A thesis entitled

"DECARBOXYLATION AND ESTER HYDROLYSIS

OF SUBSTITUTED MALONATES"

submitted by

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## ABSTRACT

Previous studies on the mechanism of thermal decarboxylation of malonic acids are critically reviewed and the results discussed in relation to similar reactions of monobasic and β-keto acids. Also recent developments in the mechanism of aliphatic ester hydrolysis are reviewed with a particular emphasis on the special problems of malonate esters such as charge interaction and neighbouring group effects.

The experimental studies have concerned the decarboxylation of halogenated malonic acids under a wide range of conditions. It is found that both the molecular acid and the monoanion of dichloro- and dibromomalonic acid readily decarboxylate, whereas the difluoro derivative is stable. This striking difference does not come from differences in intramolecular interaction, but is probably associated with the special structure of the molecular difluoromalonic acid. The acid dissociation constants for these halogenated acids have also been measured.

The hydrolysis of 2-(trimethylammonium)diethylmalonate has been studied and it is shown that decarboxylation of the corresponding half ester occurs very rapidly at room temperature. This is the only known case of decarboxylation of a malonic acid anion. Ester hydrolysis reactions have also been studied

kinetically for the p-nitrophenyl esters of 2,2-dialkyl-substituted malonic acids under conditions where both hydroxide ion and nucleophilic catalysis are important, and for the ethyl esters of dibromo and dichloroethyl-malonates in alkaline aqueous ethanol. No definitive evidence for intramolecular catalysed hydrolysis was observed in any of these reactions.

TO MY PARENTS

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# PART I

## Decarboxylation of Malonic Acids

# Chapter I

## Introduction

For more than one hundred years the decarboxylation of carboxylic acids has been a subject of interest to chemists. Their interest was due to the extreme importance of the reaction from biological point of view, as well as due to the importance which this reaction has in preparative organic chemistry. Recent studies, however, have been orientated more towards the mechanism of the reaction and in spite of many attempts to solve the problem there are many conflicting observations requiring further investigation.

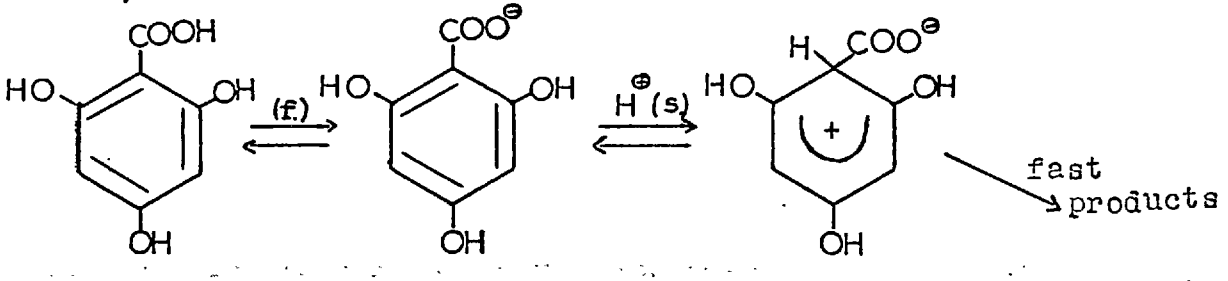
Apparently, there are several mechanistic pathways for decarboxylation depending upon the type of reacting species as well as the reaction conditions. The most general classification is probably the one based on molecularity of the reaction, since it has been shown that both unimolecular and bimolecular processes can occur. Malonic acids usually decarboxylate via the unimolecular process under thermal conditions and accordingly this introduction is concerned mainly with this type of reaction. However, a very brief survey of the bimolecular reaction is also given.

Bimolecular Mechanism.

The first suggestion for a bimolecular carboxylic acid decarboxylation mechanism came from Schenkel and Schenkel-Rudin in 1948 (equation I - 1)

$$H^{\oplus} + RCOOH \longrightarrow RH + CO_2 + H^{\oplus} \qquad \text{(eq. I - 1)}$$

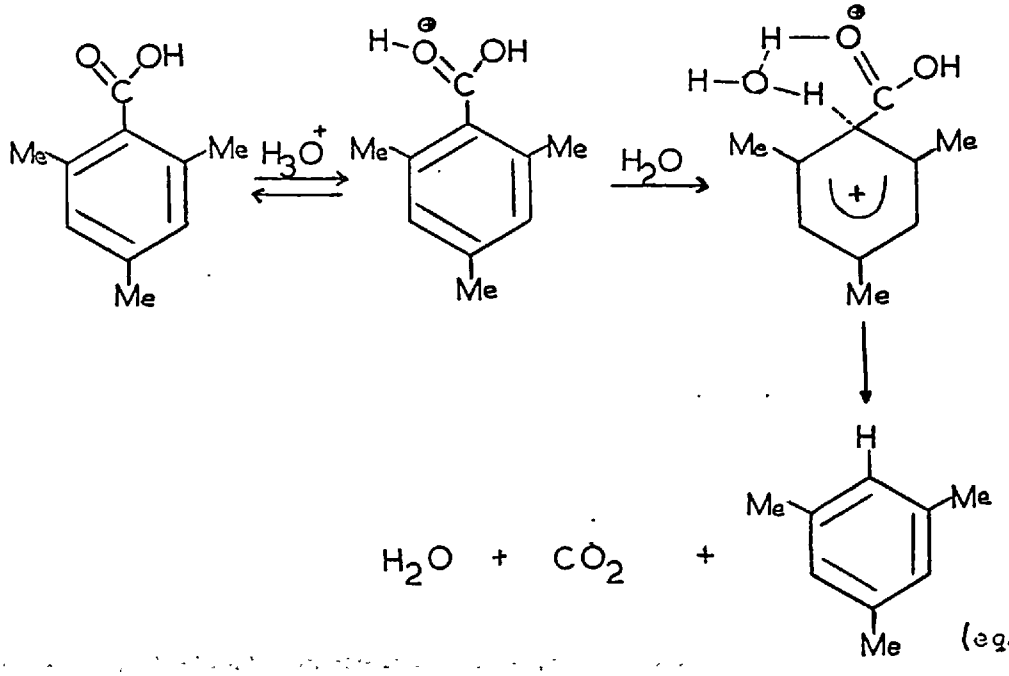
in order to explain the very ready decarboxylation of anthracene-9-carboxylic acid in acidic (sulphuric or dichloroacetic acids) rather than in basic solvents. Other acids thought to decarboxylate similarly were ortho and para-hydroxybenzoic acids[2]. Yet, it was not really known whether an undissociated acid or the corresponding anion was the reacting species. Schubert and Gardner[3] measured the rate of decarboxylation of 2,4,6-trihydroxybenzoic acid in a wide range of aqueous perchloric acid concentrations. On the bases of these measurements the most probable pathway was thought to be a rate determining proton attack on the $C_1$-carbon atom of the carboxylate ion: (equation I - 2).




(eq. I - 2)

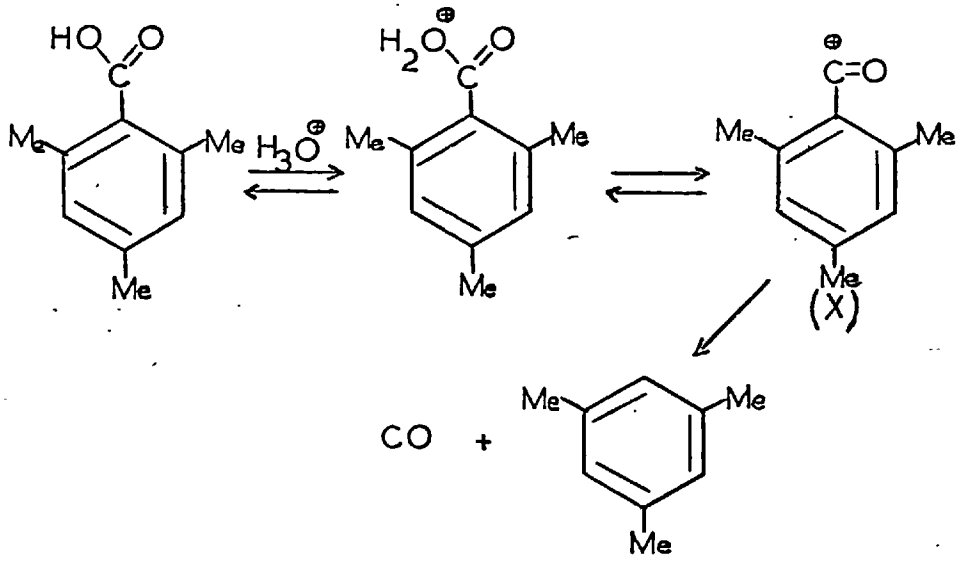
Alternatively, the undissociated acid could have decarboxylated unimolecularly. The possibility of a unimolecular decomposition of 4-substituted salicylic acids was later excluded by Willis[4,5] measurements which showed the rate constant to be increased by electron-releasing 4-substituents and the existence of a Hammet relationship when $\sigma^+$ parameters were used. Recent studies have shown that similar bimolecular processes also apply to the decarboxylation of anthranilic[6], salicylic[7] and p-amino-benzoic acids[8].

An interesting variation of the bimolecular decarboxylation mechanism occurs in the reaction of mesitoic acid[9],[10] in concentrated aqueous sulphuric acid. Decarboxylation proceeds in the solutions less than 80% $H_2SO_4$ according to the proposed mechanism (equation I - 3)




(eq. I - 3)

At higher acidity, however, the formation of a stable acyl cation (X) was observed (equation I - 4) spectrophotometrically.




(eq. I - 4)

Recent N.M.R. studies of a series of carboxylic acids have confirmed the existence of acyl cationic species in highly concentrated sulphuric acid solutions[11]. This evidence seems to suggest that bimolecular acid-catalysed decarboxylation occurs only in more dilute acidic media and may be replaced by a decarbonylation mechanism at high acidities.

There is much evidence in the literature to support the operation of most of the above reactions, particularly for aromatic acids. As this evidence is well documented in several recent reviews[12], [13], [14] the historical aspects of the so-called spontaneous (unimolecular) decarboxylation will be considered in detail, since this was the main subject of the present investigation.

Unimolecular Mechanism

It has been established experimentally that many carboxylic acids undergo spontaneous or thermal decarboxylation under suitable conditions: (equation I - 5)

$$R\text{-}CCOH \xrightarrow{\Delta} RH + CO_2 \qquad \text{(eq. I - 5)}$$

Three general classes of acids can be identified in this respect.

(a) Some $\alpha$-substituted aliphatic monocarboxylic acids containing strongly electron-withdrawing groups, or monocarboxylic acids which form zwitterions very readily.

(b) $\beta$-keto and $\beta$- $\gamma$ -unsaturated-monocarboxylic acids, and,

(c) dicarboxylic acids.

The form of the acid undergoing decarboxylation is not the same in each case and depends upon the relative value of the activation energy for the undissociated acid, monoanion or zwitterion; the most reactive one, of course, being the species with the lowest value for the energy of activation.

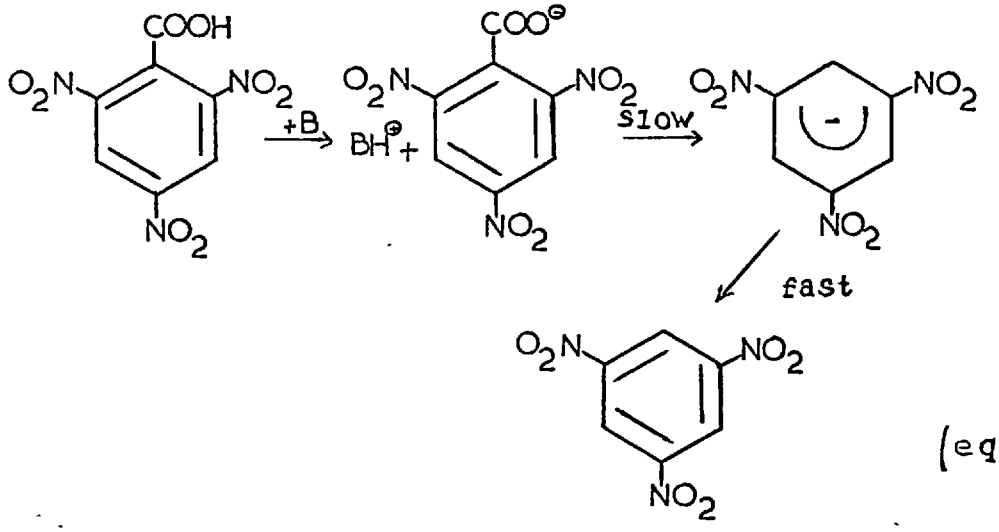
(a) Monocarboxylic Acids

The problem of whether the undissociated acid or the corresponding anion decarboxylates in the case of $\alpha$-halo-acetic acids was a matter of interest to many scientists more than thirty years ago. However, evidence such as an equal activation energy for both the sodium salt and the undissociated acid[15],[16],[17], a rate of decarboxylation about $10^7$ times slower when toluene (non-ionizing) was the solvent[15],[17], and in solvents where ionization was not favoured (like ethyl alcohol), a rate of decarboxylation proportional to the amount of added base[18], all supported the assumption that the reactive species was the anion of the halo-acid, i.e. (equation I -6)

$$X_3C\cdot COO^{\ominus} \xrightarrow{\text{slow}} X_3C^{\ominus} + CO_2$$

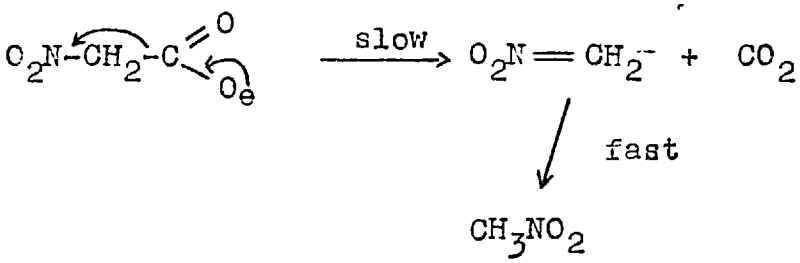
$$X_3C^{\ominus} \xrightarrow[H_2O]{\text{fast}} X_3CH + {}^{\ominus}OH \qquad \text{(eq. I - 6)}$$

Similar behaviour for 2,4,6-trinitrobenzoic acid was observed by Verhoek[19]. The rate of reaction in absolute ethanol was proportional to the amount of the base added to the solution (equation I - 7):




(eq. I - 7)

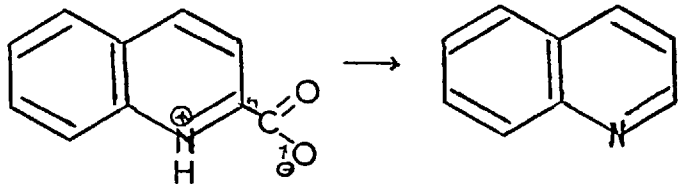
Unimolecular thermal decomposition of the anionic form of $\alpha$-nitro-acids was also observed by Pedersen[20], [21]. Since $\alpha$-nitroisobutyric acid reacted at a similar rate to $\alpha$-nitroacetic acid and the rate of bromine uptake was equal to the rate of decarboxylation of the latter, he proposed the mechanism to be




(eq. I - 8)

All the monobasic acids known to undergo decarboxylation in the anionic form have strong electron-withdrawing $\alpha$-substituents, which presumable stabilise formation of the corresponding carbanion[12].

However, several heterolytic $\alpha$-imino-acids like picolinic, quinaldic, isoquinaldic, thiazole-2-carboxylic, or 2-thiazolylacetic[1], [22],[23] acid are known to be stable in their anionic form, but to decarboxylate unimolecularly in moderately acidic media. Since the methyl betaine of quinaldic acid decarboxylates very easily[22] it was concluded that quinaldic acid itself decarboxylates as a zwitterion (equation I - 9) and the undissociated acid was assumed to be a stable species. The same explanation must apply to the other $\alpha$-imino acids,

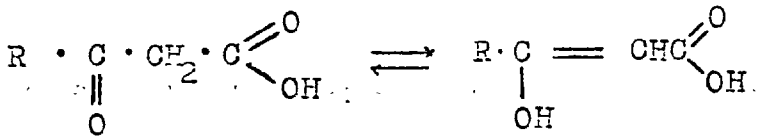


$+ CO_2$ (eq. I - 9)

with the positive charge in the zwitterion structure acting as a powerful electron-attracting group.

(b) $\beta$-keto Carboxylic and Unsaturated Acids

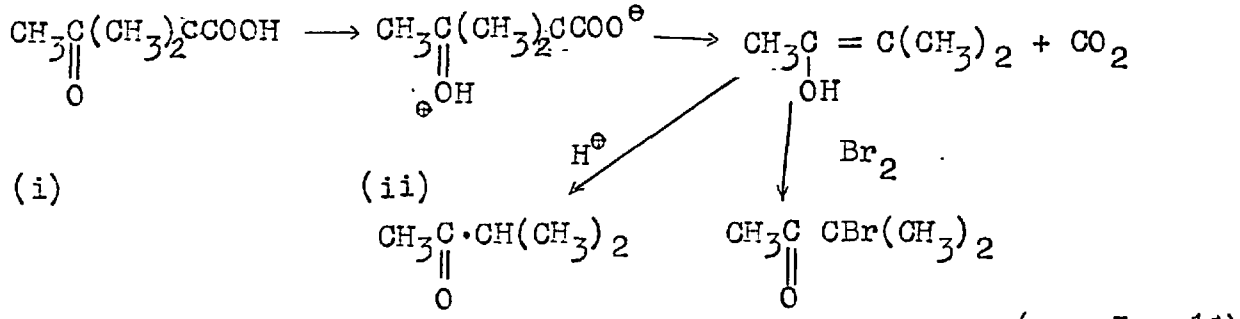
Early investigations on the rate of keto-acid decarboxylation had established stability of $\alpha$- and $\gamma$- isomers and instability of the $\beta$-keto carboxylic acids[24]. This suggested that decarboxylation was somehow related to keto-enol tautomerisation (equation I - 10). Investigations of acetoacetic acid by



(eq. I - 10)

Pollak[25], Engfeldt[26], Widmark[27], Euler[28] and Ljunggren[29] showed both the neutral acid and the anion were unstable, and that amines catalysed the reaction, but they gave no information of the nature (i.e. keto or enol) of the reactive species. However, investigations on $\alpha$, $\alpha$-dimethylacetoacetic acid[24] and $\alpha$-bromocamphorcarboxylic acid[30], which cannot enolise, proved the keto form to be the unstable one. Also, the rate of $Br_2$ or $I_2$ uptake[21], [31] which was equal to the rate of decarboxylation of both acetoacetic and $\alpha$, $\alpha$-dimethylacetoacetic acids was the indication that the enol-form intermediate was formed after the $CO_2$ cleavage.

On the bases of the experimental evidence available at the time, Pedersen[21] proposed the following mechanism for the decarboxylation of a $\beta$-keto acid (equation I - 11):



(eq. I - 11)

Zwitterion (ii) formation was believed to occur because of the weak basicity of the keto group. Once it is formed, Pedersen

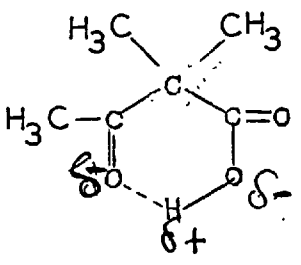
argued, positive charge of the species should make it more reactive than the normal undissociated acid or the corresponding anion. Finally, formation of an enol-intermediate (iii) was detected spectrophotometrically by Steinberg and Westheimer[32] during decarboxylation of dimethyl oxaloacetic acid in dilute aqueous solution (equation I - 12) (without buffer species

$$HOOC\cdot\underset{\underset{O}{\|}}{C}(CH_3)_2CCOO^{\ominus} \longrightarrow \underset{\underset{O_{\ominus}}{|}}{HOOCC}=C(CH_3)_2 + CO_2 \xrightarrow{H^{\oplus}} HOOC\underset{\underset{O}{\|}}{C}CH(CH_3)_2$$

(iii) (eq. I - 12)

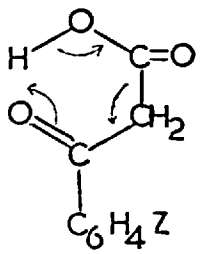
present in the solution, the enol-form is relatively stable).

Since the separation of charge is necessary for the formation of a zwitterion, the rate of decarboxylation should depend upon polarity of the solvent, if it occurs via the mechanism proposed by Pedersen. However, experiments by Westheimer and Jones[33] on dimethylacetoacetic acid decarboxylation in several solvents of different dielectric constant, showed no change in the rate of reaction. Therefore, an intermediate (iv) of a minimum polarity was suggested, actually a six-membered hydrogen bonded structure, which was in agreement with all the experimental data, particularly with the formation of an enol product.



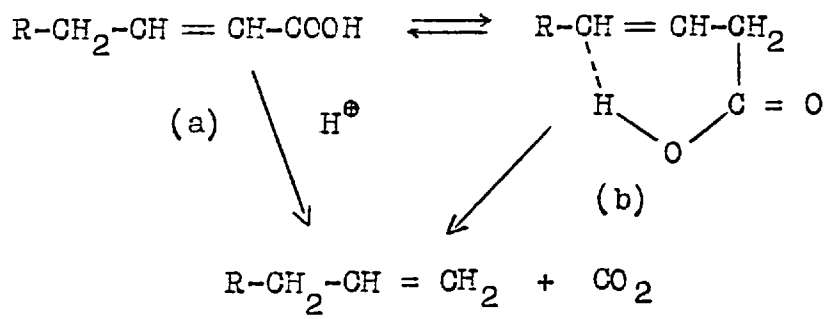
(iv)

Cryoscopic measurements in solvent benzene[34] on benzoylacetic, p-anisoylacetic and p-chlorobenzoylacetic acids indicated the existence of monomers of all of the three acids, presumably in an unionised chelated form, the one which was accepted as the active form for decarboxylation. Moreover, the influence of a substituent (Z) on the primary isotope effect ($k_H/k_D$) for several substituted benzoylacetic acids in solvent benzene[34][35] was explained most satisfactorily in terms of proton transfer in a similar cyclic transition state (v).



(v)

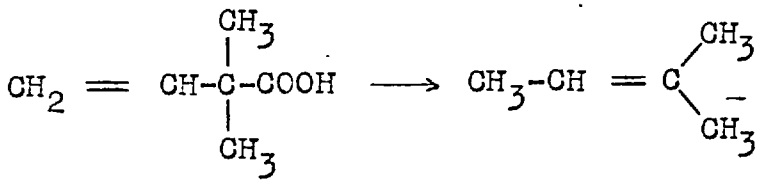
Summarising available data for the decarboxylation of $\alpha,\beta$- and $\beta,\gamma$-unsaturated carboxylic acids up till 1950 Arnold, Elmer and Dodson[36] suggested two possible pathways for the reaction to occur ( (a) and (b) in equation I - 13):



(eq. I - 13)

Both would give rise to the formation of the same product, i.e.

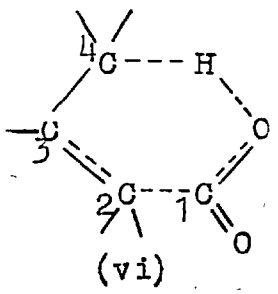
an olefin with the terminal double bond. Pathway (a) is similar to the one accepted for cinnamic acid decarboxylation[37] (i.e. acid catalysed formation of a carbonium ion which then spontaneously collapses to give the product). Pathway (b) assumes isomerisation of $\alpha,\beta$—into $\beta,\gamma$—unsaturated carboxylic acid (as a reversible process) which then decarboxylates via cyclic transition state. Therefore, (b) resembles the mechanism accepted for the decarboxylation of $\beta$—keto carboxylic acids. In order to decide between these alternative mechanisms Arnold, Elmer and Dodson examined several model reactions. Firstly, they showed that 2,2-dimethylbutene-3-oic acid a $\beta,\gamma$—unsaturated acid, which cannot isomerise into the $\alpha,\beta$—isomer by a simple prototropic shift, underwent ready decarboxylation to give only one product (equation I - 14). Secondly, $\alpha,\beta$—unsaturated



(eq. I - 14)

acids, such as 4,4-dimethylpenten-2-oic acid which cannot isomerise, do not decompose even at very high temperatures. These results clearly support mechanism (b), where the $\alpha,\beta$- and $\beta,\gamma$—isomers were in equilibrium and the latter was unstable. A more systematic study by Bigley[38] provided

convincing proof for this mechanism for decarboxylation of $\beta,\gamma$-unsaturated acids. In accord with the mechanism (equation I - 15) Bigley found: 1) the formation of a terminal olefin (if R' = H) in spite of the higher thermodynamic stability of an internal olefin; 2) formation of trans-olefins (when R' = alkyl) rather than cis isomers; 3) transfer of deuterium from the carboxyl group to the $\gamma$-carbon atom; and 4) negative values for the entropy of activation. Further investigations[39],[40],[41], however, have revealed additional observations which necessitate slight modifications to the proposed mechanism. Briefly, these show the rate of reaction in the gas-phase is the same as in the liquid-phase; $\alpha$, $\beta$ and $\gamma$ substituents all affect the rate of reaction, particularly the $\beta$-substituent; and the existence of both carbon-14 and primary hydrogen isotope effects ($k_H/k_D$).



(vi)

All of them support the idea of a multicentre transition state (vi) where bond-making and bond-breaking process in a six-membered ring have an equal importance and occur synchronously

(c) Dicarboxylic Acids

Early kinetic investigation on the decarboxylation of both mono- and di-substituted malonic acids[42],[43],[44], including unsubstituted malonic acid itself, established the first-order dependence between the reaction rate and the substrate concentration. The product of the reaction was always carbon dioxide and the corresponding monocarboxylic acid (equation I - 16):

$$X_2C(COOH)_2 \longrightarrow X_2CHCOOH + CO_2 \qquad \text{(eq. I -16)}$$

Of the three species of malonic acid (i.e. undissociated acid, monoanion and dianion) only the first two were found to be unstable, whereas the dianion did not decarboxylate even after 48 hours at 125°C[16]. Fairlough[16] measured the rate of decarboxylation of the sodium hydrogen malonate at several temperatures and found the activation energy to be identical to that obtained by Bernulli and Wege[42] for decarboxylation of undissociated malonic acid. However, the rate of reaction was five times faster for the acid than for the monoanion at the same temperature. In the case of 2,2-dibromomalonic acid studied by Muus[45], [46], the monoanion was apparently the only unstable form of the acid. The dianion was stable for a very long time,

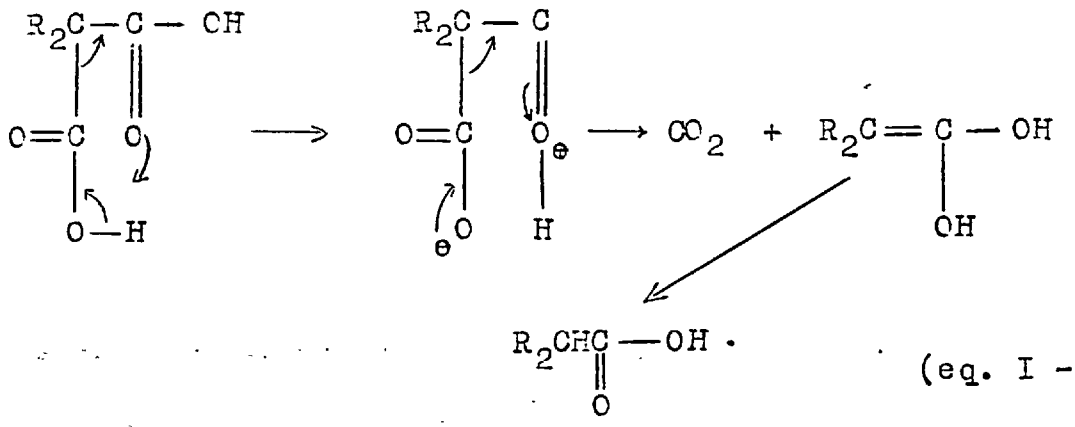
while from the pH-rate constant profile it was concluded that the undissociated acid was also a stable species. As the rate of bromine uptake was equal to the rate of decarboxylation of the monoanion, Nuus suggested the following mechanism (equation I - 17):

$$HCOC - CBr_2 - CCO^{\ominus} \longrightarrow CO_2 + HOOC\,CBr_2^{\ominus} \longrightarrow CHBr_2COOH$$

$$\overset{Br_2}{\swarrow}$$

$$CBr_3CCO^{\ominus} \qquad \text{(eq. I - 17)}$$

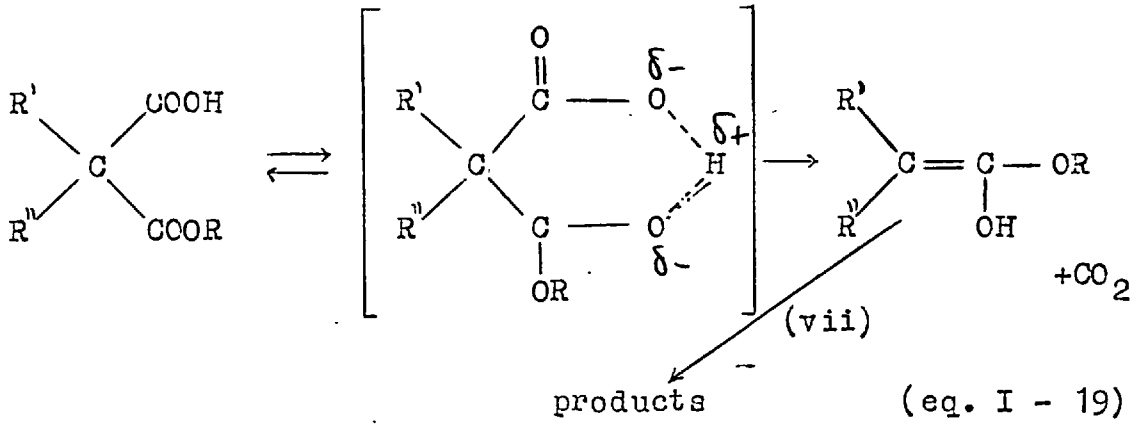
These early results were inconclusive. The data indicated that in some cases, at least, both the mono-anion and the di-acid were unstable, and in the latter respect dicarboxylic acids differed from simple monobasic acids, and were similar to $\beta$-keto and unsaturated monobasic acids. The similarity between the mechanisms for decarboxylation of $\beta$-keto- and substituted malonic acids was first pointed out by King[47] in 1947 (equation I - 18):



(eq. I - 18)

More convincing proof came from Hall's[48] experiments on decarboxylation of malonic acid at 80° and 90°C in the pH region from 0.4 to 4.9. He showed that the unionised acid was more reactive than the monoanion by a factor of 10, whereas the dianion was completely stable. This suggested that proton transfer between the carboxylic groups initiated decarboxylation.

Further progress in elucidation of the mechanism came from experiments carried out with optically active malonates. Kenyon and Ross[49] reasoned that if during the course of the reaction (according to the equation I - 19) a double bond was




(eq. I - 19)

to be formed (vii), the product of the reaction would not be optically active. Both (+) and (-) ethyl hydrogen ethylmethyl-malonate were reacted, and in agreement with their argument, gave the same racemic mixture of 2-methyl-ethylbutyrate. This was consistent with the intramolecular nature of the reaction, but gave little further information on the nature of the transition state.

A great effort has been made by a number of scientists[50] to understand the nature of the transition state by measuring the carbon isotope effect (i.e. the relative rates of decarboxylation when the carbon atom in one of the carboxyl groups was replaced by its $C^{13}$ or $C^{14}$ isotope). The experimentally observed intramolecular effect was in excellent agreement for $C^{13}$ isotope with the theoretical predictions of Bigeleisen's[51] theory. The effect was, however, considerably larger than theory for $C^{14}$ substitution[52] in unsubstituted malonic acid and particularly in the case of monobromomalonic acid. These discrepancies have never been completely resolved, and since the C-isotope effects are independent of the position of the proton in the transition state, they give no information on this aspect of the mechanism.

The significance which an 2-substituent might have on the rate of decarboxylation of malonic acids was first emphasised by Gelles[53] in 1953. Analysing the data for the rate of decarboxylation of 2-phenylmalonic acid in pH range from 0 till 6, Gelles obtained the rates at which undissociated acid and the corresponding monoanion decarboxylated at 45°C. The monoanion decarboxylated three times as fast as the undissociated acid, while the dianion was again found to be stable. Differences in the ease of the carbon-carbon bond fission for malonic[48], dibromomalonic[45] and phenylmalonic acid (Table I - 1) were attributed to the electron withdrawing ability of bromine and phenyl groups.

TABLE (I - 1)

| Acid | Molecular Acid $k_1 \times 10^4$ (hours$^{-1}$) | Monoanion $k_2 \times 10^4$ (hours$^{-1}$) |
|---|---|---|
| 2,2 —dibromomalonic | $\ll$85000 | 85000 |
| 2 -phenylmalonic | 112 | 350 |
| malonic | 1.4 | 0.2 |

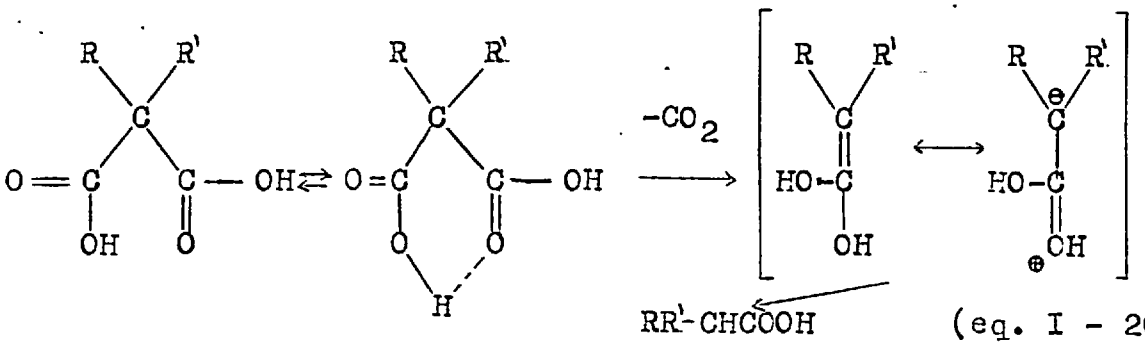
As Gelles pointed out, the same general inductive effect is reflected in the magnitude of the dissociation constants (Table I - 2).

TABLE (I - 2)

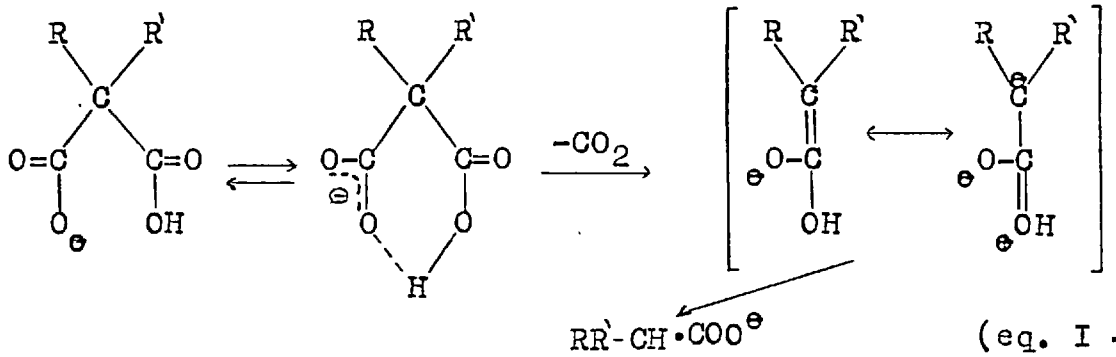
| Acid | $K_1$ (mol. l$^{-1}$) | $K_2$ (mol. l$^{-1}$) |
|---|---|---|
| 2,2 —dibromomalonic | 1 | $10^{-2}$ |
| 2 —phenylmalonic | $2.6 \times 10^{-3}$ | $9.4 \times 10^{-6}$ |
| malonic | $1.4 \times 10^{-3}$ | $2.1 \times 10^{-6}$ |

The relative reactivity of the monoanion and undissociated acid was accounted for in terms of the ease of accommodation of the negative charge developing in the carbon-carbon bond undergoing fission. When unsubstituted malonic acid undergoes intramolecular proton transfer followed by loss of carbon dioxide, electron density in the transition state is smaller for the

undissociated acid than for the monoanion. Consequently, the rate of reaction is faster for the former than for the latter species. Introduction of an electron withdrawing group in 2 -position (equation I - 20) leads to stabilisation of the developing negative charge. The rate of reaction becomes faster in general, and particularly for the monoanion (equation I - 21).




(eq. I - 20)




(eq. I - 21)

The stability of a doubly charged anion was attributed to the high electron density in the ground state of the molecule. The

fission process would have caused even higher electron density in the transition state and, obviously, the extra charge could not be accommodated very easily.

A cyclic transition state formed by an intramolecular proton transfer[12] has found its support in the values of the entropies of activation for the decarboxylation of some substituted malonic acids[54]. The values are listed in Table (I - 3):

TABLE (I - 3)

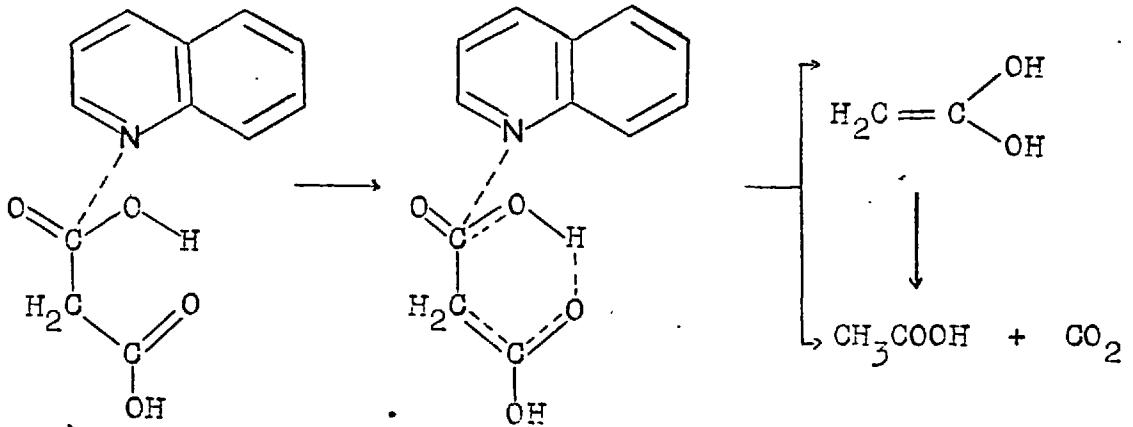
Activation Entropies (in e.u.) for the Decarboxylation of Malonic Acids

| Acid | Solvent | | | |
|---|---|---|---|---|
| | Water | | 80% Dioxan | |
| | $R_2C(COOH)_2$ | $R_2C(COO^{\ominus})COOH$ | $R_2C(COOH)_2$ | $R_2CCOO^{\ominus}COOH$ |
| Malonic | -2 | +1 | -9 | -2 |
| 2,2 -dibromomalonic | | +15 | | +4 |
| 2-phenylmalonic | -8 | +5 | -14 | -2 |

The explanation was as follows. If a cyclic structure of the acid undergoing decarboxylation was formed in a preequilibrium step, the transition state would closely resemble the initial state. Consequently, the entropy of activation should have a small value in all cases. Since formation of an intramolecularly hydrogen-bonded initial state occurs more readily for the

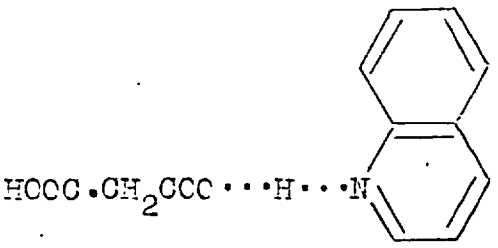
monoanion than for the undissociated acid, the entropy of activation should have less negative value for the former than for the latter species. The results in Table (I - 3) support this conclusion, but the variation in entropy with the substituent is difficult to rationalise.

Amine catalysed decarboxylation of malonic acid has been extensively studied. These results do not bear directly on the transition state of the thermal reaction, but they serve to show that a single mechanism probably operates under widely different conditions. Fraenkel, Belford and Yankwich[55] investigated a quinoline catalysed decarboxylation of malonic acid in water and dioxane solutions. Only the undissociated acid exhibited a strong quinoline catalysis in dioxane solutions where the rate of reaction was proportional to the quinoline concentration. The catalytic ability of other amines was dependent upon steric hindrance to the catalyst. These authors therefore proposed a mechanism involving solvation of the carboxylic carbon atom (equation I - 22). This was preferred over hydroxyl association



(viii)

(eq. I - 22)



(ix)

(ix), because the latter would be similar to the formation of an anion which would decrease the rate of the reaction instead of increasing it.

Extensive kinetic studies have been reported[56],[57] by Clark on the decarboxylation of malonic acid, several monosubstituted malonic acids, oxamic and oxanilic acids in their molten state and in a series of different types of solvents (ethers, acids, nitrocompounds, cresols, aldehydes, etc.). All these results have been fitted to four different, but parallel isokinetic plots, i.e. the isokinetic temperature (determined by the slope of $\Delta H^{\#}$ versus $\Delta S^{\#}$ curve) is the same in all cases. This observation was taken as the indication for the same mechanism operating under a wide variety of experimental conditions. The existence of four isokinetic lines was attributed to the different nucleophilicity of the solvents which solvate the carboxylic carbon atom in the way suggested by Yankwich and and his coworkers for quinoline.

Recently, further efforts have been made to extablish both the forming and the importance of intramoleculer proton transfer in the transition state for the decarboxylation process. Distinction between a cyclic or a dipolar transition state has been discussed by Brower[58] and coworkers on the basis of the

activation volume measurements for malonic, 2,2 —dimethyl-malonic and acetoacetic acid decarboxylations. Activation volumes for malonic acid have been found to change stepwise through a range of 14 ml. by changing the solvent from water, dimethylsulfoxide, dioxan to tetrahydrofuran (decreasing polarity). The observation was taken to indicate a transition state which is more polar than the ground state, i.e. Pedersen's[59] zwitterion transition state[11] is preferred over Westheimer and Jones'[33] intramolecular proton transfer postulate (iv). By undertaking measurement of hydrogen isotope effect ($k_H/k_D$) for malonic acid decarboxylation in molten state, Blades and Wallbridge[60] hoped to clarify the nature of the transition state. The values for $k_H/k_D$ observed at 139.8° and 145.3°C were 1.09 ± 0.02 and 1.11 ± 0.01 respectively. Such a low $k_H/k_D$ value was attributed to a very small change in stretching of O — H bond in the rate determining step of the reaction. They believed that the results favoured Yankwich and coworkers postulate[55], where coordination to the carboxylic carbon produces decomposition and proton transfer is not involved in the rate determining step. Blades and Wallbridge interpreted the relatively high value of the isotope effect for decarboxylation of 2,2 —dimethylmalonic acid ($k_H/k_D$ = 4.5)[60] as invalid since it was, most probably, the result of intramolecular proton transfer occurring after the loss of carbon dioxide.

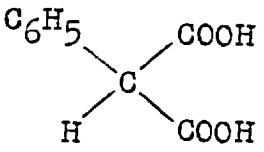
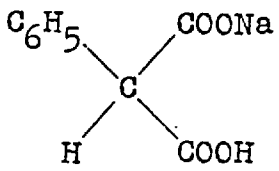
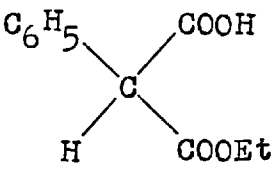
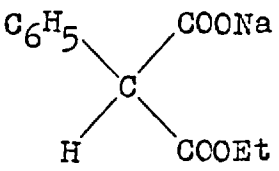
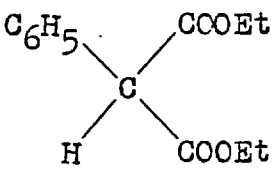
Hydrogen isotope effects for decarboxylation of malonic and 2,2-dimethylmalonic acids were reinvestigated in this laboratory[61] in aqueous HCl solutions at 90°C. In addition, the effect was measured for malonic acid at 98.4°C in dioxane solution. The experimentally obtained values are listed in Table (I - 4):

TABLE (I - 4)

| Acid | Solvent | $k_H/k_D$ |
|---|---|---|
| Malonic | $H_2O/D_2O$ | 1.23 ± 0.13 |
| Malonic | dioxane | 1.51 ± 0.15 |
| 2,2 —dimethyl-malonic | $H_2O/D_2O$ | 1.20 ± 0.14 |

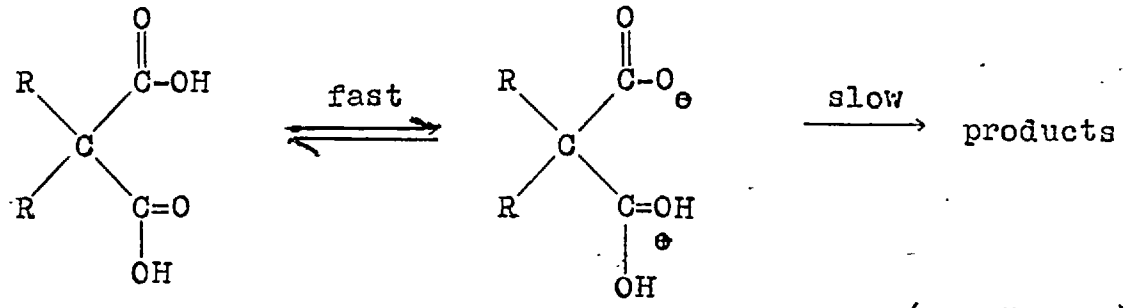
Furthermore, the rates of decarboxylation at 55.4°C in dimethylsulfoxide solvent were measured for some derivatives of 2-phenylmalonic acid. The compounds together with the first order rate constants are listed in Table (I - 5).

TABLE (I - 5)

| | Compound | | $k \times 10^3$ (sec.$^{-1}$) |
|---|---|---|---|
| a) | 2-phenylmalonic acid |  | 0.26 |
| b) | sodium 2-phenyl-malonic acid |  | 2.8 |
| c) | ethyl hydrogen 2-phenylmalonate |  | 1.0 |
| d) | sodium ethyl 2-phenylmalonate |  | No reaction |
| e) | diethyl 2-phenyl-malonate |  | No reaction |

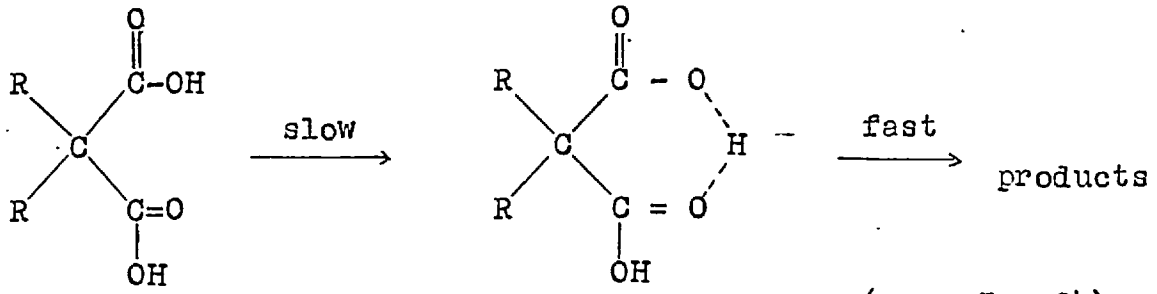
As is seen from Table (I - 5) only compounds a), b) and c) underwent reaction, while d) and e) were stable under the

conditions. Intramolecular proton transfer therefore seemed to be the essential part of the reaction, although the distinction between a preequilibrium (equation I - 23) and a rate determining




(eq. I - 23)

proton transfer (equation I - 24) could not be made from these results. Kinetic hydrogen isotope effects obtained experimentally




(equ. I - 24)

(Table I - 4) were compared with those calculated on the bases of Swain and coworkers[62] and Bunton and Shiner[63] theoretical treatments. The Swain treatment predicts that proton transfer

between oxygen atoms concurrent with carbon-carbon bond fission does not result in an appreciable primary isotope. Accordingly the calculated value for the preequilibrium transfer is 1.41 and the symmetrical transition state should give $k_H/k_D$ = 1.19 at 90°C. The Bunton and Shiner approach to the problem gives the $k_H/k_D$ = 1.54 for the preequilibrium process (equation I - 23). It was, therefore, believed that, as far as kinetic hydrogen isotope effect is concerned, a symmetric cyclic transition state was the more likely pathway for dicarboxylic acid decarboxylation.

Summary

In spite of extensive investigations, it is clear that the mechanism of thermal decarboxylation is not thoroughly understood. Only the anions of simple monocarboxylic acids appear to be unstable, whereas for keto- and unsaturated acids, it is the molecular (un-ionised) acid that decomposes. Both these reactions are important, however, in the case of some (but not all) malonic acids, and there is good evidence that both the unionised acid and the monoanion decarboxylate under thermal conditions. This process certainly involves intramolecular proton transfer between the carboxylic groups, which is probably synchronous with carbon-carbon fission. Species such as quinoline, which co-ordinate with the carboxylic carbon,

appear to catalyse the reaction. Solvent acids only appear to affect the reaction by changing the concentration of mono-anion and unionised substrate. There is no evidence of bi-molecular acid catalysed decarboxylation of the kind observed with aromatic species.

Few studies of substituent effects have been reported for malonic acid. It is clear, however, that electron withdrawing groups speed the reaction and this has been attributed to stabilisation of negative charge in the transition state. Steric effects of substituents have been ignored, although these must affect the degree of intramolecular hydrogen bonding. Accordingly, a closer investigation of substituent effects was undertaken, specifically to resolve several anomalous results for halogen substituted malonic acids. These were the ready decarboxylation of the monoanion of dibromomalonic acid, but the apparent stability of the molecular acid, and the stability of difluoromalonic acid in all its forms.

# Chapter II

## Decarboxylation of some 2-substituted Malonic Acids

The ease of decarboxylation of 2-substituted malonic acids seems to depend very much upon the nature of the substituent, as pointed out in Chapter I. Apparently, the more electron withdrawing character the substituent has, the easier the species undergoes the reaction. As was mentioned before, Geiles[53] has suggested that this kind of effect could be explained by the ability of a reacting species to accommodate the developing negative charge in the transition state. On the other hand, high electron density of a dianion might prevent the reaction since the developing charge could not be easily accommodated.

From this point of view, it is rather unusual to find and difficult to explain both the stability of difluoromalonic acid[64] and the low reactivity of undissociated dibromomalonic acid,[45][46] as well as the extreme ease with which dianion of malonic acid decarboxylates when the substituent is the trimethylammonium ion[65]. Since the reactivity of all these compounds had been investigated rather qualitatively, and not very extensively, it was thought that the reinvestigation might shed some light on their unusual reactivity, and, indirectly, on the mechanism of decarboxylation of malonic acids in general.

The present work includes decarboxylation experiments with 2,2-difluoromalonic acid, 2,2-dichloromalonic acid and also with the half hydrolysed product of 2-(trimethylammonium) diethyl malonate, which is discussed in Chapter V.

a) Experiments with 2,2-difluoromalonic acid

The results obtained by Muus[45] for the decarboxylation of dibromomalonic acid suggested that the monoanion was the reactive species. In order to find the pH where aqueous 2,2-difluoromalonic acid solutions have the highest concentration of the monoanion, dissociation constants ($K_1$ and $K_2$) of the acid were measured at 25°C. These measurements were carried out (a) without any neutral electrolyte present in the solution; (b) in 0.10 M KCl; (c) 0.20 M KCl; (d) 0.50 M KCl; (e) 1.00 M KCl; (f) 0.50 M $KNO_3$ and (g) 0.50 M LiCl, and the results are summarised in Table (II - 1).

Table (II - 1)

Dissociation Constant Measurements of 2,2-difluoromalonic Acid in Aqueous Solutions at 25°C

| Number of experimental determinations | Added electrolyte (M/l) | $K_1 \times 10^2$* (mol/l) | $K_2 \times 10^2$* (mol/l) | $K_1/K_2$ | $pK_1$ | $pK_2$ |
|---|---|---|---|---|---|---|
| 4 | – | 5.9 ± 1.5 | 1.30±0.03 | 4.5 | 1.23 | 1.89 |
| 2 | 0.10 KCl | 6.2 ± 0.07 | 1.65±0.08 | 3.8 | 1.21 | 1.78 |
| 3 | 0.20 " | 5.7 ± 0.12 | 1.77±0.04 | 3.2 | 1.24 | 1.75 |
| 3 | 0.50 " | 9.5 ± 0.18 | 2.37±0.06 | 4.0 | 1.02 | 1.63 |
| 4 | 1.00 " | 40.0 ± 5.5 | 2.86±0.15 | 14.0 | 0.40 | 1.54 |
| 2 | 0.50 $KNO_3$ | 12.2 ± 0.4 | 2.31±0.27 | 5.3 | 0.91 | 1.64 |
| 2 | 0.50 LiCl | < 0 | | | | |

a) *Mean values; b) The concentration of 2,2-difluoromalonic acid was $(2.0\pm0.5) \times 10^{-2}$ M/l

c) The listed $K_1$ and $K_2$ are "mixed constants"

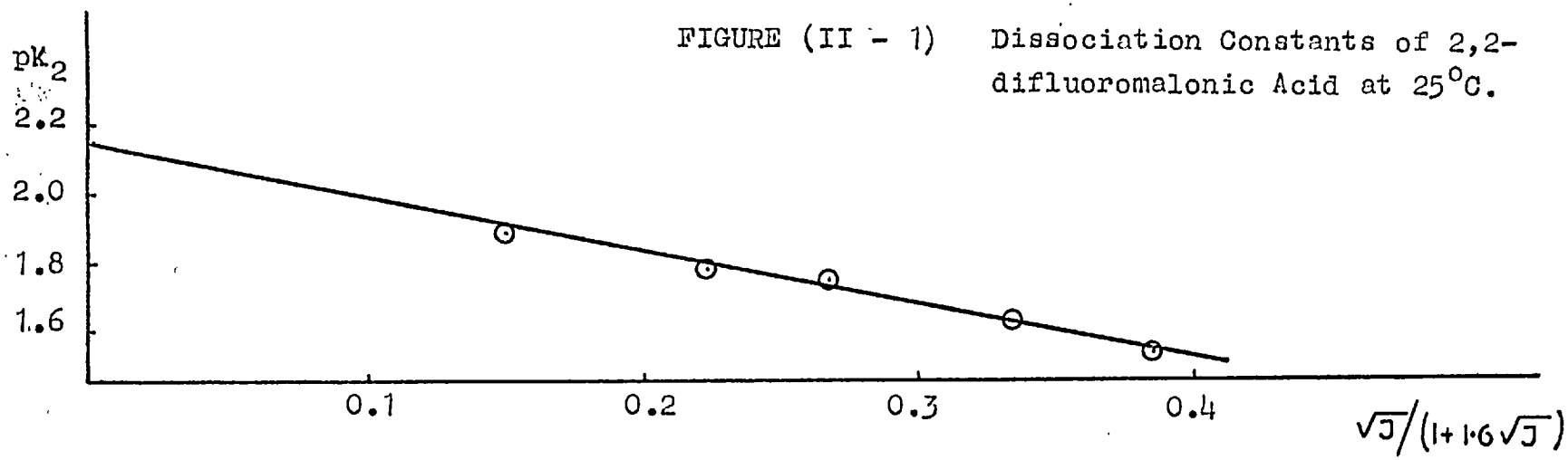
All the listed values of $K_1$ and $K_2$ in Table (II - 1) were calculated as "mixed constants"[66] (i.e. they include only the activity coefficient for the hydronium ion and concentration terms only for all the other species present in solutions). However, a reasonably good approximation for the thermodynamic dissociation constant can be obtained as an intercept of the $pK_1$ versus $\sqrt{J}/(1+\sqrt{J})$ and $pK_2$ versus $\sqrt{J}/(1 + 1.6\sqrt{J})$ plots (see Figure (II -1) ) where $J$ represents the ionic strength of the solutions. The slope of the latter line was found to be 1.45 which, within experimental error, agrees with the theoretically expected value of 1.51.

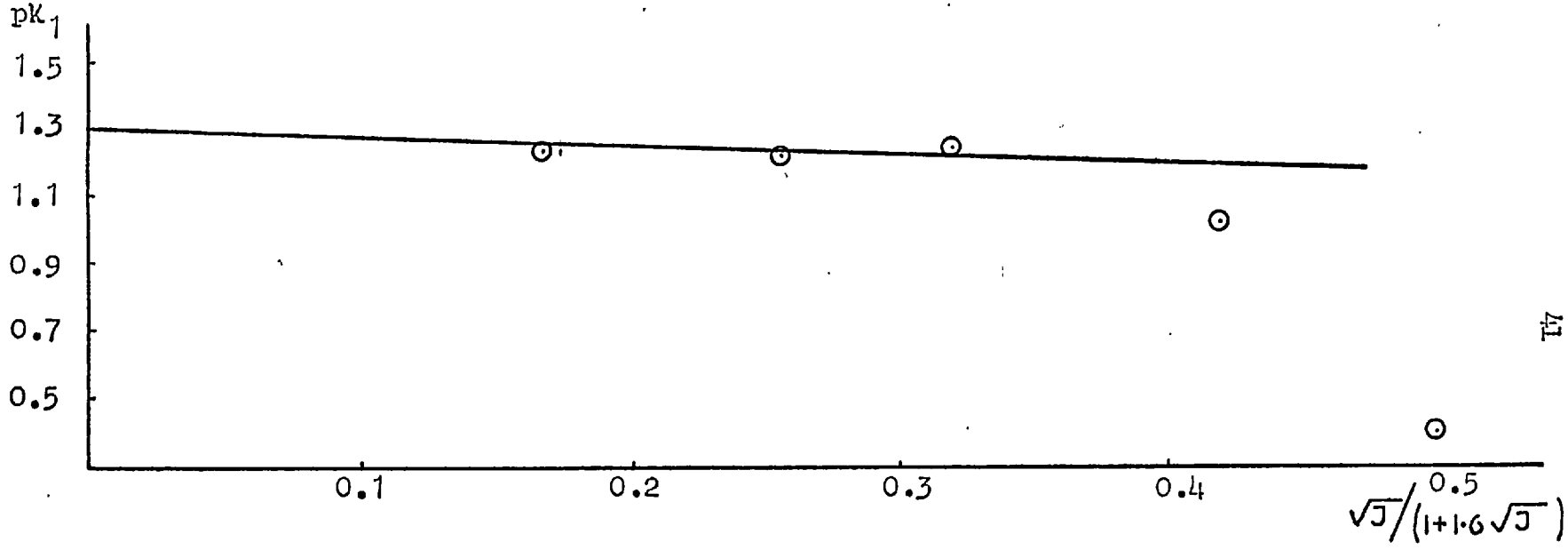
Extrapolated $pK_1$ and $pK_2$ to zero ionic strength are 1.30 and 2.12 which correspond to $K_1$ and $K_2$ of $5.0 \times 10^{-2}$ and $7.6 \times 10^{-3}$ mols/l respectively.

Appreciable deviations of the $pK_1$ values evident from Figure (II - 1) for 0.5 and 1.0 M/l KCl solutions are most probably due to the increased liquid junction potential, since the other salts, when used at 0.5 M/l had similar effects; whereas with LiCl as the added electrolyte, the calculated value of $K_1$ became negative.

Furthermore, two sets of dissociation constant measurements which contained no added neutral electrolyte in the solutions were corrected for activity coefficients according to

FIGURE (II - 1) Dissociation Constants of 2,2-difluoromalonic Acid at 25°C.



Speackman's method of thermodynamic dissociation constant determinations[67]. To obtain the mean ionic activity coefficient ( $y_\pm$ ) of an ion of valence $z^\pm$ , the Debye-Huckel[66] equation of the form

$$- \log ( y_\pm ) = \frac{0.505\ z^+ z^- \sqrt{J}}{(1 + 1.6\sqrt{J})}$$

was used. The ionic strength ( J ) was estimated in a first approximation from the equation (II - 1)

$$J = {}^1/_2 (b + [H^+] + [HA^-] + 4 [A^=] ) \qquad \text{equ.(II - 1)}$$

where b represents $[Na^+]$ and is identical with $[NaOH]$ added into the solution; $[H^+]$ was taken as the antilog of the measured pH; $[HA^-]$ and $[A^=]$ are the concentrations (M/l) of monoanion and dianion of 2,2-difluoromalonic acid respectively. These concentrations were estimated from the value of $K_2 = 1.25 \times 10^{-2}$ obtained from uncorrected calculations.

The values of $K_1$ and $K_2$ obtained as described above were $(5.15 \pm 0.30) \times 10^{-2}$ and $(7.87 \pm 0.06) \times 10^{-3}$ respectively. Although the deviation from the mean value is considerable,

particularly for $K_1$ value, it is to be expected because of the strength of first acid group. Otherwise, the $K_1$ and $K_2$ obtained graphically from Figure (II - 1) and by Speakman's activity coefficient corrections agree well.

On the basis of $K_1 = 5.75 \times 10^{-2}$ and $K_2 = 1.80 \times 10^{-2}$ (i.e. the mean value for the "mixed" $K_1$ and $K_2$ respectively) it was computed that more than 25 mole % of the monoanion was present over the pH region from 0.5 to 2.25, while the maximum concentration of approximately 50 mole % was found to be at pH = 1.50.

The experiments with 2,2-difluoromalonic acid throughout the pH region mentioned above at 75 to 80°C, did not show any apparent decarboxylation for several days in aqueous solutions, nor in strong $H_2SO_4$ solutions. No evolution of carbon dioxide could be detected at all, and the 2,2-difluoromalonic acid was recovered unchanged. The acid was also found to be stable in dimethylsulfoxide (which is known to be a favourable solvent for decarboxylation of malonic acids), over the same temperature range.

b) <u>Decarboxylation of 2,2-dichloromalonic acid in aqueous solutions</u>

The reaction for 2,2-dichloromalonic acid in aqueous solutions was investigated over a wide range of solvent acidity, from Ho = -4.83 to pH = 3.28. The first order rate constants

obtained from pH = 0.89 to 3.28 are presented in Table (II - 2); for HCl solutions (pH > 1) in Tables (II - 3) and (II - 4), while the data for $HClO_4$ solutions are summarised in Table (II - 5).

Table (II - 3) includes both the observed rate constants and their corrected values for those cases when KCl as a neutral electrolyte was present in the solutions. Corrections were necessary, since an appreciable influence of KCl (and other electrolytes) was detected on the rate of decarboxylation and this will be discussed later on. The effect due to KCl present in solutions was estimated from Figure (II - 2) where first order rate constants versus KCl concentrations in 1.00 M/l HCl are plotted using the data from Table (II - 4).

Table (II - 2)

Decarboxylation Measurements of 2,2-dichloromalonic Acid in Aqueous Buffer Solutions (total buffer concentration: AcOH/AcNa = 0.25 M/l; or the same total concentration of $ClCH_2COOH$ and $Cl_2CHCOOH$) at 25.0 ± 0.1°C

| Run | pH* | $k_{obs.} \times 10^3$ min.$^{-1}$ | - log $k_{obs.}$ |
|---|---|---|---|
| 101 | 3.28 | 0.435 | 3.362 |
| 98 | 2.66 | 1.67 | 2.777 |
| 99 | 2.56 | 2.05 | 2.688 |
| 91 | 2.26 | 3.53 | 2.452 |
| 87 | 2.21 | 3.84 | 2.416 |
| 89 | 1.86 | 5.77 | 2.238 |
| 88 | 1.71 | 6.21 | 2.207 |
| 86 | 1.55 | 7.36 | 2.133 |
| 85 | 1.48 | 7.80 | 2.109 |
| 84 | 1.42 | 7.65 | 2.116 |
| 102 | 1.06 | 9.00 | 2.046 |
| 103 | 1.03 | 8.45 | 2.073 |
| 80 | 0.96 | 7.30 | 2.137 |
| 79 | 0.89 | 7.66 | 2.116 |

a) * determined experimentally

b) Concentration of 2,2-dichloromalonic acid was approx. 0.03 M/

Table (II - 3).

Decarboxylation Measurements of 2,2-dichloromalonic Acid in Aqueous HCl Solutions at 25.0 ± 0.1°C

| Run | HCl (M/l) | Ho | $k_{obs.} \times 10^3$ ($min.^{-1}$) | Added KCl (M/l) | $k_{obs.} \times 10^3$ corrected for KCl | - log $k_{obs.}$ |
|---|---|---|---|---|---|---|
| 96 | 2.00 | -0.69 | 4.98 | | | 2.303 |
| 97 | 1.49 | -0.47 | 5.50 | | | 2.260 |
| 63 | 1.00 | -0.20 | 6.05 | | | 2.218 |
| 64 | 0.712 | -0.036 | 6.86 | 0.300 | 6.62 | 2.179 |
| 93 | 0.503 | 0.20 | 6.89 | | | 2.162 |
| 94 | 0.315 | 0.43 | 7.46 | | | 2.127 |
| 95 | 0.187 | 0.69 | 7.22 | | | 2.141 |
| 66 | 0.502 | 0.309 | 7.42 | 0.502 | 7.02 | 2.153 |
| 67 | 0.353 | 0.301 | 8.17 | 0.651 | 7.61 | 2.118 |
| 68 | 0.220 | 0.515 | 8.33 | 0.784 | 7.71 | 2.113 |

a) When KCl present Ho was accordingly corrected.
b) Concentration of 2,2-dichloromalonic acid was: 0.03 to 0.13 M/l.

Table (II - 4)

Decarboxylation Measurements of 2,2-dichloromalonic Acid in Aqueous 1.00 M/l HCl Solutions in presence of KCl at 25.0 ± 0.1°C

| Run | KCl (M/l) | $k_{obs.} \times 10^3$ min.$^{-1}$ |
|---|---|---|
| 63 | 0.00 | 6.05 |
| 72 | 1.00 | 6.80 |
| 73 | 2.00 | 7.66 |
| 74 | 3.00 | 8.44 |

a) Concentration of 2,2-difluoromalonic acid was 0.13 to 0.04 M/l.

Figure (II - 2)

Influence of KCl on Rate of 2,2-dichloromalonic acid Decarboxylation in 1.0 M HCl solution at 25°C.

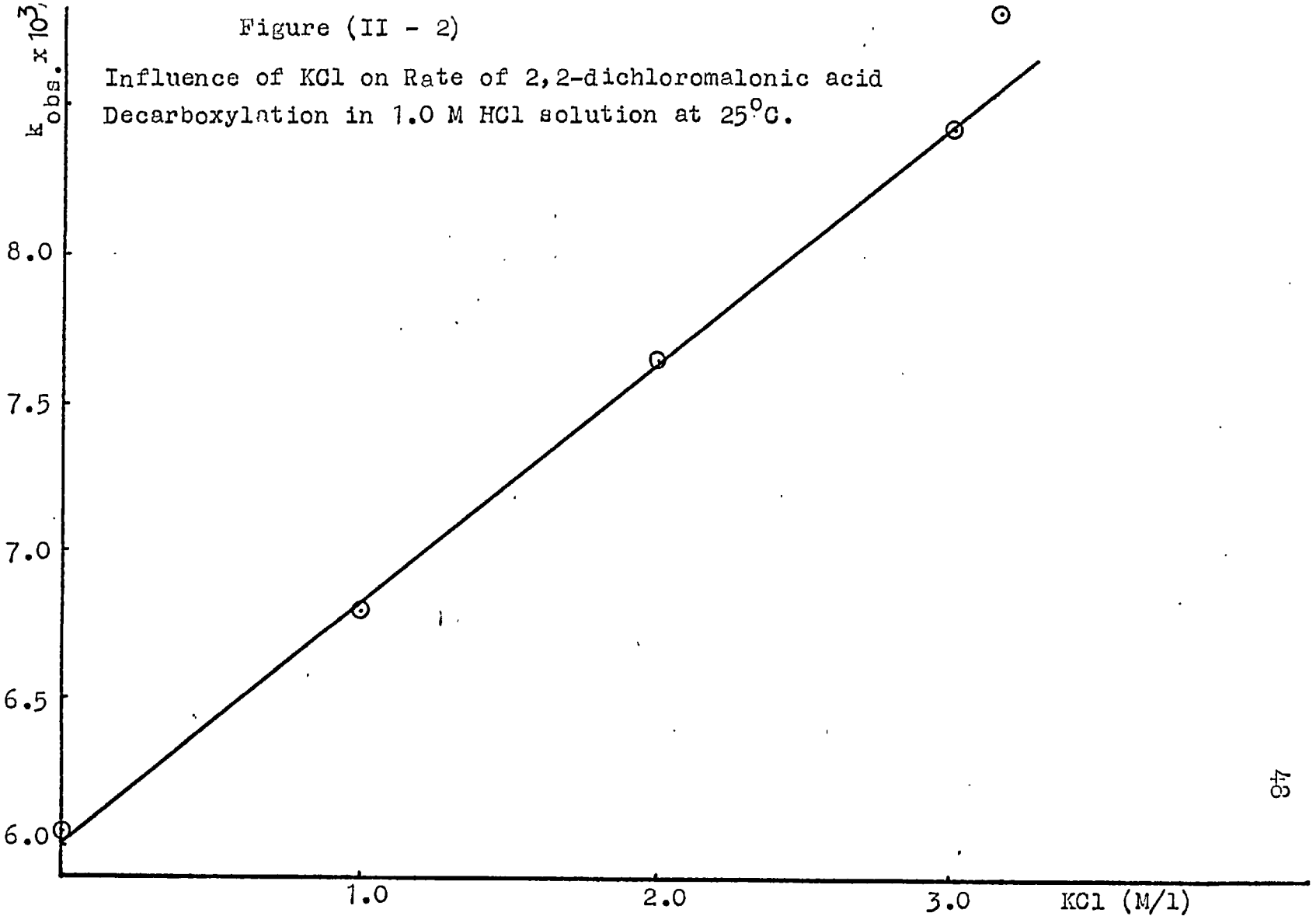


Table (II - 5)

Decarboxylation Measurements of 2,2-dichloromalonic Acid in Aqueous $HClO_4$ solutions at 25.0 ± 0.1°C

| Run | $HClO_4$ (M/l) | -Ho | $k_{obs.} \times 10^3$ min.$^{-1}$ | - log $k_{obs.}$ |
|---|---|---|---|---|
| 60 | 8.58 | 4.83 | 0.18 | 3.744 |
| 61 | 7.13 | 3.70 | 0.35 | 3.456 |
| 53 | 5.98 | 2.83 | 0.71 | 3.150 |
| 54 | 4.18 | 1.81 | 1.56 | 2.806 |
| 55 | 3.40 | 1.42 | 2.20 | 2.657 |
| 56 | 2.66 | 1.08 | 3.10 | 2.509 |
| 57 | 1.80 | 0.68 | 4.30 | 2.366 |
| 58 | 1.36 | 0.45 | 5.00 | 2.301 |
| 62 | 0.98 | 0.20 | 6.10 | 2.215 |

a) Concentration of 2,2-dichloromalonic acid was approx. 0.13 M/l.

The results in strongly acidic solutions (Tables (II - 3) and (II - 5) ) were unexpected on the conclusion drawn by Muus[45] from the investigation of 2,2-dibromomalonic acid. However, they clearly suggest that either 2,2-dichloromalonic acid is an extremely strong acid and the observed reaction is due to decarboxylation of the monoanion present in the solution, or the undissociated (molecular) form of the acid undergoes the reaction itself.

In order to analyse the data from Tables (II - 2), (II - 3) and (II - 5), first and second dissociation constants for 2,2-dichloromalonic acid were measured. These measurements were carried out at $0^{\circ}C$ since decarboxylation occurs at an appreciable rate at room temperature. These results are summarised in Table (II - 6), while in Figure (II - 3) the values of $pK_1$ and $pK_2$ are plotted versus $\sqrt{J}/(1+\sqrt{J})$ and $\sqrt{J}/(1+1.6\sqrt{J})$ respectively. The ionic strength ( J ) was determined as the sum of KCl added and the malonic acid concentrations.

Table (II - 6)

The Dissociation Constant Measurements for 2,2-dichloromalonic Acid in Aqueous Solutions at 0°C

| Number of runs included | KCl added (M/l) | Total Ionic Strength | $K_1$ (mol/l) | $K_2 \times 10^2$ (mol/l) | $pK_1$ | $pK_2$ |
|---|---|---|---|---|---|---|
| 2 | 0.02 | 0.04 | 0.211 ± 0.004 | 1.53 ± 0.02 | 0.675 | 1.815 |
| 2 | 0.10 | 0.12 | 0.180 ± 0.035 | 1.78 ± 0.05 | 0.745 | 1.750 |
| 2 | 0.20 | 0.22 | 0.164 ± 0.003 | 1.72 ± 0.10 | 0.785 | 1.764 |
| 2 | 0.50 | 0.52 | 0.230 ± 0.005 | 2.23 ± 0.05 | 0.638 | 1.651 |
| 2 | 1.00 | 1.02 | | 3.0 | | 1.52 |

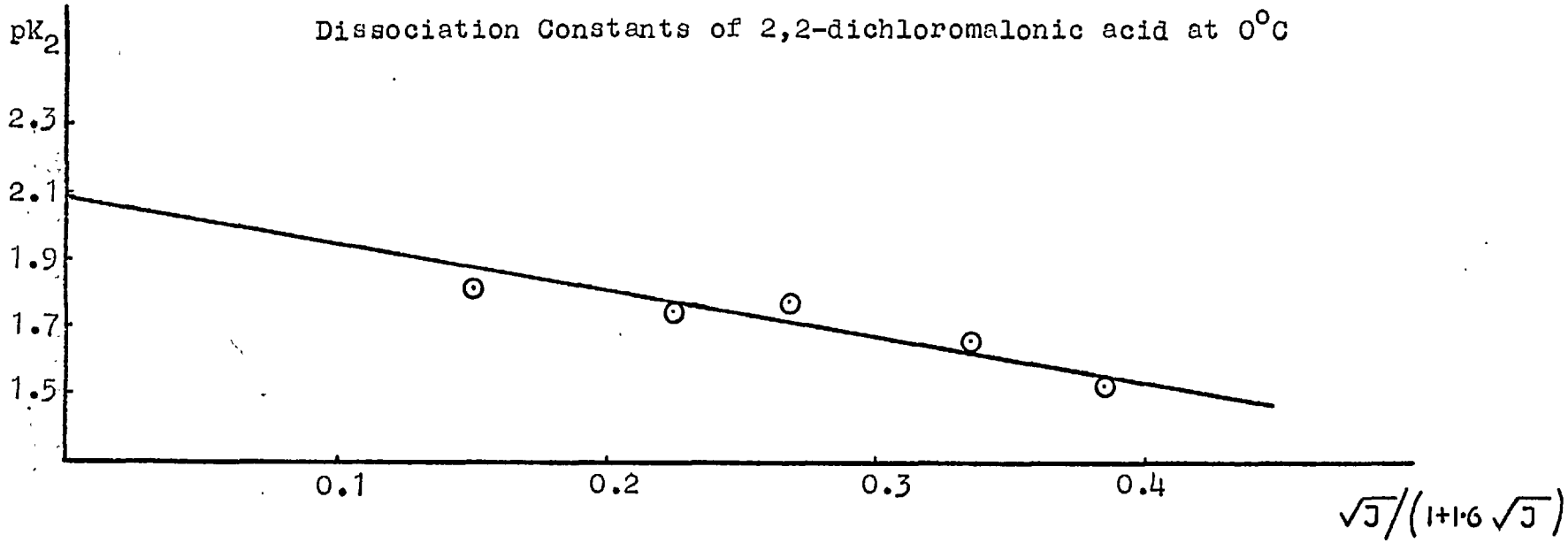
a) Concentration of 2,2-dichloromalonic acid was $(2.8 \pm 0.4) \times 10^{-2}$ M/l.

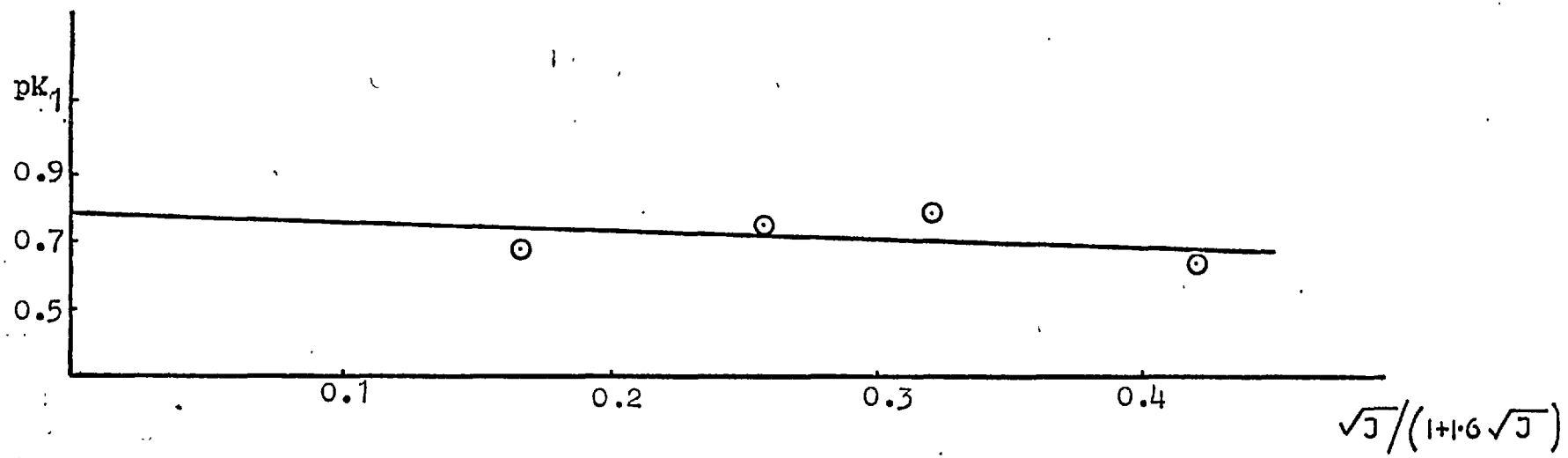
b) $K_1$ and $K_2$ as listed are "mixed constants".

c) Total Ionic Strength is a sum of KCl added and the malonic acid concentrations.

Figure (II - 3)

Dissociation Constants of 2,2-dichloromalonic acid at 0°C



The thermodynamic values of $pK_1$ and $pK_2$ obtained graphically are 0.78 and 2.08 respectively, with a maximum deviation of 0.08 log. units from the best straight lines. As for 2,2-difluoromalonic acid, the measurements of $K_1$ and the corresponding $pK_1$ for 2,2-dichloromalonic acid are more scattered than for $K_2$ and tend to deviate more from the linear plot at ionic strengths higher than 0.5.

Generally, the contribution from the undissociated acid and monoanion to the gross rate of decarboxylation was obtained by allowing for the concentration of the various species present at a given acidity. This was done in the following way:

$$\text{rate} = k_{obs.} \times \left[\text{total malonic acid concentration}\right]$$
$$= k_{obs.} \times \left( \left[H_2A\right] + \left[HA^-\right] + \left[A^=\right] \right)$$

Equ. (II-2)

where $k_{obs.}$ = first order rate constant evaluated under any experimental conditions;

$\left[H_2A\right]$ ; $\left[HA^-\right]$ and $\left[A^=\right]$ = concentrations (M/l) of undissociated acid, monoanion and dianion of malonic acid respectively.

Since the dianion is stable, $H_2A$ and $HA^-$ contribute to the total reaction, hence:

$$k_{obs.} \times \left( \left[H_2A\right] + \left[HA^-\right] + \left[A^=\right] \right)$$
$$= k_{(H_2A)} \times \left[H_2A\right] + k_{(HA^-)} \times \left[HA^-\right]$$

Equ. (II - 3)

Dividing by $[HA^-]$ gives:

$$k_{obs.} \times \left( {}^{[H_2A]}/_{[HA^-]} + 1 + {}^{[A^=]}/_{[HA^-]} \right)$$

$$= k_{(H_2A)} \times \left( {}^{[H_2A]}/_{[HA^-]} \right) + k_{(HA^-)} \qquad \text{Equ. (II - 4)}$$

The ratios $[H_2A]/[HA^-]$ and $[A^=] / [HA^-]$ are related to the acid dissociation constants $K_1$ and $K_2$ by:

$$K_1 = \frac{[HA^-]\ [H^+]}{[H_2A]} \; ; \quad [H_2A] / [HA^-] = {}^{[H^+]}/_{K_1} \qquad \text{Equ. (II-5)}$$

and

$$K_2 = \frac{[A^=]\ [H^+]}{[HA^-]} \; ; \quad {}^{[A^=]}/_{[HA^-]} = {}^{K_2}/_{[H^+]} \qquad \text{Equ. (II - 6)}$$

Substitution for the concentration ratios in equation (II - 4) gives

$$k_{obs.} \times \left( {}^{[H^+]}/_{K_1} + 1 + {}^{K_2}/_{[H^+]} \right)$$

$$= k_{(H_2A)} \times \left( {}^{[H^+]}/_{K_1} \right) + k_{(HA^-)} \qquad \text{Equ. (II - 7)}$$

or

$$Y = k_{(H_2A)} \times X + k_{(HA^-)} \qquad \text{Equ. (II - 8)}$$

where $Y = k_{obs.} \times \left( {}^{[H^+]}/_{K_1} + 1 + {}^{K_2}/_{[H^+]} \right)$

and $X = \left( {}^{[H^+]}/_{K_1} \right)$.

Thus the plot of Y versus X gives slope = $k_{(H_2A)}$ and intercept = $k_{(HA^-)}$.

It was found better, however, to evaluate $k_{(HA^-)}$ as a slope rather than the intercept. This can be done by multiplying equation (II - 7) by $(K_1/[H^+])$ throughout, which gives:

$$k_{obs.} \times \left(1 + K_1/[H^+] + K_1K_2/[H^+]^2\right) = k_{(H_2A)} + k_{(HA^-)} \times \left(K_1/[H^+]\right) \qquad \text{Equ. (II - 9)}$$

$$\text{or} \quad Y' = k_{(HA^-)} \times X' + k_{H_2A} \qquad \text{Equ. (II - 10)}$$

where $Y' = k_{obs.} \times \left(1 + K_1/[H^+] + K_1K_2/[H^+]^2\right)$

and $X' = \left(K_1/[H^+]\right)$

Species of 2,2-dichloromalonic acid (as mole % ratios) present at various pH assuming value of $K_1 = 0.204$ and $K_2 = 1.95 \times 10^{-2}$ are listed in Table (II - 7). From this it is evident that the bulk components at pH = 1 or higher are the monoanion and dianion and that the decarboxylation rates decrease with increasing pH because the dianion is stable. The rate coefficient for decomposition of the monoanion $k_{(HA^-)}$ was obtained from this data by means of equation (II - 10) and the

Table (II - 7)

Mole % Ratios of 2,2-dichloromalonic Acid ($X_{(H_2A)}$), Monoanion ($X_{(HA^-)}$) and Dianion ($X_{(A^=)}$) Calculated by assuming that $K_1 = 0.204$ and $K_2 = 1.95 \times 10^{-2}$

| pH | $X_{(H_2A)}$ | $X_{(HA^-)}$ | $X_{(A^=)}$ |
|---|---|---|---|
| 3.50 | - | 1.60 | 98.4 |
| 3.00 | - | 4.88 | 95.1 |
| 2.50 | - | 19.95 | 86.1 |
| 2.00 | 1.80 | 33.3 | 64.9 |
| 1.75 | 3.70 | 45.9 | 50.4 |
| 1.50 | 8.40 | 56.6 | 35.0 |
| 1.25 | 17.00 | 61.6 | -21.4 |
| 1.00 | 29.1 | 59.4 | 11.6 |
| 0.75 | 44.1 | 50.4 | 5.5 |
| 0.50 | 62.6 | 35.4 | 1.9 |
| 0.25 | 71.6 | 27.6 | 1.2 |
| 0.00 | 81.8 | 17.8 | 0.4 |
| -0.25 | 89.0 | 10.9 | 0.1 |
| -0.75 | 96.2 | 3.7 | - |
| -1.50 | 99.4 | 0.64 | - |
| -2.50 | 100 | - | - |

graph obtained by plotting Y' versus X' is shown in Figure (II - 4). The slope of this plot yields a value of $k_{(HA^-)}$ = $1.61 \times 10^{-2}$ min.$^{-1}$ In principle, the intercept should yield the value of $k_{(H_2A)}$, but because of its small value (relative to the values of Y'), its exact magnitude is uncertain. However, it is clear that decomposition of the diacid species is considerably less than the monoanion.

A more reliable value for the $k_{(H_2A)}$ coefficient can be obtained from studies at higher acidity, i.e. in HCl and $HClO_4$ aqueous solutions. The data in HCl solutions from Table (II - 3), plotted in accordance with equation (II - 8), is shown in Figure (II - 5). The values of $k_{(H_2A)}$ and $k_{(HA^-)}$ thus obtained are $5.50 \times 10^{-3}$ min.$^{-1}$ and $1.20 \times 10^{-2}$ min.$^{-1}$ respectively. The results for acidities higher than 1.0 M/l HCl deviate from the linear plot of Figure (II - 5) and particularly so if the measurements in $HClO_4$ solutions are included. Actually, the $k_{(H_2A)}$ and $k_{(HA^-)}$ coefficients obtained from aqueous $HClO_4$ solution measurements are $2.54 \times 10^{-3}$ min.$^{-1}$ and $3.6 \times 10^{-2}$ min.$^{-1}$ respectively.

Discussion

On the basis of the estimated mole % ratios for the various 2,2-dichloromalonic acid species (Table (II - 7) ), $k_{obs.}$ would be expected to reach a constant value at an acidity of

Figure (II - 4)

Analysis of Decarboxylation Data for 2,2-dichloromalonic Acid (pH = 0.8 to 3.2)

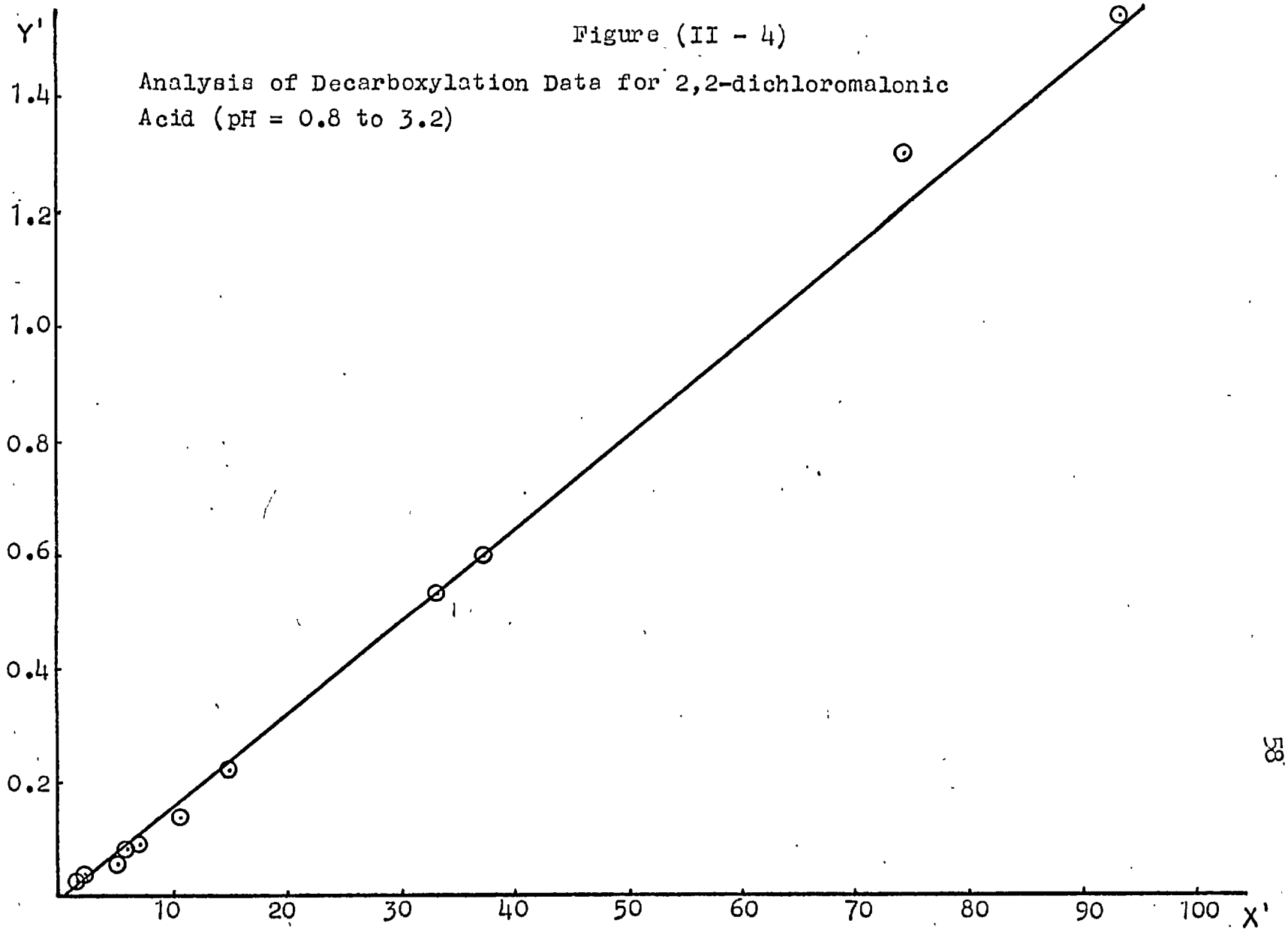
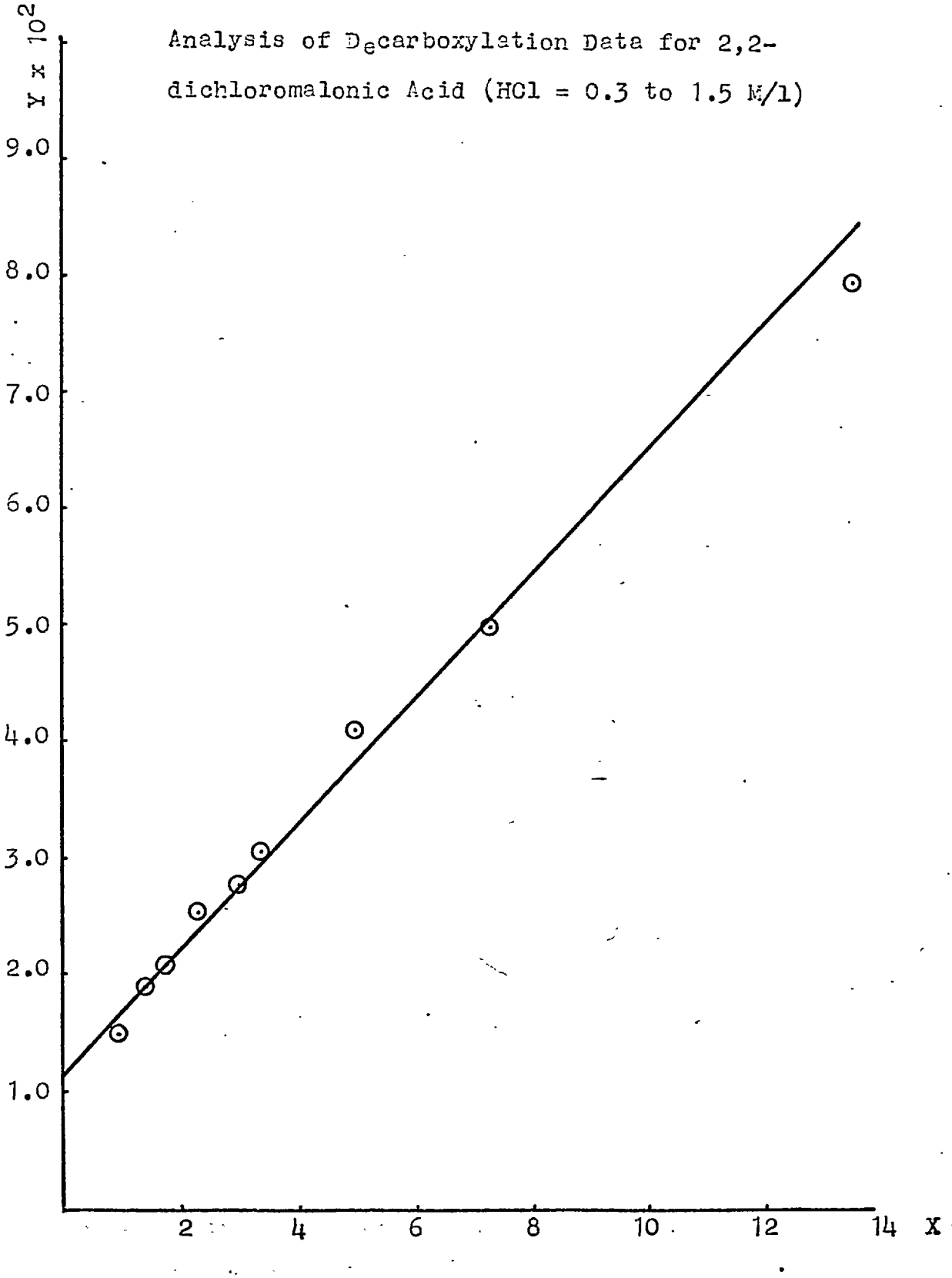


Figure (II - 5)

Analysis of Decarboxylation Data for 2,2-dichloromalonic Acid (HCl = 0.3 to 1.5 M/l)



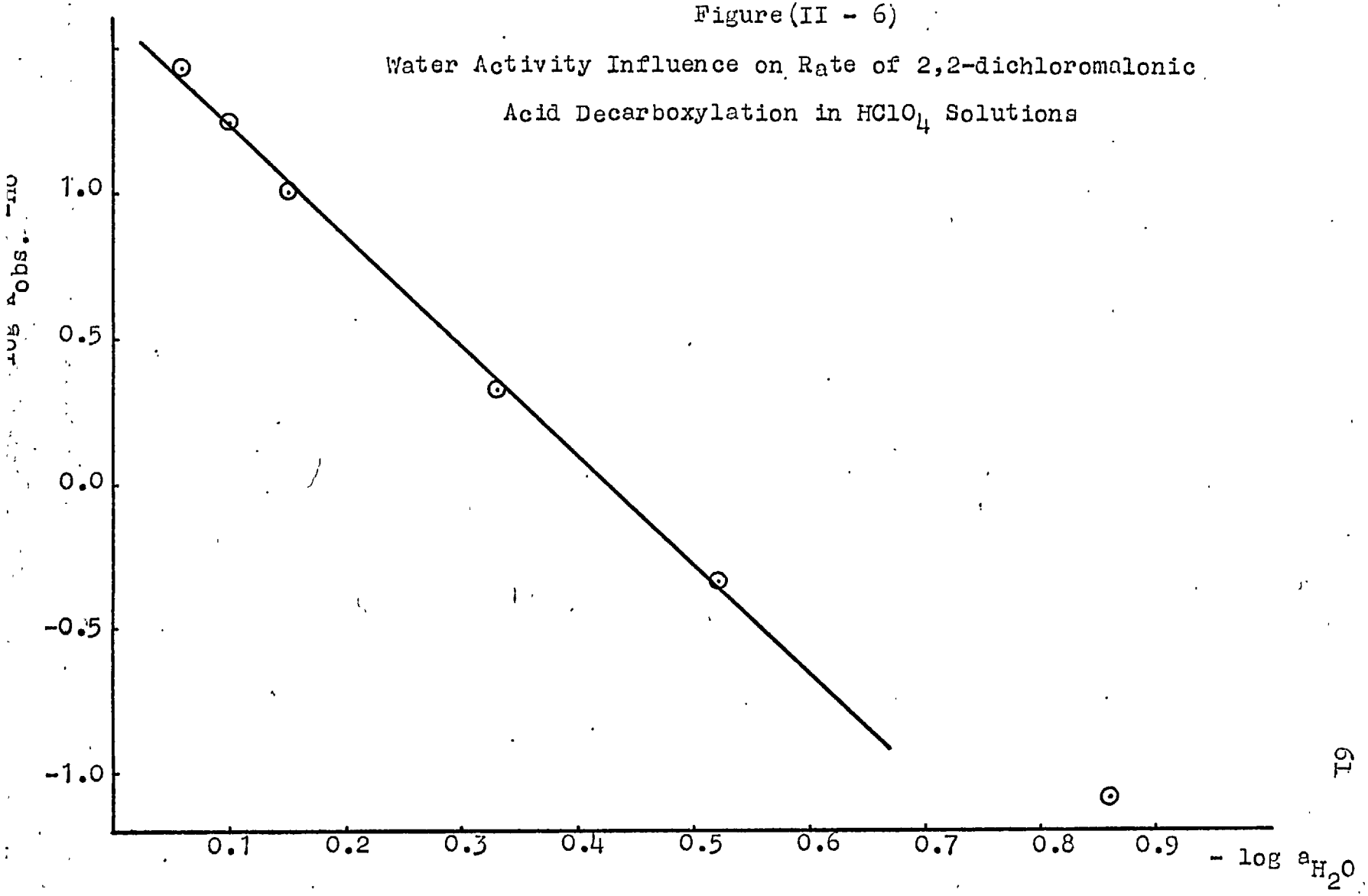
1.5 on the -Ho scale, since 2,2-dichloromalonic acid dissolved therein should be completely in the unionised form.

However, the value of $k_{obs.}$ does not reach a constant value, but instead decreases steadily at higher acidities. Apparently, over a wide range of solvent acidity, log $k_{obs.}$ varies linearly with log $a_{(H_2O)}$ where $a_{(H_2O)}$ is the activity of water [68]. The log $k_{obs.}$ versus log $a_{(H_2O)}$ dependence is shown on Figure (II - 6) for reaction in aqueous-$HClO_4$ solutions. This suggests solvation plays some part in the decomposition of the 2,2-dichloromalonic acid.

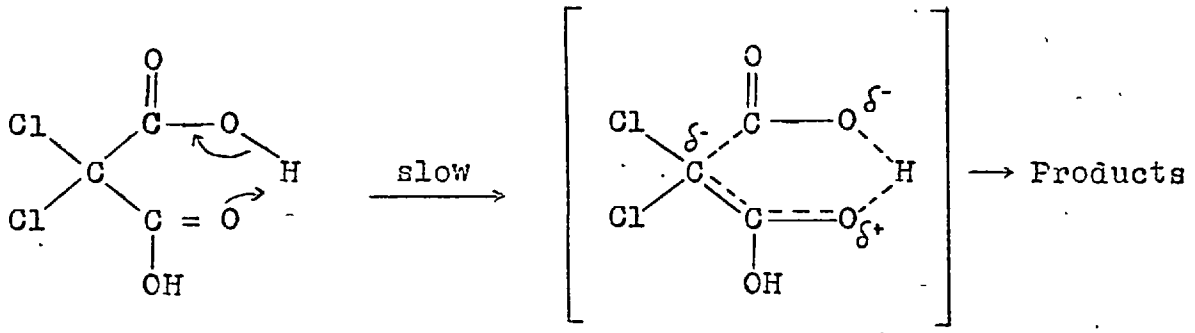
It was considered, however, that secondary salt effects (i.e. variations in the dissociation constants $K_1$ and $K_2$ values) could also operate in the strongly acidic media and thus might explain differences obtained for the $k_{(H_2A)}$ and $k_{(HA^-)}$ rate coefficients in concentrated HCl and $HClO_4$ solutions. To check this possibility, analysis of the data was done with $K_1 = 0.50$ and $K_2 = 3 \times 10^{-2}$. The value of $k_{(H_2A)}$ then changed from $2.54 \times 10^{-3}$ min.$^{-1}$ to $2.41 \times 10^{-3}$ min.$^{-1}$, which is only 5% lower. A greater change was obtained for the value of $k_{(HA^-)}$ which became nearer in value to that found for HCl solutions, i.e. $2.0 \times 10^{-2}$ min.$^{-1}$ and $1.2 \times 10^{-2}$ min.$^{-1}$ respectively. However, deviations from the linear plot expected for Figure (II - 5) were still apparent and therefore it seems probable that primary salt effects must be important. This is not

Figure (II - 6)

Water Activity Influence on Rate of 2,2-dichloromalonic Acid Decarboxylation in $HClO_4$ Solutions



unexpected for the reaction must involve considerable charge development in forming the transition state (equation (II - 11)) and obviously, the more water available, the more stabilised the




Equ. (II - 11)

transition state becomes. Thus, increasing either the neutral salt or acid concentration should decrease the reaction rate by lowering the activity of water. Another factor that might be important is the relative ease with which $CO_2$ is accommodated into the reaction solution. This effect could be estimated from the values of relative $CO_2$ solubilities ($^{S}/_{So}$) in the solutions to the solubility in pure water (see Table II - 8). The higher the solubility of $CO_2$, the lower the energy of the solvated species and, most probably, the lower the energy of the transition state. The order of reactivity of 2,2-dichloromalonic acid in KCl, $NH_4Cl$ and NaCl solutions roughly follows the decrease in $CO_2$ solubility, but the correlation is not good for LiCl and HCl solutions. It therefore seems likely that this effect is

Table (II - 8)

The Influence of an Electrolyte on the observed rate of 2,2-dichloromalonic acid decarboxylation in 1.00 M HCl Solutions at 25.0 ± 0.1°C

| Aqueous Solvent Composition (M/l) | $k_{obs.} \times 10^3$ min.$^{-1}$ | Water Activity* | $k_{obs.}/k'_{obs.}$ ** | S/So*** |
|---|---|---|---|---|
| 4 M $HClO_4$ | 1.20 | 0.792 | 0.19 | |
| 4 M HCl | 3.60 | 0.804 | 0.60 | 0.97 |
| 1 M HCl + 3 M LiCl | 3.90 | 0.811 | 0.65 | 0.83 |
| 1 M HCl + 3 M NaCl | 5.14 | 0.852 | 0.85 | 0.77 |
| 1 M HCl + 3 M $NH_4Cl$ | 7.97 | 0.873 | 1.32 | 0.91 |
| 1 M HCl + 3 M KCl | 8.44 | 0.870 | 1.40 | 0.85 |

*Water activity was calculated[69] by means of osmotic coefficients Ø using the equation $-\ln a_w = \frac{\nu . m . w}{1000} \times \text{Ø}$ where $\nu$ = number of ions into which an electrolyte dissociates; m = molality of the salt; w = molecular weight of the solvent (w = 18). $a_w$ was estimated for 3m salt solutions.

**The ratio of $k_{obs.}$ in the solution of the high electrolyte concentration and $k'_{obs.}$ in 1.0 M HCl.

***Solubility of $CO_2$ of 1 M salt solution relative to the solubility in pure water[70,71]

not very important which implies that the transition state must lie early on the reaction coordinate.

From the experimental work of Muus[45] on the decarboxylation of 2,2-dibromomalonic acid it was concluded that the monoanion form was the only reactive species whereas both the dianion and undissociated forms were stable. Actually, experiments at sufficiently high acidity to provide 100% or very nearly so, of the undissociated form of the acid were not carried out to prove this point. If the dissociation constants of 2,2-dibromomalonic acid are $K_1 = 1$ and $K_2 = 1.24 \times 10^{-2}$, then in the solution of pH = 0, 50% of the acid is undissociated and the rest is present as the monoanion. Assuming the monoanion reacts ten times faster than the undissociated acid, only 10% of the overall rate at this acidity comes from the undissociated acid which must be close to the experimental error in Muus' measurements. Accordingly, it is presumptuous to draw any conclusion from this data about the reactivity of undissociated dibromomalonic acid. However, one experiment carried out in the present work reveals that the rate of the decarboxylation of 2,2-dibromomalonic acid in 9.15 M/l $HClO_4$ is $6.1 \times 10^{-5}$ min.$^{-1}$ at 25°C which is similar to that for 2,2-dichloromalonic acid under these conditions. Likewise, the rate constant ratio $k_{(HA^-)}/k_{(H_2A)}$ for the 2,2-dibromomalonic acid is about 80 and this compares

favourably with the ratio for 2,2-dichloromalonic acid. The data for both acids are summarised in Table (II - 9) and compared with the rates of malonic and 2-phenylmalonic acids decomposition at 25°C. The ease of the accommodation of the developing charge in the transition state seems to govern the reactivity of the malonic acid series as suggested by Gelles in 1953, and there is no evidence that steric effects are important. The charge accommodation should be closely related to the type of 2-substituent which is in general self-evident from Table (II - 9) ). However, from this point of view the stability of 2,2-difluoromalonic acid is rather unusual. The strongly electron-withdrawing fluorine substituent seems to stabilise the carbon-carbon bond and thus prevents the acid decomposition and a similar effect has been reported for the decarboxylation of trifluoroacetic acid[72]. (Activation energy for trifluoroacetate decomposition is 10 Kcal. higher than for trichloroacetate ions under the same experimental conditions.) Certainly, the low polarisability of the fluorine atom is one factor which impedes accommodation of the developing charge. However, the acidity of the first carboxylic group of 2,2-difluoromalonic acid is rather low when compared with the other 2,2-dihalomalonic acids (see Table (II - 10) ). This is unusual and not observed with the halogenated acetic acids[73]. The observation suggests that 2,2-difluoromalonic acid might exist in either intramolecularly

Table (II - 9)

Relative Reactivity of Monoanion and Undissociated Species of Malonic Acids at 25°C

| Acid | $k_{H_2A} \times 10^4$ (hours$^{-1}$) | $k_{H_2A} \times 10^4$ (hours$^{-1}$) | $k_{HA^-} \times 10^4$ (hours$^{-1}$) | $k_{HA^-}/k_{H_2A}$ |
|---|---|---|---|---|
| $Br_2C(COOH)_2$ [45] | 37 (9.15 M/l $HClO_4$) | | 2900 | 79 |
| $Cl_2C(COOH)_2$ | 108 (8.5 M/l $HClO_4$) | | 7200 | 67 |
| | | 3300 | 9600 | 2.9 |
| $PhCH(COOH)_2$ [53] | | 3.6 | 7.9 | 2.2 |
| $CH_2(COOH)_2$ [48] | | 0.024 | 0.0048 | 0.21 |
| $F_2C(COOH)_2$ | | — | — | — |

a) $k_{H_2A}$ and $k_{HA^-}$ for $PhCH(COOH)_2$ and $CH_2(COOH)_2$ extrapolated from the higher temperature data

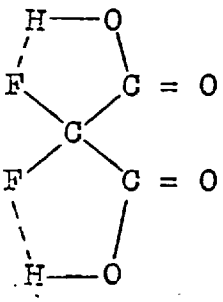
Table (II - 10)

First ($K_1$) and Second ($K_2$) Dissociation Constants of Malonic Acids

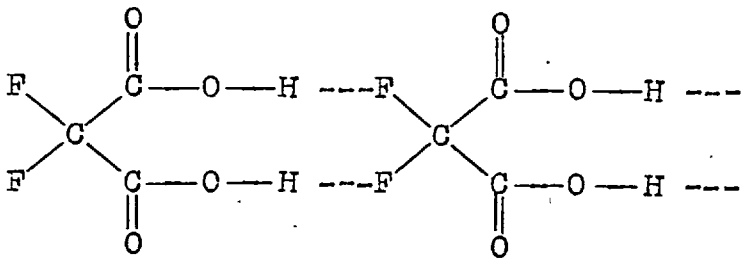
| Acid | $K_1$ (mol/l) | $K_2$ (mol/l) | $K_1/K_2$ |
|---|---|---|---|
| $Br_2C(COOH)_2$ | 1 | $10^{-2}$ | 100 |
| $Cl_2C(COOH)_2$ ≠ | 0.17 | $8.3 \times 10^{-3}$ | 20 |
| $PhCH(COOH)_2$ | $2.6 \times 10^{-3}$ | $9.4 \times 10^{-6}$ | 277 |
| $CH_2(COOH)_2$ | $1.4 \times 10^{-3}$ | $2.1 \times 10^{-6}$ | 670 |
| $F_2C(COOH)_2$ | $5.0 \times 10^{-2}$ | $7.6 \times 10^{-3}$ | 6.6 |

≠ measured at $0^{o}C$

(x) or intermolecularly ($x_A$) hydrogen-bonded forms in aqueous



(x)



($x_A$)

solutions, since the fluorine atom is known to form powerful hydrogen bonds. It is questionable, however, whether those forms of the acid would exist at temperatures as high as 70 or 80°C and cause the stability of 2,2-difluoromalonic acid and its mono-anion. Attempts to obtain evidence about the type of hydrogen-bonding from infra-red studies in $CHCl_3$ solutions did not clear the problem completely. Intensity of a broad and weak peak of bonded OH frequency from 2500 to 3300 $cm.^{-1}$ decreases as the concentration of the acid decreases but the lower frequency side of the peak decreases at noticeably faster rate. This implies that hydrogen-bonding of the ($x_A$) type is predominant in $CHCl_3$ solutions.

## Conclusion

It is evident that both molecular 2,2-dichloromalonic acid and its monoanion readily decarboxylate at 25°C, the rate constants being $k_{(H_2A)} = 4 \times 10^{-3}$ min.$^{-1}$ and $k_{(HA^-)} = 1.4 \times 10^{-2}$ min.$^{-1}$. The same conclusions can be drawn for 2,2-dibromomalonic acid, whereas 2,2-difluoromalonic acid is stable in all its forms in aqueous and dimethylsulfoxide solutions.

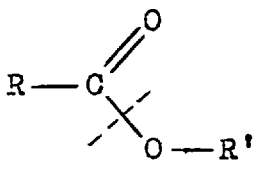
# PART II

## Hydrolysis of Malonate Esters

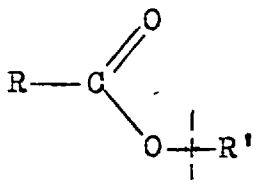
# Chapter III

## Introduction

The hydrolysis of esters generally has been widely examined and a good deal is known about the mechanism. Depending on a number of factors, but mainly the experimental conditions and the structure of the ester, either acyl-oxygen (xi) or alkyl-oxygen (xii) fission can occur. Also the reaction may



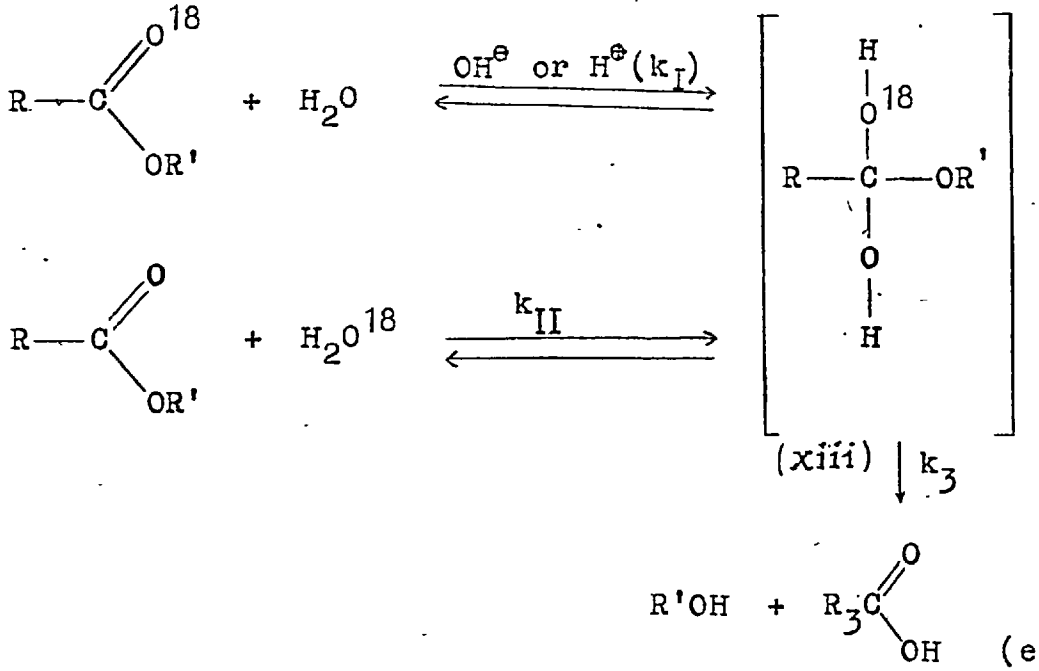
(xi)



(xii)

be catalysed by either the hydronium ion or the hydroxide ion. These various factors suggest eight different mechanisms are in principle possible[74]. Seven of these have been observed experimentally, and the so-called $B_{AC}2$ mechanism in alkaline conditions and the $A_{AC}2$ mechanism in acid conditions are the most common. There is also good evidence that in many cases tetrahedral intermediates (xiii) are involved along the reaction

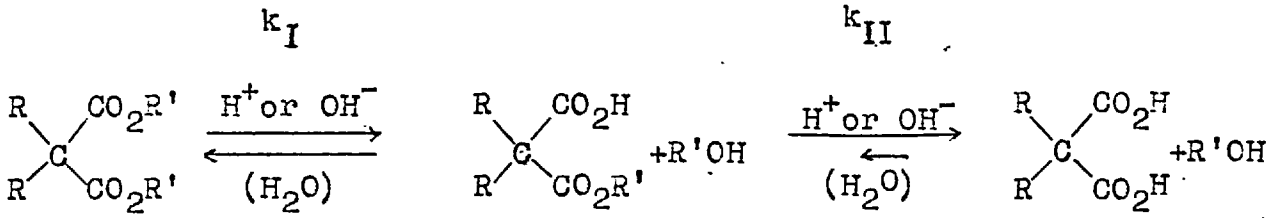
path (equation (III - 1) )[75]. Most recent work has shown that general acids and general bases may catalyse the reaction in addition to the hydronium and hydroxide ions. The nature of



this catalysis is not entirely understood, but pathways involving nucleophilic attack by general bases on the carbonyl carbon atom, and either general acid or general base catalysed breakdown of the tetrahedral intermediate, have been recognised. This catalysis is known to be especially effective when the general acid and a general base is a neighbouring group to the ester function. Generally, detailed information on the mechanism is readily available on many texts[74][75][76] and further discussion will concentrate specifically on the hydrolysis of malonate esters.

The Hydrolysis of Malonate Esters

The hydrolysis of diethylmalonate under alkaline conditions was found to be a normal second order reaction by Goldschmidt and Scholz[77] in 1903 (and checked later by Swiberly[78]) and differed only from other compounds in that two ester groups hydrolysed. This feature did, however, present a problem in that when the rates of first and second hydrolysis were similar in magnitude, no kinetic equation was available to calculate the specific rate coefficients for each ester group from the experimental data. Usually the rate constant ($k_I$) for hydrolysis of the first ester group was estimated from measurements in the first stage of the reaction neglecting hydrolysis of the second one, and for the second ester rate coefficient ($k_{II}$), the first part was neglected. Knoblauch[79], however, calculated the composition of the reaction mixture at intermediate stages in the hydrolysis of various di-esters, including diethyl malonate; and the general agreement between the calculated and the experimental composition made the principle of a two stage reaction acceptable (equation III - 2).



(eq. III - 2)

In trying to elucidate the mechanism for hydrolysis of diesters by connecting their constitution with the reactivity quantitatively, Ingold[80] came to the conclusion that factors which control the speed of hydrolysis could be classified into statistical, polar, steric and medium effects. The relative rates for two independent consecutive reactions are determined by equation (III - 3)

$$k_I/k_{II} = (\nu_1 + \nu_2)^2/2\nu_1\nu_2 \qquad \text{equ.(III-3)}$$

where $k_I$ and $k_{II}$ = rate coefficients for hydrolysis of the first and second groups, respectively, and $\nu_1$ and $\nu_2$ = the corresponding catalytic coefficients. When applied to the symmetrically constituted esters i.e. ($\nu_1 = \nu_2$) the equation (III - 3) reduces to equation (III - 4).

$$k_I/k_{II} = 2 \qquad \text{equ. (III - 4)}$$

For the catalysed hydrolysis of esters such as diethyl succinate or tartrate the rate constant ratio $k_I/k_{II}$ is very close to 2. The same applies for the alkaline hydrolysis of esters of polyvalent alcohols like glycol diacetate[81]. In these cases, a neutral substrate molecule is invariably involved for both the first and second ester group hydrolysis. However, when an ester

of a dibasic acid undergoes base catalysed hydrolysis, the substrate for the second stage of the reaction (the corresponding monoanion) is negatively charged and considerable electrostatic interaction with the hydroxide ion catalyst occurs: this may result in $k_I/k_{II} \gg 2$. The deviation from the statistical limit of $k_I/k_{II} = 2$ depends on the proximity of the two ester functions, and with a large separation the $k_I/k_{II}$ approaches its statistical value[82][79][83][84].

The interaction between a charged substituent present in the molecule and a charged catalyst approaching the reactive site is transmitted through the solvent, as well as through the molecule itself[80]. Neglecting the latter perturbation, Ingold found that the only parameter influencing the $k_I/k_{II}$ ratio is the distance ('r') between the main ionic centre in the carboxylate ion of the monoester, $ROOC(CH_2)_nCOO^{\ominus}$, and the main focus of the reaction with hydroxide ion in the carboxylic ester group[85]. The values for "r" calculated from the $k_I/k_{II}$ ratio for an irreversible reaction were compared with the results obtained from the first and second dissociation constants of the corresponding dicarboxylic acids[86]. They were in a very good agreement only for higher homologues of the series. Obviously, the effect of a substituent which is transmitted through the molecular framework could not be neglected.

Investigating the base catalysed hydrolysis of diethyl malonate and diethyl adipate in water and in 80% alcohol/water solutions, Westheimer and Jones[83] correlated the experimental data with theoretical predictions of the Kirkwood-Westheimer theory[37][38], which takes account of the electrostatic influence of a charged substituent transmitted through the solvent as well as through the molekule itself. The activated complex is represented as a region of low dielectric constant surrounded by a homogeneous solvent. For short and relatively broad molecules like malonates, most of the lines of force travel through the molecule itself and, consequently, the influence of solvent is minimised. Some experimental results proved to be in a good qualitative agreement with the predictions of their theory. Westheimer and Jones further investigated the influence of an electrolyte upon the first and second rate constants for malonate ester hydrolysis. They found $k_I$ to be practically independent of ionic strength in either of the solvents, while $k_{II}$ was strongly influenced by the neutral salt concetration and particularly so in alcohol/water solutions. This salt effect could explain the increasing $k_I/k_{II}$ ratio reported by Ritchie[82] in alcoholic solutions for malonate ester hydrolysis. However, it would not explain Ritchie's results for the $k_I/k_{II}$ ratio of a series of 2-substituted diethyl malonates under similar conditions. He found the

sequence for $k_I/k_{II}$ ratio for base catalysed hydrolysis in 50% aqueous/alcoholic solutions at 25°C to be 77.9, 28.6, 13.5 and 4.57 for the unsubstituted ester, 2-methyl, 2,2-dimethyl and 2,2-diethyl derivatives respectively. Such a pronounced influence of substituents in 2-position was unexpected, at least on the basis of Kirkwood-Westheimer's theory.

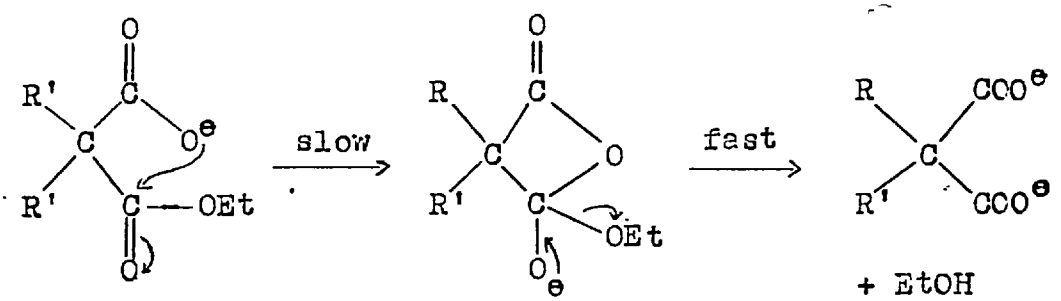
In general, however, the presence of the 2-alkyl substituents should decrease the reactivity of the compound due to the steric retardation, as well as the electron donating character of the alkyl groups. Experimental data by Ritchie[82] about the first ($k_I$) and second ($k_{II}$) rate constants (second order rate constants) of a series of 2-substituted malonates do show the decrease of the rate constants in the order: unsubstituted ester, 2,2-dimethyl and 2,2-diethyl malonates. These results are presented in Table (III-1) where it can be seen that although both the individual values of $k_I$ and $k_{II}$ decrease, the effect is higher for $k_I$ than for $k_{II}$. Or, in other words, the difference between the neutral and negatively charged species of the malonate system undergoing nucleophilic attack at the carbonyl group becomes negligible as the substitution in the 2-position increases. One possible explanation could be intramolecular carboxylate catalysis ($COO^{\ominus}$-4 participation) of the second group hydrolysis operating either in competition with intermolecular ($OH^{\ominus}$) base catalysis (in less sterically

Table (III - 1)

Second Order Rate Constants for the Base Hydrolysis of a Series of Diethyl Malonates in Aqueous/alcoholic Solutions (50 mol. %) at 25°C

| 2-substituent | $k_I \times 10^3$ | $k_{II} \times 10^4$ | $k_I/k_{II}$ |
|---|---|---|---|
| None | 16900 | 21700 | 77.9 |
| 2-methyl | 2400 | 8380 | 28.7 |
| 2,2-dimethyl | 57 | 420 | 13.6 |
| 2,2-diethyl | 1 | 24 | 4.57 |

hindered molecules) or, as the only form of the second ester group hydrolysis (see eq. (III - 5) ):




(xiv)

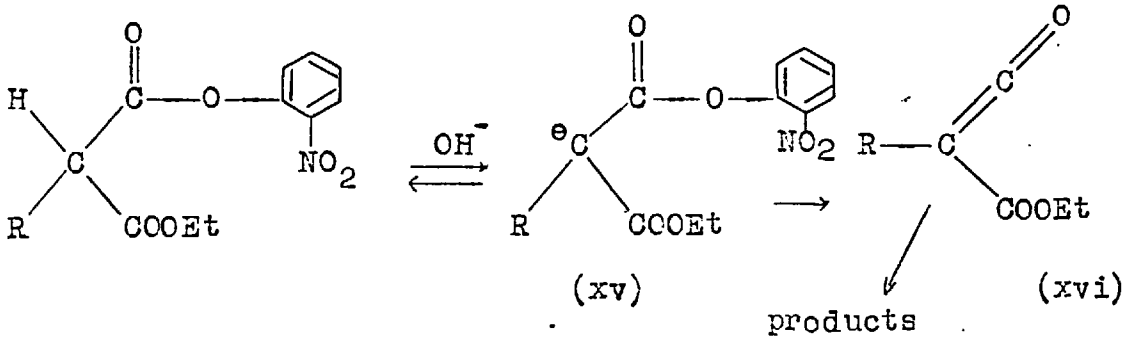
Equ. (III - 5)

Energetically unfavourable formation of a four-membered intermediate (xiv) could be compensated by the steric interaction of a bulky (gem.) ethyl group in 2-position and, therefore, result in intramolecular catalysis only. Actually, the problem has never been reinvestigated and no satisfactory explanation offered to date. In particular, steric errects from bulky substituents were not considered.

The influence of solvent on both the rate and the mechanism of dicarboxylic acid ester hydrolysis was examined by Swiberly and Kuhta[84]. They studied the alkaline hydrolysis of diethyl malonate, diethyl succinate and diethyl sebacate and found the expected decrease (on the basis of Westheimer and Jones results) in the $k_I/k_{II}$ ratio (118, 5.77 and 2.82 respectively) with substrate structure in 50% dioxan/water without added salts. However, when the concentration of dioxan was increased, the $k_I/k_{II}$ ratio decreased considerably for all substrates. Thus, for diethyl malonate $k_I/k_{II}$ changes from 165 in 20% dioxan/water to 1.46 in 82.75 wt. % dioxan/water solutions. Furthermore, since the plot of log $k_{II}$ versus solvent dielectric constant (D) passes through a minimum when D approaches 30 (the region where ion pairs formation becomes important[85]) they concluded that the mechanism for hydrolysis of the second ester group is changing from an ion-ion process in media of high dielectric constant to one involving ion-ion-pairs in media of lower

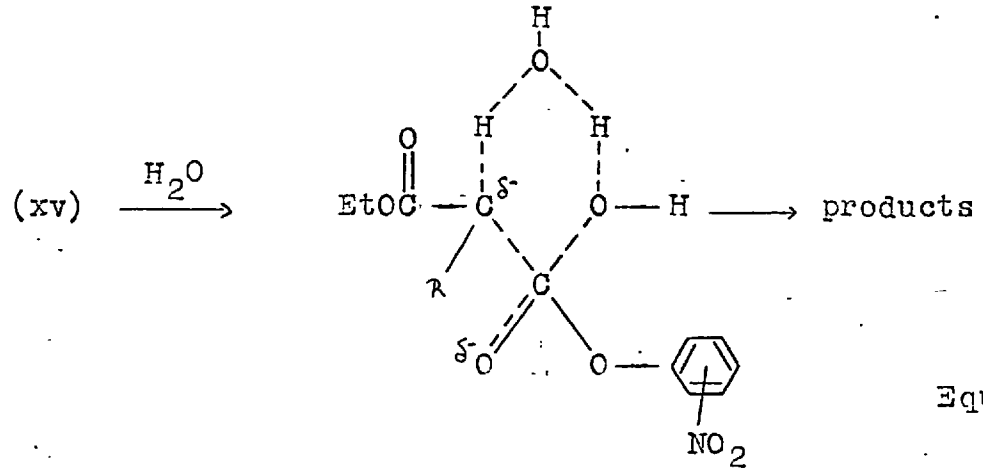
dielectric constant. Furthermore, with very low dielectric media, Swiberly and Kuhta believed the formation of ion-pairs was important for hydrolysis of both the first and second ester groups. However, this change in mechanism should not be important under the conditions of Ritchie's experiments, as aqueous solvents were used.

More recent work by Bruice and his collaborators[90] has suggested that o-nitrophenyl malonate esters along with other esters containing labile 2-H atoms (i.e. $CN{\cdot}CH_2COOR$ or $(CH_3)_2\overset{\oplus}{S}CH_2COOR$) and a good leaving group (i.e. $-o-NO_2C_6H_4O^{\ominus}$) may undergo an unusual kind of base catalysed hydrolysis involving the formation of a carbanion intermediates (xv) Eq. (III - 6). The evidence for this comes mainly from the unusual pH-rate profiles obtained for these compounds in contrast to those for substituted derivatives (such as 2,2-dimethyl o-nitrophenyl ethyl malonate) devoid of 2-H atoms. In all these cases, decomposition of the carbanion intermediate was thought to occur either spontaneously (see equation (III - 6) ) without solvent interaction (i.e. formation of an unstable



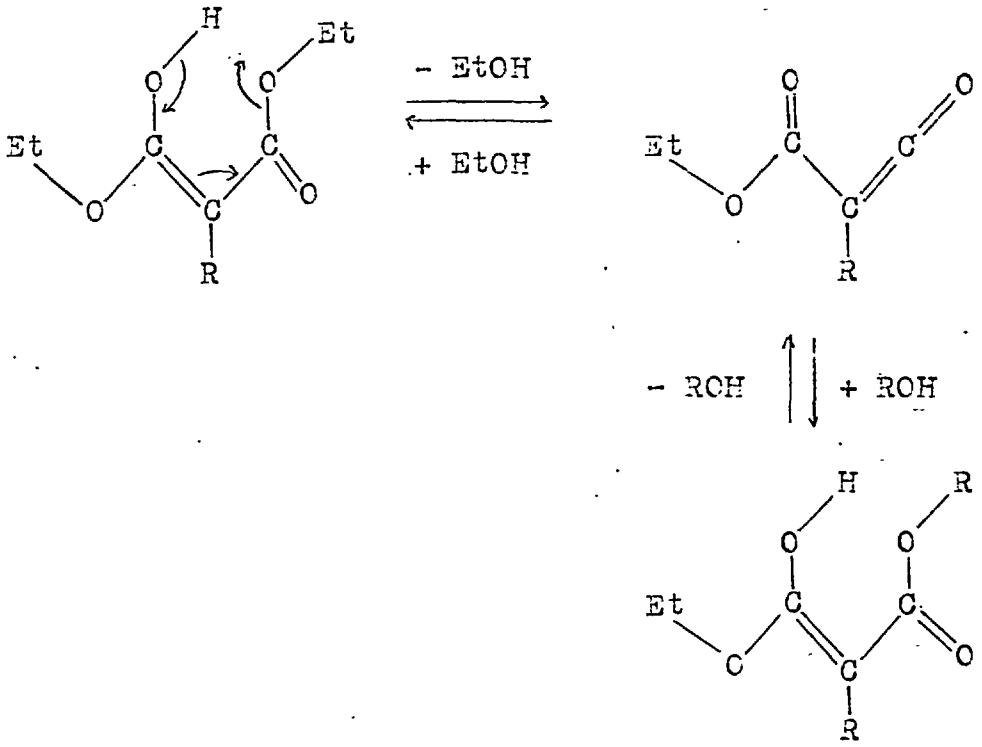

Equ. (III - 6)

ketene (xvi) or by a general base catalysed attack of water at the ester carbonyl carbon (equation (III - 7) ).




Equ. (III - 7)

Bruice and Holmquist favoured the first pathway as formation of hydroxamate with hydroxylamine and acylimidazoles in imidazole buffer solutions are most easily rationalised via the trapping of ketene intermediates. Holmquist and Bruice[90] suggested further that the uncatalysed transesterification of a series of malonates described by Rowland and coworkers[91][92] proceeds via a related ketene mechanism (equation (III - 8) ). However, this mechanism is obviously not important with disubstituted malonate esters.




equ. (III - 8)

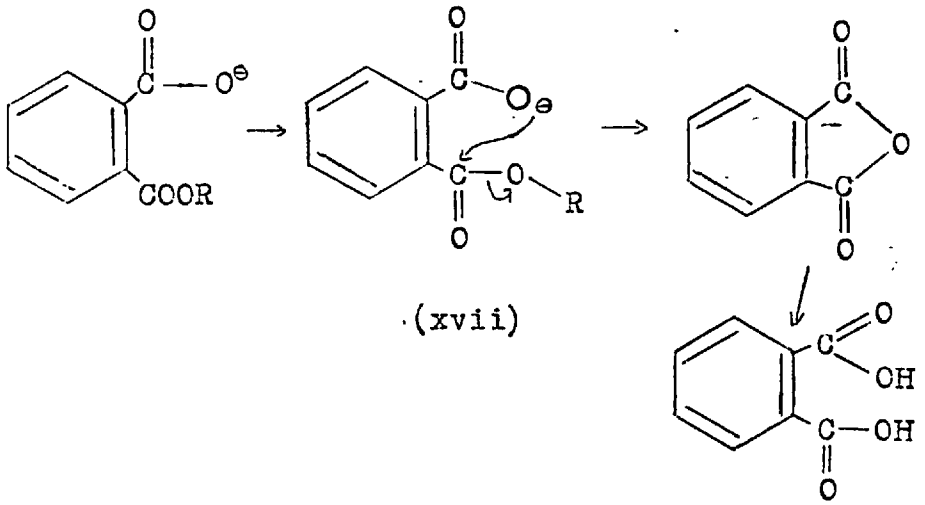
Neighbouring Group Effects

Extensive investigations over the last twenty years have established that mutual interactions between neighbouring groups have an important bearing on the rates and mechanism on many reactions. In particular, it has been established that the interaction of neighbouring nucleophilic and basic ($-O^-$, $-CO_2^-$, $-NH_2$ etc.) is important in ester hydrolysis and other carbonyl

eddition reactions. Several excellent summaries are available in review articles[93][74][94].

Interaction of this kind might be expected with the reactions of malonates, where one carboxylic group interacts with the other but, surprisingly, few attempts have been made to observe and identify neighbouring group effects in this class of compounds.

However, anchimeric assistance has been investigated extensively in other dicarboxylic acids[95][96][97][98]. One of the first investigations was by Bender and collaborators[95][96] who studied derivatives of phthalic acid and concluded the pH-rate profile for the hydrolysis of methyl hydrogen phthalate was connected with carboxylate ion assisted hydrolysis of the ester function via transition state (xvii) in equation (III - 9)



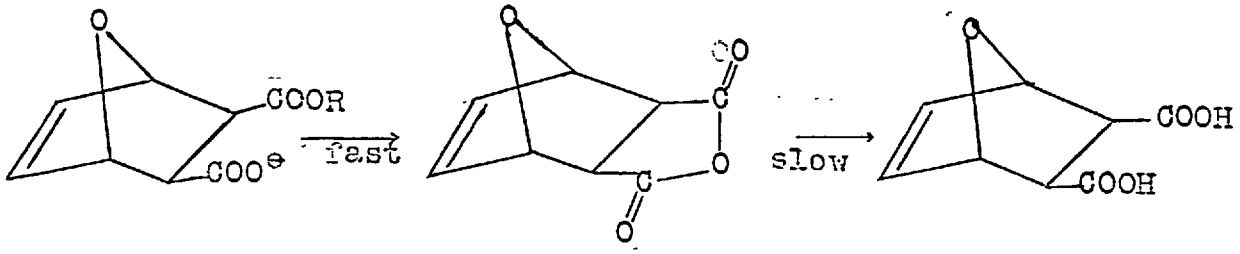
(xvii)

Equ. (III - 9)

to give a phthalic anhydride intermediate. Other related work,

on the hydrolysis of acetyl salicylate involving both pH-rate studies and $O^{18}$ exchange(99) demonstrated that carboxylate ion could act as a neighbouring base catalyst.

The pH-rate profiles for hydrolysis of phenyl hydrogen succinate and glutarate(97) have also been interpreted as evidence for intramolecular nucleophilic catalysis by carboxylate ion. Unsubstituted succinate hydrolyses about 200 times faster than glutarate in the pH independent region presumably because the smaller distance between the two carboxylic groups increases the entropy of activation for the succinate substrates. Substituent effects on the rate of intramolecular hydrolysis of dicarboxylic acid monoesters have been extensively studied by Bruice and Pandit(98). They investigated the hydrolysis of several mono p-bromophenyl esters of succinic and glutaric acid, as well as mono p-methoxyphenyl esters of maleic and 7-oxabicyclo [2,2,1] hept-2-ene-5,6-exo dicarboxylic acid. Release of phenoxide ion from maleic and 7-oxabicyclo [2,2,1] hept-2-ene-5,6-exo dicarboxylic acid esters produced a neutral intermediate which itself hydrolysed at a rate identical to that observed for the corresponding anhydride (xviii). This clearly indicates that




(xviii) Equ. (III - 10)

decomposition of the anhydride (xviii) is the rate controlling process (equation (III - 10) ). However, hydrolysis of succinic and glutaric acid anhydrides must be much faster than their formation, since these species cannot be detected in the reaction mixture. Bruice and Pandit deduced the following observation from their results:

a) Five membered rings are closed at higher speed than six-membered ones (unsubstituted succinate reacts 230 times as fast as glutarate).

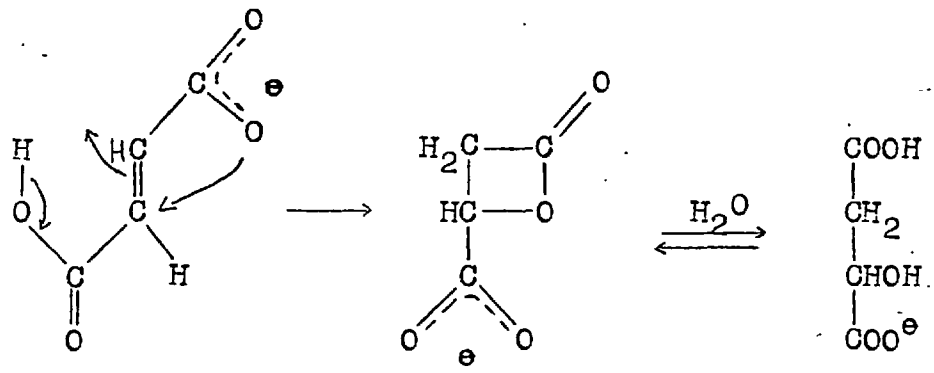
b) Ring opening (decomposition of the intermediate anhydride) is but little influenced by the size of the ring.

c) Geminal substitution (particularly at the $\beta$-position) increases the rate of ring closure and decreases the rate of ring opening.

d) Restricted rotation of the reacting carboxyl and carbophenoxy groups accelerates the rate of ring closure by a factor of $10^4$ ($1 \times 10^4$ and $5 \times 10^4$ for maleic and 7-oxabicyclo [2,2,1] hept-2-ene-5,6-exo dicarboxylic acid respectively) relative to the unsubstituted glutarate hydrolysis.

e) Non-bonding interaction between substituents in substituted glutarates and succinates results in an increase of the ring closure because the reacting centres are brought closer together[100]; whereas the rate of ring opening seems to be mainly dependent upon steric hindrance.

Bell-shaped pH-rate profiles obtained for the hydration of fumaric acid arise from the enhanced reactivity of the fumaric monoanion, i.e. both the -COOH and $CCO^{\ominus}$ groups are involved in the reaction. This is most easily explained by isomerisation to $\beta$-malo-lactonic acid which then undergoes rapid hydrolysis (equation (III - 11) ).



Equ. (III - 11)

Clearly there is good evidence for neighbouring carboxylate ion catalysed ester hydrolysis in dicarboxylic acid derivatives in which the carboxyl functions are separated by at least two carbon atoms, i.e. fumaric, maleic, succinic esters, but apart from Ritchie's experiments, there is no evidence for similar neighbouring group intermediates in malonate esters: also, malonate anhydride has never been isolated. However, this is no a priori reason why such interaction should not occur. There is, in fact, some evidence of neighbouring group interaction by $-COO^{\ominus}$ resulting with the formation of a lactone intermediate for

reactions other than ester hydrolysis. Thus anchimeric assistance by ionised carboxylic groups has been observed during hydrolysis of several aliphatic halo-acids. The hydrolysis of $\beta$-, $\gamma$-, $\delta$—halo-acids in neutral solutions gives isolable lactones[101][102][103]; hydrolysis of $\alpha$-halo-acids provides several observations indirectly supporting the reaction via an intramolecular nucleophilic displacement. For example: a) Configuration of the product is retained during hydrolysis of $\alpha$-bromopropionate[104], the rate of methanolysis of $\alpha$-bromopropionate is about twenty times faster than isopropyl bromide solvolysis[105] and hydrolysis is not appreciably affected by either solvent or neutral electrolyte concentration. Further evidence for intramolecular participation by $-COO^{\ominus}$ comes from thermodynamic activation parameters. Thus, Lane and Haine[106,107] have measured the energy and the entropy of activation for the solvolysis of a series of monobromo carboxylic acids where the bromine substituent varies from the $\alpha$ to $\varepsilon$ and $\zeta$ position. A positive value for the entropy of activation ( 11 e.u.) for $\alpha$, $\beta$ and $\gamma$ -substituted acids was interpreted as a release of water molecules in the transition state which increases the entropy of the system as a whole. However, shifting the bromine atom further away from the carboxylate ion makes the contribution of intramolecular reaction to the total reaction smaller and the

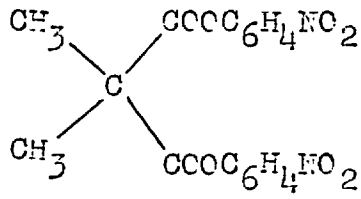
entropy of activation diminishes (- 2 e.u. for $\varepsilon$ -bromocaproate and - 13 e.u. for $\zeta$ -bromoenanthate). As far as intramolecular reaction is concerned, the enthalpy of activation changes considerably with the distance of the two reactive sites in the molecule. The greater the strain in the intermediate lactone, the greater the enthalpy of activation. Regarding 5-membered rings as being strainless, 5 Kcal. of energy is required to form four-membered ring and 7 Kcal. for three-membered ring formation. The magnitude of these energy terms would not prohibit lactone formation for the $\alpha$ - and $\beta$-bromo acids.

Accordingly, kinetic studies of malonate ester hydrolysis were undertaken in alkaline solutions to probe for the incidence of neighbouring carboxylate ion catalysis. The substrates used by Ritchie are unreactive and it is difficult to obtain rate data for hydrolysis of both the first and second groups under identical conditions. For this reason more reactive substrates were used in the present investigation.

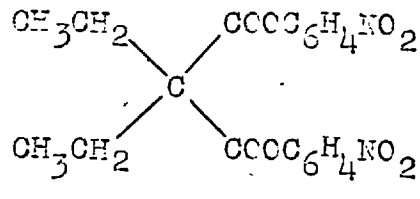
# Chapter IV

## Discussion of Results for the Base Catalysed Hydrolysis of 2,2-disubstituted Malonates

It is evident that for the hydrolysis of an unsubstituted diethylmalonate the relative reactivity of the first and second ester group is a function of the experimental conditions, but extrapolated values of $k_I/2k_{II}$ ratio to the zero ionic strength in aqueous 80% ethanol/water[83] and dioxan/water solutions[84] (when the value of the dielectric constant of the solvent was higher than 60 in the last mentioned solvent), are in reasonable qualitative agreement with predictions of the Kirkwood-Westheimer theory. However, the data for alkyl substituted ethyl malonates cannot be explained by the Kirkwood-Westheimer treatment. Substitution lowers the $k_I/2k_{II}$ ratio for ester hydrolysis and is clearly related to the nature of the alkyl substituent. The actual aim of the present work was to establish whether neighbouring group interactions are important for the hydrolysis of 2,2-disubstituted malonates. The substrates chosen for the study were 2,2-dimethyl di(p-nitrophenyl)malonate (xix); 2,2-diethyl di(p-nitrophenyl)malonate (xx); 2,2-dibromo/diethylmalonate and 2,2-dichloromalonate. The corresponding unsubstituted p-nitrophenyl malonate ester was found to be much too



(xix)



(xx)

reactive to be followed by the method described in the experimental section. Above pH = 5 neither the first nor the second ester group hydrolyses could be followed quantitatively.

The experimental pseudo-first order rate constants with excess of NaOH in 41 vol. % dioxan/water solutions are summarised in Tables (IV - 1) and (IV - 2) for substrates (xix) and (xx) respectively. The ionic strength of the solutions was adjusted by KCl to a total value of 1.00 for all of the measurements listed in the two tables. Concentration of the substrates was in the region of $2 \times 10^{-6}$ M/l. On the basis of the individual measurements, the second order rate constants $k_{I(OH^-)}$ and $k_{II(OH^-)}$ for the hydrolysis of (xix) were estimated to be $(8.3 \pm 0.3) \times 10^2$ l. $mol^{-1}$ $min.^{-1}$ and $2.6 \pm 0.1$ l. $mol^{-1} min.^{-1}$ respectively. Therefore, $k_{I(OH^-)}/k_{II(OH^-)} = 320$, or when corrected for the statistical factor $k_{I(OH^-)}/2k_{II(OH^-)} = 160$. Rate constants for this particular compound were not corrected for contribution via a water catalysed pathway since the plot log $k_{obs.}$ versus log [NaOH] has a slope of unity.

Table (IV - 1)

Hydrolysis of 2,2-dimethyl di(p-nitrophenyl)malonate with Excess of NaOH Measured in 41 vol. % Dioxan/Water Solvent at 25 ± 0.1°C

| Run | NaOH (M/l) | KCl (M/l) | $k_{1obs.}$ ($min.^{-1}$) | $k_{2obs.} \times 10^3$ ($min.^{-1}$) | $-\log k_1$ | $-\log k_2$ |
|---|---|---|---|---|---|---|
| 159 | 0.010 | 0.990 | - | 25.0 | - | 1.602 |
| 160 | 0.002 | 1.00 | - | 5.53 | - | 2.257 |
| 161 | 0.001 | 1.00 | 0.86 | - | 0.065 | - |
| 162 | 0.0006 | 1.00 | 0.479 | - | 0.320 | - |

$k_{I(OH^-)} = (8.3 \pm 0.3) \times 10^2$ l.mol$^{-1}$ min.$^{-1}$;

$k_{I(OH^-)} = 2.6 \pm 0.1$ l. mol$^{-1}$ min.$^{-1}$

$k_{I(OH^-)}/k_{II(OH^-)} = 360$

Table (IV - 2)

Hydrolysis of 2,2-diethyl di(p-nitrophenyl) malonate With Excess of NaOH; Measured in 41 vol. % Dioxan/Water Solvent at 25.0 ± 0.1°C

| Run | NaOH (M/l) | KCl (M/l) | $k_{1obs.} \times 10^2$ (min.$^{-1}$) | $k_{2obs} \times 10^4$ (min.$^{-1}$) | -log $k_1$ | -log $k_2$ |
|---|---|---|---|---|---|---|
| 151 | 0.50 | 0.50 | - | 221 | - | 1.655 |
| 152 | 0.40 | 0.60 | - | 184 | - | 1.735 |
| 153 | 0.20 | 0.80 | - | 91.2 | - | 2.040 |
| 154 | 0.05 | 0.95 | - | 24.4 | - | 2.613 |
| 155 | 0.02 | 0.98 | 23.6 | 9.30 | 0.628 | 3.032 |
| 156 | 0.01 | 0.99 | 12.0 | 5.19 | 0.920 | 3.285 |
| 158 | 0.004 | 1.00 | 5.71 | 1.90 | 1.244 | 3.720 |
| 157 | 0.001 | 1.00 | 1.84 | 0.74 | 1.735 | 4.130 |

$k_{I(OH^-)} = 11.3$ l. mol$^{-1}$ min.$^{-1}$

$k_{II(OH^-)} = (4.72 \pm 0.26) \times 10^{-2}$ l. mol$^{-1}$ min.$^{-1}$

$k_{I(OH^-)}/k_{II(OH^-)} = 240$

The data for the 2,2-diethyl malonate (xx) gives a mean value of the second order rate constant $k_{II(OH^-)}$ = (4.7 ± 0.26) x $10^{-2}$ l. mol.$^{-1}$ min.$^{-1}$ (the rate for 0.001 M NaOH was not taken into account since the deviation from log $k_{2\ obs.}$ versus log [NaOH] plot was very much higher than the standard deviation). From the log $k_{1\ obs.}$ versus log [NaOH] plot it was realised that the competition between $H_2O$ and $OH^{\ominus}$ catalysed hydrolysis was considerable. From equation (IV - 1) it is apparent that the intercept of $k_{1\ obs.}$ versus [NaOH] plot is a

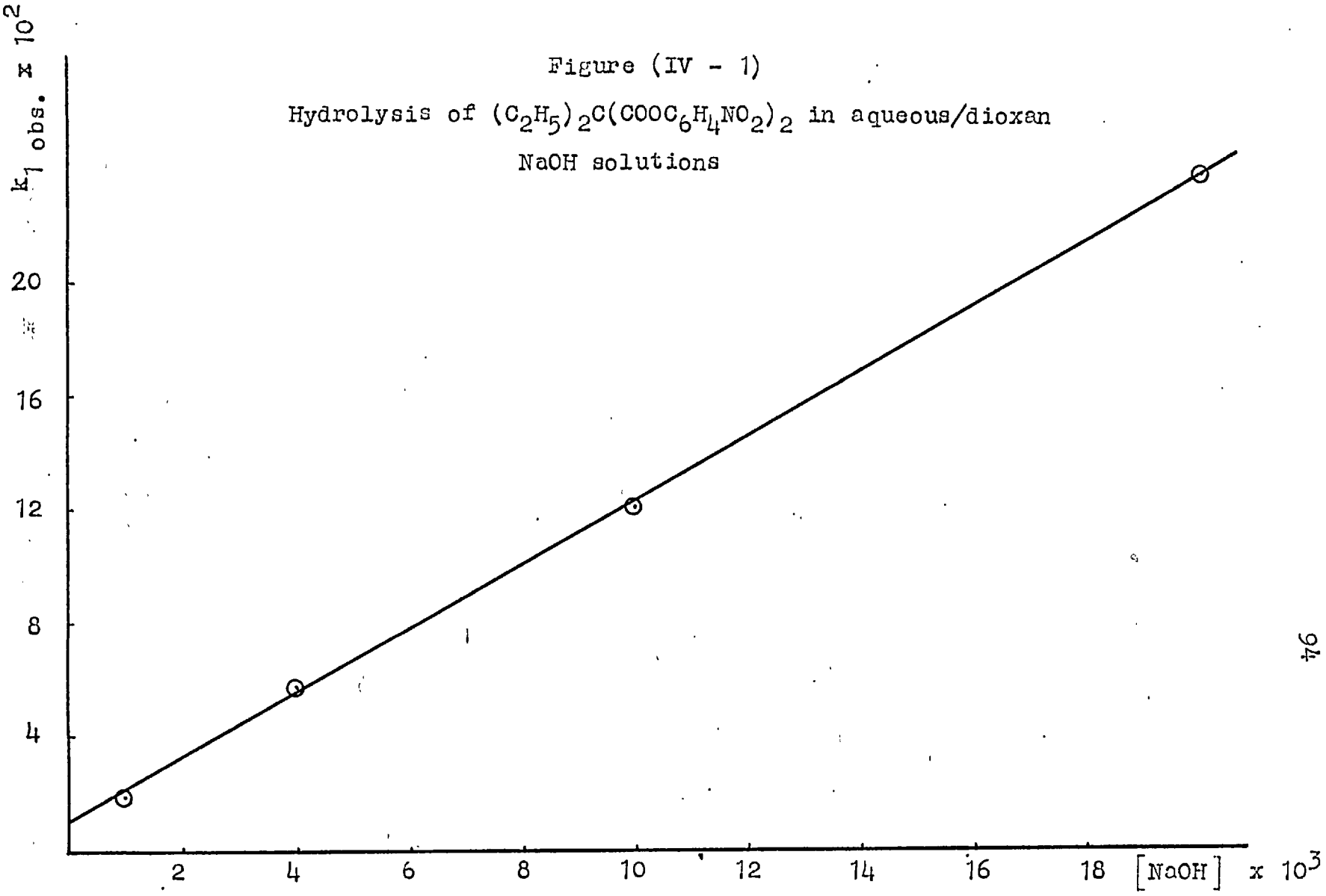
$$k_{1\ obs.} = k_{I(H_2O)} \times [H_2O] + k_{I(OH^-)} \times [OH^-]$$

Equ. (IV - 1)

constant related to the spontaneous (water catalysed) hydrolysis. Accordingly, $k_{I(OH^-)}$ = 11.3 l. mol.$^{-1}$ min.$^{-1}$ and $k_{I(H_2O)} \times [H_2O] = k_W = 1 \times 10^{-2}$ min.$^{-1}$, as estimated from Figure (IV - 1). The first and second rate constant ratio for hydroxide ion catalysed hydrolysis of (xx) is, therefore, $k_{I(OH^-)}/k_{II(OH^-)}$ = 240, or $k_{I(OH^-)}/2k_{II(OH^-)}$ = 120. Thus neither the $k_{I(OH^-)}/k_{II(OH^-)}$ ratios for 2,2-dimethyl or 2,2-diethyl p-nitrophenyl malonates is unexpectedly low, and, accordingly, neighbouring group interaction by the $-COO^{\ominus}$ does not occur under these conditions.

Figure (IV - 1)

Hydrolysis of $(C_2H_5)_2C(COOC_6H_4NO_2)_2$ in aqueous/dioxan NaOH solutions



However, this effect would be most noticeable at low $OH^{\ominus}$ concentration, where hydrolysis by the normal bimolecular path is less important. For the studies at base concentrations less than $10^{-3}$ M/l, glycine/NaOH buffer was used. The solvent composition remained as mentioned above, and the ionic strength was adjusted with KCl to the total value of 0.059 M/l. The experimental pseudo-first order rate constants together with the corresponding pH (measured) and the buffer concentrations are listed in Tables (IV - 3) and (IV - 4) for the first and second ester group hydrolysis respectively and log $k_{obs.}$ versus pH (measured) are presented in Figure (IV - 2).

Apart from $OH^{\ominus}$ and $H_2O$ acting as nucleophiles in buffered solutions, it is apparent that glycine itself catalyses the reaction. However, the structure of glycine is such that the reaction could proceed by a general acid-general base catalysed pathway as well as by nucleophilic catalysis. Therefore, the rate constant dependence upon glycine concentrations was checked for both the first and second ester group hydrolysis. From the data in Table (IV - 5) it is obvious that double buffer concentration increases the rate of reaction by a factor of 3 and 8 for the first and the second ester group hydrolysis, respectively. Thus, the first ester group seemed to be hydrolysed via a normal nucleophilic attack on the carbonyl carbon atom while the second group hydrolysis probably involved two or perhaps three molecules of glycine in the transition state.

Table (IV - 3)

Hydrolysis of the First Ester Group of $(C_2H_5)_2C(COOC_6H_4NO_2)_2$ in Presence of Glycine/NaOH buffer and Glycine with Excess of NaOH at 25.1 ± 0.2°C

| Run | pH (measured)* | mls of 0.1 M Glycine in 100 mls of Solution | mls of 0.1 M NaOH in 100 mls of Solution | $k_{1\ obs.} \times 10^2$ | $-\log k_{1\ obs.}$ |
|---|---|---|---|---|---|
| 140 | 9.71 | 28 | 12 | 0.79 | 2.102 |
| 124 | 10.15 | 24 | 16 | 1.15 | 1.940 |
| 137 | 10.16 | 24 | 16 | 0.98 | 2.008 |
| 141 | 10.14 | 24 | 16 | 1.03 | 1.987 |
| 125 | 10.47 | 22 | 18 | 1.17 | 1.932 |
| 142 | 10.83 | 20.4 | 19.6 | 1.80 | 1.745 |
| 126 | 11.10 | 20.4 | 19.6 | 1.00 | 2.00 |
| 127 | 11.91 | 19.6 | 20.4 | 2.09 | 1.680 |
| 143 | 11.46 | 19.6 | 20.4 | 3.69 | 1.433 |
| 131 | 12.33 | 19.2 | 20.8 | 4.41 | 1.356 |
| 130 | 12.36 | 18.8 | 21.2 | 4.62 | 1.335 |
| 128 | 12.68 | 18.0 | 22.0 | 9.03 | 1.044 |
| 133 | 12.94 | 16.0 | 24.0 | 16.0 | 0.796 |

Table (IV - 4)

Hydrolysis of the Second Ester Group of $(C_2H_5)_2C(COOC_6H_4NO_2)_2$ in Presence of Glycine /NaOH Buffer and Glycine with Excess of NaOH at 25.1 + 0.2°C

| Run | pH (measured) | mls of 0.1 M Glycine in 100 mls of Solution | mls of 0.1 M NaOH in 100 mls Solution | $k_{2\ obs.} \times 10^4$ | $-\log k_{2\ obs.}$ |
|---|---|---|---|---|---|
| 144 | 9.71 | 28 | 12 | 3.01 | 3.521 |
| 145 | 10.84 | 20.4 | 19.6 | 4.45 | 3.352 |
| 146 | 11.60 | 19.6 | 20.4 | 4.80 | 3.312 |
| 147 | 12.95 | 16.0 | 24.0 | 6.21 | 3.207 |

Figure (IV - 2)

Hydrolysis of (xx) in Glycine Buffer at 25°C.

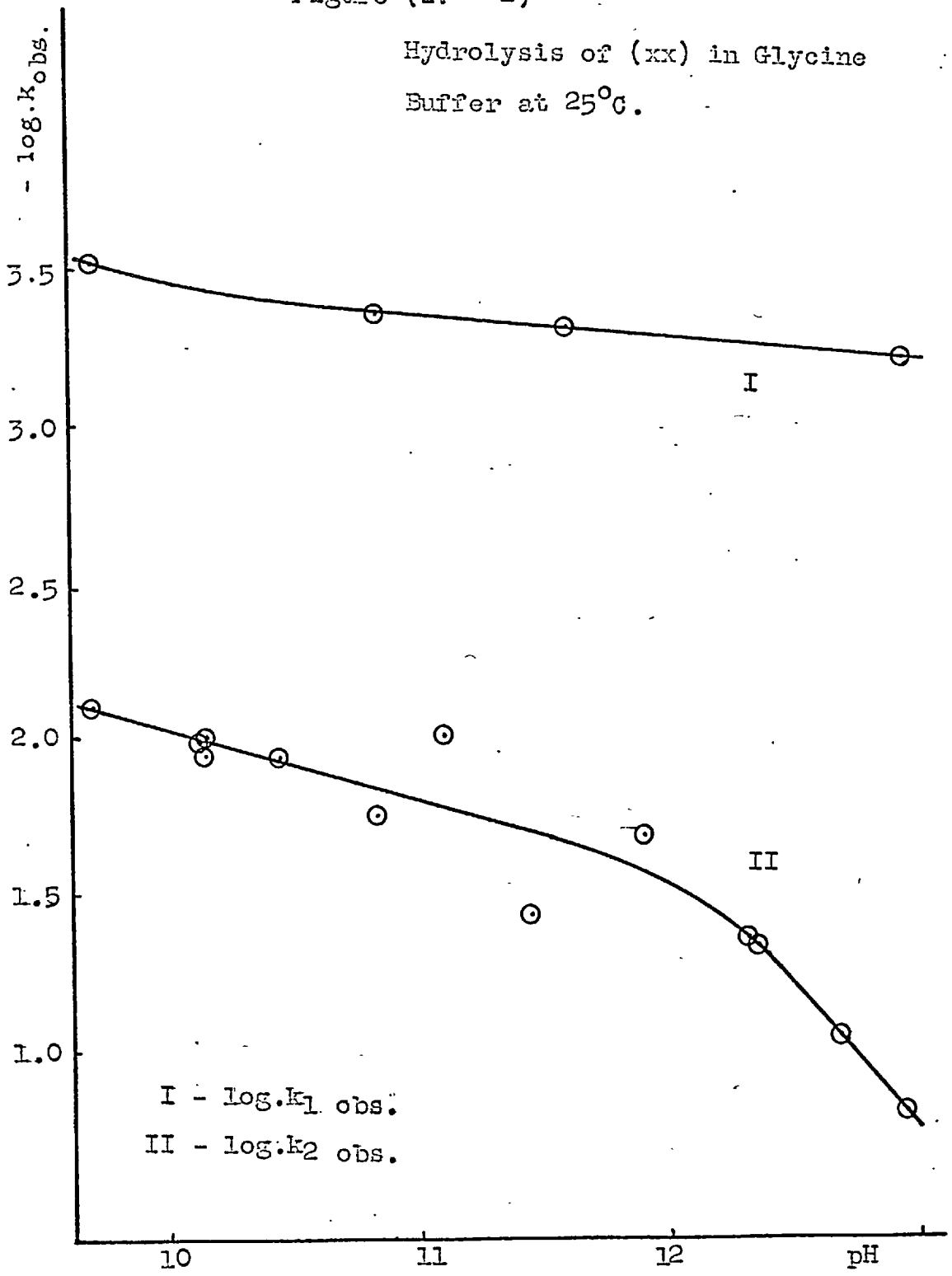


Table (IV - 5)

| Run | pH (measured) | mls. of 0.1 M $NH_2CH_2COOH$ in 100 mls of Solution | mls. of 0.1 M NaOH in 100 mls of Solution | mls(glycine)--mls.(NaOH) / mls.(NaOH) | $k_{1\ obs.} \times 10^2$ | $k_{2\ obs.} \times 10^3$ |
|---|---|---|---|---|---|---|
| 148 | 9.77 | 56.0 | 24.0 | $^{32}/_{24} = 1.33$ | 2.05 | 2.20 |
| 140 | 9.71 | 28.0 | 12.0 | $^{16}/_{12} = 1.33$ | 0.79 | |
| 144 | 9.71 | 28.0 | 12.0 | $^{16}/_{12} = 1.33$ | | 0.301 |
| 149 | 10.50 | 44.0 | 36.0 | $^{8}/_{36} = 0.22$ | 3.15 | 4.03 |
| 125 | 10.47 | 22.0 | 18.0 | $^{4}/_{18} = 0.22$ | 1.17 | |

$$k_{1\ obs.(148)}/k_{1\ obs.(140} = 2.6 \qquad k_{2\ obs.(148)}/k_{2\ obs.(144)} = 7.3$$

$$k_{1\ obs.(149)}/k_{1\ obs.(125)} = 2.7$$

Kinetic runs included in Table (IV - 5) were carried out in a system where both zwitterion and the glycine monoanion were present. In some of the measurements included in Tables (IV - 3) and (IV - 4) NaOH was in excess over the total glycine concentration and consequently in these measurements the contribution of glycine zwitterion catalysed hydrolysis to the total rate of reaction was eliminated. The measurements could, therefore, serve to check the rate of hydrolysis dependence upon the glycine monoanion concentration only and to realise the type of influence (if any) zwitterion may have on hydrolysis of the two ester groups.

However, the measured pH values of the above mentioned solutions seemed to be rather high when compared to the NaOH concentrations which remained after complete zwitterion neutralisation. Thus several NaOH solutions were made up in the same solvent with the same total salt concentration and the measured pH were compared with the calculated ones (utilising the known NaOH concentration). The data are collected in Table (IV - 6) and show the measured values to be about 1.0 pH units higher than the calculated ones. Since the electrodes were calibrated in water solutions, whereas the pH measurements of the reaction mixtures were carried out in 41 vol. % dioxan/water solvent, the difference between the two values could arise from

Table (IV - 6)

Comparison of Measured pH and Calculated Ones from known NaOH Concentrations in 41 vol.% Dioxan/Water Solvent at 25.1 ± 0.2°C

| $[NaOH] \times 10^3$ (M/l) | -log. [NaOH] (calculated) | -log. $[H^+]$ (calculated) | -log. $[H^+]$ (measured) |
|---|---|---|---|
| 40.0 | 1.40 | 12.60 | 13.58 |
| 4.00 | 2.40 | 11.60 | 12.65 |
| 2.00 | 2.70 | 11.30 | 12.34 |

an uncompensated liquid-junction potential. Due to this discrepancy in pH values, the calculated NaOH concentrations were thought to be more reliable ones in solutions where NaOH was in excess over the total glycine concentration.

Allowing for NaOH and glycine monoanion ($gly^-$) catalysis, the relationship between the various rate coefficients becomes for hydrolysis of the first ester group:

$$k_{1\ obs.} = k_{I(OH^-)} \times [OH^-] + k_{I(gly^-)} \times [gly^-] \quad \text{Eq. (IV-2)}$$

or

$$\frac{k_{1\ obs.} - k_{I(OH^-)} \times [OH^-]}{[gly^-]} = \text{Constant} \quad \text{Eq. (IV - 3)}$$

and for the second ester group:

$$k_{2\ obs.} = k_{II(OH^-)} \times [OH^-] + k_{II(gly^-)} \times [gly^-]^2 \quad \text{Eq. (IV - 4)}$$

or

$$\frac{k_{2\ obs.} - k_{II(OH^-)} \times [OH^-]}{[gly^-]^2} = \text{Constant} \quad \text{Eq. (IV - 5)}$$

The analysis of data according to the equations (IV - 3) and (IV - 5) is presented in Tables (IV - 7) and (IV - 8) (concentrations of glycine monoanion and zwitterion were calculated via the amount of total glycine and total NaOH added to the reaction mixture, while $k_{I(OH^-)}$ and $k_{II(OH^-)}$ were taken as 11.3 l. $mol^{-1}$ $min.^{-1}$ and $4.7 \times 10^{-2}$ l. $mol^{-1}$ $min.^{-1}$ respectively). The left-hand side of equation (IV - 3) appears reasonably constant (see last column in Table (IV - 7) ) as long as NaOH is

Table (IV - 7)

Analysis of Data from Table (IV - 3)

| Run | pH (measured) | Excess of [NaOH] (M/l) x $10^3$ | $k_{1\ obs.}$ x $10^2$ | $k_{I(OH^-)} \times [OH^-] \times 10^2$ | Glycine monoanion (M/l) | $(k_{1\ obs.} - k_{I(OH)} \times [OH^-]) /$ glycine monoanion |
|---|---|---|---|---|---|---|
| 140 | 9.71 | - | 0.79 | 0.05 | $1.15 \times 10^{-2}$ | $0.73 \times 10^{-2} / 1.15 \times 10^{-2} = 0.63$ |
| 124 | 10.15 | - | 1.15 | 0.16 | $1.59 \times 10^{-2}$ | $0.99 \times 10^{-2} / 1.59 \times 10^{-2} = 0.62$ |
| 137 | 10.16 | - | 0.98 | 0.16 | $1.59 \times 10^{-2}$ | $0.82 \times 10^{-2} / 1.59 \times 10^{-2} = 0.52$ |
| 141 | 10.14 | - | 1.03 | 0.16 | $1.59 \times 10^{-2}$ | $0.87 \times 10^{-2} / 1.59 \times 10^{-2} = 0.55$ |
| 125 | 10.47 | - | 1.17 | 0.34 | $1.78 \times 10^{-2}$ | $0.83 \times 10^{-2} / 1.78 \times 10^{-2} = 0.47$ |
| 142 | 10.83 | - | 1.80 | 0.77 | $1.89 \times 10^{-2}$ | $1.03 \times 10^{-2} / 1.89 \times 10^{-2} = 0.55$ |
| 127 | 11.91 | 0.8 | 2.09 | 0.91 | $1.96 \times 10^{-2}$ | $1.18 \times 10^{-2} / 1.96 \times 10^{-2} = 0.60$ |
| 143 | 11.46 | 0.8 | 3.69 | 0.91 | $1.96 \times 10^{-2}$ | $2.78 \times 10^{-2} / 1.96 \times 10^{-2} = 1.42$ |
| 131 | 12.33 | 1.6 | 4.41 | 1.81 | $1.92 \times 10^{-2}$ | $1.33 \times 10^{-2} / 1.92 \times 10^{-2} = 0.69$ |
| 130 | 12.66 | 2.4 | 4.62 | 2.71 | $1.88 \times 10^{-2}$ | $1.91 \times 10^{-2} / 1.88 \times 10^{-2} = 1.02$ |



/continued .....

Table (IV - 7) Continued

| | | | | | | |
|---|---|---|---|---|---|---|
| 128 | 12.68 | 4.0 | 9.03 | 4.52 | $1.80 \times 10^{-2}$ | $4.51 \times 10^{-2} / 1.80 \times 10^{-2} = 2.50$ |
| 133 | 12.94 | 8.0 | 16.0 | 9.04 | $1.60 \times 10^{-2}$ | $7.00 \times 10^{-2} / 1.60 \times 10^{-2} = 4.40$ |

Table (IV - 8)

Analysis of Data from Table (IV - 4)

| Run | pH (measured) | Excess of NaOH (M/l) | $k_2$ obs. x $10^2$ | $k_{II(OH)} \times [OH^-] \times 10^4$ * | Glycine monoanion (M/l) | $(k_{2\ obs.} - k_{(OH)}[OH^-]) / [\text{glycine monoanion}]^2$ |
|---|---|---|---|---|---|---|
| 144 | 9.71 | - | 3.01 | 0.02 | $1.2 \times 10^{-2}$ | $2.99 \times 10^{-4} / 1.44 \times 10^{-4} = 2.07$ |
| 145 | 10.84 | - | 4.45 | 0.32 | $1.96 \times 10^{-2}$ | $4.13 \times 10^{-4} / 3.84 \times 10^{-4} = 1.08$ |
| 146 | 11.60 | $8 \times 10^{-3}$ | 4.80 | 0.38 | $1.96 \times 10^{-2}$ | $4.42 \times 10^{-4} / 3.84 \times 10^{-4} = 1.15$ |
| 147 | 12.95 | $8 \times 10^{-3}$ | 6.21 | 3.76 | $1.60 \times 10^{-2}$ | $2.45 \times 10^{-4} / 2.56 \times 10^{-4} = 0.96$ |

* $k_{II(OH)} = 4.7 \times 10^{-2}$ l. $mol^{-1}$ $min.^{-1}$

not in an appreciable excess over glycine concentration, while it increases noticeably as the excess of NaOH increases. Since the opposite appears to hold for the second ester group hydrolysis (see last column in Table (IV - 8) ) it is more likely that this observation is a real effect rather than an experimental error of some sort. Consequently, the rate of first and second ester group hydrolysis of $(C_2H_5)_2C(COOC_6H_4NO_2)_2$ could be described by equations (IV - 6) and (IV - 7) respectively.

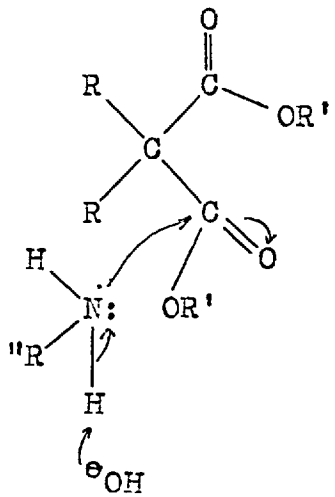
$$\text{rate}_1 = k_{I(H_2O)} \times [H_2O][S] + k_{I(OH^-)} \times [OH^-][S] + k_{I(gly^-)} \times [gly^-][S] + f_I([gly^-][OH^-][S]) \qquad \text{Eq. (IV - 6)}$$

and

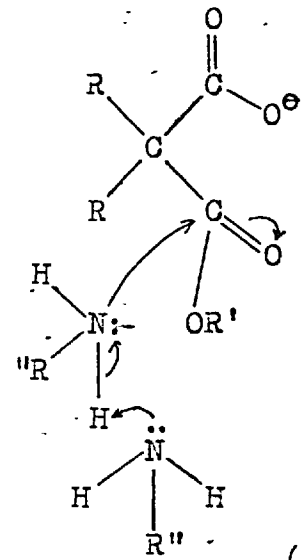
$$\text{rate}_2 = k_{II(H_2O)} \times [H_2O][S^-] + k_{II(OH^-)} \times [OH^-][S^-] + k_{II(gly^-)} \times [gly^-]^2[S^-] + f_{II}([gly^-][S^-][fly_{zw}]) \qquad \text{Eq. (IV - 7)}$$

where $[S]$ and $[S^-]$ = diester and monoester-monoanion of 2,2-diethyl di-(p-nitrophenyl) malonate concentration, respectively, while $[gly_{zw}]$ = glycine zwitterion concentration.

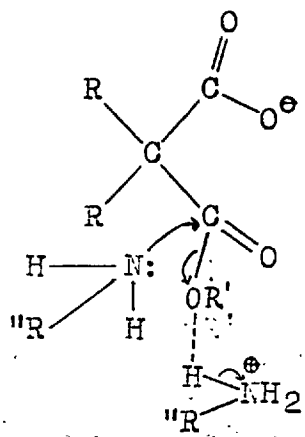
It is clear that the investigations undertaken in the present work with p-nitrophenyl malonate esters did not show an appreciable (and therefore noticeable) contribution of intramolecularly catalysed second ester group hydrolysis. Instead, general base catalysis (xxi) and (xxii) and perhaps general acid catalysis (xxiii) of the nucleophilic attack at the carbonyl carbon atom became evident. In transition states like (xxi) and (xxii) a general base ($OH^{\ominus}$ or the glycine mono-anion) removes a proton from the attacking nucleophile, thus facilitating the process, while in (xxiii) general acid catalysis occurs by protonation of the leaving phenoxide group.



(xxi)



(xxii)



(xxiii)

Experiments with 2,2-dibromo and 2,2-dichloro diethyl malonates

Experiments with these di-halomalonates were carried out in 60 wt. % ethanol/water solutions at 25°C (total ionic strength of 0.1 was maintained with KCl). The results of the measurements are summarised in Tables (IV - 9) and (IV - 10) for 2,2-dibromo and 2,2-dichloro diethyl malonates respectively, while log $k_{obs.}$ versus pH (measured) plot for the former substrate is present in Figure (IV - 3). As the Figure shows, the results are not very reproducible and further investigations were discontinued. With 2,2-dibromo substrate the NaOH required for the complete hydrolysis was regularly high for 10 to 20% while for 2,2-dichloro compound was usually low for about 10% of the calculated value. In the case of the dibromo ester, there was evidence of hydrolysis of the bromine substituent under the experimental conditions, and this could account for the increased quantities of base consumed.

However, the general trend of the log $k_{1\ obs.}$ versus pH line is linear with the slope of unity while log $k_{2\ obs.}$ versus pH is not. The increasing $k_{2\ obs.}/k_{1\ obs.}$ ratio with increasing pH of the solutions could, perhaps, be the indication of the intramolecular catalysis of the second ester group under these conditions, although it is difficult to understand why this interaction is more important at high rather than low pH.

Table (IV - 9)

Hydrolysis of First and Second Ester Group of 2,2-dibromo Diethylmalonate in 60 wt. % Ethanol/Water Solutions at 25.0 ± 0.2°C (Ionic Strength = 0.1)

| pH (measured) | $k_{1\ obs.}$ ($min^{-1}$) | $k_{2\ obs.}$ ($min^{-1}$) | $k_2/k_1$ | $-\log k_{1\ obs.}$ | $-\log k_{2\ obs.}$ |
|---|---|---|---|---|---|
| 11.40 | 0.039 | 0.019 | 0.49 | 1.41 | 1.72 |
| 11.60 | 0.069 | 0.037 | 0.54 | 1.16 | 1.43 |
| 11.80 | 0.074 | 0.032 | 0.43 | 1.13 | 1.49 |
| 11.80 | 0.120 | 0.044 | 0.37 | 0.92 | 1.35 |
| 11.90 | 0.082 | 0.037 | 0.45 | 1.09 | 1.43 |
| 12.00 | 0.213 | 0.038 | 0.18 | 0.67 | 1.43 |
| 12.30 | 0.352 | 0.046 | 0.13 | 0.45 | 1.34 |
| 12.30 | 0.177 | 0.059 | 0.34 | 0.75 | 1.23 |

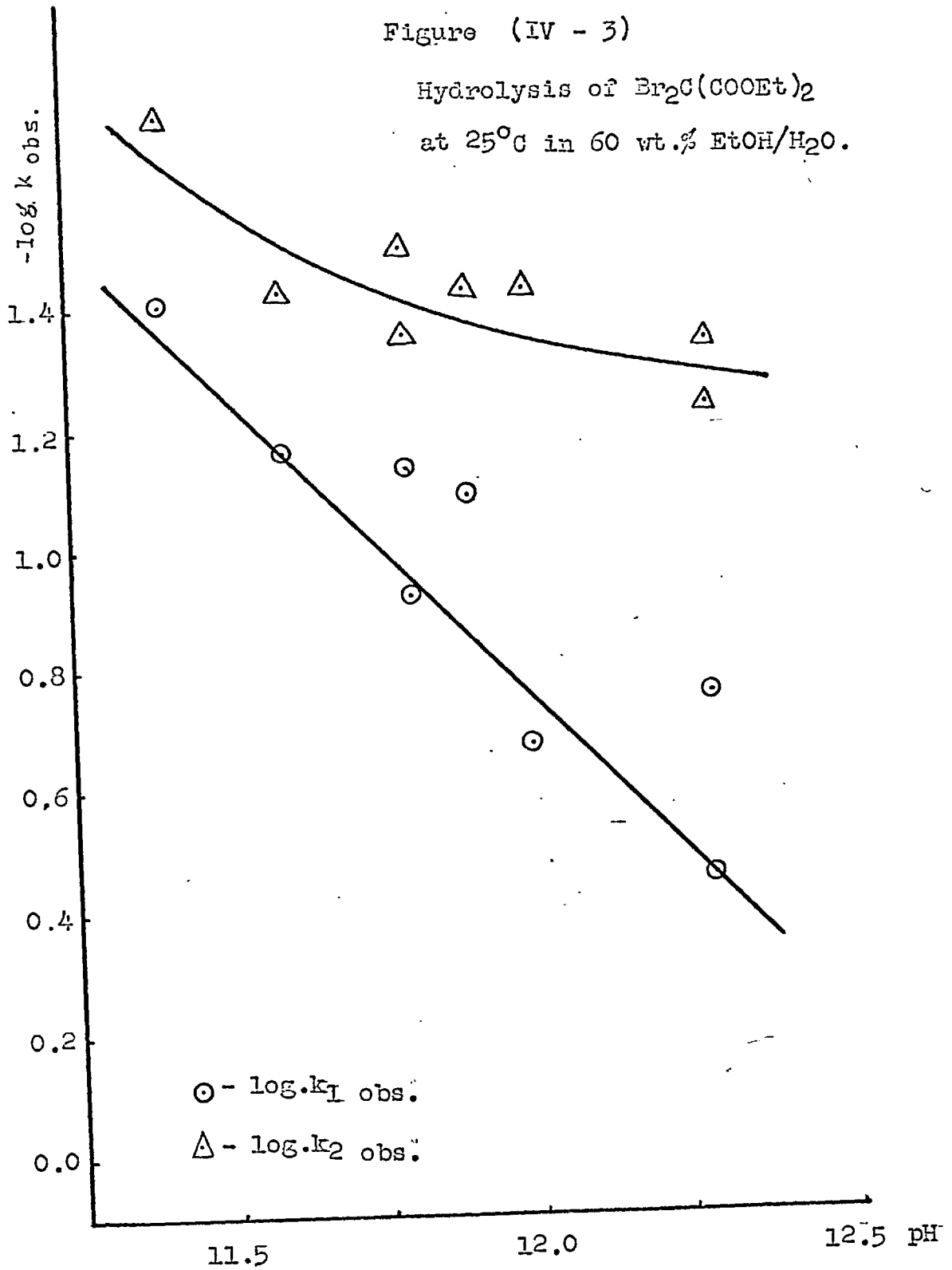
Table (IV - 10)

Hydrolysis of First and Second Ester Group of 2,2-dichloro Diethylmalonate in 60 wt. % Ethanol/Water Solutions at 25.0 ± 0.2°C (Ionic Strength = 0.1)

| pH (measured) | $k_{1\ obs.}$ ($min^{-1}$) | $k_{2\ obs.}$ ($min^{-1}$) | $k_2/k_1$ | $-\log k_{1\ obs.}$ | $-\log k_{2\ obs.}$ |
|---|---|---|---|---|---|
| 11.50 | 0.064 | 0.017 | 0.27 | 1.19 | 1.77 |
| 11.70 | 0.092 | 0.033 | 0.36 | 1.04 | 1.48 |
| 11.70 | 0.086 | 0.028 | 0.33 | 1.07 | 1.55 |

Figure (IV - 3)

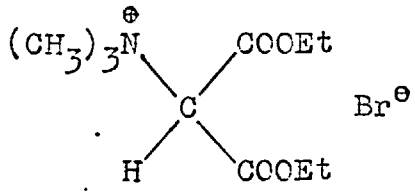
Hydrolysis of $Br_2C(COOEt)_2$ at 25°C in 60 wt.% $EtOH/H_2O$.



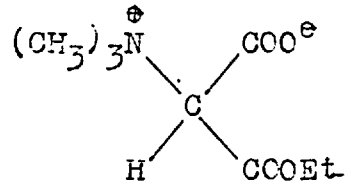
# Chapter V

## The Hydrolysis and Decarboxylation of 2-(trimethylammonium)-diethylmalonate

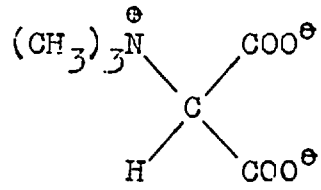
Investigation of substituted ethylmalonates suggested that electron withdrawing substituents accelerate ester hydrolysis. Thus, it was expected that 2-(trimethylammonium)-diethylmalonate (xxiv) would readily hydrolyse under mildly alkaline aqueous conditions. However, it had been reported[65] that the corresponding dianion (xxvi) was unstable and readily lost $CO_2$ at room temperature, although the half hydrolysed anion (xxv) was stable. The instability of the dianion (xxvi)



(xxiv)



(xxv)



(xxvi)

is inconsistent both with the results for other malonic acids and with the reported stability of the corresponding half ester (xxv). Accordingly, hydrolysis of this ester was investigated in aqueous solutions from pH = 8 to pH = 12, to investigate the mechanism of hydrolysis and the nature of subsequent decarboxylation.

In the present work several unsuccessful attempts were made to isolate compound (xxv) from aqueous solutions, and the only products obtained in significant amounts were the betain ester (xxvii), betain itself (xxviii) and sodium bicarbonate. This suggested that decarboxylation of at least two of the

$(CH_3)_3\overset{\oplus}{N}CH_2COOEt$ (xxvii)

$(CH_3)_3\overset{\oplus}{N}CH_2CO\overset{\ominus}{O}$ (xxviii)

malonate species occurred readily in alkaline solutions.

Kinetic measurements, however, indicated that the best condition for the isolation of (xxv) would be to hydrolyse the first ester group at pH 10 to 11, where the reaction is complete in less than five minutes (using one equivalent of NaOH) and to precipitate the products immediately. As mentioned above, the product (xxv) apparently decarboxylated on isolation from the reaction mixture.

The kinetic data for the hydrolysis experiments at various pH are summarised in Table (V - 1) and presented graphically in Figure (V - 1). Curves A and B in Figure (V - 1) represent log $k_{1\ obs.}$ and log $k_{2\ obs.}$ for base catalysed hydrolysis of the first and second ester groups of (xxiv) respectively. While curve A shows a first-order dependence between the rate coefficient and the base concentration as expected for a normal (bimolecular) base catalysed reaction, the pH independent part

Table (V - 1)

Ester Hydrolysis Measurements of 2-(trimethylammonium-bromide)-diethylmalonate in 0.1 M KCl

Solutions at 25.0 ± 0.1°C

A) First Ester Group.

| Run | pH | $k_{1\ obs.}$ ($min^{-1}$) | $k_I$ (l/mol.min) | - log $k_{1\ obs.}$ | $t_{1(\frac{1}{2})}$ (min) |
|---|---|---|---|---|---|
| 86 | 9.860 | 0.450 | 62 | 0.345 | 1.55 |
| 89 | 8.265 | $1.14 \times 10^{-2}$ | 62 | 1.943 | 61.5 |

/continued .....

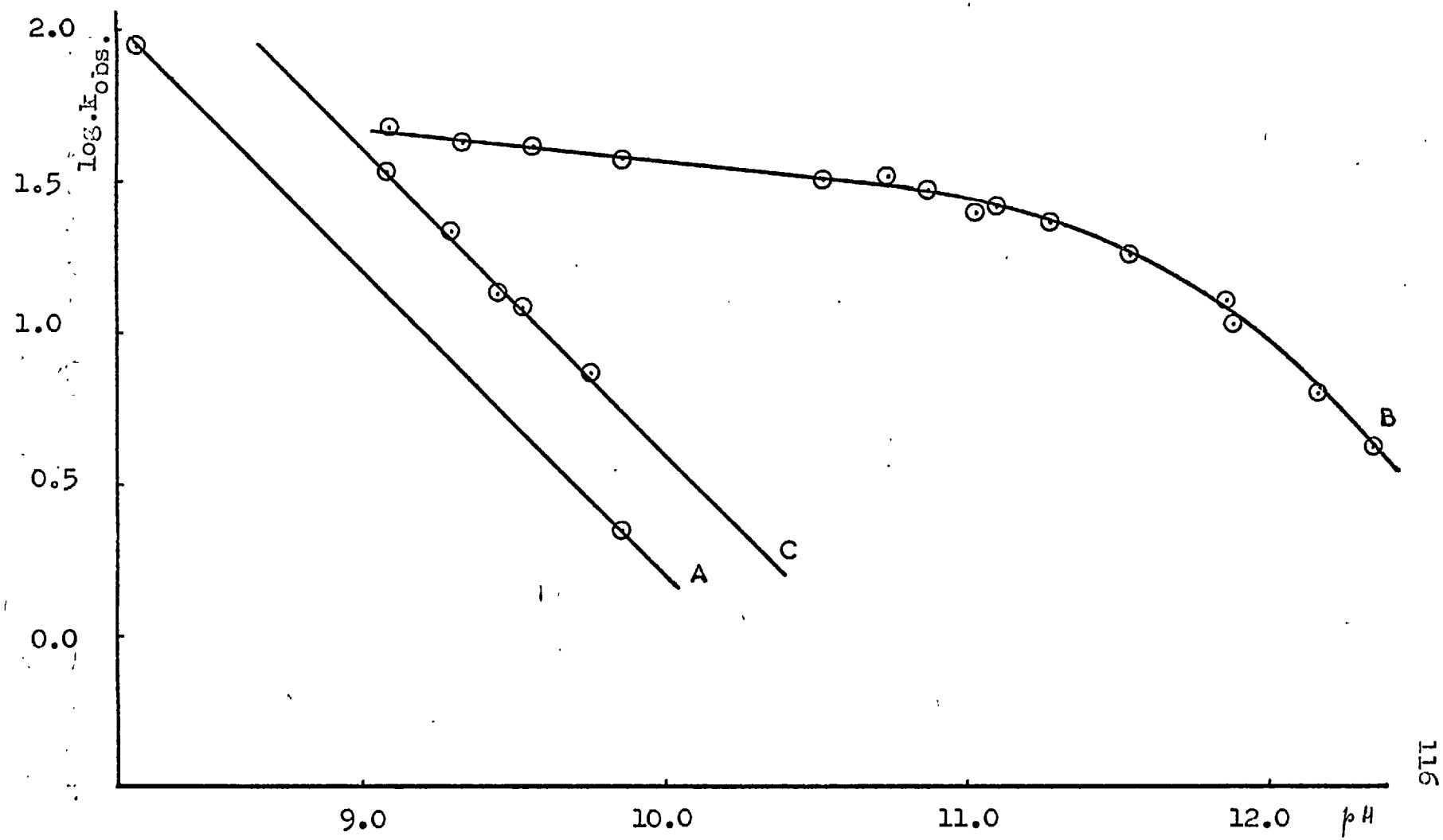
Table (V - 1)

(continued)

B) Second Ester Group.

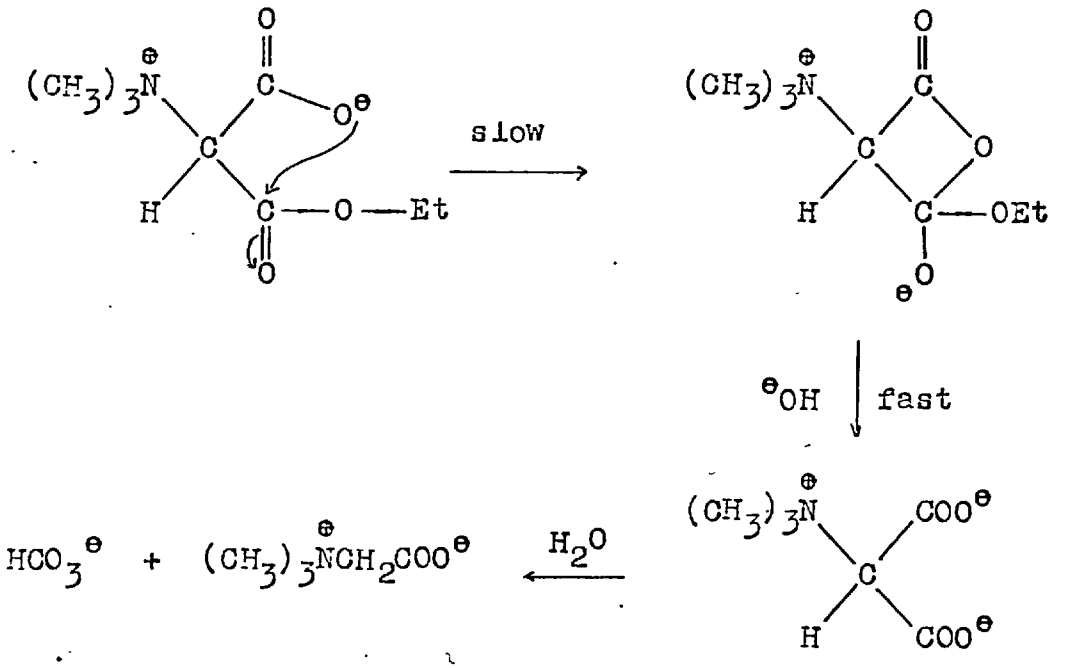
| Run | pH | $k_{2\ obs.} \times 10^2$ (min.) | $t_{2(\frac{1}{2})}$ (min.) | - log $k_{2\ obs.}$ |
|---|---|---|---|---|
| 94 | 9.085 | 2.07 | 33.8 | 1.684 |
| 93 | 9.328 | 2.36 | 29.7 | 1.627 |
| 92 | 9.565 | 2.48 | 28.2 | 1.605 |
| 86 | 9.860 | 2.66 | 26.3 | 1.575 |
| 94A | 10.522 | 3.15 | 22.2 | 1.501 |
| 96 | 10.738 | 3.07 | 22.8 | 1.513 |
| 100 | 10.862 | 3.32 | 21.0 | 1.479 |
| 95 | 11.030 | 4.01 | 17.4 | 1.398 |
| 88 | 11.103 | 3.82 | 18.3 | 1.418 |
| 97 | 11.273 | 4.19 | 16.7 | 1.378 |
| 98 | 11.540 | 5.60 | 12.5 | 1.252 |
| 99 | 11.860 | 8.23 | 8.5 | 1.085 |
| 102 | 11.877 | 9.64 | 7.25 | 1.016 |
| 101 | 12.155 | 15.9 | 4.4 | 0.799 |

Figure (V - 1)



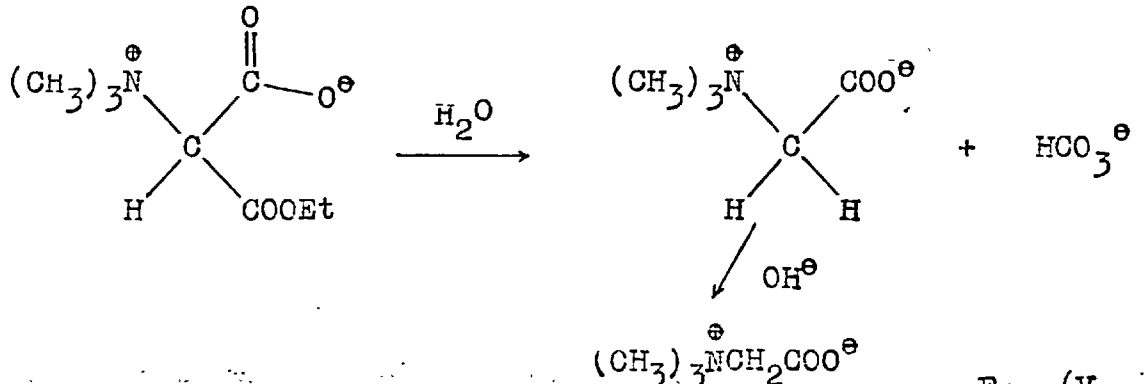
of curve B requires a different explanation, both were thought to satisify the unusual log $k_{2\ obs}$ versus pH dependence:

a) Intramolecularly catalysed hydrolysis of the second ester group according to the scheme:




Eq. (V - 1)

b) Decarboxylation of (xxv), prior to hydrolysis of the second group:




Eq. (V - 2)

Both pathways are rather unusual for a malonate monoester reaction, but not impossible. Analysis of the isolated products after hydrolysis of only one group was not definitive evidence for either pathway, since (xxv) could decarboxylate during the isolation process. To solve the problem, hydrolysis of (xxiv) in $D_2O$ was undertaken at pH 9.2 and 11.1. The reactions were carried out in the usual way (described in experimental section), but from time to time 0.5 mls. samples were taken from the reaction solution and the N.M.R. spectra of the samples were taken.

The unreacted diester (xxiv) in $D_2O$ solvent shows only three proton resonances relative to $H_2O$ at $\tau = 5.25$: 1.) $CH_3$ - triplet ( $\tau \sim 8.59$); 2.) $CH_2$ - quartet ( $\tau \sim 5.48$) and 3.) $(CH_3)_3\overset{\oplus}{N}$ - C singlet ( $\tau \sim 6.45$) (designed as A in Figures (V - 2), (V - 3) and (V - 4) ). The signal due to hydrogen at 2-C in the malonate ester does not appear in the spectrum since it undergoes rapid exchange with deuterium at pH approximately 5. The addition of a small amount of NaOD ( few% of the total amount required for the hydrolysis) at pH not higher than 9.2 results in the formation of three resonances due to the $(CH_3)_3\overset{\oplus}{N}$ - C group ( resonances A, B and C), whereas resonances due to the ethyl fraction show that the corresponding amount of the ester function has hydrolysed (see Figure (V - 3). Furthermore, comparison of the

Figure (V - 2)

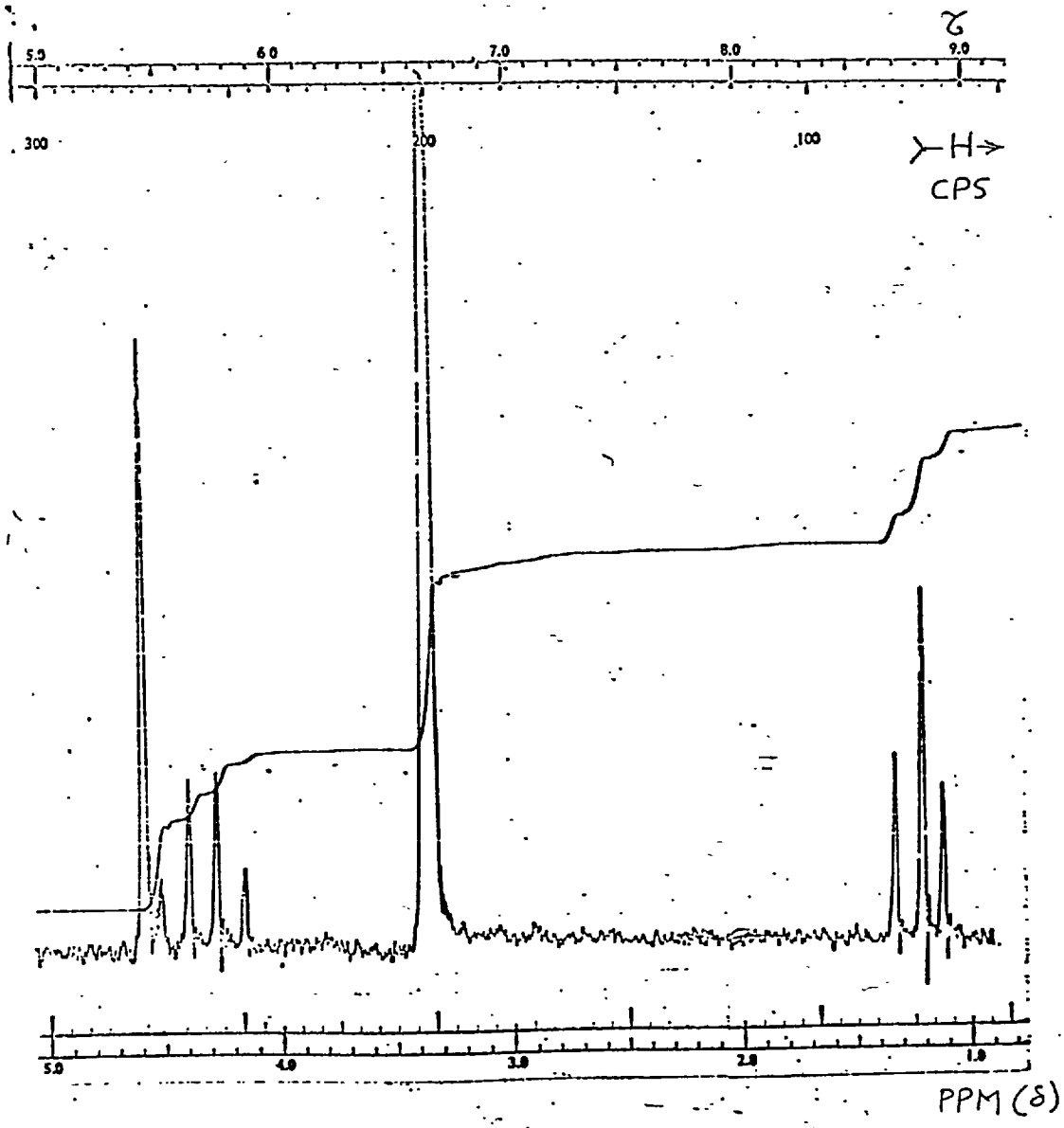
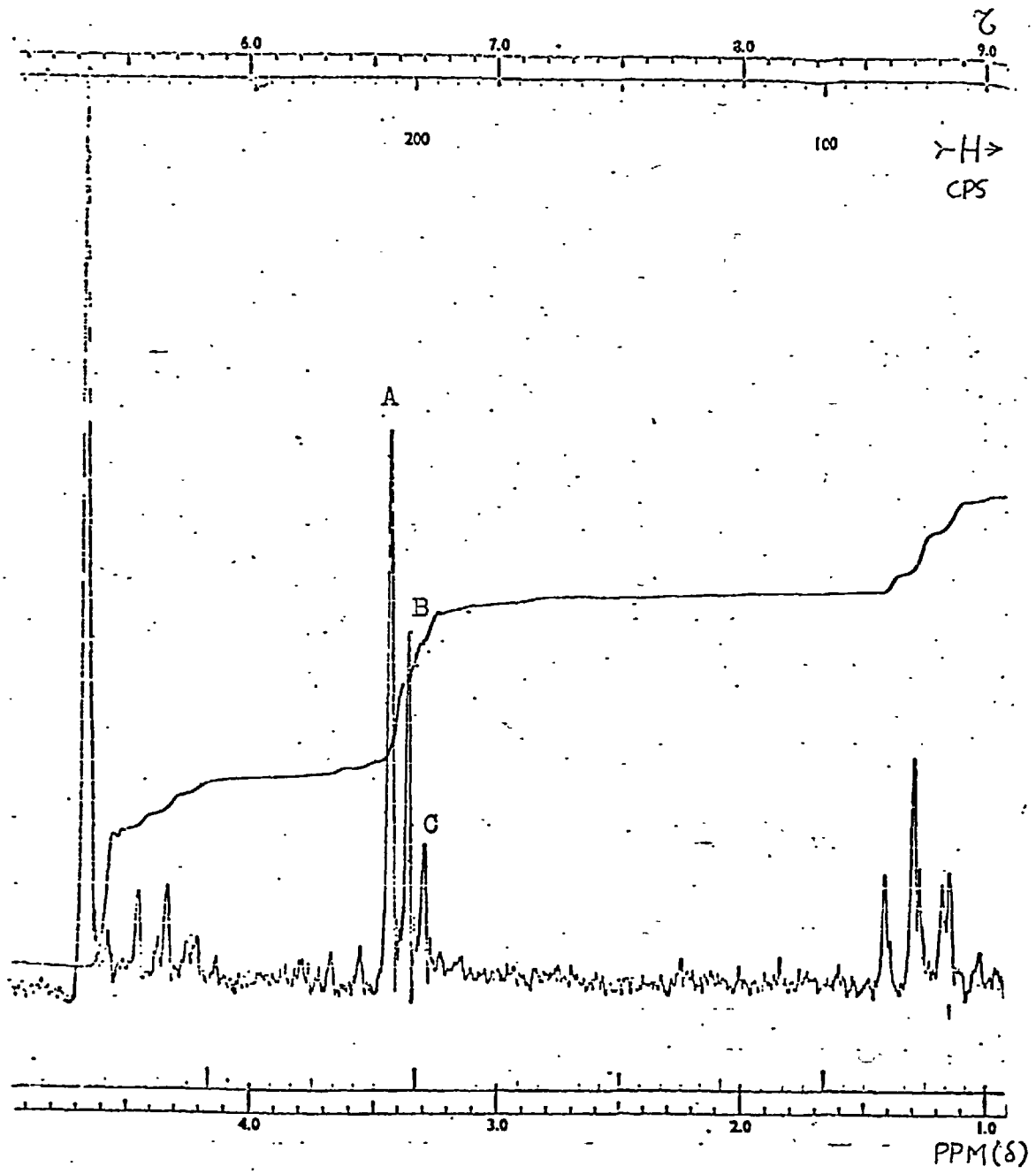


Figure (V - 3)



rate of NaOD uptake from the pH-stat measurements with the rate of disappearance of the unreacted ester measured from the N.M.R. spectra (via signal A) gives the rate constants $6.4 \times 10^{-2}$ min.$^{-1}$ and $7.2 \times 10^{-2}$ min.$^{-1}$, respectively. Subsequent addition of NaOD indicates further hydrolysis of the ester as well as the appearance of the fourth signal (D) due to $(CH_3)_3\overset{\oplus}{N}$ - C (see Figure (V - 4) ). At the end of the kinetic run this was the only signal present, showing only one product of the reaction at pH $\leqslant$ 9.2, apparently compound (xxviii).

Experiments at pH = 11.1 (see Figure (V - 5) ) showed, however, complete hydrolysis of the first ester group on rapid addition of approximately one equivalent of NaOD (signal A disappeared; B and C almost equally strong; D very small). The rate of NaOD uptake and the rate of appearance of signal D were calculated to be $4.3 \times 10^{-2}$ min.$^{-1}$ and $5.0 \times 10^{-2}$ min.$^{-1}$ respectively. Furthermore, it was observed that when any of the intermediate samples were left for one hour without further NaOD addition, signal B disappeared completely, while C increased proportionally (see Figure (V - 6) ). During this process, other resonances due to the ethyl groups did not change appreciably (actually, two quartets overlapping each other, initially, collapsed, but no evidence of hydrolysis was otherwise observed). When the whole reaction solution was treated similarly, the pH dropped from 11.1 to 8.2 and did not change further, unless

Figure (V - 4)

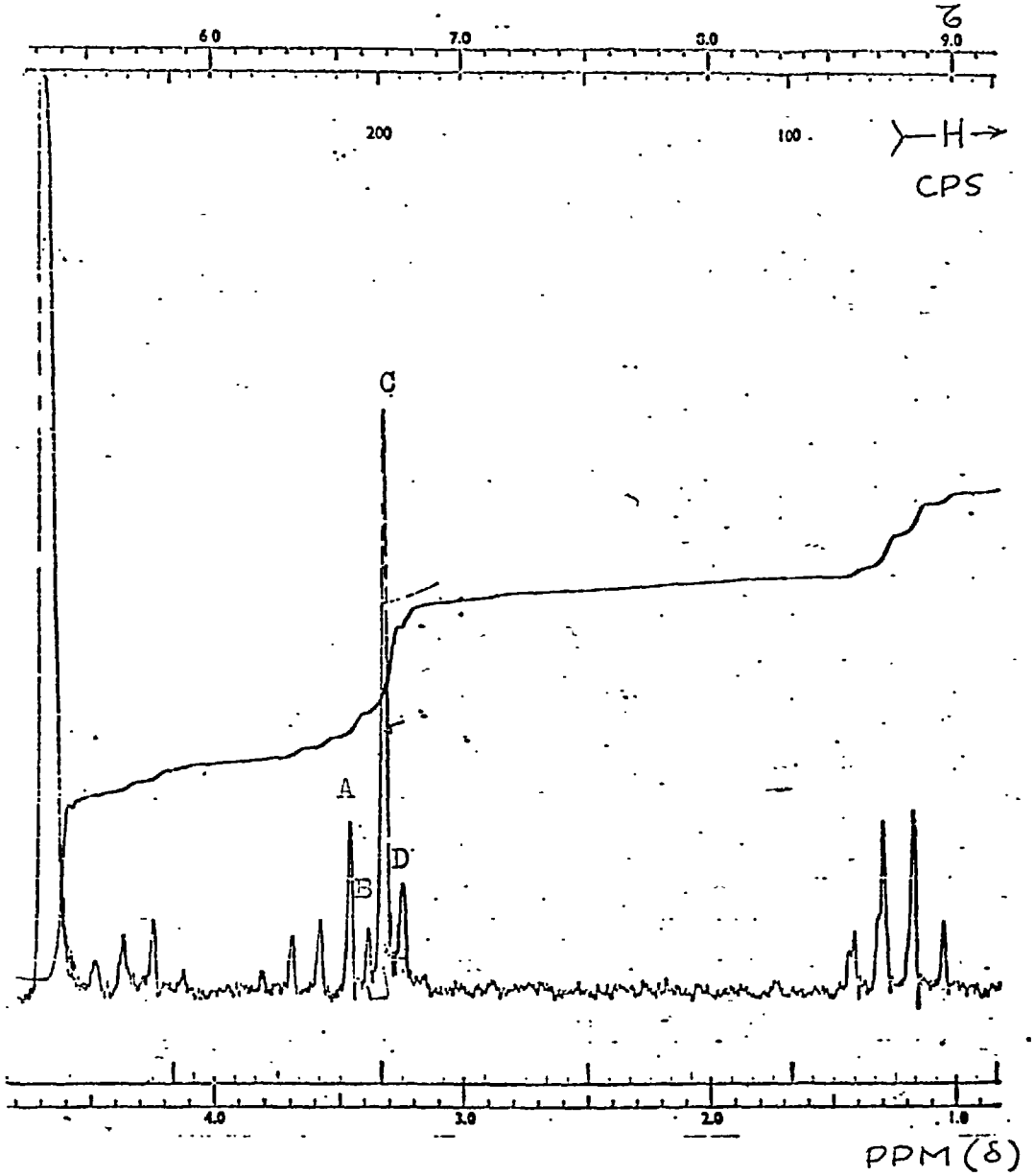


Figure (V - 5)

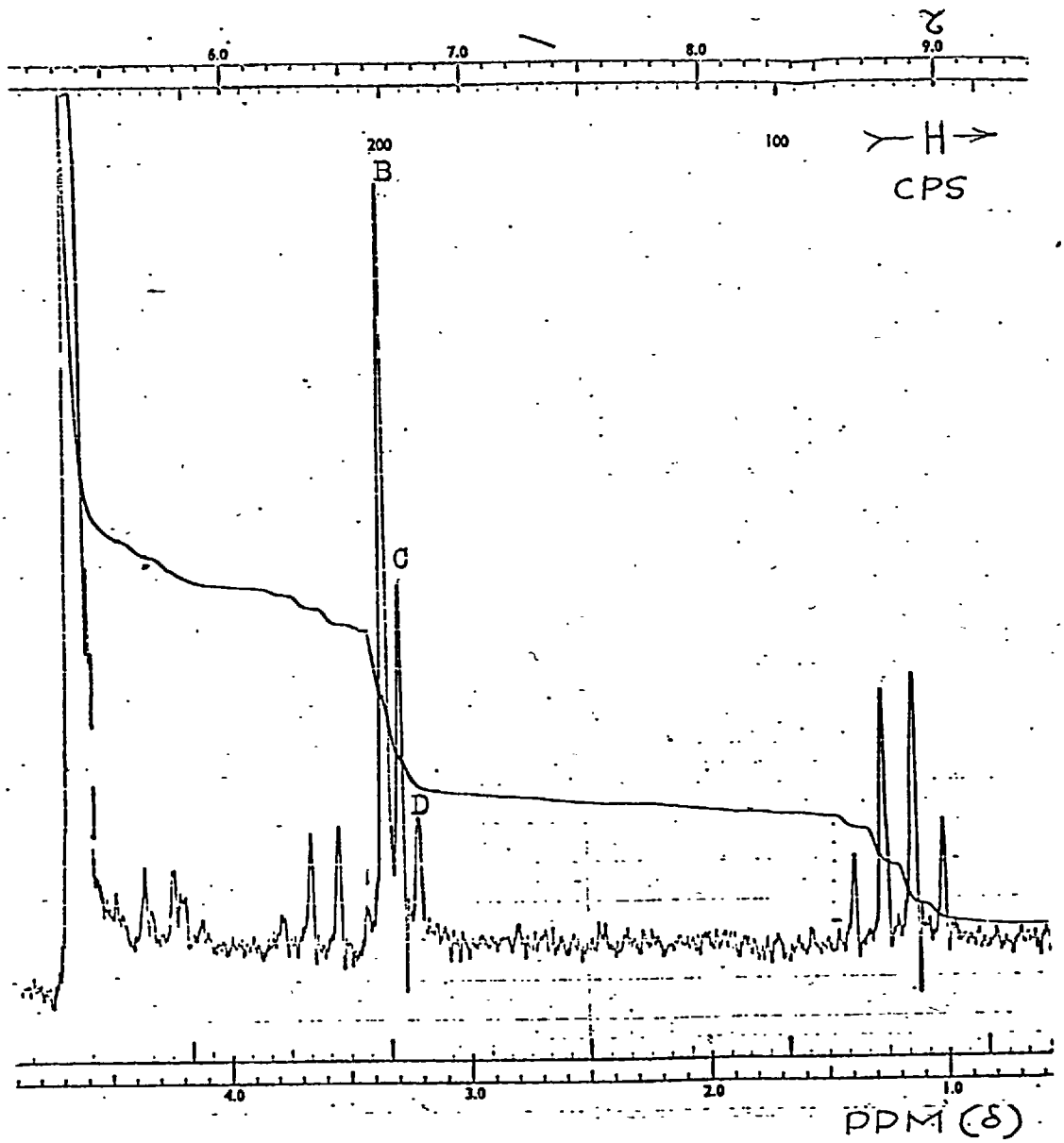
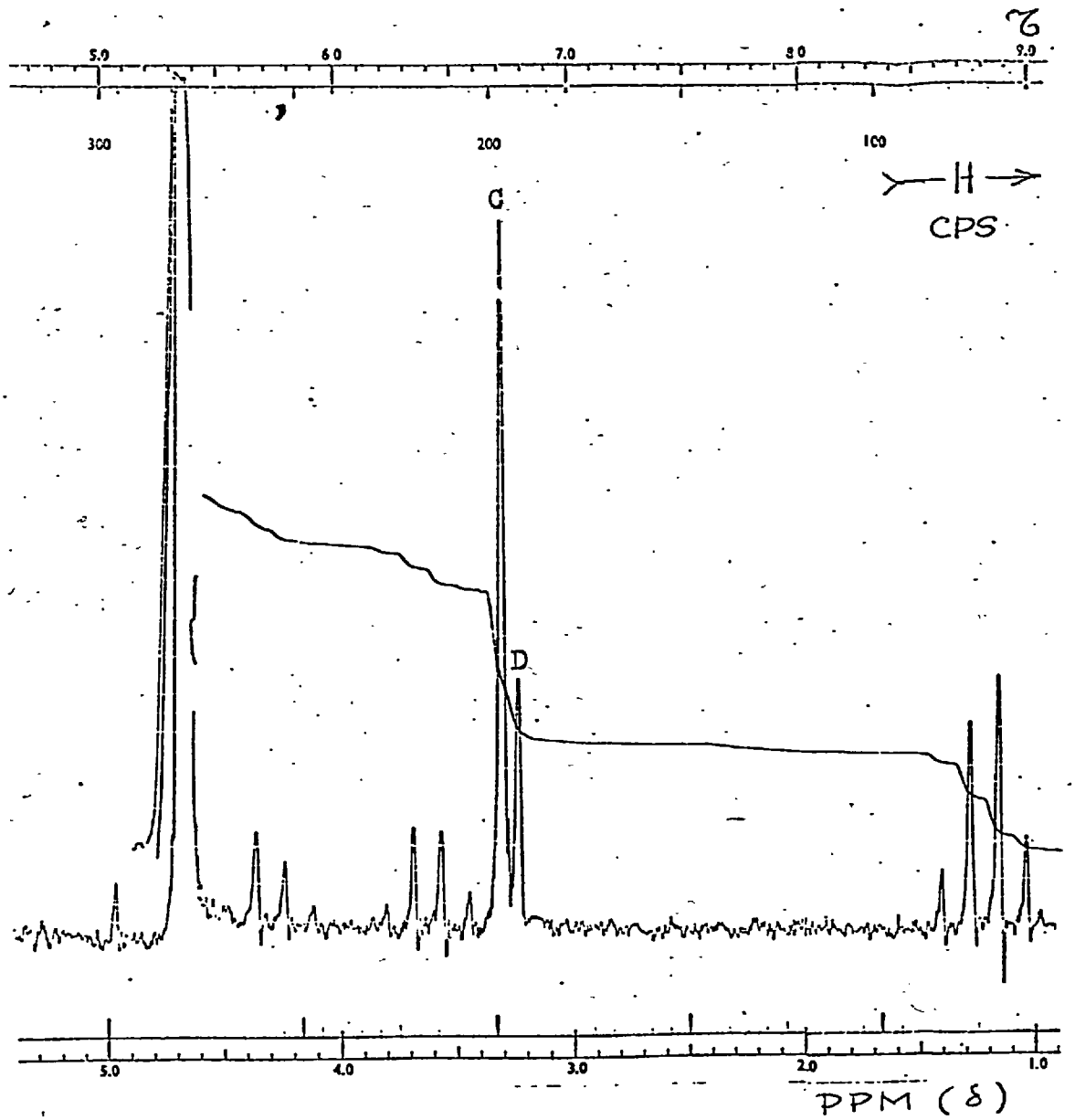


Figure (V - 6)



extra Na OD was added. Moreover, the time for the NaOD addition to obtain the previous value of pH = 11.1 (2 to 3 minutes) was enough for complete hydrolysis of the remaining ester. This experiment showed that two different species were reacting under the former and latter conditions. Disappearance of B without any consumption of NaOD, as well as the very small difference (affecting the shape rather than position) of ethyl resonances in the N.M.R. spectra pointed to decarboxylation occurring before the second ester group of (xxiv) had hydrolysed, i.e. (xxv) readily decarboxylated under mild alkaline conditions, which is contrary to Cohen and Corwen's conclusions. This was confirmed by several pH-stat hydrolysis measurements undertaken one hour after the fast hydrolysis of the first ester group of (xxiv). The results are summarised in Table (V - 2) together with the rate of hydrolysis of authentic betaine ester $(CH_3)_3\overset{\oplus}{N}CH_2COOEt\ Cl^{\ominus}$ (run No. 112) and graphically presented on Figure (V - 1) (Curve C). The close similarity in the rates shows that the betaine ester (xxvii) is formed readily at pH 9 to 10, and this species then undergoes further hydrolysis to the betaine itself. Decarboxylation of (xxv) is most probably the step which governs the rate of NaOH uptake at pH lower than 11 and, therefore, the pH independent part of curve B could be explained accordingly. Competition between decarboxylation and second ester group hydrolysis is probably occurring at pH

Table (V - 2)

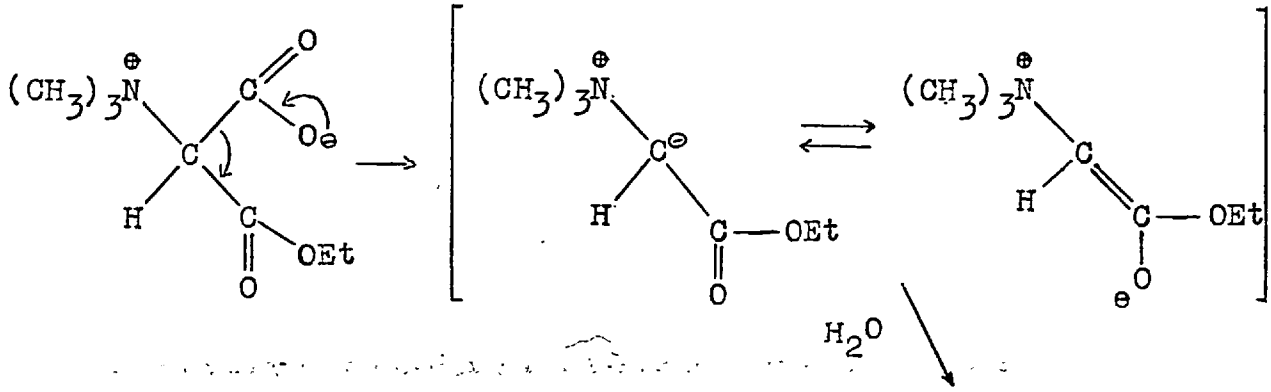
Hydrolysis of Decarboxylated Monoester of 2-(trimethylammonium bromide)-diethylmalonate in 0.1 M KCl Aqueous Solutions at 25°C

| Run | pH | $k_{obs.} \times 10^2$ ($min.^{-1}$) | $t_{(\frac{1}{2})}$ (min.) | - log $k_{obs.}$ |
|---|---|---|---|---|
| 107 | 9.085 | 2.95 | 23.7 | 1.530 |
| 110 | 9.290 | 4.25 | 16.5 | 1.372 |
| 108 | 9.525 | 8.17 | 8.5 | 1.087 |
| 111 | 9.750 | 13.5 | 5.2 | 0.869 |
| 112[≡] | 9.47 | 7.50 | 9.35 | 1.125 |

[≡] Reaction of the authentic $(CH_3)_3\overset{\oplus}{N}CH_2COOet\ Cl^{\ominus}$ betaine ester.

higher than 11, thus causing the reaction to be pH dependent. The slope of the curve B (Figure (V - 1) ) approaches unity at pH higher than 12, indicating a normal bimolecular $OH^{\ominus}$ catalysed hydrolysis of the second ester group of (xxv). Thus, the shape of the pH-rate profile does not seem to evidence for intramolecular catalysed hydrolysis.

The ease with which (xxv) and (xxvi) decarboxylate in contrast to other malonate anions is not easily rationalised. Although the trimethylammonium ion substituent is an extremely powerful electron withdrawing group, it is now more so than two chlorine atoms, for example. It is possible that electrostatic effects are more important than electron destabilisation. Nevertheless, it is apparent that loss of $CO_2$ occurs without intramolecular proton transfer which seems to be an essential part of the reaction for other malonic acids. The presence of the carbonyl group next to the reaction centre helps to accommodate the negative charge in the transition-state according to equation (V - 3), and this explains why the 2-(trimethylammonium) malonic acid reacts much more readily than betaine itself.




Eq.(V-3)

# PART III

## Experimental

# Chapter VI

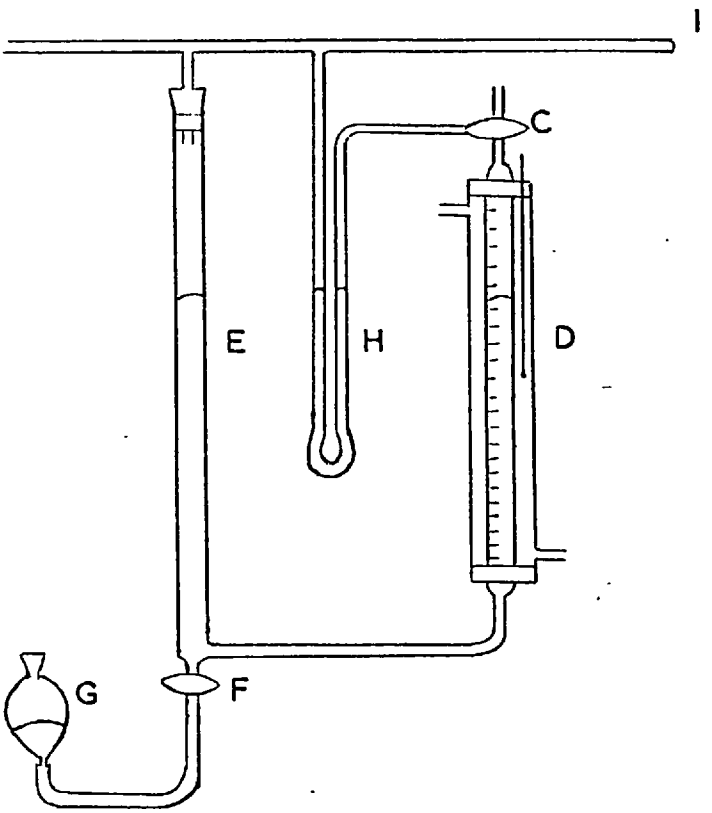
The description of experimental methods together with details of the preparations and purifications of chemical reagents and solvents used is included in the following chapter.

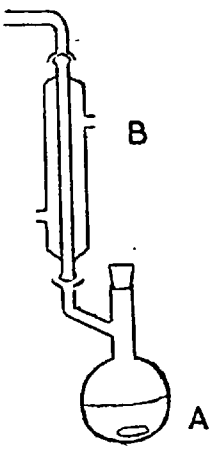
## Section 1

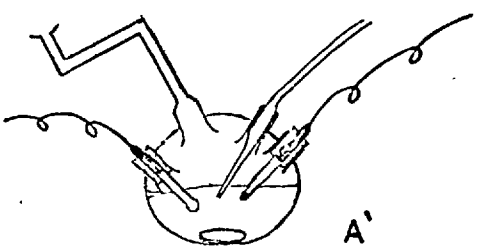
a.) The apparatus and the Kinetic Method for the Decarboxylation Experiments.

The rates of the decarboxylation reactions were followed by measuring the volume of carbon dioxide evolved at timed intervals. The gas-burette is ilustrated in Figure (VI - 1). Two different reaction flasks (A) and (A') were used depending upon the acidity of the solution. When the acidity of the reaction mixture was high and therefore constant throughout the reaction, a 50 mls. round bottom flask (A) was used. It was attacked by means of a spherical ground-glass joint to a condenser (B) which was connected by a second spherical ground-glass joint to a three-way stop-cock (C), itself attached to the top of a 100 mls. mercury-filled gas-burette (D). The gas-burette was connected to the levelling tube (E) and both of them connected to a 500 mls. mercury receiver (G) through stop-cock (F). A bent capillary (H)

Figure (VI - 1)



containing mercury, acting as a manometer, was connected with a reaction flask and a gas-burette by means of the stop-cock (C), the other end of the capillary (H) being connected to the tube (I) lying along the top of the apparatus. The reaction flask was immersed in a constant temperature bath (temperature being noted on a N.P.L. calibrated thermometer). Stirring of the reaction solution was effected by means of a teflon stirring bar contained in the flask and turned by a magnet placed below the flask in the thermostatted bath. The magnet was rotated at a constant speed by a motor to which it was connected by a metal shaft.

To ensure that all the volumes were read at a fixed constant temperature, thermostatted water of 25°C was circulated through the condenser as well as the jacket into which the gas-burette was enclosed.

Before the start of each kinetic run, the mercury was placed into the receiver (G) and the system flushed thoroughly with carbon dioxide by passing the gas through the line (I) connected to the levelling tube (E). The gas-burette and the levelling tube were filled with mercury by raising the receiver (G). The stop-cock (F) was closed to retain the mercury in the burette.

Decarboxylation Experiments type (A)

An accurately weighed sample of the organic acid to be decarboxylated (the amount required for evolution of 40 to 60 c.c. of carbon dioxide at N.T.P.) was taken in an open soda-glass vial and inserted into the reaction flask where 20 mls. of solvent saturated with carbon dioxide was present.

The volume of the evolved gas was read at atmospheric pressure which was estimated by withdrawing the mercury from the levelling tube (E) until the mercury levels on both sides of the capillary (H) were the same.

Decarboxylation Experiments type (B)

When the pH of the reaction solution was between 0.9 and 3.3, a 100 mls. four-necked round bottom flask (A') was used for the reaction. In other respects, the experimental procedure was the same as that described above. Radiometer glass type G 202 B and calomel K 901 electrodes were fitted through teflon stoppers (sealed with Araldite) into the flask. In a typical kinetic experiment, 70 mls. of aqueous buffer solution (approximate concentration of buffer was 0.27 M/l) was used as a solvent. The concentration of buffer solution was only five to six-fold higher than the usual concentration of the malonic acid. Consequently, the pH of the reaction solution was gradually

increasing during the reaction period. This difficulty was avoided by using the Radiometer pH-stat assembly consisting of a type SBR 2c titrigraph coupled to an SBU 1 syringe burette unit, TTT-11 automatic titrator and pH-meter PHM 26. The end of the syringe burette was replaced by B-14 quick-fit air leak. Addition of HCl solution (0.2 or 0.5 M/l) was automatically controlled by pH-stat assembly to ensure that the pH of the solution during the reaction remained within ± 0.01 pH units. In some experiments the rate of carbon dioxide evolved was compared with the rate of HCl uptake recorded on a TTT-11 titrigraph and found in good agreement with each other.

Calculation of Rate Coefficients

As the amount of substrate reacted is directly proportional to the volume of carbon dioxide evolved, the first order rate coefficient (k) for the (A) type of experiments could be calculated from the equation (VI - 1)

$$k = \frac{2.303}{t} \log \frac{a}{a - x} \qquad \text{Eq. (VI - 1)}$$

k = first order rate coefficient in $min.^{-1}$

t = time in min.

a = volume of carbon dioxide evolved at the end of the reaction (10 half lives), or calculated from the amount of the acid taken for a particular experiment and assuming 100% decomposition.

$x$ = volume of carbon dioxide evolved in time t.

Many of the slow reactions were not followed to completion. In those cases the theoretical volume of carbon-dioxide which should be evolved at 25°C from the known amount of the acid was used. To check this assumption, a few reactions were followed to completion and the volume of carbon dioxide evolved was found in close agreement with the calculated value.

Straight lines were obtained from plots of log $(a - x)$ versus $t$ over at least 70% of the reaction.

The infinity readings in experiments of type (B) were always high. This was probably due to difficulties in obtaining a carbon-dioxide saturated solution of the required pH. Also, the initial 20 to 30 minutes of the reaction had to be discarded (the carbon-dioxide saturation equilibria did not take place immediately) for the same reason. In these types of experiments readings were followed up to four half lives so that the Guggenheim method[108] of rate constant calculations could be applied (equation (VI - 2) ).

$$k = \frac{2.303}{t} \log (a' - x) \qquad \text{Eq. (VI - 2)}$$

Where:

$k$ = first order rate coefficient in $min.^{-1}$

$t$ = time in min.

$x$ = volume of carbon dioxide evolved in time $t$.

$a'$ = volume of carbon dioxide evolved in approx.(two half lives + t) time intervals.

Typical kinetic runs for both types of measurements are cited below. Some of the runs were repeated and agreement in the first order rate constants was better than $\pm$ 5% for measurements of (A). For the type (B) experiments, however, the reproducibility was $\pm$ 8% probably because of the slow carbon-dioxide saturation equilibria. Since the rate of reaction is quite fast in the pH region from 0.5 to 1.5; almost the first half-life had to be discarded in the calculations. Therefore, the total volume of carbon-dioxide in the calculation is smaller and the relative error in the readings becomes greater. In Guggenheim's procedure the error in readings (random or systematic) is more pronounced since the difference of two variables ( (a') and (x) ) is involved. A second source of systematic errors could arise from small leaks in the gas burette. However, from time to time the system was checked against any leakage.

Typical Kinetic Runs

The results cited in Tables (VI - 1); (VI - 2) and (VI - 3) are typical for (A) and (B) type measurements. The first order rate constants were obtained graphically, i.e. from the slope of the best straight lines drawn by plotting log (a - x) versus t(min.) (for experiments (A) ), or log (a' - x) versus t(experiments (B) ), as represented in Figures (VI - 2), (VI - 3), and (VI - 4). and (VI - 5).

Table (VI - 3) contains data for gas volume measurements together with the data for the pH-chart readings, where ($x_t$) represents the % of the syringe (2.5 mls. syringe) which had been added at time t. The agreement between the rate constants is better than $\pm$ 3%, which can be considered as very satisfactory. Rate coefficients were calculated from the chart readings only when the pH of the reaction solution was about 2 or higher.

Table (VI - 1)

Kinetic Run 55

wt. of 2,2-dichloromalonic acid, 0.3613 grs. = $2.09 \times 10^{-3}$ mols., concentration = 0.104 M/l, solvent: 20.0 mls. 3.40 M/l $HClO_4$

Bath temp. 25.0 ± 0.1°C
Jacket temp. 24.8°C
a = 50.9 c.c.

| time (min.) | x (c.c.) | (a - x) (c. c.) | log (a - x) |
|---|---|---|---|
| 15 | 2.0 | 48.9 | 1.689 |
| 35 | 4.3 | 46.6 | 1.668 |
| 48 | 5.6 | 45.3 | 1.656 |
| 70 | 7.7 | 43.2 | 1.635 |
| 90 | 9.5 | 41.4 | 1.617 |
| 120 | 12.2 | 38.7 | 1.588 |
| 155 | 15.1 | 35.8 | 1.554 |
| 215 | 19.5 | 31.4 | 1.497 |
| 260 | 22.5 | 28.4 | 1.453 |
| 320 | 25.9 | 25.0 | 1.398 |
| 350 | 27.8 | 23.1 | 1.364 |
| 380 | 29.3 | 21.6 | 1.335 |
| 400 | 30.2 | 20.7 | 1.316 |
| 440 | 32.0 | 18.9 | 1.277 |
| 480 | 33.6 | 17.3 | 1.238 |
| 522 | 35.1 | 15.8 | 1.199 |
| 546 | 35.9 | 15.0 | 1.176 |

$k = 2.24 \times 10^{-3}$ min.$^{-1}$

Figure (VI - 2)

Data in Table (VI - 1)

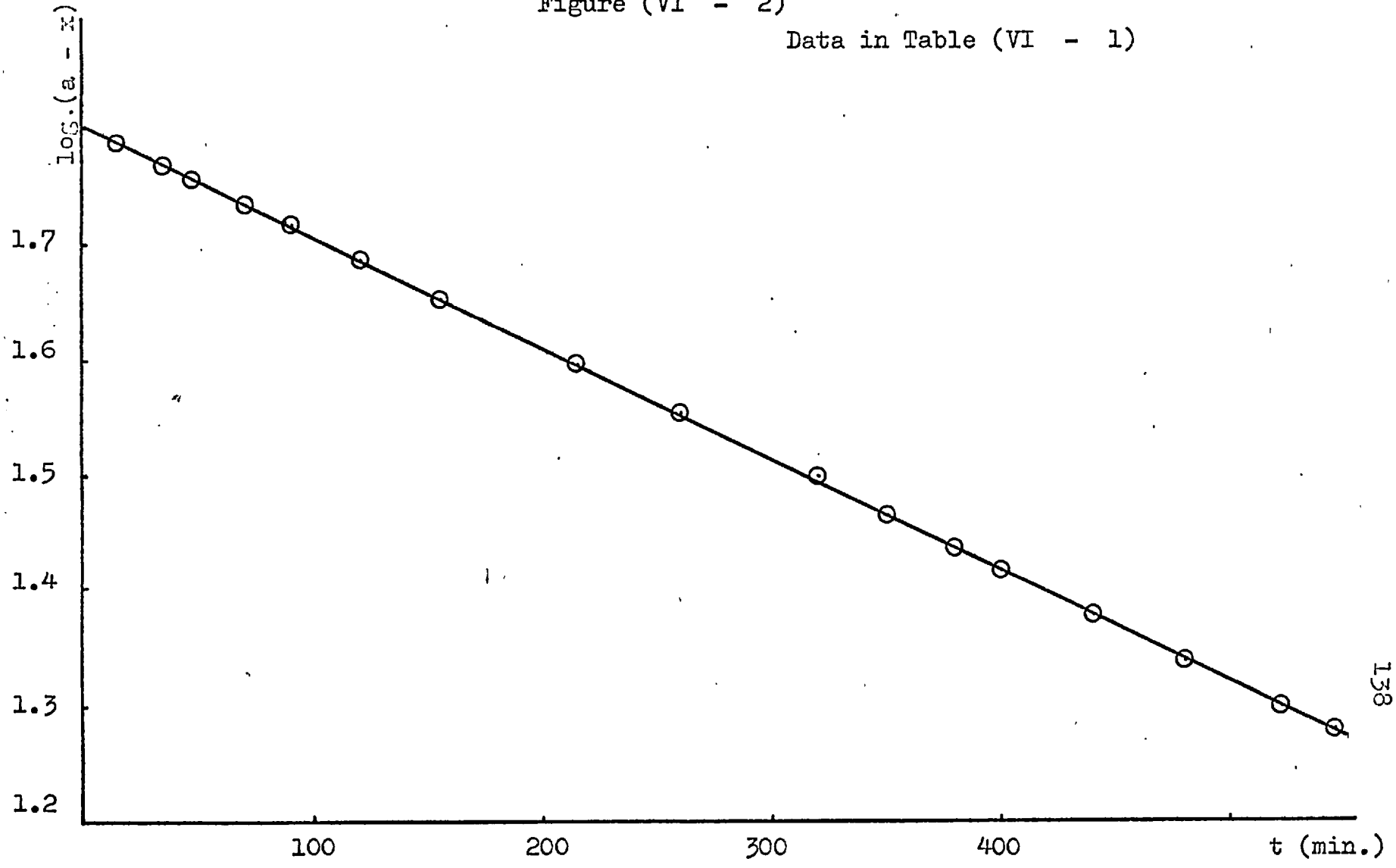


Table (VI - 2)

Kinetic run 64

wt. of 2,2-dichloromalonic acid: 0.3629 grs. = $2.10 \times 10^{-3}$ mols., concentration = 0.105 M/l

Solvent: 20 mls. 0.712 M/l HCl + 0.300 M/l KCl

Bath temp. 25.0 ± 0.1°C

Jacket temp. 24.7°C

a calculated = 51.1 c.c.

a experimental = 50.4 c.c.

| time (min.) | x (c.c.) | (a - x) (c. c.) | log (a - x) |
|---|---|---|---|
| 6 | 1.9 | 49.2 | 1.692 |
| 12 | 3.8 | 47.3 | 1.675 |
| 27 | 8.4 | 42.7 | 1.630 |
| 41 | 12.2 | 38.9 | 1.590 |
| 53 | 15.3 | 35.8 | 1.554 |
| 72 | 19.5 | 31.6 | 1.500 |
| 86 | 22.4 | 28.7 | 1.458 |
| 100 | 25.0 | 26.1 | 1.417 |
| 122 | 28.8 | 22.3 | 1.349 |
| 143 | 31.9 | 19.2 | 1.284 |
| 159 | 33.9 | 17.2 | 1.236 |
| 184 | 36.6 | 14.5 | 1.162 |
| 205 | 38.6 | 12.5 | 1.097 |
| 220 | 39.8 | 11.3 | 1.053 |
| 241 | 41.3 | 9.8 | 0.991 |
| 275 | 43.3 | 7.8 | 0.892 |
| 322 | 45.3 | 5.8 | 0.763 |

$k = 6.86 \times 10^{-3}$ min.$^{-1}$

Figure (VI - 3)
Data in Table (VI - 2)

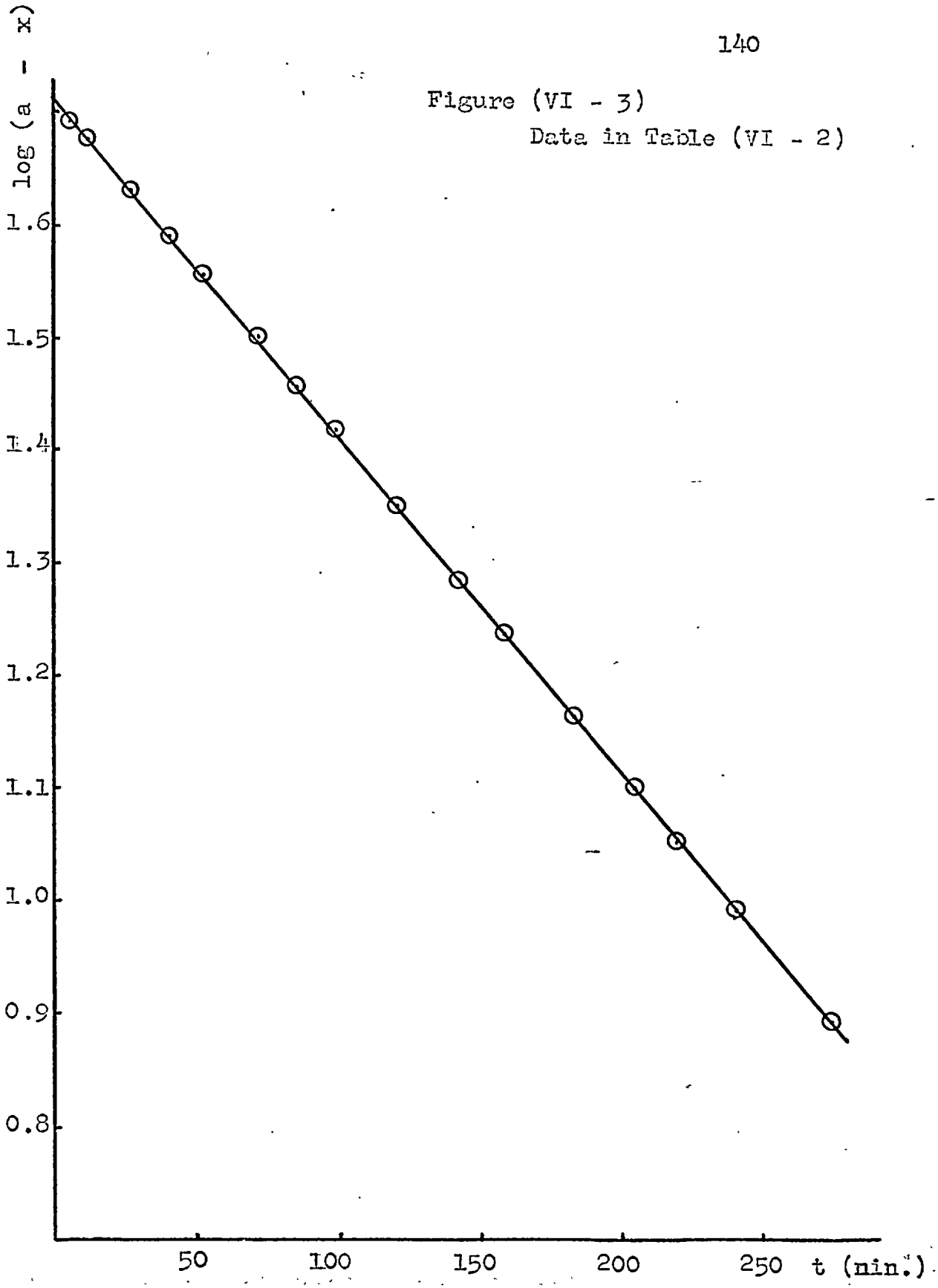


Table (VI - 3)

Kinetic Run 91.

Wt. of 2,2-dichloromalonic acid: 0.3710 grm. = $2.15 \times 10^{-3}$ mols., concentration = $3.07 \times 10^{-2}$ M/l

Solvent: 70 mls. aqueous 0.217 AcOH + 0.044 AcONa.

Bath temp. 25.1 ± 0.1°C

Jacket temp. 24.9°C

pH = 2.26

| time (min.) | x (c.c) | a' (c.c.) | (a' - x) (a' = x + X(430)) | log (a' - x) |
|---|---|---|---|---|
| 20 | 11.4 | 38.5 | 27.1 | 1.433 |
| 40 | 14.0 | 39.2 | 25.2 | 1.402 |
| 60 | 16.3 | 39.8 | 23.5 | 1.371 |
| 80 | 18.4 | 40.4 | 22.0 | 1.343 |
| 100 | 20.4 | 40.9 | 20.5 | 1.312 |
| 120 | 22.3 | 41.4 | 19.1 | 1.281 |
| 140 | 24.1 | 41.8 | 17.7 | 1.248 |
| 160 | 25.7 | 42.2 | 16.5 | 1.218 |
| 180 | 27.3 | 42.6 | 15.3 | 1.185 |
| 200 | 28.7 | 42.9 | 14.2 | 1.153 |

$k = 3.54 \times 10^{-3}$ min.$^{-1}$

Figure (VI - 4)

Data in Table (VI - 3)

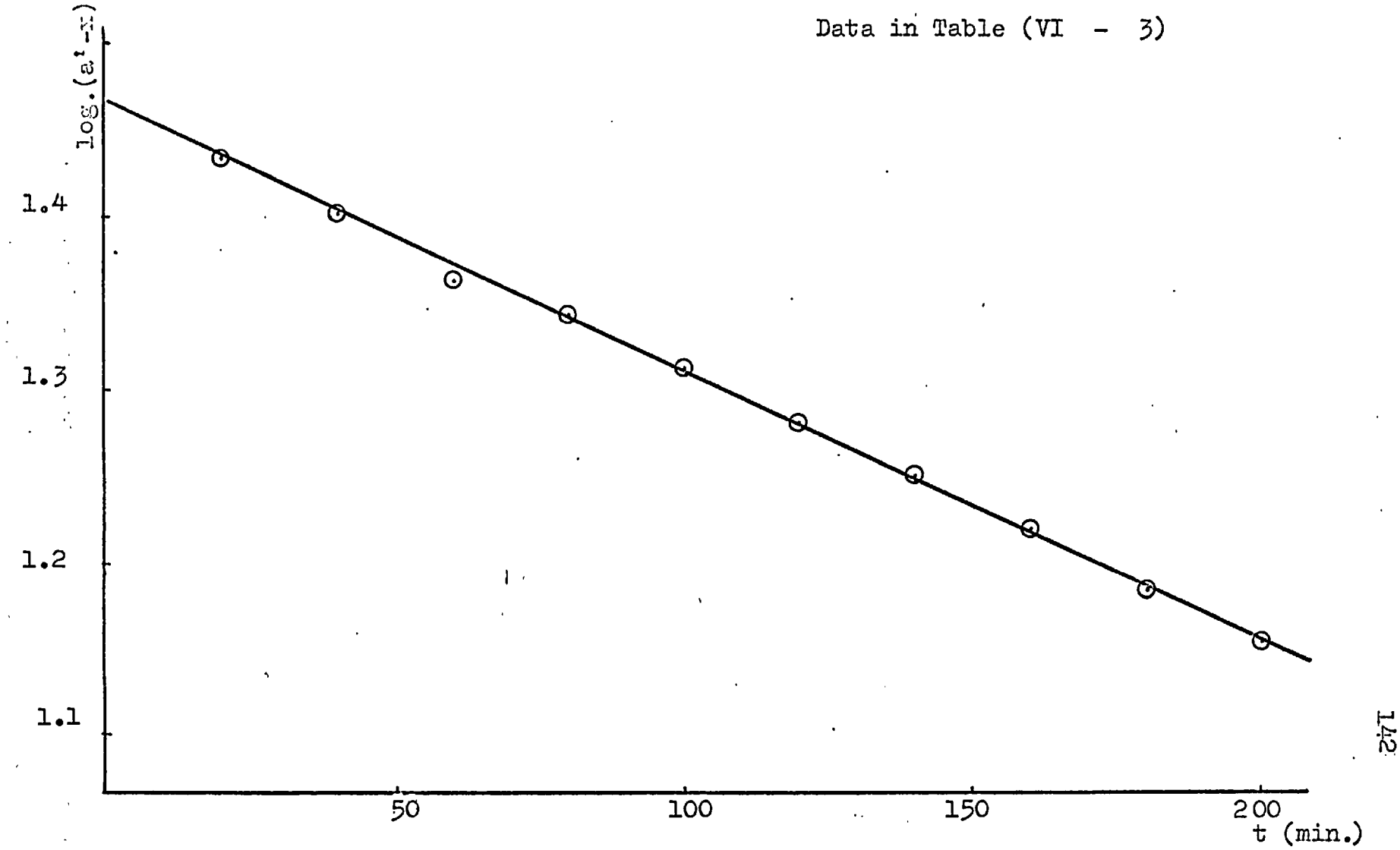


Table (VI - 3)
(continued)

pH chart readings.

| time (min.) | $X_t$ * (% of the syringe) | X'** ($X_t$ + X(200)) | (X' - $X_t$) | log (X' - $X_t$) |
|---|---|---|---|---|
| 40 | 28.0 | 135.0 | 107.0 | 2.030 |
| 80 | 55.0 | 148.0 | 93.0 | 1.968 |
| 120 | 79.0 | 158.5 | 79.5 | 1.900 |
| 160 | 100.0 | 168.8 | 68.9 | 1.838 |
| 200 | 119.8 | 177.0 | 57.2 | 1.757 |
| 240 | 135.0 | 185.0 | 50.0 | 1.699 |
| 280 | 148.0 | 191.0 | 43.0 | 1.633 |
| 320 | 158.5 | 196.1 | 37.6 | 1.575 |
| 360 | 168.8 | 202.0 | 33.2 | 1.521 |
| 400 | 177.0 | 206.0 | 29.0 | 1.462 |
| 440 | 185.0 | 209.7 | 24.7 | 1.393 |

$$k = 3.64 \times 10^{-3} \text{ min.}^{-1}$$

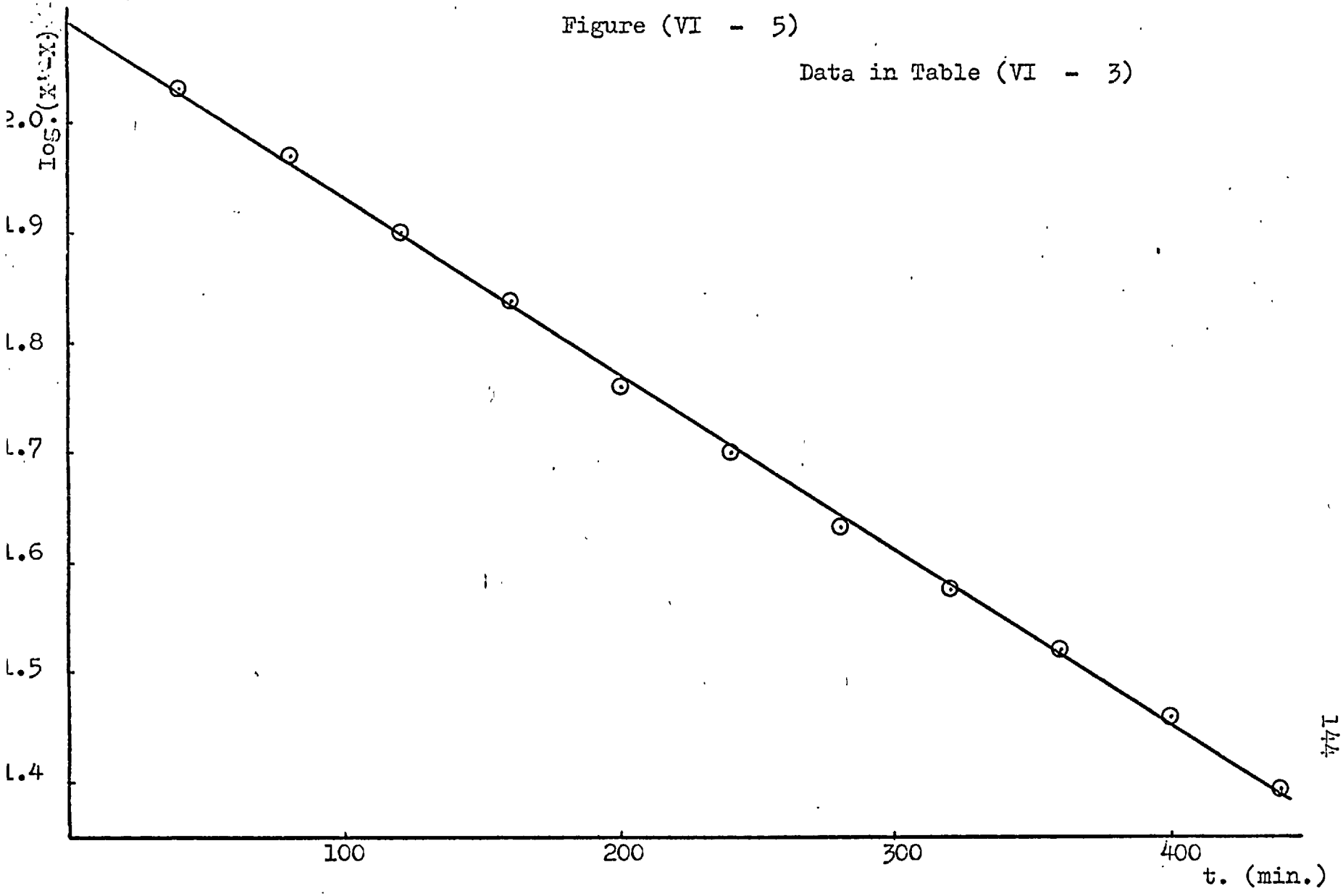
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* $X_t$ = readings at time t

** X' = readings at (200 min. + t) time.

Figure (VI - 5)

Data in Table (VI - 3)



## Section 2

### Dissociation Constant Measurements

a) Apparatus

The first ($K_1$) and second ($K_2$) dissociation constants of the halogen substituted malonic acids were measured potentiometrically utilising a Radiometer pH-meter PHM-26 assembly with a Radiometer glass electrode type G 202 B and calomel electrode K 901. The latter was placed in saturated aqueous KCl solution and was in contact with the test solution via a potassium chloride (in agar-agar) salt bridge[109] (concentration of KCl was ~4 M/l at 25°C and 1.3 M/l at 0°C).

For the measurements at 25°C, thermostatted water (25.0 ± 0.1°C) was circulated around the measuring beaker, while for the measurements at 0°C the beaker was placed in a water/ice bath.

The automatic Radiometer syringe was replaced by 10 mls. (0.05 mls divisions) automatic burette provided with a soda-lime guard tube to avoid absorption of carbon dioxide from the atmosphere.

b) Typical Dissociation Constant Measurements

Two consecutive sets of measurements under identical experimental conditions did not give reproducible enough results unless buffer solutions with pH close to that of the sample

itself were used to standardise the electrode system. Therefore, as well as a primary standard, i.e. 0.05 potassium hydrogen phthalate (pH = 4.008 at 25°C), a secondary standard 0.01 M/1 HCl+ 0.09 M/1 KCl (pH = 2.07 at 25°C) were used to calibrate the pH-meter.

An accurately weighed sample of the malonic acid was dissolved in 25 mls. of aqueous salt solution (de-ionised water) and stirred in the measuring beaker long enough for the temperature to become constant. As a titrant, BDH standard carbon dioxide free 0.10 M/1 NaOH solution was used and Analar KCl, $KNO_3$ or $NH_4NO_3$ were used to adjust the ionic strength of the solution.

0.1 M/1 NaOH titrant contained in a burette was added to this solution in 0.50 or 1.00 mls. portions and pH of the solution was determined and recorded after each aliquot of titrant until approximately 80% of the total NaOH solution was used. The amount of titrant used for complete neutralisation of the acid agreed within ± 1% with the calculated value. After every set of measurements the electrodes were checked with phthalate buffer solution; unless the reading was within 0.02 pH units with the known pH of the buffer, the results were disregarded.

Throughout the pH measurements, carbon dioxide free $N_2$ was blown through the solution to prevent the $CO_2$ absorption

from the atmosphere.

c) Calculation of the Dissociation Constants

The required dissociation constants were evaluated from the pH versus titrant volume graph using the method devised by Speakman[67]. In this, the experimental results are related to the dissociation constants by the following equation:

$$\left\{H^+\right\}^2 \; L\, y_2/N\, y_o \;=\; K_1 \left\{H^+\right\} M\, y_2/N\, y_1 \;+\; K_1K_2 \qquad \text{Eq. (VI - 3)}$$

where antilog(pH)= $\left\{H^+\right\}^{-1} = a_H^{-1}$;

$y_o$, $y_1$ and $y_2$ = activity coefficients of undissociated acid, monoanion and dianion respectively, and

$$L = \left[HA^-\right] + 2\left[A^=\right] = b + \left\{H^+\right\};$$
$$M = \left[H_2A\right] - \left[A^=\right] = a - b - \left\{H^+\right\};$$
$$N = 2\left[H_2A\right] + \left[HA^-\right] = 2a - b - \left\{H^+\right\};$$

(Thus, a = total acid concentration in mols/l,

b = the concentration of the base added in M/l).

Speakman's equation is of the form

$$Y = K_1X + K_1K_2 \qquad \text{Eq. (VI - 4)}$$

thus, $Y = \left\{H^+\right\}^2 L\, y_{2/Nyo}$ and $X = \left\{H^+\right\} My_{2/Ny_1}$

Values of X and Y were calculated from the experimental data and plotted against each other. The intercept corresponds to $K_1K_2$ and the slope to $K_1$.

The activity coefficient $y_o$ is considered to be unity, while $y_1$ and $y_2$, when included in the calculations, were estimated by Debye-Hückel equation

$$- \log y_{\pm} = 0.5\, z^2 \sqrt{J} / (1 + 1.6\sqrt{J})$$

where $z$ = the charge of the ion in question, and

$J$ = ionic strength of the solution

$$= \tfrac{1}{2} (b + [H^+] + [HA^-] + 4 [A^=])$$

Normally, activity coefficient corrections were not included (apart from two sets of titrations with no neutral electrolyte present in the solution) in the calculations, therefore, so-called "mixed constants" were evaluated by the method described above.

Typical sets of measurements and calculations are included in Tables (VI - 4), (VI - 5) and (VI - 6), together with the experimental details of the particular titration.

Table (VI - 4)

Run No.71

Wt. of 2,2-difluoromalonic acid:
0.1503 g. dissolved in 50 ml
Solvent: 25 ml of aqueous KCl solution (0.50 M/l)

Concentration:
Exp. $2.14 \times 10^{-2}$ Calc. $2.13 \times 10^{-2}$ M/l

Temperature $25.0 \pm 0.1^{\circ}C$

| mls. of 0.1 M NaOH | $[H^+] \times 10^2$ (M/l) | $a \times 10^2$ (M/l) | $b \times 10^2$ (M/l) | $X \times 10^4$ | $-Y \times 10^2$ |
|---|---|---|---|---|---|
| 1.00 | 2.29 | 2.01 | 0.384 | 10.4 | 1.12 |
| 2.00 | 1.96 | 1.94 | 0.744 | 8.91 | 1.286 |
| 3.00 | 1.67 | 1.87 | 1.071 | 7.57 | 1.443 |
| 4.00 | 1.39 | 1.80 | 1.38 | 6.47 | 1.620 |
| 5.00 | 1.14 | 1.75 | 1.66 | 5.25 | 1.74 |
| 6.00 | 0.892 | 1.69 | 1.93 | 4.08 | 1.84 |
| 7.00 | 0.665 | 1.63 | 2.18 | 3.00 | 1.92 |
| 8.00 | 0.457 | 1.58 | 2.42 | 2.04 | 2.00 |
| 9.00 | 0.263 | 1.54 | 2.65 | 1.19 | 2.14 |

$K_1 = 9.25 \cdot 10^{-2}$ $K_2 = 2.28 \cdot 10^{-2}$ $K_1/K_2 = 4.05$

Figure (VI - 6)

Data in Table (VI - 4)

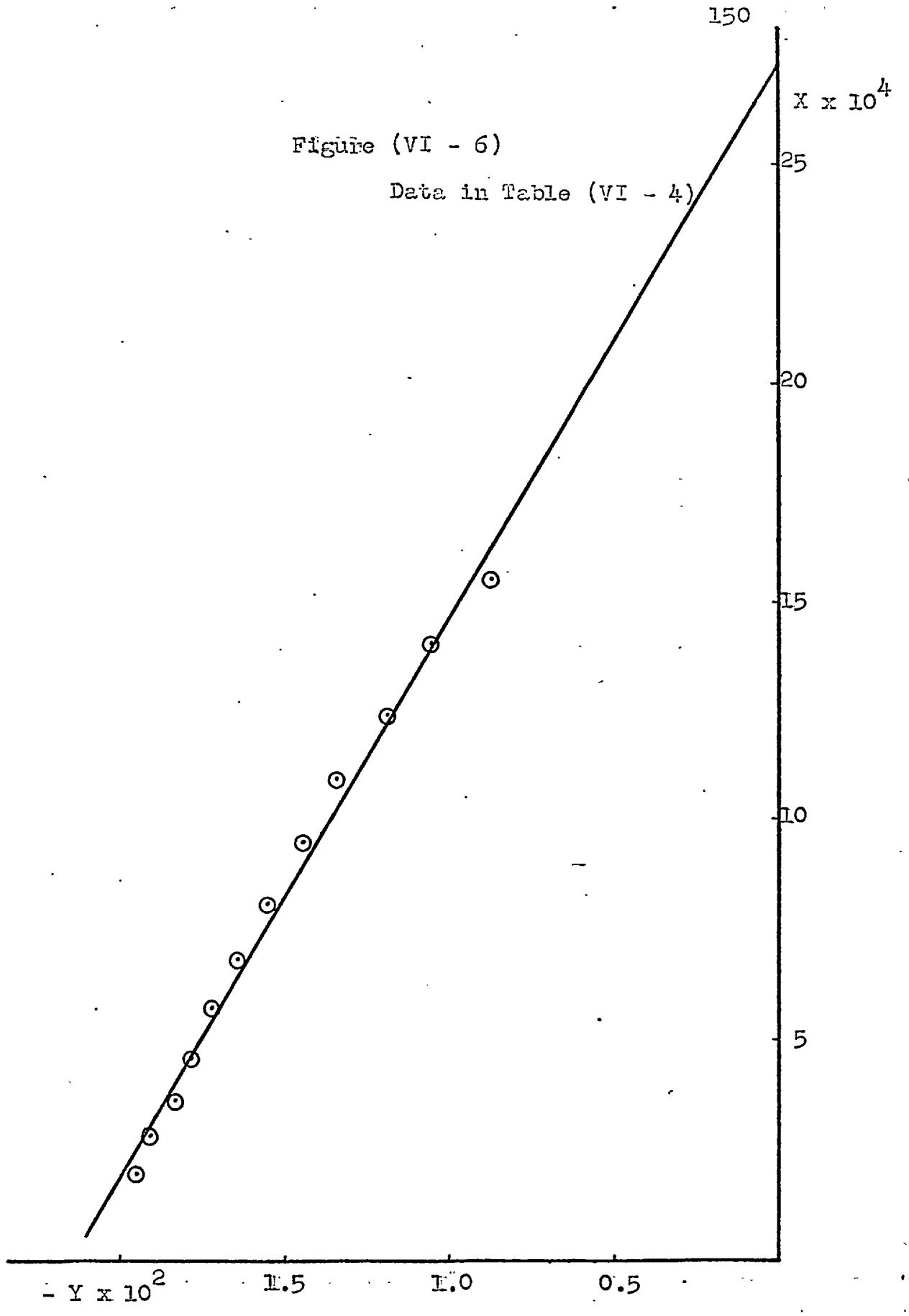


Table (VI - 5)

Run No. 84

Wt. of 2,2-difluoromalonic acid 0.2143 g dissolved in 50 ml

Solvent: 25 ml of aqueous $KNO_3$ solution (0.50 M/l)

Concentration:

Exp: $3.05 \times 10^{-2}$ M/l

Calc: $3.07 \times 10^{-2}$ M/l

Temperature $25.0 \pm 0.1^{\circ}C$

| mls. of 0.1 M NaOH | $\{H^+\} \times 10^2$ (M/l) | $a \times 10^2$ (M/l) | $b \times 10^2$ (M/l) | $X \times 10^4$ | $-Y \times 10^2$ |
|---|---|---|---|---|---|
| 1.00 | 3.177 | 2.930 | 0.385 | 15.6 | 0.87 |
| 2.00 | 2.845 | 2.823 | 0.741 | 14.1 | 1.06 |
| 3.00 | 2.518 | 2.722 | 1.071 | 12.4 | 1.19 |
| 4.00 | 2.233 | 2.628 | 1.379 | 10.94 | 1.34 |
| 5.00 | 1.958 | 2.541 | 1.666 | 9.54 | 1.45 |
| 6.00 | 1.698 | 2.458 | 1.935 | 8.16 | 1.55 |
| 7.00 | 1.455 | 2.381 | 2.187 | 6.88 | 1.64 |
| 8.00 | 1.230 | 2.310 | 2.425 | 5.73 | 1.72 |
| 9.00 | 1.020 | 2.242 | 2.648 | 4.68 | 1.78 |
| 10.00 | 0.825 | 2.18 | 2.855 | 3.72 | 1.84 |
| 11.00 | 0.644 | 2.12 | 3.057 | 2.88 | 1.92 |
| 12.00 | 0.473 | 2.06 | 3.242 | 2.05 | 1.94 |

$K_1 = 0.125$ $K_2 = 2.48 \cdot 10^{-2}$ $K_1/K_2 = 5.7$

Figure (VI - 7)

Data in Table (VI-5)

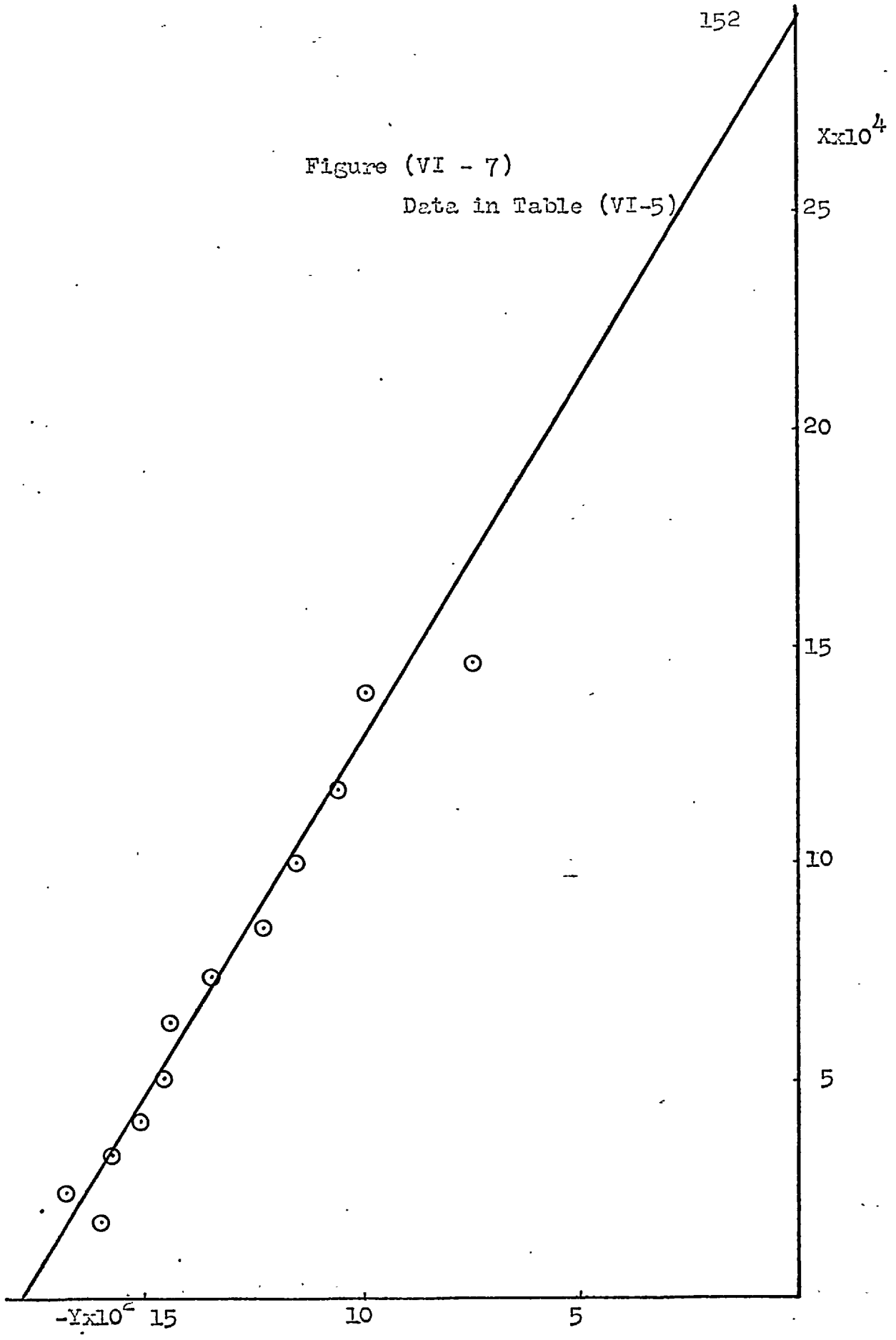


Table (VI - 6)

Run No. 99

Wt. of 2,2-dichloromalonic acid
0.2717 g in 50 ml
Solvent: 25 mls of aqueous KCl solution (0.20 M/l)

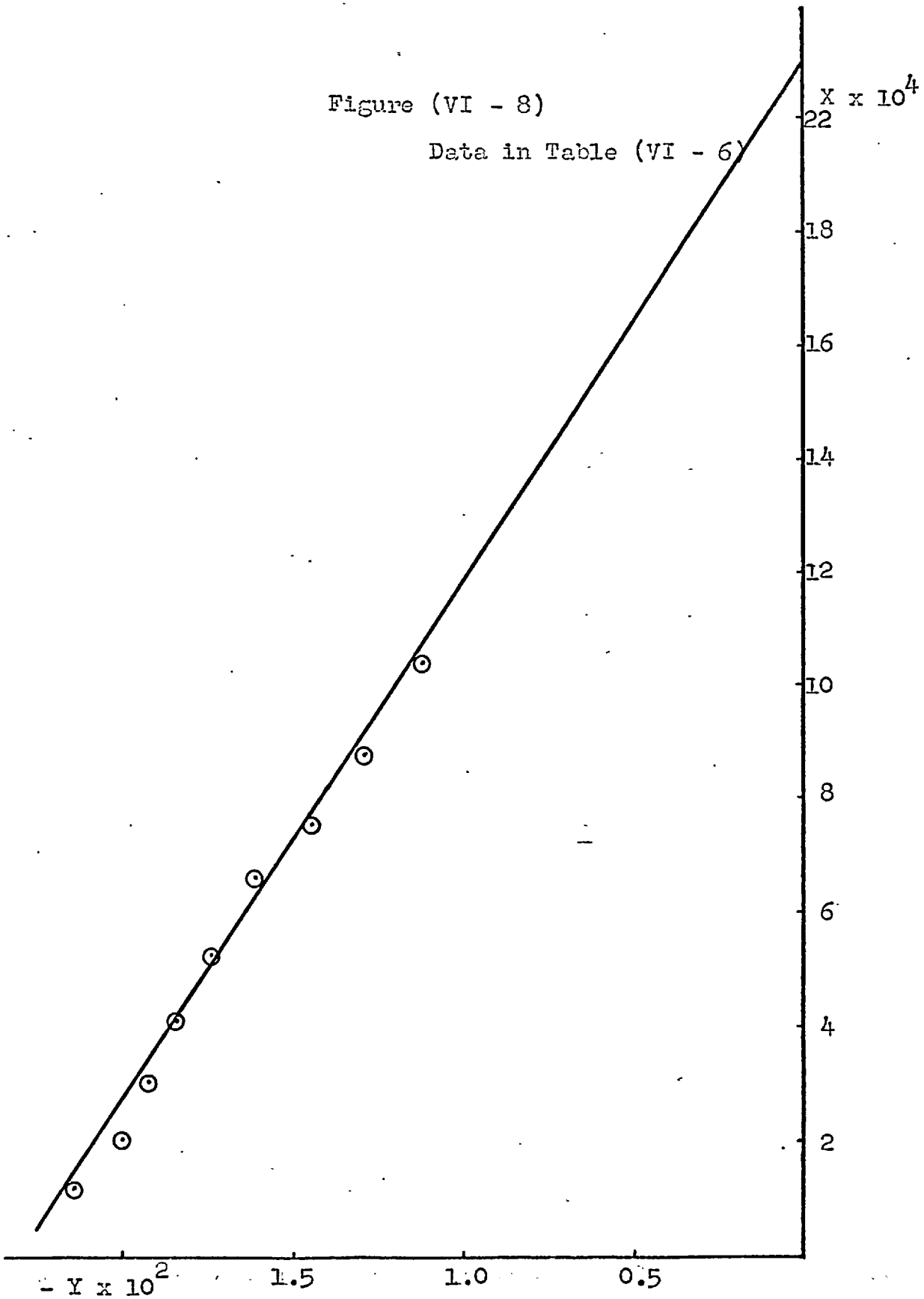
Concentration:
Exp: $3.09 \cdot 10^{-2}$ M/l
Calc: $3.15 \cdot 10^{-2}$ M/l
Temperature $0^{\circ} \pm 0.2^{\circ}$C.

| mls. of 0.1 M/NaOH | $\{H^+\} \times 10^2$ (M/l) | $a \times 10^2$ (M/l) | $b \times 10^2$ (M/l) | $X \times 10^4$ | $-Y \times 10^2$ |
|---|---|---|---|---|---|
| 1.00 | 3.162 | 2.972 | 0.378 | 14.72 | 0.746 |
| 2.00 | 2.870 | 2.862 | 0.730 | 13.95 | 0.996 |
| 3.00 | 2.522 | 2.760 | 1.055 | 11.70 | 1.061 |
| 4.00 | 2.218 | 2.665 | 1.359 | 10.05 | 1.153 |
| 5.00 | 1.936 | 2.575 | 1.642 | 8.53 | 1.235 |
| 6.00 | 1.693 | 2.492 | 1.906 | 7.44 | 1.352 |
| 7.00 | 1.458 | 2.412 | 2.152 | 6.32 | 1.439 |
| 8.00 | 1.227 | 2.342 | 2.388 | 5.08 | 1.461 |
| 9.00 | 1.020 | 2.272 | 2.610 | 4.13 | 1.516 |
| 10.00 | 0.837 | 2.208 | 2.812 | 3.34 | 1.573 |
| 11.00 | 0.673 | 2.148 | 3.010 | 2.72 | 1.684 |
| 12.00 | 0.491 | 2.088 | 3.195 | 1.81 | 1.600 |

$K_1 = 0.166$ $K_2 = 1.78 \cdot 10^{-2}$ $K_1/K_2 = 9.35$

Figure (VI - 8)

Data in Table (VI - 6)



## Section 3

### Kinetic Methods for the Studies of Malonate Ester Hydrolysis

The rates of these reactions were measured utilising two different methods: a) pH-stat and b) spectrophotometric methods.

a) pH-stat Measurements

A Rediometer pH-stat assembly (described previously in Section 1 of this Chapter) was used to follow the rates of base catalysed hydrolysis of substituted diethyl malonates. The pre-determined pH of the reaction solution was kept constant by automatically controlled additions of carbon dioxide free standard NaOH solution (or NaOH solutions standardised with standard HCl solutions). Therefore, the amount of ester which underwent hydrolysis at a time t was determined by the percentage of NaOH solution added and this volume was recorded on the recorder chart running at a constant speed. The experiments with 2,2-dihalo-diethyl malonates were carried out in 60 wt. % ethanol/water solvent because the solubility of these esters in pure water was very low. In this case, the titrant contained the same percentage of the organic solvent as the reaction solution itself.

The pH-meter electrodes were standardised by means of primary standard potassium hydrogen phthalate (0.05 M/l) and borax buffers of 0.05 M/l concentration and they were regularly

checked after every kinetic run with borax buffer solution (pH = 9.18 at 25°C). When water was the solvent the deviation from the known pH of the buffer was not higher than ± 0.02 pH units. For the ethanol/water solvent, however, deviations were much higher, usually ± 0.1 pH units. In general, the results in mixed solvents (40 wt. % dioxan/water and 50 wt. % acetone/water solutions were investigated as well) were not very satisfactory. The calculated amount of NaOH solution used for the complete hydrolysis of the ester did not agree with the experimentally determined value. The latter was always higher for approximately 10 to 20% . The reasons for these discrepancies have already been discussed in Chapter IV.

Kinetic Procedure

In aqueous solutions kinetic measurements in the pH region from 8 to 13 were undertaken for 2-(trimethylammonium bromide) diethyl malonate only, and were carried out as follows. The pH of 30 mls. of 0.1 M KCl solution was adjusted to a desired value by a trace of borax buffer and automatically controlled introduction of standardised 0.1 M NaOH solution. Thermostatted water of 25.0 ± 0.1°C was circulating around the reaction beaker throughout the time of the experiment. The system was flushed continuously with nitrogen which had been passed through a

column of soda-lime and three wash bottles containing concentrated NaOH solution and two of distilled water respectively. Approximately 10 minutes after the pH of the solvent had been adjusted, 2.0 mls of stock solution (made in 0.1 M KCl solution and brought up to the temperature of 25°C) was introduced by means of graduated syringe. The pH-stat was activated immediately and the reaction was followed at least for three half lives (or five half lives when the Guggenheim method of calculation was employed). To check the agreement between calculated and experimentally determined infinity readings, several runs were followed up until ten half lives. A large discrepancy was observed between these two. The value was low at lower pH and high in more alkaline solutions, ranging from 70 to 140 % of the required amount for complete reaction. N.M.R. and reaction product studies showed this effect arose from decarboxylation of the monoester of the substrate. The rate constant for hydrolysis of the first ester group ($k_1$) was estimated by "time ratio" method of Schwemer[110] using 15, 35, and 70% of the calculated amount of the compound which was used in the particular measurement.

The second rate constant ($k_2$) actually representing the total rate of decarboxylation and ester hydrolysis was determined independently. First ester group was hydrolysed rapidly at pH ~ 10.2 (where half life ~ 0.5 min. or higher). Five minutes after the start, the pH of the reaction solution was readjusted

either by the automatically controlled addition of the extra NaOH, or by manual introduction of a few drops of dilute HCl solution, and hydrolysis of the second ester group was then followed at the desired pH. Pseudo first order rate constants ($k_2$) were calculated by the Guggenheim method from the percentage of NaOH uptake which was obtained for four or five half lives of the total reaction.

Typical kinetic experiments of the type just described, together with the experimental details are summarised in Tables (VI - 7) and (VI - 8).

Hydrolysis in ethanol/water solutions was carried out in a similar manner, apart from the fact that a known amount of the substrate was dissolved in the total amount of solvent and the pH of the reaction mixture was autometically adjusted by the pH-stat assembly. The first and second ester hydrolysis constants were calculated by "time ratio" method of Schwemer with 15, 35 and 70% of the experimentally found infinity NaOH uptake.

b) Spectrophotometric Determinations of Rates of p-nitrophenyl Ester Hydrolysis.

The rates of base catalysed hydrolysis of 2,2-disubstituted di(p-nitrophenyl) malonates were measured by means of a Unicam spectrophotometer (SP-700) by following the appearance of

Table (VI - 7)

Kinetic Run 86

1.50 mls. Stock solution

(0.2117 g. of (xxiv) dissolved in 10 mls.

of 0.1 M KCl = $7.10 \times 10^{-4}$ M/l)

Solvent: 30.0 mls. aqueous 0.1 M KCl

pH = 9.860

| % of the reaction | % of the syringe | divisions (cm) | time (min.) |
|---|---|---|---|
| 15 | 12.8 | 3.10 | 0.775 |
| 35 | 29.8 | 9.80 | 2.45 |
| 70 | 59.6 | 69.9 | 17.47 |

| | | $k_1/k_2$ |
|---|---|---|
| $\log {}^{t_{35}}/_{t_{15}} = \log {}^{9.80}/_{3.10}$ | = 0.500 | 0.067 |
| $\log {}^{t_{70}}/_{t_{15}} = \log {}^{69.9}/_{3.10}$ | = 1.353 | -0.072 |
| $\log {}^{t_{70}}/_{t_{15}} = \log {}^{69.9}/_{9.80}$ | = 0.853 | 0.075 |

| | $k_1$ (min.$^{-1}$) |
|---|---|
| 15 = | 0.351 |
| 35 = | 1.106 |
| 70 = | 7.85 |

| | $k_1$ (min.$^{-1}$) |
|---|---|
| 0.453 | |
| 0.452 | |
| 0.450 | |

$k_1$(Average) = 0.452 min.$^{-1}$

Table (VI - 8)

Kinetic Run No. 87

1.50 mls. stock solution
(0.2117 g of (xxiv)) dissolved in
10 mls. of 0.1 M KCl = $7.10 \times 10^{-4}$ M/l
Solvent: 30.0 mls 0.10 M aqueous KCl
pH = 11.105

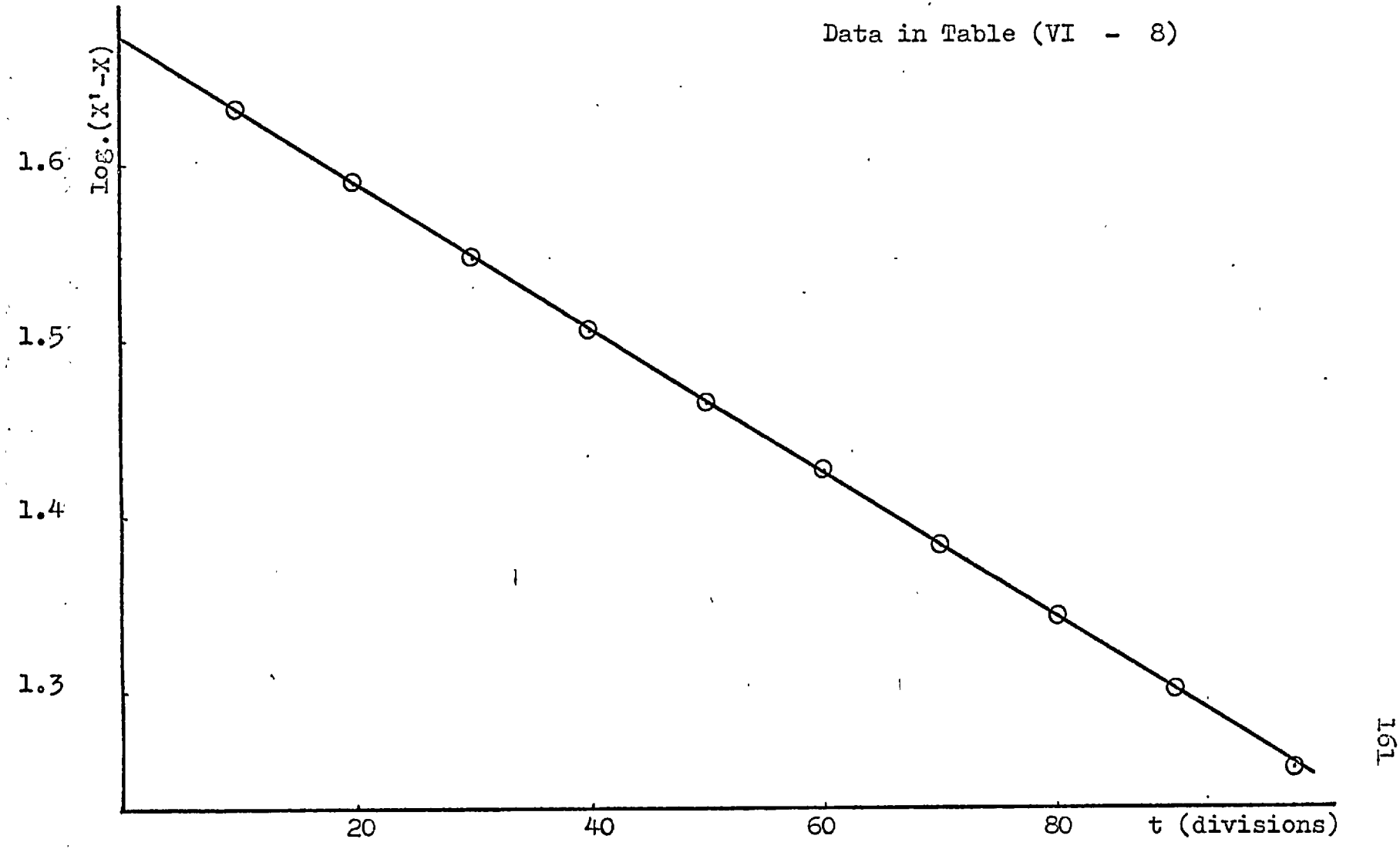
% of 2.50 mls syringe:
required 85.2%
found 115%
Temperature 25.0 ± 0.1°C

| Divisions (4 div.= 1 min.) | (% of syringe) X | ($X_t$ + X(140)= X' (% of syringe) | (X' - X) | log(X' - X) |
|---|---|---|---|---|
| 10 | 5.8 | 48.4 | 42.6 | 1.629 |
| 20 | 11.0 | 49.8 | 38.8 | 1.589 |
| 30 | 15.8 | 51.0 | 35.2 | 1.547 |
| 40 | 20.1 | 52.2 | 32.1 | 1.507 |
| 50 | 24.0 | 53.2 | 29.2 | 1.465 |
| 60 | 27.6 | 54.2 | 26.6 | 1.425 |
| 70 | 30.9 | 55.0 | 24.1 | 1.382 |
| 80 | 33.9 | 55.8 | 21.9 | 1.341 |
| 90 | 36.6 | 56.5 | 19.9 | 1.299 |
| 100 | 39.0 | 57.0 | 18.0 | 1.256 |

$k_2 = 3.84 \times 10^{-2}$ min.$^{-1}$ ; $t_{\frac{1}{2}} = 18.2$ min.

Figure (VI - 9)

Data in Table (VI - 8)



p-nitrophenol at $\lambda$ = 406 nm. Thermostatted water at 25.0°C was circulated around the measuring cell to attain constant temperature. All measurements were carried out in solvent composed of 41/59 vol. % dioxan/water (actually, 40 mls of purified dioxan plus 1.0 mls of dioxan stock solution of substrate in 100 mls of total solution).

Stock solutions of the substrate, made by dissolving a known weight in 20 mls. of purified dioxan, were used for several kinetic measurements since it was shown that the esters were stable for several weeks when dissolved in this solvent. In the presence of glycine buffer total ionic strength was 0.058 M/l, while in NaOH solutions it was 1.0 M/l. In both cases, the ionic strength was adjusted by KCl.

Pseudo first order rate constants were calculated either by "time ratio" method of Schwemer, or from the slopes of the best straight lines obtained from log (abs.$_\infty$ - abs.$_t$) versus time plots. abs.$_\infty$ and abs.$_t$ represent absorbance when the reaction went to the completion and absorbance at the time t respectively.

Kinetic Procedure

Before the start of each kinetic run the spectrophotometer was checked for stability at the required temperature of the experiment. The solvent was prepared in the volumetric flask

containing a known amount of KCl so that the total ionic strength was constant. The solvent was brought up to 25.0°C and, after the stock substrate solution had been introduced, the volume was made up to the mark by a few drops of deionised water. This reaction mixture was placed into the clean and dry cell as quickly as possible and the chart was run at a constant, known speed. When the reaction was relatively slow points were taken from time to time by recording the absorbance at a particular time, rather than by continuous monitoring.

In order to check the reproducibility of the measurements, several kinetic runs were repeated under the same experimental conditions. It was found that disagreements between two measurements could be as high as ± 10% when stock solution (about 0.10 mls.) was introduced directly to the reaction cell containing the buffer solution. The method was not satisfactory because the optical cell was not graduated and the total volume was 9.5 ± 0.5 mls. Therefore the concentration of the substrate was not accurately known. Consequently, it was necessary to prepare the reaction mixture beforehand in a volumetric flask (as described above). Using this method, the reproducibility of the measurements was satisfactory (within ± 3%).

Examples of typical spectrophotometrically measured kinetic runs together with details of the reaction conditions are given in Tables (VI - 9) and (VI - 10).

Table (VI - 9)

Kinetic Run No. 149

0.50 mls. stock solution in 50 mls. of solvent (41/59 vol.% dioxan/water)

Buffer: Glycine = 0.044 M/l plus NaOH = 0.036 M/l

pH (measured) = 10.47 10.57

pH (calculated) = 10.89

Absorbance at $t_\infty$ required ( $\lambda = 24600\ cm^{-1}$) 0.816

found 0.845

Temperature $25.0 \pm 0.1^\circ C$

"Time ratio" method of calculation

| % of the reaction | absorbance | transmittance (%) | time (min.) |
|---|---|---|---|
| 15 | 0.127 | 74.7 | 10.9 |
| 35 | 0.296 | 50.6 | 35.1 |
| 70 | 0.591 | 25.6 | 165 |

$\log {}^{t_{35}}/_{t_{15}} = \log {}^{35.1}/_{10.9} = 0.508$ $k_2/k_1$ 0.045

$\log {}^{t_{70}}/_{t_{15}} = \log {}^{165}/_{10.9} = 1.180$ 0.125

$\log {}^{t_{70}}/_{t_{35}} = \log {}^{165}/_{35.1} = 0.672$ 0.135

$k_1/k_2 = 0.130$

15 = 0.347

35 = 1.051

70 = 5.15

| $k_1 \times 10^2\ min.^{-1}$ | $k_2 \times 10^3\ min.^{-1}$ |
|---|---|
| 3.18 | 4.14 |
| 3.00 | 3.90 |
| 3.12 | 4.06 |

$k_{1(average)} = 3.10 \times 10^{-2}\ min.^{-1}$

$k_{2(average)} = 4.03 \times 10^{-3}\ min.^{-1}$

## Table (VI - 10)

Kinetic Run No. 158

1.00 mls dioxan stock solution in 100 mls. of solvent (final solvent composition: 41 mls. dioxan in 100 mls solution conteining 1.00 M/l KCl and 0.001 M/l NaOH).

Absorbance at $t_\infty$ at $\lambda = 24600\ cm^{-1}$
required: 0.816
found: 0.846
Temperature: $25.0 \pm 0.2^{\circ}C$

A) First Ester Group:

Absorbance at $t_\infty = 0.423 = a$

| time (") (40" = 60 min) | X (Absorb. at t) | (a - x) | log (a - x) + 1.000 |
|---|---|---|---|
| 0 | 0.129 | 0.294 | 1.468 |
| 2 | 0.176 | 0.247 | 1.393 |
| 4 | 0.217 | 0.206 | 1.314 |
| 6 | 0.250 | 0.173 | 1.238 |
| 8 | 0.274 | 0.149 | 1.173 |
| 10 | 0.299 | 0.124 | 1.094 |
| 12 | 0.321 | 0.102 | 1.009 |
| 14 | 0.340 | 0.083 | 0.919 |
| 16 | 0.356 | 0.067 | 0.826 |
| 18 | 0.369 | 0.054 | 0.733 |

$$k_{1\ obs.} = 5.83 \times 10^{-2}\ min.^{-1}$$

Figure (VI - 10)

Data in Table (VI - 10)

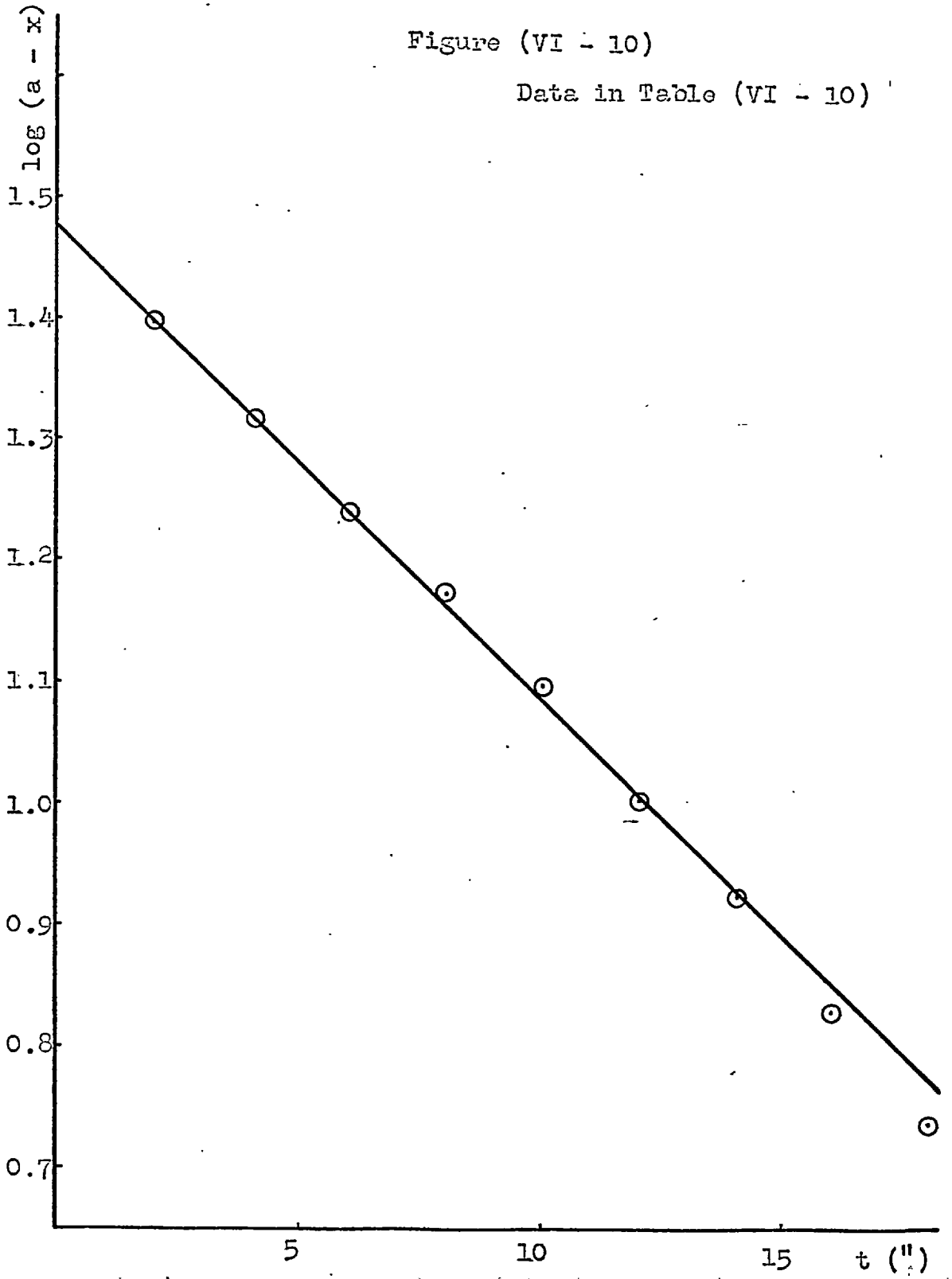


Table (VI - 10)

(continued)

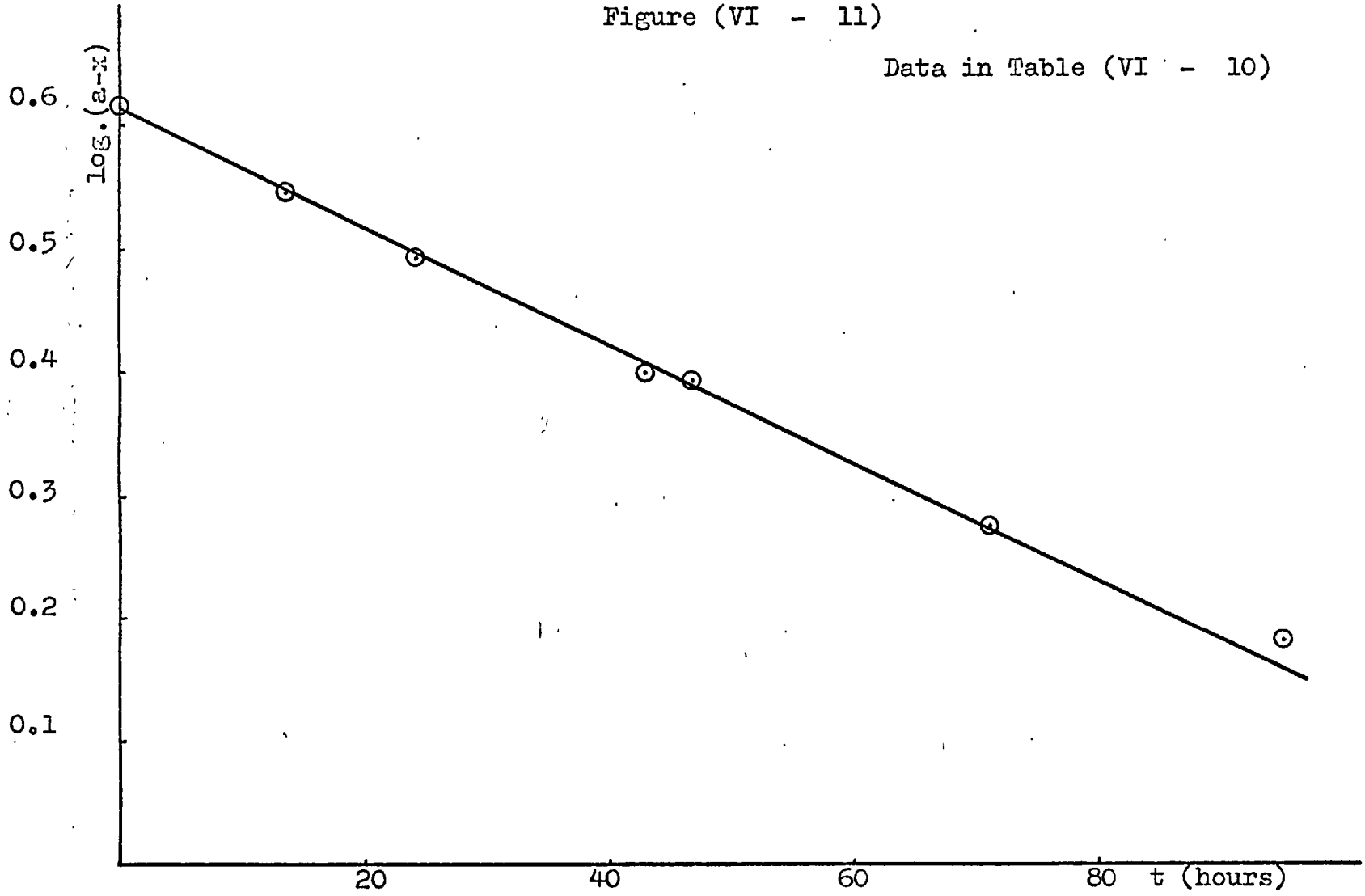
B) Second Ester Group

Absorbance $t_\infty$ = 0.846 = a

| time (hours) | X (Absorbance at t) | (a - x) | log (a - x) + 1.00 |
|---|---|---|---|
| 0.0 | 0.433 | 0.413 | 0.616 |
| 13.5 | 0.495 | 0.351 | 0.545 |
| 24.0 | 0.536 | 0.310 | 0.492 |
| 43.0 | 0.596 | 0.250 | 0.398 |
| 46.5 | 0.599 | 0.247 | 0.392 |
| 71.0 | 0.658 | 0.188 | 0.274 |
| 95.0 | 0.695 | 0.151 | 0.179 |

Figure (VI - 11)

Data in Table (VI - 10)



## Section 4

### Preparation and Purification of Reagents and Substrates

Para-nitrophenyl esters of malonic acids were prepared according to the method described by Ziegler and Junek[111] for the preparation of phenyl esters of unsubstituted as well as monosubstituted malonic acids.

1) Di-(p-nitrophenyl) malonate

A mixture of dried malonic acid (1.0 g.), p-nitrophenol (2.2 g.) and phosphoryl chloride (1.8 mls.) was heated for 15 minutes at 110°C. After cooling, the solid reaction mixture was washed several times with water and concentrated sodium bicarbonate solution until most of unreacted p-nitrophenol was removed. After several recrystallisations from glacial acetic acid the m.p. was 195 °C (Lit. m.p. 203°). Anal. found: C, 51.98; H, 2.89; N, 8.13 %. Calculated for $C_{15}H_{10}N_2O_8$: C, 52.1; H, 2.89; N, 8.09%.

2) 2,2-dimethyl di(p-nitrophenyl)malonate

2,2-dimethylmalonic acid (1.53 g.), p-nitrophenol (3.2 g.) and phosphoryl chloride (2.3 mls.) were allowed to react for 20 minutes at 130°C. After cooling the product was worked up as described above. The crude material was recrystallised several times from acetone/ethanol and dried under vacuum. The m.p. of

the compound was 157°C.

Anal. Found: C, 54.69; H, 3.79; N, 7.52 %. Required for $C_{17}H_{14}N_2O_8$: C, 54.6; H, 3.74; N, 7.49%.

4) 2,2-dimethylmalonic acid

The above compound was prepared according to the method (slightly modified) described by Thorne[112].

Diethylmalonate (4.8 g.) was added gradually to alcoholic sodium ethoxide solution (16 mls. of 9% sodium ethoxide). The thick white precipitate obtained was diluted with absolute ethanol and allowed to react with excess methyl iodide at 60° until the solution was no longer alkaline. After addition of aqueous sodium hydroxide solution, the reaction mixture was heated under reflux for two days. Dimethylmalonic acid was isolated according to the usual procedure and recrystallised from diethyl ether/methylene chloride. The m.p. of the acid was 192° (Lit. m.p. 192 - 3°C).

5) 2,2-dichloromalonic acid

The above acid was prepared by the method described by Conrad and Reibach[113]. Sulphuryl chloride (83 g.) was added to the refluxing ethereal solution of malonic acid (31.2 g. of finely ground and dry malonic acid in 300 mls. of sodium dry diethyl ether) over a period of eight to ten hours, the reaction

mixture being kept in the light. After the evolution of HCl gas had ceased, the reaction was stopped, and excess solvent removed under vacuum. The acid was precipitated by the addition of methylene chloride into the concentrated ethereal solution. Crystals obtained were washed several times with methylene chloride under an atmosphere of nitrogen and dried under high vacuum over phosphorus pentoxide. The purity of the acid was found to be 99.5% by back titration of the excess of NaOH (from 5.0 mls. of 1 M. standard NaOH solution) with standard 0.1 M. HCl solution using methyl red as indicator.

6) 2,2-difluoromalonic acid

The above compound was prepared by a method described by Evans and Tatlow[64].

Octafluorocyclohexadiene (30 g.) was oxidised with alkaline aqueous potassium permanganate (180 g. of $KMnO_4$ in 180 mls. of water and 9 g. of KOH) in a rocking autoclave at 60°C (approximately 50 hours). After filtration of precipitated $MnO_2$, the unreacted $KMnO_4$ was reduced with $SO_2$ and the solution then acidified with concentrated $H_2SO_4$ (3 - 4 mls.). The acid was extracted with diethyl ether and isolated from the solution in the usual way. The compound was sublimed several times and had the m.p. 116 - 117°C (Lit. m.p. 117 - 118°C). $^{19}F$ N.M.R. spectra (HA - 100 Hz) showed only two equivalent fluorine atoms in the molecule (solvent - diethyl ether).

The dianilinium salt of difluoromalonic acid was prepared according to the method described by the same authors[64]. Aniline was added to an ethereal solution of the acid (0.53 g. of acid in 10 mls. of ether) until no more precipitate came out. After two recrystallisations from acetone/chloroform, the salt had a m.p. of 157 - 8°C (Lit. m.p. 160°C).
Anal. Found: C, 55.2; H, 4.92; N, 8.60%. Calculated for $C_{15}H_{16}F_2O_4$: C, 55.2; H, 4.96; N, 8.89%.

7) 2,2-difluoro diethylmalonate

2,2-difluoromalonic acid (3 g) was dissolved in dry ethanol (20 mls) and refluxed for two days in presence of 2 mls. of concentrated $H_2SO_4$. The solution was cooled to 0°C, neutralised with aqueous NaOH solution and further diluted with water (approximately 50 - 60 mls.). The required ester was extracted with diethyl ether from the neutral reaction solution. The bulk of solvent was removed on a rotary film evaporator, the residue dried overnight with sodium sulphate. After removal of the drying reagent and the rest of the ether (at high vacuum and room temperature), the ester was purified by distillation under reduced pressure (b.p. 120°C/30 mm.); Lit. b.p. 94-95°C/23mm.
Anal. Found: C, 42.98; H, 5.35; F, 19.23 %. Calculated for $C_7H_{10}F_2O_4$: C, 42.8; H, 5.1; F, 19.4%.

8) 2-(trimethylammonium bromide) diethylmalonate

Slightly altered method of Cohen and Corwin[65] was employed to prepare the above compound (xxiv).

The solution of 2-bromo diethylmalonate (12 g.) and absolute ethanol (50 mls.) was gently heated and stirred. A solution of trimethylamine in absolute ethanol (33 w/v %) (slight excess) was added slowly over a period of approximately two hours, and the reaction mixture was heated at 35 to 45°C for another two hours. (Several attempts were made differing in temperature and length of the reaction time). The product of the reaction (mainly compound (xxiv)) was precipitated with sodium dry diethyl ether. Further purification included several recrystallisations from dried chloroform/carbon tetrachloride and dry diethyl ether. The isolated substance was dried under high vacuum for several days and stored in a dessiccator over phosphorus pentoxide.

Identification of the compound (xxiv)

a) Molecular weight determined via bromide titration utilising 0.1 M. $AgNO_3$ solution and potassium chromate as indicator[114]. M.W. was 298 ± 1% (For $C_{10}H_{20}NO_4Br$ M.W. = 298).

b) N.M.R. in chloroform solution indicated: one singlet corresponding to three methyl groups attached to nitrogen ( $\tau$ = 6.18); one quartet due to two ethylene groups ( $\tau$ = 5.62), and one triplet due to two methylene groups ( $\tau$ = 8.66) in alcoholic part of the ester.

c) M.p. 127°C (Lit. m.p. 122 - 123°C)[65]

d) Analysis: Found: C, 40.3; H, 6.81; N, 4.60; O, 21.42%. Calculated for $C_{10}H_{20}NO_4Br$: C, 40.3; H, 6.70; N, 4.70; O, 21.5%.

A by-product of the reaction described above was 2-(trimethylammonium bromide) ethylacetate (xxvii)The amount of(xxvii) produced varied from about 2% to 20%; the percentage increasing as the temperature of the reaction was raised. This compound was isolated from chloroform solution of the crude reaction product by precipitation with a small amount of diethyl ether and purified by recrystallisation from the same solvents. This substance melted at 154°C (Lit. m.p. 158 - 9°C). Molecular weight, determined by titration with 0.1 M. $AgNO_3$ was found to be 226 ± 0.5% (for $C_7H_{16}NO_2Br$ M.W. = 226). I.R. spectrum was almost identical to that of the same compound via different route (described below).

Analysis: Found: C, 37.14; H,6.94; N, 6.17%. Calculated for $C_7H_{16}NO_2Br$ C, 37.1; H, 7.09; N, 6.20%.

9) 2-(trimethylammonium chloride) ethylacetate

The above compound was prepared according to the method described by Jackson and Marvel[115].

An alcoholic solution of trimethylamine (excess) was added slowly to an alcoholic solution of ethylchloroacetate (prepared by acid-catalysed esterification of chloroacetic acid in absolute ethanol) and left overnight at room temperature.

The excess of solvent was removed under reduced pressure and the residue treated with diethyl ether. Crude precipitate was recrystallised from chloroform/dry ether or absolute ethanol/dry ether, and dried under vacuum for several days. Titration with 0.1 M. $AgNO_3$ showed M.W. to be 182 (for $C_7H_{16}NO_2Cl$ M.W. = 181.5). M.p. 156 - 157° (Lit. m.p. 166 - 7°C; 157 - 158°C - very hydroscopic compound). The amount of 0.1 M NaOH used for hydrolysis of the ester group (pH-stat method) agreed with calculated amount within ± 0.2%. The product of the hydrolysis was acidified with 1 M. HCl solution and precipitated with acetone. I.R. spectrum was identical with betaine hydrochloride.

Analysis: Found: C, 39.27; H, 7.74; N, 8.71%. Calculated for $C_5H_{12}NO_2Cl$ C, 39.1; H, 7.80; N, 9.12%.

10) 2,2-dibromo diethylmalonate

Commercially available (An. Eastman Chemical) compound was further purified by distillation under vacuum. The middle fraction which distilled at constant temperature was utilised for the kinetic measurements.

11) 2,2-dichloro diethylmalonate

Concentrated ethereal solution of 2,2-dichloromalonic acid (preparation of the acid described already) was further treated with absolute ethanol (excess) and HCl gas which was allowed to bubble through the solution for 24 hours[113]. The reaction mixture was then washed several times with water and the above ester extracted with diethyl ether. The bulk of the solvent was removed on a rotary film evaporator and the residue dried overnight with sodium sulphate. After removal of the drying reagent and the rest of the solvent, the ester was purified by distillation under reduced pressure (b.p. 108°C/12mm. Lit. b.p. 110-13°C/13 mm.).

Solvents and Reagents

In the equilibria and kinetic studies deionised water was utilised in making up all the solutions.

B.D.H. dioxan was purified by the method described in Vogel[116]. In order to minimise contact with the atmosphere, the dioxan container was flushed with nitrogen each time when opened.

Commercially available chloroform and carbon tetrachloride were dried over anhydrous calcium chloride, and distilled.

Absolute ethanol (Analar) was used without further purification.

Other solvents used in preparations of the compounds were used as commercially purchased.

Acids like HCl, $HClO_4$ or $H_2SO_4$ utilised for the kinetic measurements were Analar; neutral salts: KCl, LiCl, $NH_4Cl$ and $CH_3COONa$ were Analar and used without further purification.

Other reagents like sulphuryl chloride, phosphoryl chloride trimethyl amine (in absolute ethanol solution), p-nitrophenol, malonic acid, 2-bromo-diethylmalonate, chloroacetic acid and aniline were used as commercially available and without further purification.

## PART IV

### References


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