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STUDIES ON THE DECARBOXYLATION OF MALONIC ACIDS

A Thesis

Presented for the Degree of

Master of Science

in the Faculty of Science of the

University of St. Andrews

by

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St. Salvator's College,

1966.

St. Andrews.



(ii)

I declare that this thesis is a report of the results of my own research work and that it has not been submitted to any other institution for a Higher Degree.

The thesis describes the results of research work carried out at the Chemistry Department, St. Salvator's College, University of St. Andrews under the supervision of Dr. B.C. Challis, since September 1965.

(iii)

I hereby certify that Miss Shiela Kerr has spent four terms at research work under my supervision, has fulfilled the condition of University Court Ordinance 338 (St. Andrews No. 51) and is qualified to submit the accompanying thesis in application for the Degree of Master of Science.

Director of Research.

ABSTRACT

Previous studies on the mechanism of the thermal decarboxylation of monobasic, β -keto, unsaturated and dibasic carboxylic acids are reviewed. Two methods for calculating theoretically the isotope effects expected in organic reactions are also discussed.

The relative decarboxylation rates of a series of α -phenylmalonic acid derivatives in non-protonic solvents are reported, and the data give the first diagnostic evidence that an intramolecular proton transfer is essential to the process of decarboxylation.

Observed isotope effects for malonic acid in aqueous media and in dioxan, and for α,α' -dimethyl-malonic acid in aqueous media, are reported and compared with theoretical values of the isotope effect as calculated by two distinct methods. The results suggest that the mechanism of decarboxylation takes place through a cyclic hydrogen-bonded transition state. The rate of decarboxylation of malonic acid is not found to be catalysed by strong acids.

A preliminary investigation of the rate of hydrolysis of diethyl α,α' -dibromomalonate is also reported.

ACKNOWLEDGEMENTS

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SECTION I

INTRODUCTION

PART I

The Historical Survey

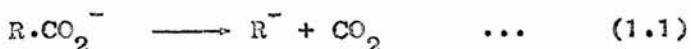
The general utility of decarboxylation as a technique for both the degradation and the synthesis of organic molecules, and its importance as a biological process, has led to innumerable investigations of this reaction over the last one hundred years. The earliest physical chemists used their results, derived mainly from studies of the rates of decarboxylation of organic acids in solution, to formulate the theory of unimolecular reactions, whereas organic chemists developed the reaction for its synthetic utility. More recently, however, the principal concern of many workers has been to elucidate the mechanism by which decarboxylation takes place.

It is apparent from these investigations that the process of decarboxylation can occur via several mechanistic pathways depending on both the acid involved and the experimental conditions. The various mechanisms are listed below and for discussion, at least, can be conveniently subdivided into unimolecular and bimolecular reactions of various kinds.

Unimolecular

(a) A reaction in which the organic acid

decarboxylates in the form of its anion, equation (1.1) has been well established for many organic acids



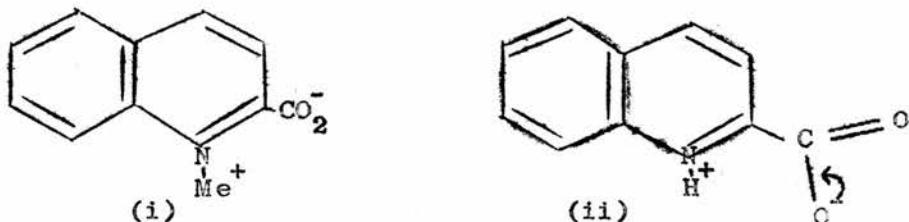
containing electron withdrawing substituents, (such as trichloroacetic and nitroacetic acids), which stabilise the carbanion R-. A detailed discussion of the evidence for this thermal, base catalysed reaction is deferred until later, in the section dealing with the thermal decarboxylation of monobasic acids.

(b) In some cases, for example in the decarboxylation of quinaldic¹ α -picolinic² and α -methyl- α -2pyridylbutyric³ acids, the anion appears to be stable whereas the free acid readily decarboxylates via a unimolecular process. The free acid is postulated to exist as a zwitterion, equation (1.2), and the activation energy for the



decarboxylation of this species might be expected to be lower than that for the corresponding acid anion: thus the zwitterion should react preferentially. Evidence for this mechanism in the case of quinaldic acid is that the

anion is stable under conditions which cause decomposition of the free acid. Also the methylbetaine of the acid (i) decomposes very readily, and therefore Brown and Hammick¹ concluded that the analogous zwitterion (ii), and not the free acid, decarboxylated.



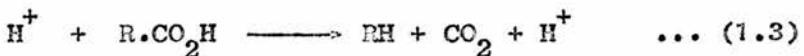
The two unimolecular reactions, (a) and (b), are really quite similar and the relative importance of each type of decomposition depends on the molecular structure of the acid concerned. In the case of acids where zwitterion formation is not favoured due to the presence of strong electron withdrawing groups, mechanism (a) predominates, the negative substituents in R- reducing the activation energy for the heterolytic fission of the carbon-carbon bond sufficiently to enable decarboxylation to occur more readily.

(c) A further series of acids, namely dicarboxylic, β -keto carboxylic and unsaturated acids, also decompose

on heating via a unimolecular path. The mechanism of these reactions is also discussed in detail later.

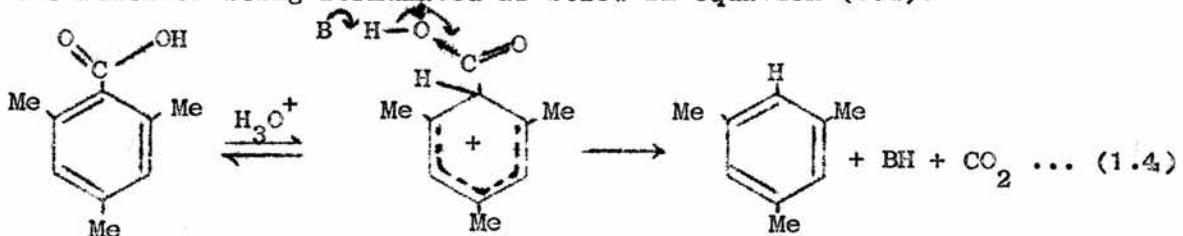
Bimolecular

(a) Decarboxylation can also proceed via a bimolecular acid catalysed path. Schenkel and Schenkel-Rudin⁴ first proposed this mechanism, equation (1.3), to account for the reaction of anthracene-9-carboxylic acid, where the rate

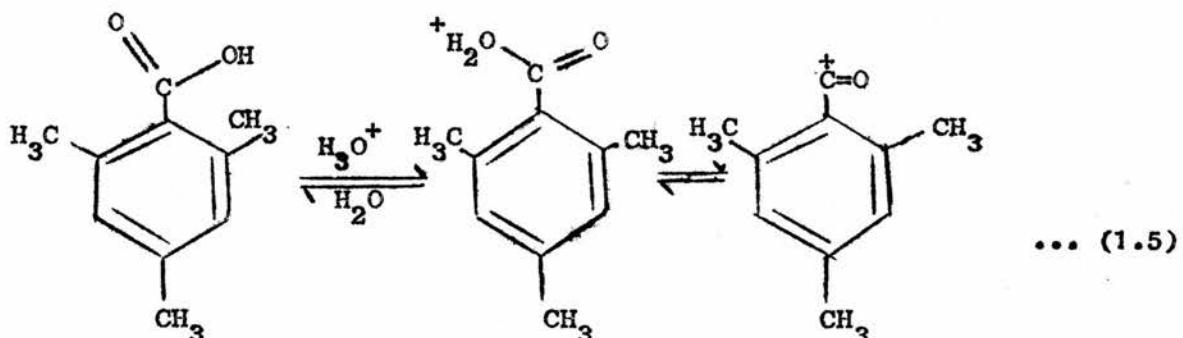


of decarboxylation increased qualitatively with increase of hydrogen ion concentration.⁵ Other acids thought to decarboxylate similarly were hydroxybenzoic acids⁶ and substituted cinnamic acids.⁷

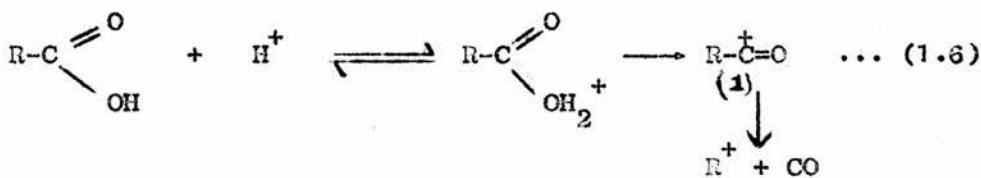
Studies of mesitoic acid⁸ showed apparent hydronium catalysis in aqueous solutions of less than 80% H_2SO_4 , the reaction being formulated as below in equation (1.4).



In more concentrated sulphuric acid solutions, however, Schubert⁹ showed by cryoscopic studies that the equilibrium below, equation (1.5), occurred with formation of a stable acyl cation.



Recent nuclear magnetic resonance studies on a series of carboxylic acids¹⁰ in very concentrated sulphuric acid solutions provided further evidence for a decarbonylation rather than a decarboxylation reaction. The mechanism of the decarbonylation reaction was postulated as in equation (1.6) to proceed via an acyl



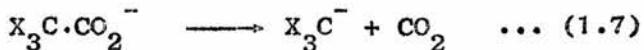
cation (i). This evidence seems to imply that a bimolecular, acid catalysed decarboxylation occurs only in more dilute acid solutions and may be replaced by a decarbonylation mechanism at high acidities.

There is considerable evidence in the literature to support the operation of nearly all these reactions. As this evidence is well documented in several recent

reviews,^{11,12,13} the historical aspects of the thermal uncatalysed reaction only will be considered in detail here, since this particular reaction was the subject of the present investigation. As mentioned previously three general classes of acids undergo thermal decarboxylation: monobasic acids containing strongly electron withdrawing groups such as nitro and halogen, β -keto and unsaturated acids, and dicarboxylic acids.

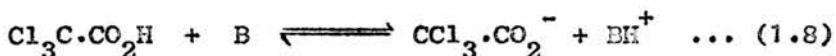
Monobasic Acids.

Early kinetic investigations by Verhoek,^{14,15} and Johnson and Moelwyn Hughes,¹⁶ on the trihalogeno-acetic acids, which gave good first order rate coefficients for decarboxylation led these workers to conclude that only the acid anions underwent decomposition, equation (1.7).

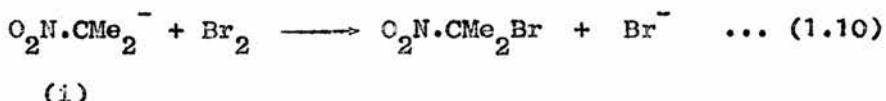
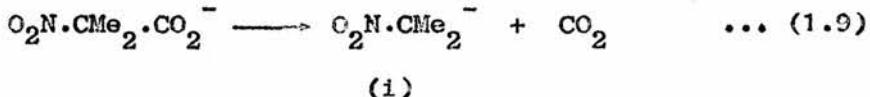


The main evidence to support their conclusion was that, although these acids were almost completely ionised in water and they did not form zwitterions, the activation energies for decarboxylation of the acids, and their sodium salts, in water¹⁷ were closely similar, suggesting that only the anion decarboxylated. Furthermore, decarboxylation in non-ionising solvents, e.g.

toluene, was found to be 10^7 times slower than the rate in water. In non-aqueous solvents, which, like non-ionising systems, would give rise to small concentrations of anion, the rate of decarboxylation was proportional to the concentration of anion formed by addition of base B, equation (1.8).



Investigations by Pedersen¹⁸ on α -nitroisobutyric acid showed this acid to decarboxylate at a rate equal to the rate of absorption by the system of added bromine. Since the product formed after normal loss of carbon dioxide, 2-nitropropane, would not react with bromine under the reaction conditions. Pedersen suggested that the data was consistent with the formation of an intermediate anion (i) which could then react with bromine, equations (1.9) and (1.10).



Similar studies on α -nitroacetic acid¹⁹ showed the

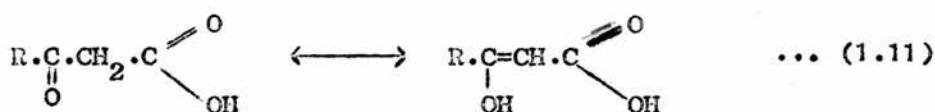
presence of an anionic intermediate formed by decarboxylation of the univalent acid anion.

There are a number of other cases where there is clear evidence that the anion readily decarboxylates whereas the acid itself does not, including 2,4,6-tri-nitrobenzoic acid in solvent alcohol²⁰ and phenylpropiclic acid.²¹

The characteristic feature of all the monobasic acids known to decarboxylate thermally in the anionic form is the presence of strong electron withdrawing substituents δ to the carboxyl group. These presumably stabilise the resulting carbanion and therefore assist in the elimination of carbon dioxide.

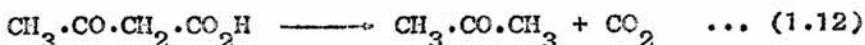
β -Keto Carboxylic and Unsaturated Acids.

The fact that β -keto carboxylic acids readily decarboxylate, but the α - and γ -isomers do not, was correlated with tautomerisation of the β -isomer to give a keto and an enol tautomer as below, equation (1.11).

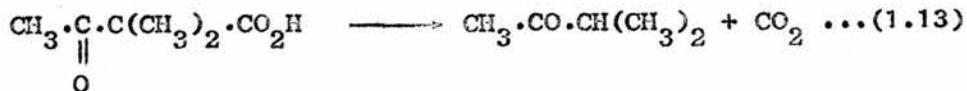


Early investigations on acetoacetic acid by Engfeldt,²² Widmark,²³ von Euler,²⁴ and Llunggren²⁵

in the 1920's showed that both the free acid and the anion were unstable in aqueous solution, but the rate of decarboxylation of the free acid, equation (1.12) was faster than that of the anion. The reaction was also

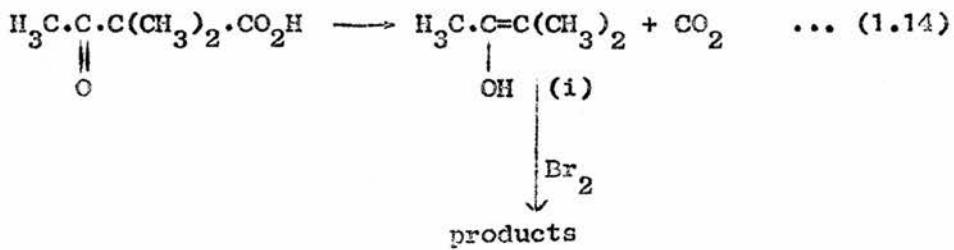


found to be strongly catalysed by primary- and slightly by secondary- amines, but was insensitive to the presence of tertiary amines. From this early work on acetoacetic acid, it was not clear whether decarboxylation occurred via the keto or the enol form. To resolve this problem Pedersen²⁶ studied α,α' -dimethyl-acetoacetic acid, equation (1.13) which could only



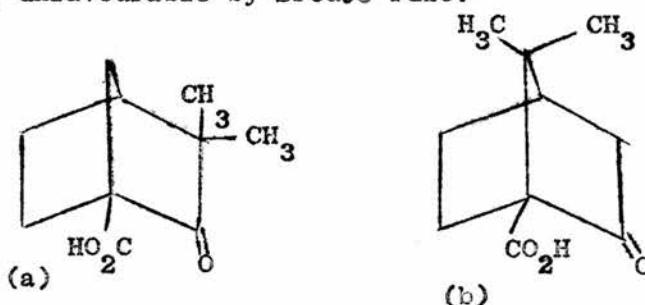
exist in the keto form, and found this to decarboxylate 4.5 times faster than the rate of decomposition of acetoacetic acid²⁵ at the same temperature. This finding clearly showed the keto form to decarboxylate, and a similar conclusion was drawn by Bredig and coworkers^{27,28} from similar studies with camphor-carboxylic acids. Since the α,α' -dimethylacetoacetic

acid, existing only in the keto form, decarboxylated quicker than acetoacetic acid existing as a mixture of keto- and enol- tautomers, the keto form was reasonably suggested as the unstable species in both cases. Further, by kinetic measurements on the bromination of α,α^1 -dimethylacetooacetic acid, and by comparison with the rate of evolution of carbon dioxide, Pedersen showed that bromine addition occurred at the same rate as keto acid decarboxylation. He therefore suggested that the decarboxylation of β -keto carboxylic acids led directly to the enol form (i) of the reaction product, which then reacted with bromine, equation (1.14).

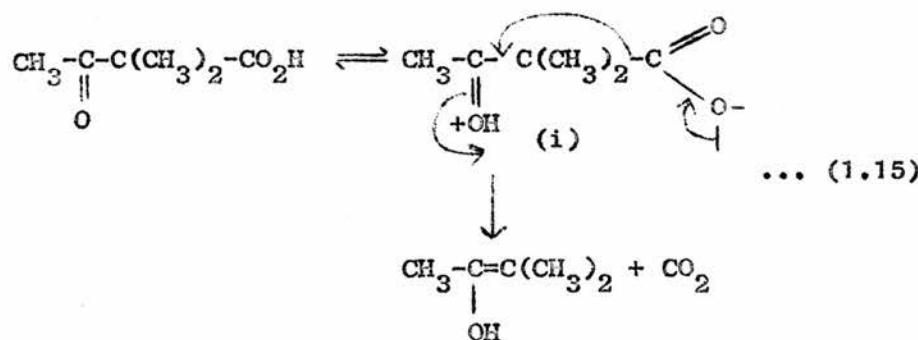


Further verification for the formation of an enol product arose from the fact that β -keto acids did not decarboxylate on heating if the enol product was unfavourable on energetic grounds. Thus bicyclic β -keto acids, such as camphenonic²³ (a) and

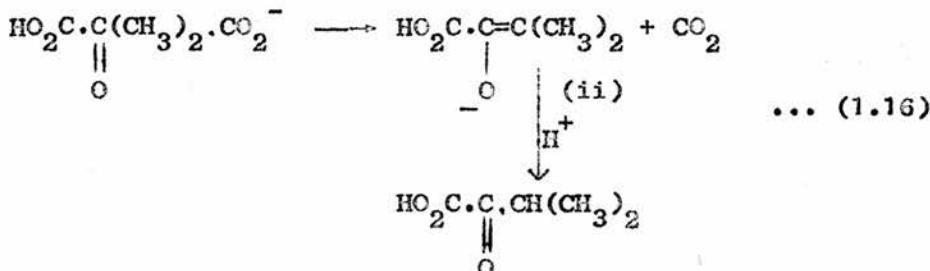
ketopinic³⁰ (b), were stable to heat because the enol tautomers resulting from decarboxylation would have double bonds at bridge-head positions, and this was very unfavourable by Bredts rule.³¹



In the light of all the evidence, Pedersen formulated a mechanism for the decarboxylation of α, α' -dimethylacetoacetic acid in which, owing to the weakly-basic properties of the keto group, there would be a slight tendency for protonation leading to the formation of a zwitterion: because of the electronic-attraction of the positive charge, this zwitterion (i) would be expected to decompose more quickly than a monovalent ion, equation (1.15).

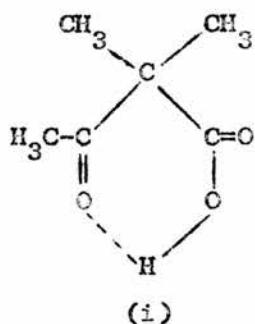


The enol intermediate postulated by both Ercdt and Pedersen was finally and completely established by a study of the decarboxylation of dimethyloxalo-acetic acid³², equation (1.16), as in this case the enol tautomer (ii) is relatively long lived and may be detected by ultraviolet spectroscopy.



The intermediate formation of a dipolar ion in the decarboxylation of β -keto acids was readily accepted by most workers until 1941. Then Westheimer and Jones³³ studied the decarboxylation of acetoacetic acid in a series of solvents of varying dielectric constant. They reasoned that, since the work of separating a positive and negative charge to form a dipolar ion should increase with decreasing dielectric constant of the medium, reactions taking place by way of a highly polar activated complex should proceed much more rapidly in solvents of high rather than low dielectric constant. This notion

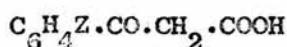
had been verified previously by other workers for the preparation of quaternary ammonium salts,³⁴ and for the hydrolyses of tertiary halides.³⁵ Westheimer and Jones, however, could find no diminution in the rate of decarboxylation in solvents of low dielectric constant, and therefore concluded that a zwitterion was not an intermediate in the reaction. As an alternative they suggested that a chelate ring (i) was the intermediate in the decarboxylation of β -keto carboxylic acids. This



conclusion was consistent with all the known experimental findings and particularly with the formation of an enol product in decarboxylation.

The mechanism of decarboxylation of β -keto acids was studied further by Swain and his coworkers³⁶ who, in 1961, measured the primary isotope effect ($\frac{k_U}{k_D}$) for a series of substituted benzoylacetic acids (i) and

their deuterated analogues (ii) in solvent benzene at 50° C. The observed variation in isotope effect



(i)



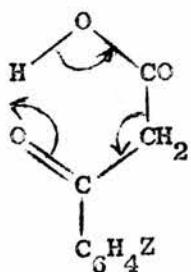
(ii)

with substituents [v. Table (II)] was regarded as being

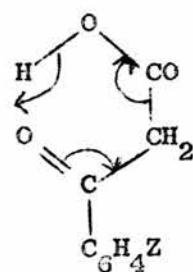
TABLE (I.I)

<u>Substituent Z</u>	$\frac{k_H}{k_D}$
m-nitro	2.8
p-chloro	1.7
H	1.4
p-methyl	0.85

more consistent, considering the physical differences between the two transition states, with a cyclic proton transfer (i) than with a cyclic hydride mechanism (ii).



(i)

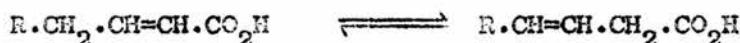


(ii)

The observation that the substituents Z- had very little effect on the OH vibrational frequencies in the ground state, as verified by infrared measurements, strongly suggested that the variation shown in TABLE (I.1) for $\frac{k_H}{k_D}$ arose from differences in the transition state configuration. In benzene, the keto acid was shown to exist in the un-ionised, chelated, form by cryoscopic experiments, and this species was thought to be the active form for decarboxylation. In water, however, the evidence was less certain, although Swain and his coworkers favoured reaction via a cyclic, hydrogen-bonded transition state over a dipolar ion. Subsequent studies, however, concerned with the determination of volumes of activation for this particular decarboxylation lead to the opposite conclusion. These results are discussed further in the section dealing with dibasic acids.

Further evidence for the formation of cyclic transition states in decarboxylation reactions comes from several studies of unsaturated acids. In a series of papers published between 1925 and 1930, Linstead and coworkers³⁷ established that α,β - and β,γ -unsaturated acids would frequently isomerise via a simple prototropic

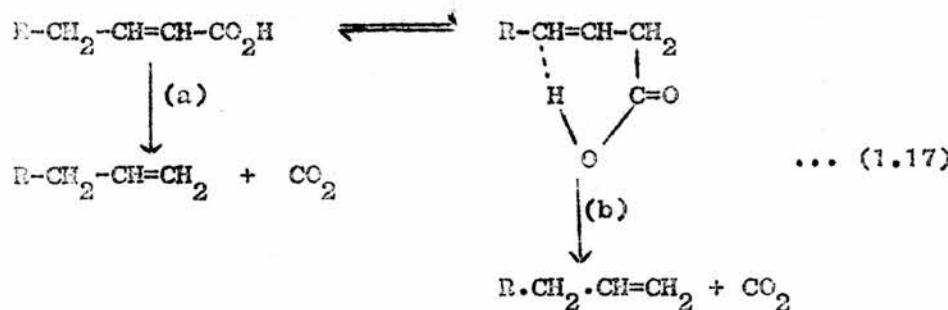
shift, and that the thermal decarboxylation of α,β -unsaturated acids (i) might actually proceed via the β,γ -isomer (ii) as an intermediate.



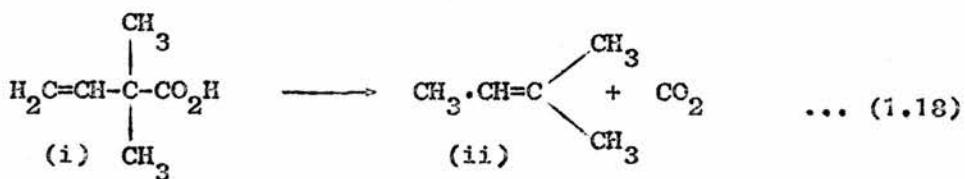
(i)

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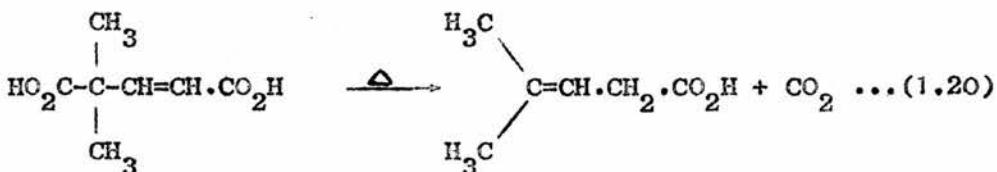
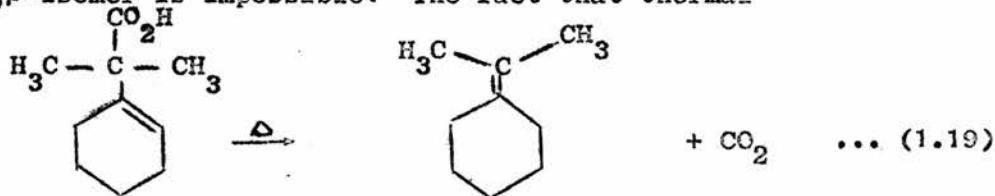
In 1950 two possible mechanisms, equation (1.17) were suggested for the thermal decarboxylation of unsaturated



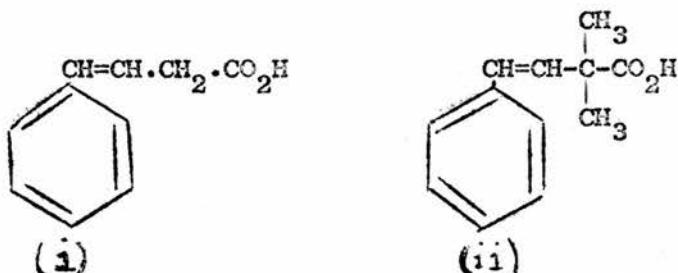
acids by Arnold, Elmer and Dodson.³⁸ (a) was essentially an acid catalysed reaction, similar to that verified for cinnamic acids,³⁹ and (b) took place via a cyclic transition state, similar to the mechanism postulated for decarboxylation of β -keto carboxylic acids. To resolve these possibilities, they studied the pyrolysis of 2,2'-dimethylbuten-3-oic acid (i) and verified the only product as 2-methylbuten-2 (ii), equation (1.18).



In the above example, as in the cases of two other acids examined by earlier workers,^{40,41} equations (1.19) and (1.20), rearrangement of the β, γ -isomer to its α, β -isomer is impossible. The fact that thermal

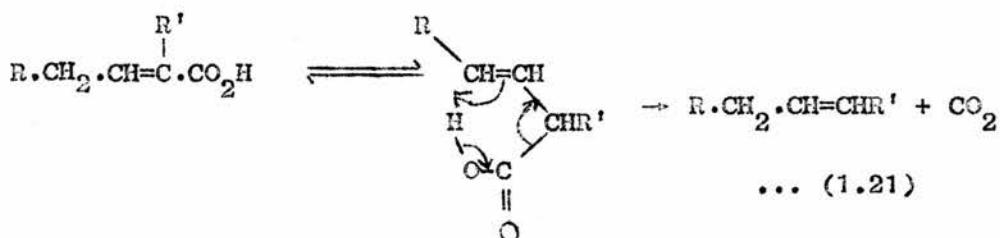


decarboxylation occurred easily in all three cases showed the β, γ -form to be unstable. On looking at 4,4'-dimethylpenten-2-oic acid, which could only exist in the α, β -form, no decarboxylation occurred even on heating for two hours at 300°C . This work inferred decarboxylation to take place by route (b) where the α, β - and β, γ -isomers were in equilibrium and the latter was unstable. The thermal stability of styrylacetic acid⁴² (i) and α, α' -dimethylstyrylacetic acid³³ (ii), where isomerisation to the β, γ -form would not be favoured due to

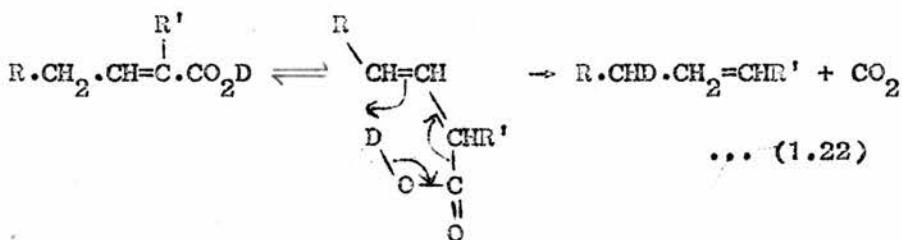


destruction of the conjugated system, points also to the thermal stability of α,β -unsaturated acids.

In 1963 Bigley⁴³ produced a convincing proof of this mechanism, equation (1.21) by showing that, when



$R' = H$, a terminal olefin was formed despite the greater stability of the internal isomer, whereas, when $R' =$ alkyl, trans olefins were formed. Furthermore, for compounds where the carboxylic hydrogen had been replaced by deuterium, product analysis showed that, concurrent with decarboxylation, the isotopic hydrogen had been transferred to the δ -carbon atom, equation (1.22).

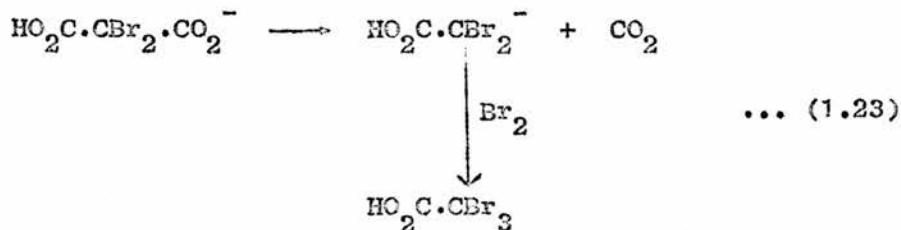


In conclusion, it is clear that the decarboxylation mechanisms of β -keto carboxylic acids and β, γ -unsaturated acids are similar and that the evidence points to the formation of a cyclic transition state in which the H atom of the ejected carboxylic group is transferred, in the former case to oxygen, and, in the latter case to the γ -carbon atom. Further evidence for the nature of the transition state in the reaction of β -keto acids is discussed in the next section, that dealing with dibasic acids for which an analogous mechanism of decarboxylation has been suggested.

Dibasic Acids.

Early studies on dibasic acids, including malonic⁴⁴ and substituted malonic acids,⁴⁵ yielded little evidence for the mechanism of decarboxylation. These investigations did establish, however, that the reaction was first order in malonic acid concentration.

Later, Muus⁴⁶ working with α, α' -dibromomalonic acid found the rate of uptake of bromine during decarboxylation equal to the decarboxylation rate, and, in aqueous solutions at various hydrogen ion concentrations, the decarboxylation rate was proportional to the concentration of the monoanion, equation (1.23).

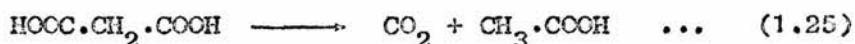
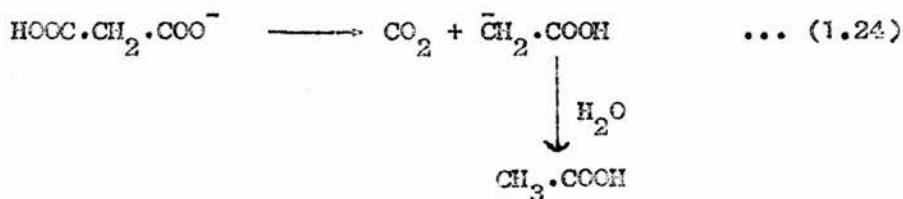


It therefore appeared that, as for monobasic acids, the monoanion and not the undissociated acid was the unstable species, but subsequent work showed subtle differences from the mechanism for monobasic acids.

In 1938 Fairclough²¹ studied the decarboxylation, in aqueous solutions, of sodium hydrogen malonate: by comparing his derived rate coefficients with those obtained for malonic acid itself by Bernoulli and Wege,⁴⁴ he found the monoanion to decarboxylate five times slower than the free acid. The dianion was observed to be completely stable to heat. A different decarboxylation mechanism must therefore exist for dibasic acids as compared to monobasic acids, and Fairclough, recognising this, drew attention to the enhanced activity of the free acid in the reactions of β -keto carboxylic and dibasic acids, and also for oxalic acid⁴⁷ as studied by Dinglinger and Schröer. The analogous behaviour of these acids strongly pointed to some similarity in their mechanism of decarboxylation.

A mechanism, like that advanced by Westheimer and

Jones for β -keto acids, was first suggested for substituted malonic acids by King⁴⁸ in 1947, but more convincing proof of the decarboxylation pathway came with Hall's work in 1948.⁴⁹ He examined the effect of both substrate concentration and hydrogen ion concentration on the decomposition rates of malonic acid. Over a pH range 0.4 → 4.89 at 20°C to 90°C, the reaction was always first order in the stoichiometric concentration of malonic acid. The rate varied, however, with solvent acidity and, although constant at pH values below 1 and above 4.5, increased with decreasing pH between these limits. The most reasonable interpretation of the data was to assume that decomposition of malonic acid occurred by two concurrent mechanisms involving the monoanion, equation (1.24), and the neutral molecule, equation (1.25), respectively.



From Fairclough's earlier work,²¹ the free acid was known to decompose faster than the monoanion. Hall

therefore suggested that increasing the hydrogen ion concentration increased the concentration of malonic acid, until, at a pH of less than 1, a maximum rate of reaction, corresponding only to the free acid decomposition, equation (1.25), was observed. At higher pH values, some monoanion would be present and the rate was therefore slower. The minimum rate of decomposition at approximately pH = 4.5 corresponded to the decomposition of monoanion itself, equation (1.24). At very high pH values above 4.5 a further drop in rate would be anticipated, owing to an increasing concentration of the stable dianion.

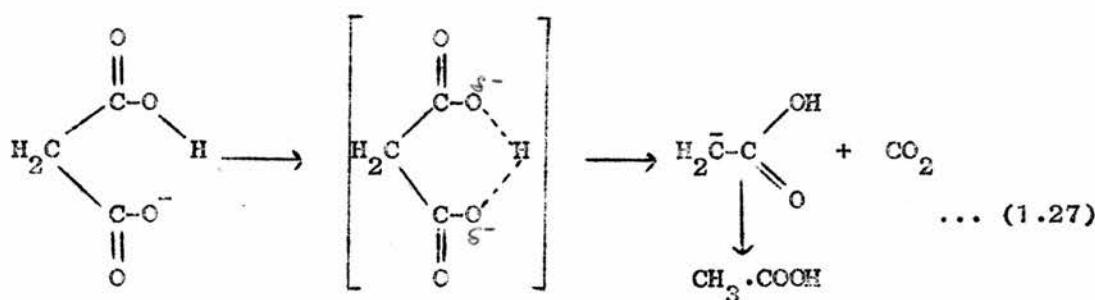
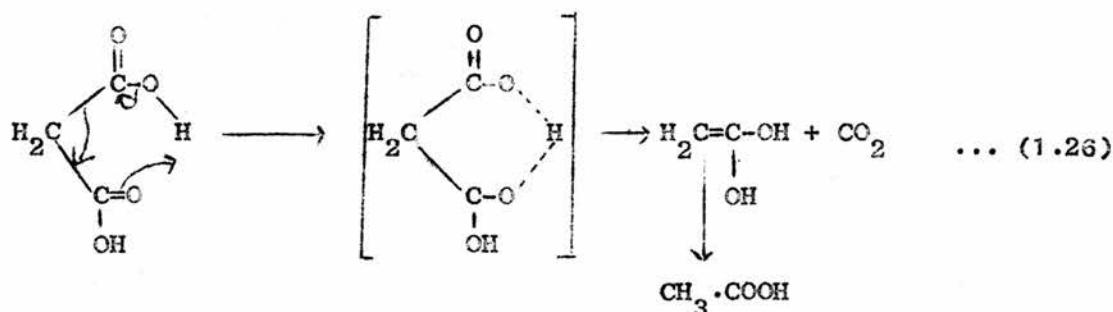
Hall found the free acid to react ten times faster than the anion[(v. TABLE (I.2)], but in deriving the rate coefficient for the anion reaction, ionisation of the acetic acid formed as product, which would change the pH value throughout the course of the reaction, was neglected. The omission of this factor casts some doubt on Hall's value for the relative rates of free acid and monoanion decarboxylation. His work accorded

TABLE (I.2)

$$k_{80} \times 10^6 \text{ sec}^{-1} \quad k_{90} \times 10^6 \text{ sec}^{-1} \quad E_{80 \rightarrow 90} \text{ K.cals.}$$

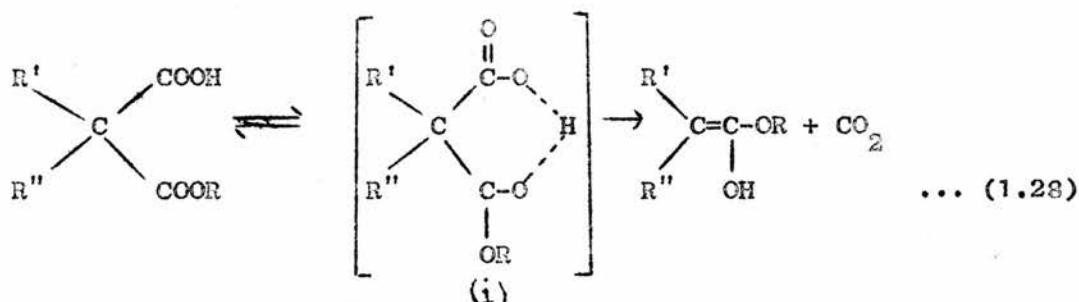
Malonic acid (k_1)	2.12	7.11	30.8
Acid Malonate ion (k_2)	0.24	0.71	28.5

well, however, with the idea of decarboxylation occurring via cyclic, hydrogen-bonded, transition states, as shown in equation (1.26) for the neutral molecule and in equation (1.27) for the monoanion, respectively, but was not unequivocal proof of their existence.



In 1951, Kenyon and Ross⁵⁰ studied the decarboxylation of a series of optically active acids in which the molecular assymmetry resided in the carbon atom α to the carboxyl group. If, during the course of the reaction, a double bond was formed between C^α and C^β as indicated by the intramolecular mechanism of decarboxylation, equation (1.28), then the assymmetry should be lost and the decarboxylation product

would inevitably be racemic. In the case of the two substituted



malonic acid derivatives investigated, both gave racemic products, consistent with the proposed mechanism, but the investigation did not provide any evidence as to the exact nature of the transition state (i).

Many investigations have been concerned with the measurement and interpretation of the C-isotope effects for decarboxylation reactions in which one carboxylic carbon of malonic acid was replaced by C^{13} or C^{14} .^{51,52,53} The data was interpreted by comparing the observed values with those obtained theoretically using the Bigeleisen method. Excellent agreement between theoretical and observed values in the case of C^{13} effects was found, but the observed values for C^{14} substitution⁵⁴ were generally very much greater than the theoretical calculations predicted. Although these results were independent of the position of the proton in the transition state⁵⁵ and did not help to elucidate this aspect of the mechanism, the anomalous results obtained using C^{14} led Gelles⁵⁶ in 1953 to study the kinetics of

the decarboxylation of α -phenylmalonic acid in aqueous solutions of various pH. Assuming the free acid only to exist in the pH range $0.7 \rightarrow 1.0$, and the monoanion to exist from pH $4 \rightarrow 6$, he found the monoanion to decarboxylate unimolecularly three times faster than the unionised acid. The dianion was stable. On comparing the data for malonic, α, α' -dibromomalonic and α -phenylmalonic acids [v. TABLE (I.3)], the introduction of electron withdrawing substituents was reflected in a greatly increased rate of fission of the carbon-carbon bond in both the unionised acid and the mono-anion.

TABLE (I.3)

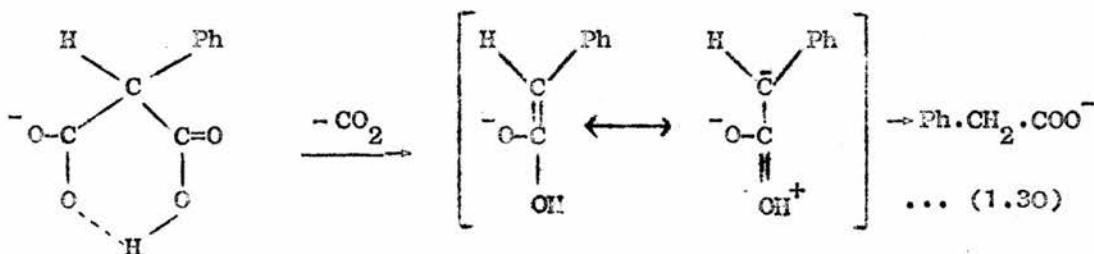
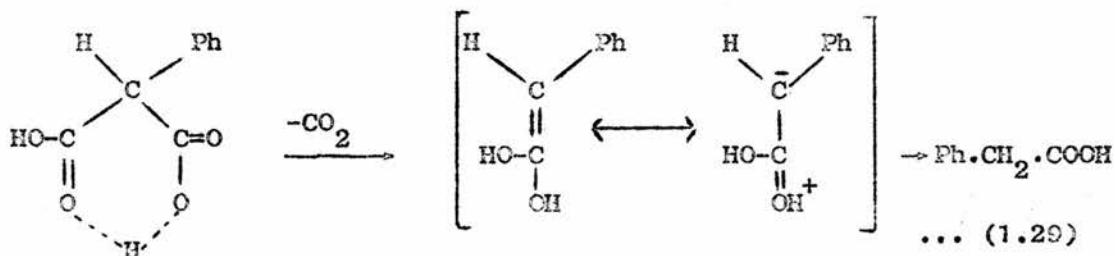
Acid	$10^4 k_e (\log_e, \text{hour}^{-1})$	$10^4 k_e^1 (\log_e \text{hour}^{-1})$
α, α' -Dibromomalonic ⁴⁶	25000	25000
α -Phenylmalonic ⁵⁶	112	350
Malonic ⁵⁰	1.4	0.2

The same general inductive effect is also apparent in the acid dissociation constants for these compounds [v. TABLE (I.4)].

TABLE (I.4)

Acid	$K_1 \text{ mole l.}^{-1}$	$K_2 \text{ mole l.}^{-1}$
Malonic	1.4×10^{-3}	2.1×10^{-6}
α -Phenylmalonic	2.6×10^{-3}	9.4×10^{-6}
α, α' -Dibromomalonic	1	10^{-2}

Gelles explained these results on the basis of an intramolecular proton transfer leading to the formation of negative charge on the α -carbon atom in the transition states, equations (1.29) and (1.30). The stability of the dianion which does not decarboxylate, could then be ascribed to the



high electron density in the carbon-carbon bonds making it difficult for the negative charge, produced on loss of carbon dioxide, to be accommodated in the transition state. In the monoanion reaction for malonic acid itself, equation (1.26), the greater electron density in the carbon-carbon bonds of the initial state would be expected to result in the negative charge, produced on loss of carbon dioxide, being accommodated less

readily than in the free acid reaction, thus resulting in an enhanced rate of reaction for the free acid, as found experimentally. In α -phenylmalonic acid, however, the inductive effect of the phenyl group was thought to assist the reaction in both cases, equations (1.29) and (1.30), by a delocalisation of the negative charge produced on loss of carbon dioxide. The introduction of the α -phenyl group would then be expected to assist formation of the more negative transition state, equation (1.30), relative to the less negative transition state, equation (1.29), leading to an increased rate of reaction for the monoanion compared to the free acid, and this also agrees with the experimental results.

Hall and Hanrahan⁵⁷ have recently compared the entropies of activation for the decarboxylation of substituted malonic acids. Their results are tabulated below [TABLE (1.5)] and qualitatively support the notion of a cyclic transition state.

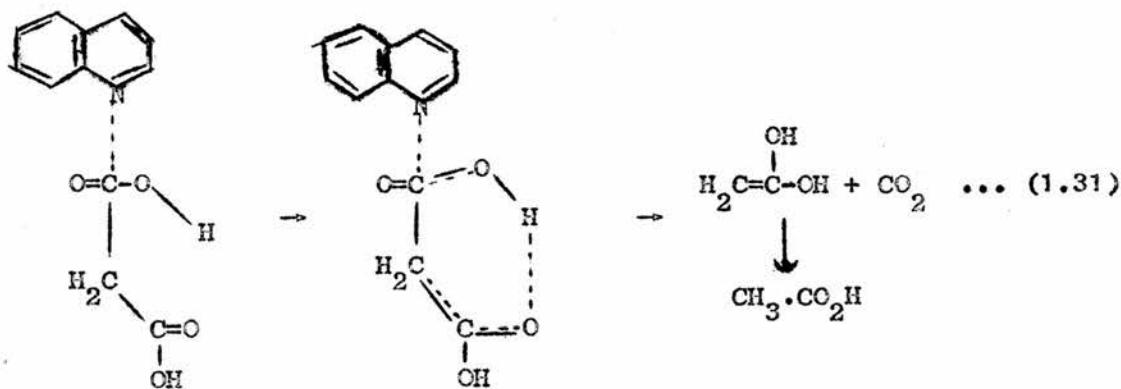
TABLE (1.5)

Acid	Solvent		80% Dioxane	
	Water	HA^-	H_2A	HA^-
Malonic	H_2A	HA^-	H_2A	HA^-
Malonic	-2	+1	-9	-2
α, α' -Dibromomalonic	-	+15	-	+4
α -Phenylmalonic	-8	+5	-14	-2

The simple explanation is that an intramolecularly hydrogen-bonded species in the initial state would lead to a less negative entropy of activation, because of the closer similarity between the initial and transition states. Since internal hydrogen-bonding is expected to be more extensive in the monoanion, than in the undissociated acid, decarboxylation of the former should proceed with a smaller, (i.e. less negative), entropy of activation. The data also showed that internal hydrogen-bonding in the initial state, was more extensive in water than in dioxane. It must be noted, however, that the differences in activation entropies are quite small, whereas the uncertainties in their estimation are reasonably large. The latter observation is particularly pertinent to the rate coefficients for the monoanion reaction, as no account was taken of the dissociation of the product α -phenylacetic acid which would change the pH of the solutions during the course of the reactions. Thus, although individual figures may have little relevance, the general trend supports reaction via an internal hydrogen-bonded transition state.

The catalysis of malonic acid decarboxylation by amines and other bases has been extensively studied. Although these results do not bear directly on the transition state

configuration of the thermal reaction, they provide insight and show that a single mechanism probably operates under widely different conditions. For the quinoline catalysis of malonic acid decarboxylation a mechanism involving solvation of the carboxylic carbon, equation (1.31) was suggested by Yankwich and coworkers.^{5C}



Carbon solvation was favoured over hydroxyl association, equation (1.32), mainly because the monoanion decomposed less rapidly than the free acid, and hydroxyl association would



represent an approach to anion formation. Further evidence in support of carbon solvation stemmed from the known interactions between carbon dioxide and amines providing

evidence of the nitrogen atom coordinating to carbon in an environment similar to that in the carboxyl group.⁵⁹ Also, larger amines exhibited steric hindrance, which affected their catalytic ability, and this effect was much larger than expected for hydroxyl association. Finally the values of the intermolecular carbon isotope effect for the diacid decarboxylation in quinoline, and its temperature coefficient, did not agree with values calculated by the Bigeleisen method for a thermal uncatalysed decarboxylation, indicating that some change occurred in the binding about the carboxyl carbon-atom in the initial state.

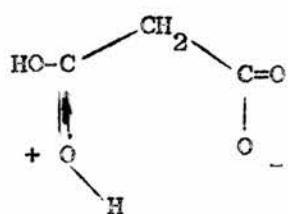
Extensive investigations on the influence of various solvents on the kinetics of the decarboxylation of malonic acid and substituted derivatives have been carried out by L.W. Clark.⁶⁰ The results in many solvents fitted a single isokinetic plot, indicating that the same mechanism, probably that involving solvation of the transition state, as suggested by Yankwich for the catalysis by amines, applied to widely varying conditions.

However, some slight modification to the mechanism suggested by Yankwich and coworkers was deemed necessary to explain the recent results for 1,1-cycloalkane dicarboxylic acids carried out by Abiel and Tien.⁶¹ Their attempt to demonstrate the

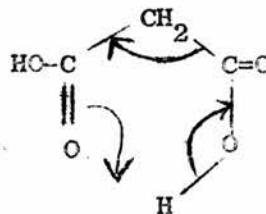
prime importance of strain in determining rates of decarboxylation, by consideration of the cyclic transition states formed in the decomposition of cyclopropane, cyclobutane and cyclopentane dicarboxylic acids led them to conclude that various complicating factors besides strain were involved, and that solvent interaction with a cyclic transition state, if it occurred, must form an intermediate lying closer to the initial than to the final state.

Further conflicting evidence on the mechanism of decarboxylation of both β -keto and dibasic acids has been cast by recent measurements of the activation volumes for several decarboxylation reactions including malonic, α,α' -dimethylmalonic, and acetoacetic acids.⁶² Thus the activation volumes for malonic acid were found to decrease stepwise through a range of 14 ml. as the polarity of the solvent decreased. Such a decrease in the values of the activation volumes has been found for other comparable reactions in which polar products result from non-polar reactants.⁶³ For example, the activation volume for the reaction of n-butylbromide with pyridine⁶⁴ decreased by 16 ml. on changing solvent from aqueous alcohol to toluene. The values for the activation volumes of malonic acid therefore tend to favour the dipolar intermediate (i), as initially

suggested by Pedersen,²⁶ rather than that proposed by Westheimer and Jones³³ (ii), although some development of charge might also be expected in the latter case.



(i)



(ii)

The authors suggested that the complications involved in determining the relation between free energy of activation and degree of solvation, as used by Westheimer and Jones, may have led to a wrong conclusion, as is also apparent from detailed studies of similar reactions.⁶⁵

Two investigations of hydrogen isotope effects for decarboxylation of dibasic acids have been reported previously. Blades and Wallbridge⁶⁶ studied the decomposition of molten $\text{CH}_2(\text{COOH})_2$ and $\text{CD}_2(\text{COOD})_2$, and found that the difference in the reaction rates ($\frac{k_{\text{H}}}{k_{\text{D}}}$) was much less than that predicted for a maximum primary isotope effect [v. TABLE(1.6)] as might be expected for intramolecular proton transfer arising from the formation of a cyclic transition state. They

concluded that such a low isotope effect could only be consistent with a mechanism in which the malonic acid was internally hydrogen-bonded in the initial state, and in which the transition state was very similar to the initial one.

TABLE (1.6).

Measured Values of $\frac{k_H}{k_D}$ for malonic acid.		Maximum Values of $\frac{k_H}{k_D}$ for a primary isotope effect.	
Temp.	$\frac{k_H}{k_D}$	Temp.	$\frac{k_H}{k_D}$
139.8°	1.09 ± 0.02	100°	6.6
145.3°	1.11 ± 0.01	200°	4.4

From both infrared⁶⁷ and thermodynamic⁶⁸ data for malonic acid and its monoanion, however, it seems very unlikely that there is any extensive hydrogen-bonding in the initial state, so their results may infer the existence of a modified type of mechanism. The other study of primary hydrogen isotope effects by Dunn and Warkentin⁶⁹ for α, α' -dimethyl-malonic acid showed a $\frac{k_H}{k_D}$ ratio of 4.5. This very different result could arise, however, from the method of kinetic analysis, involving the measurement of an intramolecular proton transfer in the intermediate, $(\text{CH}_3)_2\text{C}=\text{C}(\text{OH})\text{---OD}$.

Summary

For the thermal decarboxylation of monobasic acids, other than β -keto or unsaturated acids, the reactive species is restricted to the anions of those acids which contain strong electron withdrawing groups. The absence of any evidence to support decarboxylation of the free acid itself, except in those cases where zwitterion formation takes place, strongly suggests that the presence of, or formation of, carboxylate ion in the transition state is an important requirement of thermal decarboxylation.

Valuable circumstantial evidence of the mechanism of reaction is also given by studies of β -keto and unsaturated acids. The faster decarboxylation of the unionised acid as compared to the anion, in these cases, points to the importance of a proton transfer, either in the transition state or in a pre-equilibrium process, to give a dipolar ion which then reacts. Other evidence lends support to this conclusion, but does not allow a firm decision to be made between the two alternatives.

In the decarboxylation of dibasic acids, both the monoanion and the diacid can undergo reaction. The thermal stability of the dianion, on the other hand, has been interpreted as evidence for the importance of a proton

transfer occurring in the transition state for decarboxylation, although the formation of the dianionic product would also be energetically unfavourable. The experimental evidence circumstantially supports either the transfer of a proton in the transition state, or the pre-equilibrium formation of a dipolar ion, but does not allow any distinction to be made between these two alternatives. The measurement of hydrogen isotope effects to determine the extent of proton transfer in the transition state has led to the two conflicting values, as reported in the previous section: a value of 1.02 for malonic acid which has been interpreted as evidence against any proton transfer, and a value of 4.5 for dimethylmalonic acid, which suggests substantial proton transfer.

In view of this conflicting evidence, a detailed kinetic investigation was undertaken in an attempt to determine the mechanism of the thermal decarboxylation of several malonic acids, and the results are reported herein. This investigation followed two independent lines:

(1) An investigation of the rate of thermal decarboxylation of sodium ethyl α -phenylmalonate which contains no proton available for intramolecular transfer in the transition state. For comparison, the decarboxylation rates of hydrogen ethyl α -phenylmalonate, α -phenylmalonic acid and sodium hydrogen

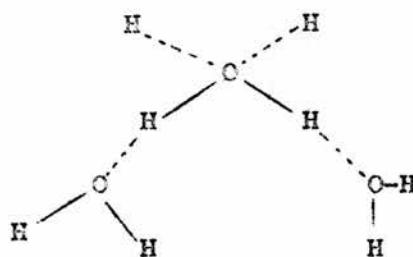
α -phenylmalonic acid was studied under similar conditions.

(2) A comparison of the thermal decarboxylation rates of malonic acid and α, α' -dimethylmalonic acid and their deuterated analogues under similar conditions. These results were analysed for evidence of transition state configuration by comparison with theoretical hydrogen-isotope effects calculated via two independent methods. The basis of these theoretical treatments is outlined below.

The Bunton and Shiner Treatment

Bunton and Shiner have discussed a scheme for calculating kinetic solvent isotope effects applicable to acid-base equilibria and also to reaction rates. The basis of their approach was that the experimental solvent isotope effects were due to changes in differential zero point energies between the initial and transition (or final), states of the reactions, (or equilibria), respectively. In aqueous media the initial, final and transition states would be bonded to solvent, the vibration frequencies of all the hydrogen bonds involved being affected. It was reasonably assumed that changes in frequency produced by bonding to acids would be proportional to the ease with which the acid tends to lose a proton i.e. its pK_a value, and in bases, similarly to their pK_b values.⁷¹ To introduce a measure of consistency the following rigid rules were proposed for all cases:-

(a) In the absence of solute, each water molecule is assumed to accept two hydrogens from, and to donate two hydrogens to other water molecules.



(b) All solute molecules are assumed to hydrogen bond to solvent water only.

(c) Solute molecules more basic than water will accept hydrogens from water for bonding, for as many electron lone pairs as are available. To calculate the frequency of these bonds the following equation (1.33) is used. The reference points for this equation are the experimentally determined

$$\nu \text{ (cm}^{-1}\text{)} = 3040 + 22.0 \text{ pK}_b \quad \dots \text{ (1.33)}$$

values of $3,000 \text{ cm}^{-1}$ ($\text{pK}_b = -1.74$) and $3,400 \text{ cm}^{-1}$ ($\text{pK}_b = 15.74$) for hydrogen donated from water to OH^- ion, and for hydrogen donated from water to water, respectively.

(d) Solute molecules more acid than water will donate hydrogens for hydrogen bonding to water by breaking one or more of the hydrogen bonds already existing in water. To calculate the frequencies here, a correlation line,

equation (1.34) is defined by the values for the hydronium ion donating to water $\omega = 2900 \text{ cm}^{-1}$ ⁷⁴ ($pK_a = -1.26$), and water donating to water as an acid $\omega = 3,400 \text{ cm}^{-1}$ ⁷⁴ ($pK_a = 16.04$).

$$\omega (\text{cm}^{-1}) = 2937 + 28.8 pK_a \quad \dots (1.34)$$

(e) The number of hydrogen bonds donated and accepted must be the same on each side of the equation.

To determine the solvent hydrogen isotope effect $(\frac{k_H}{k_D})$ theoretically, the sum of the vibration frequencies for all bonded hydrogens in the initial state $\sum \omega_H$, and for all bonded hydrogens in the transition state $\sum \omega'_H$ at absolute temperature T, were substituted into a modified Bigeleisen equation (1.35).⁷⁵

$$\sum \omega_H - \sum \omega'_H = 12.53 T \log \frac{k_H}{k_D} \quad \dots (1.35)$$

The method has been applied to a large range of reactions with moderate success but, due to insufficient values for the vibration frequencies of hydrogen bonds and the fact that the bonding and librational modes of vibration are neglected, complete agreement between the calculated and experimental values is seldom obtained. The theory is useful, however, in determining the direction of isotope effects in a series

of reactions. Although Bunton and Shiner explicitly excluded intramolecular hydrogen bonding from their considerations, their treatment has recently been applied to such situations by Eyring and coworkers⁷⁶ with a reasonable degree of success.

The Swain, Kuhn and Schowen Treatment⁷⁷

A somewhat different approach to hydrogen isotope effects in organic reactions where a proton is transferred from one oxygen (or nitrogen) to another, concomitant with carbon-carbon bond cleavage has recently been suggested by Swain, Kuhn, and Schowen. The basis of their theory is contained in three formal rules:-

(1) Electron supplying substituents lengthen the nearest reacting bonds, but have an alternating effect on more remote reacting bonds. A reacting bond is defined as one being made or broken at the transition state, i.e., one absent in either the reactants or the products of the rate determining step.

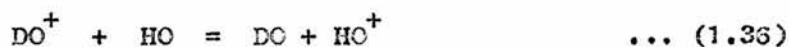
(2) A proton being transferred from one oxygen to another in an organic reaction (with bond changes on carbon in the rate determining step) will lie in an entirely stable potential at the transition state, and neither form reacting bonds nor give rise to primary hydrogen isotope effects. It will be closer to the more basic oxygen at the transition state, but increasingly remote as substituents are changed to make this oxygen less basic.

(3) The more strained, hindered, or crowded the product of a rate determining step becomes (basicities and other electrical factors remaining equal), the more the transition state should resemble the products.

Rule (2) is the fundamental one which shows that, for proton transfers between oxygen atoms, as would be expected in the cyclic transition state for the decarboxylation of β -keto and dibasic acids, no primary isotope effect should be evident but a secondary one should exist and would be calculable.

Swain assumed that non-concerted mechanisms occur and, in order to calculate secondary isotope effects for O-H-O systems he assumed any O-H bond in the reactants or products to be either $H-O^-$, $H-O^+$ or $H-O-$, whereas O-H bonds in the transition state could be intermediate. An integer n for any O-H bond is therefore taken as the fraction in energy representing the extent of conversion to products: thus for a reactant - like transition state n is equal to zero and for a product-like transition state n equals unity. The total isotope effect is given by the product of all the factors K^n for all O-H bonds, K being the limiting isotope effect corresponding to the conversion of each particular O-H bond from its initial state in the reactants to its final

state in the products. In calculating the limiting isotope effect K for the conversion of $\text{HO} \rightarrow \text{HO}^+$ and $\text{HO} \rightarrow \text{HO}^-$ the $\frac{k_{\text{H}}}{k_{\text{D}}}$ ratios are taken as 1.5 and 2.0 at 25°C respectively.²⁸ Thus for the below equilibria, equations (1.36) and (1.37), K_1 and K_2 at 25°C are 1.5 and 2.0 respectively. The isotopic



partition function ratios for the bond changes above are assumed to be independent of the environment, and the values of K_1 and K_2 are obtained empirically and found to be in good agreement with calculated values. The values of K_1 and K_2 as quoted refer to 25°C , but their temperature dependence is defined as a simple exponential dependence on T^{-1} , plus a temperature independent factor of unity. Thus K_1 at any absolute temperature T could be calculated from the below equation (1.38).

$$(K_1)_T = 1 + (K_1)_{298}^{-1} \frac{T}{298} \quad \dots (1.38)$$

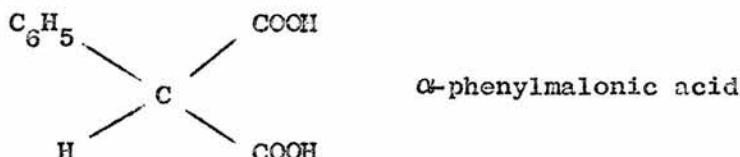
SECTION II

THE DISCUSSION OF RESULTS

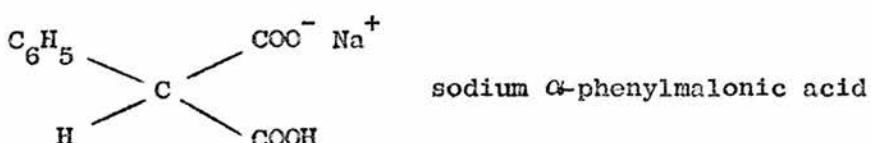
PART IThe Decarboxylation of Several α -Phenylmalonic Acids and Esters.

In order to establish the existence and the importance, or otherwise, of an intramolecular proton transfer in the process of thermal decarboxylation, the reaction of a series of related compounds in which the structure of the carboxylic moiety could be varied was studied kinetically. The selection of α -phenylmalonic acids, anions, and esters, was made solely in the interests of solubility, availability and the known ready decarboxylation of the parent acid. A consideration of the five compounds studied [(a) to (e)] shows that in compounds (a), (b) and (c) there is a proton available for intramolecular transfer, whereas in (d) and (e) there is not.

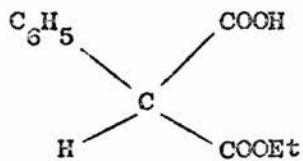
(a)



(b)

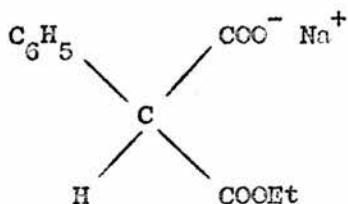


(c)



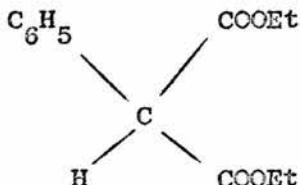
ethyl hydrogen α -phenylmalonate

(d)



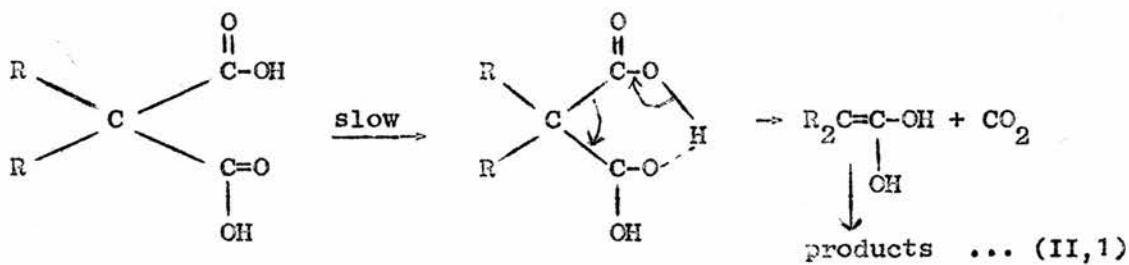
sodium ethyl α -phenylmalonate

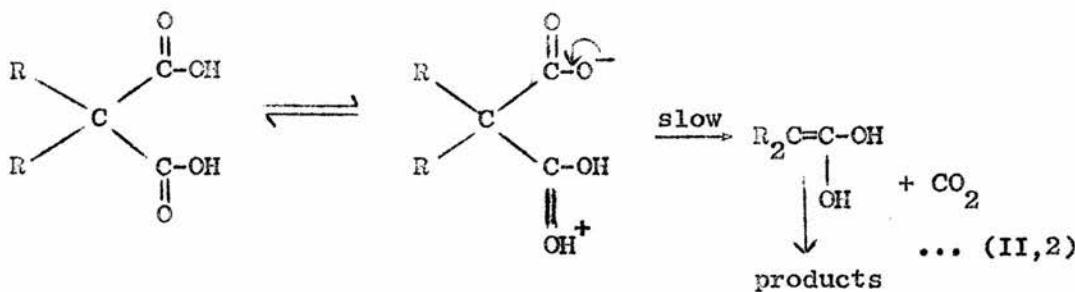
(e)



diethyl α -phenylmalonate

The two postulated mechanisms for the thermal decarboxylation of dibasic acids, as discussed in the previous section, both involve intramolecular proton transfer as illustrated by equations (II,1) and (II,2). It is therefore evident that only the compounds (a), (b) and (c)





would be expected to undergo appreciable reaction if intramolecular proton transfer is indeed kinetically significant. Since the α -phenyl group is common to all five compounds, electronic effects from its presence should be of secondary importance and hence should not appreciably affect the relative rates of decarboxylation.

The thermal decarboxylation of α -phenylmalonic ester and its anion has been studied previously.⁷⁹ Corey concluded that the monoanion of ethyl hydrogen α -phenylmalonate decarboxylated, but his experiments were carried out in aqueous solution and it is likely that hydrolysis occurred to give sodium α -phenylmalonic acid, which then decarboxylated readily, as has been shown by Gelles.⁵³ Thus, in order to eliminate any competing ester hydrolysis which could occur for compounds (c), (d) and (e) in aqueous solution, the rates of decarboxylation in this investigation were studied in a non-protonic solvent, dimethylsulphoxide. Compounds (c) and (d) were also investigated in solvent xylene. The experimental results

obtained for the rates of decarboxylation of the five compounds are tabulated in TABLE (II,1) below, and in FIGURE (II,1) the volume of carbon dioxide evolved is plotted as a function of time in typical experiments with each compound.

TABLE (II,1)

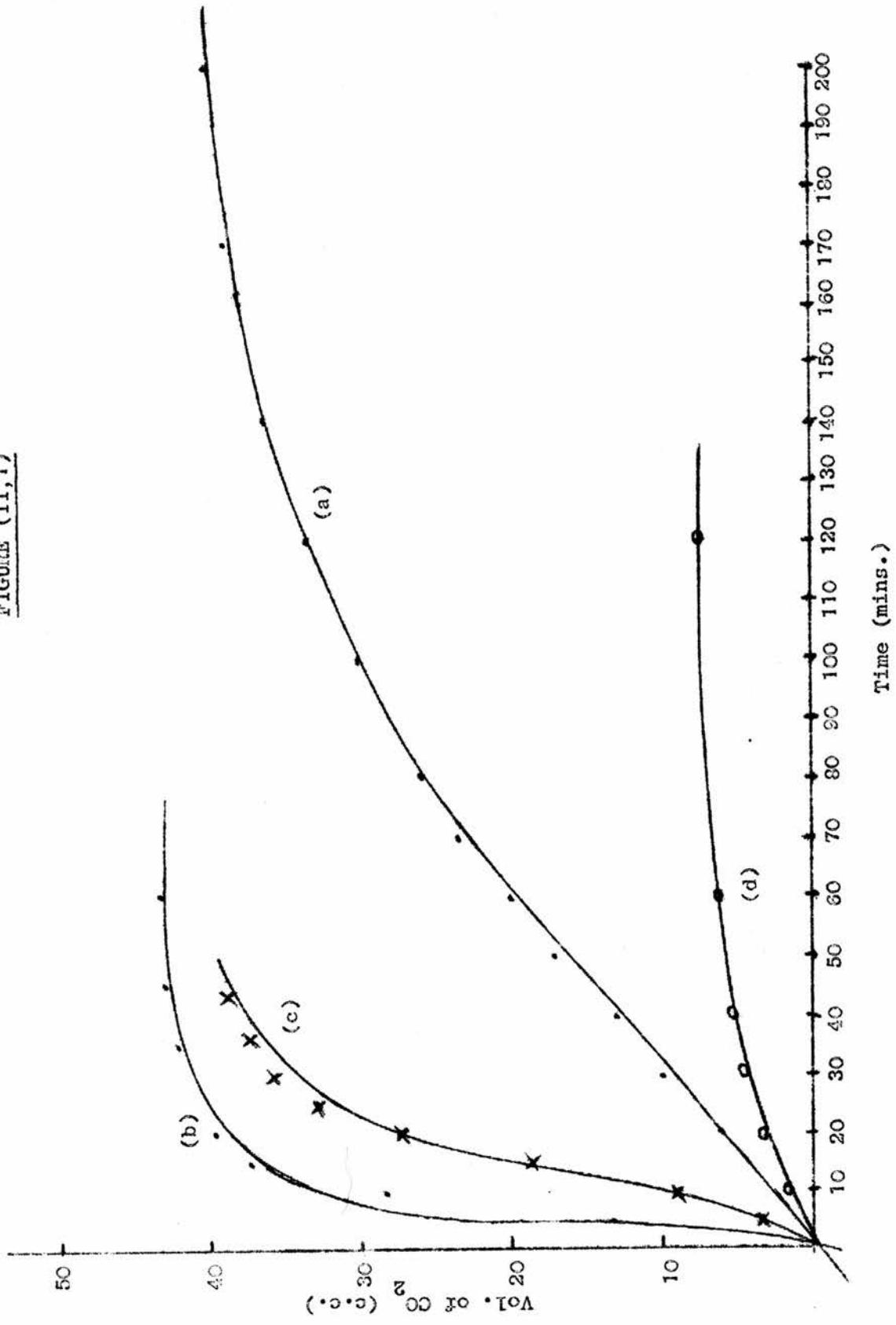
The Decarboxylation Rates of Compounds (a) to (e) Run In Dimethylsulphoxide at 55.4°

Run	Compound	$k \text{ sec}^{-1}$
35	(a)	2.6×10^{-4}
36	(b)	2.8×10^{-3} *
41		2.9×10^{-3}
40	(c)	0.91×10^{-3}
44		1.10×10^{-3}
38	(d)	no reaction
42		
43	(e)	no reaction

* 1st order rate coefficient calculated over the initial 50% of the reaction. Subsequently the reaction rate slows down and this is discussed further below.

From these results it is clearly apparent that compounds (d) and (e) are relatively stable and this conclusion implies

FIGURE (II, 1)



that intramolecular proton transfer is an integral part of the thermal decarboxylation of at least dibasic acids in dimethylsulphoxide. These results and their accordance with previous investigations are discussed further below.

Dimethylsulphoxide is known to enhance the rate of decarboxylation of malonic acid at 90°C by a factor of twenty-five compared to water as solvent,⁸⁰ and the rate of decarboxylation of α -phenylmalonic acid at 55°C, as reported in TABLE (II,1) is twenty-six times larger than the value obtained by Hall and Hanrahan for the free acid in aqueous solution.⁵⁷ Thus the catalytic effect of dimethylsulphoxide solvent on the two acids is similar. The exact cause of these rate enhancements is not entirely clear, but there is good evidence that it stems mainly from stabilisation of the polar transition state by dimethylsulphoxide.⁸¹

In a previous study of α -phenylmalonic acid and sodium α -phenylmalonic acid by Gelles⁵⁶ in aqueous solution, the monoanion was shown to decarboxylate three times faster than the di-acid, and a subsequent study by Hall and Hanrahan,⁵⁷ utilising a series of dioxan/water mixtures as solvent, also showed the monoanion to decarboxylate faster than the acid (in 80% dioxan at 55°C

a factor of ten was observed). Hall and Hanrahan also noted that the decarboxylation of sodium α -phenylmalonic acid was not first order in solutions of 90% or more dioxan but could offer no explanation for this discrepancy. The present results are consistent with these earlier findings. The monoanion of α -phenylmalonic acid was found to decarboxylate readily in solvent dimethylsulphoxide, although, as for the reaction in 90% aqueous dioxan, good first order kinetics were obtained from only measurements made throughout approximately the first 50% of the reaction. The rate coefficient cited in TABLE (II,1) was calculated for this part of the reaction. Thereafter the first order coefficient steadily decreased in value as is shown in TABLE (II,2) for kinetic experiment 36. In TABLE (II,2) values of the second order coefficient calculated in accordance with equation (II,3) are also listed and it can be clearly

$$\text{v} = k_2 [\text{sodium } \alpha\text{-phenylmalonic acid}]^2 \quad \dots \text{(II,3)}$$

seen that this coefficient also is not consistent throughout the whole reaction.

TABLE (II,2)

Time (mins)	% Reaction	$k_1 \text{ sec}^{-1}$	$k_2 \text{ litres moles}^{-1} \text{ sec}^{-1}$
2.5	31.2	2.5×10^{-3}	1.84
5	56.5	2.77×10^{-3}	2.88
7.5	68.5	2.57×10^{-3}	3.20
10.0	74.1	2.25×10^{-3}	3.17
20.0	85.3	1.59×10^{-3}	3.20
30.0	90.3	1.29×10^{-3}	3.91

The cause of this change in kinetic order was not investigated in detail. It probably arises, however, from anticatalysis by the intermediate carbanion formed in the reaction. This carbanion could protonate unreacted starting material to give the diacid, which would be expected to decarboxylate at a slower rate. It is clearly apparent, however, that in dimethylsulphoxide the monoanion (b) decarboxylates at a considerably faster rate than the parent acid (a), as is shown both by the first order rate coefficients listed in TABLE (II,1) and by a comparison of the volumes of carbon dioxide evolved, for both compounds under identical experimental conditions tabulated with respect to time, in TABLE (II,3).

TABLE (II,3)

The decarboxylation rates of compounds (a) and (b) in dimethylsulphoxide at 55.4° C

Time (mins)	Vol. of CO ₂ evolved by α-phenylmalonic acid (mls.)	Vol. of CO ₂ evolved by sodium α-phenylmalonic acid (mls.)
5	0.7	19.2
10	1.2	25.2
15	3.1	27.8
20	5.1	29.0
25	7.6	30.0
30	10.0	30.7

Having established this fact, it seems highly probable that sodium ethyl α-phenylmalonate would decarboxylate faster than ethyl hydrogen α-phenylmalonate if an intramolecular proton transfer were not essential for the reaction to occur.

Measurement of the relative rates of decarboxylation of ethyl hydrogen α-phenylmalonate and its sodium salt show, however, that the former decarboxylates by a first order process over 86% of the total reaction, whereas the latter does not undergo any significant decarboxylation

under the same conditions. The extent of hydrolysis occurring in the above two reactions does not appear to be significant, as, for ethyl hydrogen α -phenylmalonate, the rate of decarboxylation is five times faster than the corresponding rate for α -phenylmalonic acid (the compound into which it would be hydrolysed) under the same conditions. The above rate enhancement for the half-ester (c) compared to the di-acid (a) is probably due to the mesomeric effect of the ethoxide group increasing the electron density on the carboxylic oxygen and thereby facilitating the proton transfer. In the case of sodium ethyl α -phenylmalonate, any hydrolysis occurring should give rise to sodium α -phenylmalonic acid which very rapidly decarboxylates at 55.4°C . The absence of decarboxylation also suggests this certainly does not occur to any large extent, although the small volume of carbon dioxide evolved initially with this compound may arise from hydrolysis by incipient water in the solvent followed by decarboxylation. Furthermore, it was found that the addition of one equivalent of conc. hydrochloric acid to the flask containing sodium ethyl α -phenylmalonate, which had been left for several hours in dimethylsulphoxide without

appreciable reaction, caused an immediate evolution of gas, probably via the formation of ethyl hydrogen α -phenylmalonate and subsequent hydrolyses products. The observed infinity value obtained after the addition of hydrochloric acid was that expected for a complete decarboxylation of the substrate.

Diethyl α -phenylmalonate was not observed to decarboxylate in dimethylsulphoxide at 55.4°C .

Kinetic Studies in Solvent Xylene

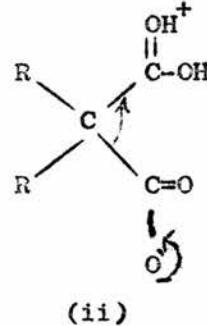
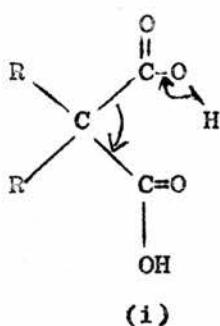
To establish that the above results, reported for ethyl hydrogen α -phenylmalonate and its sodium salt, were not a particular function of the solvent, the same compounds were also studied in solvent xylene at 90.5°C . Under these conditions ethyl hydrogen α -phenylmalonate decarboxylated and the reaction was 90% complete in thirteen hours. A good first order plot was not obtained here due to initial inhomogeneity of the system. Sodium ethyl α -phenylmalonate, on the other hand, did not decarboxylate in xylene at 90.5°C over a period of twenty-four hours: a nuclear magnetic resonance spectrum of the material remaining in the flask showed it to be the original compound, unchanged.

The stability of sodium ethyl α -phenylmalonate, under conditions which readily cause the decarboxylation of

ethyl hydrogen α -phenylmalonate suggest that an intramolecular proton transfer is vital in facilitating the decarboxylation of, at least, phenylmalonic acid and its derivatives. These results do not, however, differentiate between the two previously suggested mechanisms for the reaction, as described in equations (II,1) and (II,2).

PART 2Kinetic Hydrogen Isotope Effects

Having established that an intramolecular proton transfer occurs in the process of thermal decarboxylation, it seemed desirable to determine whether this occurred in a pre-equilibrium step to give the dipolar ion (ii), which then slowly loses carbon dioxide, or in the rate determining step itself giving a cyclic transition state, (i). It also seemed likely that measurements of kinetic hydrogen isotope



effects might distinguish between these alternatives.

The discordancy in previous measurements of the isotope effects for α, α' -dimethylmalonic acid and malonic acid itself, as mentioned in the introduction, also warranted further study. In order to maximise the hydrogen isotope effect, a system was chosen in which the change in the O-H stretching frequency occurring on passage from the initial to the transition state was maximal, or, in other words a system in which intramolecular hydrogen

bonding in the ground state was minimal. There is ample experimental evidence from pK^{68} , infrared⁶⁷ and thermodynamic measurements to indicate that bulky groups attached to the α -carbon atom increase the extent of internal hydrogen bonding. Also internal hydrogen bonding should be larger for the monoanion than for the diacid itself. Thus the present studies were carried out with malonic acid and also α, α' -dimethylmalonic acid.

The experimental conditions were regulated to give a pH value of 0.42 in the solution, which, by reference to Hall's earlier work,⁴⁹ meant that the only species present in the solution was the undissociated dicarboxylic acid. A preliminary calculation having shown that the addition of 0.63 cc. of concentrated hydrochloric acid to 20.0 cc. of deuterium oxide produced a solvent of the desired acidity containing 0.97 atom fractions of deuterium, then this solution was used for the kinetic studies with the deuterated analogues of malonic acid and α, α' -dimethylmalonic acid. To minimise random errors in determining the isotopic rate ratio, the undeuterated solutions were prepared in an identical manner. The experimental rate coefficients for the decarboxylation of malonic acid in water and dioxan, and its deuterated analogue in deuterium

oxide and dioxan, together with the rate coefficients for the decarboxylation of α, α' -dimethylmalonic acid in water and its deuterated analogue in deuterium oxide are tabulated below in TABLE (II,4). The experimental isotopic rate ratio's ($\frac{k_H}{k_D}$) are also recorded in TABLE (II,4).

In TABLE (II,4) the values of individual rate coefficients lie well within $\pm 5\%$ of the calculated mean rate coefficient. The errors in the isotopic rate ratios are assessed by assuming an overall maximum error of 10% in the mean values of the rate coefficients. The value of the rate coefficient obtained for the decarboxylation of malonic acid in aqueous media agrees reasonably well with the value of 7.11×10^6 sec⁻¹ measured by Hall⁴⁹ in 1949.

The magnitudes of $\frac{k_H}{k_D}$ obtained for malonic acid and for α, α' -dimethylmalonic acid in aqueous solution show that the kinetic isotope effects are small and similar in magnitude.

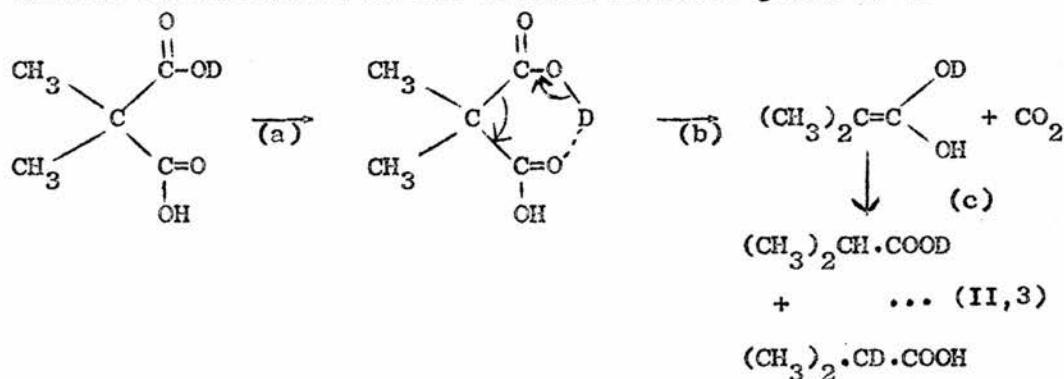
The very different value of 4.5 previously reported by Dunn and Warkentin for the ratio $\frac{k_H}{k_D}$ of α, α' -dimethylmalonic acid⁶⁹ can be explained by considering their experimental technique. The isotope effect was determined by measurement of the $\frac{D}{H}$ ratio in the carboxyl groups of a partly deuterated sample of α, α' -dimethylmalonic acid, and by comparing this figure with the $\frac{D}{H}$ ratio on the α -carbon atom of the iso-

TABLE (II,4)

<u>Substrate</u>	<u>Run No.</u>	<u>Temp.</u>	<u>Solvent</u>	<u>$k_H \times 10^6 \text{ sec}^{-1}$</u>	<u>$k_D \times 10^6 \text{ sec}^{-1}$</u>	<u>Mean Value</u>	<u>$\frac{k_H}{k_D}$</u>
Malonic acid	2	90.0°C	20 cc. H ₂ O + 0.63 cc. conc.HCl	5.75 ± 0.3)		
	5	"		5.92 ± 0.3)		
	6	"		5.79 ± 0.3)	5.83 ± 0.3	
	13	"		5.86 ± 0.3)		
						1.23 ± 0.13	
Malonic acid	3	90.0°C	20 cc. D ₂ O + 0.63 cc. conc.HCl	4.79 ± 0.24)		
	4	"		4.61 ± 0.23)	4.73 ± 0.24	
	7	"		4.79 ± 0.24)		
Malonic acid	14	98.4°C	15 cc. of dioxan	10.7 ± 0.5)		
	15	"		10.1 ± 0.5)	10.4 ± 0.5	
						1.51 ± 0.15	
Deuteriomalonic acid	19	98.4°C	15 cc. of dioxan	6.64 ± 0.33)		
	20	"		7.1 ± 0.35)	6.88 ± 0.34	
	24	"		6.9 ± 0.34)		
α, α' -dimethyl-25 malonic acid	26	90.0°C	20 cc. H ₂ O + 0.63 cc. conc.HCl	2.1 ± 0.1)	2.1 ± 0.1	
		"		2.1 ± 0.1)		
Deuterio α, α' -27 dimethylmalonic acid	27	90.0°C	20 cc. D ₂ O + 0.63 cc. conc. HCl	1.7 ± 0.1)		1.20 ± 0.14
	28	"		1.8 ± 0.1)	1.75 ± 0.1	

butyric acid obtained as a final product-equation (II,3). A

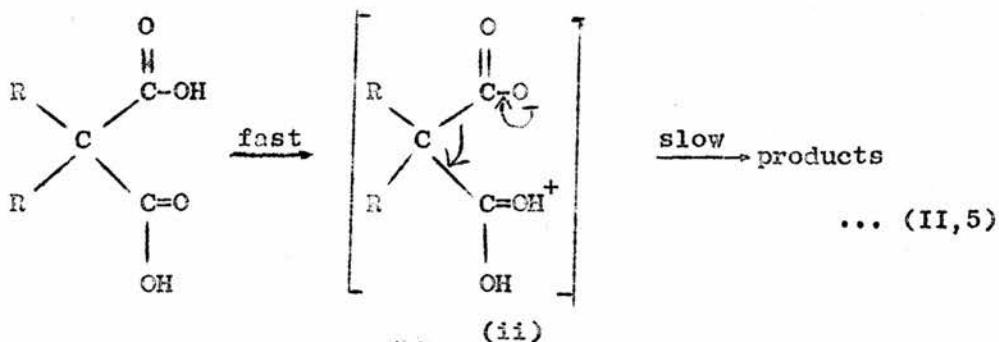
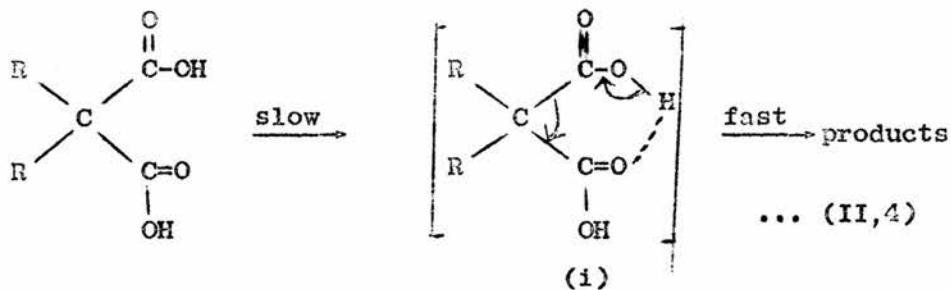
careful consideration of the overall reaction given as in



equation (II,3) suggests that the large isotope effect measured by Dunn and Warkentin probably arises from proton transfer occurring in the final product-forming step (c) of the reaction and is therefore not directly comparable with that measured in the present study.

In view of the very small kinetic hydrogen isotope effects obtained experimentally for both malonic acids, it seemed particularly important to establish whether their magnitudes are consistent with a decarboxylation mechanism involving intramolecular transfer of the isotopic species. It was also hoped that theoretical considerations might clarify the nature of the transition state for decarboxylation. The adopted method was to calculate the expected values of the $\frac{k_H}{k_D}$ ratio for the two "most likely" mechanistic pathways involving an intramolecular proton transfer,

equations (II,4) and (II,5). These differ only in respect to the timing of the intramolecular proton transfer relative to the breaking of the C-C bond and elimination of carbon dioxide.



In both cases the initial state is assumed to contain no internal hydrogen bond. In equation (II,4) the transition state is assumed to be the cyclic intermediate (i) formed by 50% transfer of the carboxylic hydrogen. In equation (II,5) this proton is transferred in a rapid pre-equilibrium step and the rate determining step does not involve translational movement of isotopic hydrogen, therefore

only secondary hydrogen isotope effects are involved.

Two methods are used to calculate the expected kinetic isotope effects, namely that of Swain et al⁷⁷ and that of Bunton and Shiner,⁷⁰ and both have been discussed previously in Section I. Although both methods should lead to similar results, they approach the problem from somewhat different viewpoints.

The Swain, Kuhn and Schowen Treatment

In this treatment K^n is the contribution for each transition state bond where K is the limiting value of $\frac{k_H}{k_D}$ for a transfer from the reactants to the products and n describes the extent of transfer in the transition state. Swain predicted that there would be no appreciable primary isotope effect for a proton transfer between two oxygen atoms.

In applying this approach to malonic acid decarboxylation, it is first necessary to correct the values of K_1 at 25°C for the below reaction, equation (II,6), to 90°C, the temperature at which the decarboxylation studies were carried out in aqueous solution.



at 25°C (298°A)

$$K_1 = \frac{k_H}{k_D} = 1.5^{77}$$

at 90°C (363°A)

$$\begin{aligned} K_1(363) &= (K_1(298)^{-1}) \frac{298}{363} + 1 \\ &= \underline{1.41} \end{aligned}$$

Considering the cyclic transition state, equation (II,4)
then $n = 0.5$ as the transition state is assumed to be
symmetrical.

$$\frac{k_H}{k_D} = (K_1)_{363}^{0.5} = 1.19$$

Considering a dipolar ion transition state as in equation
(II,5) then $n = 1$, as the proton is completely transferred.

$$\frac{k_H}{k_D} = (K_1)_{363}^1 = \underline{1.41}$$

The above calculations clearly show that an intra-molecular proton transfer via either of the postulated paths leads to a kinetic hydrogen isotope effect of similar small magnitude to those observed experimentally.

Earlier measurements of the kinetic hydrogen isotope effects for the decarboxylation of malonic acid in the molten state by Blades and Wallbridge^{6G} also led to very small values of $\frac{k_H}{k_D}$, but these workers interpreted their results as being inconsistent with the idea of an

intramolecularly hydrogen-bonded cyclic transition state.

An application of the Swain treatment to their results, however, shows that such a transition state can be consistent with their data, which is listed below:

Measured Isotope Effects:	$\frac{k_H}{k_D}$	Temp. $^{\circ}\text{C}$
	1.09 ± 0.02	139.8°
	1.11 ± 0.01	145.3°

Correcting the value of K_1 at 25°C to 139.8°C for equation (II,6).

At 25°C (298°A)

$$K_1 = \frac{k_H}{k_D} = 1.5$$

at 139.8°C (412.8°A)

$$K_{1(412.8)} = (K_{1(298)}^{-1})_{412.8}^{298} + 1$$

$$= \underline{1.36}$$

For transition state (i) in equation (II,4)

$$\frac{k_H}{k_D} = \frac{(1.36)^{0.5}}{412.8}$$

$$= \underline{1.16}$$

For transition state (ii) in equation (II,5)

$$\frac{k_H}{k_D} = (1.36)^{\frac{1}{412.8}}$$

$$= \underline{1.36}$$

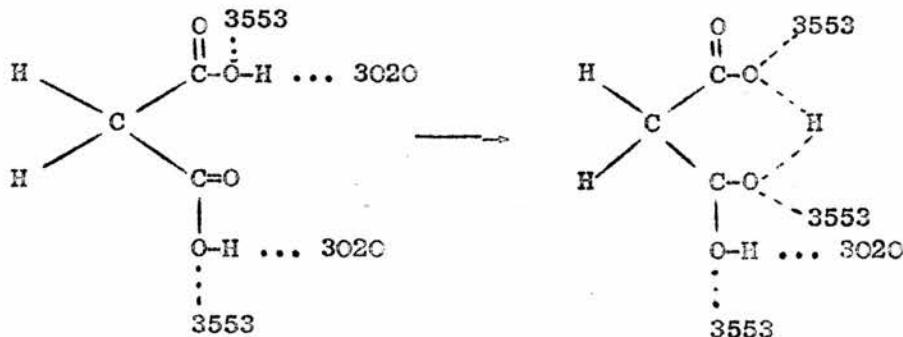
A similar calculation at the temperature 145.3°C (418.3°A) also gives for transition state (i) $\frac{k_{\text{H}}}{k_{\text{D}}} = 1.16$ and for transition state (ii) $\frac{k_{\text{H}}}{k_{\text{D}}} = 1.36$.

A comparison of the values obtained by Blades and Wallbridge at the two temperatures, namely 1.09 and 1.11, with the calculated value of 1.16 for a cyclic hydrogen-bonded transition state (i) shows that the measured values are not inconsistent with this type of mechanism. The agreement between the results reported herein, the earlier results, and the values calculated by the Swain et al. treatment for both sets of data assuming a cyclic hydrogen bonded transition state, is, in all cases, good. The value of $K_1 = 1.5$ for $-\text{OH} \rightarrow \text{OH}^+$ at 25°C . as given by Swain, referred specifically to aqueous media. It was assumed however to be independent of the medium. The measured value of $\frac{k_{\text{H}}}{k_{\text{D}}}$ for malonic acid in dioxan i.e. 1.51 suggests that this is not completely justified, although the differences between the calculated $\frac{k_{\text{H}}}{k_{\text{D}}} = 1.16$ and the measured $\frac{k_{\text{H}}}{k_{\text{D}}} = 1.51$ are very small. In the case of the molten malonic acid the differences between calculated and experimental values are negligible. This suggests that any solvent effect on the measured isotope effects is also small.

The Bunton and Shiner Treatment

According to this approach, the kinetic isotope effects observed are principally due to the differential zero-point energy changes between the initial and transition states of the reaction in the two isotopic solvents, and vibration changes of all the isotopically substituted hydrogens have to be accounted for. Bunton and Shiner therefore predict that often primary isotope effects themselves will be cancelled to some extent by a secondary solvent isotope effect which can be calculated.

Applying the Bunton and Shiner treatment to a reaction involving intramolecular proton transfer concomitant with the elimination of carbon dioxide, equation (II, 1), requires calculation of the hydrogen bond stretching frequencies for the two species below:



The dotted lines refer to hydrogen bonds of the inscribed frequency to or from solvent water molecules. The frequencies, calculated in the manner described

in the introduction (V. page 36), and the relevant pK's required for these calculations, are deduced as follows.

$$pK_{A_1} \text{ (malonic acid)} = 2.87^{82}$$

The pK_B for malonic acid has not been measured. Its value is therefore estimated by assuming that the pK_A for the conjugate acid of malonic acid is two units more negative than the corresponding pK_A for acetic acid (i.e. the difference is approximately the same as that for the acid dissociation constants of the neutral acids themselves).

$$pK_A \text{ (acetic acid)} = 4.76^{83}$$

$$pK_{A_1} \text{ (malonic acid)} = 2.87^{82}$$

$$pK_A \text{ (acetic acid } H^+) = -6.1^{84}$$

$$pK_A \text{ (malonic acid } H^+) = -8.1$$

$$\begin{aligned} \text{Thus } pK_B \text{ (malonic acid)} &= 14 + 8.1 \\ &= 22.1 \end{aligned}$$

$$\begin{aligned} \text{and } pK_B \text{ (malonic acid) per} \\ \text{oxygen atom} &= 22.4 \end{aligned}$$

The stretching frequencies of the relevant hydrogen bonds with the solvent, calculated from the appropriate pK's as discussed in the introduction (V. page 37-38), are therefore as follows.

H bond to water (donated by the acid)

$$\begin{aligned}\nu &= 2937 + 28.8 \text{ pK}_A \\ &= 2937 + 28.8 \times 2.87 \\ &= 3020 \text{ cm}^{-1}\end{aligned}$$

H bond from water (donated to the acid)

$$\begin{aligned}\nu &= 3040 + 22.9 \text{ pK}_B \\ &= 3040 + 22.9 \times 22.4 \\ &= 3553 \text{ cm}^{-1}\end{aligned}$$

Thus for the initial state, the sum of hydrogen bond frequencies becomes:

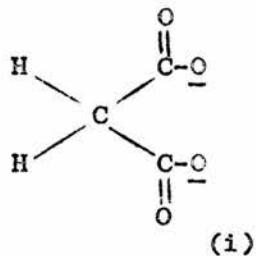
$$\begin{aligned}\sum \nu_H &= 2 \times 3553 + 2 \times 3020 \\ &= 13,146 \text{ cm}^{-1}\end{aligned}$$

and for the transition state:

$$\begin{aligned}\sum \nu_H^{-1} &= 3 \times 3553 + 3020 \\ &= 13,679 \text{ cm}^{-1}\end{aligned}$$

In forming the transition state, it is assumed that the total number of hydrogen bonds with the solvent remains unaltered. That is, on forming an intramolecular hydrogen bond with the proton being transferred from the first carboxyl group, the second carboxyl group must also receive another

hydrogen bond from solvent water. The reasonableness of this assumption is readily apparent by considering that four hydrogen bonds would be donated from water to a dicarboxylate anion in which the two negative charges are localised on two oxygen atoms. In the transition state (i), below, two



of these solvent hydrogen bonds are made with the proton undergoing intramolecular transfer. The frequency of the hydrogen bonds from water to the carboxylic oxygen atoms in the transition state are also assumed to be the same as that of their counterparts in the initial state, i.e. 3553 cm^{-1} . In other words the development of partial negative charge on these oxygens is not specifically considered. The error arising from this omission should not be very large, as hydrogen bonds to carboxylate anion itself are of the order of 3300 cm^{-1} . Both assumptions about the number and frequency of hydrogen bonds become more acceptable on realising that any charge which is developed in the transition state should be localised in the bonds undergoing fission.

Using the above values of the total hydrogen bond frequencies in the initial and transition states and utilising equation (I,35) (V. page 38), the secondary solvent isotope effect is calculated to be

$$\begin{aligned}\frac{k_H}{k_D} &= \frac{\text{antilog } \sum v_H - \sum v_H^{-1}}{12.53T} \\ &= \text{antilog } \frac{-533}{12.53 \times 363} \\ &= \text{antilog } -0.117 \\ &= 0.76\end{aligned}$$

The primary isotope effect for intramolecular proton transfer in the transition state is therefore:-

$$\begin{aligned}\left(\frac{k_H}{k_D}\right)_{\text{obs.}} &= \left(\frac{k_H}{k_D}\right)_{1^\circ} \times \left(\frac{k_H}{k_D}\right)_{2^\circ} \\ \left(\frac{k_H}{k_D}\right)_{1^\circ} &= \frac{1.23}{0.76} \\ &= 1.62\end{aligned}$$

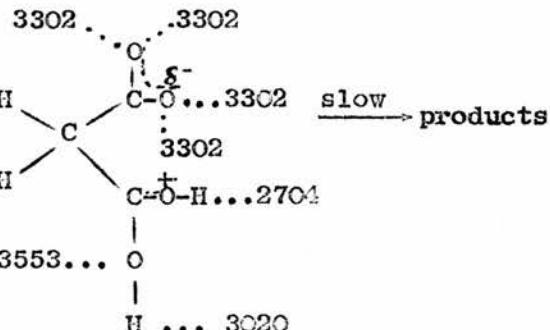
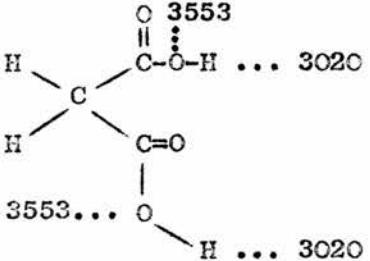
This is a particularly interesting result, because it shows that, having made reasonable allowances for the secondary solvent isotope effect, the experimental results lead to a low primary isotope effect, as suggested by Swain et al., for proton transfer to and from oxygen

accompanying reactions also involving C-C bond cleavage.

It is noteworthy that the ratio $\frac{k_H}{k_D}$ (= 1.51) in dioxane closely approaches the above calculated value of the primary isotope effect for the cyclic hydrogen-bonded transition state. This can be correlated with the fact that, in solvent dioxane, less solvent bonding would be expected on the basis of its lower basicity compared to water, and thus the secondary solvent isotope effect should be greatly reduced.

Applying the Bunton and Shiner treatment to a decarboxylation mechanism involving pre-equilibrium formation of a dipolar ion, equation (II,5) is simpler because only secondary hydrogen isotope effects would be expected. These may be calculated in an analogous manner to that previously described, by utilising the estimated pK's for the species involved in the pre-equilibrium

process as below.



As before, the dotted lines refer to hydrogen bonds of the inscribed frequency to or from solvent water

68.

molecules. The relevant pK values for the components of the pre-equilibrium are assessed as described previously (V page 37-38) and have the following values:-

$$\begin{aligned} \text{pK}_B \text{ (dipolar ion)} &= \text{pK}_B \text{ (malonate ion)} \\ &= 11.13 \end{aligned}$$

i.e. $\text{pK}_B \text{ (dipolar ion) per oxygen atom} = 11.43$

$$\begin{aligned} \text{pK}_A \text{ (dipolar ion)} &= \text{pK}_A \text{ (malonic acid H}^+) \\ &= \text{pK}_A \text{ (acetic acid H}^+)-2 \\ &= -8.1 \end{aligned}$$

The stretching frequencies of the hydrogen bonds involved are estimated as:

H bond to water (donated by the acid) = 3020 cm^{-1} (V page 64)

H bond from water (donated to the acid) = 3553 cm^{-1} (V page 64)

H bond from water (accepted by dipolar ion)

$$\begin{aligned} \textcircled{O} &= 3040 + 22.9 \text{ pK}_B \\ &= 3040 + 22.9 \times 11.43 \\ &= 3302 \text{ cm}^{-1} \end{aligned}$$

H bond to water (from dipolar proton)

$$\begin{aligned} \textcircled{O} &= 2937 + 28.8 \text{ pK}_A \\ &= 2937 + 28.8 \times -8.1 \\ &= 2704 \text{ cm}^{-1} \end{aligned}$$

Thus for the initial state:

$$\begin{aligned}\sum \nu_H &= 2 \times 3553 + 2 \times 3020 \\ &= 13,146 \text{ cm}^{-1}\end{aligned}$$

For the final state:

$$\begin{aligned}\sum \nu_H^{-1} &= 4 \times 3302 + 3020 + 3553 + 2704 - 3 \times 3,400 \\ &= 22,485 - 3 \times 3,400 \\ &= 12,285 \text{ cm}^{-1}\end{aligned}$$

Since three solvent-solvent bonds must be removed in the final state to maintain a numerical balance in the number of bonds on both sides of the equation, three frequencies of $3,400 \text{ cm}^{-1}$ are subtracted from the final state.

The calculated isotope effect using equation (I,35) on page 38 is therefore

$$\begin{aligned}\frac{k_H}{k_D} &= \text{antilog} \frac{\sum \nu_H - \sum \nu_H^{-1}}{12.53T} \\ &= \text{antilog} \frac{861}{12.53 \times 363} \\ &= \text{antilog } 0.189 \\ &= 1.54\end{aligned}$$

Thus the calculated hydrogen isotope effect for the dipolar ion mechanism, equation (II,5) via the Bunton and Shiner

treatment ($\frac{k_H}{k_D} = 1.54$) is a little larger than that determined experimentally ($\frac{k_H}{k_D} = 1.23$). It shows however better agreement with the corresponding parameter calculated via the Swain et al. treatment ($\frac{k_H}{k_D} = 1.41$) although this is not altogether surprising since both theoretical treatments are related indirectly to the same fundamental data for secondary isotope effects.

In conclusion, the above results and calculations show that the small observed hydrogen isotope effects are consistent with a decarboxylation process, for dicarboxylic acids, involving an intramolecular proton transfer. Using a reasonable model, the calculated values are in better agreement with experimental data, if this proton transfer occurs in the transition state rather than in a pre-equilibrium step.

PART 3

Decarboxylation of malonic acid in concentrated mineral acid solutions.

The decarboxylation of malonic acid was also investigated for evidence of external hydrogen ion catalysis in strongly acidic solutions. Previous workers⁴⁹ were unable to detect any such catalysis in dilute hydrochloric acid solutions, and the reaction was investigated here in 5N hydrochloric acid, and also concentrated perchloric acid solutions. The results are reported in TABLE (II,5) below.

TABLE (II,5)

The rates of decarboxylation of malonic acid at 90.0°C in conc. acid solutions.

Run	Solvent	$k \text{ sec}^{-1}$
6	0.42N HCl	5.79×10^{-6}
18	5N HCl	5.75×10^{-6}
21	3.95M HClO_4	3.54×10^{-6}
22	7.34M HClO_4	1.32×10^{-6}

These rate coefficients verify that the decarboxylation reaction is not acid catalysed and, in perchloric acid solutions, the reaction rate is even reduced. This small reduction in rate probably arises from a medium effect on

the reaction rather than from any significant protonation of the carboxylic groups. This is an interesting result, however, for it shows that, whereas intramolecular proton transfer leads to decomposition, protonation by an external source probably does not. Thus decarboxylation of dicarboxylic acids stems from the instability of the charged intermediate formed by intramolecular proton transfer.

SECTION III

EXPERIMENTAL

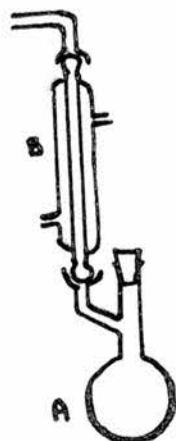
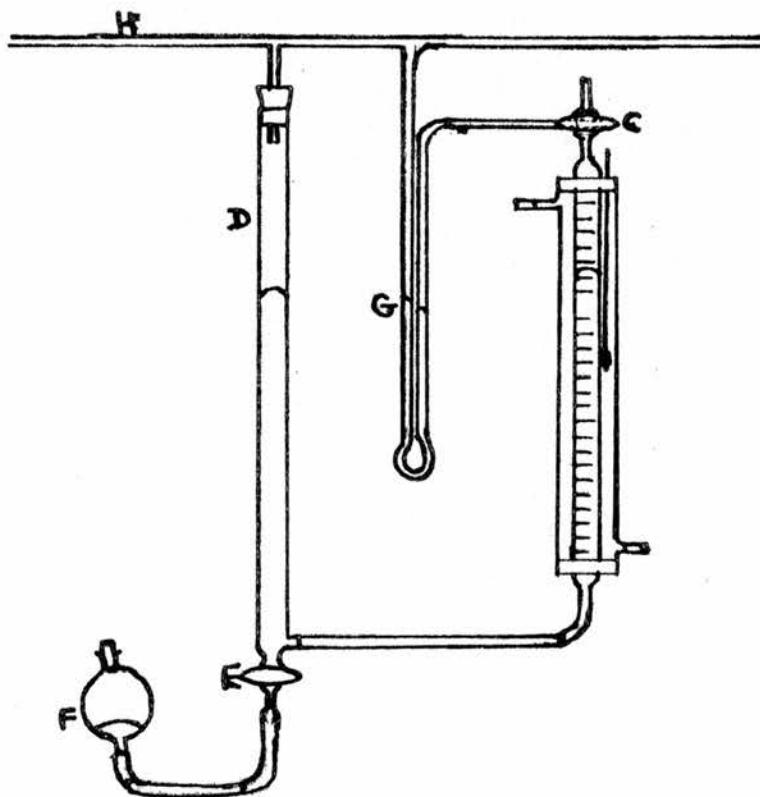
A description of the apparatus and of the experimental methods used is included in the following section, together with details of the preparation and purification of all the chemical reagents and solvents used. In all cases the rate of the decarboxylation reaction was followed by measuring the volume of carbon dioxide evolved at timed intervals.

PART 1

The Apparatus and the Kinetic Method

The apparatus used for measuring the decarboxylation rates is illustrated in DIAGRAM 1. and consisted of a 50 ml. round-bottomed flask (A) attached 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 ml. mercury-filled gas burette. The gas burette was connected to a levelling tube (D) containing mercury under atmospheric pressure. Mercury could be withdrawn from the levelling tube by means of a stop-cock (E) leading to a 500 ml. reservoir (F). To facilitate reading of the gas burette a bent capillary tube containing mercury (G) was incorporated into the system after the manner described by Schubert,² being connected on one side to the reaction flask and the gas burette by way of

DIAGRAM I.



the tap (C), and on the other side to the tube (H) lying along the top of the apparatus. Carbon dioxide was passed through the tube (H) before starting the reaction and during the course of the reaction it was open to the atmosphere. The volume of evolved gas at a pressure equal to atmospheric could be read from the burette by withdrawing mercury from the levelling tube (D) until the mercury levels on both sides of the capillary (G) were the same. To minimise temperature fluctuations and to ensure that all the volumes were read at a fixed, constant temperature, the burette was enclosed in a constant temperature jacket. A flow of water from an accurately thermoregulated bath kept at exactly 25°C , as read on an N.P.L. thermometer, was circulated through the jacket and also through the condenser, thereby minimising the unthermostatted dead space.

The round-bottomed reaction flask was immersed in a constant temperature bath containing polyethylene glycol, and the temperature was regulated to within $\pm 0.1^{\circ}\text{C}$, the exact temperature being noted on an N.P.L. thermometer. Stirring of the reaction solution was effected by means of a teflon stirring bar contained in the flask and turned by a magnet situated below the flask in the oil-bath. The magnet was rotated by a motor to which it was attached

by a metal shaft. The speed of the motor was kept constant throughout the experiments to ensure an even evolution of gas. Preliminary experiments were carried out to determine the minimum stirring rate to obtain an even evolution of gas and to establish that the rate of decarboxylation was independent of higher stirring rates.

At the beginning of each kinetic run the entire apparatus was first thoroughly flushed out, for ten minutes, with carbon dioxide gas dried by passage through silica gel, by first withdrawing all the mercury into the reservoir, and by passing the gas through the line (H) connected to the levelling tube. The gas burette and the levelling tube were then filled with mercury by raising the reservoir, and the stop-cock was closed to retain the mercury. An accurately weighed sample of the organic acid to be decarboxylated, either approximately that required to give 20 cc. of carbon dioxide at N.T.P. or, in some cases, half this volume, was contained in a sealed soda-glass vial and inserted into the reaction flask along with 15 ml. or 20 ml. of solvent. The solvent in all cases was pre-saturated with carbon dioxide by passage of the dry gas through a small volume of the solvent for fifteen minutes just prior to starting the reaction. The

mixture was heated and stirred in the oil bath with the system open to the atmosphere for about fifteen minutes or until temperature equilibrium was reached, and then the flask was connected to the burette. To start the reaction the sample tube was ruptured by a glass rod inserted through the neck of the flask. The volume of gas evolved was measured, at appropriate time intervals, in the manner described previously.

In the experiments to obtain the $\frac{k_H}{k_D}$ ratio for the malonic acid itself, in aqueous solutions, the reaction was initiated by injecting, from a graduated syringe, an accurately known weight of malonic acid dissolved in 5 ml. of water or deuterium oxide, into the flask containing the remaining 15 ml. of the solvent. The flask was fitted with a self-sealing rubber stopper, and, since the decarboxylation rate of malonic acid in aqueous solution at room temperature over a short period of time was negligible this method provided a convenient means of starting the reaction. On using solvents other than water and raising the decarboxylation temperature for subsequent experiments, a ground-glass stopper was employed to prevent leakage and the vial broken as described previously.

In all cases changes in atmospheric pressure were neglected as reasonable fluctuations in this variable

would produce an error of only 1% in the measured volumes, but the readings were taken at a constant temperature of 25°C .

Calculation of Rate Coefficients

As mentioned previously, the experimental results were obtained as volumes of carbon dioxide evolved at timed intervals. These volumes are, of course, directly related to the fraction of substrate that has undergone reaction [x in equation (III,1)]. Thus the first order rate coefficients could be calculated from equation (III,1).⁸⁵

$$k = \frac{2.303}{t} \log \frac{a}{a-x} \quad \dots \text{(III,1)}$$

k = rate coefficient in sec.⁻¹

t = time in secs.

a = volume of carbon dioxide evolved at infinite time

x = volume of carbon dioxide evolved in time t .

For many of the slower reactions, the reaction was not followed to completion. Instead the theoretical volume of carbon dioxide evolved, calculated from the known concentration of substrate, was used. To check this assumption a few reactions were followed to completion, however, and the volume of carbon dioxide evolved was equivalent to 95% or better of the theoretical value. The difference in

the rate coefficients using the theoretical and the experimental infinity values for the volume of evolved gas was found to be \pm 3%. Straight lines were obtained for plots of $\log(a-x)$ versus time, over the range studied which was at least 70% of the total reaction, showing the reactions to be first order. Typical kinetic runs are cited below and each run was repeated at least once, or until consistent values of the rate coefficient were obtained. The calculated error in determining the rate coefficient was of the order \pm 5%. Exactly the same technique was used in all related cases, and, in the isotope effect determinations, since the effects are generally quoted in terms of a rate coefficient ratio $(\frac{k_H}{k_D})$, as calculated from the measurements of the normal and deuterated malonic acids in water and deuterium oxide respectively, the overall error in determining the isotope effects should be considerably less.

Typical Kinetic Runs

The results cited in TABLES (III,1), (III,2) and (III,3) for kinetic runs 3,6 and 20 are typical of those obtained under first order conditions. In each case the rate of the reaction was taken as the slope of the best straight line graph drawn from plotting $\log(a-x)$ versus t .

TABLE (III,1)

Kinetic Run 3

Wt. of malonic acid = 0.3783 gm. Bath Temp. = 90.0°C
 Jacket Temp. = 25°C

Theoretical α corrected to
 25°C = 88.99 cc.

Solvent: 0.63 cc. conc. HCl + 20.0 cc. D_2O

Time (hours)	x c.c.	(a-x) c.c.	log (a-x)
1	3.2	85.79	1.9335
2	5.6	83.39	1.9211
3	8.0	80.99	1.9084
4	10.3	78.69	1.8954
7	15.5	73.49	1.8362
$8 \frac{11}{12}$	17.3	71.69	1.8554
$13 \frac{2}{3}$	22.3	66.69	1.8241
$18 \frac{11}{12}$	27.8	61.19	1.7866
24	33.6	55.39	1.7434
28	38.2	50.79	1.7053
34	43.0	45.99	1.6627
42	48.5	40.49	1.6074
47	52.4	36.59	1.5634
52	55.4	33.59	1.5262
57	57.4	31.59	1.4995
$67 \frac{1}{6}$	62.1	26.89	1.4296
$71 \frac{5}{6}$	64.0	24.99	1.3978
75	65.5	23.49	1.3709

$k = 4.79 \times 10^{-6} \text{ sec}^{-1}$

RUN 3

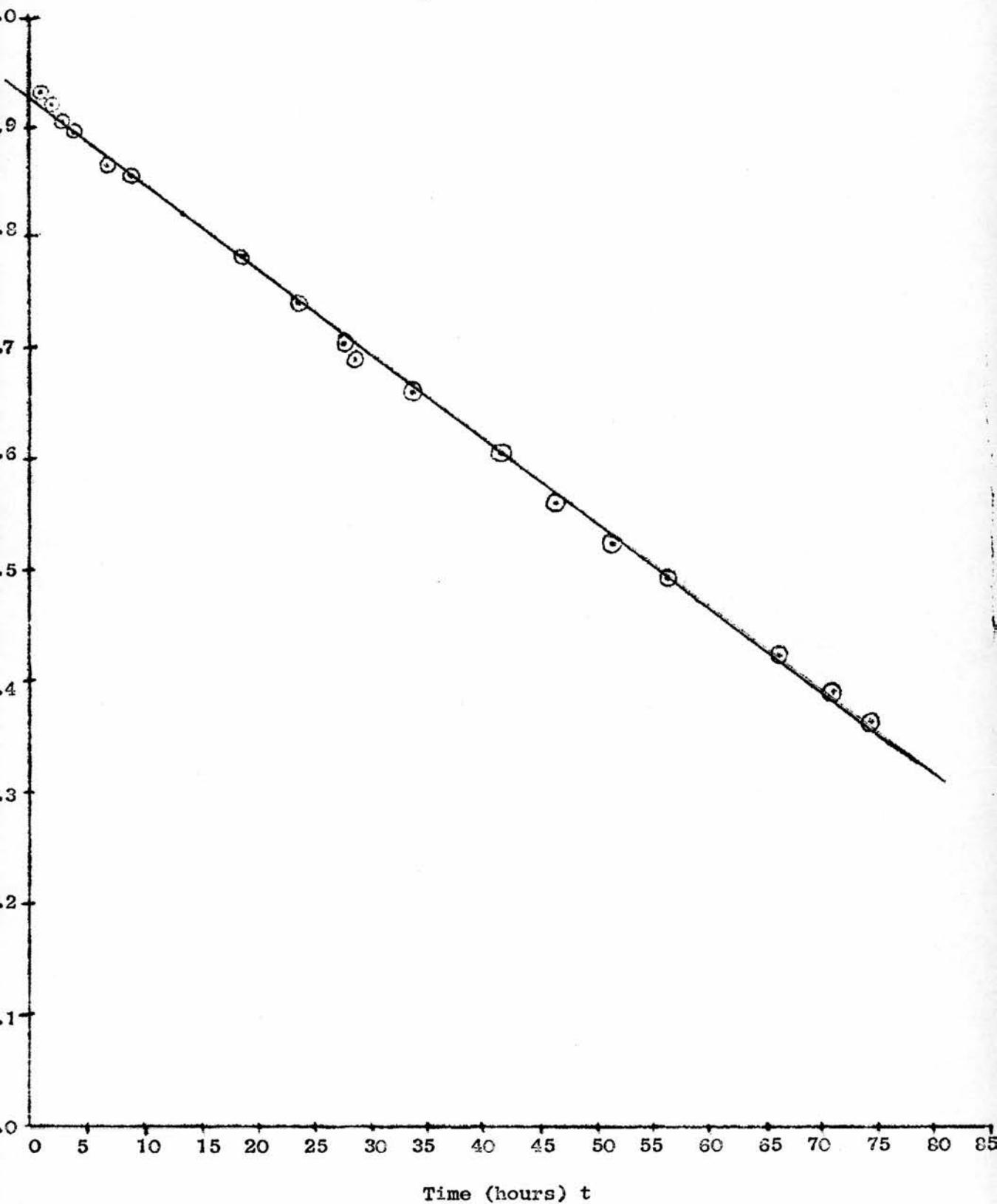


TABLE (III,2)

Kinetic Run 6

Wt. of malonic acid = 0.3581 gm. Bath Temp. = 90.0°C

Jacket Temp. = 25°C

Theoretical cc corrected
to 25°C = 84.23 c.c.Solvent: 0.63 c.c. of conc. HCl + 20.0 cc H₂O

Time (hours)	x c.c.	(a-x) c.c.	log (a-x)
2	4.4	79.83	1.9022
4	7.7	76.53	1.8839
5	10.2	74.03	1.8694
6	12.0	72.23	1.8587
9	15.5	68.73	1.8372
12 1/12	20.8	63.43	1.8023
17 1/12	26.5	57.73	1.7614
22	32.7	51.53	1.7121
24 1/6	35.2	49.03	1.6905
27	37.8	46.43	1.6668
29 1/2	40.2	44.03	1.6438
34 1/12	44.0	40.23	1.6045
42	49.6	34.63	1.5395
46	51.8	32.43	1.5109
50 1/6	54.0	30.73	1.4805
53 11/12	55.9	28.33	1.4523
58	58.8	25.43	1.4053
69 1/2	63.6	20.63	1.3145
73 1/2	65.0	19.23	1.2840

$$k = 5.79 \times 10^{-6} \text{ sec}^{-1}$$

RUN 6

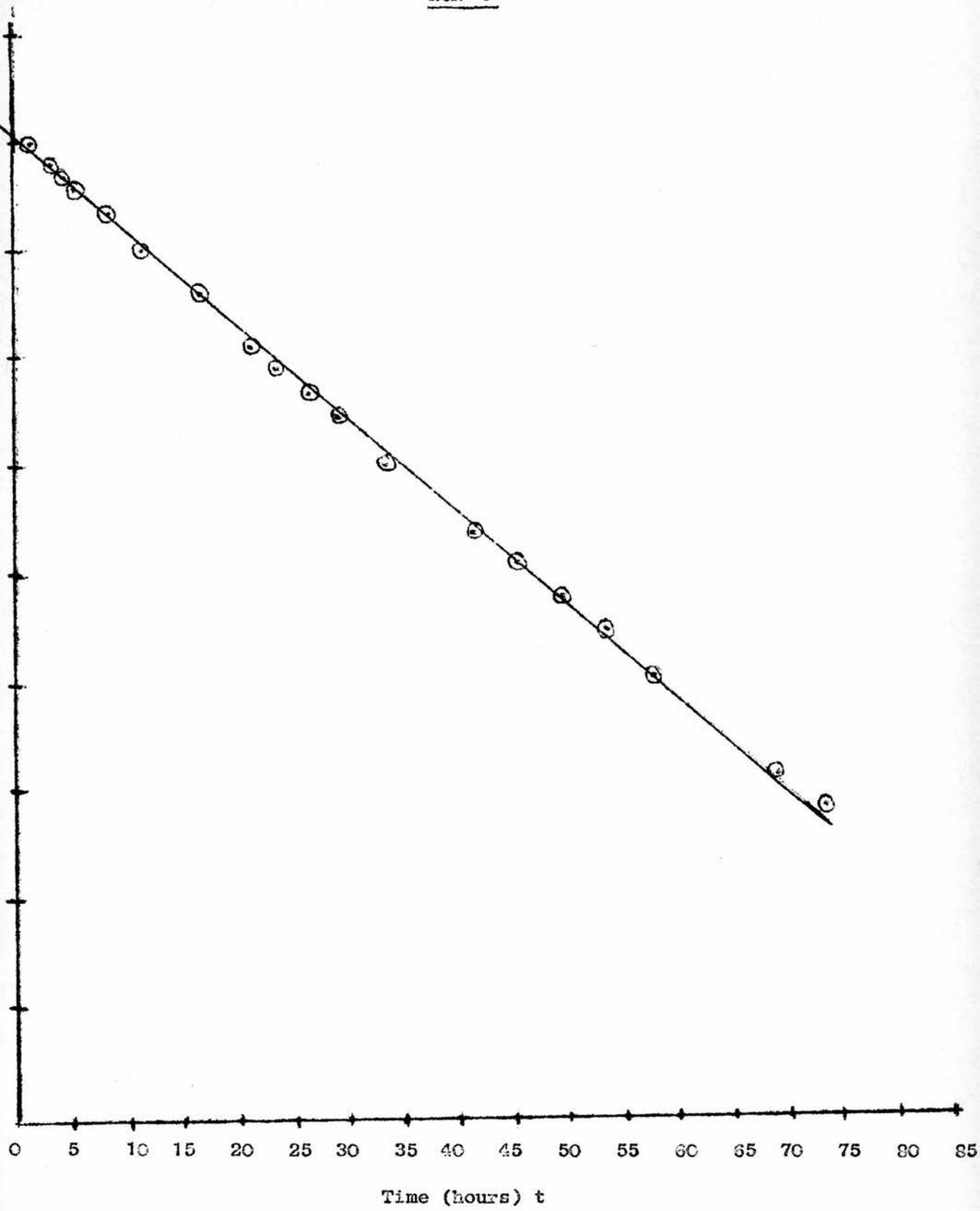


TABLE (III,3)

Kinetic Run 20

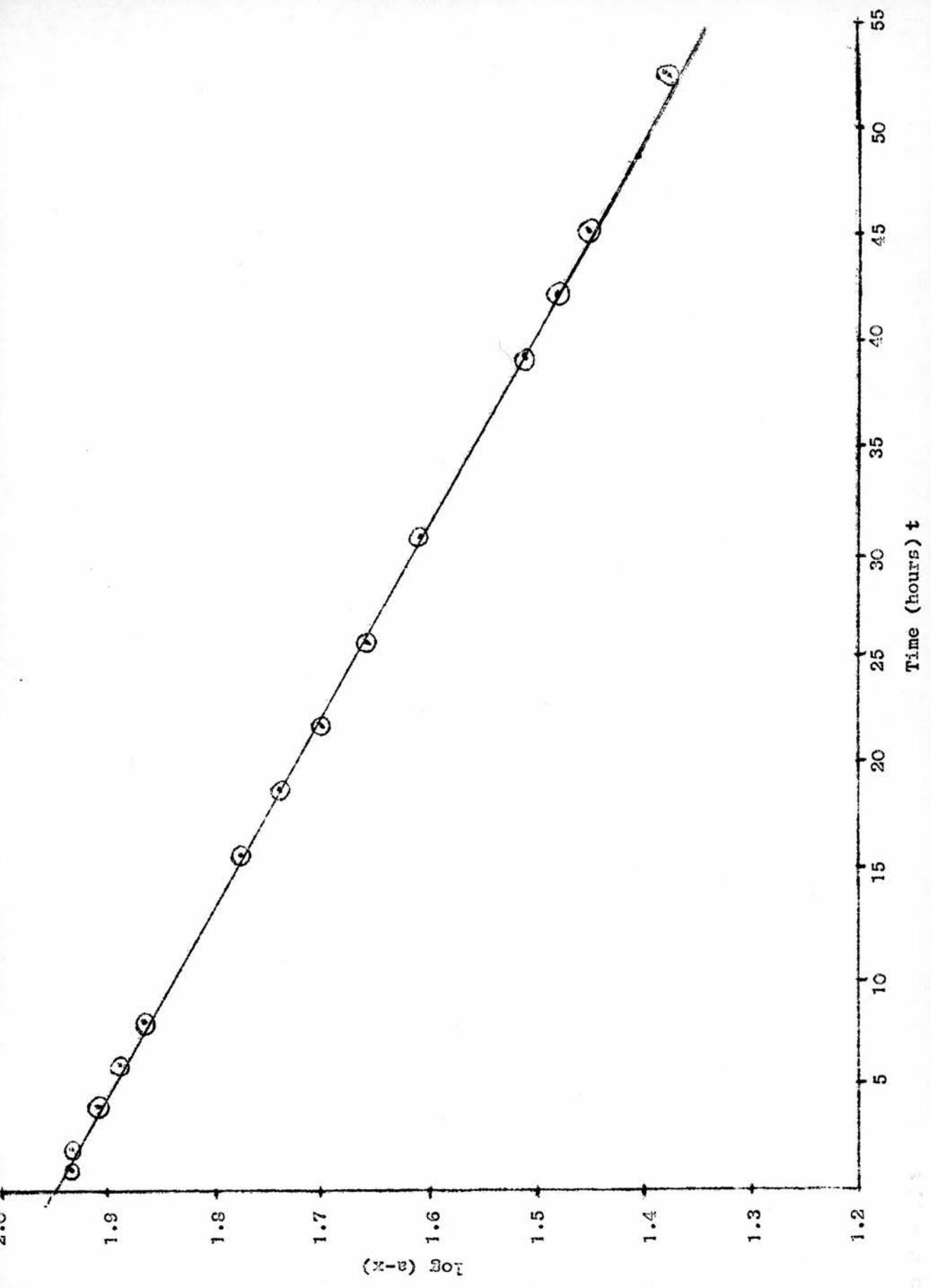
Wt. of $\text{CD}_2(\text{COOD})_2$ = 0.3251 gm. Bath Temp. = 98.4°C
 Jacket Temp. = 25°C

Theoretical α corrected
to 25°C = 88.8 c.c.

Solvent: 15 ml. of dried D_2O saturated dioxan

Time (hours)	x c.c.	(a-x) c.c.	log (a-x)
1	2.3	86.5	1.9370
2	3.2	85.6	1.9325
4	7.6	81.2	1.9096
6	11.2	77.6	1.8899
8	14.8	74.0	1.8692
16	29.0	59.8	1.7767
19	34.1	54.7	1.7380
22	38.7	50.1	1.6998
26	43.2	45.6	1.6590
31	48.2	40.6	1.6085
39 $\frac{1}{2}$	56.4	32.4	1.5105
42 $\frac{1}{2}$	58.6	30.2	1.4800
45 $\frac{1}{2}$	60.6	28.0	1.4472
49	63.4	25.4	1.4048
53	64.4	24.4	1.3874

$k = 7.1 \times 10^{-6} \text{ sec}^{-1}$



The Kinetic Method for the Decarboxylation of α -Phenylmalonic Acid Derivatives.

The decarboxylation rates of these compounds were studied in dimethylsulphoxide or xylene solvent, the solvent being in the case of dimethylsulphoxide kept dry by storage over molecular sieve. The glass apparatus was dried by leaving for twenty-four hours in an oven set at 120°C . The general procedure was the same as that already described previously but the reactions were so much faster that measured infinity values which agreed to better than 95% of the theoretical were used for each experiment. In all cases the weight of the organic compound used was that computed to give approximately 40 c.c. of carbon dioxide at N.T.P.

Calculation of Rate Coefficients

Because of the greatly increased rates of these reactions, the volumes of evolved gas at timed intervals were less accurate than those for the slower rates thus the error in determining the rate coefficients was increased to $\pm 8\%$. However, relative values of the rate coefficient were of more interest than the exact rates of decarboxylation.

Typical Kinetic Runs

The results cited in TABLES (III,4) and (III,5) for kinetic runs 36 and 44 showed that these reactions exhibited first order kinetics. The reaction rate was determined from the slope of the straight line graph drawn from plotting $\log (a-x)$ versus t , as described by equation (III,1)[V. page 77].

TABLE (III,4)

Kinetic Run 36Wt. of α -phenylmalonic acid = 0.3200 gm. Bath Temp. = 55.4°C

Jacket Temp. = 25°C

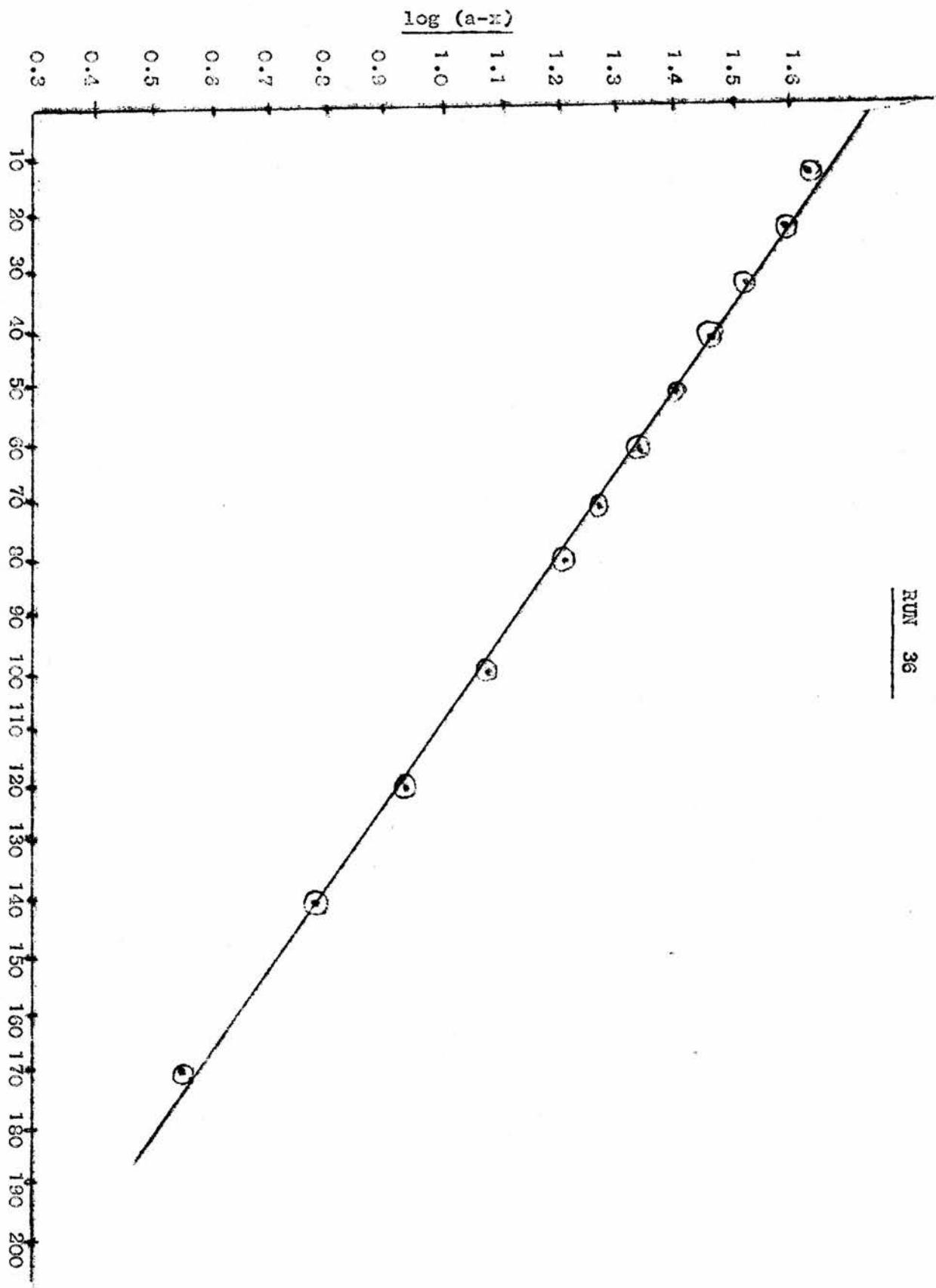
Measured α C = 42.3 c.c.Theoretical α C = 43.5 c.c.

Solvent: Dimethylsulphoxide

Time (mins.)	x c.c.	(a-x) c.c.	log (a-x)
10	1.2	41.1	1.6138
20	5.1	37.2	1.5705
30	10.0	32.3	1.5092
40	13.5	28.8	1.4594
50	17.1	25.2	1.4014
60	20.3	22.0	1.3424
70	23.5	18.8	1.2742
80	25.8	16.5	1.2175
100	30.1	12.2	1.0864
120	33.5	8.8	0.9445
140	36.3	6.0	0.7782
170	38.9	3.4	0.5315

$$\underline{k = 2.6 \times 10^{-4} \text{ sec}^{-1}}$$

RUN 36



TABLE(III,5)Kinetic Run 44Wt. of ethyl hydrogen α -phenylmalonate = 0.3751 gm.Bath Temp. = 55.4 $^{\circ}$ CJacket Temp. = 25 $^{\circ}$ CMeasured α c = 43.4 c.c.Theoretical α c = 44.1 c.c.

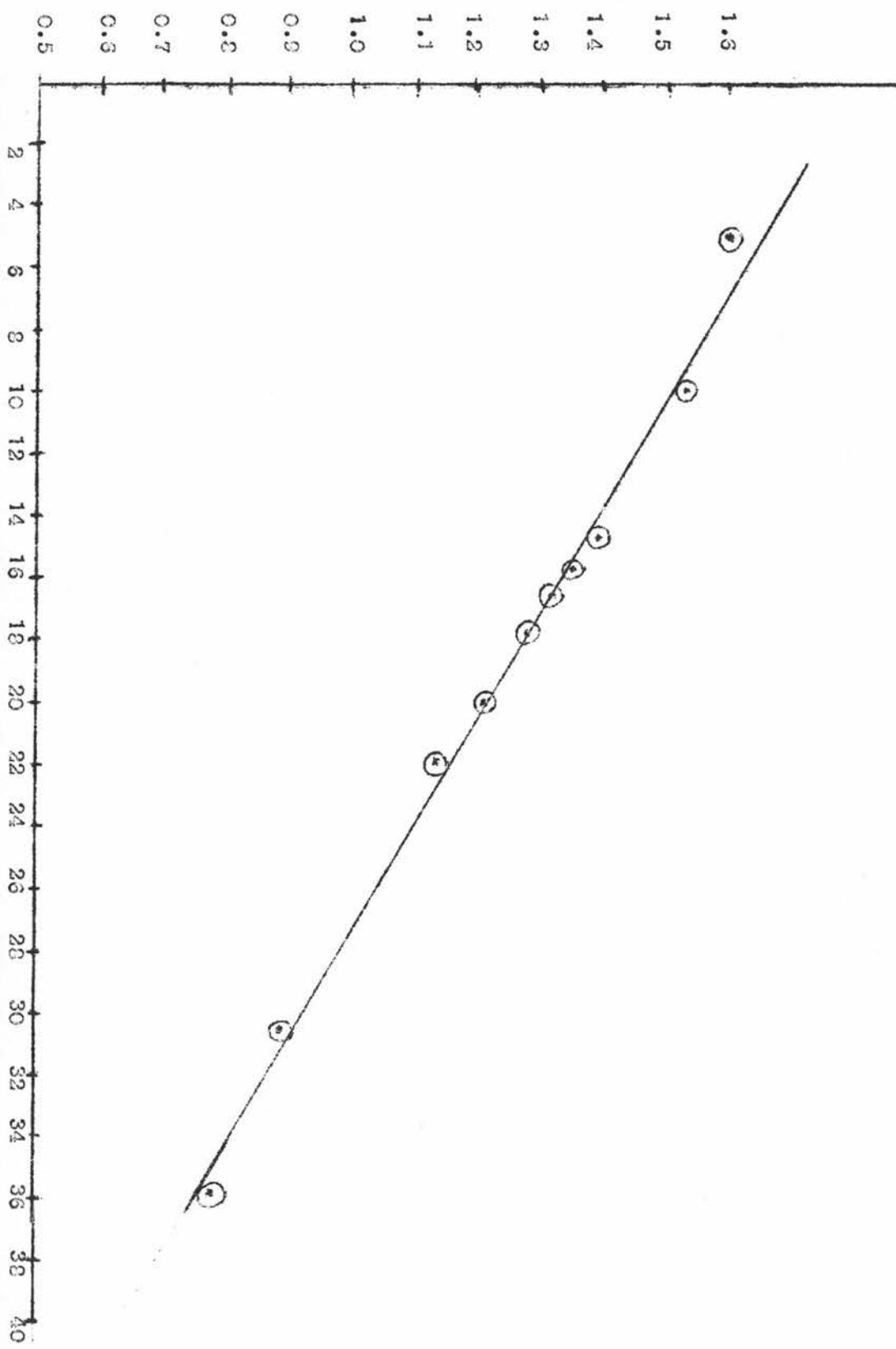
Solvent: Dimethylsulphoxide

Time (mins.)	x c.c.	(a-x) c.c.	log(a-x)
5	3.4	40.0	1.6021
10	9.0	34.4	1.5366
14 $\frac{2}{3}$	18.6	24.8	1.3945
15 $\frac{2}{3}$	20.8	22.6	1.3541
16 $\frac{1}{2}$	22.4	21.0	1.3222
17 $\frac{2}{3}$	24.3	19.1	1.2810
20	27.3	16.1	1.2068
22	29.8	13.6	1.1335
25	32.8	10.6	1.0253
30 $\frac{1}{2}$	35.8	7.6	0.8808
36	37.4	6.0	0.7782

$$\underline{k = 1.10 \times 10^{-3} \text{ sec}^{-1}}$$

RUN 44

log (a-z)



PART 2Preparation and Purification of MaterialsMalonic Acid

B.D.H. analar grade malonic acid was further purified by sublimation at 95-100°^oC and was stored in a vacuum desiccator to prevent uptake of moisture. The melting point of the malonic acid was 135°^oC, (lit. value = 135.6°^oC)⁸⁷ after sublimation and fresh samples were sublimed at regular intervals.

Tetra deuteriomalonic Acid

Tetra deuteriomalonic acid CD₂(COOD)₂ was prepared by dissolving purified malonic acid in 99.7% deuterium oxide and evaporating the resulting solution to dryness.⁸⁷ After three recrystallisations the prepared tetra deuteriomalonic acid was found to be at least 97.4% deuterated. The extent of deuteration of the carboxylic groups was examined qualitatively by infra-red spectroscopy using a Grubb Parsons spectrophotometer, when the OH absorption frequencies were removed on examining the spectrum of the deuterated compound in the form of a potassium bromide disc compared to those of the hydrogen compound. The extent of deuteration of the carboxylic groups was estimated quantitatively by nuclear magnetic resonance. A comparison between a standard

solution of the hydrogen compound in dioxan containing 0.1 gm. per c.c. and a standard solution of the deuterium one in dioxan also containing 0.1 gm. per c.c. permitted an assessment of the percentage of hydrogen present, FIGURE (III,1). The melting point of the tetradeuteriomalonic acid was 129.0°C (lit. value = $129.4 \rightarrow 130.3^{\circ}\text{C}$).⁶⁶

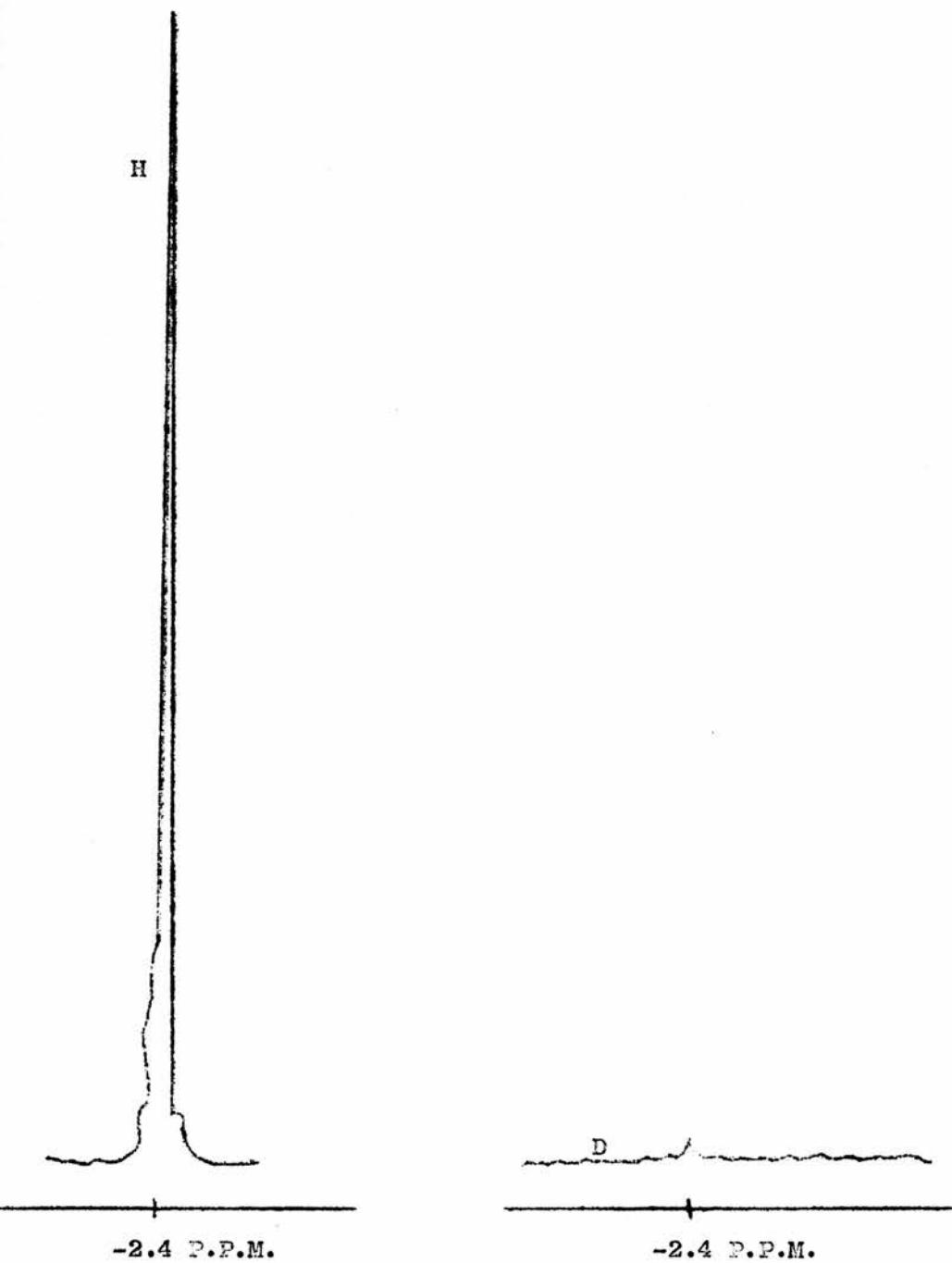
Tetradeuteriomalonic acid $\text{CD}_2(\text{COOD})_2$ was obtained from Yeda as 99.36% pure and was sublimed at $95 \rightarrow 100^{\circ}\text{C}$ before using. The melting point of the commercial sample was 129°C (lit. value = $129.4 - 130.3^{\circ}\text{C}$).⁶⁶ The rate coefficients of reactions obtained using the commercial product did not differ from those obtained using the synthesised tetradeuteriomalonic acid.

α, α' -Dimethylmalonic Acid

α, α' -Dimethylmalonic acid was prepared by the method described by Thorne⁶⁶ utilising the reaction of 160 gm. of diethylmalonate (B.D.H.) in a 9% alcoholic solution of sodium ethoxide prepared by adding 23 gm. of sodium to 760 cc. of dry ethyl alcohol, with 142 gm. of methyl iodide. After heating on a water-bath until the solution was neutral, a further 760 cc. of 9% sodium ethoxide solution and 142 gm. of methyl iodide were added and the whole again heated until the solution was neutral. After the addition of water to the solution the separated ethyl dimethylmalonate was

FIGURE (III,1)

Nuclear Magnetic Resonance Spectrum of Malonic and
Deuteriomalonic Acids in Dioxan, showing the Carboxylic
OH Peaks.



washed with water, dried over calcium sulphate and distilled, the fraction distilling between $193 \rightarrow 195^{\circ}\text{C}$ being collected. The ester was saponified with a 50% aqueous potassium hydroxide solution. After neutralising the solution with hydrochloric acid, washing with diethyl ether to remove traces of the unchanged ethyl dimethylmalonate and then acidifying with more hydrochloric acid, the liberated acid was extracted from the solution with diethyl ether. It was recrystallised first from water and then from diethyl ether. After several recrystallisations from diethyl ether the acid melted at $188-189^{\circ}\text{C}$ (lit. value = 192°C).⁸⁹ The neutralisation equivalent was 65.0 ± 0.2 (calculated value = 66).

Di Deutero α,α' -Dimethylmalonic Acid

This was prepared from α,α' -dimethylmalonic acid by dissolving the acid in deuterium oxide, in a manner exactly analogous to that described for the deuterio-malonic acid. Nuclear magnetic resonance studies of the deuterated compound in dioxan failed to show any hydrogen peak.

α -Phenylmalonic Acid.

The method of Basterfield and Hamilton⁹⁰ as described for the dimethyl ester was used to saponify

the commercially available diethyl ester (Aldrich Chemical Co.). 5.7 Grams of ethyl α -phenylmalonate were dissolved in 50 cc. of diethyl ether and mixed with 100 cc. of an approximately 4% (by weight) aqueous solution of sodium hydroxide. The two-phase system was shaken thoroughly for an hour at room temperature after which the aqueous layer containing sodium α -phenylmalonate was separated, extracted with diethyl ether to remove traces of unchanged ester and finally acidified with dilute sulphuric acid. The acidic aqueous phase was again extracted with diethyl ether and the ether removed on a rotary-film evaporator at room temperature. The resulting acid, after several recrystallisations from diethyl ether-petroleum ether (b.pt. 100-120°C) mixtures melted at 152°C (lit. value = 152-153°C)⁹¹. The neutralisation equivalent was 90.6 \pm 0.2 (calculated value = 90.0).

Sodium α -Phenylmalonic Acid

The preparation of this compound was carried out as described by Basterfield and Tomecko.⁹² Thus an aqueous solution of α -phenylmalonic acid was treated with rather less than one equivalent of sodium hydroxide. The solution was then evaporated to dryness under vacuum, and the residue washed thoroughly with sodium-dried diethyl ether. The resulting salt melted at 185°C with decomposition.

(lit. value = 184 - 188°C).⁹²

Ethyl Hydrogen α-Phenylmalonate

Ethyl hydrogen α-phenylmalonate was prepared by the method described by Corey.⁷⁹ A mixture of 12.2 gm. of diethyl α-phenylmalonate (Aldrich Chemical Co.) and 2.9 gm. of potassium hydroxide in 80 ml. of 50% aqueous ethanol (by volume) was allowed to stand at room temperature for approximately thirty minutes until the solution was neutral. The crude half-ester was obtained by acidifying the solution with dilute hydrochloric acid, and then extracting with diethyl ether. On removal of the ether at room temperature using a rotary-film evaporator, the crude half-ester was obtained and purified by several recrystallisations from methylene chloride and petroleum ether (b.pt. 100-120°C) mixtures. After drying the material obtained melted at 76°C (lit. value = 76-77°C).

The decarboxylation product of the half-ester, phenylacetic acid is also noted in the literature to melt at 76°C. In order to establish the preparation of ethyl hydrogen α-phenylmalonate the following additional tests were applied:

- (1) A mixed melting point of the product with phenylacetic acid showed the mixture to melt over a range from 60-66°C, which is considerably lower than the 76°C

quoted for both phenylacetic acid and ethyl hydrogen α -phenylmalonate. This inferred the two components of the mixture to be different.

(2) Infra-red data on the solid material suspended in a nujol mull, obtained using a Perkin Elmer 237 instrument is shown in FIGURE (III,2). The spectrum shows the presence of two carbonyl groups, the absorptions at 1720 cm^{-1} and 1665 cm^{-1} being attributed to the C=O of the carboxylic acid group, while the absorption at 1745 cm^{-1} corresponded to the C=O of the ester. The C-O stretch absorbed at 1170 cm^{-1} and the OH absorption bands were found between 2,500 and $2,700\text{ cm}^{-1}$ and were comparable with those found in a similar spectrum of phenylacetic acid, but the latter failed to exhibit absorptions at 1745 cm^{-1} and 1170 cm^{-1} , FIGURE (III,3), as would be expected if these absorptions corresponded to the ester group absorptions.

(3) Nuclear magnetic resonance studies of the compound run in deuteriochloroform established the presence of an ethyl group FIGURE (III,4). The integrated peak areas corresponded to those expected for ethyl hydrogen α -phenylmalonate. The neutralisation equivalent was 200 (calculated value = 208).

Sodium Ethyl α -Phenylmalonate

This compound was prepared by treating a solution of

FIGURE (III,2)

Infrared Spectrum of Ethyl Hydrogen α -Phenylmalonate

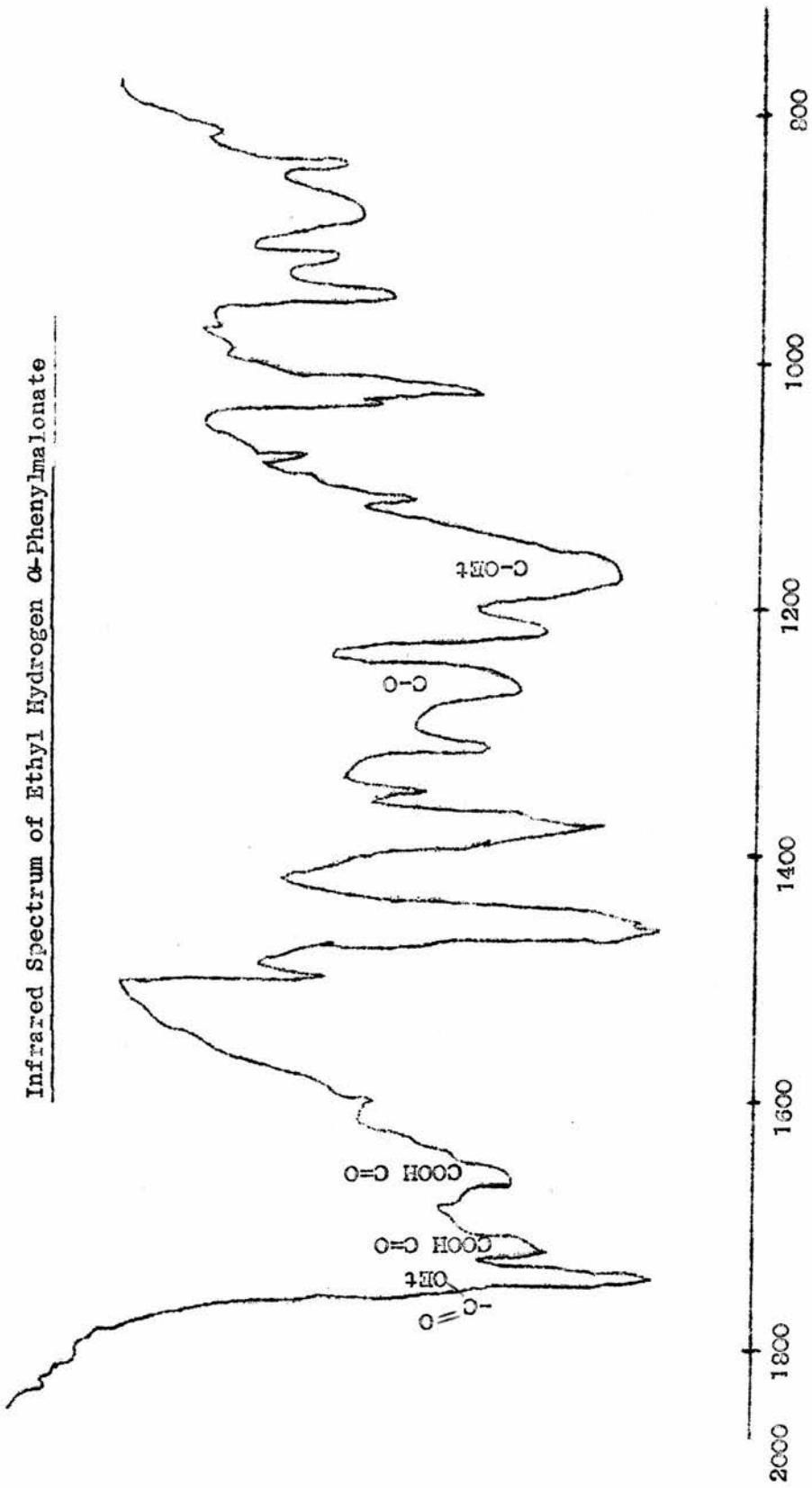
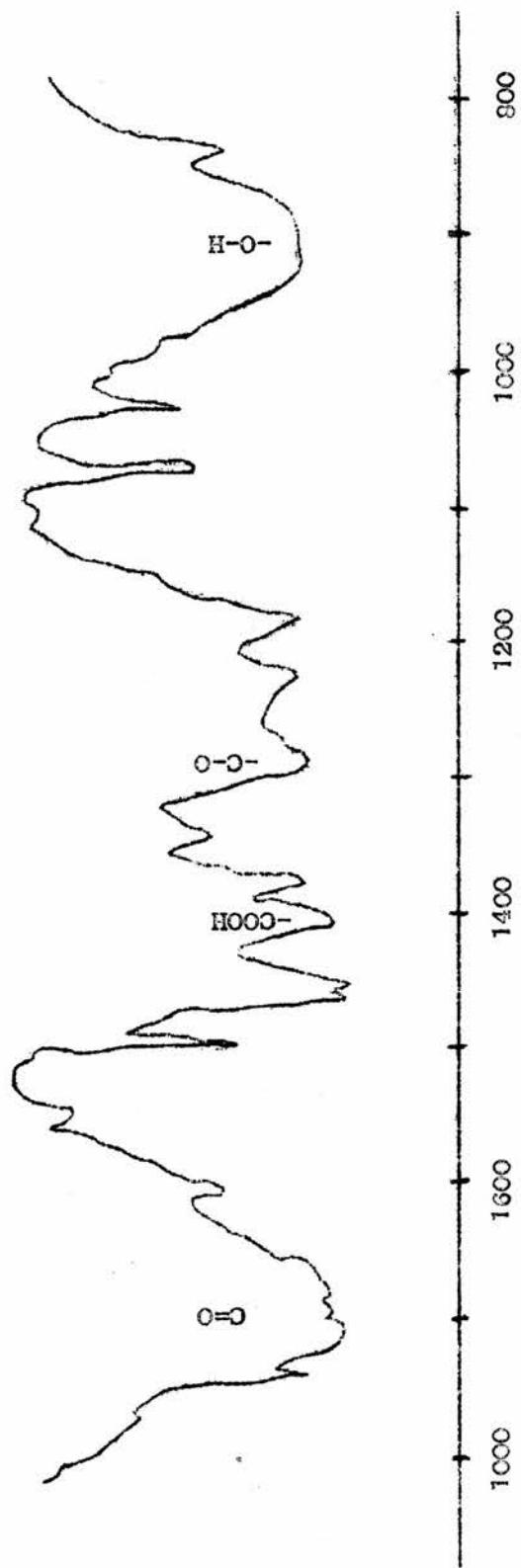


FIGURE (III,3)

Infrared Spectrum of Phenylacetic acid



ethyl hydrogen α -phenylmalonate in the minimum amount of dry ethanol, with one equivalent of approximately 1M. analar sodium hydroxide dissolved in dry ethanol. The reaction flask was cooled in an ice bath to slow down any competing ester hydrolysis. A small amount of the disodium salt which precipitated out of the solution and whose structure was verified by nuclear magnetic resonance, FIGURE (III,5) was removed by centrifugation. The ethanol solution was evaporated to dryness at room temperature under vacuo, and the resulting salt washed with dry diethyl ether to remove any traces of ethyl hydrogen α -phenylmalonate. After drying the salt it was observed to melt with decomposition above 115°C . In order to establish the structure of this compound several physical tests were carried out.

(1) An infra-red spectrum of the solid suspended in nujol exhibited no OH absorptions between $2,500\text{ cm}^{-1}$ and $2,700\text{ cm}^{-1}$ as found for the half-acid. At lower wave numbers FIGURE (III,7) an absorption at 1740 cm^{-1} was attributed to the C=O absorption of the ester group and one at 1170 cm^{-1} to the C-O of the ester group and these can be compared with the spectrum of ethyl hydrogen α -phenylmalonate FIGURE (III,2). A comparison of FIGURE (III,7) with the spectrum of the disodium salt of α -phenylmalonic acid FIGURE (III,6) suggested the absorptions

FIGURE III, 4.

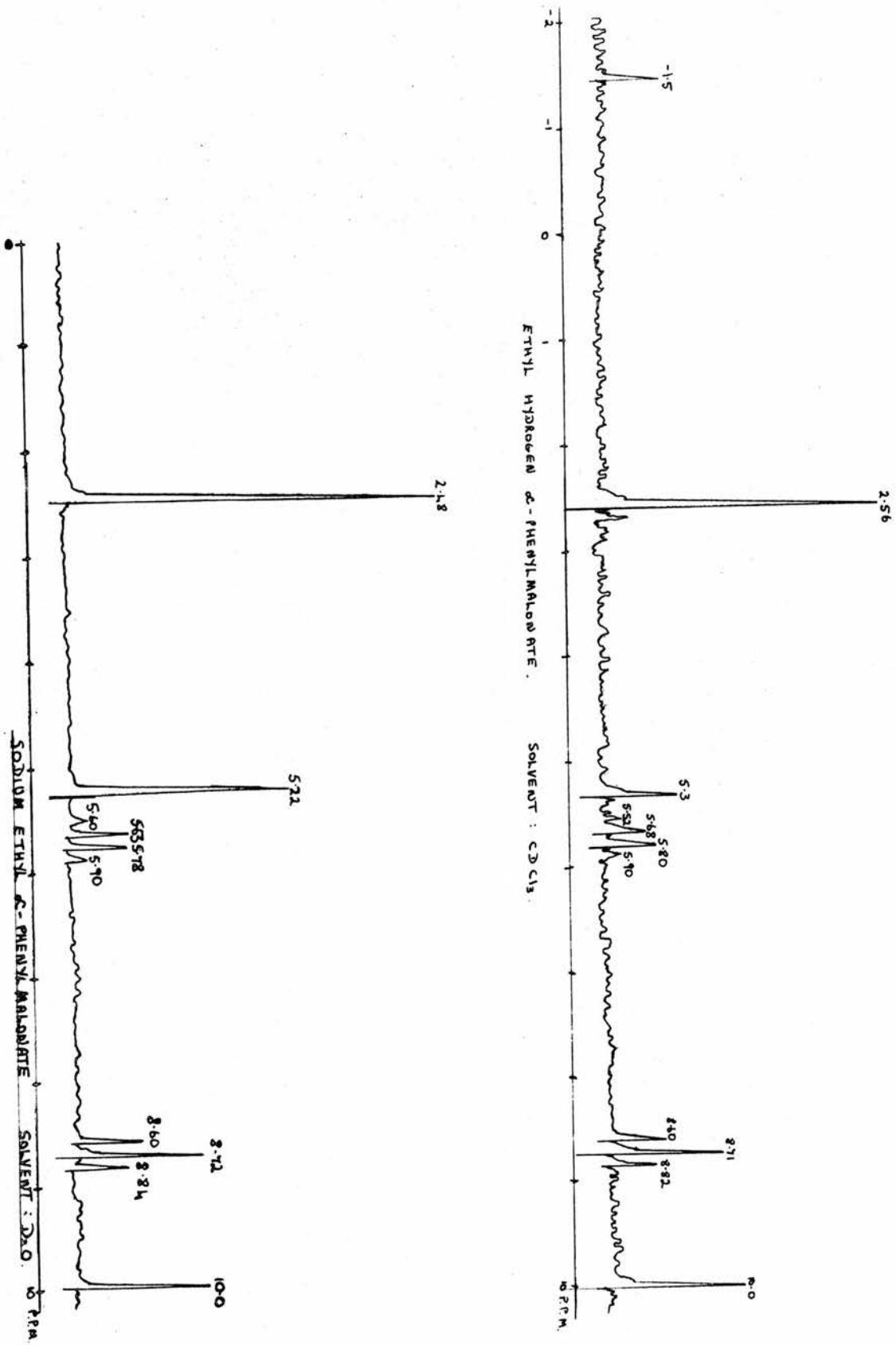


FIGURE III, 5

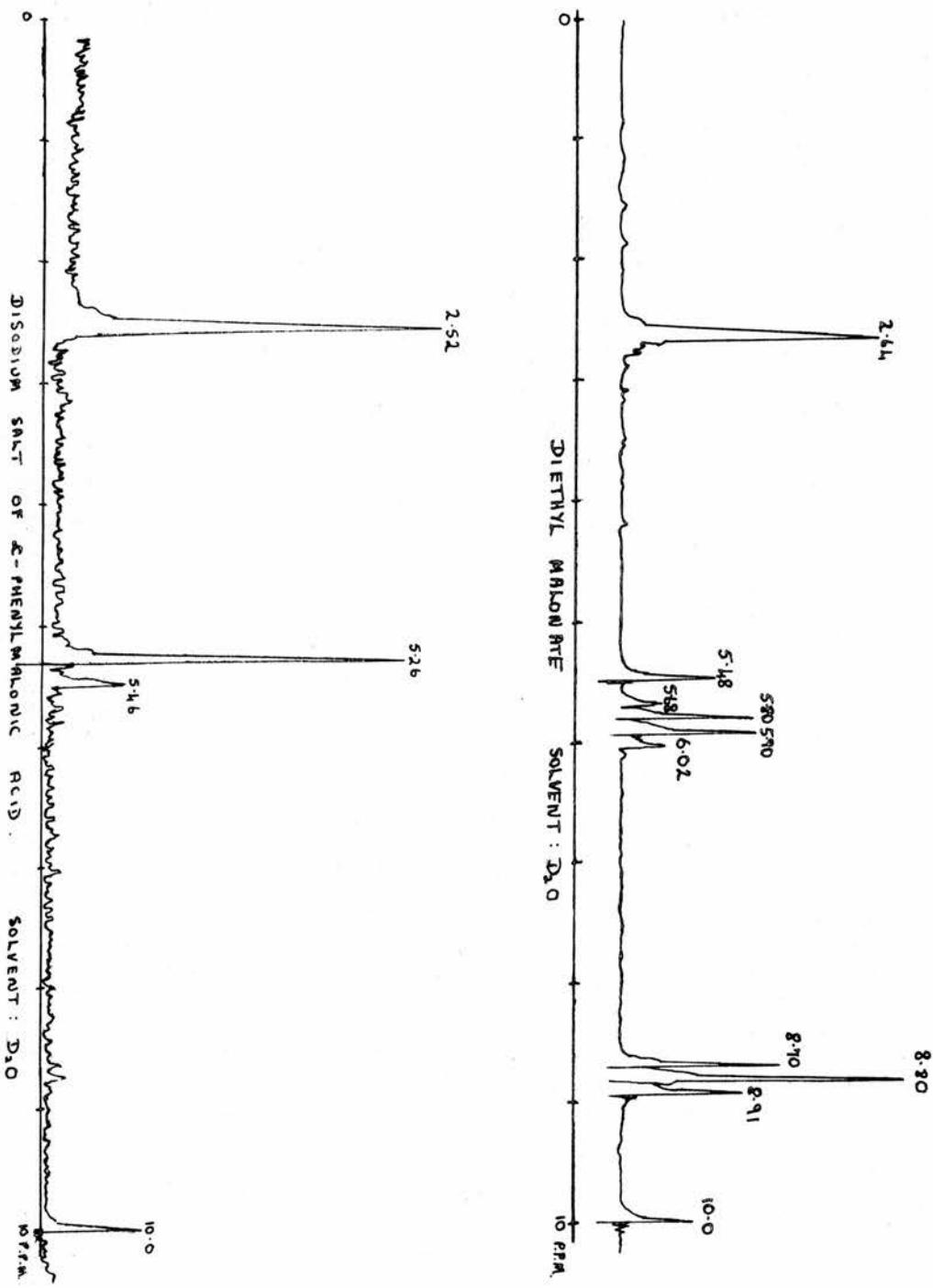


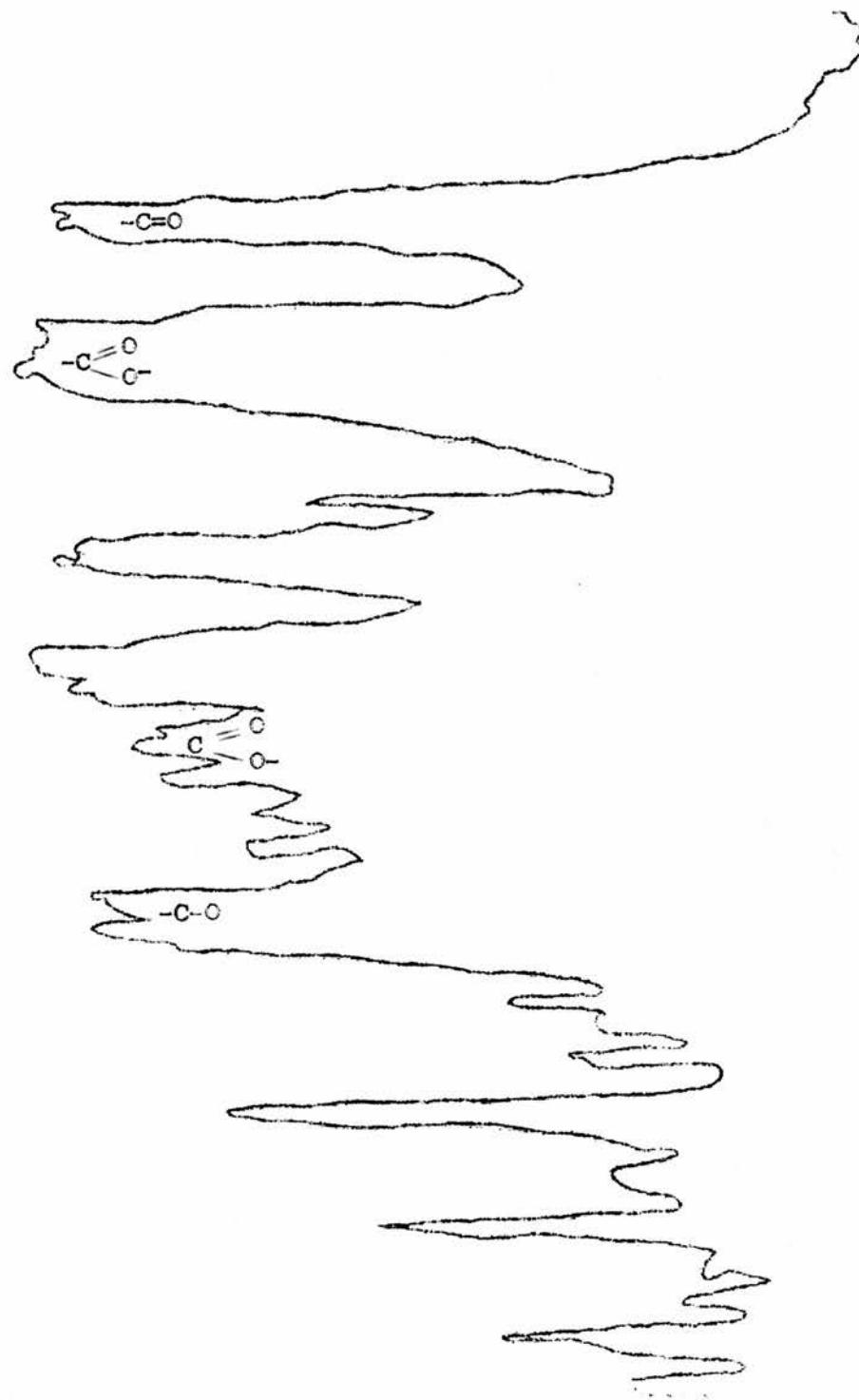
FIGURE (III,6)

Infrared Spectrum of Disodium Salt of α -Phenylmalonic Acid



FIGURE (III,7)

Infrared Spectrum of Sodium Ethyl α -phenylmalonate



at 1600 cm^{-1} and $1300 - 1350\text{ cm}^{-1}$ corresponded to carboxylate ion absorptions. These bands occurred in the ranges $1610 - 1550\text{ cm}^{-1}$ and $1420 - 1300\text{ cm}^{-1}$ as defined by Bellamy⁹³ for the absorption bands corresponding to carboxylate ion.

(2) Studies of the compound by nuclear magnetic resonance using deuterium oxide as a solvent, established the presence of an ethyl group FIGURE (III,4) and the integrated peak areas agreed well with those expected for sodium ethyl α -phenylmalonate.

Analysis. Calculated for $C_{11}H_{11}O_4Na$: C, 57.39; H, 4.78; Na, 9.99. Found: C, 56.95; H, 4.54; Na, 9.75.

Solvents

In the kinetic studies only deionised pure water was utilised in making up all the solutions.

The deuterium oxide was commercially obtained from Norsk-Hydro as, at least, 99.7% pure and was used without further purification.

Dimethylsulphoxide obtained from B.D.H. was purified by distillation from calcium hydride, in an atmosphere of nitrogen, and then kept dry by storage over molecular sieve.

B.D.H. Dioxan was purified by the method described in Fieser⁹⁴ and dried by storage over molecular sieve. For the experiments using deuteriomalic acid in dioxan, the solvent

was first saturated with deuterium oxide and then dried. Before use the dioxan was investigated using nuclear magnetic resonance and no trace of water could be detected when the sample was compared with a sample containing 20% water.

Ethyl alcohol was purified by the method described in Vogel.⁹⁵

Diethyl ether was dried by distillation from sodium and stored over sodium metal.

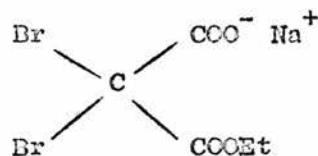
Xylene commercially purchased as sulphur free was redistilled and dried over sodium wire.

SECTION IV

APPENDIX AND BIBLIOGRAPHY

Appendix 1. A preliminary investigation of the rate of base catalysed hydrolysis of diethyl dibromomalonate in aqueous-ethanol solution.

A brief study of the base catalysed hydrolysis of diethyl dibromomalonate was carried out to determine the experimental conditions necessary to prepare the monosodium salt of the half ester (i) in optimum yield. This particular compound was considered an ideal substrate for studying the



(i)

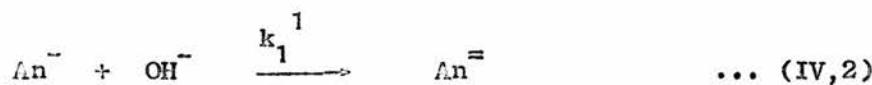
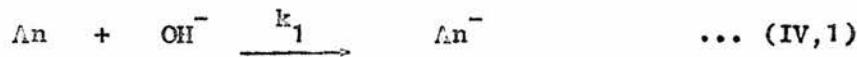
importance of internal proton transfer in facilitating thermal decarboxylation in aqueous solutions, as its estimated rate of ester hydrolysis under these conditions was considerably less than the reported rates of decarboxylation of both α,α' -dibromomalonic acid and its monocation. A literature survey showed that no half esters of the parent acid had been previously isolated. Thus the rates of hydrolysis of both the first and second ester groups of diethyl dibromomalonate were investigated and these results are reported herein. For comparison, the rates of hydrolysis

of the first and second ester groups of diethylmalonate were also investigated under similar experimental conditions.

Experimental

The hydrolysis reaction was followed with the aid of a Radiometer pH-stat assembly consisting of a type SBR2 titrigraph coupled to an SBUL syringe burette and a TTA3 titration assembly. The kinetics were carried out at a predetermined constant pH to provide a constant excess of base; under these conditions the reaction is pseudo first order in ester concentration. A pure aqueous medium was unsatisfactory for the study of diethyl dibromomalonate due to the insolubility of this compound and, instead, the solvent used was a 60% aqueous-ethanol mixture. The base added was a standard solution of sodium hydroxide also in 60% aqueous ethanol to prevent any alteration of the medium on addition of base.

Base catalysed hydrolysis of the diester, represented as An , takes place as described by equations (IV,1) and (IV,2). The ratio of the rate coefficients $\frac{k_1}{k_1^1}$ for successive



first order reactions can be calculated by the "time-ratio" method put forward by Schwemer⁹⁶ and described by Frost and Pearson.⁹⁷ The percentage reaction, deduced from the volume of standard base added, was plotted against time and values of the ratio $\log \frac{t_x}{t_y}$, where t_x and t_y were the times necessary to complete x% and y% of the reaction respectively, were compared with calculated values, set in tabular form, for various ratios of $\frac{k_1}{k_2}$.⁹⁸ The magnitude of the rate constant k_1 was also calculable from the tables and, on substitution into equation (IV,3) gave the half-life of a bimolecular reaction. In this way the time (where $[A_0]$ =

$$t_{\frac{1}{2}} = \frac{1}{k_1 [A_0]} \quad \dots \text{ (IV,3)}$$

initial concentration of the ester) required to produce the half-hydrolysed ester in optimum yield, following the addition of base to the diester, can be calculated from a knowledge of $t_{\frac{1}{2}}$ and the ratio $\frac{k_1}{k_2}$.

In an actual kinetic experiment, a known weight of the diester was dissolved in a known volume (approx. 10 c.c.) of 60% aqueous ethanol. This solution was well stirred, under an atmosphere of nitrogen, in a thermostatted container at a constant 25°C. The pH-stat, set to the predetermined value, was then activated. After the initial rapid addition of standard base to bring the solution up to the predetermined

pH, the rate of hydrolysis was followed by the addition of further base to maintain the pH. The % reaction was therefore directly proportional to the quantity of base added at a constant pH.

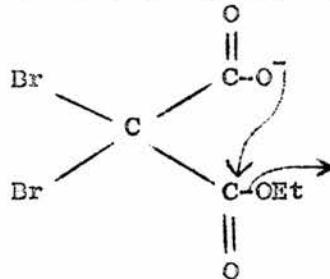
Discussion of Results

In 60% aqueous ethanol at pH = 11.9, the first hydrolysis for diethyl malonate went to completion in about two hours, but the second hydrolysis was considerably slower. The value of the ratio $\frac{k_1}{k_2}$ was estimated as at least 0.005 which is smaller than the value of 0.015 reported previously for the reaction under slightly different conditions.⁹⁹

For diethyl dibromomalonate under similar conditions, hydrolyses of both ester groups took place readily and proceeded to completion. It was found to be impossible to adjust the conditions so that $\text{Br}_2\text{C}(\text{COOEt})\text{COO}^-$ was formed without considerable hydrolysis of the second ester group occurring. It was apparent that the rate coefficient for the second hydrolysis (k_2^1) of diethyl dibromomalonate was very much faster, relative to the rate coefficient for the first hydrolysis (k_1^1) than for diethyl malonate itself. The calculated ratio $\frac{k_1^1}{k_2^1}$ from the titration curve by the "time-ratio" method of Schwemer had a value of 0.1, which corresponded to the maximum rate of the addition of

base by the radiometer. Thus the actual $\frac{k_1^{-1}}{k_1}$ ratio was probably larger.

The greatly enhanced rate of the second hydrolysis (k_1^{-1}) for diethyl dibromomalonate, relative to that for diethylmalonate, may arise from inductive withdrawal of electrons by the two bromine atoms facilitating attack by the second hydroxide ion on the intermediate anion. This effect, however, would also facilitate the initial attack by hydroxide ion on the diester. It therefore seems possible that other interactions, for instance neighbouring group participation by the carboxylate ion in $\text{Br}_2\cdot\text{C}(\text{COOEt})\cdot\text{COO}^-$, may be important. Participation



by this group promoting ester hydrolyses has been described recently by Thanassi and Bruice¹⁰⁰ for the hydrolyses of the monoesters of phthalic acid. There are, however, no previous reports of neighbouring group participation by carboxylate ion in three carbon systems in which considerable strain would have to be induced for this interaction to occur. It is noteworthy that in dibromomalonic ester, the bulk of the bromine atoms exerts considerable steric inhibition and tends to force the carboxylic moieties close together.

Since it was apparent that the preparation of pure $\text{Br}_2\text{C}(\text{COOEt})\text{.COO}^-$ could not be achieved by base catalysed hydrolysis, attention was directed to the preparation of the half-ester of phenylmalonic acid. A more thorough investigation of the relative rates of hydrolysis of diethyl dibromomalonate and related compounds should provide interesting information concerning the possibility of carboxylate participation in these systems.

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