STUDIES ON THE MECHANISM OF SOME ACID CATALYZED DECARBOXYLATIONS

By

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By Indian standards it would be extremely superfluous for me to thank Dr. Dunn. In India we do not thank our parents and teachers simply because the words are too empty to express our everlasting sentiments for them.

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ABSTRACT

The rates of decarboxylation of anthranilic acid and its 4-methyl and 4-methoxy derivatives have been studied in aqueous perchloric acid solutions upto 3M. Electron releasing substituents increase the rate of ring-protonation about equally for an acid and its anion, and decrease the ratio of decarboxylation to deprotonation of the protonated acid. No convincing evidence for decarboxylation by cleavage of COOH+ is obtained.

The rates of decarboxylation of 2,4-dimethoxybenzoic acid have been measured in aqueous perchloric and sulfuric acid solutions. On the basis of deuterium solvent isotope effects and C^{13} carboxyl isotope effects, a concerted mechanism has been proposed for its decarboxylation.

A preliminary study of the acid-catalyzed decomposition of a triazine produced by coupling diazotized anthranilic acid with pyrroline showed that the decomposition is not a decarboxylation. A tentative mechanism is proposed for the reaction.

I. LITERATURE REVIEW

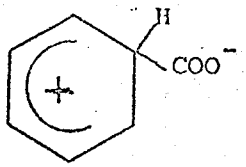
A. General

Organic chemists early recognized the importance of decarboxylation and applied it as a standard method for the degradation and synthesis of molecules. Physical chemists have used decarboxylation technique in their fundamental studies of reaction kinetics in solution. An extension of this work followed in the investigation of the mechanistic processes for thermal and catalytic decarboxylations.

Decarboxylations have been studied in the melt, solid, gas phase, aqueous and nonaqueous solutions and have been carried out by a number of procedures. Included among these are anodic, metal catalysed and photochemical methods. The most extensive studies have been made in acid- and base-catalyzed and thermal decompositions, excellent reviews of which have been made by Brown (8), Willi (44), and Long (20).

Decarboxylation of an acid RCOOH involves separation of H and R from the COO moiety. Since the H will usually leave as H^+, i.e. without electron , R normally leaves with an electron pair. Hence electron withdrawl in R caused, for example, by an electron attracting substituent, can be expected to accelerate the reaction. Aromatic carboxylic acids offer wide variations in the electron withdrawal in properties of R and, as a consequence there appears to be several operative mechanisms for decarboxylation. Evidence has accumulated to show that for some acids, it is the carboxylate anion which decomposes. For some other classes of aromatic acids the decomposing species is ArCOOH itself, and for still others acid-catalysis is observed, suggesting that the decomposing species is $ArCOOH_2^+$. From

studies by several groups with amino substituted aromatic carboxylic acid, there is evidence that a species of the structure as shown below, enters as an intermediate.



To generalize these possibilities the following formulations of electrophilic substitution have been put forward (8) analogous to the original terminology used in aliphatic nucleophilic substitution reactions (16).

S_E1 Mechanism

$$RCOO^- \longrightarrow R^- + CO_2 \quad \ldots \quad (a)$$

$$\underset{(H^+RCOO^-)}{RCOOH} \longrightarrow RH + CO_2 \quad \ldots \quad (b)$$

where H^+RCOO^- refers to the Zwitterion form of an acid, which contains a basic functional group.

S_E2 Mechanism

$$RCOOH + H^+ \longrightarrow RH + CO_2 + H^+ \quad (c)$$

$$RCOO^- + H^+ \longrightarrow RH + CO_2 \quad (d)$$

The S_E1 mechanism (a) has been demonstrated by a great deal of experimental evidence for aromatic systems containing strong electron withdrawing groups. There is a direct loss of CO_2 from a carboxylate species, leading to the formation of a carbanion.

$$ArCOO^- \longrightarrow CO_2 + Ar^- \quad (slow)$$

$$Ar^- + BH^+ \longrightarrow ArH + B \quad (fast)$$

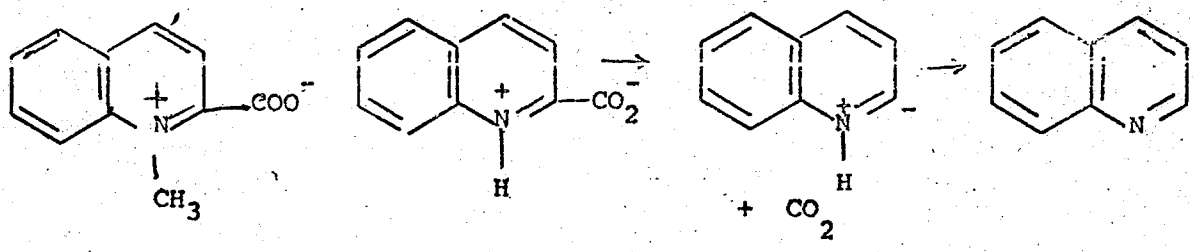
A good example of mechanism (a) is the decarboxylations of 2,4,6-trinitrobenzoic acid (39,40) and trihaloacetic acid (18,41). With 2,4,6-trinitrobenzoic acid the rate of decarboxylation is a maximum under conditions where it is completely dissociated into ions. Also, addition of base to aqueous or alcoholic solutions of this aromatic acid increases the rate of decomposition. Mathematical analysis of the data shows that a reaction of first order with respect to the anion is involved.

$$V = k_1 [ArCOO^-]$$

Evidence for the existence of the intermediate carbanion formed has also been indicated. For example, Pederson (27) showed that the addition of bromine has no effect on the rate of decarboxylation of the α-nitro isobutyrate anion even though the product is changed from 2-nitropropane to 2-bromo-2-nitropropane. He showed that the 2-nitropropane could not be brominated under the experimental conditions used. This shows that the bromine is reacting with an intermediate formed in the decarboxylation reaction.

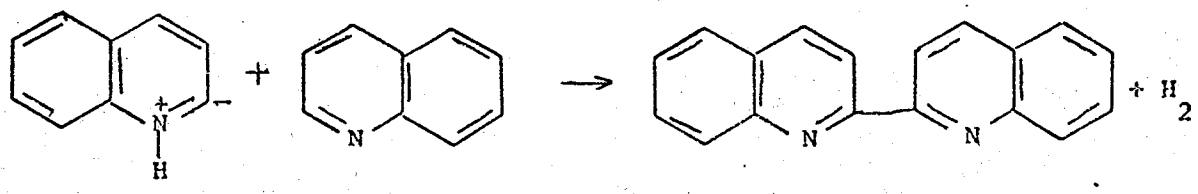
Examples of the $S_{E}1$ mechanism (b) can be found by examining the case in which the acid molecule is able to exist as the zwitterion. Brown (8) has pointed out that the activation energy needed for decarboxylation of a zwitterion could be predicted to be less than that for the corresponding acid anion on electronic grounds, thereby anticipating the rate constant for the $S_{E}1$ (b) process to be greater than for the $S_{E}1$ (a) or purely anionic decomposition

Nitrogen-containing acids of the α-amino type, such as picolinic, quinaldinic and isoquinaldinic acids, have been extensively studied by Brown, Hammick and coworkers (9). The activating electron acceptance here arises from the hetero N atom whose greater electronegativity compared to carbon becomes important. First order kinetics were observed in the decarboxylation of quinaldinic acid in quinoline. There is good evidence to show that the decarboxylation probably proceeds through the zwitterion form. They showed that the methylbetain (I) of the acid decarboxylates readily and therefore the analogous zwitterion (II) is probably the form of the acid that decarboxylates.



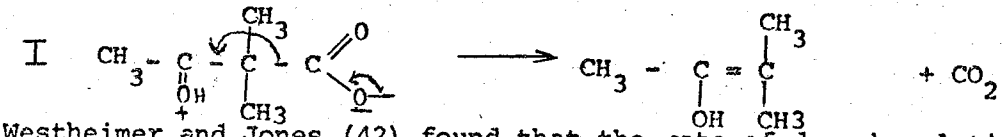
I II III

The existence of the α-quinolyl carbanion intermediate (III) was supported by the fact, that in carrying out the decarboxylation in such reagents as aldehydes, ketones, quinoline, and aromatic nitro compounds, one could isolate from the reaction mixtures other substances, an example of which is given by α-α'-diquinolyl (IV).

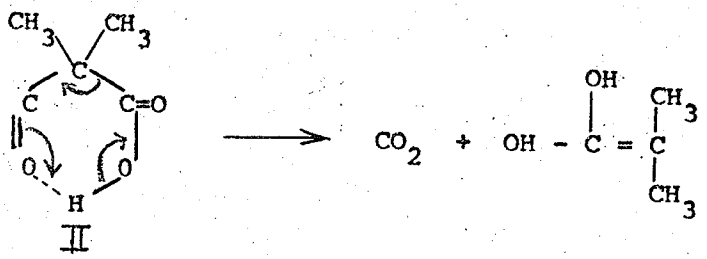


IV

For several β-keto acids it has been demonstrated that the decarboxylation involves both the anion and the zwitterion forms of the acids. Since α,α-dimethylacetoacetic acid which cannot exist in an enolic form, is readily decarboxylated. Pederson (27) concluded that it is the zwitterion form of this acid that decarboxylates:



Westheimer and Jones (42) found that the rate of decarboxylation of this acid (α,α-dimethylacetoacetic acid) is virtually independent of the dielectric constant of the solvent. Since a reaction which takes place by way of a polar intermediate should proceed more rapidly in solvents of high dielectric constant, they therefore concluded that Pederson's zwitterion cannot be an intermediate. Instead, these authors suggested that it is the hydrogen bonded form (II) of the acid that decarboxylates.



An S_E2 mechanism for decarboxylation of aromatic acids was first proposed by Schenkel and Schenkel-Rudin (36) as they showed quantitatively that anthracene-9-carboxylic acid decomposed more rapidly in acidic solvents (chloroacetic acid and sulfuric acid) than in basic (7,8-benzoquinoline) or neutral solvents. They also pointed out that the α-carbon atom in anthracene-9-carboxylic acid has a high electron density, which favours the attraction of a proton.

Two possibilities arise. The proton may attack the undissociated acid molecule:

$$H^+ + RCOOH \xrightarrow{k_1} HR + CO_2 + H^+ \quad S_E2 \text{ mechanism (c)}$$

yielding a kinetic equation of the type shown below.

$$\text{Rate} = k_1[H^+][RCOOH]$$

On the other hand, the reaction could take place between a proton and the acid anion:

$$H^+ + RCOO^- \xrightarrow{k_2} HR + CO_2 \quad \ldots S_E2 \text{ mechanism (d)}$$

When the kinetic equation would be

$$\text{Rate} = k_2[H^+][RCOO^-]$$

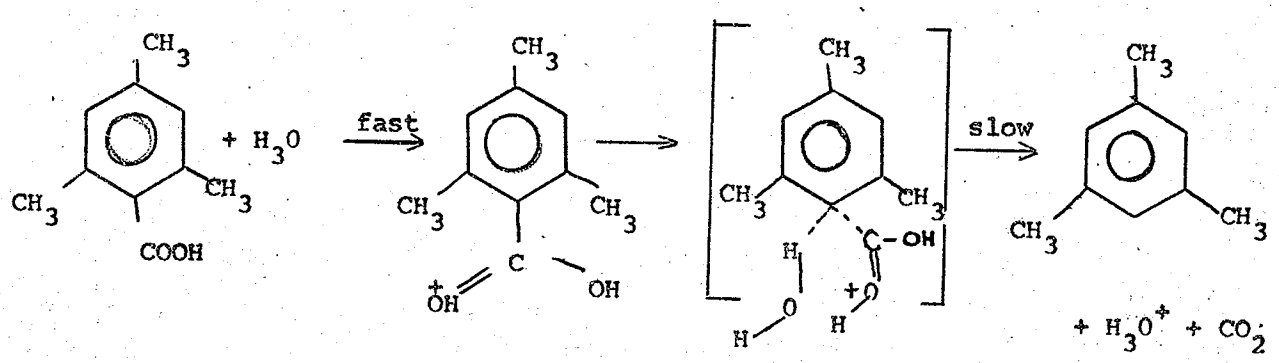
For either mechanism the rate is dependent on the attraction between the α-carbon atom of the acid and a proton. Since the formation of the anion will increase the electron density on the α-carbon atom, it may be expected that the second mechanism (S_E2 d) written above will require less activation energy than the first. However, it is possible that both mechanisms will occur, singly or simultaneously, and an analysis has to be made for each type of acid studied.

In the decarboxylation of various 2,4,6-trialkylbenzoic acids experimental data were obtained in concentrated sulfuric acid solutions (33,35).since in dilute aqueous solutions no noticable reaction occurs. Schubert (32) investigated the decarboxylation of mesitoic acid in sulfuric acid and demonstrated a proportionality between the pseudo first order rate constants and the concentration

of the hydroxonium ion in aqueous acid containing 80-100% of sulfuric acid. The rate is therefore given by the equation:

$$\text{Rate} = k[H_3O^+][\text{acid}]$$

and hence the reaction was suggested to occur by a S_E2 mechanism of the following type:



Bothner-By and Bigeleisen (5) measured the carboxyl-C^{13} kinetic isotope effects for the decarboxylation of natural mesitoic acid in 86% sulfuric acid solution at 92°C. Stevens et al (38) have simultaneously measured the C^{13} and C^{14} isotope effects under the same conditions, using a sample of mesitoic acid with 0.8% C^{14} in the carboxyl group. Below is a summary of the results of both sets of workers.

TEMP (°C)	ISOTOPE	$100(k/k^* - 1)$	Ref
60 ± 0.5	C^{13}	3.8 ± 0.1	38
61.2 ± 0.5	C^{13}	3.7 ± 0.3	5
92.0 ± 0.1	C^{13}	3.2 ± 0.1	5
60.0 ± 0.5	C^{14}	10.1 ± 0.5	38

These results indicate that caboxyl carbon bond-breaking occurs in the slow step of the decarboxylation, in agreement with Schubert's proposed mechanism.

B. Hydroxy and Alkoxybenzoic acids.

A much clearer situation is found with the more reactive hydroxy and alkoxy benzoic acids in which the rate of decarboxylation can be measured in weakly acidic aqueous solutions. The first reliable kinetic data which take into account the acidity constant of the compound were obtained on 2,4,6-trihydroxybenzoic acid (9,34). Since this acid and its anion absorb UV light much more strongly than the decarboxylation product phloroglucinol (1,3,5-trihydroxybenzene), the decomposition reaction can be followed by spectrophotometric means. Keeping the hydrogen ion concentration constant by the use of buffered solutions, pseudo first order rate constants k_1 were obtained. With increasing perchloric acid concentration the k_1 value first increased until at about $C_{HClO_4} = 1\,\underline{M}$ an upper limit was reached. Furthermore, the UV spectra of acid ArCOOH and anion $ArCOO^-$ differ sufficiently that it is possible to determine from absorbance extrapolated to time t = 0 the extent of dissociation of the trihydroxybenzoic acid under the prevailing conditions. In this manner Schubert and Gardner (34) find a proportionality between k_1 and $[ArCOOH]/C_{HA} = [ArCOOH]/([ArCOOH] + [ArCOO^-])$, the fraction of undissociated acid at equilibrium.

Schubert and his coworkers (35) have studied the decarboxylation of 2,4,6-trimethoxybenzoic acid in concentrated solutions of perchloric acid. From spectral changes in 20-64% mineral acid they find that

the ionization of the organic acid (B) to $RCOOH_2^+$ (BH^+) and to RCO^+ (AC^+) is complete in 47% and 64% acid respectively. The rate data is in agreement with a unimolecular mechanism having the rate expression

$$\log k_{obsd} + H_o - \log \frac{[B]}{[B]_{stoich}} = \text{const.}$$

$$[B]_{stoich} = [B] + [BH^+] + [AC^+]$$

upto 20% perchloric acid. In this region of acidity $[BH^+]$ and $[AC^+]$ are negligible and $[B]_{stoich} = [B]$. Between 20-47% mineral acid where there is appreciable ionisation to (BH^+), k_{obsd} is found to be increasing faster than required by the unimolecular mechanism. Therefore, the following bi- or termolecular mechanism has been proposed for decarboxylation in this region of acidity.

bimolecular

$$RCOOH + HA \longrightarrow R{+}\begin{matrix}COOH\\H\end{matrix} + A^-$$

$$R^+\begin{matrix}COOH\\H\end{matrix} + A^- \longrightarrow RH + CO_2 + HA$$

termolecular

$$HA + RCOOH + A^- \longrightarrow A^- + RH + CO_2 + HA$$

or

$$HA + RCOOH_2^+ + A^- \longrightarrow A^- + RH + COOH^+ + HA$$

The mechanism of decarboxylation of substituted salicylic acids, and in particular the decarboxylation of p-aminosalicylic acid, was investigated by Willi and his coworkers (45-49) in dilute aqueous solutions of strong acids to which KCl is added to constant ionic strength (I=0.1N). The pK values of the aromatic carboxylic acids were determined independently of the kinetic measurements by poten-

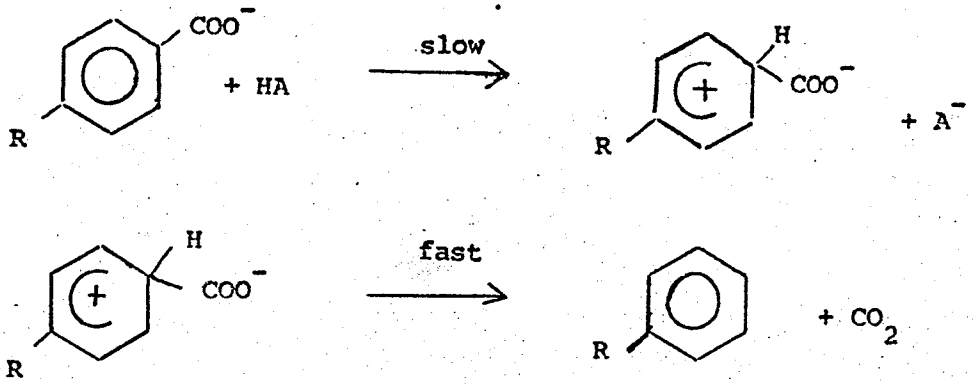
tiometric measurements on partially neutralized solutions of the same ionic strength and temperature. From the acidity constant and the H^+ concentration the extent of neutralization of the substrate under the conditions of the kinetic experiments can be calculated. There is found the same dependence between k_1 and the position of the dissociation equlibrium for salicylic acid as for 2,4,6-trihydroxybenzoic acid. Kinetic solvent-isotope effects on the decarboxylation of 4-hydroxy salicylic acid in water and deuterium oxide were determined (49) that gave further support to the bimolecular mechanism. The rate equations are:

$$\text{rate} = k_H^A [A^-][H^+] \quad \text{and}$$

$$\text{rate} = k_D^A [A^-][D^+]$$

where $[A^-]$ is the salicylate anion concentration and $[H^+]$ and $[D^+]$ are respectively the hydronium and deuteronium ion concentrations. The value, $k_H^A / k_D^A = 1.76$ was taken to indicate that the rate-determining step was a proton attack on the salicylate ion.

Furthermore, Willi (48) utilized the Hammett relationship to determine the electron requirement at the reaction centre by recording the decomposition rates of 4-methyl-, 4-methoxy-, 4-hydroxy- and 4-aminosalicylic acids in aqueous solutions. The rates were increased and the activation energies decreased as the electron-donating power of the substituent increased. The good correlation between the logarithm of the bimolecular rate constant and Brown's $\sigma+$ substituent constant supported a two step bimolecular mechanism.



However, a concerted mechanism (in which carbon-carbon bond-breaking and carbon-hydrogen bond-making occur simultaneously) cannot be completely excluded.

Using unenriched samples of 2,4-dihydroxybenzoic acid, Lynn and Bourns (25) observed a carboxyl-C^{13} isotope effect of 0.60±0.05% at 85°C for the reaction in aqueous perchloric acid solutions of varying concentrations (0.002 - 0.01M). The magnitude of this isotope effect is about five to seven times smaller than those previously observed in reactions in which the carbon-carbon bond-breaking occurs in the rate-determing step. While this is in agreement with Willi's mechanism, it could also be argued to be in favor of the concerted mechanism for the case in which the C-C bond has been only slighly altered after the reactant has passed into the activated state.

Lynn and Bourns shed further light on this problem by measuring the carboxyl-c^{13} isotope effect in acetic acid-sodium acetate buffer solutions of different concentrations. The k_{12}/k_{13} ratio

increased with increasing acetate ion concentration, a situation readily accounted for by the two step process. As the acetate ion concentration is increased, there would be an increasing tendency for this stronger base to abstract a proton from the intermediate and regenerate the reactants. This would decrease the concentration of the intermediate to such an extent that its decomposition will become rate controlling.

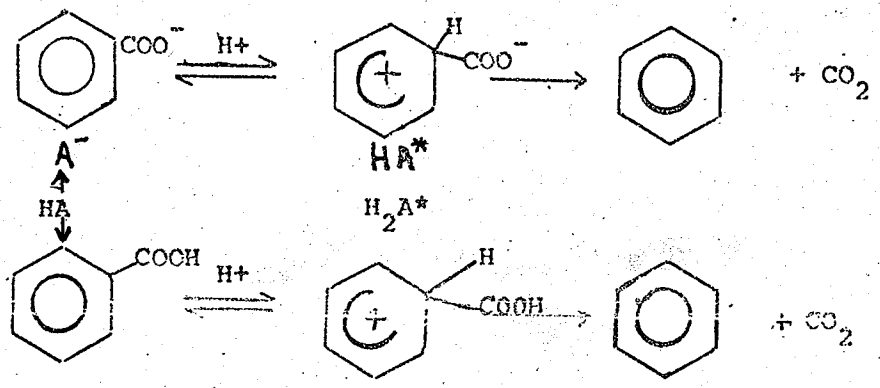
Their results are summarized below:

pH	CH_3COOH	CH_3COONa	$100(K/K^+ - 1)$
4.50	0.10	0.067	0.5 ± 0.1
5.15	0.05	0.15	1.1 ± 0.1
5.32	0.33	1.00	1.8 ± 0.1

Bourns (44) has measured the C^{13} carboxylic carbon isotope effects and deuterium solvent isotope effects on the decarboxylation of 2,4,6-trihydroxybenzoic acid. The C^{13}-carboxylic carbon isotope effect changes from 1.0042 in 10^{-3} M perchloric acid to 1.042 in 8.35 M where as the deuterium solvent isotope effect (k_{H_2O}/k_{D_2O}) changes from 3.41 in 0.014 M perchloric acid to k_{H_2O}/k_{D_2O} = 1.33 in 6.12 M perchloric acid.

Bourns and Willi (8) argue that in the lower region of acidity, the C^{13}-carboxylic carbon isotope effects and deuterium solvent isotope effects are in agreement with the slow protonation of the anion. But at high acidity the isotope effects indicate slow decarboxylation of the species.

Loss et al (24) argue that if the mechanism changes from the slow protonation of the anion to rate determining decomposition of the species H_2A^* as acidity increases, the rate ought to go faster in D_2O than in H_2O at high acidity. This is because acids are generally weaker in D_2O than in H_2O so that the equilibria $[HA] + [H^+] \rightleftharpoons [H_2A^*]$ and $[A^-] + [H^+] = [HA^*]$ will be shifted to the right in D_2O solutions.



In fact, k_{H_2O}/k_{D_2O} decreases as acidity increases but never becomes less than unity. They therefore point out that the equilibria $[A^-] + [H^+] \rightleftharpoons [HA^*]$ will also be shifted to the right in D_2O so that the observed deuterium solvent isotope effects can be accounted for if only HA^* decarboxylates.

C. Aminobenzoic acids

The stability of the three monoaminobenzoic acids in boiling aqueous solution was investigated by McMaster and Shriner (26). Anthranilic acid was found to decarboxylate by a first-order process twice as fast as p-aminobenzoic acid, while m-aminobenzoic acid had not decarboxylated after 3 hours under similar conditions.

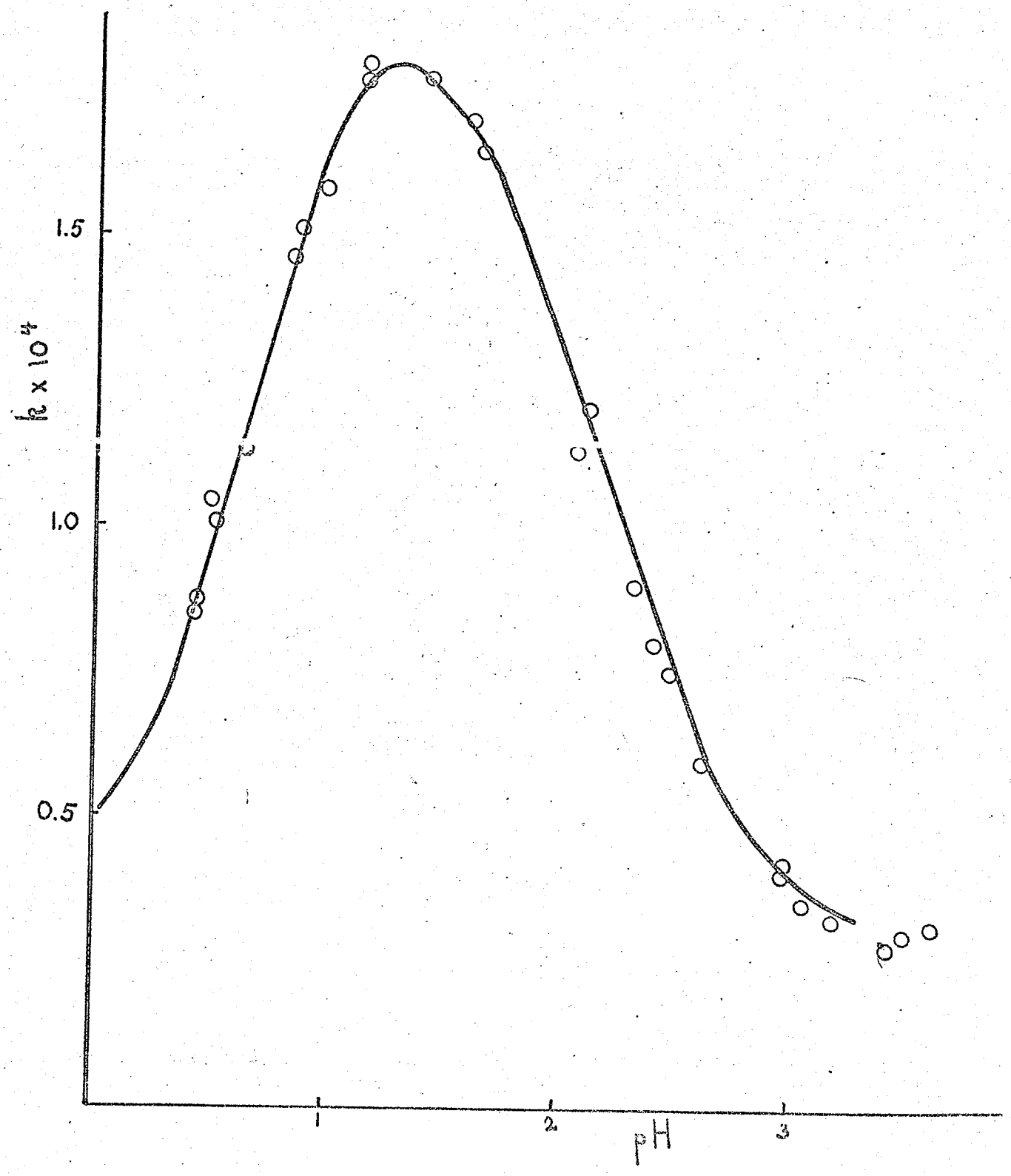
Stevens and coworkers (37) have further investigated the kinetics of the thermal aqueous and acid-catalyzed decarboxylation of anthranilic acid. These workers suggested that the reaction occurs by a mechanism involving proton attack on the α-carbon atom. The absence of a carboxyl-C^{13} kinetic isotope effect in 1M sulfuric acid led to the conclusion that the protonation of the anion at carbon 1 was the slow step. Dunn and Prysiashniuk (11A) decarboxylated a series of meta and para substituted anthranilic acids in nitrobenzene and concluded that the rate determining step was the attack by proton from one anthranilic acid molecule on the carbon α to the carboxyl group of the second molecule.

Dunn, Leggate and Scheffler (11) studied the effect of changing pH upon the rate and mechanism of decarboxylation of 4-methoxy-anthranilic acid at a constant ionic strength (0.50). The observed dependence of the rate constant (k) upon pH is shown graphically in figure I. Examination of this curve shows that k is a maximum at a pH of about 1.1-1.4, and decreases at both higher and lower pH values. Any mechanism proposed for this reaction must explain the shape of the curve in figure I and the value of the pH at the maximum value of k.

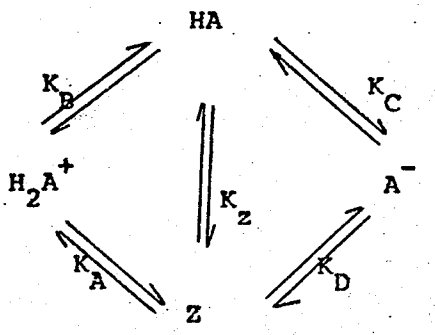
Kinetic studies of aromatic amino acids in aqueous solutions are complicated by the fact that there are four organic species in equilibrium with hydronium ion (4). The species, referred to as the Bjerrum species, can be represented by $HOOC\text{-}Ar\text{-}\overset{+}{N}H_3$ (abbreviated H_2A^+), $HOOC\text{-}Ar\text{-}NH_2$ (HA), $\overset{-}{O}OC\text{-}Ar\text{-}N^+H_3$ (Z), and $\overset{-}{O}OC\text{-}Ar\text{-}NH_2$ (A^-). The

FIGURE 1.

pH dependence of rate constants for decarboxylation of 4-methoxyanthranilic acid at 60°C.


1.5
1.0
0.5
k x 10⁴
1
2
3
pH

equilibria are shown in equation (2.1) with the hydrogen ion omitted.



... (2d)

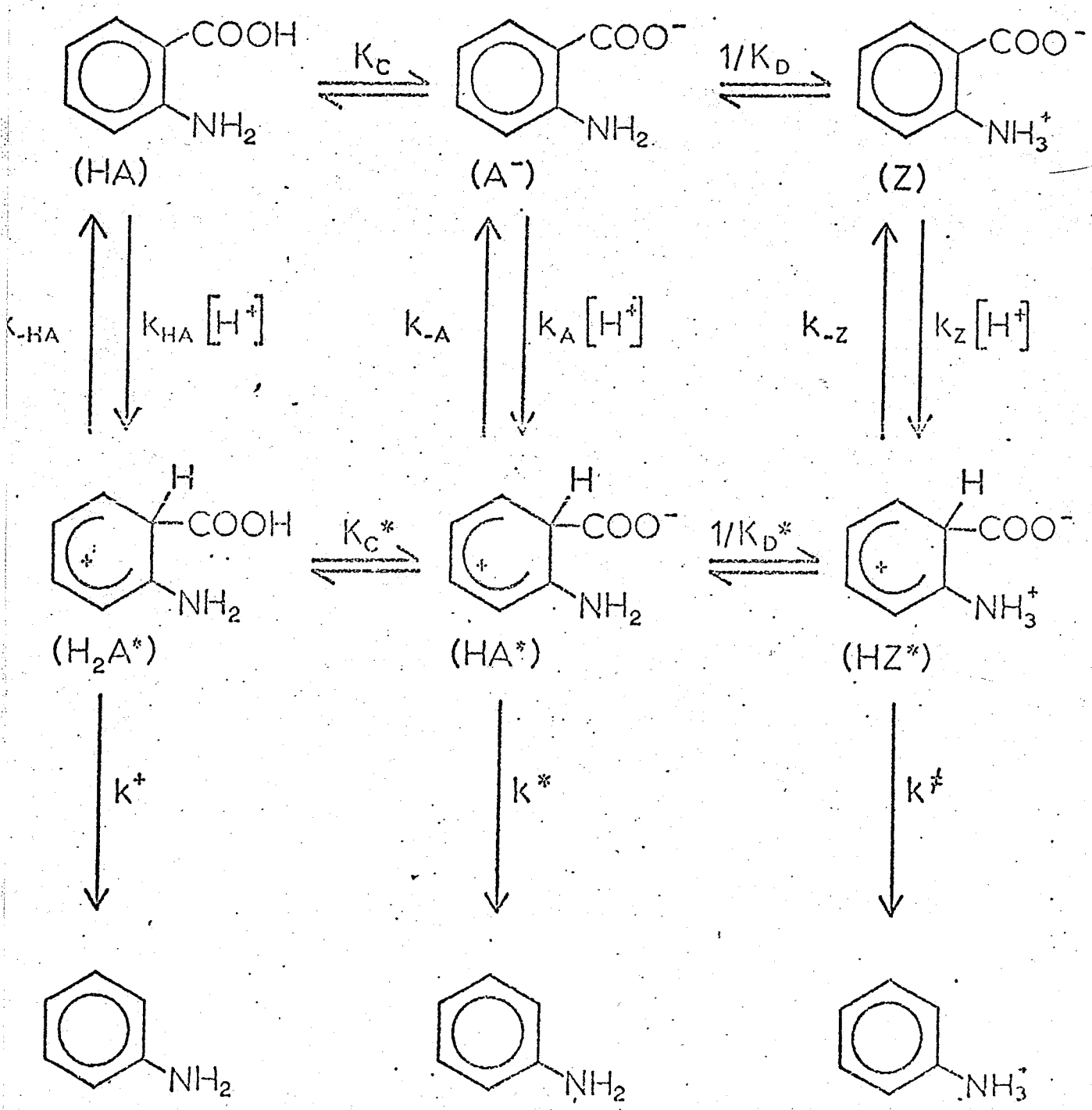
Dunn et al noted that the shape of the rate vs pH curve is very similar to that of the [HA] or [Z] vs pH curve. Each has a maximum at intermediate pH and approaches zero at either end of the pH scale, but the rate curve is displaced towards lower pH. There are three obvious possibilities which might account for this discrepancy.

1. The reaction involves simultaneous decarboxylation of two or more Bjerrum species.
2. Decarboxylation results from a reaction between different Bjerrum species.
3. A fifth Bjerrum species is formed by further protonation of the cation.

Since the pH at the rate maximum could not be accounted for by reaction of any combination of Bjerrum species, it was concluded that decarboxylation must take place via some intermediate which is not part of the Bjerrum system.

Dunn et al have proposed a mechanism for the reaction in which the non-Bjerrum intermediates H_2A^*, HA^* and HZ^* are formed

by protonation of the α-carbon of HA, A^- and Z respectively. This mechanism is shown below.



(2.2)

Assuming that all three non-Bjerrum intermediates decarboxylate, the following expression has been derived (11) for the rate of decarboxylation.

$$\frac{-d[C]}{dt} = [N]\{k_A K_2 + (k_{HA}K_B/K_1 + K_2K_A/K_1)[H^+]\} \times \frac{K^* + (K^+/K_C^* + k^{\ddagger}/K_D^*)(H^+)}{K^* + K_A + \{(K^+ + K_{-HA})/KC^* + (k^{\ddagger} + k_{-Z})/KD^*\}[H^+]}$$

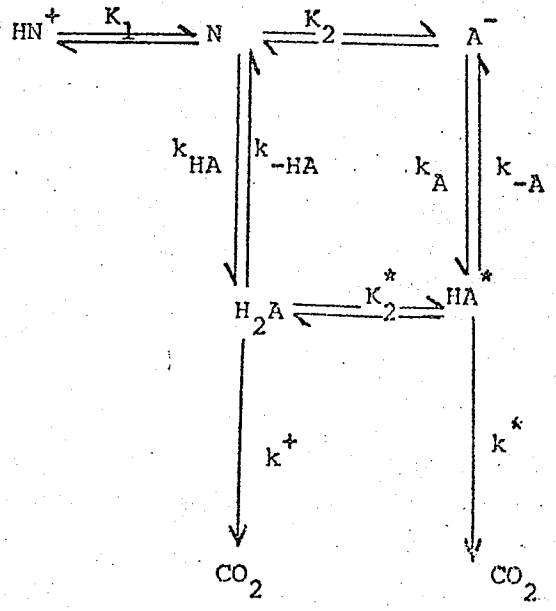
where $[N] = [HA] + [Z]$ (2.3)

and K_1 and K_2 are defined as

$$H_2A^+ \overset{K_1}{\rightleftharpoons} H^+ + N \quad (2.4)$$

$$N \overset{K_2}{\rightleftharpoons} H^+ + A^- \quad (2.5)$$

Since the ratio [HA]/[Z] is independent of pH, HA and Z may be combined under the single symbol N. Equation 2.2 may then be simplified to

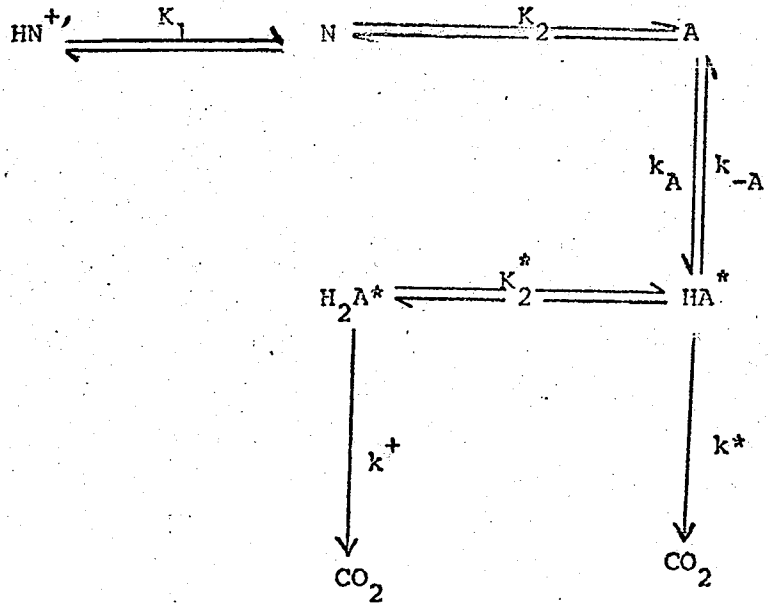


(2.6)

The rate expression then simplifies to:

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H^+]}{K_1 + [H^+]} \times \frac{k^* K_2^* + k^+ [H^+]}{(k^* + k_{-A}) K_2^* + (k^+ + k_{-HA}) [H^+]} \qquad (2.7)$$

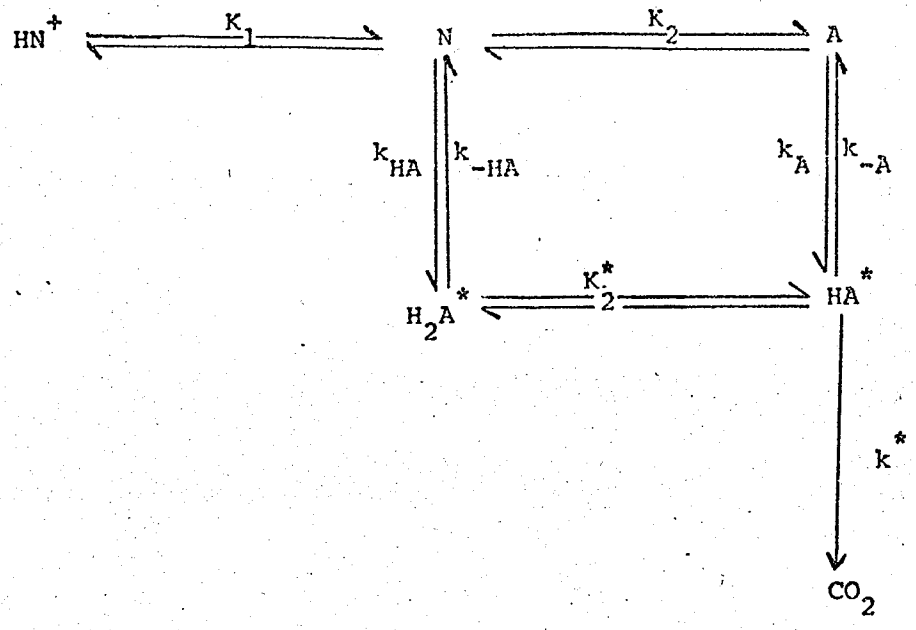
As it stands, equation (2.7) does not fit the data, because the $[H^+]^2$ terms of the numerator prevent the rate from becoming small at low pH. For the rate to decrease at low pH it will require either that $k_{HA} = 0$ or that $k^+ = 0$, but not both. That is, in order for equation (2.2) to represent the mechanism H_2A^* must participate, but either it is not formed directly by protonation of HA and Z or it does not decarboxylate. In the former case the mechanism becomes



(2.8)

$$k = \frac{k_A K_1 K_2}{K_1 + [H^+]} \times \frac{k^* K_2^* + k^+ [H^+]}{(k^* + k_{-A}) K_2^* + (k^+ + k_{-HA}) [H^+]}$$

and in the latter case



$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 \cdot [H^+]}{K_1 + [H^+]} \times \frac{k^* K_2^*}{(k^* + k_{-A}) K_2^* + (k^+ + k_{-HA})[H^+]} \qquad (2.9)$$

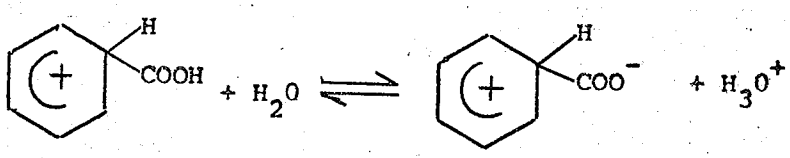
Dunn et al concluded that mechanism (2.8) requires a kinetic isotope effect at both low and high pH values whereas mechanism (2.9) requires an isotope effect at low pH value but can accommodate an effect or none at high pH.

Dunn and Buccini (10) solved the problem by measuring the carboxyl C^{13} kinetic isotope effect for 4-methoxyanthranilic acid at 60°C in aqueous solutions of different pH and constant ionic strength. The kinetic isotope effects are summarized below:

pH	$100(k/k^* - 1)$
-0.3	4.2±0.1
1.3	1.4±0.1
4.0	0.2±0.1

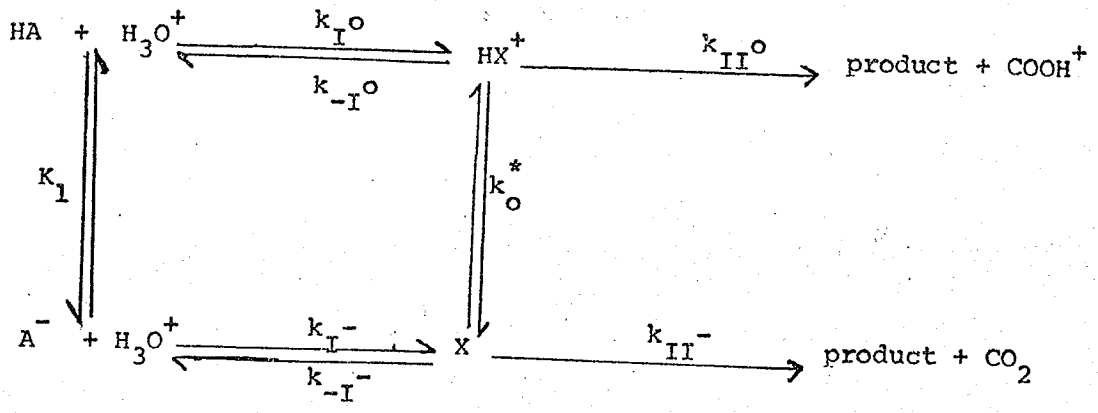
Thus, a large effect was found at low pH, and no isotope effect was found at high pH. Therefore, the reaction proceeds via mechanism (2.9), in which both of HA and Z may be protonated to form H_2A^* and HZ^*, but neither H_2A^* nor HZ^* decarboxylate directly.

Willi and his coworkers (51) argue that in the acid-catalyzed decarboxylation reactions, it is to be expected that in weakly acidic solutions, the decomposition of the intermediate X should proceed more rapidly than the other intermediate HX^+, because



HX+ X

the cleavage of the COO^- group from the sigma-complex X (leaving behind the electron pair) can take place more easily than that of the $COOH^+$ group from the sigma-complex HX^+. But in moderately acidic solutions since the ionization of the carboxylic group is suppressed, it is to be expected that the decomposition of the intermediate HX^+ would become significant compared to that of the intermediate X. Their complete scheme of all possible reaction steps is



for which the simplified rate expression takes the form:

$$k = \frac{(h_o + a)}{(h_o + b)} d \times \frac{1 + mh_o}{1 + p\,h_o} \qquad (2.10)$$

This has the same form as equation (2.7) and Willi's constants may be equated to those of equation (2.7) as follows:

If we assume with Willi that

$$k_{-A} << k^*$$

$$a = \frac{k_A K_2}{k_{HA}} \qquad m = \frac{k^+}{k^{**} K_2}$$

$$b = K_1$$

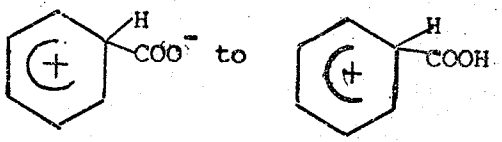
$$d = k_{HA} K_1 \qquad p = \frac{k^+ + k_{-HA}}{k^* K_2^*}$$

and it is assumed that m is negligible (that is, that HX^+ does not decarboxylate). Equation (2.10) then simplifies to:

$$\frac{h_o + a}{k(h_o + b)} = \frac{1 + p\,h_o}{d} \qquad (2.11)$$

Willi and coworkers observe that the plots of the left hand side of equation (2.11) vs h_o are linear for p-aminosalicylic acid (51) and anthranilic acid (50) so that there is no evidence of $COOH^+$ decarboxylation in these acids. However, they do notice a deviation in the plot for p-aminobenzoic acid (51) which they attribute to $COOH^+$ decarboxylation in this acid.

Since h_o increases more rapidly with acid concentration, a rate expression of the form $k = nh_o$ is usually plotted in the form $\log k = \log n - H_o$. This should give a line of unit slope if the acid dependence of the reaction is proportional to h_o. It is commonly found that such plots are linear but do not have unit slope, i.e. the reactions obey some other acidity functions than h_o (21).

The author has plotted Willi's data on p-aminobenzoic acid log k vs. $-H_o$, since a and b in equation (2.11) are negligible. A linearity is observed but the slope of the line is away from unity. It is therefore easier to explain the deviation by means of an appropriate acidity function rather a change in mechanism from the decomposition of the species  to

D. Azulene-1-carboxylic acid.

In decarboxylation of mesitoic and p-aminobenzoic acids where the $COOH^+$ decarboxylation has been proposed (32,51), the change from slow protonation to the slow decomposition has been found at those acidities where an acidity function other than pH has to be used. The whole subject of acidity function is debatable on the grounds that every reaction ought to have its own acidity function (29). The conclusions drawn from using acidity functions are certainly open to criticism. The acid-catalyzed decarboxylation of azulene-1-carboxylic acid seems to be a novel case since the changeover from slow protonation to slow decarboxylation occurs in the pH region of acidity.

Long and coworkers (23,23A) studied the decarboxylation of azulene-1-carboxylic acid in weakly and strongly acidic solutions and have proposed the following mechanism.

$$AzCOOH \underset{k2}{\overset{k_1}{\rightleftharpoons}} AzH^+COOH \underset{k_6}{\overset{k_5}{\rightleftharpoons}} \overset{+}{Az}HCOO^- + H+$$

$$\overset{+}{Az}HCOO^- \xrightarrow{k_7} AzH + CO_2$$

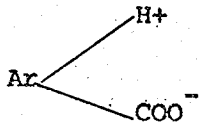
Thus:

$$k = \frac{k_1 [H^+]}{1 + \frac{k_2 k_6}{k_5 k_7} [H^+]} \qquad (2.12)$$

Equation 2.9 may be equated to equation 2.12 after deleting the constants k_A, k_{-A} and K_2.

Long and coworkers have measured the C^{13}-carboxylic carbon isotope effects and deuterium solvent isotope effects on the decarboxylation of azulene-1-carboxylic acid. The C^{13}-carboxylic carbon isotope effect changes from 1.0082 in 0.006 M perchloric acid to 1.043 in 0.32 M where as the deuterium solvent isotope effect changes from 2.15 to 1.17 between these acidities.

The analysis of the kinetic data and the additional evidence collected from C^{13}-carboxylic carbon isotope effects and deuterium solvent isotope effects led them to conclude that the particular important reaction intermediate in the decarboxylation process is the carbon protonated ampholyte



of the above structure.

II. Object of present work

From previous chapter it is obvious that aromatic acids in solution show several types of decarboxylation behaviour, depending on the character of the aromatic nucleus and on the substituents present. The acids investigated by several workers show that CO_2 is a better leaving group compared to $COOH^+$, except for mesitoic acid where $COOH^+$ decarboxylation is conclusive.

The object of the present work is to study the effects of substituents on various rate constants in anthranilic acids with the hope of gaining information which would make it possible to chose a carboxylic acid for which cleavage of $COOH^+$ would be readily demonstrated.

The results on anthranilic acids showed that the 4-methoxy is most likely to show $COOH^+$ decarboxylation. However, it could not be studied at higher acidities due to the cleavage of the methoxy group. Therefore, the 2,4-dimethoxybenzoic acid was chosen. since, it is a weak acid and so the rates are convenient to measure at relatively low temperatures. Also because it has no amino group its rate of decarboxylation is not decreased by protonation at high acidities.

III. RESULTS AND DISCUSSIONS

Decarboxylations were followed by recording the change in optical density of 10^{-4} M solutions at a wavelength where the acid absorbs but the decarboxylation product does not. The plots of the logarithm of the optical density vs time for all the acids investigated (2,4-dimethoxybenzoic acid, 4-methoxy, 4-methyl and anthranilic acid itself) were good straight lines, showing that the reaction is first order with respect to each acid. A representative run for each carboxylic acid is shown in figures A-1, A-2, A-3 and A-4. Some duplicate runs were carried out and the pseudo first order rate constants were calculated from the plots. Their estimated precision is within ± 2%.

FIGURE A.1

A typical plot of log Q_D versus time for the decarboxylation of anthranilic acid at 80°C

Fig.1

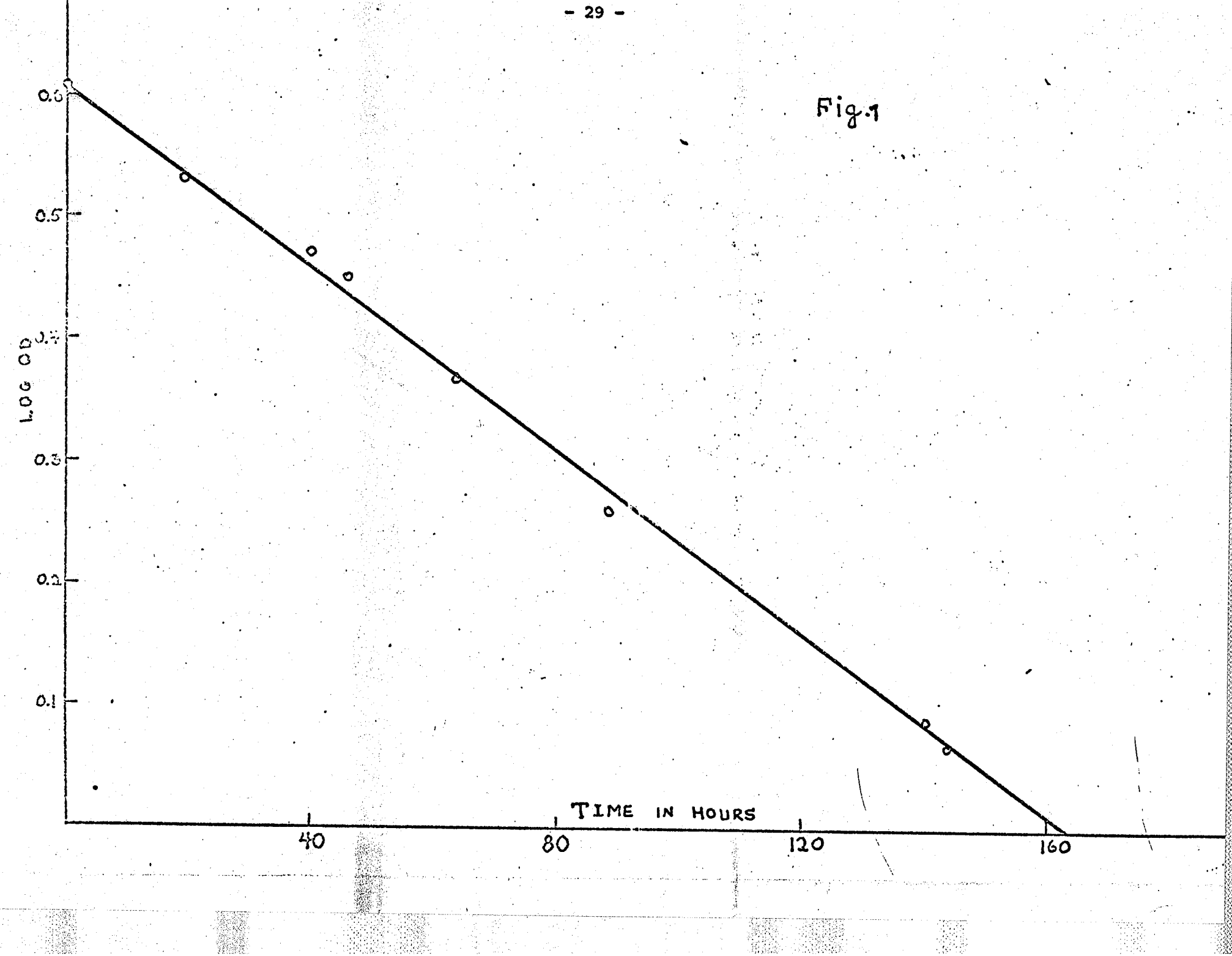


FIGURE A.2

A typical plot of log OD versus time for 4-methylanthranilic acid at 80°C

Fig. A.2

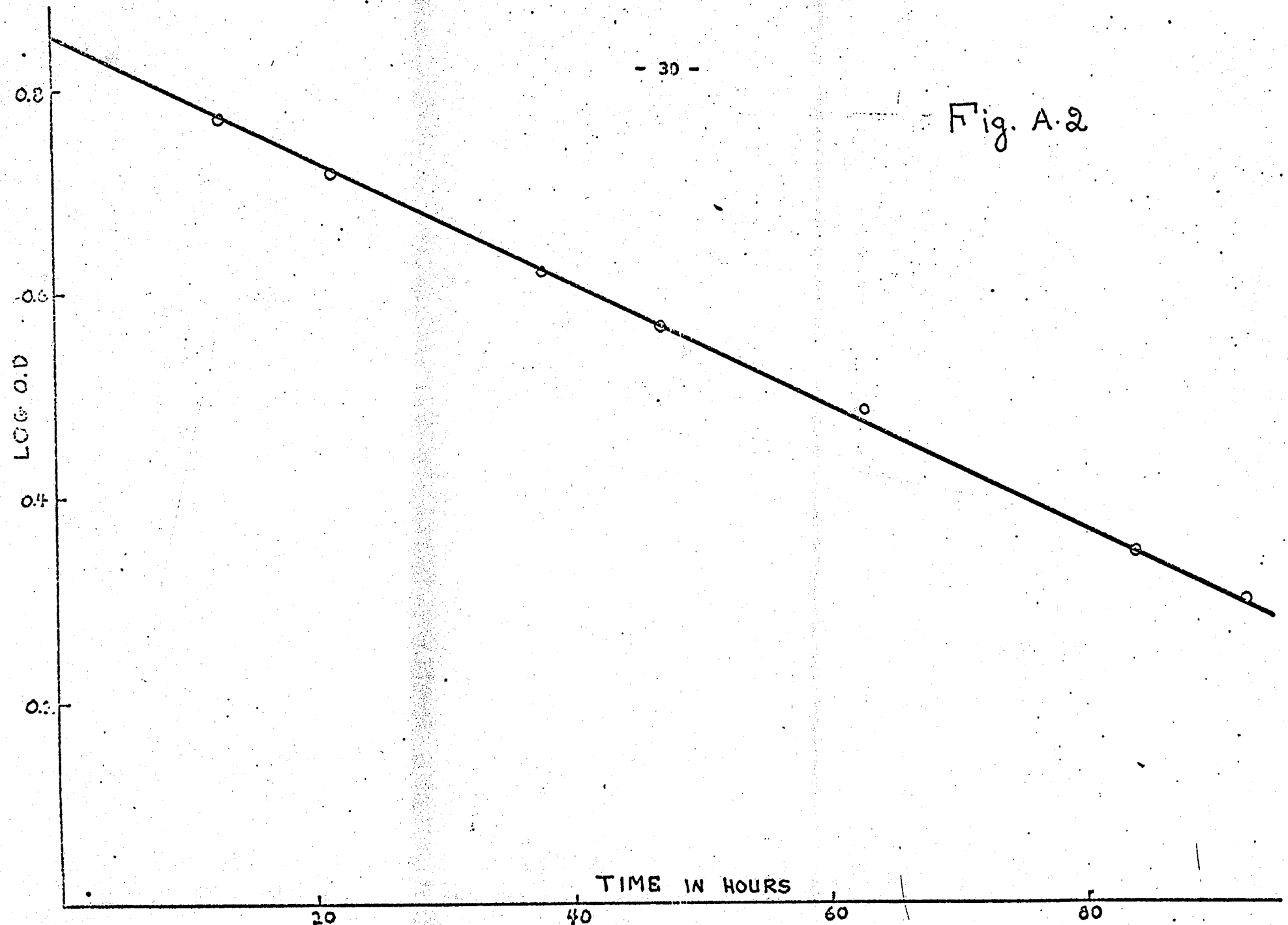


FIGURE A.3

A typical plot of log OD versus time for the decarboxylation of 4-methoxyanthranilic acid at 80°C

Fig. A-3

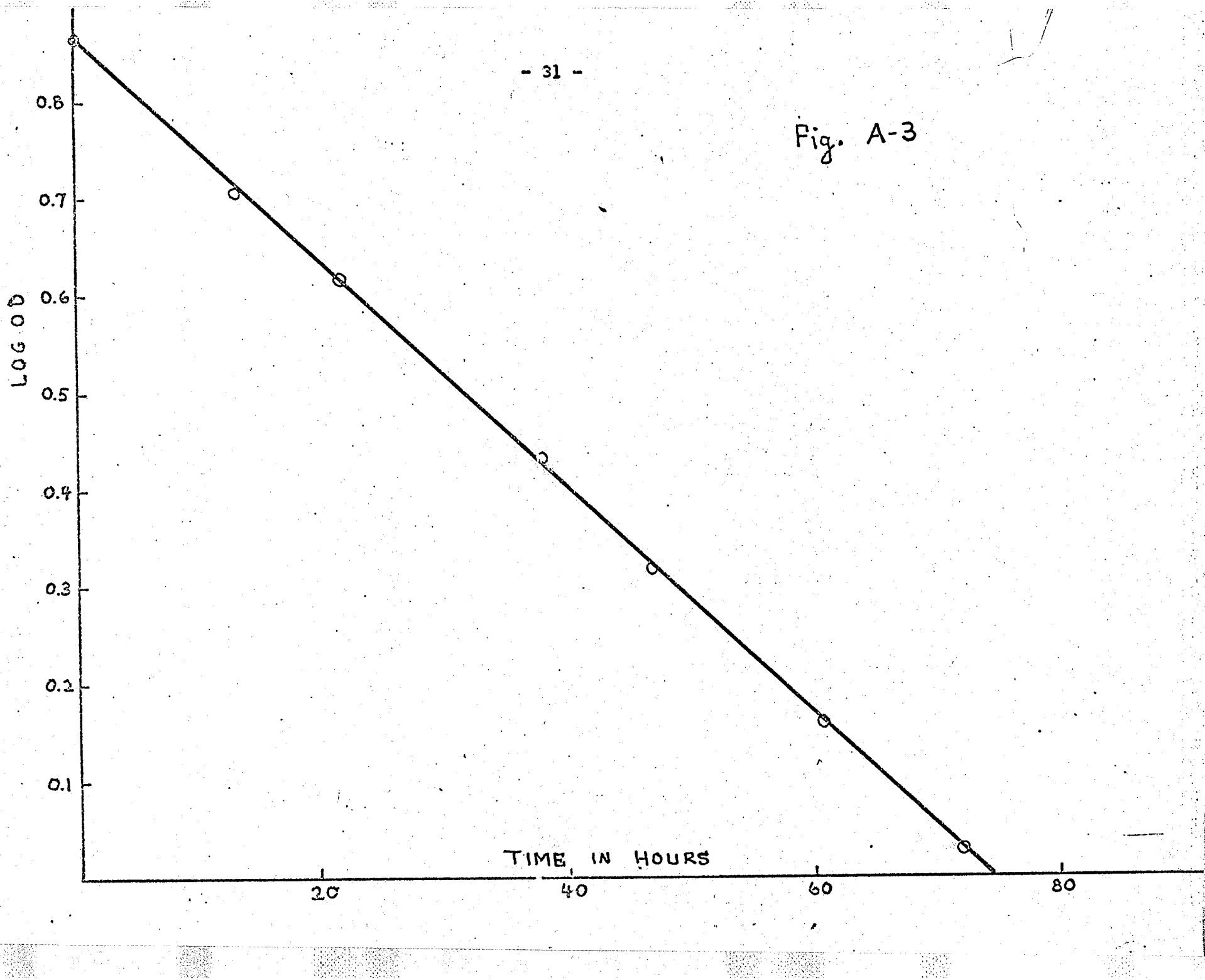


FIGURE A.4

A typical plot of log OD versus time for 2,4-dimethoxybenzoic acid at 70°C

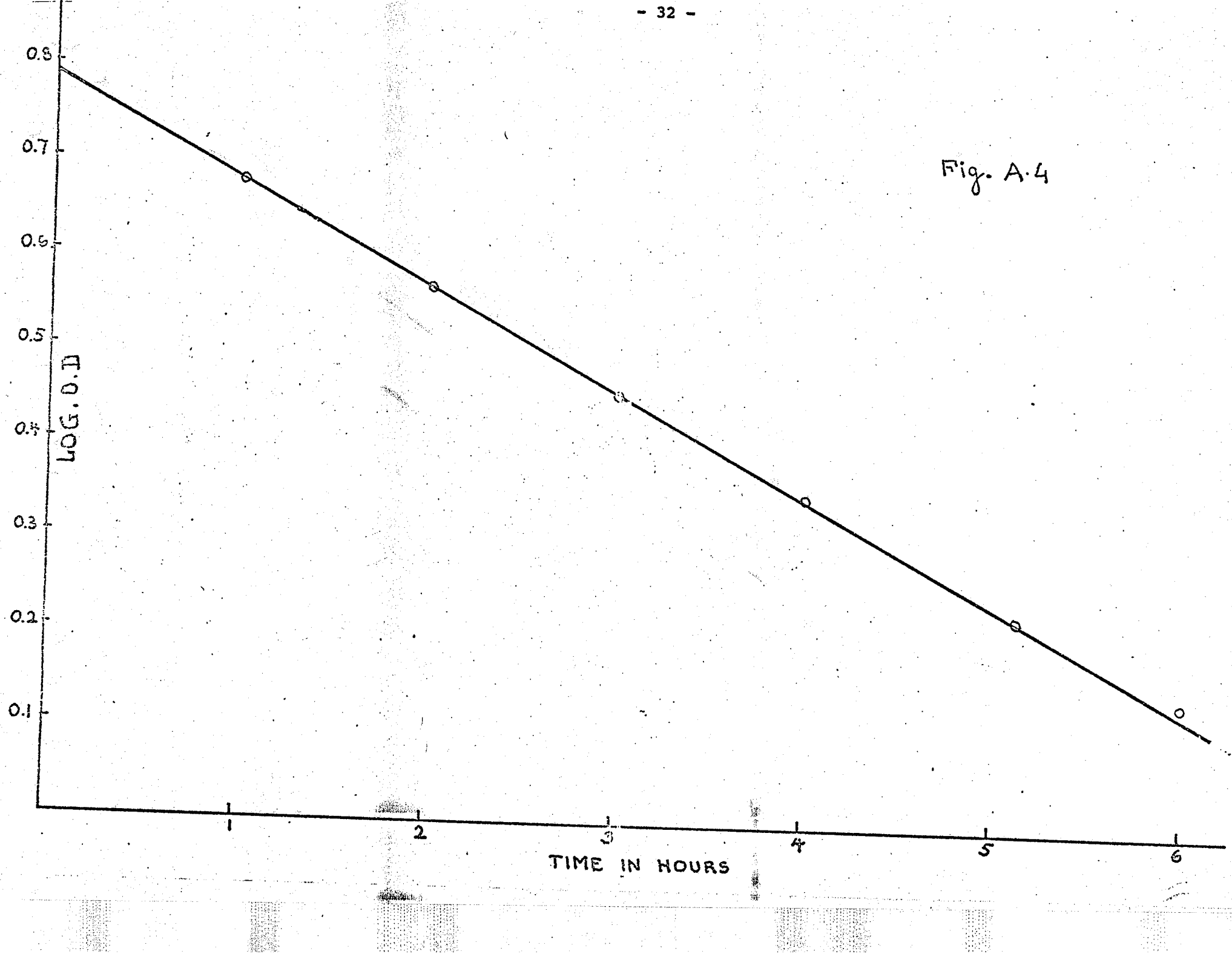


Fig. A.4

A. Aminobenzoic Acids.

In the previous work from this laboratory (10,11) the general mechanism for decarboxylation of substituted anthranilic acids was proposed, for which the overall rate constant was shown to be

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H^+]}{K_1 + [H^+]} \times \frac{k^* K_2^* + k^+ [H+]}{(k^* + k_{-A}) K_2^* + (k^+ + k_{-HA})[H+]} \qquad (A.1)$$

For 4-methoxyanthranilic acid at 60°C there is no C^{13}- carboxyl kinetic isotope effect at low acidity, so k_{-A} is small compared to k*, and because there is such an isotope effect at high acidity k+ is smaller compared to k_{-HA} (10). Hence equation (A.1) reduces to:

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H+]}{K_1 + [H+]} \times \frac{k^* K_2^* + k+ [H+]}{k^* K_2^* + k_{-HA}[H+]} \qquad (A.2)$$

It was also shown that for 4-methoxyanthranilic acid upto 2M HCl, $k^+[H^+]$ is negligible compared to $k^* K_2^*$, leading to the rate expression

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H+]}{K_1 + [H+]} \times \frac{1}{1 + \frac{k_{-HA} [H^+]}{k^* K_2^*}} \qquad (A.3)$$

The question then arises whether the $k^+[H+]$ term may become significant at higher values of $[H^+]$. An evaluation of k*/k+ ratio, or the establishment of a lower limit for it, would be of interest as a measure of the relative reactivities of CO_2 and $COOH^+$ as electrophilic leaving groups.

Willi, Won and Vilik have reported (51) that the decarboxylation of anthranilic acid fits equation A.3 upto $H_o = -1.4$

(4M HCl) so that there is no evidence for cleavage of $COOH^+$ in this acid. Similarly, Longridge and Long (23) find only CO_2 cleavage from azulene-1-carboxylic acid upto H_o = -2.8 (6M $HClO_4$). For p-aminobenzoic acid, however, Willi and Vilk find some deviation from equation A.3 beginning at H_o = -0.68 (2M HCl) which is explained as a small contribution from the term $K^+[H+]$ of equation A.2 corresponding to cleavage of COOH+ (50). This makes it evident that the relative rates of cleavage of COO and COOH+ vary with the nature of the acid undergoing decarboxylation. It was the object of the present work to investigate the effects of substituents on the various rate constants of equation (A.2) with the hope of gaining information which would make it possible to chose a carboxylic acid for which cleavage of $COOH^+$ would be readily demonstrated.

Electron attracting substituents reduce the rate of decarboxylation of anthranilic acids to values inconvenient for measurement (11). So anthranilic acid and its 4-methyl and 4-methoxy derivatives were chosen for examination of the substituent effect. Table A.I shows their rates of decarboxylation at 80° as a function of pH. It has been shown that at pHs greater than 1 there is no appreciable $C-^{13}$ carboxyl kinetic isotope effects in the decarboxylation of anthranilic acid (38) or 4-methoxy anthranilic acid (10). Consequently, the right hand fraction in equation A.1 or A.2 must equal unity at low acidity, since the rate constants for carbon-carbon bond breaking, k* and k+, appear only in this fraction. Under these conditions equation A.1 and A.2 reduce to

$$k\left(1 + \frac{[H^+]}{K_1}\right) = k_A K_2 + k_{HA}[H+] \qquad (A.4)$$

The data from table A.1 were used to calculate according to equation A.4. The calculations are shown in table A.I and are plotted in figures A-5, A-6 and A-7. The k_A and k_{HA} values so obtained are shown in Table A.II. Since the pH data of

TABLE (A.1) SHOWING THE CALCULATIONS ACCORDING TO EQN. (A.4)

pH	$[H^+]10^3$	$k\ sec^{-1} \times 10^6$	$[K_1 + [H^+]] \times 10^{-3}$	$\frac{k(K_1 + [H^+])}{K_1} \times 10^6\ sec^{-1}$
Anthranilic acid				
2.53	2.96	2.06	9.68	2.97
2.88	1.32	1.76	8.03	2.10
3.13	7.48	1.60	7.47	1.77
3.29	5.13	1.53	7.23	1.65
3.54	2.86	1.42	7.00	1.48
4-methyl anthranilic acid				
2.53	2.96	$1.67\ sec^{-1} \times 10^5$	7.47	$2.76 \times 10^5\ sec^{-1}$
2.85	1.39	1.50	5.91	1.96
3.14	0.72	0.60	5.01	1.06
3.56	0.28	0.86	4.79	0.92
3.84	0.14	0.84	4.65	0.86
4-methoxyanthranilic acid				
2.47	3.35	$2.67\ sec^{-1} \times 10^4$	12.09	$3.69 \times 10^4\ sec^{-1}$
2.81	1.55	2.09	10.29	2.44
3.26	0.55	1.40	9.29	1.48
3.53	0.30	1.32	9.01	1.36
3.81	0.15	1.15	8.90	1.17

FIGURE A.5

PLOT OF $k(K_1+[H+])/K_1$ VERSUS $[H+]$
FOR ANTHRANILIC ACID

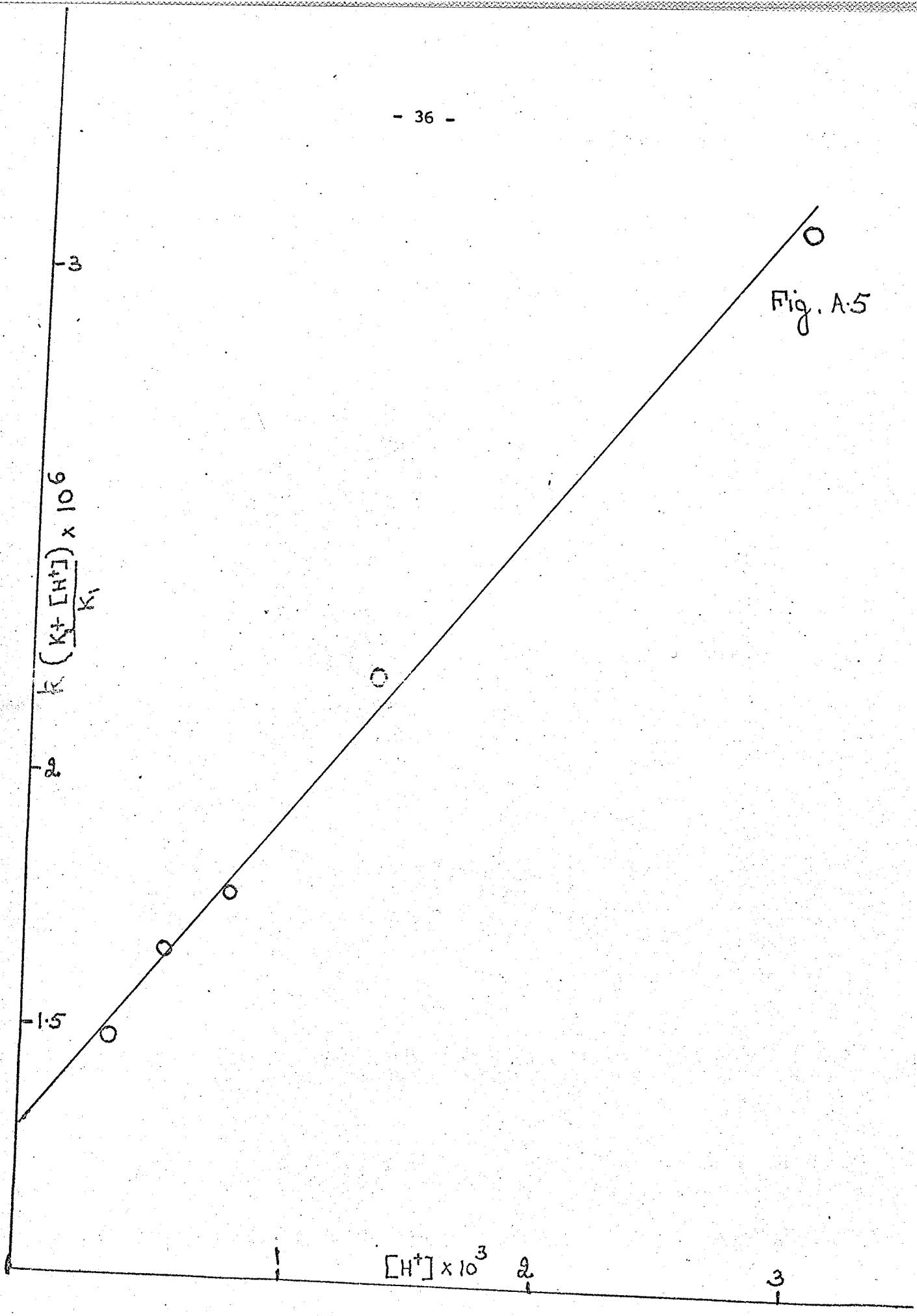


Fig. A.5

FIGURE A.6

PLOT OF $k(K_1 + [H+])/K_1$ FOR

4-METHYLANTHRANILIC ACID

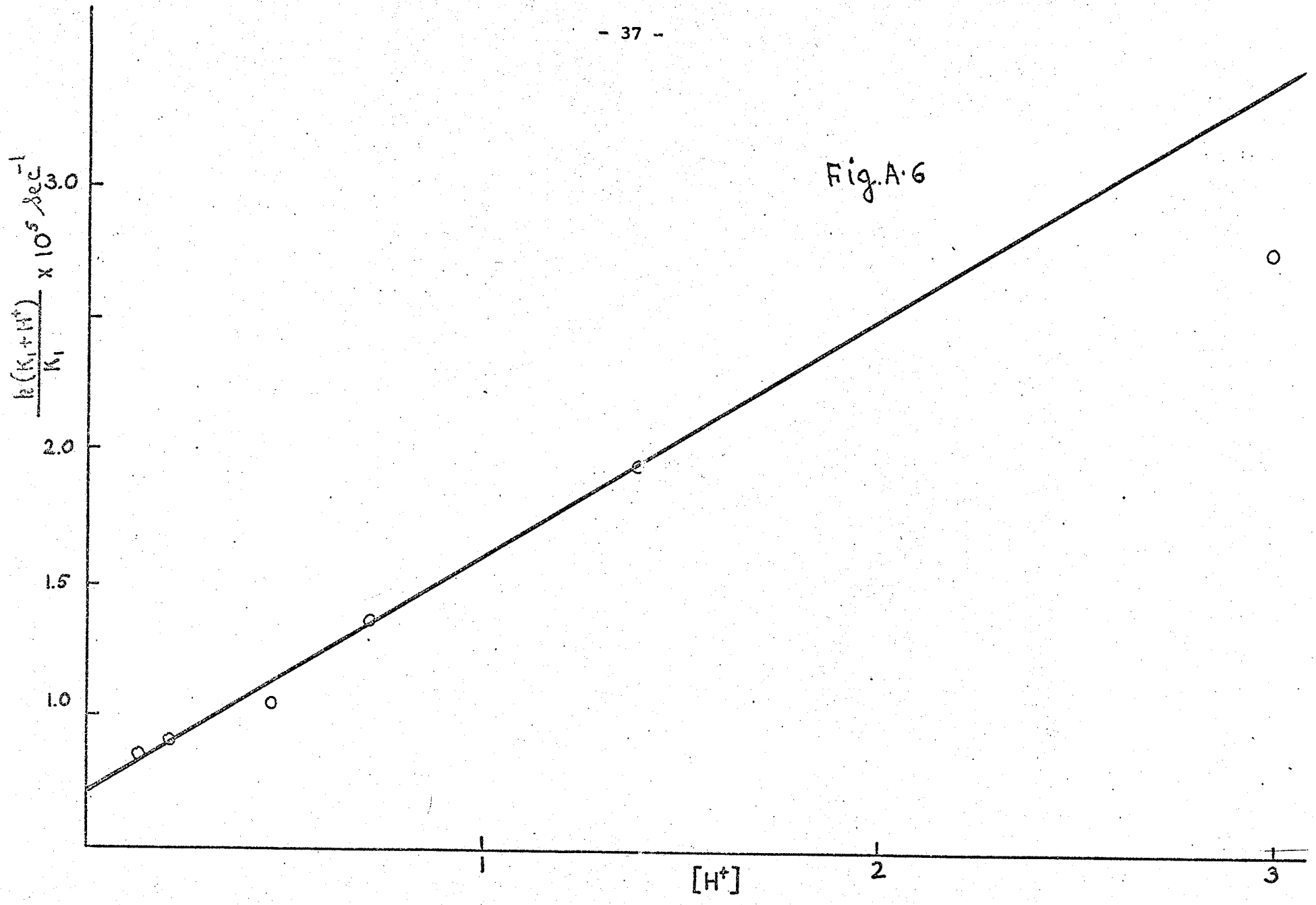


Fig. A·6

FIGURE A.7

PLOT OF $k(k_1 + [H+])/K_1$ FOR
4-METHOXYANTHRANILIC ACID

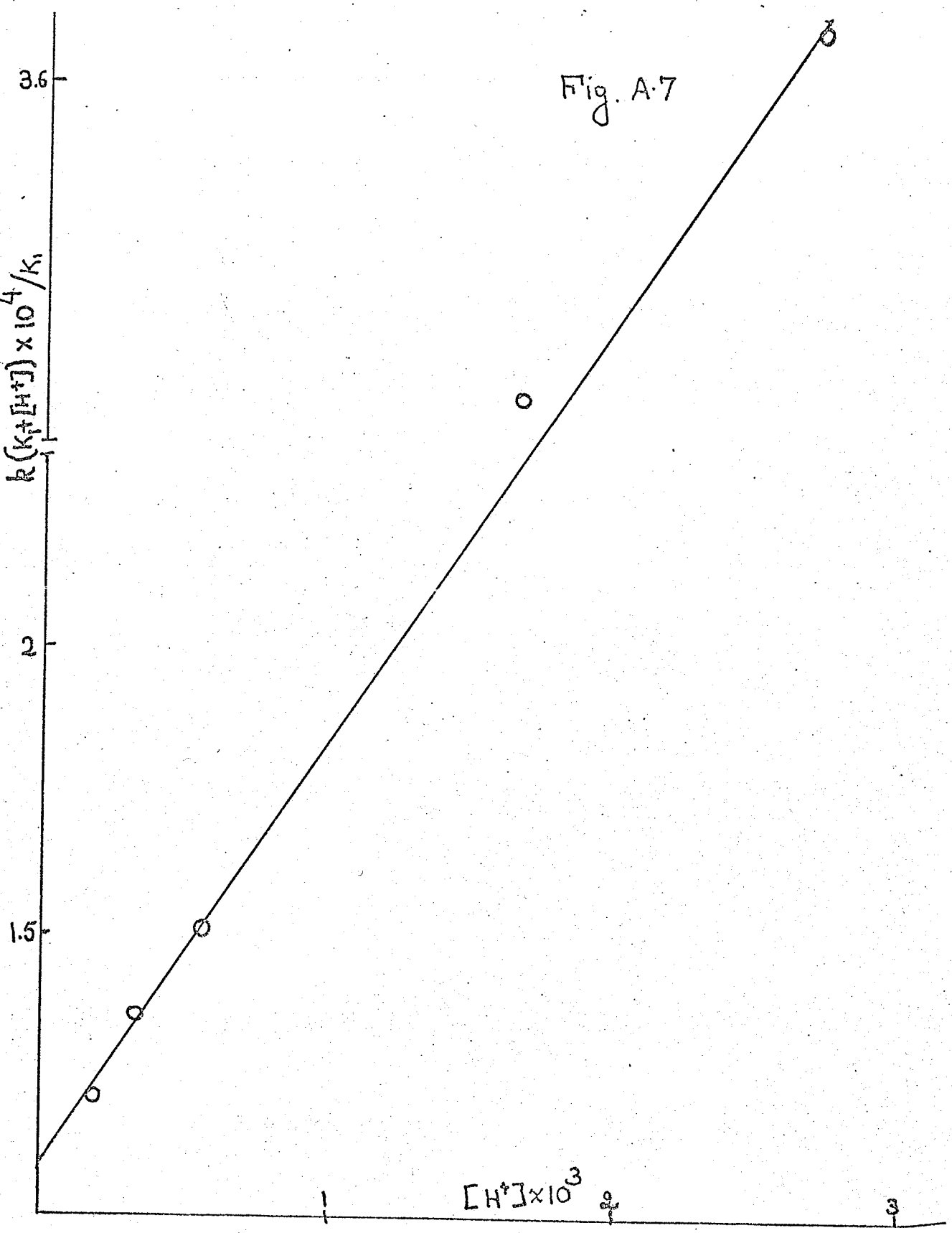


Fig. A·7

TABLE A.2

RATE AND EQUILIBRIUM CONSTANTS FOR THE DECARBOXYLATION OF ANTHRANILIC ACIDS.

T°C	Eq.	CONSTANT	ANTHRANILIC	4-METHYL	4-METHOXY
25		K_1 (M)	6.72×10^{-3}	4.51×10^{-3}	8.74×10^{-3}
25		K_2 (M)	1.40×10^{-5}	8.45×10^{-6}	1.33×10^{-4}
80	A_4	K_A ($s^{-1}M^{-1}$)	0.096	0.82	8.3
80	A_4	k_{HA} ($s^{-1}M^{-1}$)	5.7×10^{-4}	8.9×10^{-3}	7.8×10^{-2}
80	A_5	k_{HA} ($s^{-1}M^{-1}$)	3.8×10^{-4}	5.2×10^{-3}	1.1×10^{-1}
80	A_5	$k_{-HA}/k^*K_2^*$	0.28	0.42	0.89

Table A.I were obtained at 25°C, as were the available values of K_1 and K_2 (19), the k_A and k_{HA} results shown in table A.II are only approximate. However, they should not be in error by more than a factor of two, and the errors will be in the same direction for all three acids, so comparison between the rate constants for protonation of the neutral acids, k_{HA} and of anion k_{-A}, should be valid. Both increase by a factor of about ten each time the 4-substituent is changed from hydrogen to methyl to methoxy. This effect is in the direction to be expected from electron releasing groups on a process which increases positive charge on the aromatic ring.

Since the relative rates of protonation of an acid and its anion is only slightly affected by 4-substituents and since K_1 and K_2 are also not much affected by substituents (19), it is evident that substituents will have little influence on the ratio of rates of formation of the protonated intermediates derived from acid and anion, respectively.

It remains to determine the substituent effects on the ratios of rates of decarboxylation of protonated acid and protonated anion intermediates; that is, to measure the effects of substituents on the right hand fraction of equation A.2. For this purpose it is necessary to measure the rates of decarboxylation at higher acidities. When [H+] exceeds both K_1 and $k_A/k_{HA}K_2$ (i.e. at about 0.1 M $HClO_4$ and higher) the left hand fraction of equation A.3 reduces to $k_{HA}K_1$. If it is now assumed that $k+[H+]$ is negligible compared to $k^*K_2^*$, as was shown to be true for the 4-methoxy acid at 60°C (10), equation A.3 becomes

$$1/k = \frac{1}{k_{HA}K_1} + \frac{k_{-HA}/\ k^*K_2^*}{k_{HA}\ K_1}\ [H+] \qquad (A.5)$$

Table A.III shows the data for decarboxylation of the three acids at 80° C in 0.6 - 3 N $HClO_4$. At these acidities it is no longer possible to maintain constant ionic strength, and [H+] is not a reasonable approximation for hydrogen ion activity,

TABLE A. III

DECARBOXYLATION OF ANTHRANILIC ACIDS IN AQUEOUS PERCHLORIC ACID SOLUTION AT 80±01°C

MOLARITY	ANTHRANILIC $kx10^{6}sec^{-1}$	4-METHYL $kx10^{6}sec^{-1}$	4-METHOXY $kx10^{4}sec^{-1}$
0.10	2.45	29.2	8.44
0.25	2.36	-	8.96
0.60	2.04	16.6	5.12
1.00	1.81	11.7	3.03
1.40	1.59	8.53	2.45
2.00	1.06	6.41	1.35
3.00	0.52	2.34	0.47
4.12	0.41	0.85	0.23
4.98	-	0.48	0.06

so in applying the data to equation A.5, h_o must be used instead of [H+]. The data are plotted in figures A-8, A-9, and A-10, and the results are shown in table A-IV. For sulfuric and hydrochloric acids h_o is somewhat larger at 80^o than at 20^o (12) so no doubt the same be true for perchloric acid. However, this temperature correction would be the same for all three acids, so it would not alter the trend shown in table A.IV where $k_{-HA}/k^*K_2^*$ increases as the substituent changes from hydrogen to methyl to methoxy.

The linear plots obtained from equation A.5 show that all three acids are still obeying equation A.3 at acidities upto 3M $HClO_4$ as had previously been observed for anthranilic acid by Willi and coworkers (51). This means that cleavage of COOH+ is still negligible.

In order to estimate which acid might be expected to show COOH+ cleavage at the lowest acidity it is necessary to return to the more general equation A-2. At acidities where $h_o >> k^*K_2^*/k_{-HA}$ equation A.5 reduces to

$$k = \frac{k_{HA} K_1}{k_{-HA}} (k^*K_2^*/[H+] + k+) \qquad (A.6)$$

As has been pointed out earlier (p.24) plots of rate constants vs. h_o at high acidities are often not linear because h_o is not the appropriate acidity function for the reaction concerned. However, plots of log k vs. $-H_o$ are usually linear with non unit slopes. Consequently, it will be preferable to assume that k+ is negligible so that

$$\log k = H_o + \log k_{HA} K_1 \frac{k^*K_2^*}{k_{-HA}} \qquad (A.7)$$

A contribution from k+ will be indicated by a deviation of the plot of log k vs H_o towards higher rates at higher acidities.

FIGURE A.8

PLOT OF 1/k vs. h_o for
anthranilic acid

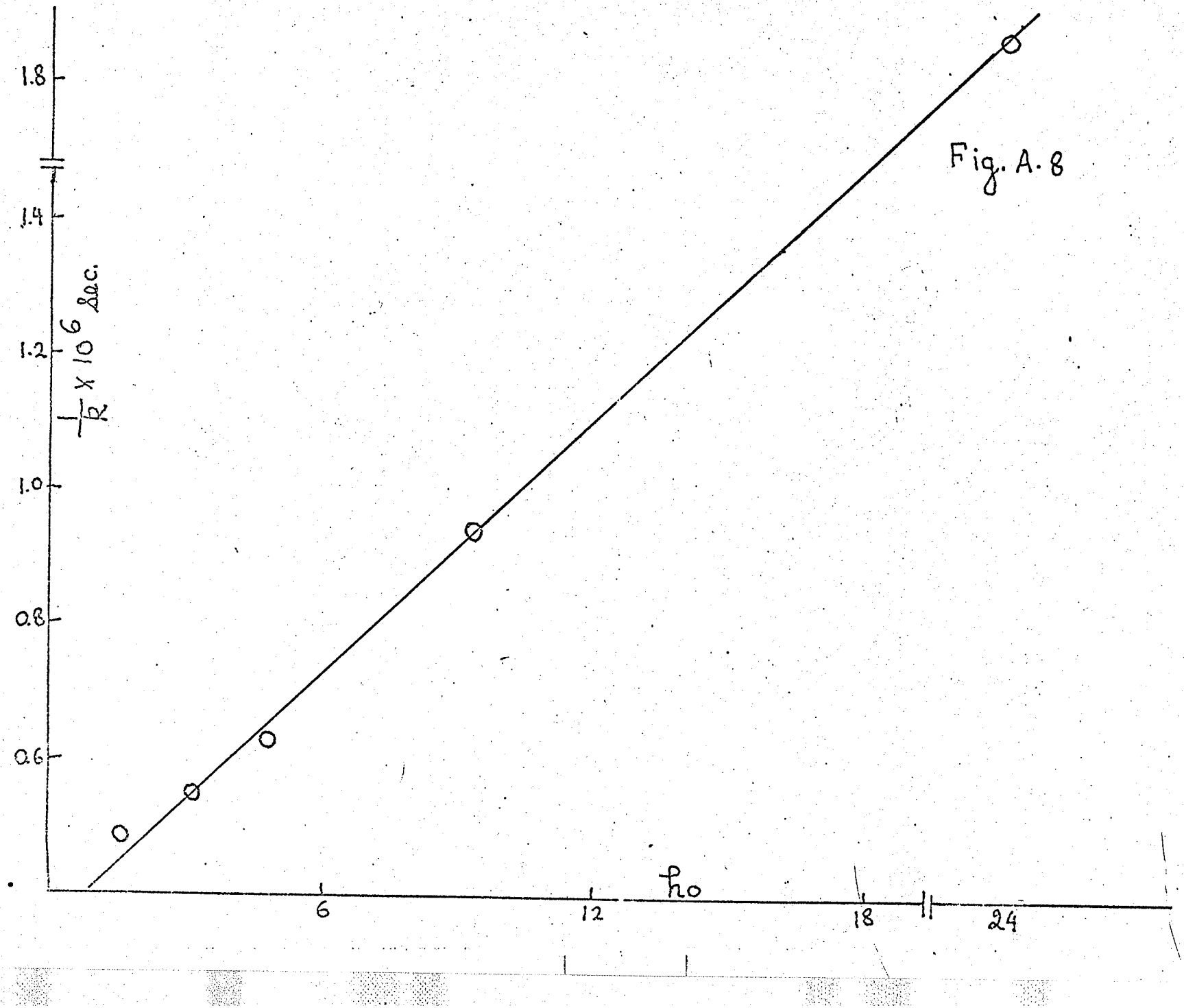


Fig. A. 8

FIGURE A.9

PLOT OF 1/k Vs. h_o FOR

4-METHYLANTHRANILIC ACID.

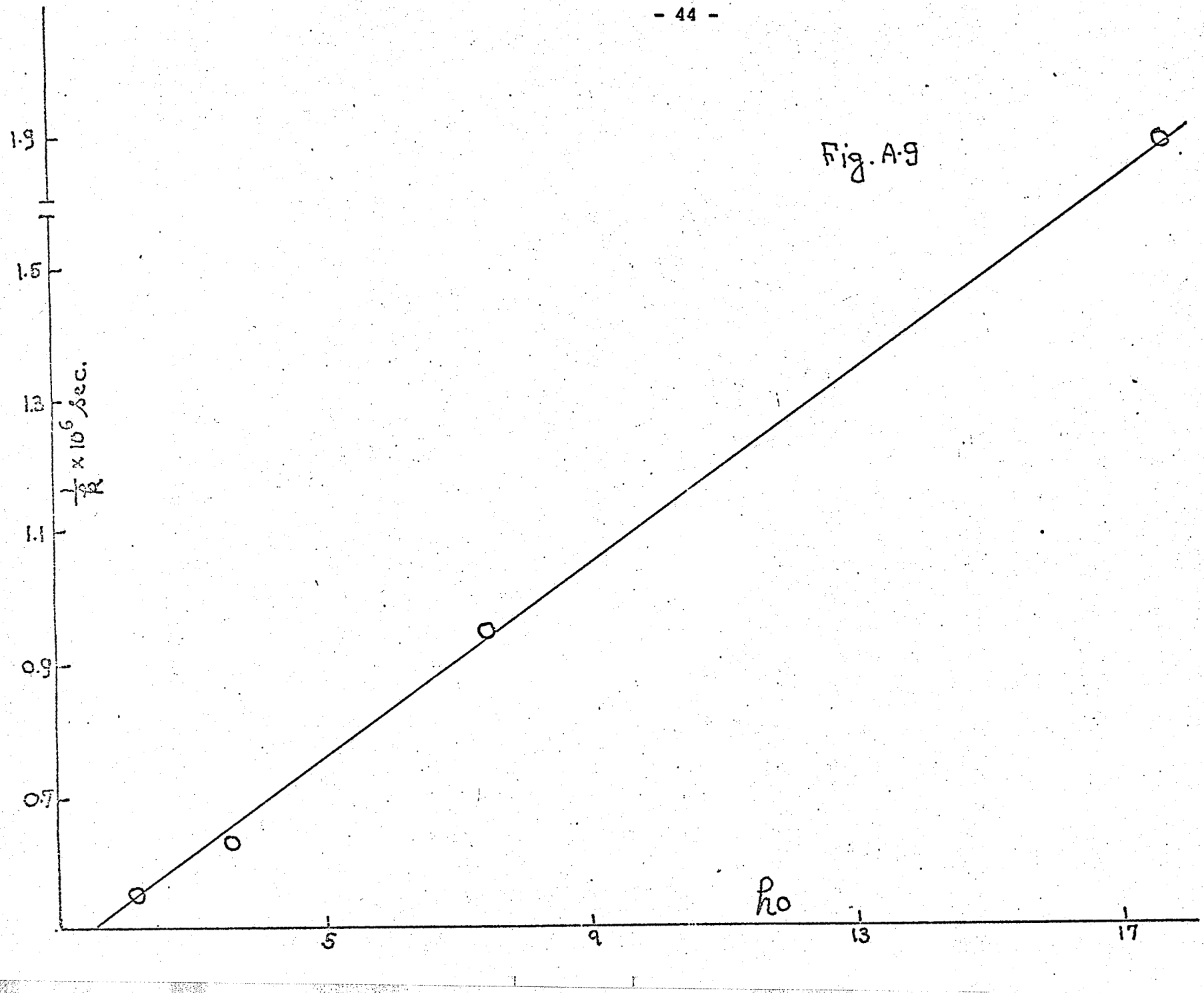


Fig. A.9

FIGURE A.10

PLOT OF 1/k Vs. h_o FOR
4-METHOXYANTHRANILIC ACID

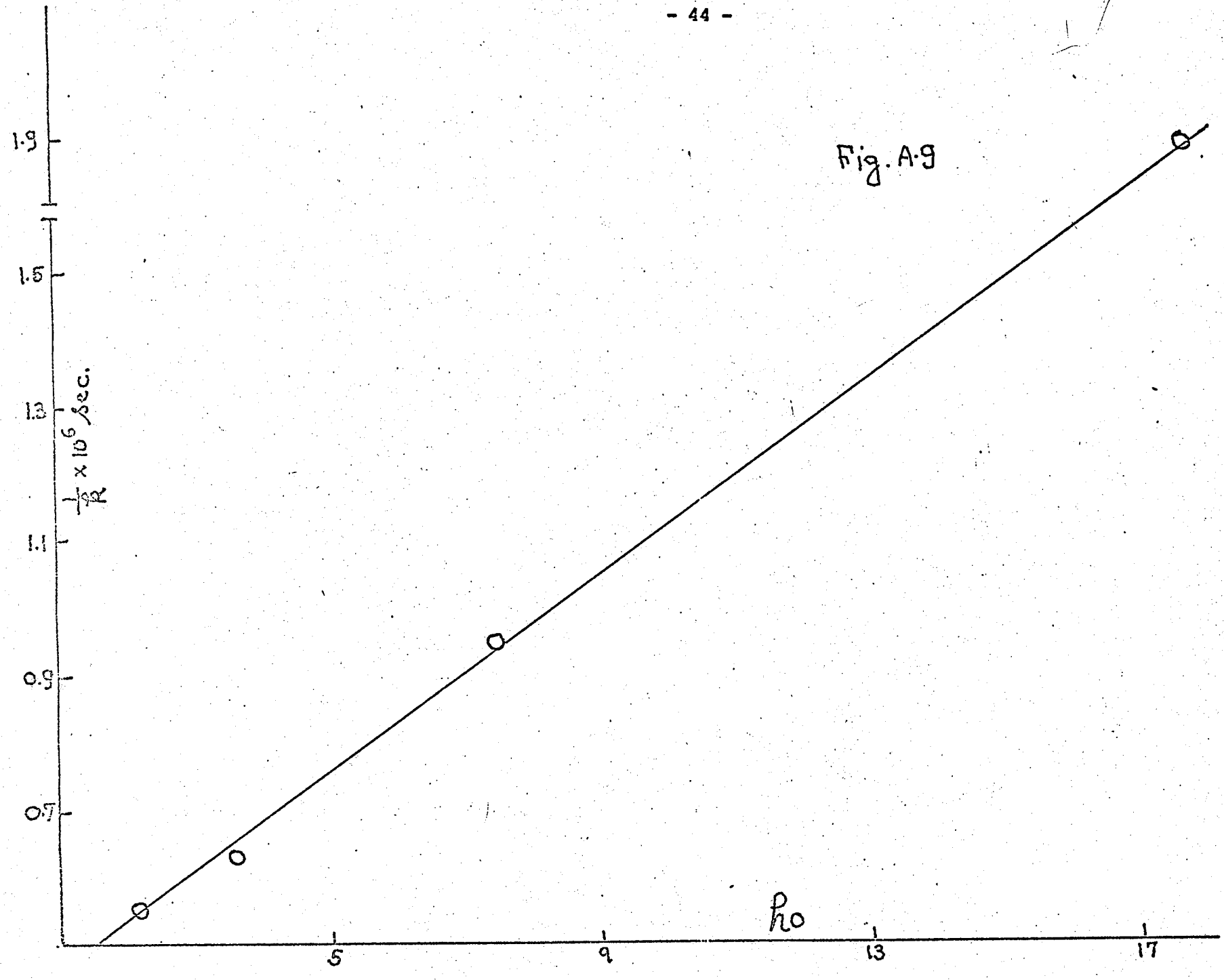


Fig. A-9

TABLE A.IV

SIMPLIFIED RATE EXPRESSIONS FOR SPECIFIC RANGES OF ACIDITY

Equation	k	$[H^+]$ or h_o range	$HClO_4$ range: anthranilic	4-methyl	4-methoxy
(A-4)	$\frac{k_A K_1 K_2 + k_{HA} K_1 [H+]}{K_1 + [H+]}$	upto $\frac{k^* K_2^*}{]0 k_{-HA}}$	upto 0.35M	upto 0.24M	upto 0.]2M
(A-5)	$\frac{k_{HA} K_1}{1 + \frac{k_{-HA}}{k^* K_2^*}[H+]}$	$\frac{k^* K_2^*}{10 k_{-HA}}$ to $\frac{10 k^* K_2^*}{k_{-HA}}$	0.35M to 3.5M	0.24M to 3.2M	0.]2M to 2.5M
(A-7)	$\frac{k_{HA} K_1 k^* K_2^*}{k_{-HA}[H+]}$	$\frac{10 k^* K_2^*}{k_{-HA}}$ to $\frac{k^* K_2^*}{10 k^+}$	3.5M to (6M?)	3.2M to ?	2.5M to ?
(A-6)	$\frac{k_{HA} K_1}{k_{-HA}} \left(\frac{k^* k_2^*}{[H+]} + k^+ \right)$	above $\frac{k^* K_2^*}{10 k^+}$			

The acidity ranges over which the various simplified rate expressions apply have been calculated from the data of table A.II and are listed in table A.IV. They show that equation A.7 and A.6 become applicable at lower acidities for 4-methoxybenzoic acid than either of the others. It would therefore appear to be the easiest one to test for COOH+ decarboxylation in the form of a contribution from k+ to equation A-6. Of course this does not mean that 4-methoxy is the acid most likely to show COOH+ decarboxylation, since the substituent effect which diminishes $k^*K_2^*$ may very well diminish k+ also.

Rates become inconveniently low at high acidities so the reaction temperature was increased to 115°C. Under these conditions the 4-methoxy acid gave erratic and irresproducible results, possibly because of cleavage of the methoxy group. Anthranilic acid behaved well, however, and tables A-V and A-VI give the rates in both perchloric and sulfuric acid respectively. It appears from figure A.11, where the rates are plotted according to equation A.7, that the data in the two strong acids are not consistent. The rates in perchloric acid seem to drift upwards with increasing acidity as would be expected if COOH+ cleavage were beginning to become important about 6M perchloric acid. In sulfuric acid solutions, however, no such deviation occurs. Apparently some of the approximations involved in relating rates to H_o especially rates at one temperature to H_o at another, are not justified. Consequently, it must be concluded that rate data at high acidities do not give reliable answers to the question of COOH+ decarboxylation.

Another tool which has been widely used to detect changes in mechanism is the kinetic isotope effects. In the present case isotope effects for the mechanism under consideration can be predicted from the rate expressions in table A.IV. Since the only rate constants affected by isotopic substitution in the carboxyl group are those for the C-C bond breaking steps, k* and k+ Table IV, equation 6, shows that the C^{13}-carboxyl kinetic isotope effect should change from zero to full in the

TABLE A.V

Rates of decarboxylation of anthranilic acid at 115±0.01°C in aqueous perchloric acid solution

MOLARITY	$k\ sec^{-1} \times 10^6$
1.00	66.80
2.00	43.80
2.50	38.41
3.00	21.82
4.12	11.30
4.98	5.38
5.50	3.28
5.99	2.25
6.48	1.67
7.20	0.98
7.45	0.67
7.95	0.68

TABLE A. VI

RATES OF DECARBOXYLATION OF ANTHRANILIC ACID IN AQUEOUS SULFURIC ACID SOLUTION AT 115±1°C

% H_2SO_4	$kx10^6 sec^{-1}$
10	70.95
15	52.68
20	47.38
25	34.14
30	21.10
35	12.70
40	7.26
45	3.96
50	1.35
55	0.62
60	0.15

FIGURE A.II

PLOT SHOWING log k VERSUS H_o FOR ANTHRANILIC ACID AT 115°C

○ H_2SO_4 – O – Open Circles

◍ $HClO_4$ – ⊜ – Shaded »

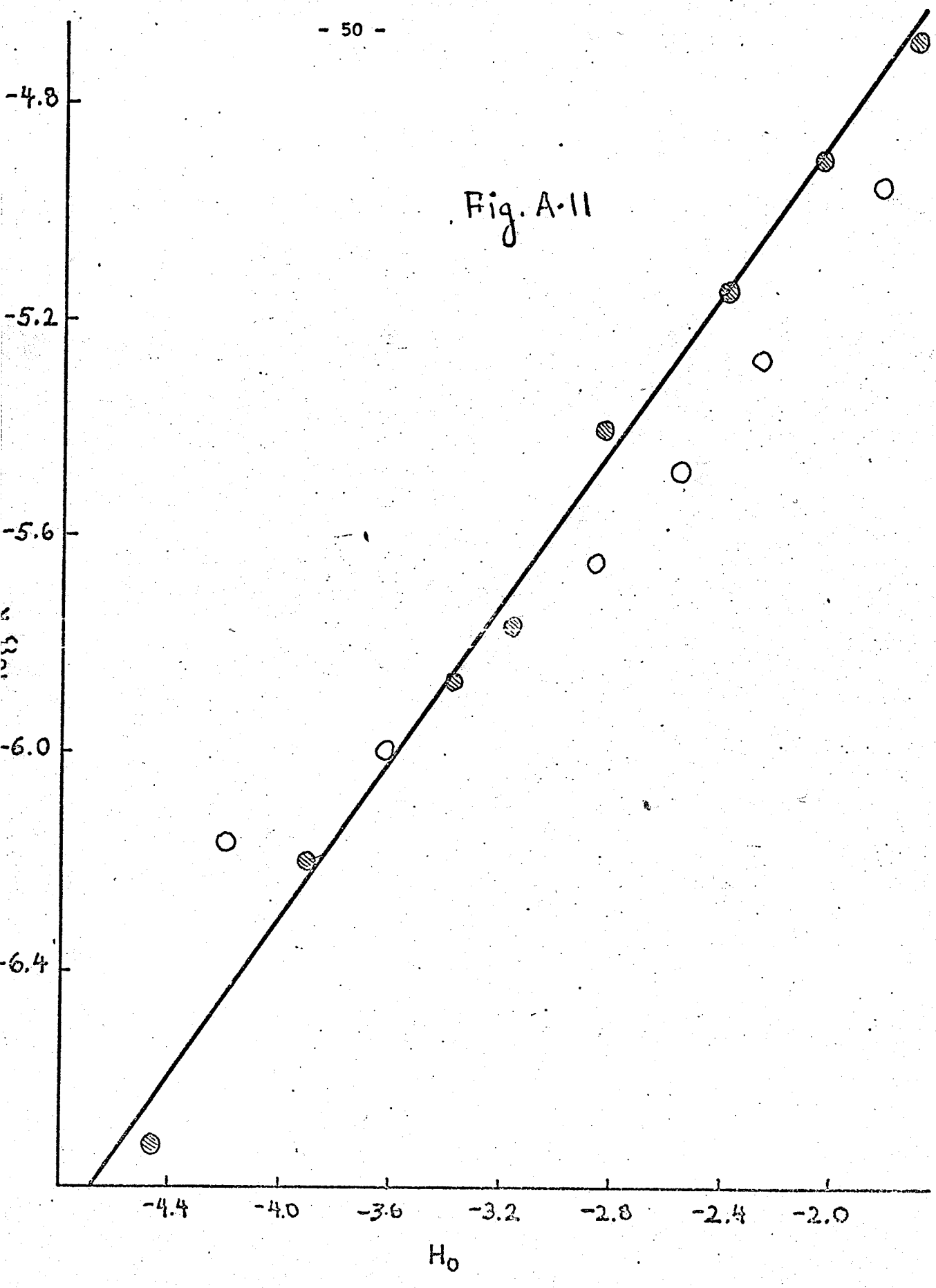


Fig. A-11

range 0.12 to 2.5 M perchloric acid for 4-methoxyanthranilic acid and in the region 0.35 to 3.5M for anthranilic acid itself. It has been found that whereas 4-methoxyanthranilic acid has C^{13}-carboxyl isotope effect of 1.5% at pH = 1.3 (10), the corresponding isotope effect for anthranilic acid is barely detectable in 1M sulfuric acid (38). In order to check the prediction of a C^{13}-kinetic isotope effect for anthranilic acid at high acidities, the isotope effects have been measured upto 5M sulfuric acid at 115°, table A.VII. A full C^{13}-isotope effect of 3.5% has been obtained.

The change in carbon isotope effect with acidity reflects the change in mechanism from slow protonation equation A.4, to slow COO cleavage equation A.7, but it can hardly be used to detect the onset of COOH+ cleavage equation A.6, because the difference in ^{13}C-isotope effect between COO and COOH+ cleavage will no doubt be too small to detect.

However, the change from slow COO cleavage ($k^*K_2^*$) to slow COOH+ cleavage (k_+) is accompanied by the disappearance of the ionization constant K_2^* from the rate expression (equation A.6). It would therefore appear possible to detect the change by means of a solvent deuterium isotope effect. Since K_2^* represents the ionization of an organic acid it would be decreased by deuteration of the solvent (1). Consequently, the rate ratio k_D/k_H for the overall reaction should increase as K_2^* disappears from the numerator of the rate expression at high acidities in equation A.7. The results of an attempt to detect this change are shown in figure A.12.

Since $DClO_4$ was not available, changes in acidity were necessarily accompanied by changes in the deuterium content of the solution. Since the dependence of rates on the isotopic composition of solvent is complex (1), rates for each of three perchloric acid concentrations were measured over a range of deuterium concentrations upto the maximum attainable. The results are shown in tables A.VIII - X, and are plotted in figure A.12 where the ratio of the rate in partly deuterated solvent to that in undeuterated solvent, k/k_H, is plotted as a function of the mole fraction of deuterium in the solvent.

TABLE A.VII

KINETIC CARBON ISOTOPE EFFECTS ON THE DECARBOXYLATION OF ANTHRANILIC ACID IN SULFURIC ACID AT 115°C

$[H_2SO_4]$M	% REACTION	CO_2ANALYSIS	MEAN	100(k/k*-1)
2.0	100	(45/44)		
		0.010365	0.010377	-
		0.010384		
		0.010382		
2.0	15	0.010372		
		0.010370	0.010371	0.0
		0.010371		
		0.010372		
10.0	15	0.010036		
		0.010041		
		0.010020	0.010038	3.6
		0.010064		
		0.010019		
		0.010051		

TABLE A-VIII

RATES OF DECARBOXYLATION OF ANTHRANILIC ACID IN 1.33N PERCHLORIC ACID WITH VARYING AMOUNTS OF D_2O
TEMPERATURE 115±1°C

WEIGHT OF $HClO_4$	WEIGHT OF D_2O	WEIGHT OF WATER	mfd *	RATE$\times 10^5$ sec^{-1}
1.87550	-	8.79130		7.56
1.87635	3,32430	5.83365	0.316	5.08
1.87670	5.49855	3.85390	0.525	4.04
1.87595	7.73805	1.81280	0.741	2.99
1.87670	9.82700	-	0.933	2.24

* mfd = mole fraction of deuterium, defined on p.101

TABLE A-IX

RATES OF DECARBOXYLATION OF ANTHRANILIC ACID IN 4.80N PERCHLORIC ACID WITH VARYING AMOUNTS OF D_2O TEMPERATURE 115±1°C

Weight of $HClO_4$	Weight of D_2O	Weight of H_2O	mfd *	rate x 10^6 sec
6.69980		5.86370		7.46
6.70580	1.11165	4.89740	0.123	7.16
6.70495	2.20380	3.98560	0.241	6.50
6.70395	3.3056	2.93940	0.365	5.47
6.70300	5.50140	0.93125	0.609	4.37
6.70220	6.51525	-	0.722	3.85

* mfd = mole fraction of deuterium, defined on p.101

TABLE A-X

RATES OF DECARBOXYLATION OF ANTHRANILIC ACID IN 7.2N PERCHLORIC ACID WITH VARYING AMOUNTS OF D_2O TEMPERATURE 115±1°C

Wt. of $HClO_4$	Wt. of D_2O	Wt. of water	$kx10^7 sec^{-1}$	mfd*
9.96375	-	3.96690	9.83	
9.95835	-	3.94490	9.80	
9.97430	4.45590	-	6.40	0.545
9.95735	4,51850	-	6.29	
9.97185	1.11560	2.94440	8.72	0.138
9.95965	2.20030	2.02935	8.08	0.270
9.96300	3.32040	1.00471	7.04	0.408

* mfd = mole fraction of deuterium, defined on p.101

FIGURE A.12

SHOWING THE PLOT OF k/k_H VERSUS
MOLE FRACTION OF DEUTERIUM

1.33 N – + – crosses
4.8 N – O – Open Circles
7.2 N – ⊖ – Shaded "

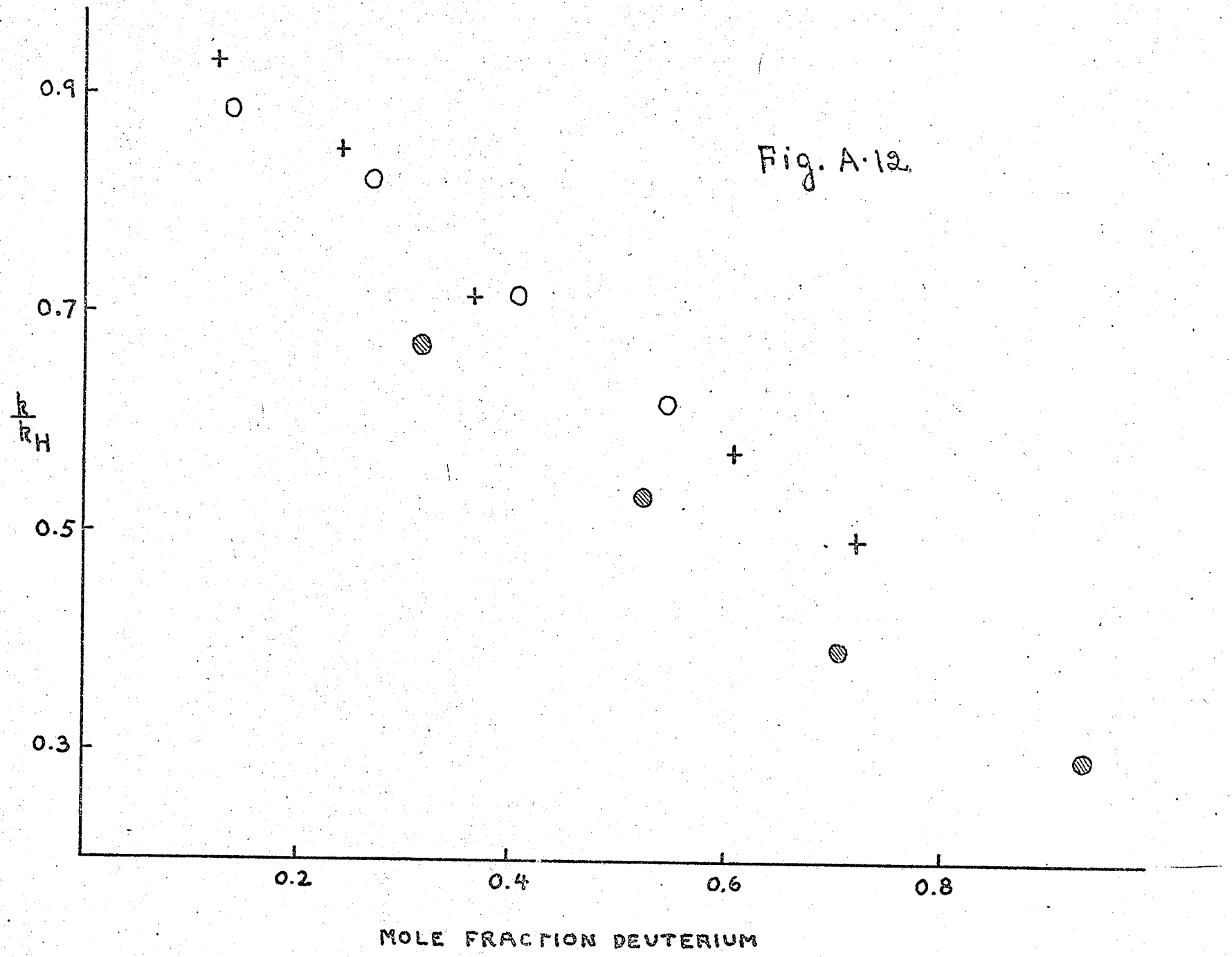


Fig. A-12.

Summary of deuterium solvent isotope effects on decarboxylation of anthranilic acid at 115±1° in sulfuric acid.

MOLARITY	RATE IN (H_2SO_4+H_2O) sec^{-1}	RATE IN (D_2SO_4 + D_2O) sec^{-1}	k_{H_2O}/k_{D_2O}
0.007	2.91×10^{-5}	1.29×10^{-5}	2.25
0.052	1.02×10^{-4}	0.33×10^{-4}	3.07
1.71	7.62×10^{-5}	2.13×10^{-5}	3.57
2.56	4.45×10^{-5}	1.40×10^{-5}	3.20
5.5	7.48×10^{-6}	2.30×10^{-6}	3.21
7.5	1.51×10^{-6}	0.504×10^{-6}	3.07

Since $H_o = D_o$ at the same acid concentration (15), the rate ratios should reflect the solvent deuterium isotope effects on the various rate and equilibrium constants in the rate expression. It is seen that k/k_H increases somewhat between 1.33 M and 4.8M acid as the importance of the term $k_{-HA}/k^*K_2^*$ in equation A.5 increases. Similar increases were observed for azulene-1-carboxylic acid by Longridge and Long (23) and for 2,4,6-trihydroxy benzoic acid by Bourns (6). But between 4.8 M and 7.2 M perchloric acid there is no detectable change in the solvent isotope effect.

The experiment was repeated in sulfuric acid, where complete deuteration is possible using D_2SO_4 and D_2O. The results (table A.XI) are identical to that found in $HClO_4$ and D_2O.

It may reasonably be concluded, therefore, that there is no evidence for cleavage of COOH+ in acidities upto about $H_o = -4$. This means that $k^*K_2^*/k+ > 10^4$. Although K_2^* is unknown, it is probably considerably less than 1, so that the rate constant for CO_2 cleavage, k*, must be greater than that for COOH+ cleavage, k+, by 10^5 or more.

B, 2,4-Dimethoxybenzoic acid.

In the preceding section it was found that $COOH^+$ decarboxylation is most likely to be found in acids with strong electron-releasing substituents, such as 4-methoxy. The conditions most favorable for $COOH^+$ decarboxylation are obviously highly acidic solutions, where the concentration of H_2A^* should greatly exceed that of HA*. However, the anthranilic acids used in the previous section do not lend themselves to the test for $COOH^+$ decarboxylation for two reasons. First, they are strong acids, for carboxylic acids, so that very high acidities are required to suppress their ionisation, and, second, at these high acidities protonation of the amino group greatly decreases the rate of the reaction so that high reaction temperatures are necessary. The combination of high acidity and high temperature led to side reactions (possibly cleavage of the methoxy group) in the decarboxylation of 4-methoxyanthranilic acid.

It was therefore decided to continue the search for $COOH^+$ decarboxylation with 2,4-dimethoxybenzoic acid. This acid offers several potential advantages over the acids used upto now. It is a much weaker acid than the substituted salicylic acids used by Bourns (6,7) so that less extreme acidities will be required to suppress anion formation. It has no very basic substituents, such as the amino groups of the aminobenzoic acids used by Willi (45-51) and Dunn (10,11), so that high temperatures will not be required at high acidities. and it is less basic than the 2,4,6-trimethoxybenzoic acid used by Schubert (35) so that protonation of the carboxyl group and acylium ion formation will not interfere with decarboxylation at moderate acidities.

Rates of decarboxylation of 2,4-dimethoxybenzoic acid at 70°C and various acidities are shown in tables B-I and B-II.

TABLE B.I

RATES OF DECARBOXYLATION OF 2,4-DIMETHOXY-BENZOIC ACID IN AQUEOUS SULFURIC ACID SOLUTION AT 70°C

MOLARITY BY TITRATION	WT % H_2SO_4	MOLARITY BY CALCULATION	$kx10^5$ sec^{-1}
0.29			0.28
0.60			0.40
0.61			0.46
0.72			0.54
1.10			1.27
1.43			1.84
1.78			2.25
2.65			4.52
	24.627	2.85	5.24
	27.477	3.23	6.57
	34.835	4.31	12.05
	44.495	5.88	22.58
	46.409	6.23	26.87
	52.429	7.34	31.98
	56.561	8.12	30.39
	62.204	9.30	28.66
	67.214	10.42	21.43
	69.519	10.91	10.87

RATES OF DECARBOXYLATION OF 2,4-DIMETHOXY-BENZOIC ACID IN AQUEOUS PERCHLORIC ACID AT 70°C

MOLARITY	$kx10^5$ sec^{-1}
1.02	1.39
1.34	2.35
1.69	3.25
1.89	4.05
2.23	4.47
2.38	5.92
2.76	7.63
3.69	13.75
3.69	17.53
4.65	26.46
4.74	27.00
5.01	30.37
5.06	32.64
5.84	39.76
6.12	43.75

TABLE B.III

C^{13}-Kinetic isotope effects observed on decarboxylation of 2,4-dimethoxybenzoic acid at 70° in perchloric acid.

MOLARITY	EXTENT OF REACTION (%) (*)	$C^{13}O_2/C^{12}O_2$	100(k/k*-1)
6.0	100	0.010746	
		0.010741	
		0.010736	
		0.010741	
	MEAN	0.010741	
6.0	7.81	0.010569	1.6
	8.57	0.010516	1.4
—	19.41	0.010612	1.4
	8.00	0.010510	1.4
4.1	13.30	0.010592	1.4
	11.85	0.010611	1.2
	11.20	0.01600	1.2
0.1	9.70	0.010732	0.0
	10.15	0.010730	0.0

(*) The percent of reaction was measured manometrically.

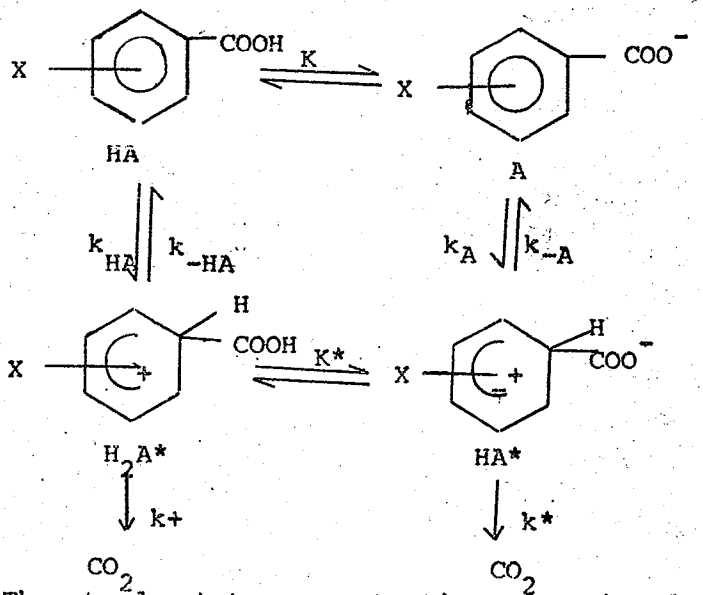
TABLE B.IV

SUMMARY OF CARBON KINETIC ISOTOPE EFFECTS OBSERVED IN THE DECARBOXYLATION OF 2,4-DIMETHOXYBENZOIC ACID IN SULFURIC ACID AT 60°

MOLARITY	EXTENT OF REACTION	$C^{13}O_2/C^{12}O_2$	MEAN	100(k/k* - 1)
5.10	100%	0.010730		
		0.010738	0.010736	
		0.010748		
5.10	15%	0.010512		
		0.010506	0.010507	2.2
		0.010504		
		0.010506		
2.55	15%	0.010605		
		0.010608	0.010607	1.1
		0.010607		
		0.010608		
0.50	15%	0.010730		
		0.010735	0.010733	0.0
		0.010735		

C^{13}-carboxyl kinetic isotope effects are shown in tables B-III and B-IV. It is seen that the rate increases with increasing acidity upto about 7M sulfuric acid and, then decreases sharply. The carbon isotope effect increases from zero at 0.5M sulfuric acid to about 2% in 5M acid. From the latter fact it is evident that the mechanism of decarboxylation for this acid changes from rate determining protonation at low acidities to rate determining decarboxylation at high acidities, just as it does for the salicylic and anthranilic acids previously investigated.

A general mechanism for acid-catalyzed decarboxylation of anthranilic acid was proposed by Dunn et al (10). In principle this general mechanism (2.2) could be modified to accommodate the decarboxylation behaviours of other classes of aromatic acids.



(B.1)

The steady state concentration of H_2A^* and HA^* are given by:

$$[H_2A^*] = \frac{[HA^*]\,[H^+]}{K^*} \qquad (B.2)$$

$$[HA^*] = \frac{k_{HA}[HA][H^+] + k_A[A^-][H^+]}{\frac{k_{-HA}}{K^*}[H^+] + k_{-A} + k^+/k^*[H^+] + k^*} \qquad (B.3)$$

and the rate of decarboxylation by

$$\frac{d[CO_2]}{dt} = k[C] = k^{+}[H_2A^*] + k^*[HA^*] \qquad (B.4)$$

where $[C] = [HA] + [A^-]$ (the total concentration of aromatic acid)

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

$$[C] = \frac{[A^-][H^+]}{K + [A^-]} = [A^-](H^+/K + 1)$$

$$\text{or } [A^-] = \frac{(C)K}{[H^+] + K}$$

$$\text{and } [HA] = \frac{[C][H^+]}{K(H^+/k + 1)} = \frac{(C)(H^+)}{[H^+] + K} \qquad (B.5)$$

substituting these values of $[A^-]$ and $[HA]$ in equation B.3

$$[HA^*] = \frac{\dfrac{k_{HA}[C][H^+]^2}{[H^+] + K} + \dfrac{k_A[C]K[H^+]}{[H^+] + K}}{K^{\ddagger} + k_{-A} + (k^+/k^* + k_{HA}/k^*)[H^+]} \qquad (B.6)$$

The values of $[HA^*]$ and $[H_2A^*]$ are substituted in equation (B.4), the rate of decarboxylation is then

$$k = \frac{k_AK[H^+] + k_{HA}[H^+]^2}{K + [H^+]} \times \frac{k^*K^* + k^+[H^+]}{K^*(k^* + k_{-A}) + (k^+ + k_{-HA})[H^+]} \qquad (B.7)$$

This may be taken as a general rate expression for acid-catalyzed decarboxylation of aromatic acids other than amino acids.

The ionization constant of 2,4-dimethoxybenzoic acid has not been reported, so it was determined spectrophotometrically at 25°C and ionic strength = 1. The optical density measurements of various buffered solutions of this acid were carried out at 280 mμ. At this wavelength the absorbance due to free acid [HA] is much more significant than due to the anion [A^-]. The data are shown in table B-V and are plotted in figure B-1.

For ionization of a monoprotic acid in water,

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

the ionization constant may be expressed by

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

where the quantities in brackets represent molar concentrations or, at high ionic strengths, activities. If the total concentration of acid (ionized plus unionized) is C, then

$$K = \frac{[H^+]\ [A^-]}{C - [A^-]} = \frac{[H^+]\ (C - [HA])}{[HA]}$$

so that

$$[A^-] = \frac{KC}{[H^+] + K} \quad \text{and} \quad [HA] = \frac{C[H^+]}{[H^+] + K}$$

Since hydronium ion does not absorb in the visible or ultraviolet regions, the total absorbance, A, of the equilibrium solution of HA is given by:

$$A = A_{HA} + A_A$$

where A_{HA} is the absorbance of the equilibrium concentration of unionized acid HA, and A_A is the absorbance of the equilibrium concentration of anion A^-. For a 1 cm cell the Beer-Lambert relationship converts the preceding equation to

$$A = \varepsilon_{HA}[HA] + \varepsilon_A[A^-]$$

where ε = molar absorptivity.

When the expression for [HA] and [A^-] derived above are introduced, this becomes

$$A = C \times \frac{\varepsilon_{HA}[H^+] + \varepsilon_A K}{[H^+] + K}$$

TABLE B-V

EXPERIMENTAL DATA OF pH AND CORRESPONDING ABSORBANCE OF THE VARIOUS BUFFERED SOLUTIONS OF 2,4-DIMETHOXY-BENZOIC ACID AT 25°C

$\mu = 1.0$ $t = 25^{\circ}C$

$C = 2.5 \times 10^{-4} M$ $\lambda = 280$ mμ

BUFFER	pH	ABSORBANCE
1,0N HCl	0	0.988
HCl	1.999	0.988
HCl	2.500	0.970
Tartaric acid + K-tartarate	3.050	0.950
"	3.555	0.920
"	3.683	0.882
"	4.533	0.600
"	4.744	0.530
"	5.900	0.420
"	6.800	0.400
1.0N NaOH		0.400

FIGURE B-1

PLOT OF pH AND CORRESPONDING OPTICAL DENSITIES OF THE VARIOUS BUFFERED SOLUTIONS OF 2,4-DIMETHOXYBENZOIC ACID

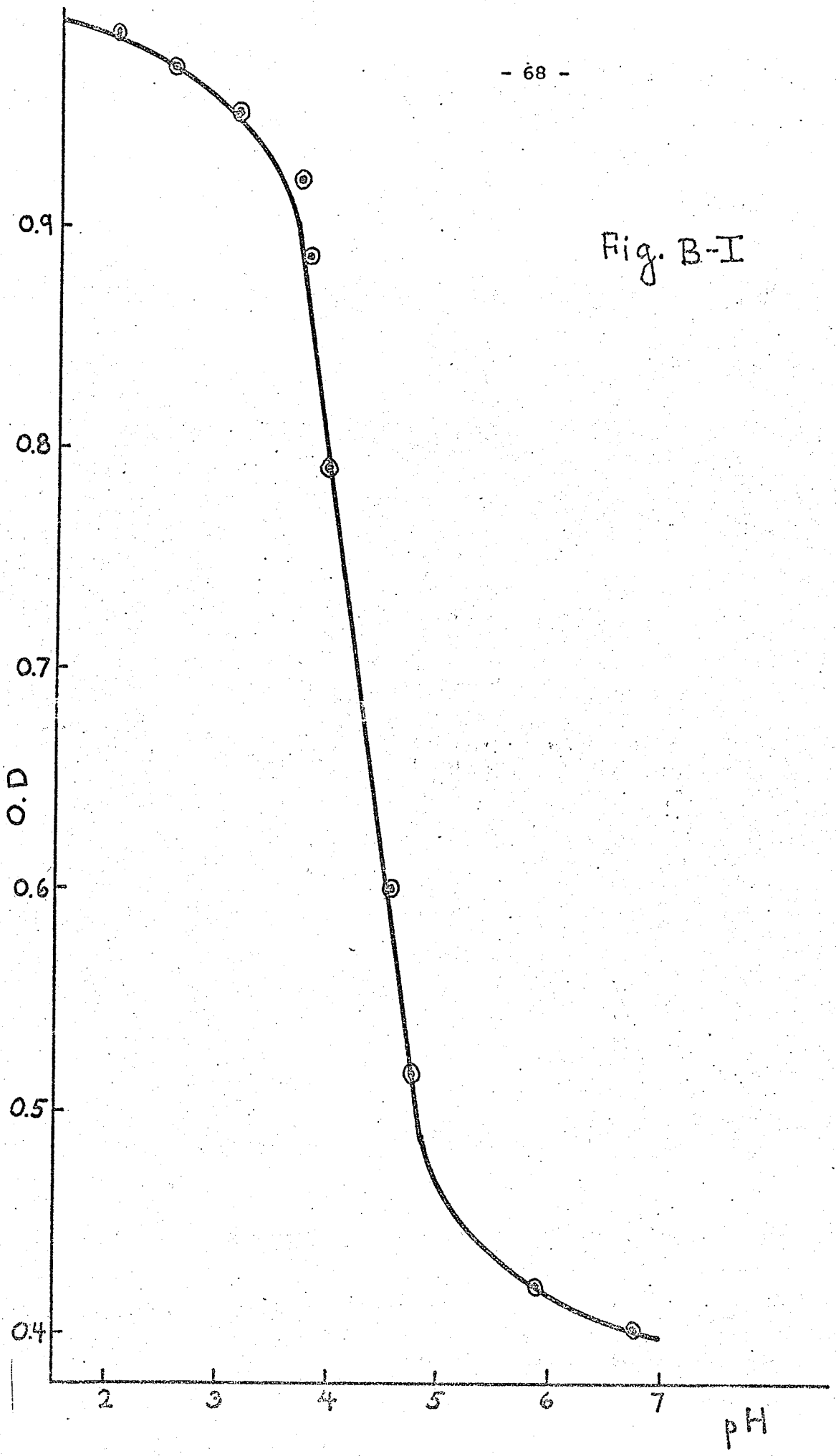


Fig. B-I

Since A, $[H^+]$ and C are observable quantities, the above equation contains only three unknowns: K, ε_{HA} and ε_B. The computor program prepared by Leggate and Dunn (19) was used to calculate K.

2,4-Dimethoxybenzoic acid is a weak acid having a pK of 4.31. Hence, when $[H^+] > 10\ K = 4.90 \times 10^{-4}$ or pH < 3.31, the equation (B.7) simplifies to:

$$k = (k_A K + k_{HA}[H^+]) \times \frac{k^*K^* + k^+[H^+]}{K^*(k^* + k_{-A}) + (k^+ + k_{-HA})[H^+]} \qquad (B.8)$$

Since at lower acidites there is no C^{13} kinetic isotope effect the right hand fraction involving k^+ and k^* (rate constants for decarboxylation steps) must disappear, which is possible only if $k^* >> k_{-A}$. The equation (B.8) then reduces to

$$k = k_A K + k_{HA}[H^+] \qquad (B.9)$$

The data from table B-VI are plotted in figures B.2 and B-3 using $[H^+]$ and h_o respectively, and although there is considerable scattering, it is evident that h_o gives a better fit. From the slope and intercept of the plot it follows that $k_A = 3 \times 10^{-2}\ sec^{-1}$ and $k_{HA} = 6 \times 10^{-4}\ sec^{-1}$. That is, the rate constant for ring protonation of the anion A^-, is about a hundred times greater than that for protonation of the free acid, HA. This ratio is similar to that found for 4-methoxyanthranilic acid (10).

At higher acidities two possibilities arise:
(1) k^+ is negligible. The essence of this postulation is that both species H_2A^* and HA^* participate as kinetic intermediates but only HA^* decomposes at a measurable rate.
(2) k^+ becomes significant at high acidities. Although CO_2 is a better leaving group compared to $COOH^+$, at higher acidities where most of the organic acid exists as unionized acid, the concentration of H_2A^* will increase considerably, so that the decarboxylation of $COOH^+$ may become significant in the rate expression.

TABLE B-VI

RATES OF DECARBOXYLATION OF 2,4-DIMETHOXYBENZOIC ACID IN AQUEOUS PERCHLORIC ACID SOLUTION AT 70°C. μ=1 (with NaCl)

MOLARITY	$kx10^5$ sec^{-1}
0.027	0.042
0.048	0.06
0.096	0.12
0.138	0.17
0.212	0.24
0.300	0.28
0.381	0.37
0.530	0.55
0.589	0.63
0.739	0.93
0.813	1.00
0.889	1.23

FIGURE B.2

PLOT OF k VERSUS $[H^+]$
for 2,4-dimethoxybenzoic acid

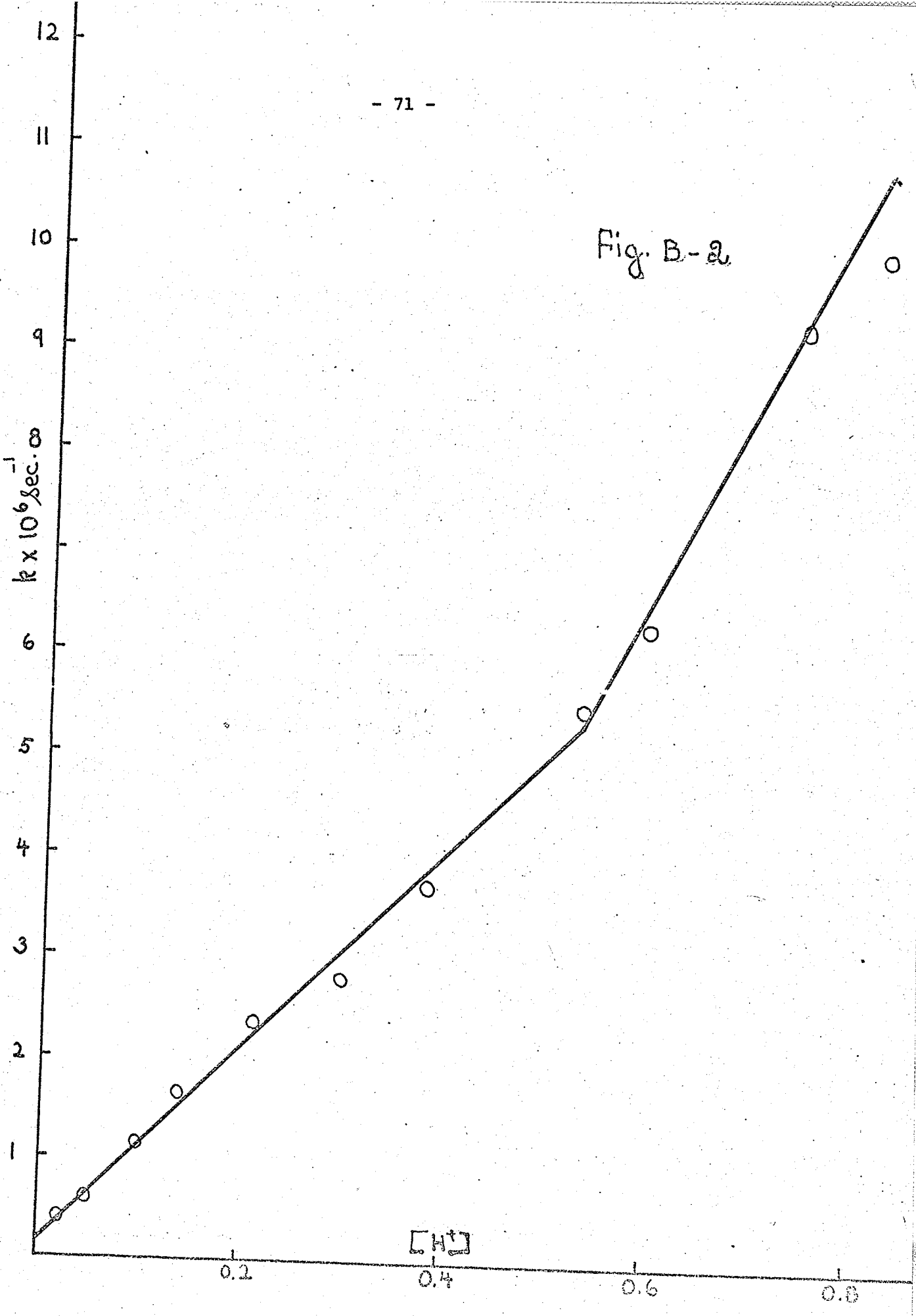


Fig. B-2

FIGURE B-3

SHOWING THE PLOT OF k VERSUS h_o
for 2,4-dimethoxybenzoic acid

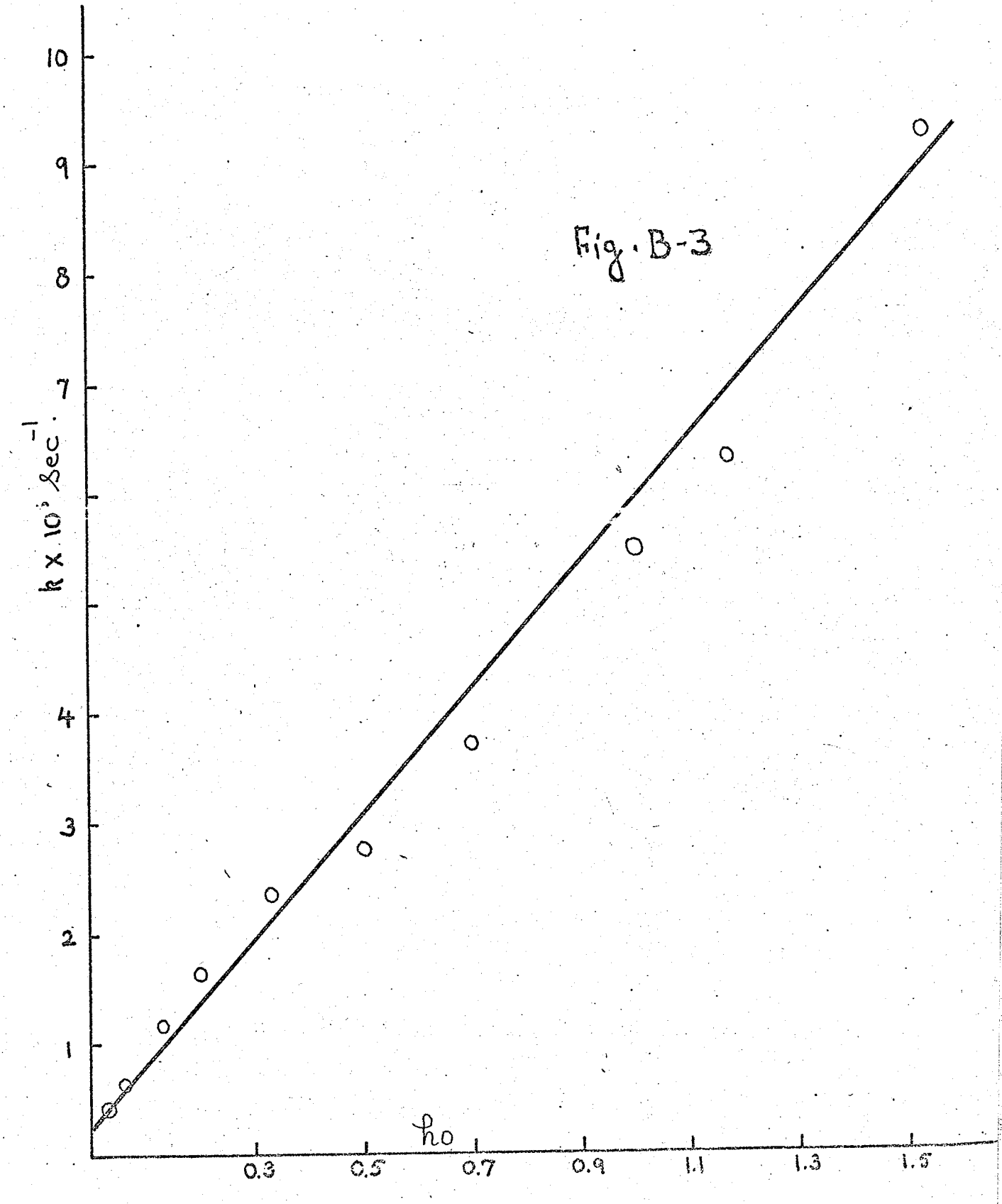


Fig. B-3

If k^+ is negligible, equation (B.8) simplifies to

$$k = k_{HA}[H^+] \times \frac{k^*K^*}{k^*K^* + k_{-HA}[H^+]} \qquad (B.10)$$

at moderate acidities, and changes to

$$k = \frac{k_{HA}}{k_{-HA}} \times k^*K^* \qquad (B.11)$$

at high acidities. But if k^+ is significant the equation (B.8) changes from

$$k = (k_A K + k_{HA}[H^+]) \quad \frac{k^*K^* + k^+[H^+]}{k^*K^* + (k^+ + k_{-HA}[H^+]} \qquad (B.12)$$

at moderate acidities to

$$k = (k_A K + k_{HA}[H^+]) \times \frac{k+}{k^+ + k_{-HA}} \qquad (B.13)$$

at high acidities. Therefore the present problem is to decide between mechanisms corresponding to equation B.11 and (B.13)

The mechanism corresponding to equation (B.11) essentially requires that the rate should become independent of the acidity at high acidities. This has been well established for azulene-1-carboxylic acid (23A) and 2,4,6-trihydroxybenzoic acid (34) where the rates start to level off around 0.5M and 1M perchloric acid respectively. Another possible reason for the rate levelling off at high acidities might be due to conversion of the species $R\text{-}C\overset{O}{\underset{OH}{<}}$ to $R\text{-}C\overset{O}{\underset{OH_2}{<}}^+$. However this protonation usually occurs at very high acidities (32). Thus for mesitoic acid the rate begins to level off around 86% H_2SO_4 and at this high acidity the above mentioned species is the main reaction intermediate (32).

Mechanism (B.11), then, predicts that the rate should level off at the point where $k_{-HA}[H^+]$ exceeds k^*K^* and should then decrease when protonation of RCOOH to $RCOOH_2^+$ begins. The mechanism (B.13), on the other hand, requires that the rate should not level off until the formation of $R\text{-}C\overset{O}{\underset{OH_2}{<}}^+$ begins, and should never decrease, since the decrease in rate

expected from $R-\overset{O}{\overset{\|}{C}}-OH_2^+$ formation will be compensated by the increase in rate expected by the $[H^+]$ term in the numerator of equation (B.13). For 2,4-dimethoxybenzoic acid pK_{BH^+} is found to be -5.5 on the H_o scale (56). Therefore mechanism (B.13) predicts that the rate should not begin to level off until the acidity reaches about $H_o = -4.5$, while mechanism (B.11) predicts that levelling off should begin at lower acidities, and the rate should begin to decrease at about $H_o = -4.5$. In correlating rates with acidity, the choice of a suitable acidity function is highly critical. The treatment of indicator protonation equilibria, as originally developed by Hammett and Deyrup (14) included the expectation that in a given acidic medium, the degree of protonation would depend only on the acidity constant of the protonated indicator and its net electric charge. This led to the establishment of the acidity function H_o, to which all electrically neutral bases were expected to conform. Hammett's prediction of behavioral uniformity of uncharged bases, in media of high dielectric constant, at least, remained unchallanged for many years, but it is now abundantly evident that different structural classes of bases, even of a single charge type, do respond differently to changes in solvent acidity, thus generating their own peculiar acidity functions. Recently (29) data are presented on the equilibrium protonation of certain azulene carbon bases, with which a new Hammett type acidity function, Hc, has been constructed by Reagan. In acid catalysed decarboxylations the protonation occurs at carbon atom 1 on the ring. In principle, therefore, the Hc function ought to be better than H_o for our purpose. The data from tables B.I and B.II are plotted in figure B-6 using Hc function. From the plots it is found that the slopes in the two acids are

identical and furthermore, they are far from unity. Figure B-4 shows the log k Vs H_o plot. In this case the slopes in the two mineral acids are nearly identical and close to unity. This would make it appear that H_o is a better function than H_c.

The fact that the rates start to level off at $H_o < -2$, figure B-4, in both mineral acids suggests that the mechanism corresponding to equation (B.11) is operative in the decarboxylation of 2,4-dimethoxybenzoic acid. Also the fact that the rate of decarboxylation decreases sharply at $H_o < -5$ supports the proposal that the intermediate H_2A^* does not itself decarboxylate. Figure B-4 shows that the rate behaviour of 2,4-dimethoxybenzoic acid is precisely that predicted by equation (B.11). The rate starts to level off at $H_o = -5$. The rate profile therefore, suggests very strongly that decarboxylation of $COOH^+$ is negligible.

Additional evidence comes from deuterium solvent isotope effects. When the protonation step is rate determining step, a value of k_{H_2O}/k_{D_2O} of from 2 to 3 would be expected. At higher acidities when the decarboxylation step is rate determining one would expect a smaller isotope effect (20). The available data, Table B VII are in accord with this expectation.

On examination of the C^{13}-kinetic data more analytically, the question then arises whether the small isotope effect (2.2%) observed at 5M sulfuric acid will become full (4%) at still higher acidities or that a concerted process is operative in the decarboxylation process.

Bourns (25) has emphasized that although a stepwise mechanism has been established for a large number of electrophilic aromatic substitution processes, there are some reactions such as decarboxylation, where the kinetic intermediate species is so short lived that unless their existence is proved, the possibility of a one step (or concerted) reaction mechanism cannot be ruled out. The decarboxylation of 2,4-dimethoxybenzoic acid would appear to come under this category. It is conceivable that instead of the stepwise mechanism, a concerted process could apply in which protonation of the acid, the formation of the

FIGURE B.VI

PLOT SHOWING THE PLOT OF log k VERSUS $-H_c$

△ – $HClO_4$ point

○ – H_2SO_4 point

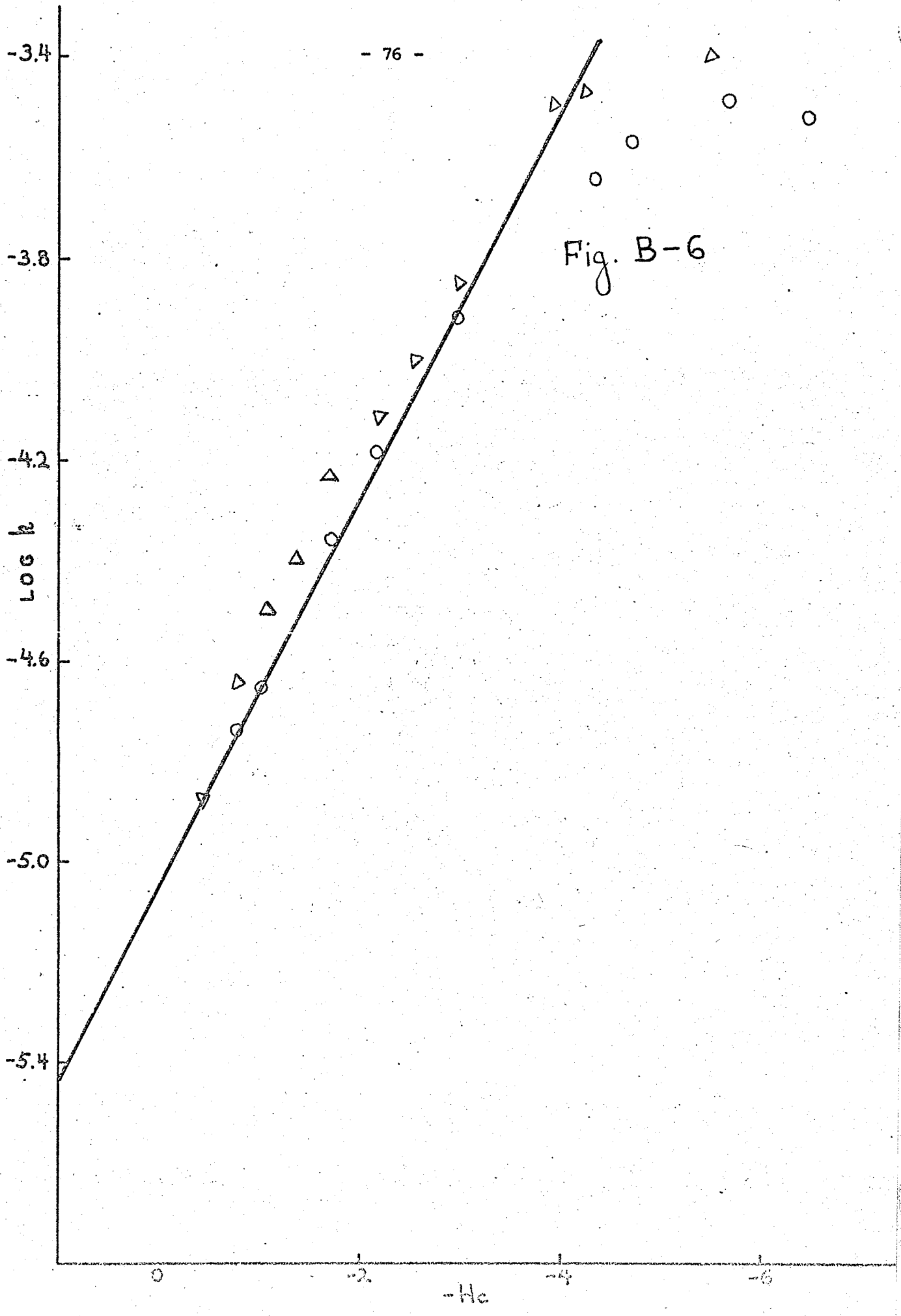


Fig. B-6

FIGURE B.4

PLOT OF log k VERSUS H_o

△ — $HClO_4$ point

○ — H_2SO_4 point (H_o by normality)

⊜ — H_2SO_4 point (H_o by weight percent acid)

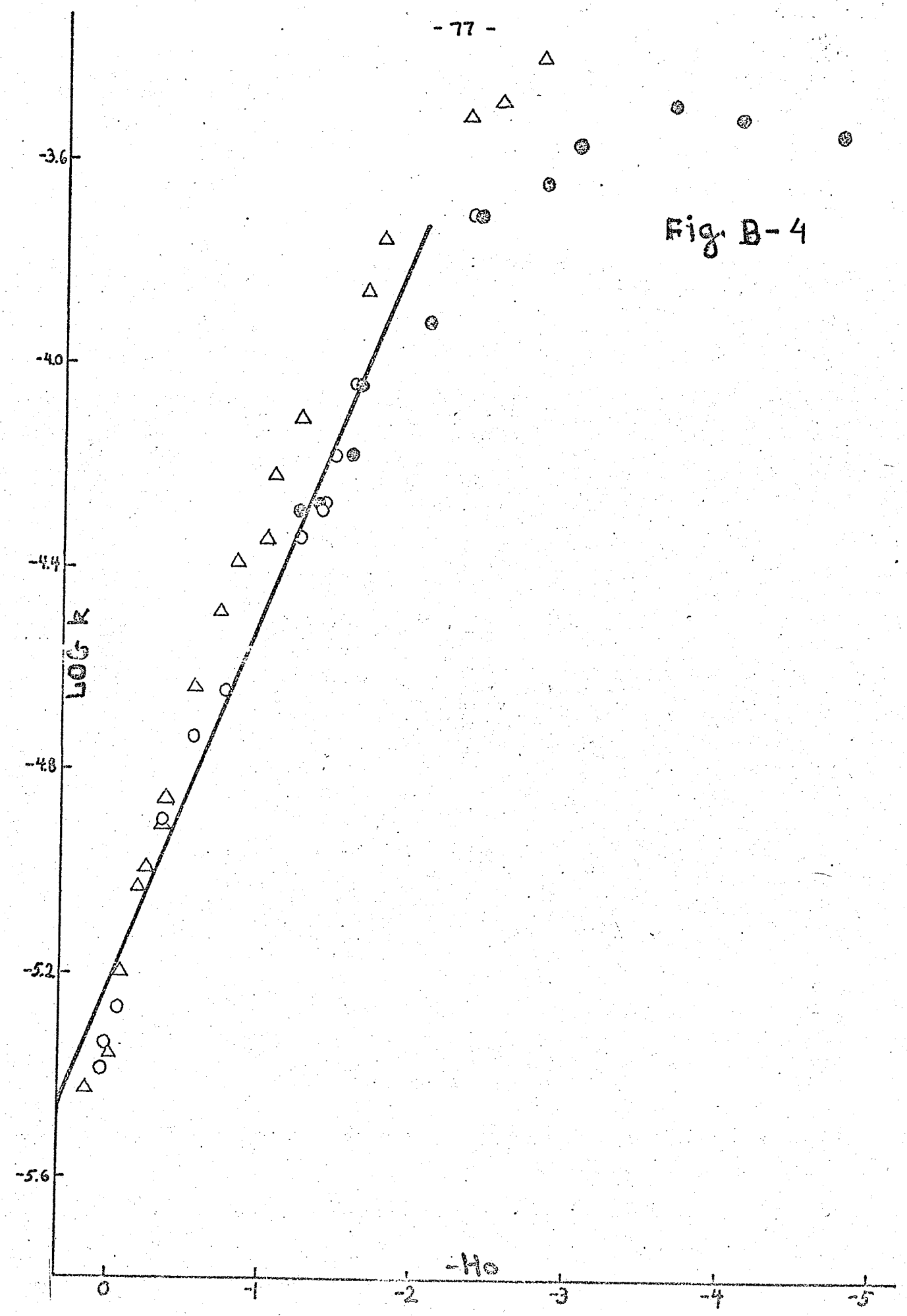


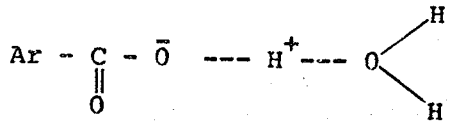
Fig. B-4

TABLE B.VII

SUMMARY OF DEUTERIUM SOLVENT ISOTOPE EFFECT IN $HClO_4$ AND D_2O FOR 2,4-DIMETHOXY-BENZOIC ACID AT 70°C

MOLARITY	$kx10^5 sec^{-1}$ in H_2O	$kx10^5 sec^{-1}$ in D_2O	k_{H_2O}/k_{D_2O}
0.15	0.21	0.10	2.10
1.33	2.35	1.38	1.70
2.76	7.63	5.40	1.41
3.94	17.53	13.00	1.35
4.74	27.00	20.70	1.30
5.06	32.64	23.60	1.38
6.12	43.75	39.64	1.10

ampholytes HA* and H_2A^* and the rupture of the carbon-carbon bond takes place in a single step with



as the transition state. Huang and Long (23A) have further argued that on a concerted mechanism with the above mentioned transition state, a smaller change in solvent deuterium isotope effect is expected in going from rate determining protonation to rate determining decarboxylation step since the departing proton in the reaction coordinate would still make a sizeable contribution to the isotope effect. Furthermore the concerted mechanism would require the magnitude of the C^{13}-isotope effect to be independent of the acid strength since the species H_3O^+ is not involved in any reversible process. By contrast, the stepwise mechanism predicts a significant change in deuterium solvent isotope effect and an increase in the magnitude of the C^{13}-isotope effect with increase in acid strength by favoring the deprotonation step and thus causing the decarboxylation step to be increasingly rate determining.

Deuterium solvent isotope effects have been measured on the decarboxylation of 2,4-dimethoxybenzoic acid. Since these effects are very much dependent on the deuterium content of the medium, they have been corrected to 100 percent deuterium figure B-5. The corrected values are shown in Table (VIII). The change in deuterium solvent isotope effect in going from acid dependent to acid independent phase, is certainly not as large as would be expected from a stepwise mechanism. In azulene-1-carboxylic acid (20) and 2,4,6-trihydroxybenzoic acid (44) where a stepwise mechanism has been established, larger changes in deuterium solvent isotope effects have been observed.

FIGURE B-5

PLOT SHOWING THE DEUTERIUM SOLVENT ISOTOPE EFFECTS VERSUS MOLE FRACTION OF DEUTERIUM

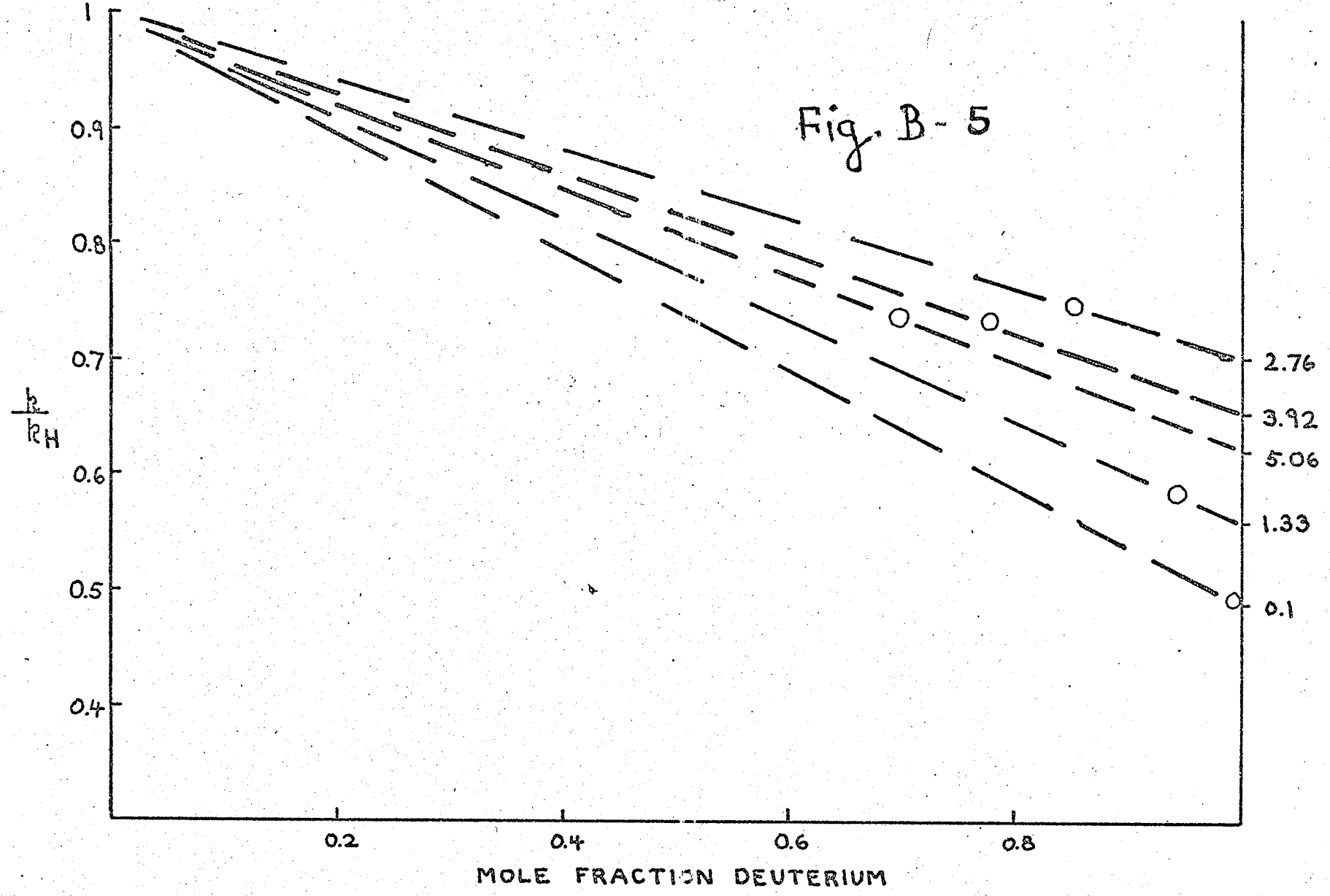


Fig. B-5
1
0.9
0.8
0.7
0.6
0.5
0.4
k/kH
2.76
3.92
5.06
1.33
0.1
0.2
0.4
0.6
0.8
MOLE FRACTION DEUTERIUM

TABLE B-VIII

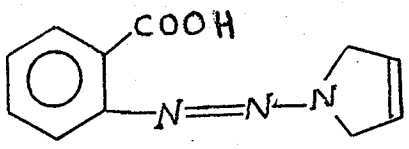
SUMMARY OF DEUTERIUM SOLVENT ISOTOPE EFFECTS ON 2,4-DIMETHOXYBENZOIC ACID AT 70° IN PERCHLORIC ACID SOLUTIONS

MOLARITY	k/k_H observed	k_D/K_H corr.
0.15	0.495	0.490
1.33	0.588	0.560
2.76	0.751	0.708
3.94	0.735	0.658
5.06	0.740	0.623

A second and perhaps more convincing piece of evidence in support of a concerted mechanism comes from C^{13}-kinetic isotope effects observed in perchloric acid solutions, Table B-III. Here the rate levels off with increasing acidity while the isotope effect is still only about 1.4%. This would seem to rule out a stepwise mechanism because the isotope effect should become full (4%) before it levels off.

C. 2-(1-Diaza-3-pyrrolino)-benzoic acid (A)

Wong (52) has prepared the compound A by condensing benzene-diazonium-2-carboxylate with 3-pyrroline. It was assigned the structure



on the basis of elemental analysis and its IR and NMR spectra.

It was also observed by him that the pyrolysis of this compound at its melting point (140°) under nitrogen atmosphere gave 1-phenyl-3-pyrroline, benzoic acid and pyrrole.

Since some of the decomposition products must be formed by decarboxylation, and since A differs from an N,N-dialkyl anthranilic acid only in having the amino group separated from the other carbon atom by the -N=N- link, it was thought that the decomposition might resemble that of anthranilic acid.

A was found to decompose readily in aqueous solution at 40°C and the rate of decomposition could be followed by the change in optical density. The only product of decomposition had an elemental analysis corresponding to anthranilic acid and its UV and IR spectra confirmed this identification.

The rates of decomposition of compound A have been measured in several buffer solutions. The results are shown in table (C-I) and are plotted in figure (C-I). It is seen that the rate is slow at pH below 2.00, and independent of acidity between pH 3 and 7. It was also found that solution of A in 1N NaOH is stable.

The following (tentative) mechanism has been proposed for its decomposition.

TABLE C-I

RATES OF DECOMPOSITION OF I AT 40°C $\mu = 1$

		$k \times 10^5$
1.00 N	HCl buffer	0.75
0.751	"	0.85
0.608	"	0.89
0.496	"	1.19
0.401	"	1.44
0.300	"	1.92
0.202	"	2.54
0.165	"	2.82
0.150	"	2.73

Tartaric acid + KH tartarate buffer

pH before experiment	pH after expt.	
1.033	1.030	4.78
1.290	1.294	5.99
1.345	1.340	6.26
1.592	1.597	9.56
2.030	2.035	8.82
2.960	2.964	10.44
3.340	3.340	10.43
3.462	3.459	10.67
3.557	3.558	9.17
3.855	3.850	10.13
4.030	4.033	9.90
4.510	4.515	11.30
4.969	4.973	9.98
5.996	5.980	10.88
7.050	7.125	11.40

1N NaoH extremely slow

FIGURE C-1

pH DEPENDENCE OF RATE CONSTANTS
FOR DECOMPOSITION OF A AT 40° C

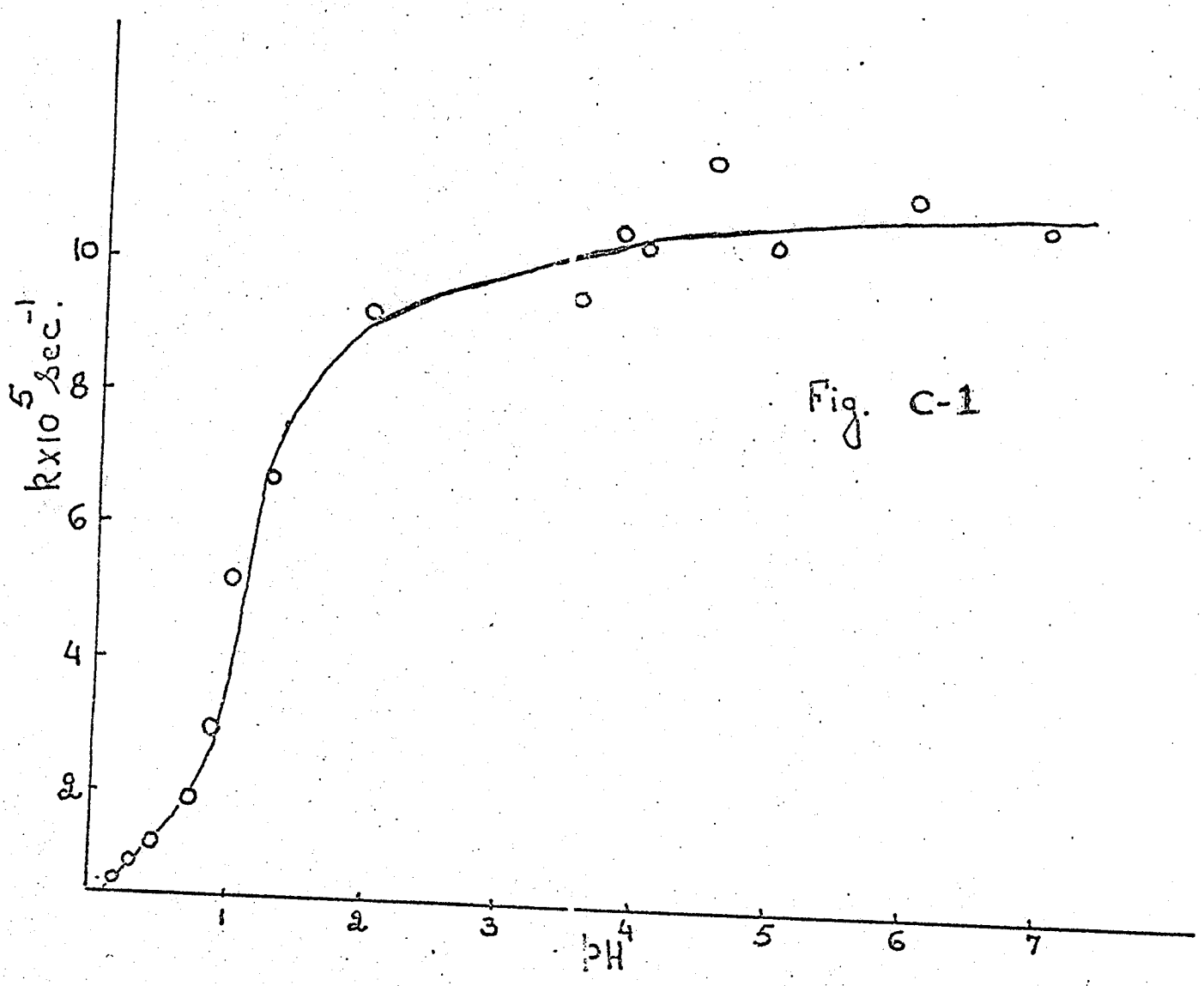
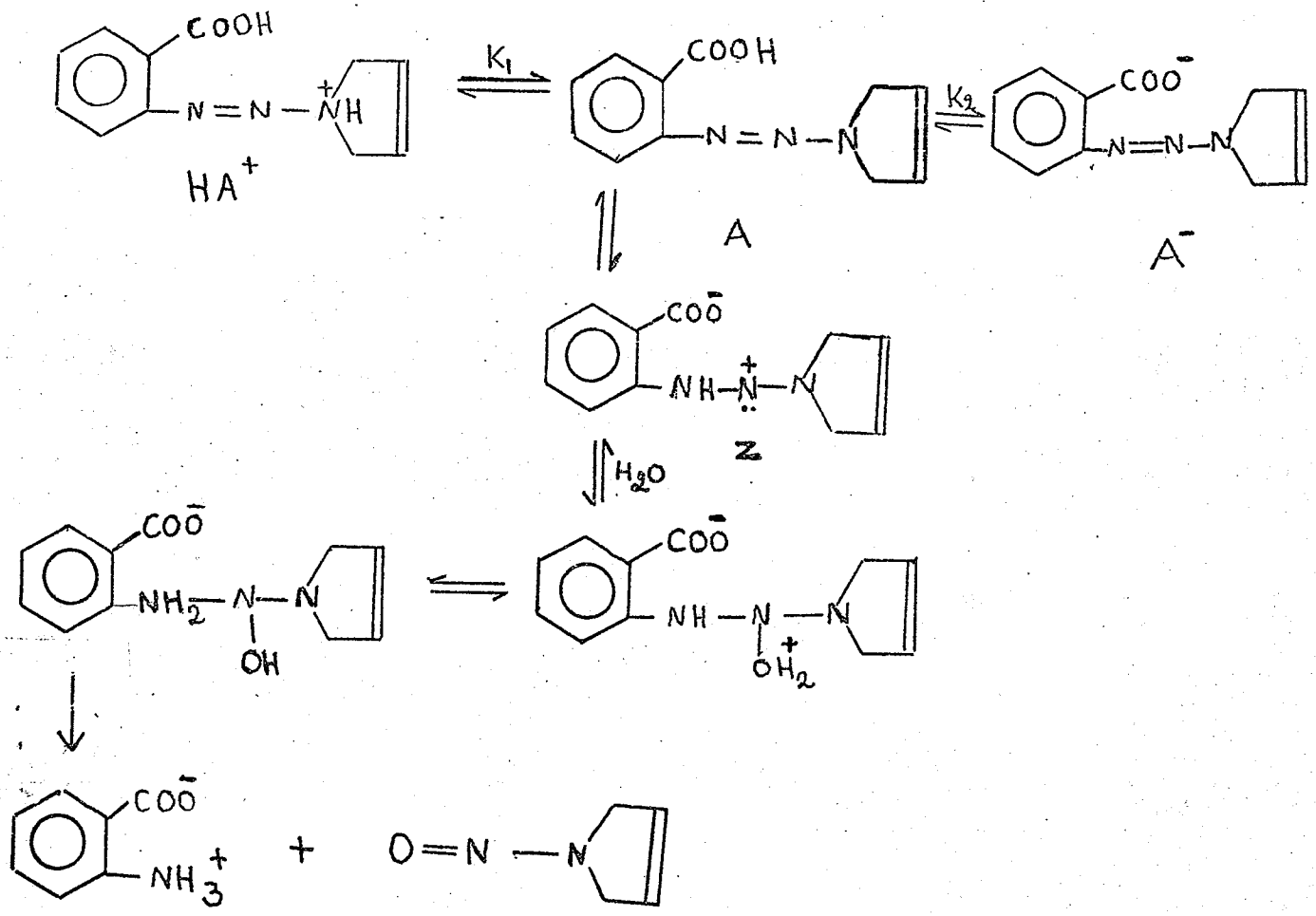
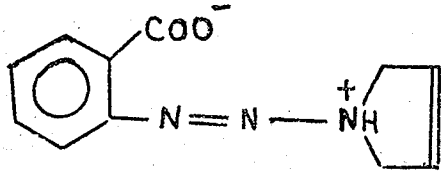


Fig. C-1



The most basic nitrogen in A is probably the pyrroline nitrogen and therefore it is postulated that in acidic solutions A is protonated to HA^+ at this site. Since decomposition is slow in acidic and basic solution it is proposed that only A decomposes. Since HA^+ does not decompose it would appear that decomposition requires protonation of A at a site other than the pyrroline Nitrogen, and since A^- does not decompose it is suggested that the o-carboxyl group provides the necessary proton to convert A to the zwitterion Z. The zwitterion to be expected in largest concentration would be



but this could hardly lead to the formation of anthranilic acid. It is therefore, proposed that the zwitterion Z, although present in lower concentrations, is the one leading to anthranilic acid. Attack by water on the positive nitrogen of Z could lead to the steps shown to anthranilic acid and 1-nitroso-3-pyrroline. The latter compound was not isolated, in fact no product originating from pyrroline was recovered. This is perhaps not surprising considering the oxidizing properties of the nitroso group and the reducing properties of pyrroline. The crude decomposition product was dark in color and this may indicate that pyrroline residues were lost through oxidation and by polymerization.

If the above mechanism is correct it requires that pK_1 for A should be about 2.5 and that pK_2 should be greater than 7. Attempts were made to determine the pK's of A, but decomposition in aqueous solutions was significant at 20°C so the attempts were abandoned.

Since to arrive at the precise mechanism would require an extensive investigation, and because it is evidently not a decarboxylation, it was felt that persuit of this reaction mechanism would not contribute to the original object of the present investigation. The investigation was therefore not carried on further. It is hoped this work will be further continued in this laboratory.

CONCLUSIONS

1. The decarboxylation of anthranilic acid and its 4-methyl and 4-methoxy derivatives has been examined in solutions of high acidity and no evidence for $COOH^+$ decarboxylation has been found.

2. It has been shown that, of the three anthranilic acids examined, the 4-methoxyanthranilic acid is the one in which $COOH^+$ decarboxylation is most likely to be found.

3. 2,4-dimethoxybenzoic acid was thought to be one which might show $COOH^+$ decarboxylation at moderate acidities, but only CO_2 decarboxylation was found even upto acidities where the rate falls off due to protonation of the carboxy group.

4. The decomposition of 2-(1-diazo-3-pyrrolino)benzoic acid in aqueous solutions has been found to give anthranilic acid as one of the principal products. The reaction is therefore not a decarboxylation. Its rate of decomposition has been studied as a function of pH, and a mechanism is suggested for the reaction, but the investigation is not carried to completion.

IV EXPERIMENTAL

A. Materials

1. Aromatic acids

Anthranilic acid (Matheson Coleman and Bell) was crystallized twice from ethanol, vacuum dried and finally sublimed under vacuum. The product had a melting point of 144.6 - 148.8°C (literature value : 146°C (31)).

4-Methoxyanthranilic acid (Leggate and Dunn (19)) was further sublimed under vacuum. The product had a melting point of 180.9 - 181.5°C [literature value: 180-181°C (31)].

4-Methylanthranilic acid (Aldrich Chemical Co.) was crystallized from ethanol, dried under vacuum and finally vacuum sublimed. The product had a melting point of 177.4-178.3°C [literature value: 178-180°C (43)].

2,4-dimethoxybenzoic acid (Aldrich chemical Co.) was cryztallized from ethanol and dried under vacuum. Same batch was used for all C^{13}-isotope work.

2. 2-(1-diaza-3-pyrrolino)benzoic acid

The compound was prepared by the method of Wong (52).

A solution of anthranilic acid (2.74 g) in absolute ethanol (30 ml) was cooled to 0° in an ice cold bath and then treated with concentrated hydrochloric acid (2 ml). Isoamyl nitrite (5 ml) was added dropwise to the stirred solution over a period of approximately 10 minutes. A light yellow solution was obtained over a period of approximately 10 minutes. On addition of anhydrous ether (30 ml) the diazonium salt precipitated. The precipitate was collected in a funnel and was washed with anhydrous ether (3x5 ml). The funnel containing the precipitate was then transferred to a clear filter flask, and the smallest convenient volume (about 5 to 10 ml) of cold water was then added to the funnel to dissolve

the diazonium salt. The aqueous solution was then stirred at 0°C with silver oxide powder (3 g) for 2 hours. After removal of the solid by filteration, the solution was poured into a mixture of absolute ethanol (100 ml) and anhydrous ether (50 ml), previously cooled to 0°. Additional anhydrous ether was added until the diazoniumcarboxylate began to crystallize. After 10 to 20 minutes standing at 0°, the product was collected, washed with cold anhydrous ether (5 ml) and stored in a dessicator. The yield of benzenediazonium-2-carboxylate was 40% (1.2 g).

3-pyrroline (1.5 g) was added very slowly to a benzene (70 ml) solution of benzenediazonium-2-carboxylate (2.4 g). The solution was warmed at 60°C in an oil bath for 1 hour. Half of the benzene was then removed under reduced pressure and the remaining solution was cooled in an ice bath. Crystalline needles separated and were recrystallized by warming in benzene to 60°C. With subsequent cooling to give (1.4 g) of o-(N-diaza-3-pyrrolino)benzoic acid. The prdouct had a melting point 138-140°C (decomposed).

B. Buffer solutions.

Buffer solutions were prepared as suggested by Bates (3) using phthalate in the pH region 2-4 (adjusting the ionic strength of 0.1 with NaCl), and hydrochloric acid for pH's less than 2. All pH measurements were made with a Radiometer model 4C pH meter with shielded glass (G202B) and Calomel (k 100) electrodes in cells thermostated to 25 ± 0.1°C. Measured pH's were reproducible and are assumed to be accurate to ± 0.01 unit. The meter was calibrated against National Bureau Standards tetraoxalate and hydrogen phthalate buffers.

Standard solutions of perchloric and sulfuric acid were made by dilution of the bottle acids. These solutions were further standardized by titration with standard sodium hydroxide solution using a micro burette. Very highly concentrated solutions of sulfuric acid were made by weighing. Exact weight percent solutions of sulfuric acid were made by the method of Zalewski (55).

C. Rate Measurements

1. Anthranilic acids.

The change in concentration of substituted anthranilic acid with time was followed spectrophotometrically by measurements made in alkaline solution where all the acid is in the anionic form, and at wavelengths where the absorbance of the reaction product is negligible. These were 310 mu for anthranilic acid, 315 for 4-methyl and 320 for 4-methoxyanthranilic acid.

The rate measurements were carried out at 80±0.1°C and 115±0.1°C. At these high temperatures the evaporation losses were found to be considerable so the ampoule method was used. Ten to 15 mg of the substituted benzoic acid was dissolved in 25 ml of the solution. Ten ampoules (2 ml capacity) each containing about 1.5 ml of the stock solution were sealed and kept in the thermostated bath. The ampoules were withdrawn from time to time and the reaction was quenched by placing them in ice cooled water. Approximately 1 ml of the solution was withdrawn and immediately injected into weighed 25 ml volumetric flasks containing 15 ml of 1N NaOH solutions. The flasks were reweighed and the weights of the aliquots were calculated as a difference in weight. After dilution to the mark with 1N NaOH the solutions were ready for the spectrophotometric determination of the concentration of the anion. The optical density per gram of the aliquots was calculated.

2. 2,4-dimethoxybenzoic acid

It was found experimentally that 2,4-dimethoxybenzoic acid undergoes decomposition when heated in aqueous solutions of sulfuric and perchloric acids. The rate of decomposition increases with increasing temperature and increasing acidity. The decomposition was recorded on a Beckman D.K. spectrophotometer.

A clean and identical spectrum was recorded at all regions of acidity at 70°, that showed a single decomposition product.

2.5 g of 2,4-dimethoxybenzoic acid was dissolved in 50 ml of 6N perchloric acid and the mixture was heated at 70°C in an oil bath for 12 hours. The reaction mixture was cooled, saturated with NaCl and was extracted with petroleum ether thrice (total 50 ml). The ether extract was neutralized with sodium bicarbonate solution, washed several time with water and dried with anhydrous sodium sulfate. After distilling off the ether, an oily product (1.5 g) was obtained. From its infrared spectrum and boiling point, it was characterized to be meta-dimethoxybenzene. It was therefore concluded that 2,4-dimethoxybenzoic acid undergoes decarboxylation reaction.

Rate measurements for this acid were carried out at 70±0.1°C. A stock solution was prepared by dissolving 50 mg of the acid in 5 ml of absolute ethyl alcohol and diluting this to 250 ml with distilled water. The solution was found to be stable at room temperature for several days. 0.5 ml of this stock solution when diluted to 25 ml gave an optical density between 0.7 and 0.6. Rates were determined by the ampoule technique. The ampoules were withdrawn from time to time, the reaction was quenched in ice cooled water. The solution was brought to room temperature and its optical density was recorded at 270, 260 and 250 mu, where the product m-dimethoxybenzene does not absorb.

3. 2-(1-diaza-3-pyrrolino)benzoic acid

0.5 g of 2-(1-diaza-3-pyrrolino)-benzoic acid (hereafter to be called A) was dissolved in 250 ml of 1N NaOH. The solution was found to be stable since its ultraviolet spectrum did not change over for several months. 0.5 ml of this stock solution when diluted to 100 ml with buffer solutions gave an optical density between 0.6 and 0.7

A was found to decompose into B at a convenient rate in aqueous solution at 40°C, Figures E-1 and E-2 show the corresponding process in 1N HCl and pH 6.8 respectively. The rate of the reaction was followed by the change in O.D. at 270 mμ. Ampoule method as previously described was used. Figure E-3 shows the plot of log OD vs time. A good first order plot was obtained upto three half life at all acidities.

One 1 gm of the compound A was dissolved in 50 ml of water. The solution was heated to 40° for two days in an oil bath. The solution was saturated with NaCl and was then extracted with benzene several times. On distilling off benzene 0.5 g of a dark solid material was obtained which was further purified by several recrystallizations from benzene, when 0.2 g of a solid (melting point 145°) was obtained. The compound was identified to be anthranilic acid from its uv and I.R. (Figures E_4, E_5, E_6) and elemental analysis.

	C	H	N
Calculated	61.31	5.11	10.21
Found	61.22	4.98	10.11

The same product (B) was obtained when the decomposition was carried out in 1N HCl.

No product originating from pyrroline could be isolated. The initial decomposition product is very dark in color and several recrystallizations are required to remove the anthranilic acid. Since pyrroline is subject to easy oxidation, reduction, and polymerization reactions, it seems possible that decomposition product originating from the pyrroline part of A may be lost in the isolation procedure.

FIGURE E-1

SHOWING THE DECOMPOSITION OF
COMPOUND A IN 1N HCl

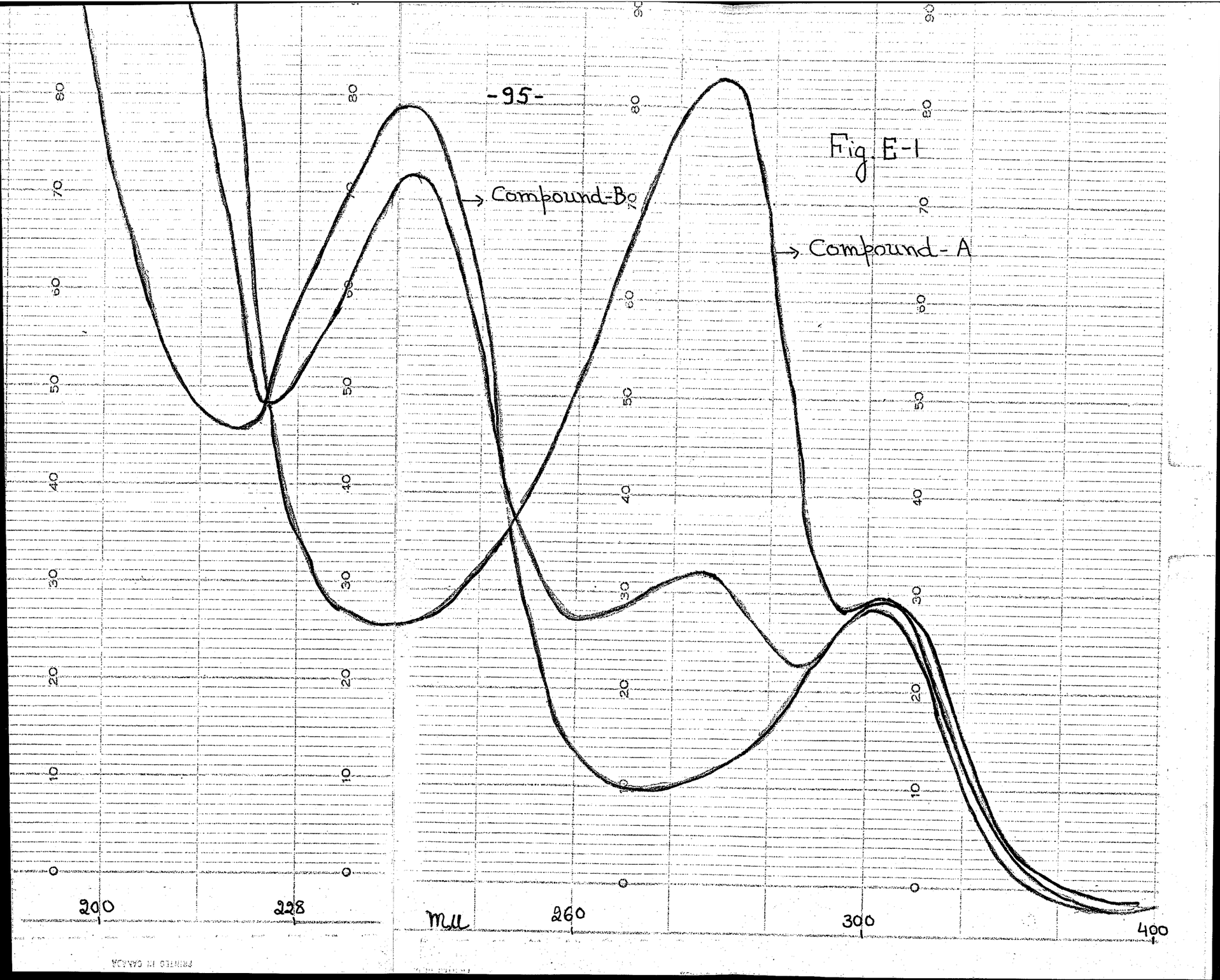


Fig. E-1

FIGURE E-2
SHOWING THE DECOMPOSITION OF
COMPOUND A IN pH 6.8

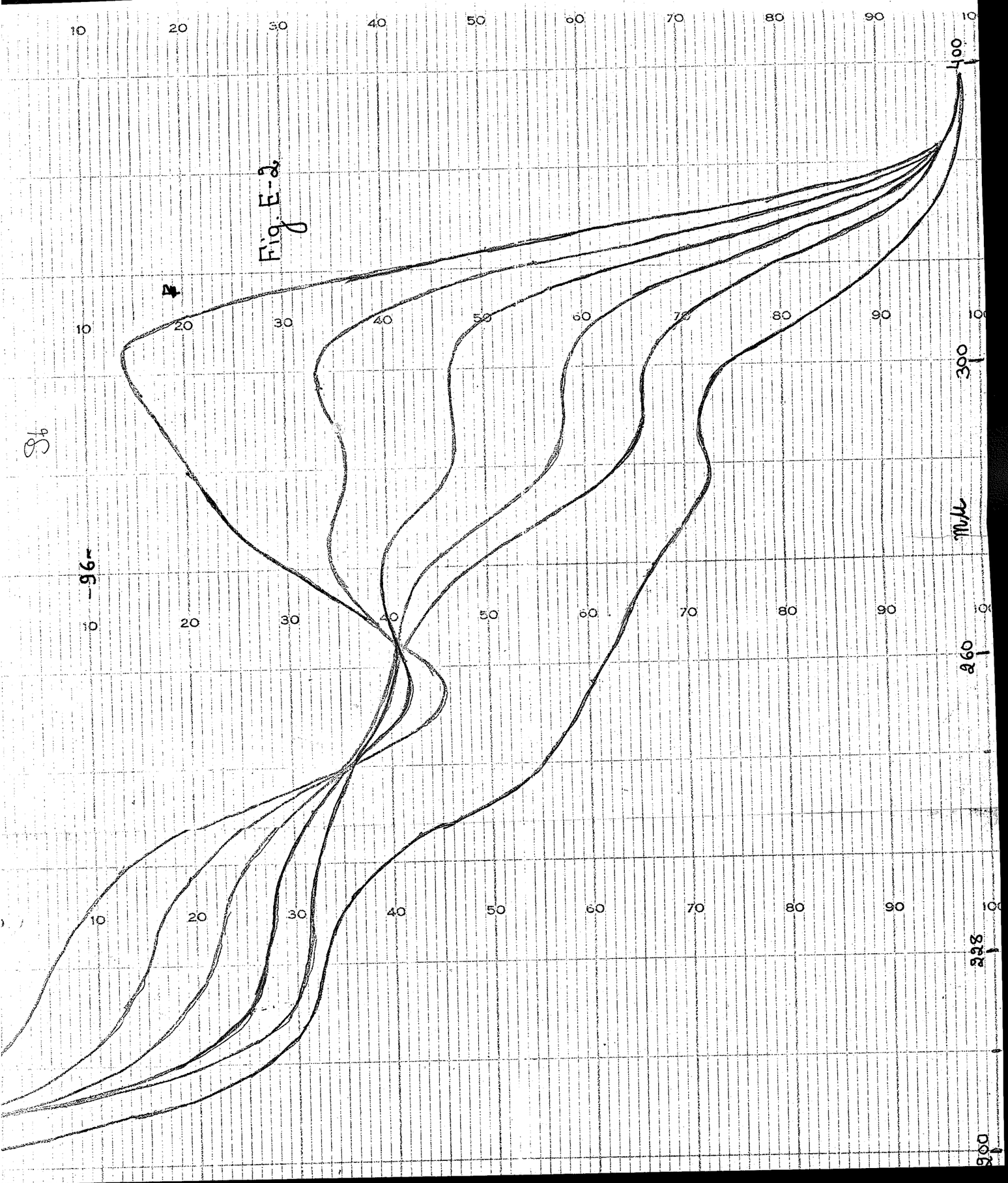


Fig. E-2
10
20
30
40
50
60
70
80
90
100
400
300
260
228
200
-96-
Mμ

FIGURE E-3

SHOWING THE PLOT OF log OD
VERSUS TIME FOR THE DECOMPOSITION
OF COMPOUND A

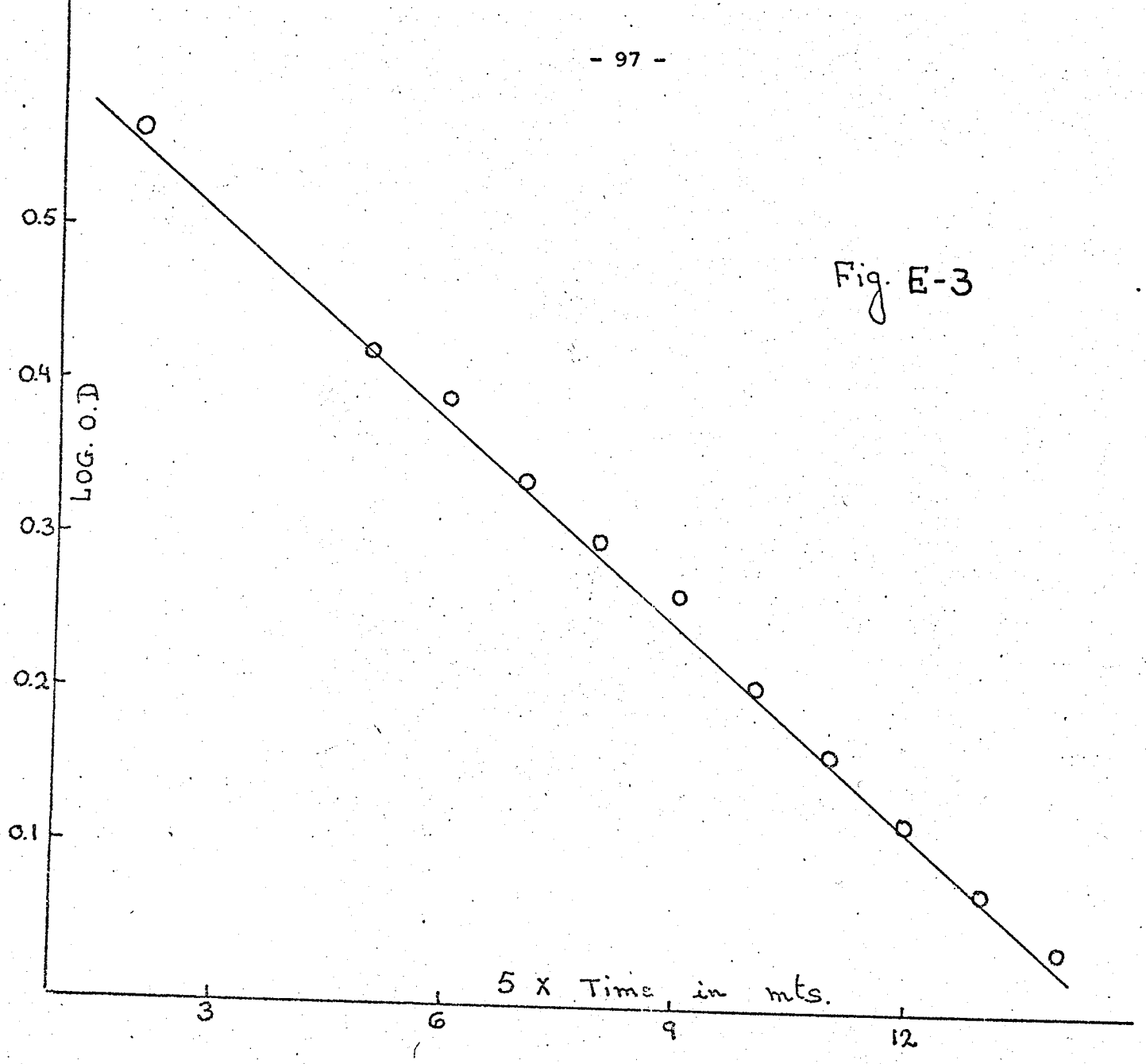


Fig. E-3

FIGURE E-4

SHOWING THE UV SPECTRUM OF
ANTHRANILIC ACID IN

I - 1N HCl

II - pH 7.0

I

100

128

0

m/e- 260

300

400

Fig. E-4

Fig. E-5 I.R. OF B IN KBr

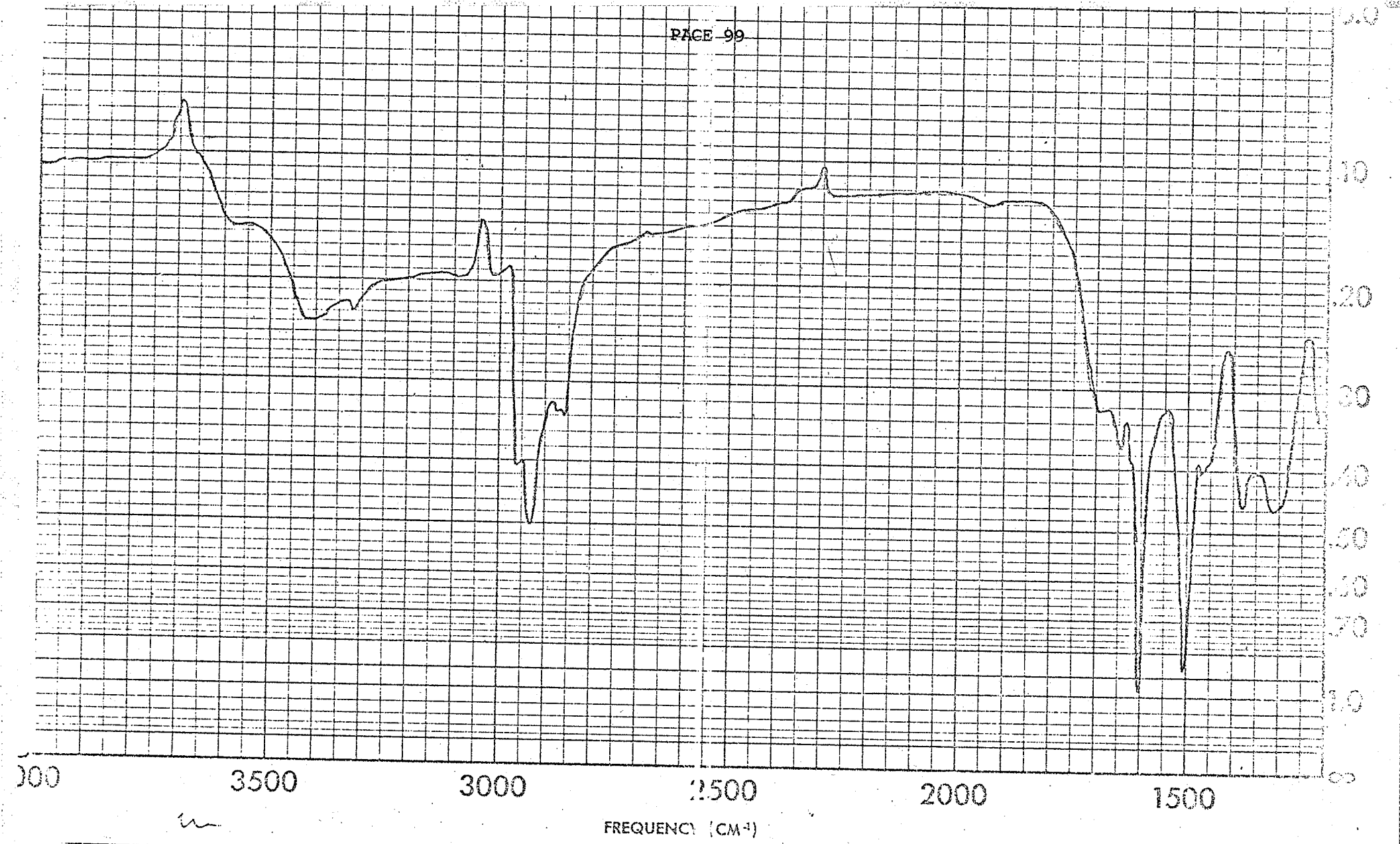
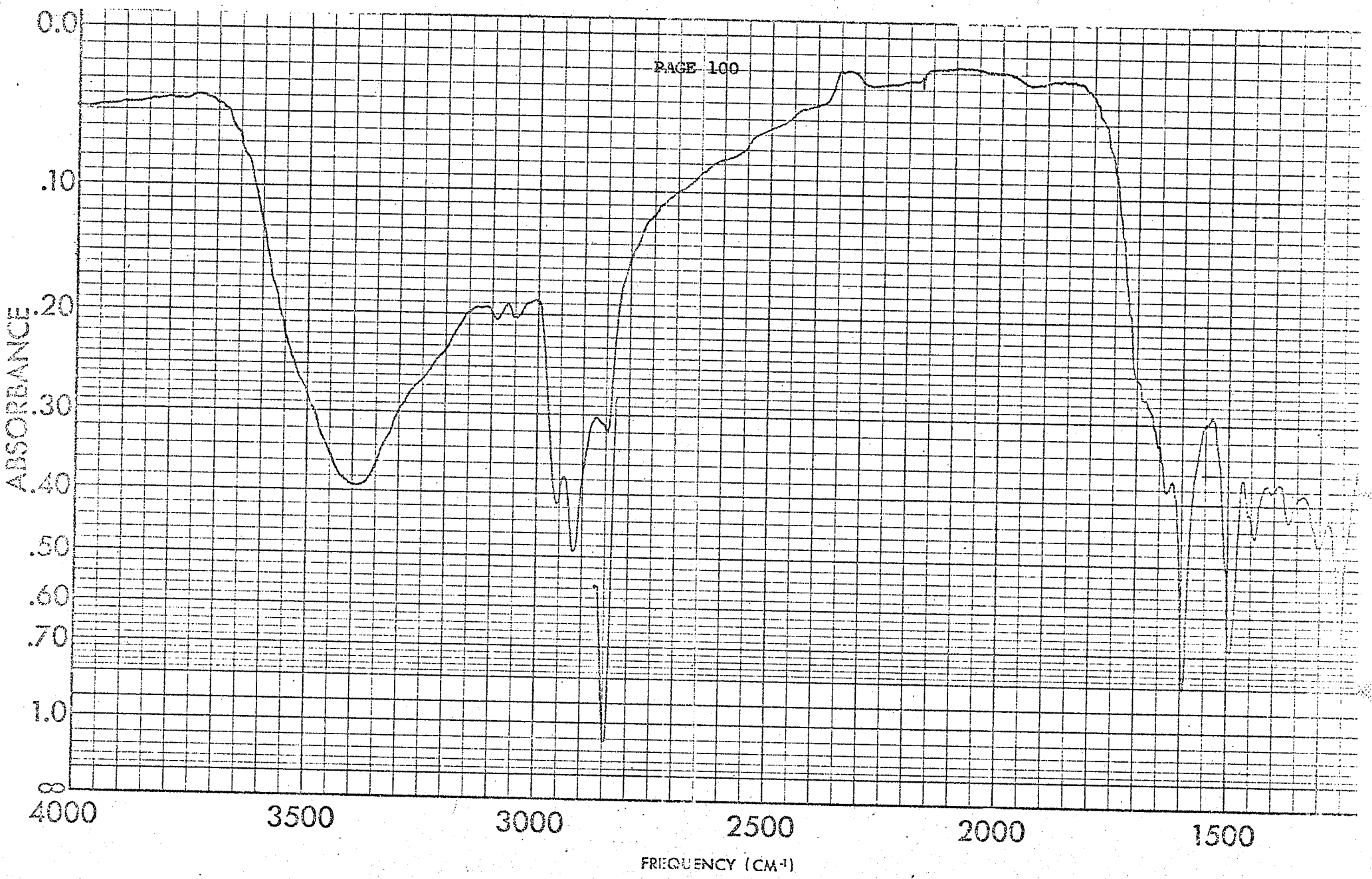

3500
3000
2500
2000
1500
FREQUENCY (CM⁻¹)

FIGURE E-6

I.R. of Anthranilic acid in KBr.


0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
FREQUENCY (CM-1)

D. Deuterium solvent isotope effects

1. In $HClO_4$ and D_2O

The bottle perchloric acid was titrated against standard NaOH solution and was found to be 73%. Equal volumes of this acid were withdrawn into several previously weighed volumetric flasks (10 ml). The flasks were reweighed and those two were picked up that contained nearly the same amount of perchloric acid. The flasks were diluted accurately to the mark, one with H_2O and the other with D_2O and were weighed again. 5-10 mg of the acid (anthranilic) was dissolved and rates in H_2O and D_2O were measured using the ampoule technique as described before. It was also established for two sets of experiments (as shown below) that the rate measurements showed acceptable agreement even though the weights of perchloric acid differed in the second place of decimal.

RUN NO.	WT. OF $HClO_4$	WT. OF D_2O	WT. OF H_2O	$kx10^7$ sec^{-1}
S_{12}	9.9637		3.9669	9.83
S_{13}	9.9583		3.9449	9.80
S_{14}	9.9743	4.4559		6.40
S_{15}	9.9573	4.5185		6.29

The mole fraction of deuterium in the solvent was calculated as follows:

$$\text{mole fraction D} = \frac{\text{gram atom D}}{\text{gram atom D + gram atom H}}$$

gram atom D = wt. D_2O x 2/20

gram atom H = H from H_2O added + H from H_2O in $HClO_4$ + H in $HClO_4$.

$$= (\text{wt. } H_2O + 0.27 \text{ wt.} HClO_4) \times 2/18 + 0.73 \text{ wt. } HClO_4/100.5$$

2. In H_2SO_4 + H_2O and D_2SO_4 + D_2O

Equal volumes of H_2SO_4 and D_2SO_4 were withdrawn using a micropipette into two previously weighed volumetric flasks (25 ml). The flasks were diluted upto the mark with H_2O and D_2O respectively and were reweighed. The solutions were found to be of equal strength (within the experimental error) by titration and by calculation from the weight percent of the acid. One example is shown below.

	H_2SO_4	D_2SO_4
weight of empty flask	19.30370	17.23080
wt (flask + 7 ml acid)	31.81940	30.08255
wt. with solvent	51.06120	51.50900
Normality by titration	10.12N	10.18N
Normality calculated from wt. percent of acid	10.02N	10.10N

E. C^{13}-carboxyl kinetic isotope effects.

1. Determination of extent of reaction in decarboxylation

Dunn and Buccini (10) measured the extent of reaction by measuring the amount of carbon dioxide evolved in the reaction. In this procedure great care has to be exercised in transferring the carbon dioxide quantitatively from the reaction vessel into the CO_2 collecting bulbs.

In this work, the extent of reaction was measured spectrophotometrically. This procedure was found to be simpler than earlier method. For both anthranilic acid and 2,4-dimethoxybenzoic acid, it was experimentally determined that the rate of decarboxylation was independent of the carboxylic acid concentration. In case of 2,4-dimethoxybenzoic acid, two solutions A and B each containing 1 mg and 100 mg of the acid respectively were decarboxylated in 5N perchloric acid. The optical densities of A were measured directly where as solution B was diluted to 100 times with 5N perchloric acid each time. The two rates (k) so determined (30.37×10^5 and 30.49×10^5) were well within the experimental error. This fact was verified in several other runs.

2. The high vacuum system

The high vacuum system shown schematically in next page was used to collect and purify the CO_2 produced in the decarboxylation reaction. A rotary oil pump and a mercury diffusion pump were used to attain the high vacuum. A McLeod gauge was connected into the system to measure the vacuum. The system was of a conventional design and only parts requiring any special description are shown in the figure.

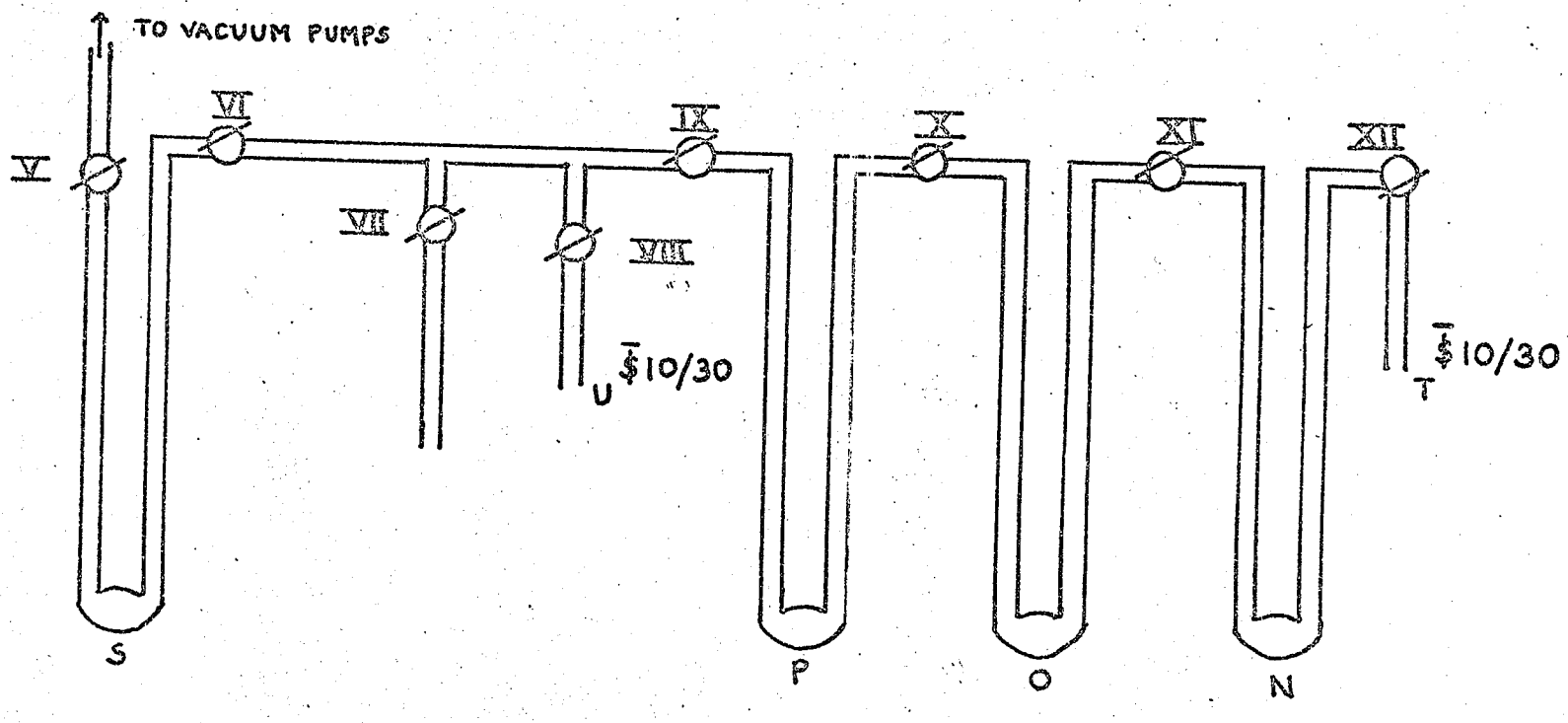
3. Procedure

Four samples were prepared for each run. The samples for complete decarboxylation were prepared by dissolving 30 mg of the carboxylic acid (2,4-dimethoxybenzoic acid) in 6N perchloric acid. The reaction vessel was a 250 ml flask containing a ground glass joint (B/24) and a stop cock (A). The reaction vessel

FIGURE E.7

SHOWING THE ESSENTIAL PARTS OF
VACUUM LINE

Fig. E-7



was attached to the high vacuum system at U keeping the stopcock IX closed. The reaction mixture was frozen in dry ice-acetone bath and was degassed till a high vacuum was obtained. The stop cock A was then closed and the reaction vessel was allowed to come to the room temperature. The mixture was frozen again and was degassed. This process was repeated four to five times to ensure that all the dissolved carbon dioxide and oxygen has been removed from the reaction mixture. All the four samples so prepared were kept together in the oil bath at $60\pm0.1^{\circ}$ for 30 hours (to ensure complete decarboxylation). The samples were then taken out from the bath and the reaction was chilled in ice cooled water. The vacuum line was flamed thoroughly to ensure that there were no organic impurities in the system. The sample (CO_2) collecting bulb was attached at T and the reaction vessel at U to the vacuum line keeping the stopcock A closed. The whole system was evacuated till a high vacuum was obtained in the McLeod gauge. The stop cocks VI, X, XI and XII were then closed. Bulb P was immersed in liquid nitrogen bath and stop cock A was opened keeping the reaction vessel in ice cooled water. The reaction mixture was stirred by means of a magnetic stirrer for one hour. Assuming that all the carbon dioxide has been transferred by this time quantitatively into the bulb P, the stop cocks A and IX were closed. Bulb P was brought to the room temperature and then it was cooled in dry ice-acetone bath whereas bulb O was immersed in liquid nitrogen bath. After fifteen minutes the stopcock X was opened, thereby transferring the carbon dioxide from bulb P to O. Water and other high boiling impurities were trapped in bulb P. The CO_2 collected in the bulb P was further purified by distillation under high vacuum through the bulbs O and N and was eventually collected in the sample bulb immersed in liquid nitrogen.

Samples for partial decarboxylations were prepared by dissolving 200 mgs of the organic acid in 100 ml of the solution. All the samples were kept in the oil bath together and were taken

out at the same time (corresponding to 15% reaction). The carbon dioxide so produced was purified and collected as described above.

All CO_2 analysis of the isotopic ratio C^{12}/C^{13} (mass $\frac{44}{45}$) were carried out with a Atlas mass spectrometer GD 150.

Prior to each analysis, the samples were scanned and no interfering impurities were found to be present.

The isotope effect, 100 (k_{12}/k_{13} - 1), was calculated from the equation

$$k_{12}/k_{13} = \frac{\log (1 - f)}{\log (1 - f \frac{R_f}{R_o})}$$

where R_f is the ratio $C^{13}O_2/C^{12}O_2$ when the fraction of acid decarboxylated is f, and R_o is the same ratio when decarboxylation is complete.

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