

STUDIES ON THE MECHANISM OF
SOME ACID CATALYZED DECARBOXYLATIONS

By

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ABSTRACT

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

The rates of decarboxylation of 2,4-dimethoxybenzoic acid have been measured in aqueous perchloric and sulfuric acid solutions. On the basis of deuterium solvent isotope effects and C¹³ carboxyl isotope effects, a concerted mechanism has been proposed for its decarboxylation.

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

I. LITERATURE REVIEW

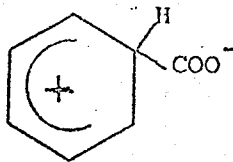
A. General

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

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

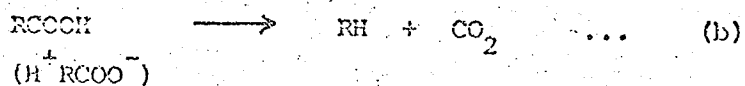
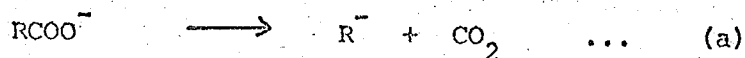
Decarboxylation of an acid RCOOH involves separation of H and R from the COO moiety. Since the H will usually leave as H^+ , i.e. without electron, R normally leaves with an electron pair. Hence electron withdrawal in R caused, for example, by an electron attracting substituent, can be expected to accelerate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

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



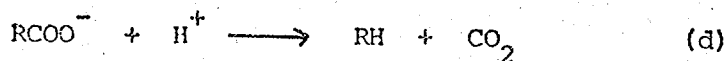
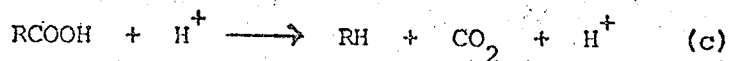
To generalize these possibilities the following formulations of electrophilic substitution have been put forward (8) analogous to the original terminology used in aliphatic nucleophilic substitution reactions (16).

S_E1 Mechanism

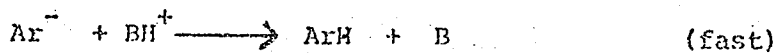
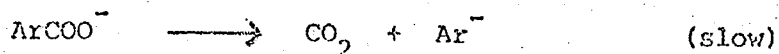


where H^+RCOO^- refers to the Zwitterion form of an acid, which contains a basic functional group.

S_E2 Mechanism



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



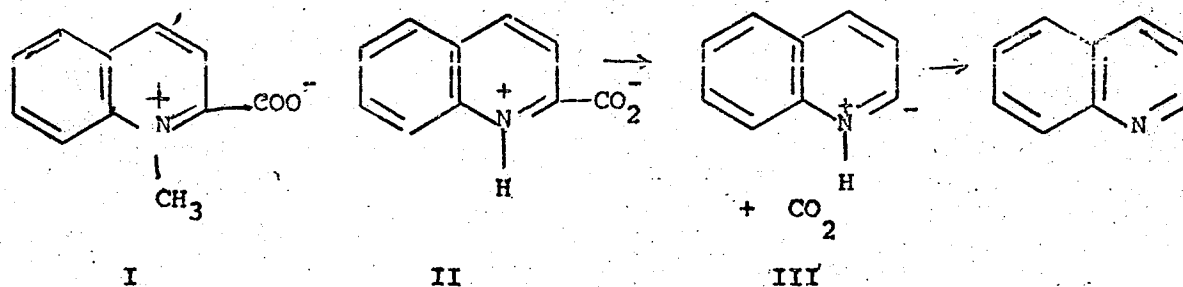
A good example of mechanism (a) is the decarboxylations of 2,4,6-trinitrobenzoic acid (39,40) and trihaloacetic acid (18,41). With 2,4,6-trinitrobenzoic acid the rate of decarboxylation is a maximum under conditions where it is completely dissociated into ions. Also, addition of base to aqueous or alcoholic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

$$V = k_1 [\text{ArCOO}^-]$$

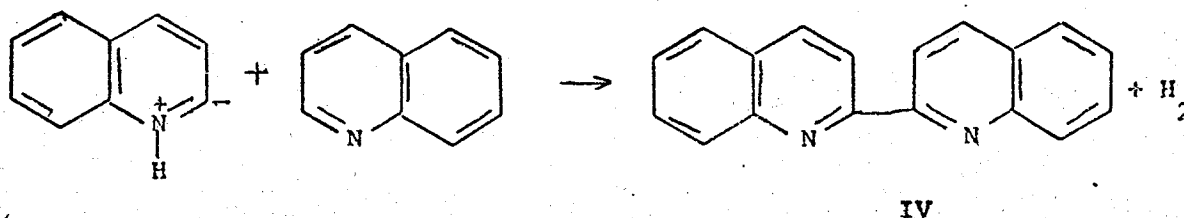
Evidence for the existence of the intermediate carbanion formed has also been indicated. For example, Pederson (27) showed that the addition of bromine has no effect on the rate of decarboxylation of the *o*-nitro isobutyrate anion even though the product is changed from 2-nitropropane to 2-bromo-2-nitropropane.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

Examples of the S_{E1} mechanism (b) can be found by examining the case in which the acid molecule is able to exist as the zwitterion. Brown (8) has pointed out that the activation energy needed for decarboxylation of a zwitterion could be predicted to be less than that for the corresponding acid anion on electronic grounds, thereby anticipating the rate constant for the S_{E1} (b) process to be greater than for the S_{E1} (a) or purely anionic decomposition

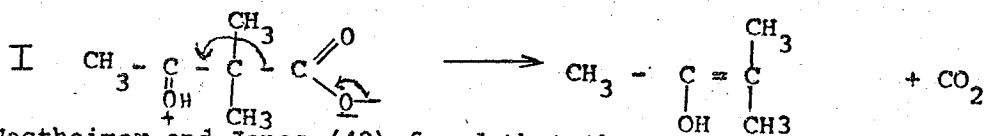
Nitrogen-containing acids of the α -amino type, such as picolinic, quinaldinic and isoquinaldinic acids, have been extensively studied by Brown, Hammick and coworkers (9). The activating electron acceptance here arises from the hetero N atom whose greater electronegativity compared to carbon becomes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



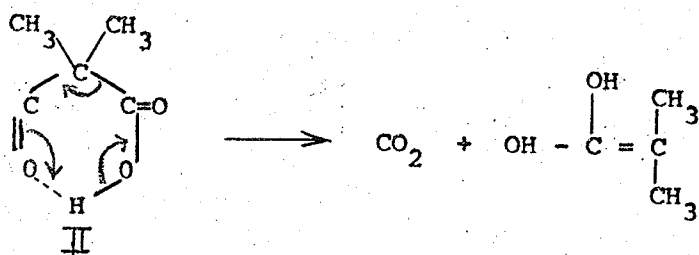
The existence of the α -quinolyl carbanion intermediate (III) was supported by the fact, that in carrying out the decarboxylation in such reagents as aldehydes, ketones, quinoline, and aromatic nitro compounds, one could isolate from the reaction mixtures other substances, an example of which is given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



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

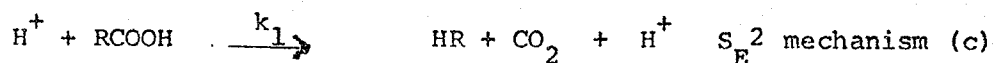


Westheimer and Jones (42) found that the rate of decarboxylation of this acid (α,α -dimethylacetoacetic acid) is virtually independent of the dielectric constant of the solvent. Since a reaction which takes place by way of a polar intermediate should proceed more rapidly in solvents of high dielectric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



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

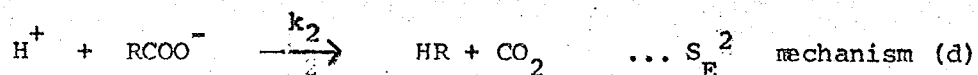
Two possibilities arise. The proton may attack the undissociated acid molecule:



yielding a kinetic equation of the type shown below.

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

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



When the kinetic equation would be

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

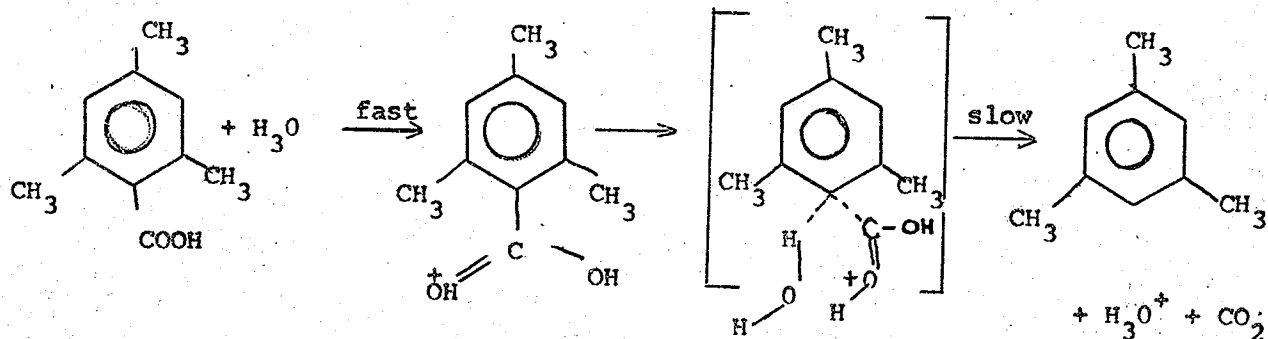
For either mechanism the rate is dependent on the attraction between the α -carbon atom of the acid and a proton. Since the formation of the anion will increase the electron density on the α -carbon atom, it may be expected that the second mechanism (S_E^2 d) written above will require less activation energy than the first. However, it is possible that both mechanism^s will occur, singly or simultaneously, and an analysis has to be made for each type of acid studied.

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

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

$$\text{Rate} = k[\text{H}_3\text{O}^+][\text{acid}]$$

and hence the reaction was suggested to occur by a $S_{\text{E}}2$ mechanism of the following type:



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

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

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

B. Hydroxy and Alkoxybenzoic acids.

A much clearer situation is found with the more reactive hydroxy and alkoxy benzoic acids in which the rate of decarboxylation can be measured in weakly acidic aqueous solutions. The first reliable kinetic data which take into account the acidity constant of the compound were obtained on 2,4,6-trihydroxybenzoic acid (9,34). Since this acid and its anion absorb UV light much more strongly than the decarboxylation product phloroglucinol (1,3,5-trihydroxybenzene), the decomposition reaction can be followed by spectrophotometric means. Keeping the hydrogen ion concentration constant by the use of buffered solutions, pseudo first order rate constants k_1 were obtained. With increasing perchloric acid concentration the k_1 value first increased until at about $C_{\text{HClO}_4} = 1\text{M}$ an upper limit was reached. Furthermore, the UV spectra of acid ArCOOH and anion ArCOO^- differ sufficiently that it is possible to determine from absorbance extrapolated to time $t = 0$ the extent of dissociation of the trihydroxybenzoic acid under the prevailing conditions. In this manner Schubert and Gardner (34) find a proportionality between k_1 and $[\text{ArCOOH}]/C_{\text{HA}} = [\text{ArCOOH}]/([\text{ArCOOH}] + [\text{ArCOO}^-])$, the fraction of undissociated acid at equilibrium.

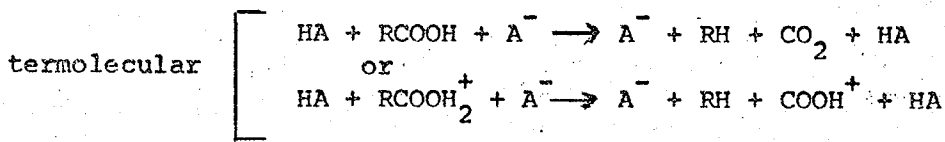
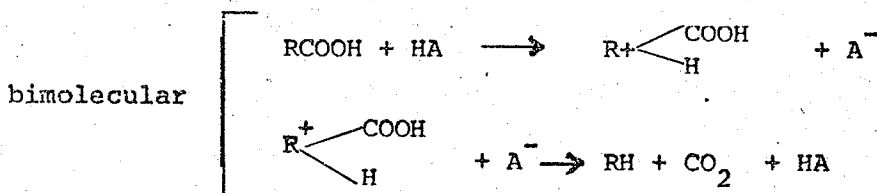
Schubert and his coworkers (35) have studied the decarboxylation of 2,4,6-trimethoxybenzoic acid in concentrated solutions of perchloric acid. From spectral changes in 20-64% mineral acid they find that

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

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

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

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



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

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

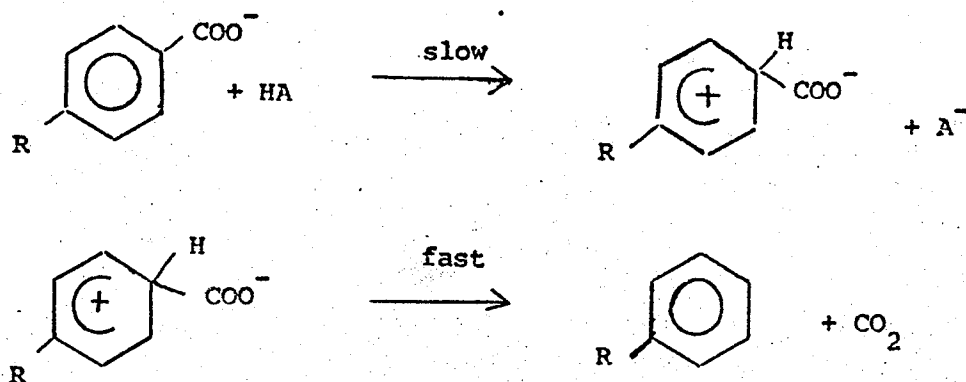
$$\text{rate} = k_{\text{H}}^{\text{A}} [\text{A}^-] [\text{H}^+] \quad \text{and}$$

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

where $[\text{A}^-]$ is the salicylate anion concentration and $[\text{H}^+]$ and $[\text{D}^+]$ are respectively the hydronium and deuterium ion concentrations.

The value, $k_{\text{H}}^{\text{A}} / k_{\text{D}}^{\text{A}} = 1.76$ was taken to indicate that the rate-determining step was a proton attack on the salicylate ion.

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



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

Using unenriched samples of 2,4-dihydroxybenzoic acid, Lynn and Bourns (25) observed a carboxyl-C¹³ isotope effect of $0.60 \pm 0.05\%$ at 85°C for the reaction in aqueous perchloric acid solutions of varying concentrations (0.002 - 0.01M). The magnitude of this isotope effect is about five to seven times smaller than those previously observed in reactions in which the carbon-carbon bond-breaking occurs in the rate-determining step. While this is in agreement with Willi's mechanism, it could also be argued to be in favor of the concerted mechanism for the case in which the C-C bond has been only slightly altered after the reactant has passed into the activated state.

Lynn and Bourns shed further light on this problem by measuring the carboxyl-C¹³ isotope effect in acetic acid-sodium acetate buffer solutions of different concentrations. The k_{12}/k_{13} ratio