THE MECHANISM OF
THE THERMAL DECARBOXYLATION OF ANTHRANILIC ACID

by

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ABSTRACT

The decarboxylation of anthranilic acid in aprotic solvents has been found to be second-order with respect to anthranilic acid. Electron-donating substituents in the acid molecule were observed to accelerate the reaction while electron-withdrawing substituents were observed to slow the reaction. An application of the Hammett equation was made to the reaction and a reaction constant of - 1.35 was obtained.

The isotope effect accompanying the thermal decarboxylation of anthranilic acid having deuterium in its carboxyl group was determined. The ratio k_H/k_D was found to be 2.66.

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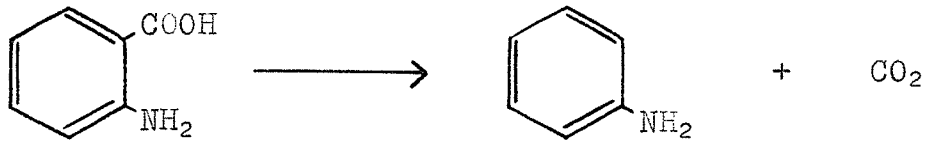
THE THERMAL DECARBOXYLATION OF ANTHRANILIC ACID

INTRODUCTION

When anthranilic acid (o-aminobenzoic acid) is heated above its melting point, it decarboxylates to yield aniline as indicated in the following equation:



This decomposition also occurs when the aqueous solution of anthranilic acid is boiled and this aqueous decomposition has been found to be catalyzed by mineral acids. Moreover, the C^{13} isotope-effect for the decarboxylations of anthranilic acid was observed to be equal to unity. On the basis of these observations, it was concluded that the decarboxylation of anthranilic acid must be a bimolecular reaction, with the attack of a proton on the acid molecule constituting the rate-determining step (37).

However, Krueger (25), who attempted to prepare o-deuteroaniline by decarboxylating partially deuterated anthranilic acid in the melt, observed that an unusually high amount of deuterium was obtained in the ring of the aniline. This result could not be explained by the mechanism proposed above for this reaction.

The object of this investigation was to study the effects of substituents in the anthranilic acid molecule on the rate

of decarboxylation to determine the reaction centre and to show whether or not the reaction could consist of a proton-attack on anthranilic acid. It was also proposed to make a deuterium isotopic study for the reaction to establish whether or not the proton-attack is the rate-determining step.

HISTORICAL REVIEW

The Mechanism for Decarboxylation

In recent years evidence has accumulated that the decarboxylation of carboxylic acids can occur either by a unimolecular or a bimolecular mechanism. Moreover, it has been realized that the process is essentially a replacement reaction:

$$H^* + RCO_2H \longrightarrow H^*R + CO_2 + H$$

Such replacements in other molecular species (e.g. replacement of a halogen by a hydroxyl group in alkyl halides) have long been known to take place by the S_N1 and S_N2 mechanisms of Hughes and Ingold (21) and it has been suggested that the two modes of decarboxylation can be classified analogously as uni- and bimolecular electrophilic replacement processes (21, 34):

S_E1 (a) $RCO_2H \longrightarrow HR + CO_2$

(b) $RCO_2^- \longrightarrow R^- + CO_2$

S_E2 (a) $RCO_2H + H^+ \longrightarrow HR + CO_2 + H^+$

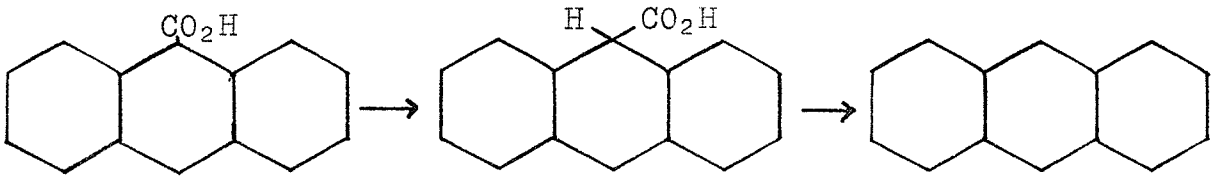
(b) $RCO_2^- + H^+ \longrightarrow HR + CO_2$

The S_E1 mechanism has been verified in a large number of cases and the reader is referred to an extensive review by Brown (5) for examples. This mechanism requires the loosening of the R-C bond to be the rate-determining process, with the implication of a rate unaffected by acids and facilitated by the introduction of substituents into R that diminish electron density at the atom α to the carboxyl group. It has been found that this mechanism proceeds through the anion form of the acid and is therefore base-catalyzed.

The number of carboxylic acids which are known to decarboxylate according to the S_E2 mechanism is, however, relatively small. The rate of a S_E2 process will be determined by the attack of a proton at the α carbon atom and will show bimolecular kinetics involving acid-catalysis. It will be facilitated by substituents in R that increase electron density at the α carbon atom.

Schenkel and Schenkel-Rudin (34) first suggested in 1948 that some organic acids are decarboxylated by a bimolecular electrophilic substitution mechanism when they found that 9-anthracenecarboxylic acid decarboxylated more readily in acidic solvents than in basic solvents. They proposed that the rate of the reaction is determined by the attraction of a proton by the carbon atom α to the carboxyl group, and that

the reaction proceeds through an intermediate as indicated in the following equation:



The kinetics of the reaction are then governed by the equation:

$$\text{rate} = k\,[H^+]\,[RCO_2H]$$

Several other acids have been found to decarboxylate according to the S_E2 mechanism. Schubert (35) studied the decarboxylation of mesitoic acid (2,4,6-trimethylbenzoic acid) in concentrated sulphuric acid and showed that a proportionality exists between the pseudo-first-order constants and the concentrations of the hydroxonium ion in the sulphuric acid. The change in the rate constant with hydroxonium concentration was interpreted on the basis that the rapid and reversible formation of the protonated acid, $RCO_2H_2^+$, is followed by the rate-determining step, the reaction of $RCO_2H_2^+$ with water to yield mesitylene, carbon dioxide and H_3O^+.

(1) $RCO_2H + H_3O^+ \rightleftharpoons RCO_2H_2^+ + H_2O$

(2) $RCO_2H_2^+ + H_2O \longrightarrow RH + H_3O^+ + CO_2$

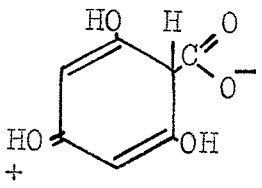
Beringer and Sands (1) later studied the rates of decarboxylation of several mesitoic acids with substituents meta to the carboxyl group. They found that the decomposition is facilitated by electron-donating substituents and hindered by electron-withdrawing substituents. It may be concluded therefore, that the reaction is favoured by a high electron density on the α-carbon atom. Bothner-By and Bigeleisen (4) and Stevens (38) have observed that when C^{13} is placed in the carboxyl group of mesitoic acid a C^{13} isotope effect is obtained, that is, the reaction is slowed down by substituting C^{13} for C^{12} in the carboxyl group. This seems to indicate that the breaking of the C-C bond is part of the rate-determining process for the decarboxylation of mesitoic acid.

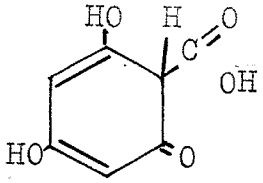
Schubert and Gardner (36) investigated the decarboxylation of 2,4,6-trihydroxybenzoic acid in various concentrations of perchloric acid. They observed that the rate constant increases quite rapidly up to 10.7 percent perchloric acid, then decreases slowly for higher concentrations. It was concluded that, rather than showing acid-catalysis in the usual sense, the data are consistent with a mechanism of a bimolecular transfer of a proton from the solution to the carboxylic acid anion as indicated in the following equation:

$$RCO_2^- + H^+ \longrightarrow RH + CO_2$$

This equation represents either a single process, such as direct replacement by a proton, or a multistep reaction

possibly involving an intermediate such as I or II:

I 

II 

Liquori and Ripamonte (27) have found that the decarboxylation of p-aminosalicylic acid in aqueous solutions of various acid concentrations is similar to the examples already discussed in that the rate constant increases and then decreases slightly with increasing mineral acid concentration. The maximum rate constant was obtained for the pH corresponding to the isoelectric point for the given temperature. This observation led these workers to conclude that the acid decarboxylates essentially in the molecular form.

Brown, Hammick, Scholefield, and Elliott (6, 7) have studied the acid-catalyzed decarboxylation of some o- and p-hydroxybenzoic acids. They determined the activation energies for the decarboxylation of these acids and the results are given in Table I. These results indicate that decarboxylations by the S_E2 mechanism are favoured by a high electron density at the reaction centre because the hydroxy groups are electron donating groups.

The S_E2 mechanism for decarboxylation can therefore be summarized as follows:

TABLE I

Arrhenius Activation Energies for the

Decarboxylation of Benzoic Acids

Acid	E (cal./mole)	
benzoic	> 39,000	
2-hydroxybenzoic	33,600	
2,4-dihydroxybenzoic	29,200	
p-aminosalicylic	19,400	(27)
2,4,6-trihydroxybenzoic	13,600	

(1) The reaction is acid-catalyzed.

(2) The reaction is favoured by a high electron density at the reaction centre.

(3) The attack of a proton on the α-carbon atom is the rate-determining step.

The attack of a proton on the α-carbon atom can occur in three different ways, and thus far no evidence has been offered to indicate how this attack does occur. The possible modes of proton-attack are:

(1) A concerted reaction,

$$RCO_2H + H^+ \longrightarrow RH + CO_2 + H^+$$

(2)
$$RCO_2H + H^+ \rightleftharpoons RCO_2H_2^+$$
$$RCO_2H_2^+ \xrightarrow{\text{slow}} RH + CO_2 \; H^+$$

(3) $RCO_2H + H^+ \xrightarrow{slow} RCO_2H_2^+$

$RCO_2H_2^+ \xrightarrow{fast} RH + CO_2 + H^+$

No evidence has been offered to indicate whether the reaction proceeds from the molecular form or from the anion form, that is, mechanism S_E2 (a) or (b).

The Decarboxylation of Anthranilic Acid

Pawlewski (30) was first to report that anthranilic acid decarboxylates when heated above its melting point, and that it is a first order reaction. McMaster and Shriner (28) found that decarboxylation also occurred when an aqueous solution of anthranilic acid was boiled and that this reaction exhibited first order kinetics.

Stevens, Pepper and Lounsbury (37) found that the decarboxylation of anthranilic acid from boiling water was first order with regard to the acid initially, but that the rate constant decreased as the reaction progressed, due to the high concentration of aniline in the solution near the completion of the reaction. The reaction was observed to be catalyzed, by mineral acids up to a concentration of 1 N, but for more acidic solutions the rate decreased. This seems to indicate that anthranilic acid decarboxylates according to the S_E2 mechanism.

Stevens also made a C^{13} isotope study for this reaction. Samples of carbon dioxide from the partial thermal, aqueous,

and aqueous acid-catalyzed decarboxylations of anthranilic acid having C^{13} in the carboxyl group were analyzed by a mass spectrometer, and it was found that under all conditions the isotope effect was close to unity. This shows that the reaction proceeds according to equation (3), which is given on the previous page, rather than according to equations (1) and (2). The absence of a C^{13} isotope effect for anthranilic acid indicates a mechanism different from that for mesitoic acid for which a C^{13} isotope effect has been observed as previously discussed.

Stevens proposed that the possible sites for proton attack on the anthranilic acid molecules are:

(a) the carbon atom α to the carboxyl group of the neutral molecule,

(b) the oxygen atom of the neutral molecule,

(c) the carbon atom α to the carboxyl group of the zwitterion,

(d) the oxygen atom of the zwitterion.

Path (d) was eliminated on the basis that decarboxylation would not occur by attack of a single proton on the oxygen of the zwitterion.

It has been found that the ratio of neutral molecules to zwitterions is greater for p-aminobenzoic acid than for anthranilic acid (3), and hence one might expect p-aminobenzoic acid to decarboxylate faster than anthranilic acid if the reaction proceeds by path (a) or (b). However, the

rate for p-aminobenzoic acid is reported to be only one-half the rate for anthranilic acid (28). From this it has been concluded by Stevens that the decarboxylation from the zwitterion would be the preferred mechanism, that is, path (c) would be the most likely mode of proton attack on the molecule.

Stevens further argued that whereas in the neutral molecule there is a high electron density at the α-carbon atom because of the mesomeric effect of the ortho amino group, no mesomeric effect would be present in the zwitterion where the inductive effects of the NH_3^+ and CO_2^- groups probably balance each other fairly closely. From this, it was concluded that the attack of the proton on the α-carbon atom of the zwitterion would require a higher activation energy than a similar attack on the neutral molecule, and therefore, mechanism (c) would less likely show an isotope effect than mechanism (a) and is to be preferred on this basis.

On the whole, the mechanism favoured by the evidence available is the attack of a proton on the carbon atom α to the carboxyl group of the zwitterion followed by a rapid cleavage of the C-C bond. However, proton attack on the α-carbon atom of the neutral molecule cannot be excluded.

OBJECT AND METHODS OF THE PRESENT INVESTIGATIONS

If the decarboxylation of anthranilic acid is a bimolecular reaction in which the attack of a proton is the rate-determining step, then the presence of electron donating groups on the benzene ring of the anthranilic acid molecule should facilitate the decomposition and electron withdrawing groups should hinder it. Moreover, a deuterium isotope effect should be expected for the reaction.

It was therefore proposed to first determine whether the decarboxylation was really bimolecular. The method which was thought would be the best to elucidate this point was to carry out the decarboxylation in an aprotic solvent. In this way the solvent would not enter the reaction directly but would serve only to dilute the reacting acid molecules, making it possible to obtain reaction rates which could be easily followed by choosing a proper temperature. This method also made it possible to carry out the reaction at various anthranilic acid concentrations to show the order of the decarboxylation.

It was also proposed to study the effect of substituents on the anthranilic acid molecule on the decarboxylation. The prime purpose of this investigation was to make an application of the Hammett equation (17) to the decarboxylation of anthranilic acid. A total of nine anthranilic acids with substituents in the 4 and 5 carbon atom positions were

investigated. The substituents in these positions were, therefore, either meta to the carboxyl group and para to the amino group, or vice versa. Because the substituent constants are usually quite different for the meta and para position, this would provide the means of determining the reaction centre, that is, whether the rate-determining step occurs at the carboxyl group or at the amino group.

It was also planned to study the rates of decarboxylation of anthranilic acid with various substituents on the amino group to determine the effect of such substituents on the reaction.

Finally, it was proposed to make a deuterium isotope study for the decarboxylation. If the rate-determining step consists of a proton-attack on the α-carbon atom of the acid molecule, then carrying out the reaction in a solvent not capable of supplying protons means that the protons must come from the acid molecules themselves. Therefore, the rate of decarboxylation for anthranilic acid in which the hydrogens on the carboxyl and amino groups are replaced by deuterium atoms should be expected to be slower than for anthranilic acid itself because the heavier deuteron is expected to attack the α-carbon atom more slowly than a proton. Moreover, it was previously pointed out that Krueger observed an unusually high amount of deuterium in the ring of the aniline obtained by decarboxylating partially deuterated anthranilic acid, and it was proposed to check this observation under the conditions of this investigation.

EXPERIMENTAL WORK

PREPARATION OF SUBSTITUTED ANTHRANILIC ACIDS

Preparation of 4-bromoanthranilic acid: This compound was prepared from o-toluidine by a series of reactions as indicated in the following equations:

$$2\text{-}NH_2\text{-}C_6H_4\text{-}CH_3 \xrightarrow{Ac_2O} 2\text{-}CH_3CONH\text{-}C_6H_4\text{-}CH_3 \xrightarrow{Br_2}$$

$$4\text{-}Br\text{-}2\text{-}CH_3CONH\text{-}C_6H_3\text{-}CH_3 \xrightarrow{[O]} 4\text{-}Br\text{-}2\text{-}CH_3CONH\text{-}C_6H_3\text{-}COOH$$

$$\xrightarrow{H_2O} 4\text{-}Br\text{-}2\text{-}NH_2\text{-}C_6H_3\text{-}COOH$$

o-Acetotoluidide was prepared by the method of Berkenheim and Livshits (2). o-Toluidine, 100 ml. (0.93 mole), was refluxed with 102 ml. (1.00 mole) of acetic anhydride in 200 ml. of benzene for one hour. The benzene was then distilled and the residue was poured over ice. The crude product was recrystallized from benzene and 106 gm. (70% of theoretical) of o-acetotoluidide, m.p. 110-111°C (literature (2) 109-111°C), were obtained.

The bromination of o-acetotoluidide was carried out by an adaption of the method of Wheeler (42). o-Acetotoluidide, 30 gm. (0.20 mole), in 300 ml. of glacial acetic acid at 15-16°C was treated with 10.5 ml. (0.20 mole) bromine. After one hour the solution was poured into cold water and the hydrogen bromide salt was collected. The salt was decomposed by boiling in one liter of water for one hour; the hot

filtrate yielded most of the product and repeated boiling of the residue yielded the balance. Thirty-seven gm. (84% of theoretical) of 4-bromo-o-acetotoluidide, m.p. 158-159°C (literature (42) 159-160°C), were obtained.

The 4-bromoacetotoluidide was oxidized to the corresponding acid by the method of Justoni (24). Seven gm. (0.03 mole) of 4-bromoacetotoluidide were suspended in 3.5 liters of water at 85°C and 10 gm. magnesium sulfate and 15 gm. potassium permanganate were added. The solution was allowed to remain at 80°C overnight. After cooling, the manganese dioxide was filtered out, the solution was acidified with hydrochloric acid and the precipitated acid was collected. Five and a half gm. (65% of theoretical) of 4-bromoacetoanthranilic acid were obtained which after recrystallization from hot water melted at 214-215°C (literature 215-216°C).

The acetyl derivative was hydrolyzed by boiling 5.5 gm. (0.022 mole) with 50 ml. 1:1 sulphuric acid for one hour; diluting and neutralizing the solution yielded 4 gm. (90% of theoretical) of 4-bromoanthranilic acid. The tan-coloured crystals melted at 217-218°C (literature (24) 219-220°C) after two recrystallizations from dilute ethanol.

Preparation of 5-bromoanthranilic acid: This derivative was prepared by brominating anthranilic acid by the method of Wheeler (42). Anthranilic acid, 25 gm. (0.18 mole), was dissolved in 250 ml. of glacial acetic acid and the solution

was cooled to 15 - 16°C. Bromine, 29.4 gm. (0.18 mole), was added slowly enough to keep the temperature from rising. After one hour the solution was poured into cold water. The precipitated hydrobromide salt was collected and washed with benzene. The salt was decomposed by boiling up in 250 ml. water three times, the hot filtrate yielded 26 gm. (65% of theoretical, literature 75% of theoretical) of 5-bromoanthranilic acid. The acid melted at 215-217°C (literature (42) 215-216°C) after recrystallization from dilute ethanol.

Preparation of 4-nitroanthranilic acid: This compound was prepared by the method of Hillers, Lokenbacks, and Majs (19) by the following series of reactions:

$$2\text{-}CH_3CONH\text{-}C_6H_4\text{-}CH_3 \xrightarrow{HNO_3} 4\text{-}NO_2\text{-}2\text{-}CH_3CONH\text{-}C_6H_3\text{-}CH_3 \xrightarrow{[O]}$$

$$4\text{-}NO_2\text{-}2\text{-}CH_3CONH\text{-}C_6H_3\text{-}COOH \xrightarrow{H_2O} 4\text{-}NO_2\text{-}2\text{-}NH_2\text{-}C_6H_3\text{-}COOH$$

Sixty gm. (0.40 mole) of o-acetotoluidide (prepared as described previously) dissolved in 400 ml. concentrated sulphuric acid were nitrated for four hours at -5°C with 40 ml. concentrated nitric acid in 120 ml. concentrated sulphuric acid. The acid solution when poured over the ice yielded 35 gm. (45% of theoretical; literature 70%) of 4-nitroacetotoluidide, m.p. 135-140°C (literature (19) 150-1°C). Several recrystallizations from hot water of this crude product yielded the compound with m.p. 149-150°C.

The oxidation of the 4-nitroacetotoluidide was carried out by treating 10 gm. (0.051 mole) in 3 liters of water at 95°C with 25 gm. of potassium permanganate in the presence of 12 gm. magnesium sulphate and allowing the solution to remain at about 90°C overnight. Seven gm. (61% of theoretical, literature 72%) of the acid were obtained with a m.p. of 215-216°C (literature 214-216°C) after recrystallization from water. Heating 10 gm. (0.044 mole) of this acetyl derivative in 30 ml. alcohol and 120 ml. concentrated hydrochloric acid for two hours on a water bath yielded the acid. Seven and a half gm. (90% of theoretical, literature 92%) of bright red crystals of nitro-anthranilic acid were obtained. After several recrystallizations from water, this compound melted at 262-264°C with decomposition (literature (19) m.p. 263-264d). 4-nitroanthranilic acid was also prepared from 4-nitro-o-toluidine by a method similar to that used for the preparation of 5-nitroanthranilic acid which is outlined below. The acid obtained by this method possessed properties similar to the acid obtained by the above method.

Preparation of 5-nitroanthranilic acid: The method used for this preparation was that of Iguchi (22) and is outlined in the following equations:

$$5\text{-}NO_2\text{-}2\text{-}NH_2\text{-}C_6H_3\text{-}CH_3 \xrightarrow{Ac_2O} 5\text{-}NO_2\text{-}2\text{-}CH_3CONH\text{-}C_6H_3\text{-}CH_3 \xrightarrow{[O]}$$

$$5\text{-}NO_2\text{-}2\text{-}CH_3CONH\text{-}C_6H_3COOH \xrightarrow{H_2O} 5\text{-}NO_2\text{-}2\text{-}NH_2\text{-}C_6H_3COOH$$

Iguchi reported that boiling 4-nitrotoluidine in an excess of acetic anhydride for two hours and pouring the solution into water yielded the acetyl derivative. When this procedure was followed for the preparation of both 4- and 5-nitro-o-acetotoluidide it was observed that the compounds thus obtained possessed melting-points substantially lower than was expected for the nitroacetotoluidides. For example in the case of 5-nitrotoluidine, a compound was obtained with a melting-point of 115°C, whereas 5-nitro-o-acetotoluidide is known to melt at 200°C. It was found that the right product was obtained when this low-melting compound was boiled in very dilute hydrochloric acid for several hours. It is therefore possible that the low-melting compounds obtained by this method are diacetyl derivatives of the toluidines. The following method was therefore developed for the acetylation. Fifty gm. (0.33 mole) of 5-nitro-o-toluidine were refluxed with 138 gm. (1.35 mole) of acetic anhydride for two hours, water was added cautiously to the hot solution and the solution was boiled for several minutes to destroy the excess acetic anhydride. Dilution of this solution yielded 44 gm. (70% of theoretical) of 5-nitro-o-acetoluidide, m.p. 198-200°C (literature 201°C). The corresponding acid was obtained by oxidation as described in the previous preparation. The 5-nitroanthranilic acid obtained was recrystallized from hot water and melted at 268-269°C with decomposition (literature (22) 270d).

Preparation of 4-chloroanthranilic acid: This compound was prepared according to the method of Cohn (11) which is given by the following equations:

$$4\text{-Cl-2-NH}_2\text{-C}_6\text{H}_3\text{-CH}_3 \xrightarrow{Ac_2O} 4\text{-Cl-2-CH}_3\text{CONH-C}_6\text{H}_3\text{-CH}_3 \xrightarrow{[O]}$$

$$4\text{-Cl-2-CH}_3\text{CONH-C}_6\text{H}_3\text{-COOH} \xrightarrow{H_2O} 4\text{-Cl-2-NH}_2\text{-C}_6\text{H}_3\text{-COOH}$$

It was found that acetylation of 4-chloro-o-toluidine did not occur by refluxing with acetic anhydride. The following procedure was therefore developed for this acetylation. Two and a half gm. (0.177 mole) of 4-chloro-o-toluidine were dissolved in 100 ml. glacial acetic acid and the solution was heated to boiling. Seventy-five ml. (0.67 mole) of acetic anhydride were added cautiously through the condenser and the mixture was refluxed for fifteen minutes. A yield of 27 gm. (91% of theoretical) of the acetyl derivative was obtained, m.p. 131-132°C (literature 131°C). The oxidation was carried out with potassium permanganate as described in previous preparations. Hydrolysis of the 4-chloroaceto-anthranilic acid yielded white crystals of the acid, which after recrystallization from dilute alcohol melted at 234-235°C (literature (11) 235-236).

Preparation of 5-methylanthranilic acid: This acid was prepared by a series of reactions as indicated in the following equations:

$$3\text{-}CH_3\text{-}C_6H_4\text{-}COOH \xrightarrow{HNO_3} 3\text{-}CH_3\text{-}6\text{-}NO_2\text{-}C_6H_3\text{-}COOH \xrightarrow{[H]} 3\text{-}CH_3\text{-}6\text{-}NH_2\text{-}C_6H_3\text{-}COOH$$

The nitration of m-toluic acid was carried out according to the method of Giacolone and Russo (13). Twenty gm. (0.20 mole) potassium nitrate in 120 ml. concentrated sulphuric acid was added cautiously to 20 gm. (0.147 mole) of m-toluic acid dissolved in 120 ml. concentrated sulphuric acid, the temperature being kept at 0°C. The solution was poured on ice and the mixture of 2-nitro and 6-nitro derivatives of m-toluic acid was collected; 2-nitro-m-toluic acid is insoluble in hot water while 6-nitro-m-toluic acid is soluble and the separation of the two isomers is made in this way. The yield was 13 gm. (36% of theoretical; literature is 32%) of 6-nitro-m-toluic acid; m.p. 131-132°C (literature (13) 135-136°).

The nitro compound was reduced to the amino acid by the method of Wheeler and Hoffman (43). Four gm. (0.022 mole) of 6-nitro-m-toluic acid were dissolved in 100 ml. concentrated ammonium hydroxide and 50 gm. (0.17 mole) of ferrous sulphate heptahydrate in 200 ml. of water were added. The solution was brought to a boil and after dooling the inorganic salts were filtered out. The solution was carefully acidified and freezing the solution yielded 3 gm. (90% of theoretical) of 5-methylanthranilic acid. The light brown crystals

melted at 175-177°C (literature (43) 177°C) after recrystallization from dilute alcohol.

Preparation of 4-aminoanthranilic acid: This compound was prepared by the reduction of 4-nitroanthranilic acid according to the method of Wheeler and Hoffman (43). Six gm. (0.033 mole) of the nitro derivative were dissolved in 150 ml. concentrated ammonium hydroxide and 75 gm. (0.25 mole) of ferrous sulphate heptahydrate dissolved in 300 ml. water were added. After boiling the solution for one hour the inorganic salts were filtered out and freezing the acidified solution yielded 2 gm. (40% of theoretical) of 4-aminoanthranilic acid. The light brown crystals melted at 134-136°C (literature (43) 138d) after recrystallization from dilute ethanol.

Preparation of acetoanthranilic acid: Anthranilic acid was acetylated by boiling in an excess of acetic anhydride. Five gm. (0.037 mole) of anthranilic acid were refluxed for one hour with 25 gm. (0.23 mole) of acetic anhydride. Water was added and the solution was boiled to destroy the excess acetic anhydride. On diluting and cooling the solution, 5 gm. (80% of theoretical) of acetoanthranilic acid were obtained, with m.p. 184-185°C (literature (43) 185°) after one recrystallization from ethanol.

The attempted preparation of 4-methylanthranilic acid: An attempt was made to prepare 4-methylanthranilic acid by the

following series of reactions but it was observed that reduction did not occur when 2-nitro-4-methylbenzoic acid was reacted with sulphate in ammonium hydroxide.

$$4\text{-}CH_3\text{-}C_6H_4\text{-}CH_3 \xrightarrow{HNO_3} 4\text{-}CH_3\text{-}2\text{-}NO_2\text{-}C_6H_3\text{-}CH_3 \xrightarrow{[O]}$$

$$4\text{-}CH_3\text{-}2\text{-}NO_2\text{-}C_6H_3\text{-}COOH \xrightarrow{[H]} 4\text{-}CH_3\text{-}2\text{-}NH_2\text{-}C_6H_3\text{-}COOH$$

The intermediate nitro acid was prepared by the method of Show-Hsuan (39). To 50 ml. (0.41 mole) of p-xylene, at 10°C, 68 ml. of fuming nitric acid was added during four hours and the mixture was poured into a liter of ice water. The oily layer was separated and treated with a solution of 240 ml. nitric acid in 240 ml. water by refluxing the solution for 48 hours. On cooling, the precipitate was filtered off, dissolved in dilute sodium hydroxide and steam distilled to remove p-xylene and 2-nitro-p-xylene. The solution was acidified and an extraction with ether was made to separate the product from terephthalic acid. The residue obtained on evaporation of the ether was treated with 200 ml. hot toluene, the toluene was filtered and evaporated, the residue was recrystallized from hot water to give 10 gm. (18% of theoretical; literature (39) 20%) of 2-nitro-4-methylbenzoic acid, m.p. 162-163°C (literature (39) 164.5°C).

An attempt was made to reduce the nitro acid to the amino acid by a method similar to that employed for the preparation of 5-methylanthranilic acid, but apparently no reduction occurred even after the mixture was heated for six hours.

THE PREPARATION OF DEUTERATED ANTHRANILIC ACID

Deuterated anthranilic acid was prepared by the method described by Krueger (25). Anthranilic acid (23 gm., 0.167 mole) was dissolved in 54 ml. of purified dioxane and 5.0 gm. (0.250 mole) of deuterium oxide were added. The acid was brought into solution by occasional shaking of the tightly stoppered flask, and the solution was allowed to equilibrate at room temperature overnight. The solvent was then removed by distillation under partial pressure, with special precautions to dry the air before allowing it to enter the system and to keep the temperature of the solution below 55°C. The solvent was collected by means of a trap immersed in a dry ice - acetone mixture, and was saved for future exchanges. The acid thus dried was exchanged with more deuterium oxide as described above. A total of four exchanges with heavy water were made. After removing the solvent the final time, the flask was warmed gradually to 85°C by means of a water bath and the system was maintained at 15 mm. pressure for about two hours. The acid, which had solidified on the walls of the flask, was broken up by gently tapping the flask and was transferred quickly to a dry bottle and placed in a desiccator. This acid will be referred to as deuterated anthranilic acid D.

THE KINETICS OF DECARBOXYLATION

The rates of decarboxylation were determined by absorption of the evolved carbon dioxide on ascarite which was weighed at regular intervals.

The apparatus was set up as shown in figure I. The reacting vessel, (a), consisted of a 25 ml. test tube-shaped vessel equipped with a ground-glass joint in such a way that it fitted directly into a one litre flask which served as a vapor bath and which was heated by an electric heating mantle. A gas inlet, (b), was built into the reaction vessel in such a way that it extended to the bottom of the vessel. The top of the vessel was equipped with a ground-glass joint into which fitted a small cold water condenser, (c), to remove most of the liquids from the gas stream. A n-butylphthalate bubbler, (d), was utilized to remove most of the aniline that might have been present in the gas stream and the final traces of organic liquids were removed in the sulphuric acid bubbler, (e). A U-tube of anhydrous calcium sulphate, (f) well packed with glass wool was placed immediately before the ascarite tubes to remove any sulphuric acid that may have been spattered over by a sudden evolution of gas. Changing over from one ascarite tube to another was accomplished by means of a three-way stop-cock, (g). The outlet of the ascarite tube (h), was protected from the atmosphere by a tube, (i), containing calcium sulphate and ascarite.

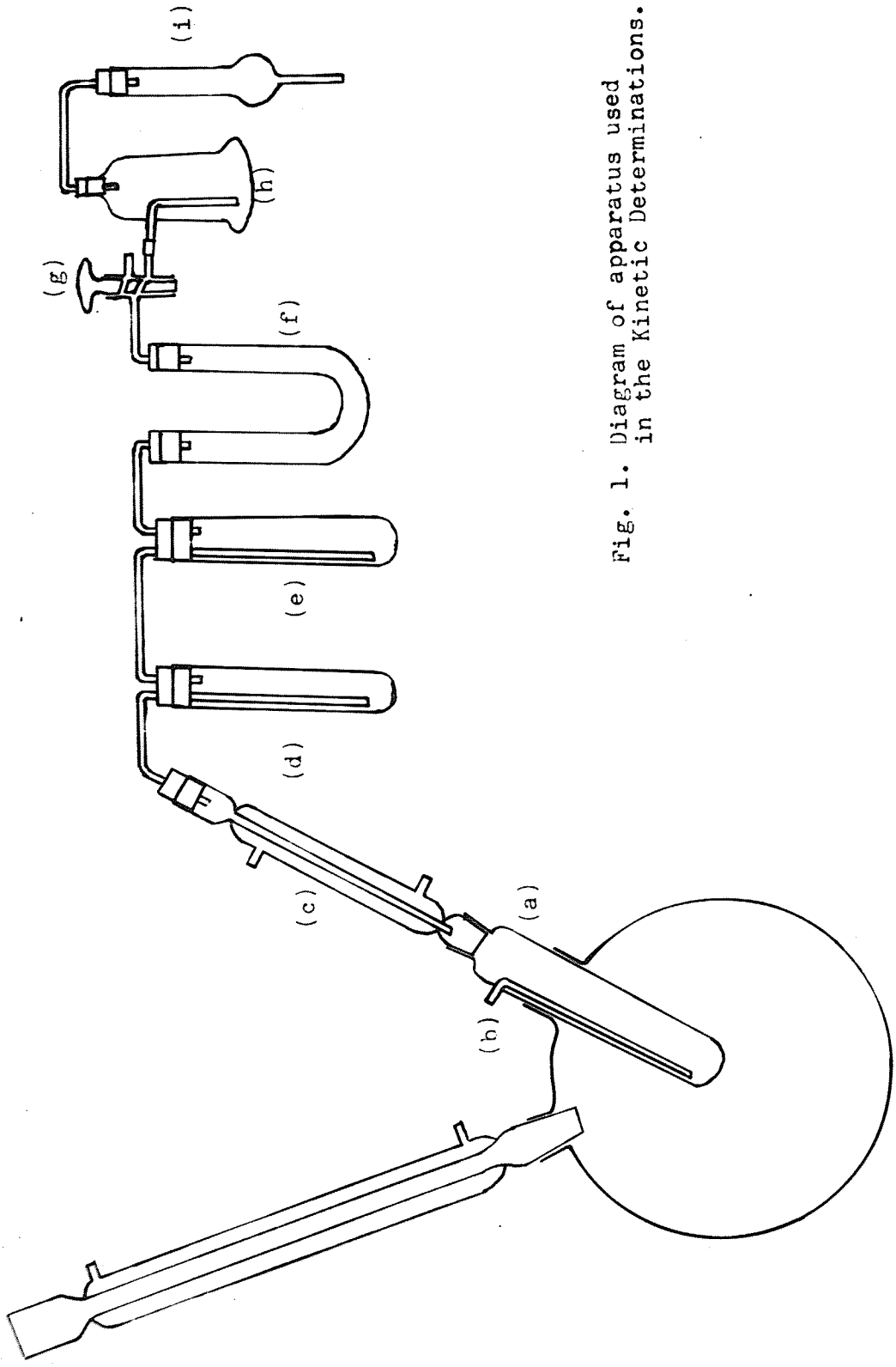


Fig. 1. Diagram of apparatus used in the Kinetic Determinations.

The reactions were carried out at the boiling points of the solvents employed. A liquid with a slightly higher boiling point was used for the vapor bath, and this provided for gentle boiling of the reaction solution. Phenyl ether proved to be ideal for this purpose because of its ability to withstand long periods of boiling without decomposition.

The boiling solvent was advantageous in several ways. In the first place, it provided a simple method for maintaining constant temperature conditions at the high temperature required. The maximum variations in temperature between individual determinations were $\pm$ 0.5°C, but the variation in temperature during a single determination was found not to exceed $\pm$ 0.2°C, as determined by means of a thermocouple and potentiometer. The large variation in temperature between individual trials resulted from the various concentrations of acids used because of the high molal boiling point elevation constant for nitrobenzene. The boiling solvent provided for rapid solution of the acid samples on introduction into the reaction vessel, and very little time was required to return the temperature to the boiling point of the solvent after the addition of the sample which resulted in unavoidable cooling. This method also allowed the bubbling of nitrogen through the solution to sweep the carbon dioxide to the ascarite tubes and to aid in rapid solution of the acid samples.

Ten ml. of solvent were usually used for each trial.. After the solvent was brought to a boil and the nitrogen was adjusted to a suitable rate, the ascarite tube was connected and the acid sample was introduced by means of a boat-shaped vessel through the opening occupied by the condenser (c). About 0.4 mole of acid sample was used for each trial.

Nitrobenzene and 1-methylnaphthalene were chosen as solvents after various possibilities were considered. Nitrobenzene proved to be particularly suitable because of its excellent solvent properties; 1-methylnaphthalene was also used because it was found that the aniline produced in the reaction could be easily separated by distillation, and this was necessary in the isotopic study.

REACTIONS IN NITROBENZENE

An extensive study of the kinetics of decarboxylation for the anthranilic acids was made in nitrobenzene. All the acids that had been prepared were found to decarboxylate without apparent side-reactions, and usually the solubility of an acid was sufficient to get a rate of reaction that could be easily followed.

The nitrobenzene was carefully purified and dried before use. Fisher Scientific Co. (rectified) product was fractionated with a Vigreux column (fourteen inches long), and the initial

and final fractions were discarded. The product was then dried with calcium sulphate for 48 Hours. The fraction boiling at 210-210.5°C/745 mm. was collected.

The data for a typical trial for anthranilic acid are given in table II. The rate constant, k, is calculated for each individual measurement by use of the second order rate equation:

$$k\,t = \frac{x}{a(a - x)} ,$$

where t = time in seconds

a = initial concentration of acid in moles/liter

x = moles of CO_2 produced to time t.

The rate constant is also obtained by plotting $1/(a - x)$ versus t and obtaining the slope of the line by the least squares method. In both of these determinations of k, the first point is disregarded because it is obviously too low. This is explained on the basis that in the initial stages of the reaction the carbon dioxide is formed too rapidly to be swept completely to the ascarite tube by the slow stream of nitrogen. The last point is also disregarded because it too is low, probably because the high concentration of aniline near the end of the reaction hinders the reaction. This is the reason used by Stevens (37) who observed the same behaviour for the reaction in the melt. The least squares plot is given in figure 2.

TABLE II

A Typical Decarboxylation of Anthranilic Acid

in Nitrobenzene at 210.5°C.

Time, hrs.	x	(a - x)	1/(a - x)	k_2 moles^{-1}-liter-sec.$^{-1}$
0	0	0.647	1.545	-
3.0	0.186	0.463	2.160	5.75×10^{-5}
4.5	0.255	0.392	2.550	6.30
6.0	0.307	0.342	2.925	6.40
7.5	0.342	0.305	3.275	6.42
9.0	0.374	0.275	3.635	6.45
12.0	0.420	0.227	4.40	6.48
18.0	0.470	0.177	5.99	6.15
				mean 6.46 ± .04

The rate constant obtained by taking the mean of the k's calculated for each point is 6.46×10^{-5} while the value obtained by applying the least squares method to a plot of $1/(a - x)$ versus t is 6.50×10^{-5}. Because of the close agreement in k's obtained by the two methods, most of the other calculations of k are made by taking the mean of the values calculated for the individual points. In the case of 4-aminoanthranilic acid, k is calculated by the three-quarter life method because the rate of the reaction is too fast to obtain a number of readings by the method employed.

Although a first order reaction plot is not given in this discussion, the possibility that the reaction is first order is eliminated on the basis that the half-life of the reaction is inversely proportional to the initial concentration

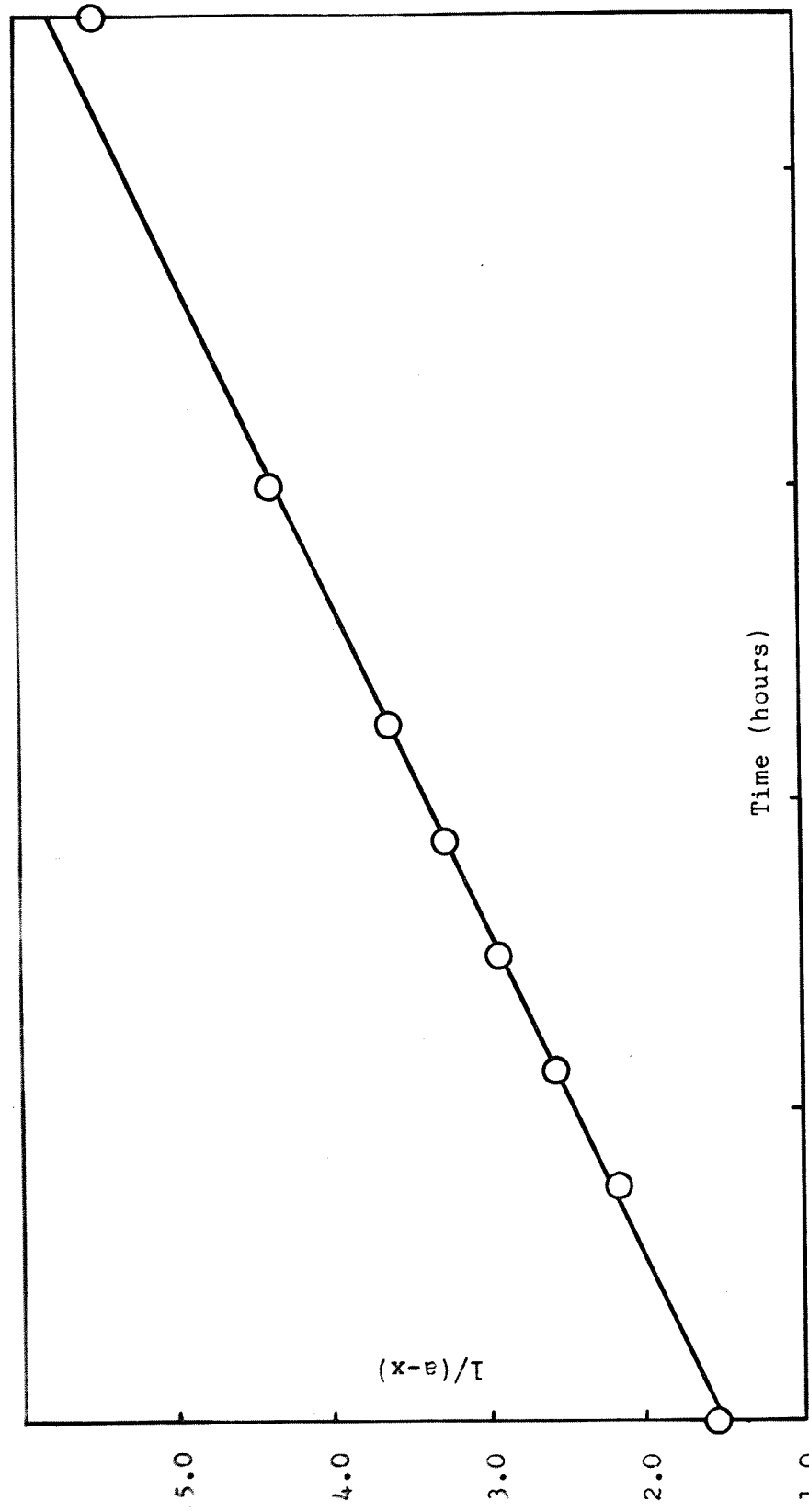


Fig. 2. A Typical Plot of 1/(a-x) versus Time for the Decarboxylation of Anthranilic Acid in Nitrobenzene.

of acid, as indicated in table III, whereas a first order reaction is characterized by a half-life independent of the concentration. The kinetic results in nitrobenzene are given in table III.

TABLE III

The Rates of Decarboxylation of Anthranilic Acids in Nitrobenzene at 210.5°C.

Trial No.	Acid	Conc. (moles-l^{-1})	Half-life (hrs.)	k_5 (x 10^5 moles-$_1$-l_{sec}-1)	k (mean)
1	anthranilic	0.542	8.2	6.12	
2		0.322	-	5.90	
3		0.647	6.7	6.41	6.17 ± 0.14
4		0.332	12.6	6.25	
5		0.441	-	6.15	
6	5-chloro-	a 0.362		1.87	
7	anthranilic	0.358		1.80	1.92 ± 0.12
8		0.483		2.10	
9	4-chloro-	0.324		3.05	
10	anthranilic	0.360		3.30	3.18 ± 0.09
11		0.320		3.20	
12	4-bromo-	0.239		2.78	2.66 ± 0.12
13	anthranilic	0.307		2.54	
14	5-bromo-	0.133		2.45	2.37 ± 0.08
15	anthranilic	0.123		2.30	
16	5-methyl-	0.212		9.35	
17	anthranilic	0.171		9.70	9.61 ± 0.18
18		0.365		9.80	
19	4-nitro-	0.399		0.180	
20	anthranilic	0.348		0.167	0.175 ± 0.013
21		0.228		0.192	
22		0.364		0.153	

The Rates of Decarboxylation of Anthranilic Acids in Nitrobenzene at 210.5°C.

Trial No.	Acid		Conc. ($moles\text{-}l^{-1}$)	Half-life (hrs.)	k ($\times 10^5 moles\text{-}l^{-1}sec^{-1}$)	k (mean)
23	5-nitro-		0.181		0.500	0.527 ± 0.027
24	anthranilic		0.208		0.555	
25	4-amino-		0.112	0.11	310	
26	anthranilic		0.093	0.12	300	
27			0.084	0.17	290	
28			0.064	0.19	270	300 ± 15
29			0.059	0.18	310	
30			0.051	0.22	320	
31			0.044	0.28	280	
32	N-methyl-anthranilic	b	0.465		43	
33	aceto-anthranilic		0.159		0.61	
34	N-phenyl-	b	0.255	14	6.88	6.69 ± 0.19
35	anthranilic		0.133	28	6.50	
36	deuterated		0.423		3.20	
37	anthranilic		0.395		2.81	3.14 ± 0.22
38			0.565		3.40	
39	anthranilic + deuterated anthranilic		0.225 0.203		4.22	
40	anthranilic		0.554		1.11	1.10 ± 0.02
41	(180°C)		0.695		1.08	
42	p-amino-	b	0.418	16 c	1.25	1.32 ± 0.07
43	benzoic		0.265	24	1.39	

(a) The 5-chloroanthranilic acid was Eastman Kodak Co. Product and was used after recrystallization from alcohol, m.p. 204-205°C.
(b) Eastman Kodak Co., product was used without further purification.
(c) One-quarter life.

REACTION IN 1-METHYLNAPHTHALENE

It was found that only three substituted anthranilic acids would dissolve in 1-methylnaphthalene, and hence the rates of decarboxylation for only these acids were determined in the solvent.

The 1-methylnaphthalene was purified before use. Eastman (practical) product was distilled with a fouteen inch Vigreux column and the initial and final fractions were discarded. The product was then dried with sodium metal at room temperature for 48 hours. The fraction boiling at 240-241°C/744 mm. was collected.

The data of a typical reaction of anthranilic acid in 1-methylnaphthalene are given in table IV. The rate constant is calculated for this example by both methods employed for the reaction in nitrobenzene. The plot of $1/(a - x)$ versus time is given in figure 3.

TABLE IV

A Typical Decarboxylation of Anthranilic Acid in 1-methylnaphthalene at 242.0°C.

Time, hrs.	x	(a - x)	1/(a - x)	k, mole^{-1}.l.$^{-1}$sec.$^{-1}$
0	0	0.597	1.67	-
2	0.223	0.374	2.68	1.40×10^{-4}
4	0.338	0.260	3.84	1.52
6	0.398	0.199	5.02	1.54
8	0.440	0.157	6.37	1.63
11	0.470	0.127	7.86	1.58
18	0.508	0.089	11.20	1.43
				mean 1.57 ± 0.04

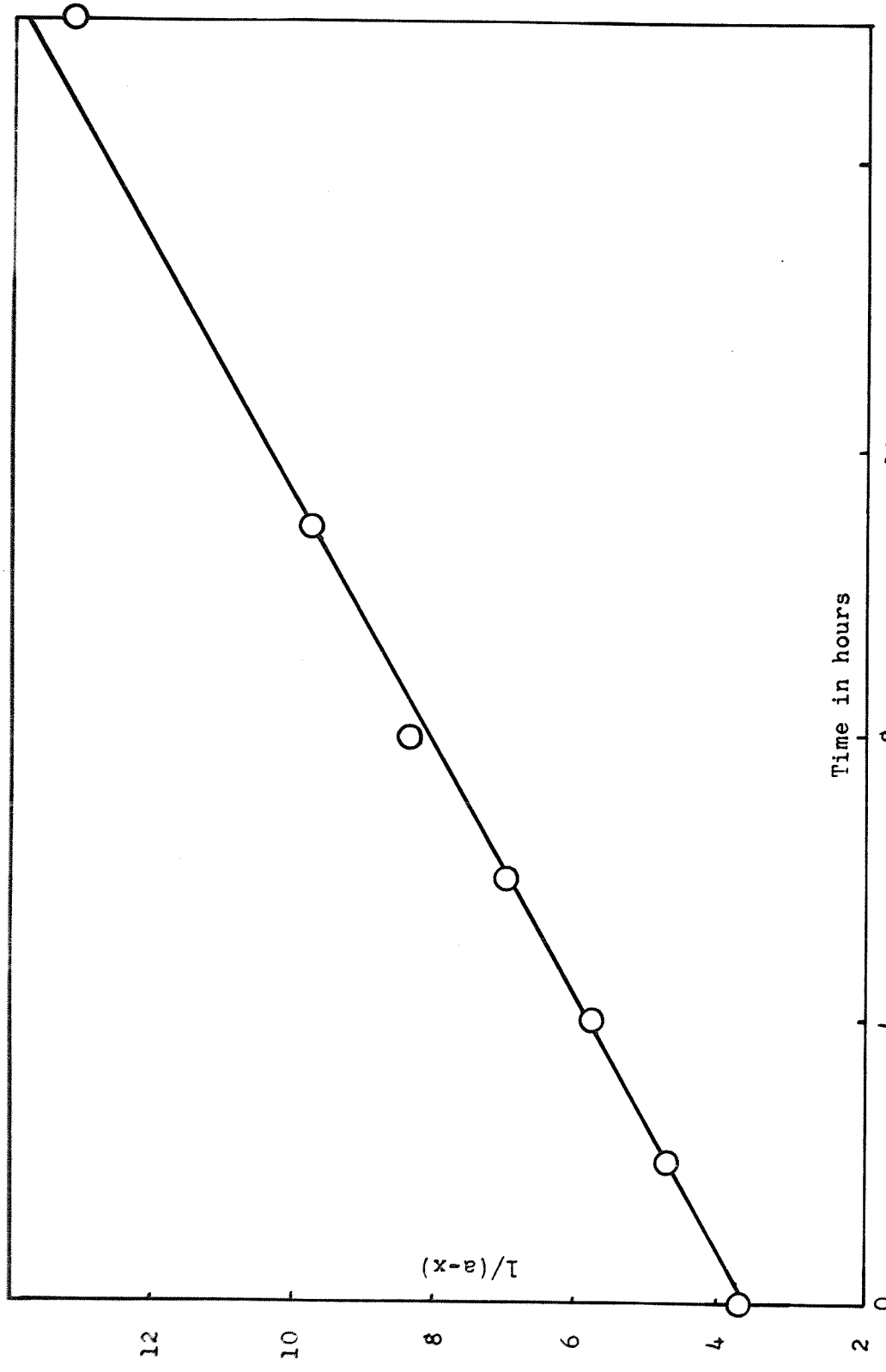


Fig. 3. A Typical Plot of 1/(a-X) versus Time for the Decarboxylation of Anthranilic Acid in 1-methylnaphthalene.

It is found that for this case the rate constant is 1.57×10^{-4} by the method of the integrated equation for a second order reaction and 1.59×10^{-4} from a least squares treatment of the $1/(a - x)$ versus time plot. All the other k's are obtained by the former method, therefore. All the results of the kinetics in 1-methylnaphthalene are given in table V.

TABLE V

The Rates of Decarboxylation of Anthranilic Acids in 1-methylnaphthalene at 242 ± 0.5°C.

Trial No.	Acid	Conc. (moles-l.$^{-1}$)	Half-life (hrs.)	k ($\times 10^{4}$)	k (mean) (moles-l.$^{-1}$sec.$^{-1}$)
44	anthranilic	0.514	3.60	1.52	
45		0.556	3.30	1.58	1.58 ± 0.04
46		0.597	3.00	1.57	
47		0.171	9.15	1.65	
48	4-chloro-	0.380		1.14	1.17 ± 0.03
49	anthranilic	0.169		1.20	
50	5-chloro-	0.440		0.76	0.74 ± 0.02
51	anthranilic	0.485		0.72	

A first order plot is not given here because, as in nitrobenzene, it is quite obvious from the half-life of the reactions that the reaction could not be first order.

THE ISOTOPIC STUDY

The kinetics of decarboxylation of deuterated anthranilic acid in nitrobenzene were studied and the results are given in table III.

The aniline produced on decarboxylation of partially deuterated anthranilic acid in 1-methylnaphthalene was isolated to study the distribution of deuterium in the aniline. A sample of deuterated anthranilic acid (17.891 gm., 0.129 mole) obtained by mixing 8.086 gm. (0.0578 mole) of anthranilic acid D with 9.805 gm. (0.0715 mole) of anthranilic acid, prepared as described previously, was decarboxylated in 50 ml. of 1-methylnaphthalene by refluxing the solution for 16 hours under an atmosphere of nitrogen. Most of the aniline was then separated from the solvent by a simple distillation, and the final separation was made with a 14 inch Vigreux column. The product was colorless and had a boiling point of 180-182°C/ 730 mm.

Determination of deuterium in the deuterated anthranilic acid.

The deuterated anthranilic acid was analyzed for deuterium by the combustion method which has been described in detail by Brynko (10) and Warkentin (41) and will not be discussed here. The water samples in this investigation were analyzed on one gradient, utilizing the water-deuterium oxide standards of Rodewald (33). The results are listed in table VI.

TABLE VI

Analysis of Deuterium in Deuterated Anthranilic Acid D

Determination	Acid sample	Mole % D_2O om the combustion water	Atom % Deuterium in the acid D (a)
1.	0.1864 gm. D acid 1.1048 gm. H acid	4.80	77.7
2.	0.1608 gm. D acid 0.9012 gm. H acid	5.05	78.0
3.	0.1736 gm. D acid 0.9954 gm. H acid	5.10	79.7
		mean 4.98 ± 0.12	mean 78.5 ± 0.08

(a) Atom % deuterium for the total of three position on the acid molecule, namely one on the carboxyl group and two on the amino group.

The analysis for deuterium in the aniline.

The distribution of deuterium in the aniline obtained as described on the previous page was determined spectrophotometrically by the method of Rodewald (33) on a Perkin-Elmer Model 21 instrument.

This method could not be used to determine the amount of deuterium on the amino group and the amount in the benzene ring simultaneously. It was therefore necessary to remove the deuterium from the amino group by a method developed by Krueger (25). About 7 ml. of aniline were dissolved in 100 ml. of liquid ammonia and the solvent was allowed to evaporate overnight. The aniline was then distilled under reduced pressure at 80-85°C/5 mm. and possessed $n_D^{22} = 1.5836$.

Spectrophotometric analysis at the 4.415 peak showed that all N-D bonds had been converted to N-H bonds.

The amount of deuterium in the ring of the aniline was then determined utilizing a Beers' law plot obtained by Rodewald for the 4415 millimicron peak. The value thus obtained was 46.5% deuterium in the ring of the aniline.

Decarboxylation of other Benzoic Acids in Nitrobenzene.

An attempt was made to decarboxylate various benzoic acids other than anthranilic acids in nitrobenzene. It was observed that p-aminobenzoic acid decarboxylated quite readily and the results are given in Table III. It is interesting to note that this acid decarboxylated according to second-order kinetics. m-Aminobenzoic acid did not decarboxylate in boiling nitrobenzene.

The decarboxylation of p-hydroxybenzoic acid in nitrobenzene provided an interesting reaction. It was observed that the reaction was very slow initially but gradually increased up to a certain point and then remained very nearly constant till the concentration of acid became low and thereafter decreased rapidly. The S-shaped curve, resulting when a plot of time versus moles of carbon dioxide is made is characteristic of a reaction in which a product catalyzes the reaction. This indicates that phenol catalyzed the decarboxylation of p-hydroxybenzoic acid.

It was observed that o-toluic, p-nitrobenzoic and benzoic acids did not decarboxylate in boiling nitrobenzene.

DISCUSSION OF RESULTS

The results are discussed under the following topics:

(1) The order of the reaction.

(2) Application of Hammett's equation to the reaction.

(3) The deuterium isotope effect.

(4) The mechanism of the reaction.

The Order of the Reaction.

The results of this investigation indicate that the decarboxylation of anthranilic acid obeys the second-order rate equation. Not only are fairly constant specific-rate constants obtained when the second-order rate equation is applied to the reaction, but also the periods of the half-life for the reaction are inversely proportional to the first power of the initial acid concentrations, a property characteristic of second-order reactions, and this definitely shows that the reaction is not first order. The behaviour was exhibited in both nitrobenzene and 1-methylnaphthalene, indicating that the reaction obeys second-order kinetics in aprotic solvents.

The nature of the reaction is unchanged by substituents on the benzene ring of anthranilic acid as indicated in the case of 4-aminoanthranilic acid where the half-life of reaction is inversely proportional to the initial concentration of acid. Furthermore, substituents in the amino group do not affect the order of reaction as is observed in the case of N-phenylanthranilic acid.

It is also interesting to note that the decarboxylation of p-aminobenzoic acid in nitrobenzene obeys second-order kinetics.

Application of Hammett's Equation to the Reaction.

The Hammett equation has provided an exceedingly valuable relationship for correlating the effect of substituents on rates and equilibria. The equation may be written as:

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

where k can be a rate or an equilibrium constant for a reaction involving a given substituent, k_o is that for the reaction with no substituent, and σ and ρ are constants. σ depends only upon the substituent, while ρ is a reaction constant, dependent upon the reaction and the external conditions (17). A negative ρ indicates that the reaction concerned is promoted by electron donating groups and hence is favoured by a high electron density at the reaction center. Similarly a positive ρ indicates that the reaction is favoured by a low electron density at the reaction center. Although the equation has been applied to a large variety of reactions, this investigation represents the first time it has been applied to a decarboxylation.

It has generally been considered that the equation is most successful when the substituents exert their effects

primarily through electrostatic interactions (16) with resonance interactions being largely responsible for observed deviations (40). Unusually large deviations have been met in electrophilic aromatic substitution reactions. It has been observed that in Hammett equation plots for reactions the points lie near a straight line for all the substituents except those capable of supplying electrons to the ring by resonance. These groups, p-Cl, p-Br, p-Me, p-MeO, and p-NH_2, are all more reactive than would be expected, the relative magnitudes of the deviations increasing with ability of the groups to donate electrons by resonance (8, 26, 31).

The failure of the Hammett equation to correlate directive effects in electrophilic aromatic substitution was attributed to major resonance interactions which were not incorporated into the usual σ-constants (31). Considerable success has been realized in correlating the available data in electrophilic aromatic substitution (9) by means of a set of σ-constants which incorporate a resonance factor (8). This set of constants is usually referred to as Brown's σ-constants.

Hammett-equation plots have been made here using both Hammett's σ-constants as compiled by Jaffe (23) and Brown's σ-constants as compiled by Brown and Okamoto (8).

Three Hammett-equation plots are given for the reaction in nitrobenzene and the data for these is given in Table VII. The first plot, figure 4, and the second, figure 5, are made

on the assumption that the reaction center is at the carboxyl group or at the carbon atom α to the carboxyl group. Figure 4 is made using Hammett's σ-constants while figure 5 is made using Brown's σ-constants. The last plot, figure 6, is made using Hammett's σ-constants and is based on the assumption that the reaction-center is at the amino group rather than at the carboxyl group.

The data for a Hammett equation plot for the reaction in 1-methylnaphthalene are given in table VIII. The plot itself is not given, but it is observed from the table that a linear relationship exists between log k/k_o and Brown's σ-constants for the small number of results.

It is observed that the point corresponding to the $\underline{p}$-NO_2 substituent is much too low in all the plots and hence is neglected in calculating the reaction constants. There is no obvious reason for this deviation and it may suggest that Brown's σ-constant for the $\underline{p}$-NO_2 group should be more positive.

The method of least squares was used to obtain the following reaction constants:

(1) - 0.858 for the reaction in 1-methylnaphthalene.

(2) - 1.56 for the reaction in nitrobenzene using Hammett's σ-constants, and neglecting the points corresponding to the $\underline{p}$-NH_2 and $\underline{p}$-NO_2 substituents.

(3) - 1.35 for the reaction in nitrobenzene using Brown's σ-constants and neglecting the point corresponding to the $\underline{p}$-NO_2 substituent.

TABLE VII

Data for the Hammett Equation Plots

for the Reaction in Nitrobenzene

Substituent	log k/k_o	Hammett's σ^a	Brown's σ^a	Hammett's σ^b
4-amino	1.69	- 0.66	- 1.3	- 0.16
5-methyl	0.19	- 0.069	- 0.066	- 0.17
hydrogen	0	0	0	0
4-chloro	- 0.29	0.227	0.114	0.373
4-bromo	- 0.37	0.232	0.150	0.391
5-chloro	- 0.51	0.373	0.399	0.227
5-bromo	- 0.42	0.391	0.405	0.232
5-nitro	- 1.07	0.710	0.674	0.778
4-nitro	- 1.72	0.778	0.790	0.710

(a) This set of substituent constants is based on the assumption that the reaction center is at the carboxyl group.
(b) This set of substituent constants is based on the assumption that the reaction centre is at the amino group.

TABLE VIII

Data for the Hammett Equation Plot

for the Reaction in 1-methylnaphthalene

Substituent	log k/k_o	Brown's σ-constant
hydrogen	0	0
4-chloro	- 0.114	0.114
5-chloro	- 0.340	0.399

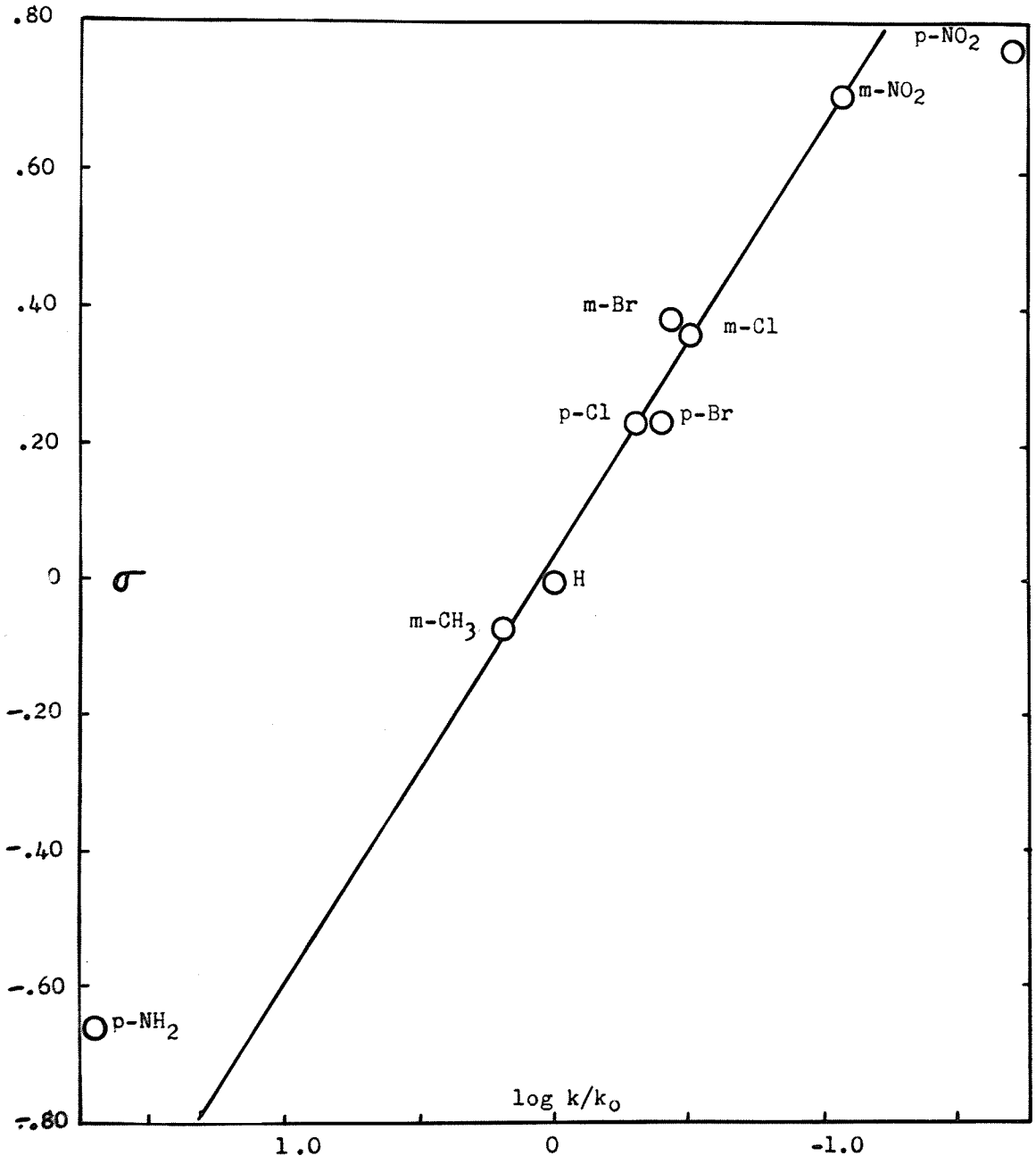


Fig. 4. Hammett-equation Plot for the reaction in Nitrobenzene using Hammett's σ -constants.

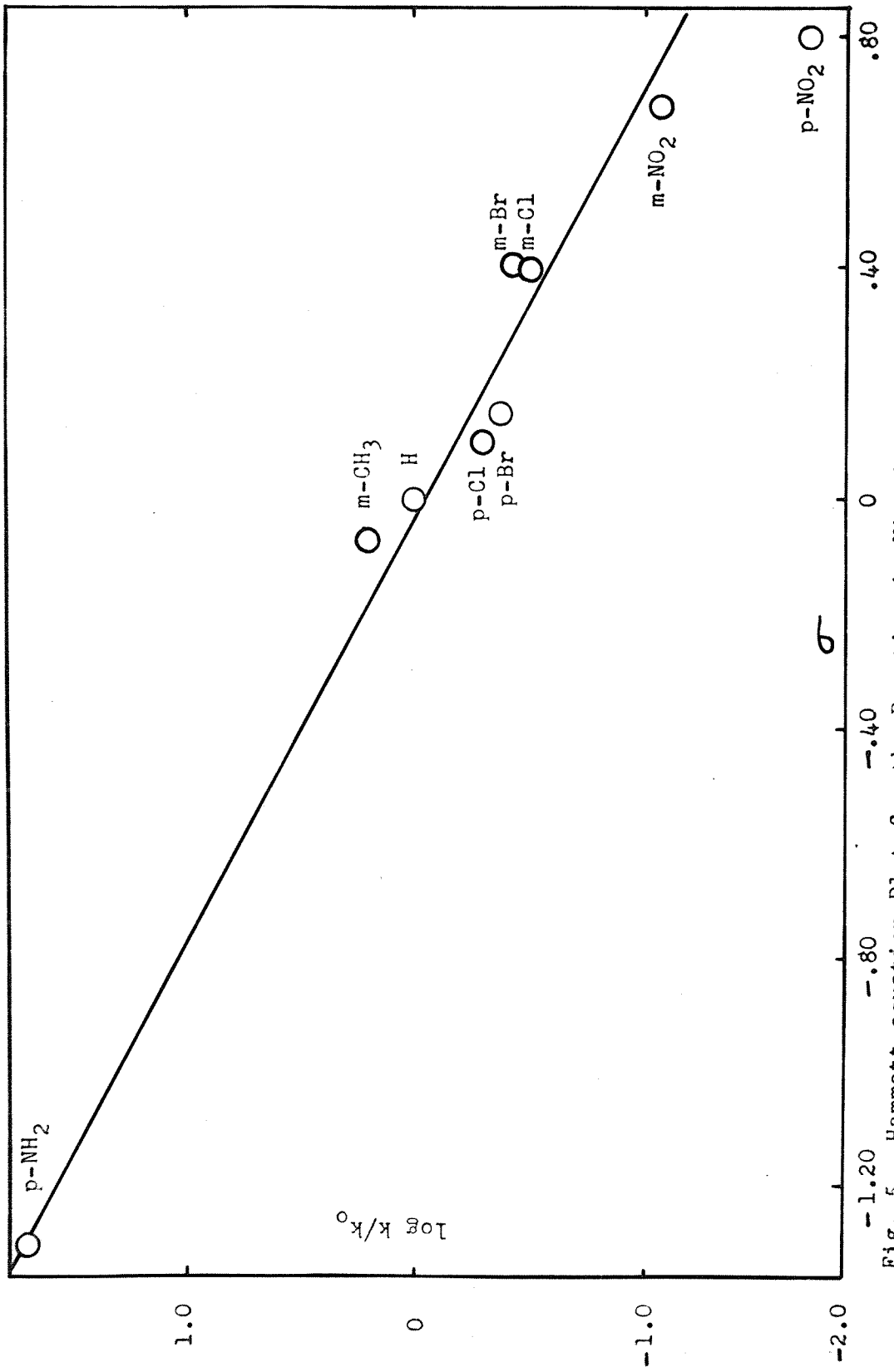


Fig. 5. Hammett-equation Plot for the Reaction in Nitrobenzene using Brown's σ -constants.

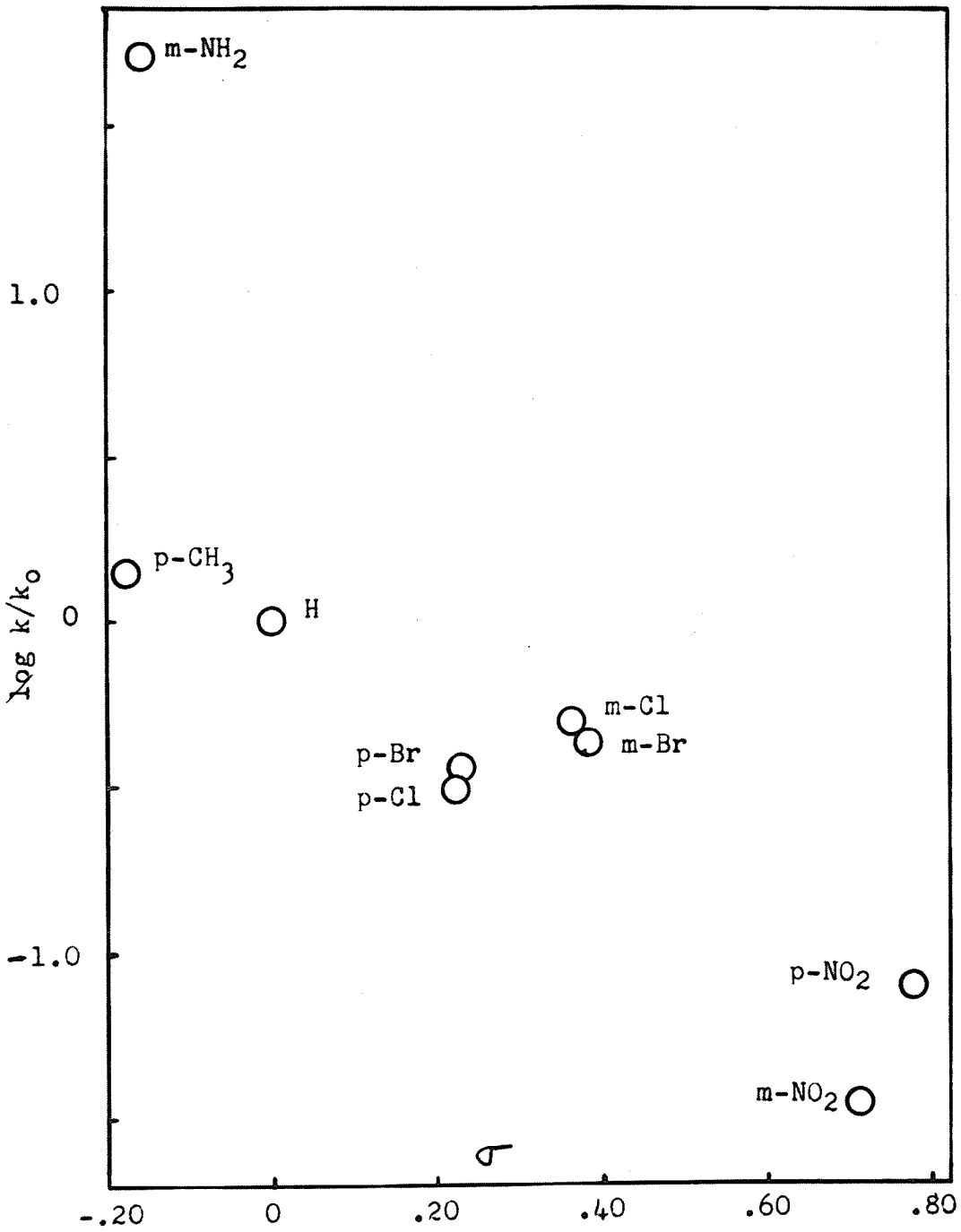


Fig. 6. Hammett-equation Plot for the Reaction in Nitrobenzene using Hammett's σ -constants and considering the amino group to be the Reaction-centre.

It is observed that a much better Hammett equation plot is obtained for the reaction when the carboxyl group or its α-carbon atom is considered to be the reaction-center (figure 4) than when the amino group is considered to be the reaction-center (figure 6). This indicates that the rate-controlling process of the decarboxylation of anthranilic acid occurs at the carboxyl group or its α-carbon atom.

Moreover, a better plot is obtained when Brown's σ-constants are used (figure 5) than when Hammett's constants are used (figure 4). It has been pointed out that Brown's constants apply to electrophilic aromatic substitution and this indicates that the decarboxylation of anthranilic acid is essentially the replacement of the carboxyl group by a proton. Consequently, this is proof that the reaction is the attack of a proton on the α-carbon atom of the acid molecule.

The Deuterium-Isotope Effect for the Reaction.

It is observed that when deuterium is substituted in the carboxyl and amino groups of anthranilic acid the rate of decarboxylation is decreased (trials 36 -39, table III). The acid used in trials 36 - 39 has been found to contain 78.5 atom-percent deuterium in the three labelled positions. The following calculation was used to obtain the rate-constant for anthranilic acid with 100 atom-percent deuterium in the labelled positions, that is, k_D as compared to k_H for anthranilic acid itself.

The apparent rate of decarboxylation of anthranilic acid will be obtained from:

$$\frac{d\left[CO_2\right]}{dt} = k' \left[A_H + A_D\right]^2$$

where A_H = anthranilic acid, A_D = deuterated anthranilic acid, k' = rate constant for partially deuterated anthranilic acid D. The apparent rate can also be written as

$$\frac{d\left[CO_2\right]}{dt} = k_H \left[A_H\right]^2 + k_H \left[A_H\right]\left[A_D\right] + k_D \left[A_D\right]^2 + k_D \left[A_H\right]\left[A_D\right]$$

or $$k' \left[A_H + A_D\right]^2 = \left(k_H \left[A_H\right] + k_D \left[A_D\right]\right) \left[A_H + A_D\right]$$

hence, $$k' \left[A_H + A_D\right] = k_H \left[A_H\right] + k_D \left[A_D\right] .$$

Substituting $k_H = 6.17 \times 10^{-5}$, $k' = 3.14 \times 10^{-5}$, $A_H = 0.215$, $A_D = 0.785$, k_D is found to be 2.32×10^{-5}. Therefore, the isotope-effect for the decarboxylation is

$$\frac{k_H}{k_D} = \frac{6.17 \times 10^{-5}}{2.32 \times 10^{-5}} = 2.66$$

The results of this isotopic study indicate that an unusually high amount of deuterium is obtained in the ring of the aniline obtained on decarboxylation of partially deuterated anthranilic acid, in agreement with the results obtained by Krueger (25) for the reaction in the melt. In explaining this observation, it would help to know the distribution of deuterium in the deuterated anthranilic acid.

An approximation of the deuterium distribution in the neutral anthranilic acid molecule may be obtained from the following equilibria for benzoic acid and aniline, for which the values of the equilibrium constants at room temperature are known (15).

(1) $\text{ØCOOH} + \text{HOD} \underset{}{\overset{K_1}{\rightleftharpoons}} \text{H}_2\text{O} + \text{ØCOOD}$

$$K_1 = \frac{[\text{H}_2\text{O}]\ [\text{ØCOOD}]}{[\text{HOD}]\ [\text{ØCOOH}]} = 0.52$$

(2) $\text{ØNH}_2 + \text{HOD} \underset{}{\overset{K_2}{\rightleftharpoons}} \text{H}_2\text{O} + \text{ØNHD}$

$$K_2 = \frac{[\text{H}_2\text{O}]\ [\text{ØNHD}]}{[\text{HOD}]\ [\text{ØNH}_2]} = 1.11 \qquad (18)$$

Combination of equilibria (1) and (2) yields:

(3) $\text{ØNH}_2 + \text{ØCOOD} \underset{}{\overset{K_3}{\rightleftharpoons}} \text{ØCOOH} + \text{ØNHD}$

$$K_3 = \frac{[\text{ØCOOH}]\ [\text{ØNHD}]}{[\text{ØCOOD}]\ [\text{ØNH}_2]} = 2.135$$

(4) $\text{ØNH}_2 + \text{ØND}_2 \underset{}{\overset{K_4}{\rightleftharpoons}} 2\ \text{ØNHD}$

$$K_4 = \frac{[\text{ØNHD}]^2}{[\text{ØNH}_2]\ [\text{ØND}_2]} = 4 ,$$

which is a statistical equilibrium constant.

These equilibria are applied to anthranilic acid by considering it to be an equimolar mixture of aniline and benzoic acid. In one mole of the deuterated anthranilic acid used in this study there would be 0.352 x 3 = 1.055 gram-atom of deuterium present, i.e.

$$(5) \quad [\text{ØNHD}] + 2[\text{ØND}_2] + [\text{ØCOOD}] = 1.055$$

$$(6) \quad [\text{ØNH}_2] + [\text{ØNHD}] + [\text{ØND}_2] = 1$$

$$(7) \quad [\text{ØCOOH}] + [\text{ØCOOD}] = 1$$

Relations (3), (4) and (5) may be incorporated into the cubic equation,

$$(8) \quad [\text{ØCOOD}]^3 + 47.5\,[\text{ØCOOD}]^2 + 27.8\,[\text{ØCOOD}] - 15.1 = 0$$

which has a solution $[\text{ØCOOD}] = 0.34$, through which the following concentrations can be obtained:

$$[\text{ØND}_2] = 0.13 \qquad [\text{ØNHD}] = 0.46$$

$$[\text{ØNH}_2] = 0.41 \qquad [\text{ØCOOH}] = 0.66$$

From this calculation we get the following constant ratio:

$$\frac{\text{D/H amino group}}{\text{D/H carboxyl group}} = 1.08$$

This indicates that the deuterium in partially deuterated anthranilic acid is evenly distributed between the amino and carboxyl groups.

The anthranilic acid used in this part of the investigation contained 35.2 atom-percent deuterium on the basis of the three replaceable hydrogens in anthranilic acid, or it may be expected that the acid consisted of very nearly 35 atom-percent deuterium in the carboxyl group. The aniline contained 46.5 atom-percent deuterium on the basis of one hydrogen in the ring of the aniline. This is an unexpectedly high amount of deuterium in the ring of the aniline and the results cannot be explained in terms of a simple mechanism for the reaction.

The Mechanism of the Decarboxylation of Anthranilic Acid.

The results of this investigation support Stevens' (37) suggestion that the decarboxylation of anthranilic acid consists of a proton attack on anthranilic acid. The negative reaction-constant obtained for the reaction shows that the reaction favours a high electron-density at the reaction-center, indicating that the rate-determining process consists of a proton-attack at the reaction center. The existence of a deuterium isotope-effect for the reaction proves that the proton-attack must be the rate-determining step.

Whereas Stevens proposed that the reaction proceeds in the zwitterion form of anthranilic acid, the results of this study suggest that the reaction proceeds in the molecular form of anthranilic acid. As pointed out above, the reaction favours a high electron-density at the reaction centre and

a high electron-density does exist at the carboxyl group of a neutral anthranilic acid molecule due to the mesomeric effect of the o-amino group. In the zwitterion, however, the electron-density at the reaction-center would be comparatively lower because the inductive effects of the NH_3^+ and CO_2^- groups probably balance each other fairly closely. On this basis, the reaction proceeds with the acid in the molecular form in which the amino group acts as a strong electron-donor to the reaction-center.

We may assume that the mechanism is concerted, with the introduction of the proton and the removal of the carboxyl group occurring in a single step. Alternately, we may assume that there is a definite intermediate in the reaction. On the basis that there is no C^{13} isotope effect, the reaction is not concerted, and the intermediate must be formed in the rate-controlling step and then rapidly decarboxylated.

The following conclusions can therefore be drawn from the results of this investigation:

(1) The reaction is bimolecular.

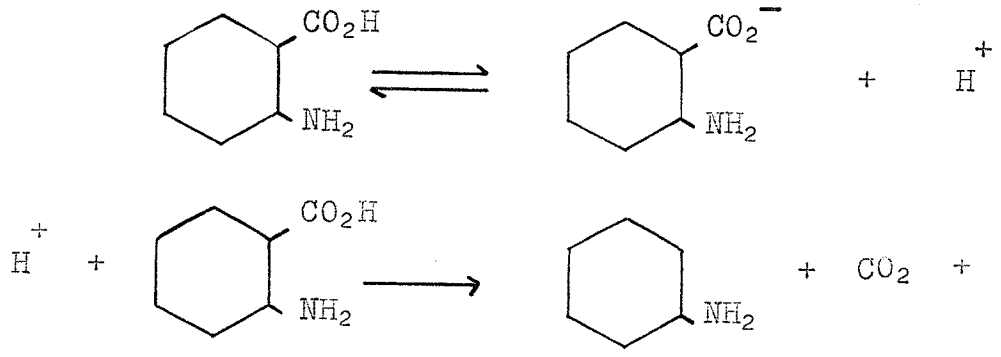
(2) The reaction-center is the carbon atom α- to the carboxyl group.

(3) The rate-determining step is the proton-attack on the α-carbon atom.

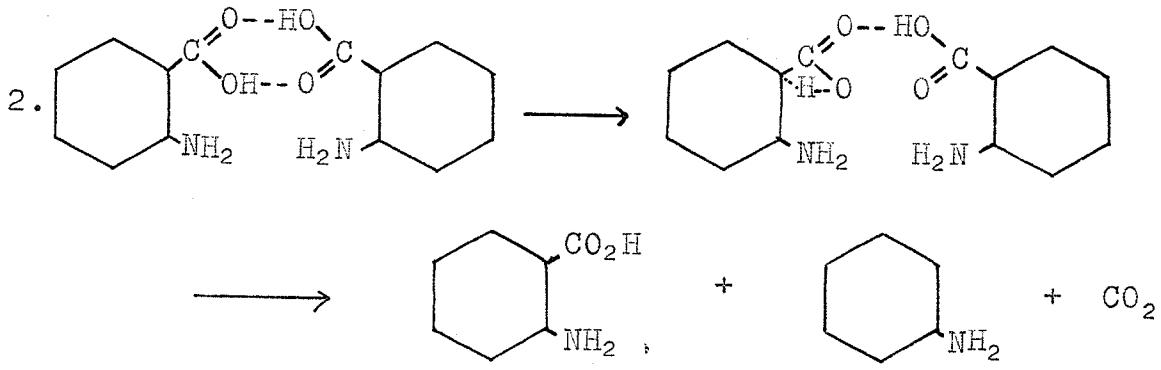
(4) The reaction occurs in the molecular form of the acid.

While the reaction is bimolecular, it cannot be readily realized whether one molecule acts merely as a proton donor to a second molecule, or if two molecules are associated in the form of a dimer, as is well known to be the case for many carboxylic acids during the decomposition of one acid molecule. The following mechanisms are therefore possible for the reaction:

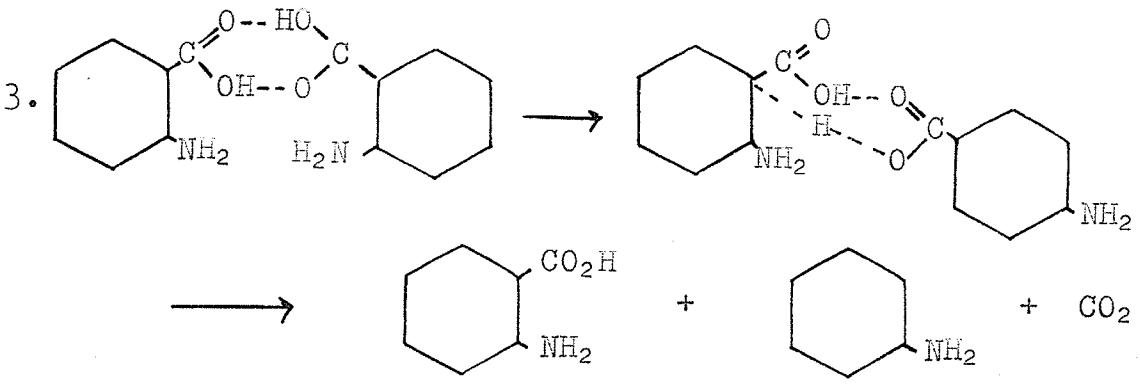
1.



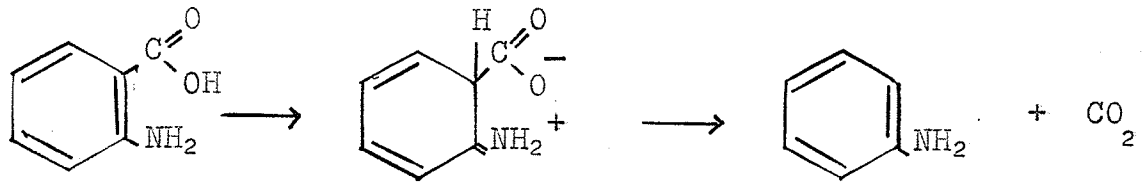
2.



3.



In all three of these possibilities the following stages of reaction may be postulated:



The results of the isotope-study indicate that the reaction is more complicated than merely a transfer of a proton from one molecule to another (mechanism 1) because the unusually high amount of deuterium in the ring of the aniline cannot be accounted for by this mechanism. It is therefore quite likely that some complex intermediate is involved and that his intermediate consists of two acid molecules hydrogen-bonded together.

While various types of hydrogen-bonding may occur in anthranilic acid, the most likely is that between two carboxyl groups. In partially deuterated anthranilic acid, the hydrogen bonds would consist of protium and deuterium bonding, some investigators claim that the deuterium bonding is slightly stronger than protium bonding (12). On the other hand, some researchers claim that protium bonding is stronger than deuterium bonding (32).

If deuterium bonding is weaker than protium bonding, then it is possible to account for the high amount of deuterium in the aniline in the following way. If the reaction does

occur in the dimer form of the acid, one of the hydrogen bonds would have to be broken before the proton could attack the reaction-center. Therefore, the dueterium bond would be broken more readily and would be the species participating in the substitution of the carboxyl group more often. If all the assumptions were correct this could be the explanation for the high deuterium concentration in the ring of the aniline.

CONCLUSIONS

(1) The decarboxylation of anthranilic acid is a bimolecular reaction in which the rate-determining step is the proton attack on the α-carbon atom.

(2) The reaction proceeds in the molecular form of the acid in which the amino group acts merely as a powerful electron-donor to the reaction-center.

(3) A hydrogen isotope-effect of 2.66 is involved in the reaction.

(4) Hammett's reaction constant is - 1.35 for the reaction in nitrobenzene.

(5) Intermolecular hydrogen bonding is suggested as a factor that might account for the results obtained.

RECOMMENDATIONS FOR FUTURE INVESTIGATIONS

The deuterium isotope-effect should be determined for the decarboxylations of p-aminobenzoic acid which has been shown to be a bimolecular reaction, similar to the decarboxylation of anthranilic acid in this respect. A study of the distribution of deuterium in the aniline produced on decarboxylation of partially deuterated p-aminobenzoic acid would indicate whether the reaction is the same as the decarboxylation of anthranilic acid. This would establish whether the o-amino group in anthranilic acid is responsible for the unusually high amount of deuterium in the ring of the aniline, or whether this effect is the results of intermolecular hydrogen bonding as proposed.

It would be interesting to see whether deuterium isotope effects exist for the decarboxylation of other acids which decarboxylate by the S_E2 mechanism. Mesitoic, salicylic, and p-hydroxybenzoic acids would be suitable for such studies.

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