

THE MECHANISM OF DECARBOXYLATION
OF ANTHRANILIC ACIDS IN AQUEOUS SOLUTION

by

Immo E. Scheffler

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"The organization of Science today is so dominated by the needs of research, with its emphasis on novelty, that the tremendous span and volume of existing scientific knowledge tends to be taken for granted. The fact that this or that theory is modified or discarded tends to be generalized into a dismissal of all that was known up till about five years ago as out of date. The great conceptual network of principles still valid, stretching back to Newton and even to Archimedes, the historical insight and experience built into the design of all modern instruments and terminology, the evolutionary and synoptic perspectives inherent in the world picture presented by Science, the greater part of its vocabulary, and the increasing body of established fact, all contribute to the indispensable and continuing inheritance of modern Science. The failure to communicate the latest news in Science may be less serious than the failure to assimilate this common heritage."

Patrick Meredith (58)

PREFACE

This is my first venture into chemical research. Looking back, I remember with pleasure the hours spent in the company of my fellow-students. I am very grateful for the guidance and inspiration, and for the knowledge communicated by my teachers in the far and near past.

Very special thanks are due to Dr. G. E. Dunn, who awakened my interest in physical organic chemistry at a very early stage of my education in chemistry. He suggested the topic of this investigation and then stood by with invaluable advice and criticisms. His open door at all times invited to helpful discussions.

I also wish to thank the National Research Council for a bursary.

ABSTRACT OF M.Sc.THESIS

submitted by Immo E. Scheffler

The Mechanism of Decarboxylation of Anthranilic Acids
in Aqueous Solution

The ionization constants of 4-methoxyanthranilic acid in aqueous solution of ionic strength 0.1 at $(60 \pm 2)^\circ\text{C}$ were determined to be: $\text{pK}_1 = 2.09 \pm 0.30$ (1.93 ± 0.05), and $\text{pK}_2 = 4.73 \pm 0.05$ (4.69 ± 0.03).

The rates of decarboxylation of this acid were then measured at 60°C in buffer solutions of ionic strength 0.1 and 0.5 in the pH range from 0 to 4. A rather sharp maximum was observed at a $\text{pH} \sim 1.0$, and there was some qualitative evidence for general acid catalysis. The kinetic data could not be interpreted either by postulating the unimolecular decomposition of one of the species H_2A^+ , HA (or z^\pm) and A^- in the rate determining step, or by suggesting a rate determining attack of a proton on one of these, or by a combination of both of these mechanisms. A modified $\text{S}_{\text{E}}2$ mechanism is put forward, in which a relatively stable intermediate participates in several competing reactions, one of which leads to the loss of carbon dioxide.

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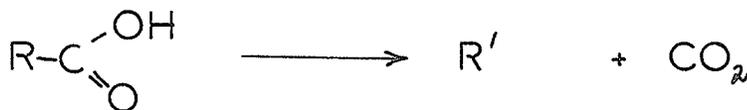
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CHAPTER I

I. INTRODUCTION

Decarboxylation reactions have for a long time been of considerable importance in synthetic organic chemistry. Syntheses via the malonic ester and via acetoacetic ester are familiar examples. Attention has also been drawn to the significance of decarboxylations in biochemical mechanisms (14,27,31)

In a very general sense the reaction involves the loss of carbon dioxide from an acid:



The nature of the product (R') depends on the nature of the group R- and possibly on the conditions of the reaction.

A variety of mechanisms have been suggested (6, 26B, 31, 44, 57), each applicable to certain types of acids (β -keto acids, aromatic acids, acids with highly electro-positive α -carbons). Decarboxylations have been studied in the melt, in non-aqueous and aqueous solvents, and many reactions are known to be subject to acid catalysis, metal ion catalysis and enzyme catalysis. In chapter II a number of possible mechanisms will be indicated.

Many examples involving aliphatic acids can be found in the review by Brown (6) and in the discussions by Hine

(268) and Kosower(31). Only a few have been included here to illustrate certain fundamental ideas. The work concerned with thermal decarboxylations of aromatic acids is presented in some detail; it is intended to represent a complete coverage of those studies found in the literature in which the emphasis was on the elucidation of the mechanism rather than on synthesis.

In chapter IV of this thesis the experimental results of a study of the thermal decarboxylation of 4-methoxyanthranilic acid in aqueous solution will be reported and discussed in the light of, and in contrast to, similar studies reported in the literature.

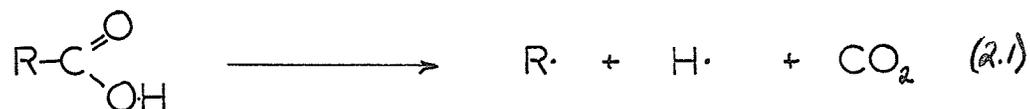
The considerations leading to the formulation of the problem are introduced following the review of the literature.

CHAPTER II

REVIEW OF THE LITERATURE

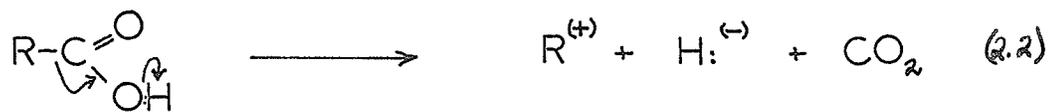
I. THE UNIMOLECULAR MECHANISM

General discussion. There is no evidence for free radicals in thermal decarboxylations (6), and homolytic fission may be disregarded.

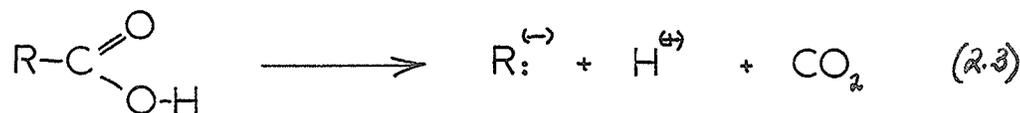


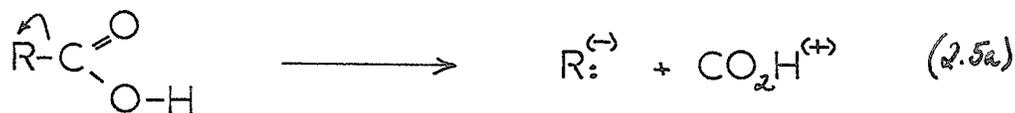
The remaining possibility, heterolytic fission, is further indicated by the effect of solvents on the rates of decarboxylation, and by the fact that the reaction is often subject to ion catalysis.

Since there are no cases known in which hydrogen gas is evolved as one of the reaction products, hydride ions are certainly not involved in decarboxylations in protic solvents and bond fission as indicated by (2.2) can also be ruled out.



Hence, the following rearrangement of the bonding electrons seems to be most probable:





Since proton transfers (between oxygen atoms) occur extremely rapidly, reactions (2.3) and (2.5) may not be kinetically distinguishable. However, there is good evidence on the basis of which it may be concluded that the decarboxylating species is the anion (6):

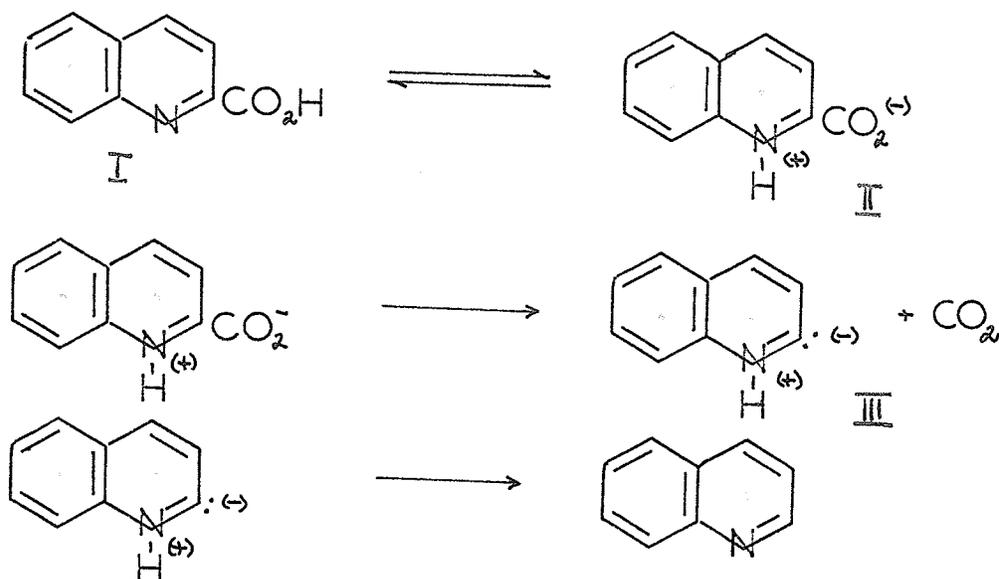
1. some acids which are completely ionized in water decarboxylate quite readily;
2. the same activation energies have been found for the decarboxylation of the sodium salts of these acids;
3. the rate of decarboxylation is reduced by a factor of 10^7 in nonionizing solvents;
4. in nonaqueous solvents the rate is found to be proportional to the concentration of the anion produced by the addition of stronger bases.

Decomposition of the free acid. There is no good, conclusive evidence for the exclusive, unimolecular

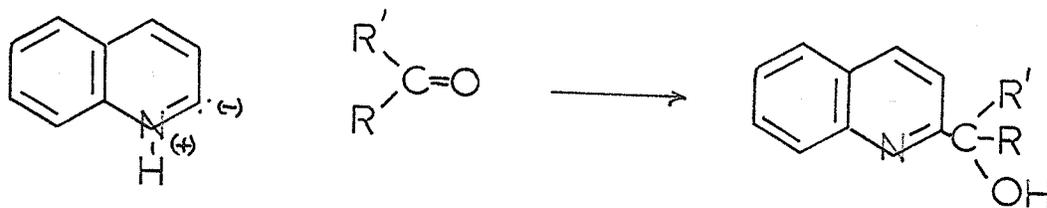
decomposition of the free acid by mechanism (2.3). The activation energy for the fission of a $R_3C-CO_2^-$ bond is expected to be less than that for fission of a $R-C-CO_2H$ bond.

Rates of decarboxylations which appear to depend on the concentration of the free acid are observed for acids capable of forming a zwitterion the concentration of which is proportional to that of the free acid.

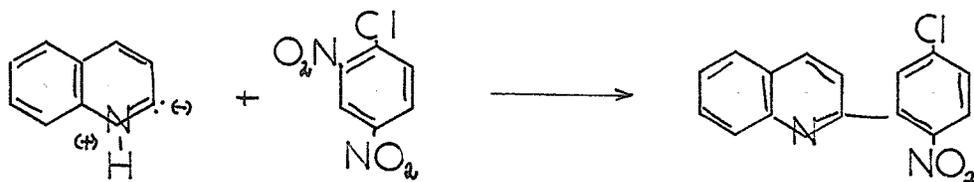
Example 1 (9) :



The existence of a stable intermediate such as (III) is indicated by its reaction with the solvent, e.g. in aldehydes or ketones (9,21):

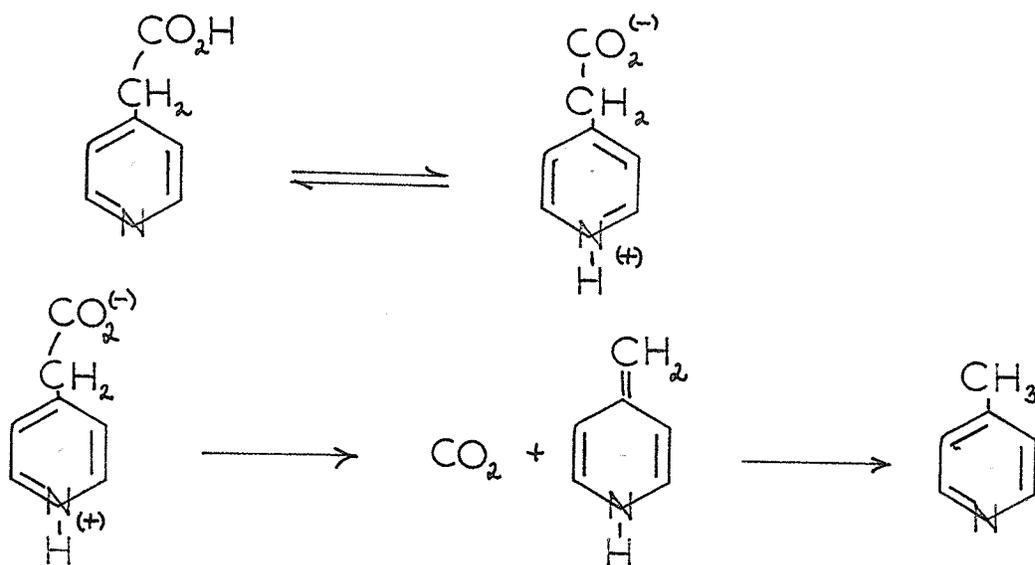


Another interesting reaction observed by Brown and Hammick (9) in the decarboxylation of quinaldinic acid in quinoline containing 2,4-dinitrochlorobenzene is the following:

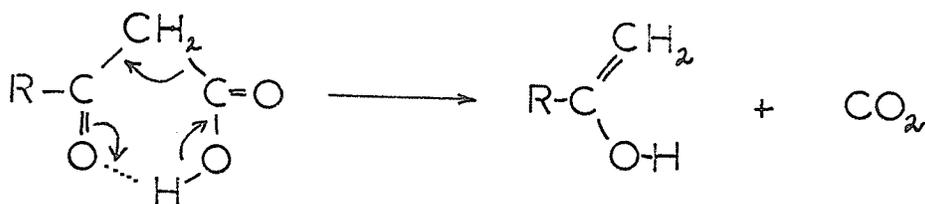


These side reactions were formulated after identification of the products.

Example 2 (17) :



The decarboxylation of β keto acids is faster than the decomposition of the corresponding anion due to the formation of a cyclic transition state which may be considered similar to a zwitterion(55).



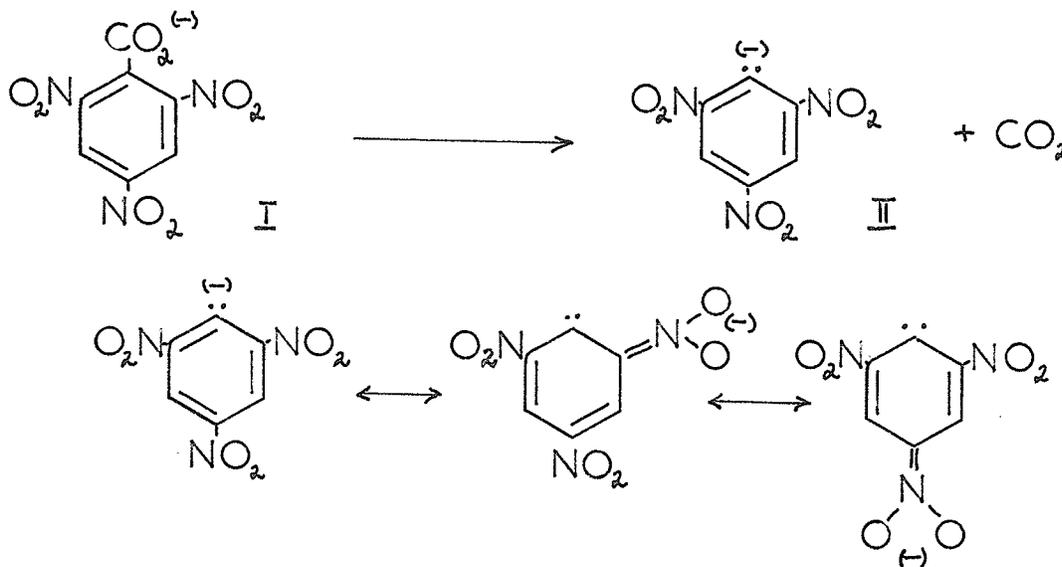
The intermediate formation of the enol can be shown by its reaction with reagents like Br_2 , which have no influence on the rate of decarboxylation.

Decomposition of the anion. The unimolecular decomposition of the anion proceeds via a carbanion intermediate which presumably reacts very quickly with the solvent. Assuming that the transition state resembles the carbanion, factors which will stabilize the carbanion will also lower the activation energy of the reaction. In other words, a dispersal of the negative charge within the remaining part of the molecule will lead to an increase in the rate. Charge dispersal can occur as follows:

1. the α -carbon (or carbon-1 in the case of aromatic acids) may be conjugated with electron accepting groups;

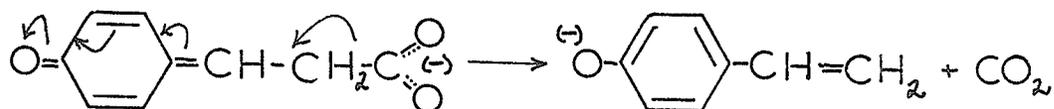
a) the decarboxylation of 2,4,6-trinitrobenzoic acid has been studied by several authors (53, 24, 30).

Observed solvent and isotope effects are consistent with the following mechanism:

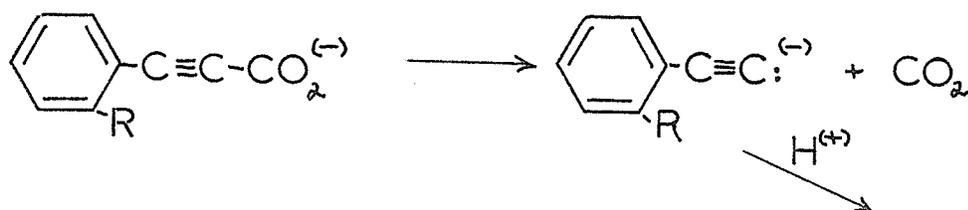


It is probable that trinitrobenzene exchanges deuterium via a similar intermediate having a carbene carbon.

- b) on the basis of the dependence of the rate on the pH Cohen and Jones (16) postulated the following intermediate species in the decarboxylation of p-hydroxycinnamic acid:

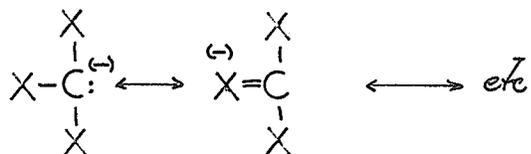


2. Decarboxylation of the simple anion may also be possible if the electronegativity of the bonding orbitals of the α -carbon is sufficiently high to allow the acceptance of the electron pair (31).



Decarboxylation occurs in aqueous solution at 120°C if R is hydrogen and the rate is not too much faster if R is a nitrogroup.

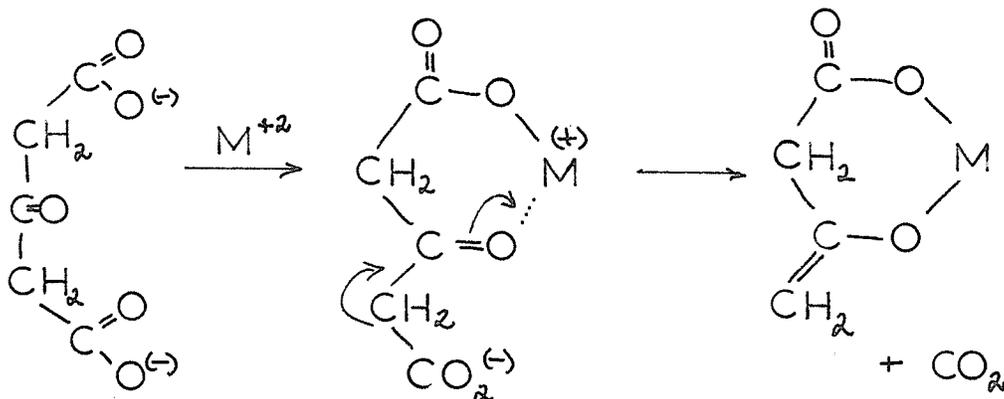
Trihaloacetic acids also decarboxylate easily because of the effect of the halogens on the electron density around the α -carbon. When X is chlorine, bromine or iodine the intermediate carbanion can be further stabilized by charge dispersion into the upper orbitals of the halogen atom.



It is noticeable that trifluoroacetic acid is relatively stable.

The resulting negative charge on $\text{C}\alpha$ after loss of CO_2 may also be stabilized if a positive charge already resides on that group. The mechanism of the decarboxylation of zwitterions fits into this category. Another example is the decarboxylation of the 1-methylbetaine of pyridine-2-carboxylic acid investigated by Kosower (3/).

The role of the metal ion in catalyzed decarboxylations is a partial neutralization of the negative charge remaining on the fragment after the loss of CO_2 (26, 425).



Monoesters of the same acid presumably would decarboxylate at a much slower rate.

II. THE BIMOLECULAR MECHANISM

Kinetics. For a weak acid in aqueous solution the well known relationship holds:

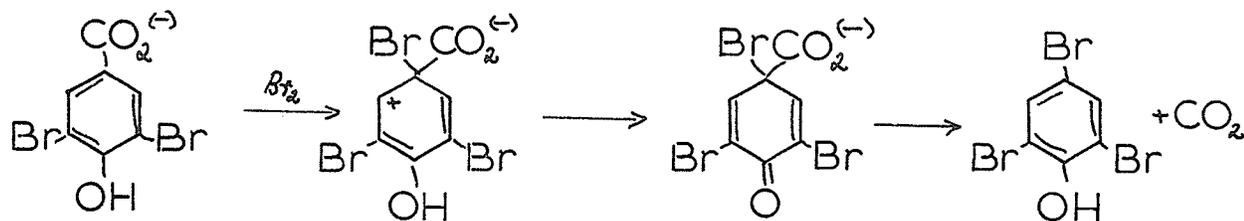
$$K_A = \frac{a_{A^-} a_{H_3O^+}}{a_{HA}} \quad a = \text{activity}$$

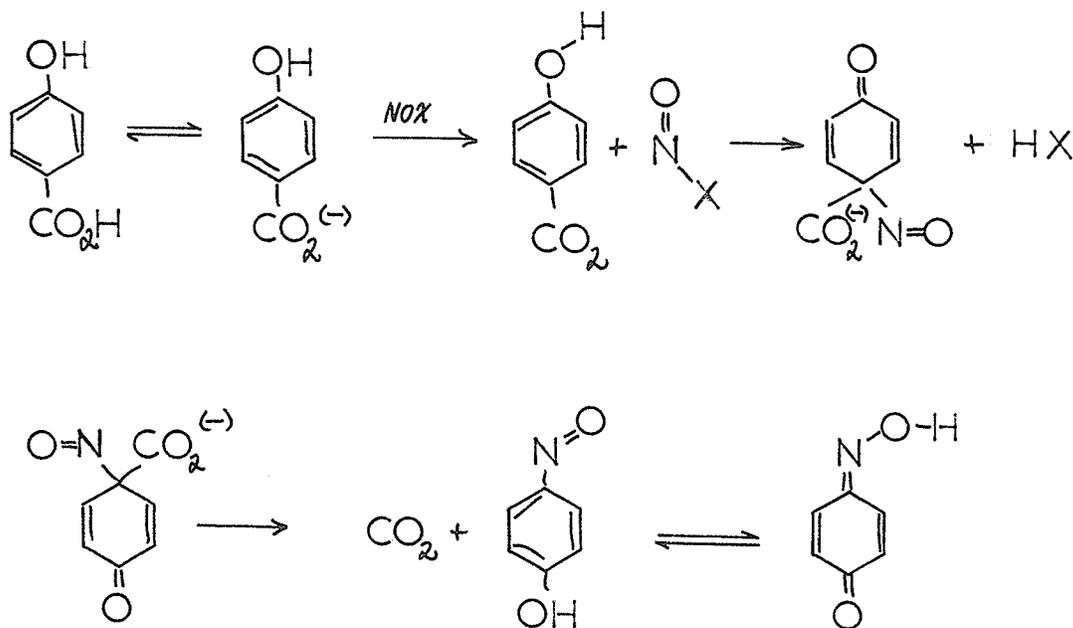
The rate expressions for the unimolecular decomposition of the neutral acid (HA) and for a bimolecular mechanism involving the anion (A⁻) and a hydronium ion are the following:

$$\begin{aligned} R_{HA} &= k_1 [HA] & [HA] &\approx a_{HA} \\ R_{A^-} &= k_2 [A^-] [H_3O^+] & [A^-] &\approx a_{A^-} \\ &= k_2 K_A [HA] \end{aligned}$$

The two mechanisms are thus kinetically indistinguishable.

Evidence. Good evidence for a bimolecular mechanism has been obtained in bromo-decarboxylations (25) and nitroso decarboxylations (57). The species replacing the carboxyl group is not involved in the acid-base equilibrium and hence it cannot be eliminated from the rate expression.





Tedder and Theaker (57) observed that the decarboxylation can be suppressed by raising the hydrogen ion concentration of the medium (repression of the ionization of the acid). The same authors report further, that neither methylsalicylate nor p-anisic acid decarboxylated under similar conditions, in support of the above mechanism.

Measurements of a kinetic isotope effect by Willi (57E) in the decarboxylation of 4-hydroxysalicylic acid in water and deuterium oxide give support to the bimolecular mechanism.

$$R_1 = k_H^A [A^-] [H^+]$$

$$R_2 = k_D^A [A^-] [D^+]$$

A value of 1.76 for the ratio k_{RH}^A/k_D^A is taken to indicate that the slow transfer of the proton to the anion is the rate determining step.

III. DECARBOXYLATION OF AROMATIC ACIDS

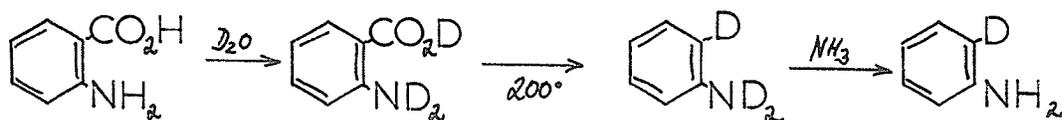
A variety of examples have already been given in the general discussion. In the following a slightly more detailed summary of the experimental evidence will be presented.

In the melt. One of the earliest observations of the decarboxylation of an aromatic acid (anthranilic acid) in the melt was that of Pawlewski (42). Stevens and his collaborators (49) confirmed that anthranilic acid loses carbon dioxide in a "first order reaction" when heated above its melting point. No isotope effect was found with C¹³ in the carboxyl group.

It may be pointed out here that the possibility of a bimolecular reaction in the melt is not excluded by the observation of the "first order" of the reaction. (To assign an order to the reaction in a melt is rather meaningless for the case where the product escapes.) A proton transfer between two species present in the melt may lead to a stable intermediate which may either be "deactivated" by loss of the proton to an other species in solution or lose carbon dioxide

to form products. This scheme is analogous to that suggested by Lindemann for pseudounimolecular reactions in the gas phase at relatively high pressures. To carry the analogy further, if the melt is diluted by an inert, aprotic substance, second order decarboxylation reactions should be found.

Dunn et al. (19) attempted to prepare deuterated aniline by decarboxylation in the melt of deuterated anthranilic acid in the following sequence of reactions:



The observed very high deuterium content of the product obtained from partially deuterated anthranilic acid can be accounted for by two alternative explanations:

(1) decarboxylation may take place by a mechanism such that deuterium migrates in preference to protium; or (2) deuterium enters more than one position in the ring. There is some support for the latter possibility from the observation (54) that on decarboxylation of simple aromatic acids with $\text{Ca}(\text{OD})_2$ deuterium is found at several positions in the ring.

It may be concluded that decarboxylations in the melt are relatively complex mechanistically, or that some deuterium exchange occurs between the product and the unreacted acid

which is not taken into consideration.

In aprotic solvents. Dunn and Prysiasniuk (18) studied the rates of decarboxylation of substituted anthranilic acids in nitrobenzene. The aprotic solvent was chosen to determine, whether the proton shift to the ring occurred inter- or intra-molecularly, whether the neutral acid or the zwitterion was involved and hence whether the proton was donated from the carboxyl or from the amino group.

The kinetic order of the reaction (2nd with respect to anthranilic acid), the relative increase in rate in the presence of electron releasing substituents, the observed deuterium isotope effect and an interpretation of the data by a Hammett relationship led to the conclusion that the rate determining step involved the attack by a proton of one anthranilic acid molecule on the C-1 of a second molecule.

In a similar study by Dunn and Janzen (20) salicylic and substituted salicylic acids were decomposed in quinoline. The reaction was first order with respect to the acid. Quinoline was chosen as solvent to allow the study of a larger number of substituents, after it had been found that the rates of some of the substituted acids in nitrobenzene were too slow to be measurable. The interesting result was, however, that in the latter solvent the order with respect to salicylic acid was second.

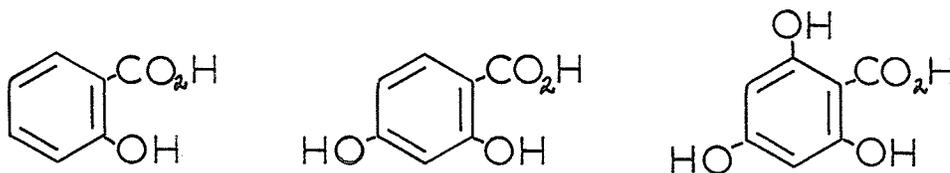
Electron donating substituents in the para position enhanced the rate. It was concluded that the proton from the carboxyl group was first transferred to the quinoline, followed by an electrophilic substitution at the ring carbon α to the carboxyl group. Whether the overall proton transfer occurs after complete dissociation or within an ion pair had yet to be established. Hence, the effect of quinoline was examined in detail by Dunn and Rodewald (2013), who concluded that the weaker acids decarboxylate through a transition state stabilized by quinoline whereas ion pair formation was thought to be involved in the case of the stronger acids.

Schenkel and Klein (45) report the kinetic data on the decarboxylation of picolinic acid in the melt, in phenanthrene, quinoline, tetrahydroquinoline at various temperatures without attempting to suggest a mechanism. The paper is noteworthy since it contains an extensive listing of the literature dealing with the mechanism of decarboxylations up to about 1940.

Decarboxylation in protic, anhydrous solvents. Whereas presumably no acid-base equilibria are involved in aprotic hydrocarbon solvents, such equilibria must be considered if the solvent can act as a base or as a proton donor.

Brown, Hammick and Scholefield (8) studied the rates of decarboxylations of a series of hydroxybenzoic

acids in resorcinol over a temperature range from 110-240°C.



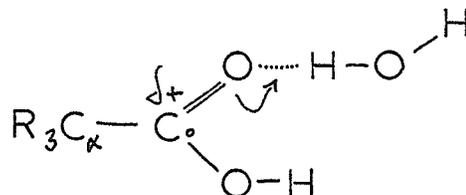
The activation energy decreased with successive substitution of hydroxyl groups in the ortho and para positions of benzoic acid. This result was interpreted in support of a bimolecular mechanism involving the attack of a proton donor on the carbon 1 where the electron density is increased by the substituents. The specific role of the solvent is not discussed.

Resorcinol has also served as solvent in the thermal decarboxylation of benzoic acid (at 255°C) and of p-chlorobenzoic acid studied by Muhammad (39,40) .

Mixed solvents. The kinetics of decomposition of 2,4,6-trinitrobenzoic acid in dioxane-water mixtures are interesting. Trivich and Verhoek (53) found that the order of the reaction changed continuously from first order in almost pure water to one half order in solutions of high dioxane content. A maximum in the rate of the reaction was observed when the composition was about 60% dioxane. At the same time the activation energy was measured to be inversely proportional to the dioxane content. The authors showed that the change in the order of the reaction is the result of the

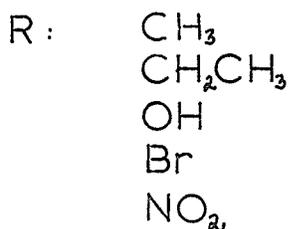
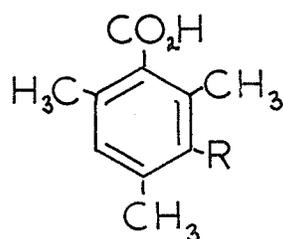
varying degree of dissociation of the acid if the anion is the decarboxylating species. In solutions of low dioxane content the acid is almost completely dissociated, the concentration of the anion is almost equal to the total concentration of the acid, and hence, the reaction is first order. In mixtures for which the dissociation constant is very small the concentration of the anion is approximately proportional to the square root of the total concentration of acid; the reaction order approaches the value of one half. The maximum in the rate was explained by the operation of two opposing solvent effects: The reduced solvation of the anion at higher dioxane concentrations leads to a suppression of the dissociation of the acid and consequently to a lowering of the concentration of the decomposing species, but at the same time the activation energy of the reaction is lowered by a reduction of the difference in the solvation of the anion and the transition state. As suggested by Verhoek (53) compared to the anion (page 7; species I) the negative charge is dispersed over a much larger space in the transition state which is assumed to be similar in structure to the intermediate (page 7; species II). Up to about 60% dioxane the solvent effect on the activation energy predominates, hence the rate increases, but at higher dioxane content the suppression of the ionization causes the rate to decrease drastically.

Schenkel and Schenkel-Rudin(44) offer a slightly more specific explanation of the solvent effect on the activation energy as observed by Trivich and Verhoek(53). The increased activation energy at the higher water content is attributed to hydrogen bonding:



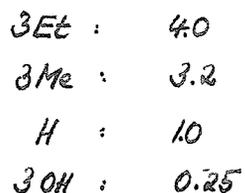
The decreased electron density on the carboxyl carbon (C_{κ}) inhibits the heterolysis of the $C_{\kappa}-C_{\circ}$ bond.

In concentrated aqueous acids. An investigation of the rates of decomposition of substituted mesitoic acids in 82.1% phosphoric and in 83.0% sulfuric acid has been carried out by Beringer and Sands (2).



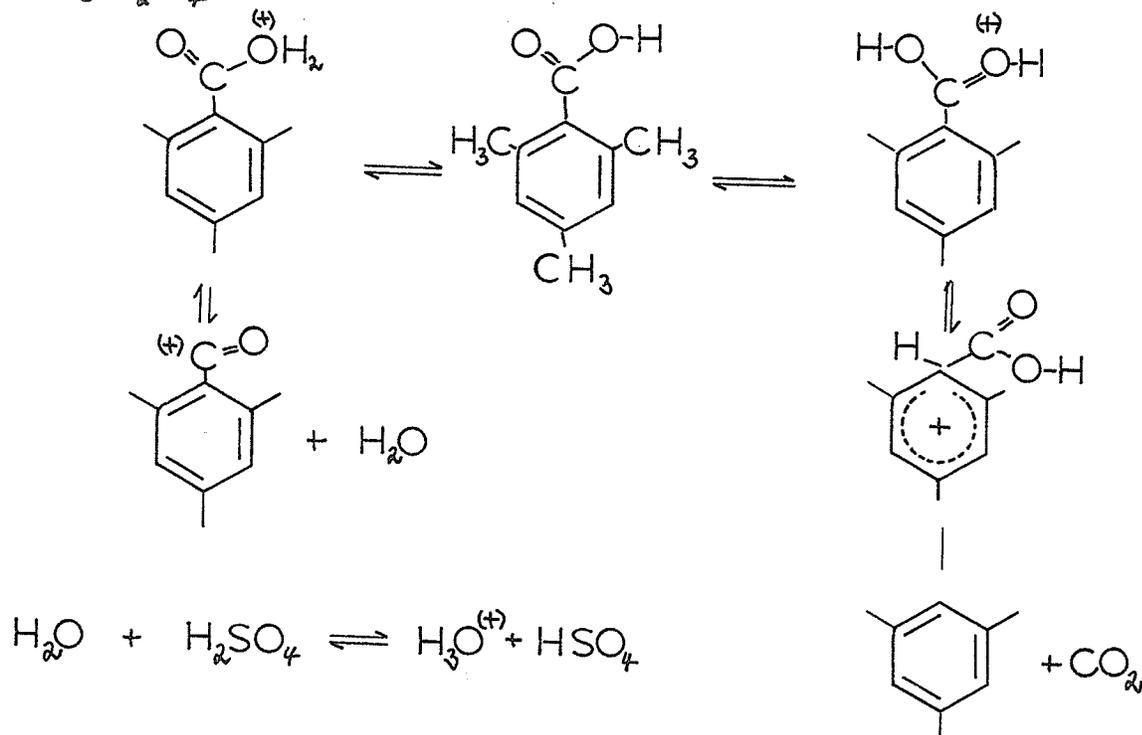
When R is Me, Et or OH, decomposition occurs between $48^{\circ} - 86^{\circ}C$ in sulfuric acid, whereas much higher temperatures are needed when the substituent is a bromo- or nitrogroup (140° and $170^{\circ}C$ respectively).

At 70° in sulfuric acid the relative rates are:



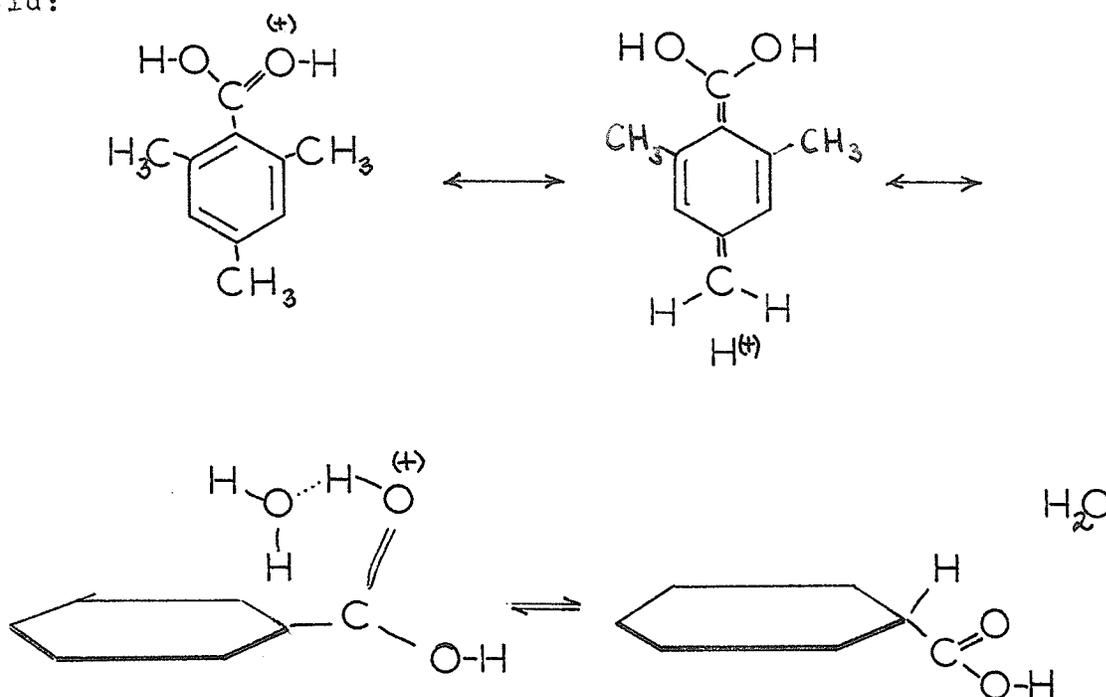
The ratio $k(\text{subst.})/k(H)$ increases at lower temperature. In phosphoric acid the rates of decomposition of mesitoic and 3-(OH) mesitoic acid were the same at 119°C. The relative rate of the substituted acid (3-OH) was higher above this temperature and lower below this temperature. When extrapolated values (at 90°C) were compared, mesitoic acid decarboxylates about 160 times faster in sulfuric acid than in phosphoric acid.

In an earlier paper (1949) Schubert (46) suggests the following scheme for the decarboxylation of mesitoic acid in strong H_2SO_4 :



Schubert and his collaborators later extended these investigations (48); they compared the rates of decarboxylation of 2,4,6-trialkylbenzoic acids in H_2SO_4 of varying composition.

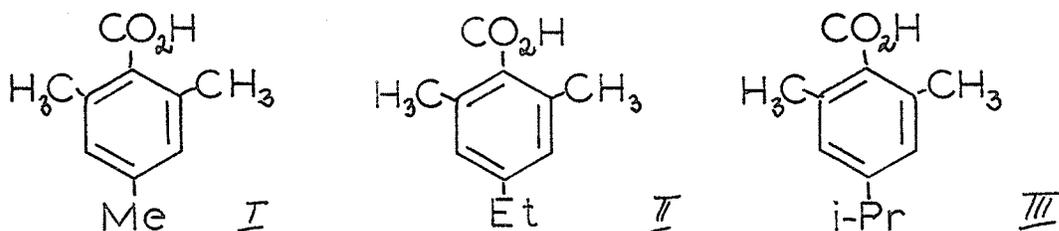
Since the rate was proportional to the concentration of hydronium ion, the presence of H_2O in the transition state was deduced. It was further suggested that the carboxyl group was out of the plane of the ring, that is to say, the bulky orthogroups sterically inhibited resonance in the protonated acid:



Spectrophotometrically the degree of ionization of mesitoic acid to $Ar-CO_2H_2^+$ and $ArCO^+$ was measured: appreciable protonation of the carboxyl group occurred at $>70\%$ H_2SO_4 , and at $>90\%$ H_2SO_4 most of the acid was present in the form of the acylium ion ($ArC^+=O$).

The data were not in agreement with a mechanism involving the unimolecular decomposition of the protonated species $\text{ArCO}_2\text{H}_2^+$ and it was concluded that molecular sulfuric acid catalysis must play a large role in any bimolecular mechanism.

The curves obtained in the plot of $k(\text{obsd.})$ vs. % H_2SO_4 for the three acids (I - III) paralleled each other closely, indicating that the ionization equilibria



were not greatly affected by the parasubstituent, and furthermore, the rates of the three acids did not differ appreciably. On the other hand, the necessity of the activating effect of the p-alkylsubstituent was shown by the stability of 2,6-dimethylbenzoic acid under similar conditions.

The very much faster rate for 2,4,6-triisopropylbenzoic acid was explained by a rise in the energy of the ground state of the reacting species (I B or II B) by steric hindrance of resonance of the $-\text{CO}_2\text{H}$ group with the ring.

