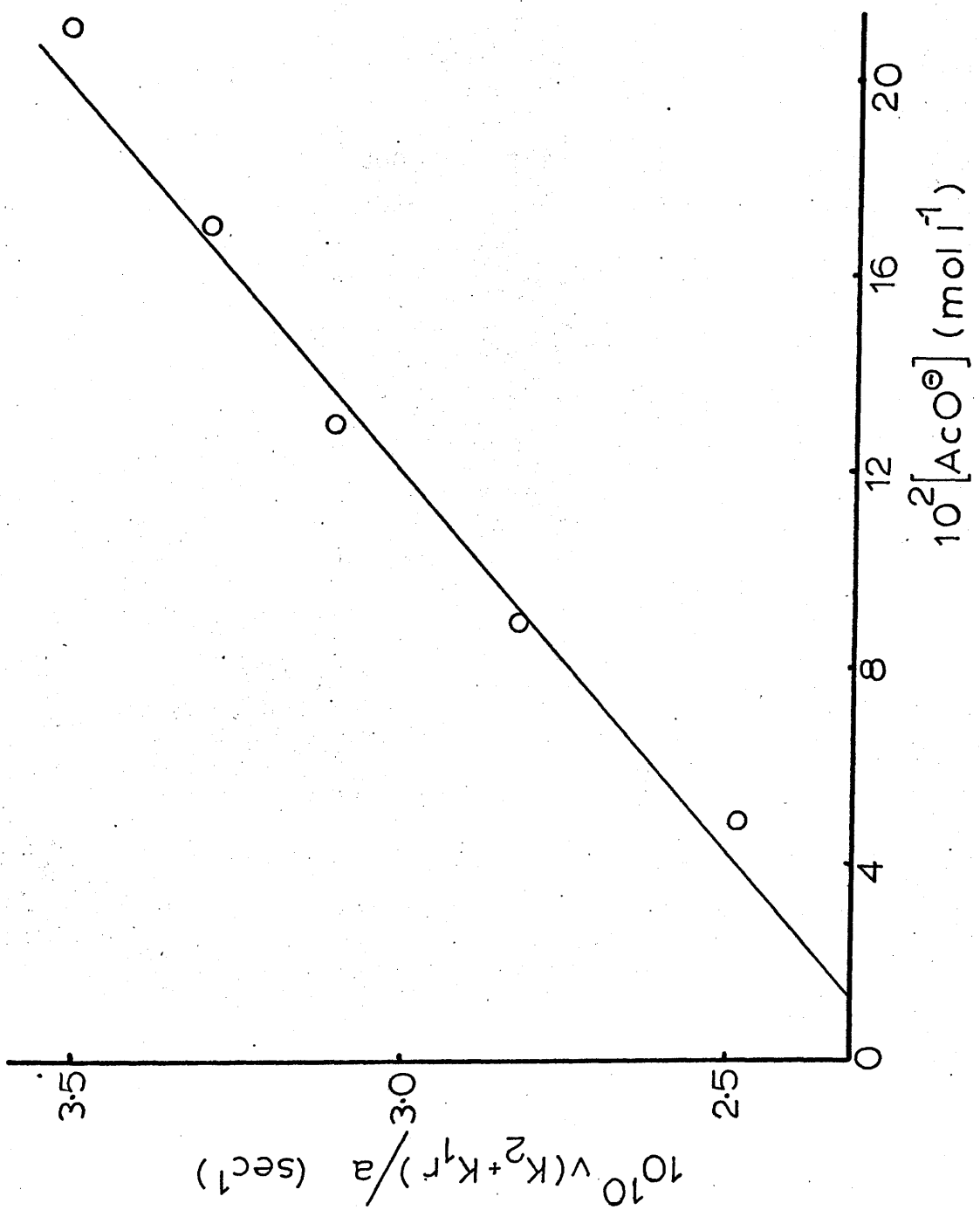


TABLE 15

Rate of ionization of ortho-acetylbenzoic acid in pyridine buffers at 25°C. (B.G.Cox)

$r = 0.1$

$I = 0.15M$

$[A^-] \simeq 0.02M$ throughout

$$k_{calc} = 2.15 \times 10^{-6} + 2.33 \times 10^{-5}|\text{pyridine}|$$

$10^3[\text{pyridine}]$ (M)		24	48	73	97	120
$10^8 k$	obs	300	335	381	437	484
	calc	271	327	385	431	495

Ortho-isobutyrylbenzoic acid (XI)

Kinetic method - Spectrophotometric

Apparatus and materials - as described

The rates of ionization in self buffered, 0.2M acetate buffer (r = 0.1) and 0.1M pyridine buffer (r = 0.1) are given in Table 16. No intermolecular catalysis by acetate ions or pyridine was detected. A value of 5.02×10^{-6} sec^{-1} was obtained for the intramolecular base catalysed first-order velocity constant, k_1.

TABLE 16

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.01	98	49.2	502

Rate of ionization in acetate buffered solution at 25°C

r = 0.1

I = 0.3M

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k$
0.1	94	200	2.9	474	504

Rate of ionization in pyridine buffered solution at 25°C

r = 0.1

I = 0.2M

$10^4[A^-]$	10^2[pyridine]	$10^{10} v$	$10^8 k$
100	10	497	497

2-Acetyl-3-nitrobenzoic acid (XII)

Kinetic Method - Because the product absorbed at the same wavelength as the triiodide ion resulting in non-linear spectrophotometric traces, the 'Dead Stop' method was used to determine the rates of ionization

Apparatus and materials - as described

Table 17 contains the information necessary to determine the rate of ionization in self buffered solution. This data has been chosen to illustrate a typical plot of 10^7N against time, Fig.16, in which the slope gives the rate of disappearance of iodine. From this a first-order velocity constant of 5.74×10^{-7} sec^{-1} was obtained.

Tables 18 and 19 contain results obtained in experiments which determined the rate of ionization in acetate and pyridine buffers. Because of the low pK_a of this acid no corrections to the anion concentration were necessary. Plots of the observed first-order velocity constant against the concentration of acetate ions and of pyridine gave a catalytic constant for acetate ions, k_{13}, of 1.76×10^{-6} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 4.3×10^{-6} l mol^{-1} sec^{-1}.

TABLE 17

Rate of ionization in self buffered solution at 25°C

$I = 0.2M$

$[A^-] = 0.02M$

$10^4[H^+] = 0.01M$

10^7N = moles l^{-1} iodine

t = time (min.)

t	10^7N
0	820
10	750
20	679
30	612
40	540
60	405
75	300
90	200

A plot of 10^7N vs t gives

$$\text{slope} = -11.49 \times 10^{-6} \text{ l mol}^{-1} \text{ sec}^{-1}$$

$$k_{obs} = 57.4 \times 10^{-8} \text{ sec}^{-1}$$

TABLE 18

Rate of ionization in acetate buffers at 25°C

$r = 0.1$

$I = 0.3M$

$k_{calc} = 56.2 \times 10^{-8} + 1.76 \times 10^{-6}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10}v$	10^8k_{obs}	10^8k_{calc}
0.1	200	40	2.9	120.2	60.1	63.3
0.1	200	80	2.9	146.0	73.5	70.3
0.1	200	120	2.9	159.6	79.8	77.4
0.1	200	160	2.9	164.6	82.3	84.4
0.1	200	200	2.9	181.6	90.8	91.4

TABLE 19

Rate of ionization in pyridine buffers at 25°C

$r = 0.1$

$I = 0.2M$

$[A^-] = 0.02M$ throughout

$k_{calc} = 55.9 \times 10^{-8} + 4.0 \times 10^{-6}[pyridine]$

$10^2[pyridine]$ (M)		2	4	6	8	10
10^8k	obs	62.3	72.8	82.3	86.9	95.2
	calc	63.9	71.9	79.9	87.9	95.9

2-Acetyl-4,5-dimethylbenzoic acid (XIV)

Kinetic Method	- Spectrophotometric
Apparatus and materials	- as described

The rates of ionization in self buffered, acetate buffered and pyridine buffered solutions are given in Table 20. Figures 17 and 18 show typical plots from which the catalytic constants for acetate ions and pyridine molecules were determined. It has been assumed that the acetate ion and the pyridine molecule are the only species involved in the intermolecular catalysis.

A catalytic constant for acetate ions, k_{13}, of 2.25×10^{-6} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 13.2×10^{-6} l mol^{-1} sec^{-1} was obtained. A value of 2.65×10^{-6} sec^{-1} was obtained for the rate constant, k_1, of the intramolecular base catalysed reaction.

TABLE 20

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.01	99	26.4	267
0.2	0.01	148.5	39.0	263
0.2	0.01	198	52.4	265

Mean $k = 2.65 \times 10^{-6}$ sec^{-1}

Rate of ionization in acetate buffered solution at 25°C

$r = 0.1$

$I = 0.3M$

$k_{calc} = 2.69 \times 10^{-6} + 2.25 \times 10^{-6}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k_{obs}$	$10^8 k_{calc}$
0.1	97	40	2.9	271	279	274
0.1	97	80	2.9	278	286	283
0.1	97	120	2.9	287	296	292
0.1	97	160	2.9	297	306	301
0.1	97	200	2.9	305	314	310

Rate of ionization in pyridine buffered solution at 25°C

$r = 0.1$

$I = 0.2M$

$[A^-] = 0.01M$ throughout

$k_{calc} = 2.65 \times 10^{-6} + 13.2 \times 10^{-6}[pyridine]$

$10^2[pyridine]$ (M)		2	4	6	8	10
$10^8 k$	obs	288	320	346	367	396
	calc	288	318	344	370	395

FIG 17

PLOT OF $10^8 k_{obs}$ v's $[AcO^{\ominus}]$ FOR

2-ACETYL-4,5-DIMETHYLBENZOIC ACID

AT 25°C

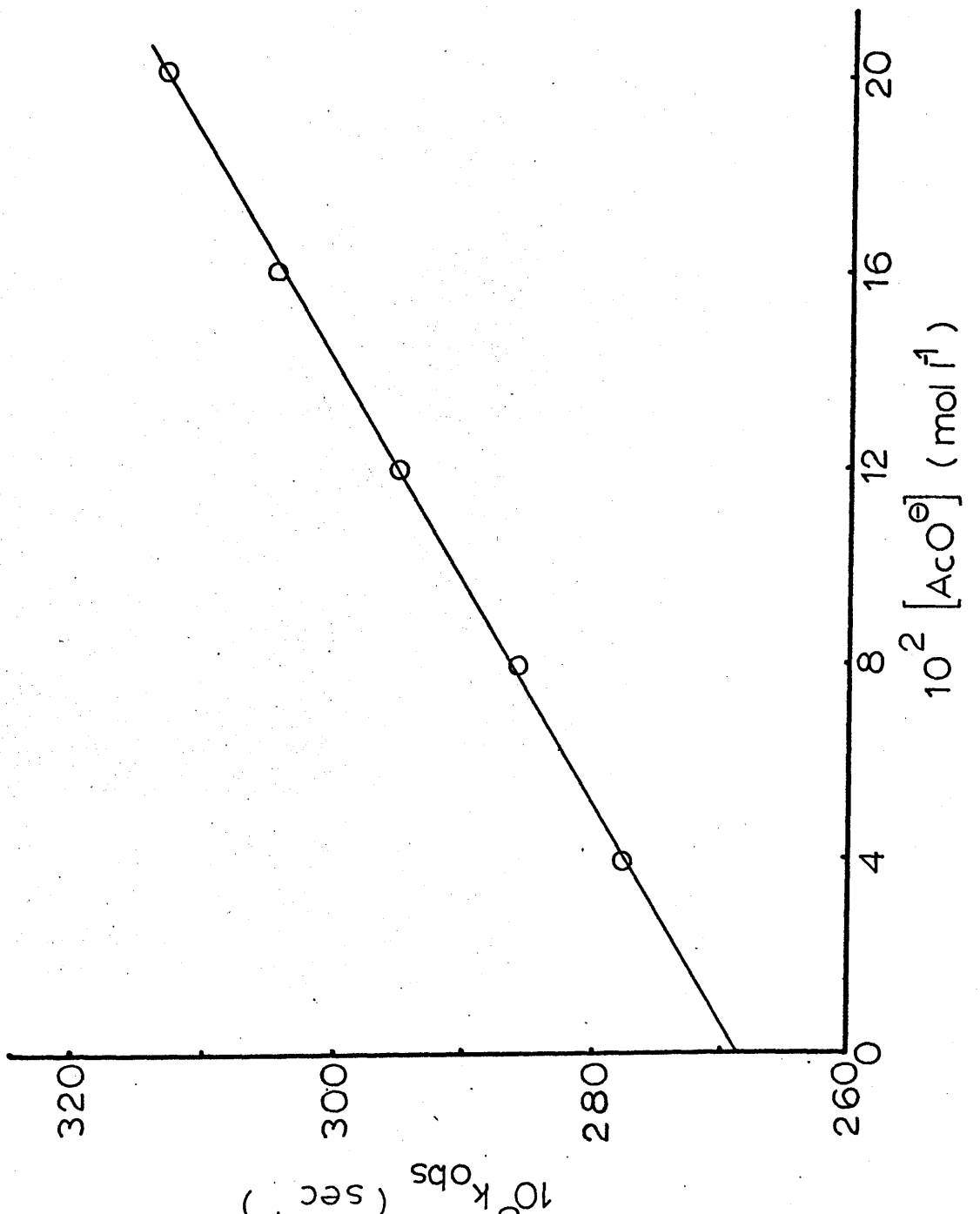
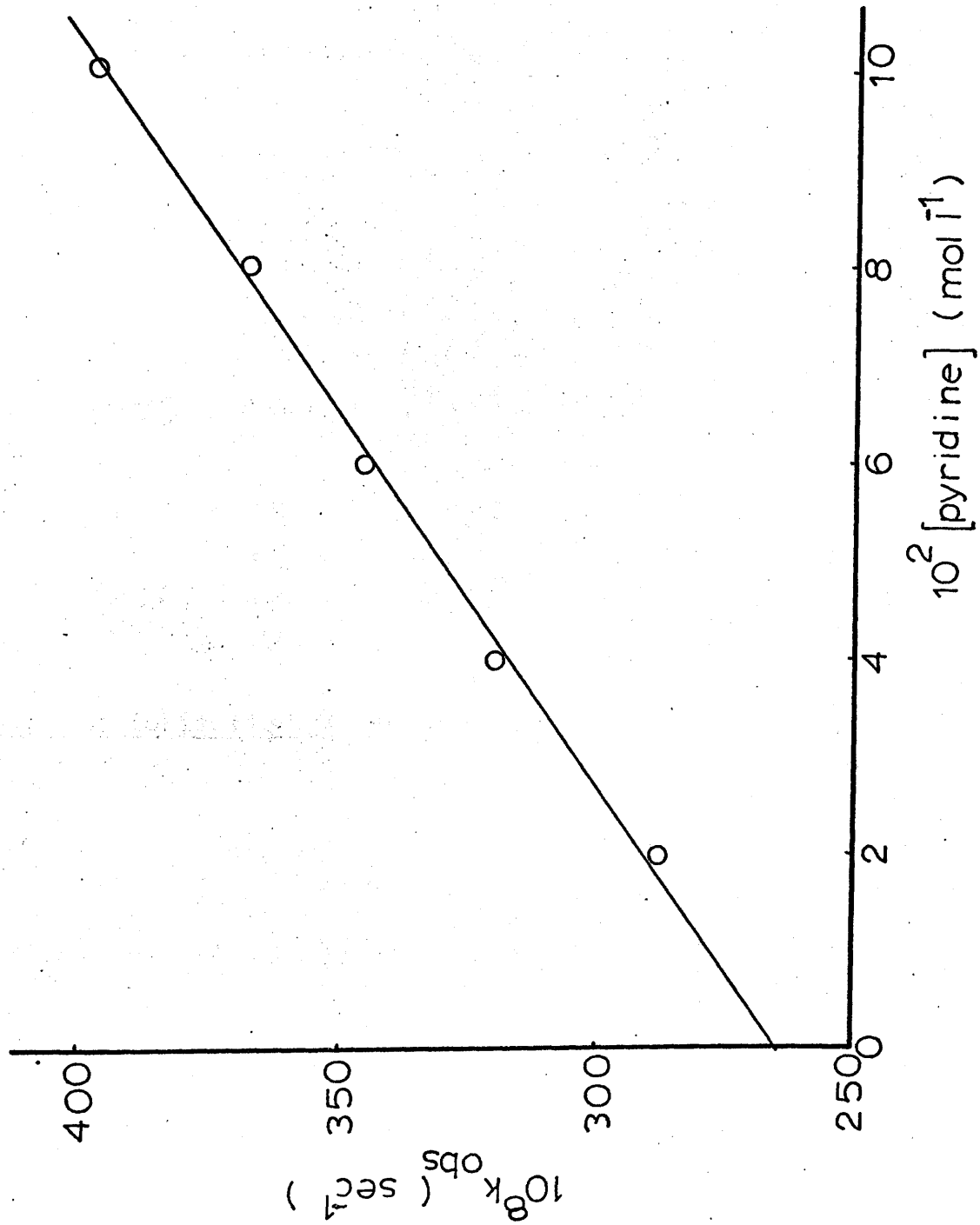


FIG 18

PLOT OF $10^8 k_{obs}$ v's [pyridine] for

2-ACETYL-4,5-DIMETHYLBENZOIC ACID

AT 25°C



2-Acetyl-4,5-dimethoxybenzoic acid (XV)

Kinetic Method - Spectrophotometric

Apparatus and materials - as described

Table 21 gives the rates of ionization in self buffered, acetate buffered and pyridine buffered solutions. A catalytic constant for acetate ions, k_{13}, of 4.73×10^{-6} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 31.1×10^{-6} l mol^{-1} sec^{-1} was obtained. A value of 3.36×10^{-6} sec^{-1} was obtained for the rate constant k_1.

TABLE 21

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.01	98.5	33.07	336

Rate of ionization in acetate buffered solution at 25°C

r = 0.1

I = 0.3M

$k_{calc} = 3.33 \times 10^{-6} + 4.73 \times 10^{-6}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k_{obs}$	$10^8 k_{calc}$
0.1	96	40	2.8	338	352	352
0.1	96	80	2.8	354	369	371
0.1	96	120	2.8	376	392	390
0.1	96	160	2.8	392	408	408
0.1	96	200	2.8	410	427	427

Rate of ionization in pyridine buffered solution at 25°C

r = 0.1

I = 0.2M

$[A^-]$ = 0.01M throughout

$k_{calc} = 3.84 \times 10^{-6} + 31.1 \times 10^{-6}[pyridine]$

$10^2[pyridine]$ (M)		2	4	6	8	10
$10^8 k$	obs	448	512	564	621	704
	calc	446	508	570	532	694

2-Acetyl-6-methylbenzoic acid (XVI)

Kinetic Method - Spectrophotometric

Apparatus and materials - as described

Table 22 contains the rates of ionization in self buffered, acetate buffered and pyridine buffered solutions. A catalytic constant for acetate ions, k_{13}, of 22.7×10^{-8} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 8.03×10^{-6} l mol^{-1} sec^{-1} was obtained. A value of 3.32×10^{-8} sec^{-1} was obtained for the base catalysed intramolecular first-order velocity constant, k_1.

TABLE 22

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.01	97	0.315	3.25
0.2	0.01	97	0.329	3.39

mean k = 3.32×10^{-8} sec^{-1}

Rate of ionization in acetate buffers at 25°C

r = 0.1

I = 0.3M

$k_{calc} = 3.24 \times 10^{-8} + 22.7 \times 10^{-8}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k_{obs}$	$10^8 k_{calc}$
0.1	93	41	2.7	4.06	4.37	4.17
0.1	93	81	2.7	4.57	4.91	5.09
0.1	93	121	2.7	5.50	5.91	6.00
0.1	93	161	2.7	6.32	6.80	6.91
0.1	93	201	2.7	7.41	7.97	7.82

Rate of ionization in pyridine buffers at 25°C

r = 0.1

I = 0.2M

$[A^-]$ = 0.01M throughout

k_{calc} = $4.56 \times 10^{-8} + 8.03 \times 10^{-6}$[pyridine]

10^2[pyridine] (M)		2	4	6	8	10
$10^8 k$	obs	18.9	38.0	53.9	69.4	83.5
	calc	20.6	36.7	52.7	68.8	84.8

2-Acetyl-3-naphthoic acid (XVII)

Kinetic Method - Spectrophotometric

Apparatus and materials - as described

Table 23 contains the rates of ionization in self buffered, acetate buffered and pyridine buffered solutions. A catalytic constant for acetate ions, k_{13}, of 1.00×10^{-6} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 8.45×10^{-6} l mol^{-1} sec^{-1} was obtained in the usual way. A value of 1.05×10^{-6} sec^{-1} was obtained for the velocity constant k_1.

TABLE 23

Rates of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.01	98	10.4	106
0.2	0.01	147	15.9	108
0.2	0.01	196	20.1	102

mean $k = 1.05 \times 10^{-6}$ sec^{-1}

Rates of ionization in acetate buffers at 25°C

$r = 0.1$

$I = 0.3M$

$k_{calc} = 1.06 \times 10^{-6} + 1.00 \times 10^{-6}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k_{obs}$	$10^8 k_{calc}$
0.1	95	40	2.75	105	110	110
0.1	95	80	2.75	108	114	114
0.1	95	120	2.75	112	118	118
0.1	95	160	2.75	116	122	122
0.1	95	200	2.75	120	126	126

Rates of ionization in pyridine buffers at 25°C

$r = 0.1$

$I = 0.2M$

$[A^-] = 0.01M$ throughout

$k_{calc} = 1.07 \times 10^{-6} + 8.45 \times 10^{-6}[pyridine]$

$10^2[pyridine]$ (M)		2	4	6	8	10
$10^8 k$	obs	123	142	154	177	190
	calc	124	141	158	175	192

8-Acetyl-1-naphthoic acid (XVIII)

Kinetic Method - It was found that this compound absorbs at the same wavelength as the triiodide ion. The Gilford 2400 spectrophotometer, incorporating a back-off mechanism, was used to compensate for the absorption of the keto-acid. A normal trace was then obtained for the kinetic runs.

Table 24 contains results for the rates of ionization for self buffered, 0.2M acetate buffered (r = 0.01) and 0.1M pyridine buffered (r = 0.01) solutions. Because the rates of ionization were studied at about pH7 for self buffered and acetate buffered and above pH7 for pyridine buffered reactions a blank was monitored simultaneously in each case so that correction for iodine oxidation could be made. A value of 0.65×10^{-8} sec^{-1} was obtained for k_1. No intermolecular catalysis due to acetate ions was observed. A rate enhancement was observed in pyridine buffered solution.

Apparatus and materials - as described.

TABLE 24

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^9 v$	$10^8 k$
0.2	0.001	98	0.64	0.65

Rate of ionization in acetate buffered solution at 25°C

r = 0.01

I = 0.3M

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10} v$	$10^8 k_{obs}$
0.01	100	200	0.125	0.66	0.66

Rate of ionization in pyridine buffered solution at 25°C

r = 0.01

I = 0.2M

$k_{calc} = 0.65 \times 10^{-8} + 8.45 \times 10^{-7}[pyridine]$

$10^4[A^-]$	$10^2[pyridine]$	$10^{10} v$	$10^8 k_{obs}$
100	10	9.1	9.1

Trans-2-acetylcyclohexanecarboxylic acid (XIX)

Kinetic Method - Spectrophotometric

Apparatus and materials - as described

The rates of ionization in self buffered, acetate buffered and pyridine buffered solutions are listed in Table 25. A value for the first order velocity constant k_1, of 5.65×10^{-8} sec^{-1} was obtained. A catalytic constant for acetate ions, k_{13}, of 15.1×10^{-8} l mol^{-1} sec^{-1} and for pyridine, k_{py}, of 34.4×10^{-8} l mol^{-1} sec^{-1} were obtained as before.

TABLE 25

Rate of ionization in self buffered solution at 25°C

I	$10^4[H^+]$	$10^4[A^-]$	$10^{10}v$	10^8k
0.2	0.01	196	11.04	5.6
0.2	0.01	196	11.18	5.7

mean $k = 5.65 \times 10^{-8}$ sec^{-1}

Rate of ionization in acetate buffers at 25°C

$r = 0.1$

$I = 0.3M$

$k_{calc} = 5.96 \times 10^{-8} + 15.1 \times 10^{-8}[AcO^-]$

r'	$10^4[A^-]$	$10^3[AcO^-]$	$10^6[H^+]$	$10^{10}v$	10^8k_{obs}	10^8k_{calc}
0.1	94	40	2.6	6.20	6.6	6.6
0.1	94	80	2.6	6.75	7.2	7.2
0.1	94	120	2.6	7.15	7.6	7.8
0.1	94	160	2.6	7.88	8.4	8.4
0.1	94	200	2.6	8.45	9.0	9.0

Rate of ionization in pyridine buffers at 25°C

$r = 0.1$

$I = 0.2M$

$[A^-] = 0.01$ throughout

$k_{calc} = 5.60 \times 10^{-8} + 34.4 \times 10^{-8}[pyridine]$

$10^2[pyridine]$ (M)		2	4	6	8	10
10^8k	obs	6.31	6.89	7.75	8.35	9.02
	calc	6.29	6.98	7.67	8.25	9.04

DISCUSSION

For ease of reference the rate constants obtained are listed in Table 26. The 'mixed' and 'true' acid dissociation constants and pK_a values for each keto-acid are summarized in Table 27.

TABLE 26

Summary of Rate Constants

k_1 = Intramolecular first-order velocity constant in self buffered solution. (sec^{-1})

k_1' = Intramolecular first-order velocity constant obtained from the intercept of the plots k_{obs} vs $[AcO^-]$. (sec^{-1})

k_1'' = Intramolecular first-order velocity constant obtained from the intercept of the plots k_{obs} vs [pyridine]. (sec^{-1})

k_{13} = catalytic constant for acetate ions (1 mol^{-1} sec^{-1})

k_{py} = catalytic constant for pyridine (1 mol^{-1} sec^{-1})

Compound	10^8k_1	$10^8k_1'$	$10^8k_1''$	10^8k_{13}	10^8k_{py}
X	205	205	215	400	2330
XI	502	-	-	-	-
XII	57.4	56.2	55.9	176	400
XIV	265	269	265	225	1320
XV	336	333	384	473	3110
XVI	3.32	3.24	4.56	22.7	803
XVII	105	106	107	100	845
XVIII	0.65	-	0.65	-	84.5
XIX	5.65	5.96	5.60	15.1	34.4

TABLE 27

Summary of K_a and pK_a Values

K_a = 'Mixed' acid dissociation constant

$pK_a = -\log K_a$

K_a^T = 'True' acid dissociation constant (from nitramide experiments)

$pK_a^T = -\log K_a^T$

Compound	$10^6 K_a$	pK_a	$10^5 K_a^T$	pK_a^T
X	74.10	4.13	30.9	3.51
XI	28.20	4.55	21.0	3.68
XII	549.0	3.26	83.2	3.08
XIII	78.75	4.10	100	3.00
XIV	57.83	4.24	22.4	3.65
XV	37.50	4.43	23.4	3.63
XVI	20.70	4.68	35.5	3.45
XVII	33.88	4.47	22.9	3.64
XVIII	3.05	5.52	-	-
XIX	24.55	4.61	4.68	4.33

A) Ortho-acetylbenzoic acid

(i) Self buffered solutions

In the introduction it was assumed that only intramolecular base catalysis need be considered and a simplified rate expression of the form

$$v = k_1[A^-]$$

was considered adequate to describe the system. It was suggested that other possible catalytic processes contribute little to the observed rate and estimates of these contributions can be fairly readily obtained.

Bell and Lidwell (71) have studied the base catalysed halogenation of compounds of the type $CH_3COCHR_1R_2$, where R_1 and R_2 are not strongly electronegative substituents, in which catalysis by water molecules produced rate constants of approximately 10^{-10} l mol^{-1} sec^{-1}. It has also been shown that catalysis by water molecules, acting both as an acid and a base, in the halogenation of acetone give rate constants of the same order of magnitude (72). It is therefore reasonable to assume that in the present system the water catalysed ionization reactions may be ignored (i.e. k_{11} and k_{12}).

Bell and Lidwell also reported rate constants for the catalysis of the same compounds by hydroxide ions. These were found to be about a factor of 10^6 greater than the corresponding rate constants obtained for catalysis by acetate ions. Assuming a similar relationship for the present system gives a value for the catalytic constant for hydroxide ions of about 4 l mol^{-1} sec^{-1}. However, the presence of a negatively charged carboxylate ion in a position ortho to the acetyl group can be expected to restrict the approach of the hydroxide ion and consequently reduce its efficiency. This would explain the results obtained by Harper and Bender in their study of ortho-isobutyrylbenzoic acid, where they obtained a catalytic constant for the hydroxide ion catalysed ionization, k_{10}, of $4.4 \pm 1.6 \times 10^{-3}$ l mol^{-1} sec^{-1}. Making

a statistical correction for the difference in the number of α-hydrogens between ortho-acetylbenzoic acid and ortho-isobutyrylbenzoic acid the value for k_{10} becomes approximately 1.3×10^{-2} l mol^{-1} sec^{-1}. Assuming that the statistical correction is valid and that no further corrections to the Harper and Bender value are necessary then at the highest pH used in the present work, where $[OH^-] = 10^{-8}M$, then $k_{OH^-}[OH^-]$ becomes approximately 1.3×10^{-10} sec^{-1}.

The possibility of intermolecular proton transfer from the keto-acid to hydroxide ions, k_9, as an alternative to intramolecular proton transfer by the carboxylate ion will be discussed later.

Harper and Bender give a value of approximately 1.1×10^{-6} l mol^{-1} sec^{-1} for the catalytic constant k_7, the intermolecular hydronium ion catalysed reaction with ortho-isobutyrylbenzoic acid. A statistical correction to the ortho-acetylbenzoic acid system would give a figure of 3.3×10^{-6} l mol^{-1} sec^{-1} and at pH2 the observed first-order velocity constant would only amount to approximately 3×10^{-8} sec^{-1}.

An indication of the magnitude of the rate of the intermolecular ortho-acetylbenzoate catalysed reaction, k_3, can be obtained in a number of ways. During the present work the catalytic constant for the acetate catalysed ionization of ortho-acetylbenzoate was found to be about 4×10^{-6} l mol^{-1} sec^{-1}. The reactivity of the benzoate ion is about one-third that of the acetate ion in enolization reactions (72) giving an estimate of 1.3×10^{-6} l mol^{-1} sec^{-1} for $k_{benzoate}$. The benzoate ion is less sterically hindered than the keto-acid anion because of the absence of an ortho-substituent and it is therefore to be expected that the catalytic constant for the latter ion would be even smaller. Assuming a value of 5×10^{-7} l mol^{-1} sec^{-1} as an upper limit to the value of k_3 and with a concentration of $10^{-2}M$ for ortho-acetylbenzoate then an estimate for the first-order velocity constant of 5×10^{-9} sec^{-1} is obtained.

Further evidence to suggest intermolecular catalysis by the keto-acid anion of this order of magnitude is based upon the iodination of para-acetylbenzoic acid where no intramolecular catalysis can occur (28). At pH6 the observed

rate for the disappearance of iodine in the presence of 2×10^{-2}M substrate is 7.6×10^{-9} sec^{-1} giving a catalytic constant for the anion (assuming no other catalysis) of 3.8×10^{-7} l mol^{-1} sec^{-1}. This value is slightly lower than that estimated for the ortho-acetyl benzoate ion above.

k_3 can also be estimated by using the Brönsted relationship

$$k_B = G(1/K_a)^{\beta}$$

where k_B is the catalytic constant for the anion of the acid A, K_a the acid dissociation constant of the acid A and G and β are constants. Substituting the appropriate values into the expression

$$k_3 = k_{13}(K_{AcOH}/K_{HA})^{\beta}$$

where $k_{13} = 4 \times 10^{-6}$ l mol^{-1} sec^{-1}

$K_{AcOH} = 1.758 \times 10^{-5}$

$K_{HA} = 3.1 \times 10^{-4}$

$\beta \simeq 0.8$

gives

$$k_3 \simeq 4 \times 10^{-7} \text{ l mol}^{-1} \text{ sec}^{-1}$$

which is in very good agreement with the estimates already obtained. The value of K_{HA} used is the 'true' acid dissociation constant estimated from the catalytic effect of the anion on the decomposition of nitramide.

Harper and Bender obtained a value of $1.5 \pm 0.2 \times 10^{-7}$ sec^{-1} for the first-order velocity constant k_2 for the intramolecular acid catalysed ionization of ortho-isobutyrylbenzoic acid. It has already been shown that ortho-acetylbenzoic acid exists as the chain tautomer (20%) and as the ring tautomer (80%) and this implies that only one-fifth of the keto-acid in the system will be able to exhibit intramolecular acid catalysis. For a solution of 10^{-2}M ortho-acetylbenzoic acid and introducing a statistical factor of 3 for the increase in the number of available hydrogens the predicted rate of disappearance of iodine would be approximately 10^{-9} mol l^{-1} sec^{-1}.

The last six results in Table 12 relate to experiments at pH < 4 in which there is an appreciable amount of unionized keto-acid. If any intramolecular acid catalysis were apparent then the value of the first-order velocity constant would tend to increase with decrease in pH. In fact the results tend to be below the mean value of k at low pH. It is doubtful whether this trend is due to any catalytic effect. An appreciable correction to the anion concentration is required and this depends considerably on the values assumed for the activity coefficients. The uncertainty of the correction, due to the use of the Davies Equation up to an ionic strength of 0.3M, is of the same order of magnitude as the observed discrepancy.

This argument can also apply to the intermolecular hydronium ion catalysed ionization of the keto-acid anion as this process is kinetically undistinguishable from the intramolecular acid catalysed process.

Further analysis is complicated by the fact that the unionized keto-acid can exist as two tautomers in aqueous solution.

However the constancy of the first-order velocity constant with varying buffer ratio indicates that the intramolecular base catalysed process is dominant and that the effect of all the other catalytic processes is negligible. This seems to justify the use of the simplified rate expression. Therefore in future calculations and with reference to the other keto-acids studied a value for the intramolecular base catalysed ionization of ortho-acetylbenzoic acid of 2.05×10^{-6} sec^{-1} has been used. The last five results in Table 12 have been neglected because of the large uncertainty in the correction applied.

(ii) Acetate buffered solutions

It was shown earlier that the rate constants k_{13}, k_{14}, k_{15} and k_{16} can be estimated by completing a series of experiments at various acetate buffer ratios, r, a graph of $v(K_2 + K_1 r)/a$ against $[AcO^-]$ giving a slope of

$$k_{13}K_2 + r(k_{14}K_1 + k_{15}K_2) + k_{16}K_1 r^2 \qquad (17)$$

However, this method is only valid if the buffer ratio remains constant throughout each series of experiments. It is seen from Table 13 that the true buffer ratio varies appreciably in the more acid acetate buffers because of the relatively high hydrogen ion concentration in the system. Therefore $v(K_2 + K_1 r)/a$ has been calculated using the corrected buffer ratios, see Table 14. Values for expression (17) were obtained from the slopes of the plots of $v(K_2 + K_1 r)/a$ against $[AcO^-]$ for each buffer ratio (see Fig.13, 14 and 15). The average value of r for each series of experiments was substituted into the relevant expression and the value of the various rate constants calculated. Thus

for r = 0.1

$$k_{13}K_2 + 0.1(k_{14}K_1 + k_{15}K_2) + 0.01\, k_{16}K_1 = 4.7 \times 10^{-10} \text{ l mol}^{-1}\text{sec}^{-1}$$

for r = 0.96

$$k_{13}K_2 + 0.96(k_{14}K_1 + k_{15}K_2) + 0.92\, k_{16}K_1 = 4.9 \times 10^{-10} \text{ l mol}^{-1}\text{sec}^{-1}$$

for r = 9.2

$$k_{13}K_2 + 9.2(k_{14}K_1 + k_{15}K_2) + 84.64\, k_{16}K_1 = 6.5 \times 10^{-10} \text{ l mol}^{-1}\text{sec}^{-1}$$

Solving these equations for k_{13}, $(k_{14}K_1 + k_{15}K_2)$ and k_{16} gives

$$k_{16} = -6.7 \times 10^{-9} \text{ l mol}^{-1} \text{ sec}^{-1}$$

The error in sign could be attributed to experimental error and the result indicates that catalysis by acetic acid on ortho-acetylbenzoic acid is too small to measure accurately. Assuming k_{16} to be zero gives

$$k_{13} \simeq 4.00 \times 10^{-6} \text{ l mol}^{-1} \text{ sec}^{-1}$$

$$k_{14} \simeq (6.3 \times 10^{-7} - 4.23\, k_{15}) \text{ l mol}^{-1} \text{ sec}^{-1}$$

$$k_{15} \simeq (1.47 \times 10^{-7} - 0.24\, k_{14}) \text{ l mol}^{-1} \text{ sec}^{-1}$$

An estimate of the various contributions at different acetate buffer ratios can now be made.

At r = 0.1

$$k_{13}K_2 = 4.69 \times 10^{-10} \text{ l mol}^{-1} \text{ sec}^{-1} \equiv 99.5\%$$

At r = 1.0

$$k_{13}K_2 = 4.69 \times 10^{-10} \text{ l mol}^{-1} \text{ sec}^{-1} \equiv 95.8\%$$

$$r(k_{14}K_1 + k_{15}K_2) = 1.89 \times 10^{-11} \text{ l mol}^{-1} \text{ sec}^{-1} \equiv 3.9\%$$

At r = 10.0

$$k_{13}K_2 = 4.69 \times 10^{-10} \text{ l mol}^{-1} \text{ sec}^{-1} \equiv 72.6\%$$

$$r(k_{14}K_1 + k_{15}K_2) = 1.89 \times 10^{-10} \text{ l mol}^{-1} \text{ sec}^{-1} \equiv 29.3\%$$

The results justify the use of the simplified rate expression for acetate buffered solutions at buffer ratios $r \leq 1.0$. At r = 10.0 the results indicate that the processes involving (AcO^- + HA) and (AcOH + A^-) become more important. Rather large corrections have had to be made, however, for the hydrogen ion concentration which depends considerably on the values assumed for the activity coefficients. It must also be remembered that at this buffer ratio the concentration of acetic acid reached 2M, which constitutes a considerable change in the reaction medium. Even so there seems to be reasonable correlation between the calculated and observed first-order velocity constants.

The figure obtained for k_{13} (4.00×10^{-6} l mol^{-1} sec^{-1}) is consistent with a value of 2.3×10^{-6} l mol^{-1} sec^{-1} obtained by extrapolating to 25°C the results of Evans and Gordon (64) for the acetate catalysed bromination of acetophenone in 75% aqueous acetic acid at 45°, 55° and 65°C.

(iii) Pyridine buffered solutions

Calculated first-order velocity constants have been obtained from the expression

$$k_{calc} = 2.15 \times 10^{-6} + k_{py}[\text{pyridine}] \text{ sec}^{-1}$$

the results corresponding reasonably well with those observed (Table 15). The value of 2.33×10^{-6} l mol^{-1} sec^{-1} for the catalytic constant k_{py} was obtained from the slope of the plot of $10^8 k$ against [pyridine]. The intercept, which corresponds to k_1, is slightly greater than the previously accepted value, but contributions to the observed velocity by the hydroxide ion at this higher pH has not been considered.

B) The keto-acids except ortho-acetylbenzoic acid

With all the keto-acids studied, except for 8-acetyl-1-naphthoic acid, the results obtained for the rates of ionization in acetate buffered solutions clearly showed a contribution due to proton abstraction by acetate ions. This can be accounted for by the addition of a term $k_{13}[AcO^-][A^-]$ to the simplified rate expression, $v = k_1[A^-]$. There are slight discrepancies between the calculated and observed first-order velocities but this cannot be explained by adding extra terms involving [AcOH] and $[OH^-]$ to the rate expression.

In pyridine buffered solutions intermolecular catalysis by pyridine molecules was indicated and the increase in rate has been accounted for by including the term k_{py}[pyridine]$[A^-]$ in the simplified rate expression. In general the intramolecular first-order velocity constant obtained from pyridine buffered solutions was slightly higher than that obtained from self buffered solutions. It is thought that this was due to catalysis by hydroxide ions because of the higher pH of these solutions.

For clarity, the ionization of the other keto-acids in self buffered, acetate and pyridine buffered solutions will be considered together.

Substituents, by exerting mesomeric and inductive effects, will alter not only the basic strength of the carboxylate ion but also the reactivity (acidity) of the acetyl group. Also, substituents adjacent either to the carboxylate ion or the acetyl group will inhibit the co-planarity of these groups with the benzene ring and will therefore not only reduce the effectiveness of the intramolecular proton transfer process but also reduce or destroy the mesomeric effect associated with these groups. The acidity of the acetyl group, relative to that in ortho-acetylbenzoic acid,

can be estimated by comparing the catalytic constants for the intermolecular acetate ion proton transfer reaction. This assumes that no further steric interaction between the acetate ion and the keto-acid has been introduced by the additional substituent. This comparison is best made using the acetate ion rather than pyridine because the latter molecule is more susceptible to steric influence.

The value of the observed intramolecular base catalysed rate of ionization for ortho-isobutyrylbenzoic acid was in complete agreement with that obtained by Harper and Bender (31). No acetate ion or pyridine catalysis was detected although pyridine is more effective in promoting the ionization of ketones. This supports the argument that the lone α-hydrogen of the isopropyl group is shielded from intermolecular attack and that only intramolecular catalysis can occur under the experimental conditions studied.

The results obtained for the keto-acids whose added substituents do not interfere sterically with the acetyl and carboxylate groups are as expected. The increase in basicity of the carboxylate ion, due to methyl or methoxy groups in the 4,5 position, results in an increase in the intramolecular proton transfer reaction. 2-Acetyl-3-naphthoic acid can be considered to be ortho-acetylbenzoic acid substituted with a benzene ring fused in the 4,5 position. The 'true' acid dissociation constant indicated a weaker acid than ortho-acetylbenzoic acid and therefore it would be expected that the intramolecular rate of ionization would be greater. In fact the reverse was observed.

From Table 26 it can be seen that the value for the intermolecular acetate ion catalysed reaction is less than that for ortho-acetylbenzoic acid indicating that the acetyl group is less acidic. This decrease in rate could also be explained by reduced conjugation of the enolate ion in the 10-π system as compared to the 6-π system because of the greater delocalization of charge and therefore the resulting intermediate would not be stabilized to the same extent as in the benzenoid system.

With all the other keto-acids studied substituents in the 3 and 6-position interfere sterically with either the acetyl group or carboxylate group.

In the discussion on ring-chain tautomerism it was stated that considerable steric effects occur when a substituent is placed in the 6-position, adjacent to the carboxyl group. The twisting of this group out of the plane of the benzene ring which results from this substitution can also be considered to occur for the anion. The transition state for the intramolecular base catalysed ionization will be planar and therefore the twisting of the carboxylate ion out of the plane will result in a higher free energy of activation. Under identical conditions it is therefore to be expected that the keto-acids which exhibit steric interference will ionize at a slower intramolecular rate than those unaffected sterically. The intramolecular rate for 2-acetyl-6-methylbenzoic acid was slower than that for ortho-acetylbenzoic acid. The magnitude of this effect cannot be explained by the slight increase in acidity of this compound compared with that of ortho-acetylbenzoic acid (ΔpK_a^T = -0.05 pK_a unit) and it is thought to be almost entirely due to steric interference of the methyl group with the carboxylate ion. The low value obtained for the intermolecular acetate ion catalysed reaction may be due to shielding of the acetyl group protons from approach of the acetate ion by the negatively charged carboxylate group. It is to be expected that approach by the neutral pyridine molecule will be easier and in fact a relatively higher value was obtained for k_{py} for 2-acetyl-6-methylbenzoic acid. The relationship between k_{py} and k_{13} will be discussed more fully later.

2-Acetyl-3-nitrobenzoic acid is more acidic than the parent keto-acid and it is the acetyl group that is preferentially twisted out of the plane of the ring (10). It was expected that this twisting of the acetyl group would reduce the effectiveness of the negative mesomeric effect and therefore increase the acidity of the acetyl protons. The overall effect, however, was a lowering of the rate of intramolecular proton transfer

suggesting that the decrease in basicity of the carboxylate ion is the more dominant effect. The relatively low values obtained for the intermolecular reaction rates can be explained by the reduction in the number of directions of approach available to the acetate ion or pyridine molecule.

From the foregoing discussion it was thought that 2-acetyl-3,4,5,6-tetrachlorobenzoic acid would show a decrease in rate similar to that of the 6-methyl- and 3-nitro-derivatives. However no zero-order traces could be obtained for this keto-acid, the rate of disappearance of iodine decreasing with time even when a number of successive additions of iodine were made. It is doubtful whether there was any significant amount of impurity present because results of elemental analysis and equivalent weight determination compare favourably with the calculated values. If multiple halogenation was occurring then the rate of disappearance of iodine should have increased with time because of an increase in acidity of the remaining hydrogens of the monoiodinated acetyl group. Multiple iodination also seems unlikely because of the suggested formation of a lactone (XXI) similar to that found after iodination of ortho-isobutyrylbenzoic acid. Incomplete scavenging may be the reason for the unexpected kinetic runs obtained.

It can be seen from Table 26 that the rates of ionization in self buffered, acetate buffered and pyridine buffered solutions for 8-acetyl-1-naphthoic acid are much slower than those for ortho-acetylbenzoic acid. Capon and his collaborators (73) compared the intramolecular acid catalysed hydrolysis of 8-methoxymethoxynaphthoic acid with that of 2-methoxymethoxybenzoic acid and found that the substituted naphthoic acid showed reduced catalytic efficiency over the substituted benzoic acid. This reduction in efficiency was attributed to the carboxyl group being less well orientated for proton transfer due to twisting out of the plane of the naphthalene ring. The same reasoning can be used to explain the marked decrease in the intramolecular base catalysed ionization of 8-acetyl-1-naphthoic acid. Not only will the carboxylate

group be twisted out of the plane of the ring because of the close proximity of the two groups but an 8-membered cyclic transition state (including the proton being transferred) will be involved as compared to a 7-membered cyclic transition state for the benzenoid system. As this was the only keto-acid where the rate of ionization was determined at pH7, it is quite possible that only a small proportion of the observed rate in self buffered solution is due to intramolecular catalysis the remainder being due to intermolecular catalysis between two anions or to abstraction of a proton by hydroxide ions. It is assumed that no acetate catalysis was detected because of efficient shielding by the carboxylate ion. The value obtained for k_{py} could well include some catalysis due to hydroxide ions, the pH of the solutions being greater than 7.

Trans-2-acetylcyclohexanecarboxylic acid was the other keto-acid that showed intramolecular base catalysis. Proton abstraction is possible from two sites, either from the acetyl group or the ring carbon attached to this group. In the former case a 7-membered cyclic transition state will be involved, although the groups are not as suitably orientated as they are in the benzenoid system. With proton abstraction from the ring carbon a 5-membered cyclic transition state will be involved. It is thought that the ring hydrogen will be more acidic than the acetyl hydrogens because of the negative inductive effects of both the acetyl and carboxyl groups. Because the 5-membered transition state is preferred (8) and the ring hydrogen is thought to be more acidic it should be removed more easily intramolecularly than the acetyl hydrogens. The kinetic data do not indicate the site of proton abstraction. An N.M.R. spectrum of the keto-acid clearly indicates the presence of methyl protons but the ring hydrogen is not clearly shown because of the complexity of the spectrum. It was not possible to determine the relative magnitude of the two processes by a deuterium exchange reaction because integration was not sensitive enough to pick out the ring hydrogen.

With most of the keto-acids studied the acetyl and carboxyl groups are subjected to steric interaction from

substituents in adjacent positions and therefore it is not possible to apply the Hammett relationship

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

where

k_o = observed first-order velocity constant for ortho-acetylbenzoic acid

k = observed first-order velocity constant for the other keto-acids.

The intramolecular rate constant, k_1, for any of the compounds studied is dependent upon the basicity of the carboxylate group and the reactivity of the acetyl group. Therefore the Brönsted relation

$$\log k = G + \beta pK_a^T$$

is not immediately applicable. An attempt was made to modify k_1 by dividing by k_{13} thereby allowing for the effect of the reactivity of the acetyl group. However this assumes equal interaction between the acetate ion and all the keto-acid anions. This assumption is not believed to be strictly valid. It was not possible to correct for the decreased basicity of those keto-acids whose carboxylate groups are not coplanar with the aromatic ring. No correlation was observed.

The Relationship between k_{py} and k_{13}

If there is no steric interaction or repulsion of like charges involved during the intermolecular base catalysed ionization of the keto-acid anion by acetate ions or pyridine molecules then the following relationship should hold

$$k_{py}/k_{13} = (K_{AcOH}/K_{py})^{0.8} = 2.4$$

The value of 0.8 has been chosen as being typical for this type of reaction. Table 28 lists the values of k_{py}/k_{13} for the keto-acids studied.

For keto-acids where there is no steric interaction between further substituents and the acetyl and carboxyl groups the ratio of $(k_{py}/k_{13})^{0.8}$ is in the range 4.1 - 5.5. These values are greater than the theoretical value indicating that the reaction with acetate ion may be being retarded by a repulsive interaction with the substrate anion.

The low value of 2.1 obtained for 2-acetyl-3-nitrobenzoic acid reflects the steric hindrance imposed by the nitro group in the 3-position to the approach of the bulkier pyridine molecule.

The value of 2.0 obtained for trans-2-acetylcyclohexanecarboxylic acid is also on the low side. This may be an indication that the ring hydrogen is preferentially removed. Approach to the ring hydrogen is partially blocked by the cyclohexane ring and therefore should be more difficult for the bulkier pyridine molecule than the acetate ion. Approach to the acetyl group should be easier which would presumably give a higher value.

Efficient shielding of the acetyl group by the carboxylate ion could explain the high value obtained for 2-acetyl-6-methylbenzoic acid.

TABLE 28

Values obtained for the ratio k_{py}/k_{13}

Compound	$(k_{py}/k_{13})^{0.8}$
X	4.1
XI	-
XII	2.1
XIV	4.1
XV	4.5
XVI	17.2
XVII	5.5
XVIII	-
XIX	2.0

The Relationship between Inter- and Intramolecular Processes

Inter- and intramolecular processes can be compared by introducing the concept of 'effective concentration', c_i. This concept illustrates the significance of intramolecular basic catalysis compared with the corresponding intermolecular basic catalysis. c_i is the concentration (in mol l^{-1}) at which inter- and intramolecular processes would make equal contributions to the reaction rate. In this work the 'effective concentration' is defined as

$$c_i = k_1/k_3$$

where

k_1 = intramolecular first-order velocity constant, sec^{-1}

k_3 = intermolecular second-order velocity constant involving two keto-acid anions, 1 mol^{-1} sec^{-1}

Thus, c_i represents the concentration of A^- that needs to be present so that the intermolecular rate involving two keto-acid anions equals the intramolecular rate due to the carboxylate ion. The 'effective concentration' can also be determined for acetate ions or pyridine molecules by replacing k_3 by k_{13} or k_{py} respectively.

A value of $\sim 4 \times 10^{-7}$ 1 mol^{-1} sec^{-1} for k_3 has already been estimated for ortho-acetylbenzoic acid using the Brönsted relationship

$$k_3 = k_{13}(K_{AcOH}/K_{HA})^{\beta}$$

and estimates for k_3 have been made in the same way for all the keto-acids studied except for ortho-isobutyrylbenzoic acid and 8-acetyl-1-naphthoic acid. In both cases no acetate catalysis was detected and in the latter case no value for K_a^T was determined. The values estimated for k_3 and c_i are listed in Table 29.

TABLE 19

Estimates for k_3 and c_i

Keto-acid	k_3(1 mol^{-1} sec^{-1})	c_i(mol l^{-1})
X	4.0×10^{-7}	5.0
XII	8.0×10^{-7}	7.1
XIV	2.9×10^{-7}	9.0
XV	6.0×10^{-7}	5.6
XVI	2.1×10^{-8}	1.6
XVII	1.3×10^{-7}	8.2
XIX	6.9×10^{-8}	0.8

Because of the approximations involved the values obtained for c_i are only good to a factor of approximately 2. Most of the values obtained for c_i are in the range 5 - 9 mol l^{-1} except for 1.6 mol l^{-1} for 2-acetyl-6-methylbenzoic acid and 0.8 mol l^{-1} for trans-2-acetylcyclohexanecarboxylic acid indicating that intramolecular basic catalysis is not as efficient for these two compounds.

The values obtained for c_i are considerably less than 56 mol l^{-1}, the value quoted by Harper and Bender (31) for ortho-isobutyrylbenzoic acid, although the values are not strictly comparable. Harper and Bender compared the catalytic constant for the intramolecular carboxylate ion catalysed reaction against the catalytic constant for the iodination of isobutyrophenone catalysed by benzoate ions, rather than with any intermolecular process involving the ortho-isobutyrylbenzoate ion itself. This treatment would decrease Harper and Bender's value for the effective molarity.

If the 'effective concentration' is calculated for 5-ketohexanoic acid, the aliphatic keto-acid studied by Bell and Fluendy (8) with the most efficient intramolecular process, then a value of 1 mol l^{-1} for the levulinate ion is obtained. Clearly intramolecular basic catalysis is more efficient for

non-sterically hindered aromatic acids than for the aliphatic keto-acids.

The low values obtained for c_i may be due to the relatively loose transition state associated with proton transfer reactions (63,74). This results in a relatively small loss in entropy when compared to the entropy loss in forming a tight transition state.

POSSIBLE ALTERNATIVE MECHANISMS TO EXPLAIN THE APPARENT INTRAMOLECULAR CATALYSIS

The mechanism for ionization in self buffered solution can either be considered as intramolecular abstraction of methyl protons by the keto-acid anion or as transfer of methyl protons from the undissociated acid to hydroxide ions. These mechanisms can be represented by (XXII) and (XXIII) respectively.

The magnitude of k_1, about 2×10^{-6} sec^{-1} for ortho-acetylbenzoic acid, is much too great to be attributed to intermolecular catalysis by water molecules on the anion, since for ketones not containing strongly electronegative substituents the process has rate constants of about 10^{-10} sec^{-1} (71). This information has already been used in justifying the use of a simplified rate expression.

It is possible to estimate a value of the catalytic constant k_{OH^-} for mechanism (XXIII) in the following way.

The rate of disappearance of iodine for intramolecular catalysis is represented by the equation

$$v = k_1[A^-] \qquad (18)$$

and the rate of disappearance of iodine for intermolecular catalysis of OH^- on HA by

$$v = k_{OH^-}[OH^-][HA] \qquad (19)$$

Equating (18) and (19) gives

$$k_1[A^-] = k_{OH}[OH^-][HA]$$

$$k_{OH^-} = k_1[A^-]/[OH^-][HA] \qquad (20)$$

By definition

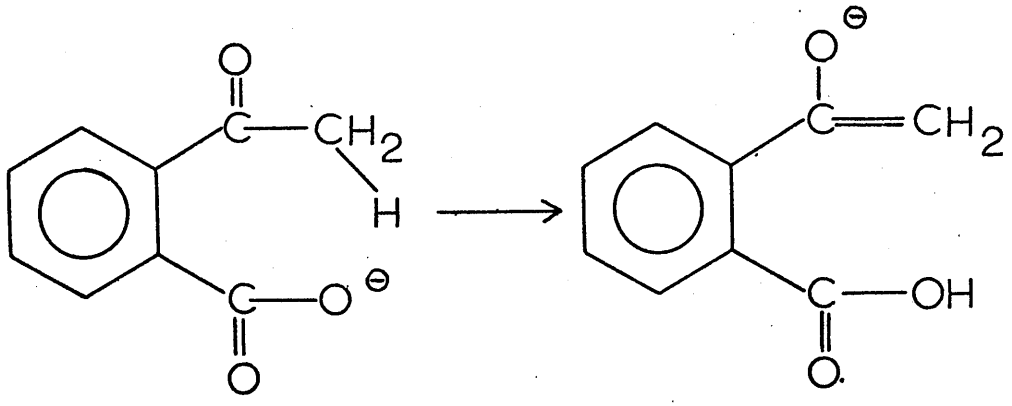
$$[OH^-] = K_w/[H^+] \qquad (21)$$

and

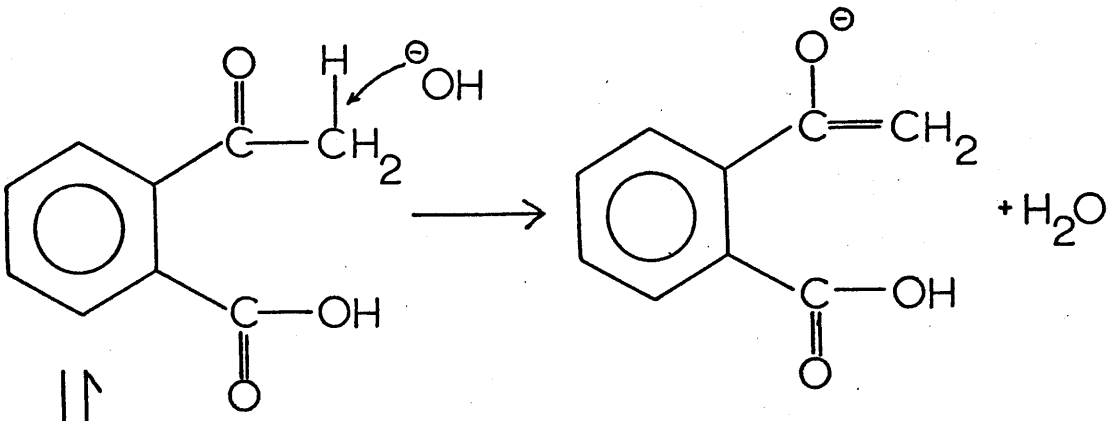
$$[A^-]/[HA] = K_a/[H^+] \qquad (22)$$

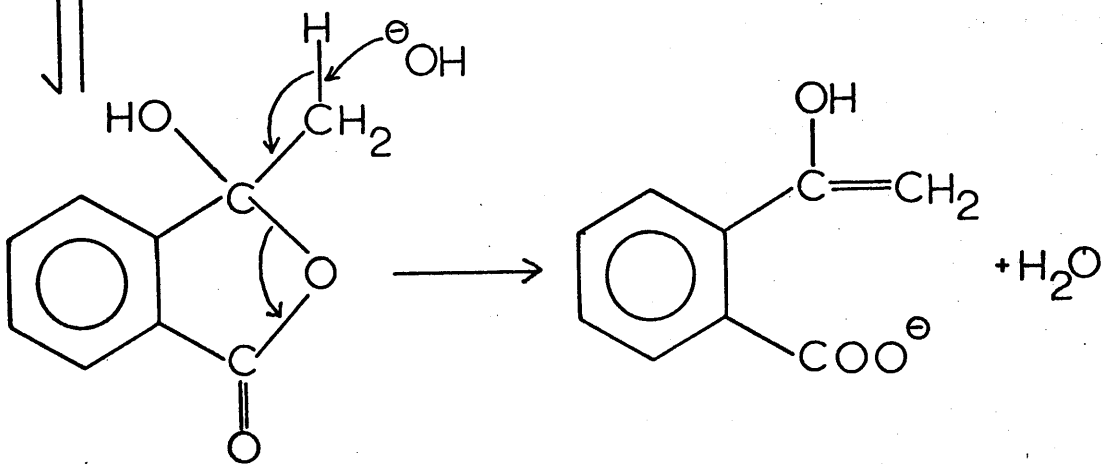
Substituting (21) and (22) into (20) gives

$$k_{OH^-} = k_1 K_a/K_w$$

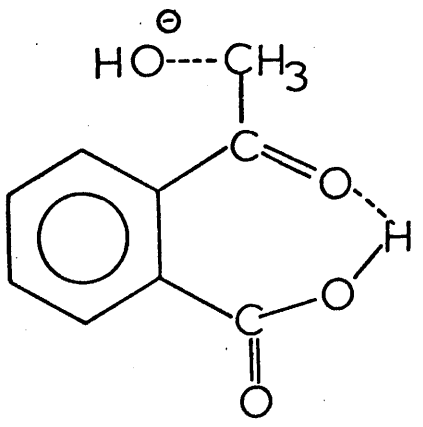


XXII

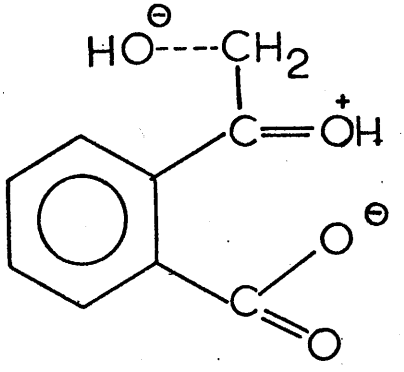




XXIII



XXIV



XXV

Substituting known values for ortho-acetylbenzoic acid (for example) into this equation where

$$k_1 = 2.08 \times 10^{-6} \text{ sec}^{-1}$$
$$K_a = 7.41 \times 10^{-5}$$
$$K_w = 1.0 \times 10^{-14}$$

gives

$$k_{OH^-} \simeq 15{,}400 \text{ l mol}^{-1} \text{ sec}^{-1}$$

Jones and his co-workers (75) have measured proton abstraction by hydroxide ions from a number of substituted acetophenones and have obtained velocity constants of the order of 1 l mol^{-1} sec^{-1}. The figure just calculated therefore seems unusually high and tends to disprove the mechanism involving hydroxide ions. It therefore seems likely that the observed rate is primarily due to abstraction of protons from the acetyl group by the ortho-carboxylate group. Calculation of k_{OH^-}, in the above manner, for the other keto-acids studied indicates that intramolecular abstraction of protons from the acetyl group is the more likely mechanism for all except 8-acetyl-1-naphthoic acid (Table 30).

TABLE 30

Estimation of k_{OH^-}

Keto-acid	k_{OH^-} (l mol^{-1} sec^{-1})
X	15,400
XI	25,000*
XII	31,500
XIV	15,300
XV	12,600
XVI	69
XVII	3,300
XVIII	2
XIX	139

* Harper and Bender (31)

8-Acetyl-1-naphthoic acid is a special case, the value of k_1 being distorted by the poor orientation of the acetyl and carboxylate groups.

On kinetic grounds other mechanisms could be written involving transition states of the types shown, (XXIV) and (XXV), both leading to the enol. Although (XXIV) is shown as being concerted it does not follow that this is actually the case since just the same kinetic result is achieved if the substrate first associates with the acid (intramolecular hydrogen bonding) and is subsequently attacked by the base, or vice versa. The value of the catalytic constant $k_{OH^-,HA}$ is approximately 2×10^4 l mol^{-1} sec^{-1} for most of the keto-acids which means that the carboxylic acid group must enhance the rate by a factor of about 10^5. This seems very unlikely since Page (76) has shown that proton transfer from bicyclo-|2.2.2|-octan-2-one 1 carboxylic acid by water is assisted by intramolecular acid catalysis, but only increasing the rate by a factor of 10^2.

This system involves a 6-membered cyclic transition state whereas the system being studied involves a 7-membered transition state and therefore this increase in rate will probably be less than 10^2.

CHAPTER 4

GENERAL CONCLUSIONS

GENERAL CONCLUSIONS

The percentages of ring and chain tautomers were determined by comparing the 'mixed' and 'true' acid dissociation constants for each keto-acid and the results compare favourably with published results obtained by other methods (although comparison is not strictly valid because of differing experimental conditions).

As expected, all the keto-acids studied exhibited, to some degree, intramolecular basic catalysis and no unexpected results were obtained except for 2-acetyl-3,4,5,6-tetrachlorobenzoic acid for which no zero-order traces were obtained. It was concluded from the detailed study of ortho-acetylbenzoic acid that only intramolecular basic catalysis was observable under the general conditions used for self buffered solutions ($\sim$ pH6). The only intermolecular process detected in the presence of an acetic acid-sodium acetate buffer at a buffer ratio of 0.1 was due to acetate ions, catalysis by acetic acid becoming more important at higher buffer ratios. All the keto-acids except ortho-isobutyrylbenzoic acid and 8-acetyl-1-naphthoic acid, exhibited intermolecular acetate catalysis and even the latter compound exhibited intermolecular pyridine catalysis.

No correlation between the 'true' acid dissociation constant and the intramolecular first-order velocity constant was possible because of the diverse nature of the substituents used and the varied positions of these substituents in relation to the acetyl and carboxylate groups.

From the higher values obtained for the effective molarity for aromatic keto-acids compared to those for the aliphatic keto-acids it seems clear that intramolecular basic catalysis is more efficient for the non-sterically hindered aromatic acids. This increase in efficiency of the intramolecular process can be explained in terms of the loss of internal rotational motions in going from the aliphatic to the aromatic system, as previously suggested. The values of the effective molarity are low when compared with the effective molarities obtained from other favourable processes and it has been suggested that this may be due to the relatively loose transition state associated with proton transfer reactions.

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APPENDIX 1

Activity Coefficients and Acid Dissociation Constants used in this Work

For I = 0.2 $f_{\pm} = 0.7683$

For I = 0.3 $f_{\pm} = 0.7638$

Compound	K at I = 0.2	K at I = 0.3
X	12.70×10^{-5}	12.83×10^{-5}
XI	4.78×10^{-5}	4.83×10^{-5}
XII	93.08×10^{-5}	94.06×10^{-5}
XIII	13.35×10^{-5}	13.49×10^{-5}
XIV	9.81×10^{-5}	9.91×10^{-5}
XV	6.36×10^{-5}	6.43×10^{-5}
XVI	3.51×10^{-5}	3.55×10^{-5}
XVII	5.35×10^{-5}	5.41×10^{-5}
XVIII	5.17×10^{-6}	5.23×10^{-6}
XIX	4.16×10^{-5}	4.21×10^{-5}