STUDIES ON THE MECHANISMS OF DECARBOXYLATION OF PYRIDINE- AND PYRROLE- CARBOXYLIC ACIDS IN AQUEOUS SOLUTION

by

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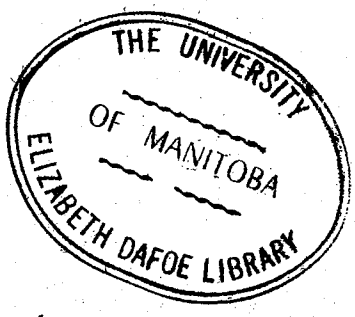

TO MY WIFE

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ABSTRACT

The rates of decarboxylation of pyridine-carboxylic acids have been studied at high temperature in aqueous solution with varying pH and constant ionic strength. The unsymmetrical shapes of the rate versus pH curves indicate that the decarboxylation of these acids is not the decomposition of a single species. A probable mechanism, involving the decarboxylation of both the neutral species and the anion, is postulated. The results of the C^{13}-kinetic isotope effects on pyridine-2-carboxylic and pyridine-2, 3-dicarboxylic acids agree with the proposed mechanism.

The pH dependence on rate at constant ionic strength for pyrrole-2-carboxylic acid has also been examined. The results, together with the C^{13}-kinetic isotope effects, indicate that its decarboxylation mechanism resembles that of anthranilic acid.

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I. INTRODUCTION

A number of areas of Chemistry have profited immeasurably through the use and study of the process of decarboxylation. The frequent occurrence of decarboxylation in the degradative and synthetical procedures of organic chemistry and during the enzymic reactions of biochemistry, and the use of the decarboxylation reaction to illustrate the fundamentals of reaction kinetics in solution, are a sufficient indication of its importance. Organic chemists early recognised the value of decarboxylation and applied it as a standard method for the degradation and synthesis of molecules. Physical chemists have used decarboxylation techniques in their fundamental studies of reaction kinetics in solution. An extension of this work followed in the development of mechanistic studies of the decarboxylation process particularly by thermal and catalytic means. Success in this direction has given impetus to investigations of the mechanism of enzymic decarboxylative reactions in the biochemical field.

Decarboxylations of organic acids have been studied in the melt (56), solid (19; 82), gas phase (5), aqueous (27; 93), and non-aqueous solution (26; 30);

and have been carried out by a number of procedures. Included among these are anodic (88), metal-catalyzed (41; 87), photochemical (38; 73), and more recently, high-pressure (10) methods. Enzymic reactions have been observed to be the cause of numerous biochemical decarboxylations (57).

An excellent review of the data is given by Brown (14), and many examples involving aliphatic acids can be found in the discussions by Hine (45) and Kosower (57). More recently, Willi (96) and Long (62) also present very thorough and up to date discussions of the subject. A variety of mechanisms have been suggested by these authors, each applicable to certain types of acids.

In the succeeding chapter of this dissertation, the mechanisms of decarboxylation will be discussed and examples from the literature will be given. In view of the relevance to our work, a special section will be centered upon the decarboxylation of aromatic amino acids in aqueous solution. Works published on the decarboxylation of pyridine- and pyrrole-carboxylic acids will be covered at the end of the chapter.

II. LITERATURE REVIEW

A. GENERAL

In a very general sense, decarboxylation of an acid RCOOH involves separation of H and R from the CO_2 moiety, and the combination of R with H. The mechanisms of decarboxylation vary with the sequence in which these processes take place.

Evidence has accumulated to show that decarboxylations may occur either by a unimolecular or by a bimolecular mechanism. The unimolecular decomposition of acid molecules was known many years ago from kinetic investigations. Many organic acids were proved to decarboxylate in the form of their anions:

$$RCO_2^- \longrightarrow R^- + CO_2$$

However, some organic acids are known to be decarboxylated more readily as free acids:

$$RCO_2H \rightleftharpoons H^+RCO_2^- \longrightarrow HR + CO_2$$

The bimolecular mechanism was first suggested by Schenkel and Schenkel-Rudin (76) in 1948:

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

The occurrence of this mechanism was supported by later studies.

Since decarboxylation can be considered to be essentially a replacement of the carboxyl group by hydrogen, the following formulations of electrophilic substitution have been put forward (14; 49; 76), analogous to the original terminology used in aliphatic nucleophilic substitution reactions:

S_E1 (a) $H^+RCO_2^- \longrightarrow HR + CO_2$

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

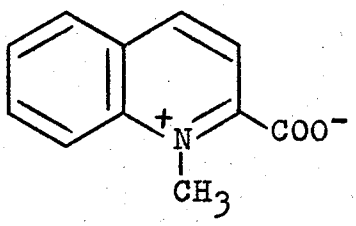
S_E2 (a) $RCO_2H + H^+ \longrightarrow RH + CO_2 + H^+$

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

Electrophilic substitution by a unimolecular process, designated as S_E1, can conceivably occur by the decarboxylation of the free acid molecule (or zwitterion) or anion. The symbol S_E2 is used to describe the electrophilic replacement by a bimolecular mechanism.

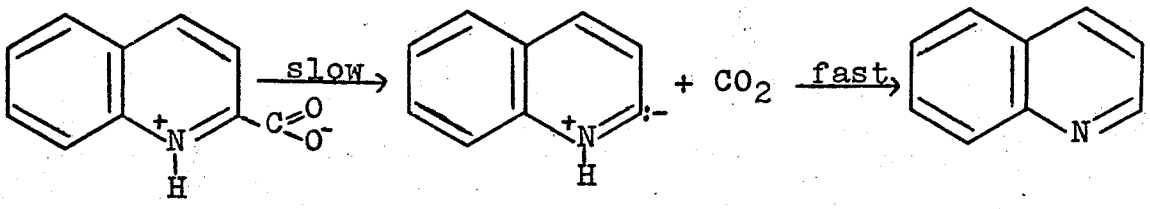
B. UNIMOLECULAR MECHANISM

Examples of the S_E1 (a) mechanism can be found by examining the case in which the acid molecule is able to exist as the zwitterion. Nitrogen-containing acids of the α-amino type, such as picolinic, quinaldinic and iso-quinaldinic acids, have been studied by Brown, Hammick and co-workers (1; 11; 12; 31). 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 evidence to show that the decarboxylation probably proceeds through the zwitterion form. They showed that the methyl betaine, 1-methylquinolinium -2-carboxylate (I), which could not



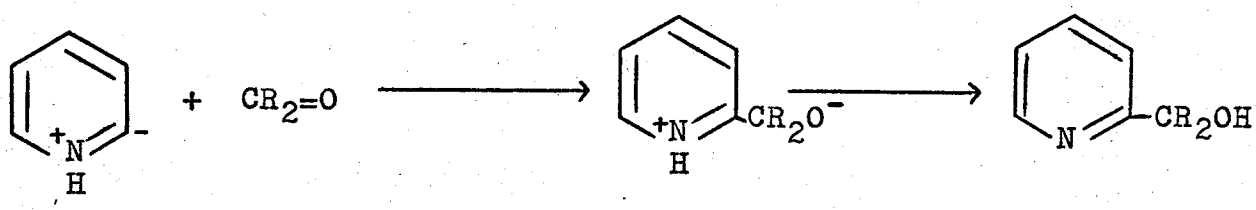
I

tautomerize to a non-zwitterionic form, decomposed relatively rapidly, and therefore the analogous zwitterion (II) is probably the form of the acid that decarboxylates.



II III IV

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 (VII):



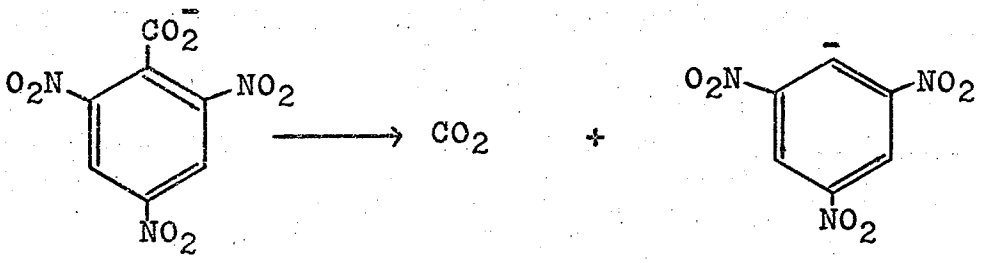
V VI VII

Among the best examples of aliphatic acids which decarboxylate by an S_E1 (b) mechanism are trihalogenoacetic acids. These acids cannot form zwitterions, but the

negative substituents reduce the activation energy for the heterolytic fission of the carbon-carbon bond sufficiently to enable decarboxylation to occur at observable temperatures. The kinetic work of Verhoek and his colleagues (2; 22; 42; 84; 86) and of Johnson and Moelwyn-Hughes (50) has proved that trifluoro-, trichloro- and tribromo-acetic acids decompose as the anions:

$$X_3C\text{-}CO_2^- \longrightarrow X_3C^- + CO_2$$

Some other acids capable of yielding fairly stable carbanions also have been found to decarboxylate by first-order reactions of their anions, e.g, phenylpropiolic acid (34), and 2,4,6-trinitrobenzoic acid (84; 85). 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. It is perhaps surprising to note the stability of the 2,4,6-trinitrophenyl anion (IX), evidenced by the relative ease of decomposition of the related carboxylate anion (VIII), but this is further supported by the observation of deuterium exchange of trinitrobenzene in alkaline ethanol solution (53).



VIII IX

For several β-keto acids, it has been demonstrated that the decarboxylation involves both the anion and the zwitterion forms of the acids. The relative rates of decomposition of anions and of the undissociated acids for several β-keto acids have been measured and are summarized in Table I.

TABLE I

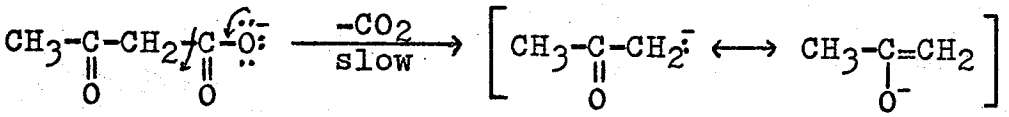
RELATIVE RATES OF DECOMPOSITION OF β-KETO ACIDS AND THEIR ANIONS IN WATER

Acid	Relative k		Temp., °C	Ref.
	Acid	Anion		
Acetoacetic	53	1	37	90
α,α-Dimethylacetoacetic	180	1	18	71
Camphor-3-carboxylic	34	1	98	9
Dihydroxymaleic	1	40	20	37
Acetonedicarboxylic	1	2.5	50	37
Malonic	10	1	90	43

The kinetic equation for the decarboxylation of acetoacetic acid in aqueous solution has the form (90):

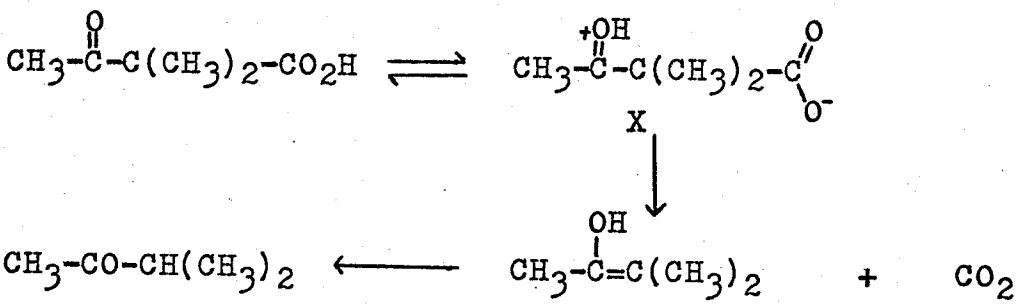
$$\text{rate} = k\left[CH_3COCH_2CO_2H\right] + k'\left[CH_3COCH_2CO_2^-\right]$$

That part of the reaction due to the acetoacetate anion was believed to proceed by the carbanion mechanism (90):

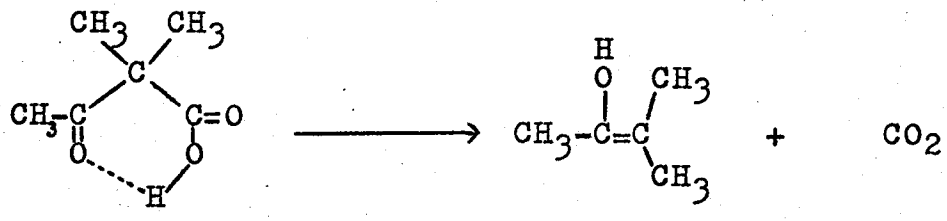


$$\xrightarrow[\text{fast}]{+\ H_2O} (CH_3)_2C{=}O \quad + \quad OH^-$$

In a study of the reaction as a whole, Pedersen used α,α-dimethylacetoacetic acid to avoid the type of keto-enol tautomerism that could complicate the study of acetoacetic acid itself (71). Since α,α-dimethylacetoacetic acid, which cannot exist in an enolic form, is readily decarboxylated, Pedersen (72) concluded that it is the zwitterion form of this acid (X) that decarboxylates:

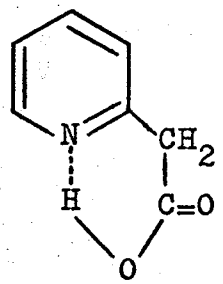


Westheimer and Jones (89) found that the rate of decarboxylation of α,α-dimethylacetoacetic acid is virtually independent of the dielectric constant of the solvent. Since a reaction which takes place by way of a polar intermediate should proceed more rapidly in solvents of high dielectric constant, they therefore concluded that Pedersen's zwitterion (X) cannot be an intermediate. Instead, these authors suggest that it is the hydrogen-bonded form of the acid (XI) which is decarboxylated.



XI

These two views must be almost identical, since the zwitterion (X) is very likely a contributor to the hydrogen-bonded structure (XI), because the nuclear configurations involved are identical. Similarly, the decarboxylation of 2-pyridylacetic acid may occur through a hydrogen-bonded form (XII). However, this idea cannot be extended to 4-pyridylacetic acid (25).



XII

C. BIMOLECULAR MECHANISM

It is only within the last twenty years that decarboxylation by a bimolecular mechanism (S_E2) has been firmly established. Schenkel and Schenkel-Rudin (76) first suggested in 1948 that some organic acids are decarboxylated by a bimolecular electrophilic substitution mechanism:

$$H^+ + RCO_2H \xrightarrow{k_1} HR + CO_2 + H^+ \quad \cdots\cdots S_E2(a)$$

in which the rate is determined by the attraction of a proton by the carboxylic acid. The kinetics are then governed by the equation:

$$\text{rate} = k_1[H^+][RCO_2H]$$

Two possibilities arise. The proton may attack the undissociated acid molecule yielding a kinetic equation of the type shown above. On the other hand, the reaction could take place between a proton and the acid anion:

$$H^+ + RCO_2^- \xrightarrow{k_2} HR + CO_2 \quad \cdots\cdots\cdots S_E2\ (b)$$

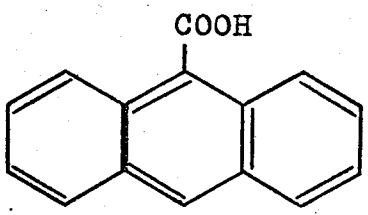
when the kinetic equation would be:

$$\text{rate} = k_2[H^+][RCO_2^-]$$

For either mechanism, the rate is dependent on the attraction between a proton and the carbon atom alpha to the carboxyl group. Reaction generally occurs at an unsaturated carbon atom, thereby allowing the new carbon-hydrogen bond to form completely in the rate-determining step without the necessity for a simultaneous breakage of the carbon-carbon bond. C-H bond formation is also expected to be favoured by electron-donating substituents and aromatic rings bearing such groups bonded to the beta-carbon of the carboxylic acid. A more common and favourable situation would be to have the alpha-carbon itself part of the aromatic ring system. Molecular structures of this type would be expected to disperse the positive charge of the carbonium ion intermediate and presumably the transition state leading to it.

Since the formation of the anion will increase the electron density on the alpha-carbon atom, it may be expected that the second mechanism ($S_E2(b)$) will require less activation energy than the first ($S_E2(a)$). However, it is possible that both mechanisms will occur, singly or simultaneously, and an analysis has to be made for each type of acid studied.

An example of an acid which is decarboxylated by the S_E2 mechanism was found by examining the case in which the anthracene-9-carboxylic acid (XIII) decomposed



XIII

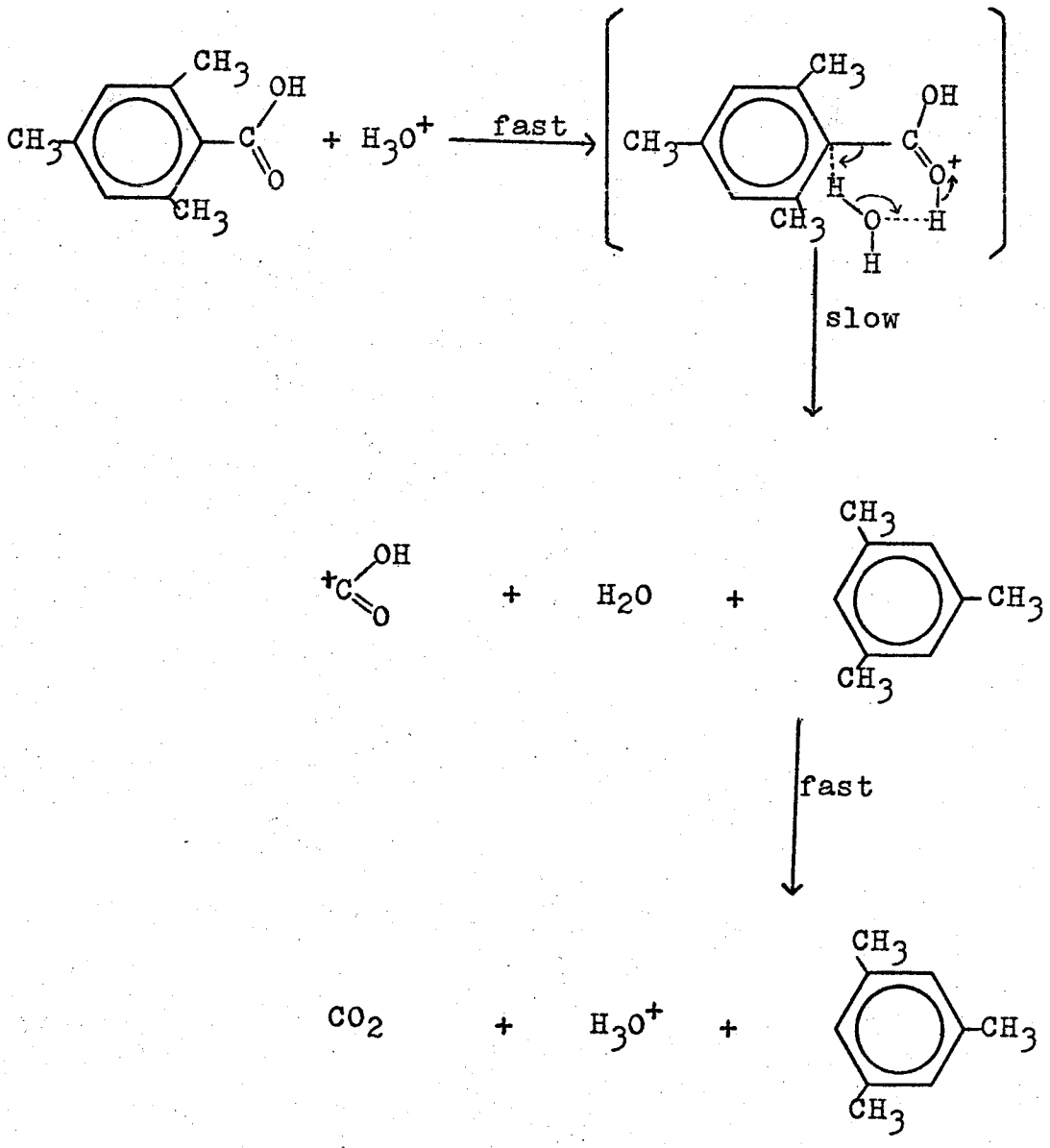
more rapidly in acidic solvents (chloroacetic and sulfuric acid) than in basic (7,8-benzoquinoline) or neutral solvents (75). Anthracene-9-carboxylic acid possessed certain structural features that could accommodate a bimolecular decomposition. The alpha-carbon, being in the 9-position, is more reactive to electrophiles because of its relatively high electron density. Furthermore, the carboxyl group in this position is sterically compressed by the peri-hydrogen atoms (67).

Other evidence for a bimolecular mode of attack in decarboxylation was put forward by Schubert and his co-workers (77; 78) in their study of mesitoic acid in strong sulfuric acid solutions. In their work, they found 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, and therefore proposed that the decarboxylation occurred by a specific hydroxonium catalysis having the rate equation in the form:

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

Hence, the reaction was suggested to occur by a S_E2 mechanism of the following type:



Bothner-By and Bigeleisen (8) 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. (82) 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:

Temperature (°C)	Isotope	$100(k/k^* - 1)$ in %	Ref.
60 ± 0.5	C^{13}	3.8 ± 0.1	82
61.2 ± 0.5	C^{13}	3.7 ± 0.3	8
92.0 ± 0.1	C^{13}	3.2 ± 0.1	8
60.0 ± 0.5	C^{14}	10.1 ± 0.5	82

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

D. AROMATIC AMINO ACIDS IN AQUEOUS SOLUTION

Benzoic and most monosubstituted aromatic acids are very stable in aqueous solution. Decarboxylation occurs at measurable rates only when there are present either several nitro groups or, conversely, groups with especially high electron-donating power. Thus, for example, o- and p-aminobenzoic acids (64) are slowly decomposed in aqueous acid solution at 70°C. The hydroxybenzoic acids are more stable; their decarboxylation is only observed below the boiling point of water when, along with the o- or p-hydroxy group, a further electron-donating group is present.

A number of aromatic amino acids have been observed to undergo decarboxylation in aqueous solution under relatively mild conditions.

$$NH_2ArCOOH \longrightarrow ArNH_2 + CO_2$$

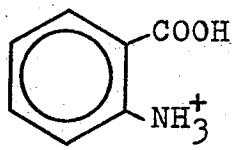
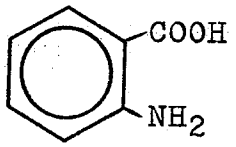
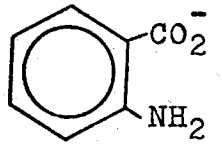
The earliest studies were those of McMaster and Shriner (64) who studied the stability of the three monoaminobenzoic acids in boiling aqueous solution. The extent of reaction was determined by titrating the undecomposed amino acid with alkali. Anthranilic acid was found to decarboxylate

by a first-order process twice as fast as p-aminobenzoic (these authors attributing this to the proximity of the ortho-amino group), while m-aminobenzoic acid had not decarboxylated after three hours under similar conditions. Since the work of McMaster and Shriner, mechanistic investigations of decarboxylation of aromatic amino acids in aqueous solution have been concentrated upon anthranilic (82), p-aminobenzoic (95) and p-aminosalicylic acids (61; 74; 92).

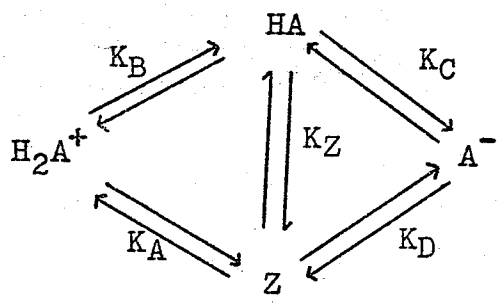
Kinetic studies of amino acids in aqueous solution are complicated by the fact that they may be present as neutral molecule, zwitterion, cation or anion. Any one or more of these organic species may decarboxylate. Although the ratio of neutral molecule to zwitterion is independent of pH, the proportions of the other species present in solution vary with the acidity of the solution. Consequently, the rates of decarboxylation of amino acids in aqueous solution may vary with the acidity of the solution, and the manner in which they vary may be expected to yield information about the nature of the organic species undergoing decarboxylation.

Bjerrum (6) has proposed that in aqueous solution

of an amino acid, four organic species are in equilibrium with each other, and they are present in a proportion depending on the hydrogen ion concentration. Taking anthranilic acid as an example, these species, referred to as Bjerrum species, may be represented by the following symbols:

Organic species	Abbreviation	
	H_2A^+	Cation
	HA	Neutral species
	Z	Zwitterion
	A^-	Anion

The equilibria are shown below with the hydronium ions omitted.



It is also expedient to let [N] refer to the total concentration of ampholyte, i.e.

$$[N] = [HA] + [Z]$$

where the concentrations (or, at high ionic strength, the activities) of HA and Z are represented by [HA] and [Z]. Since the ratio $[Z]/[HA] = K_Z$ varies with ionic strength, but not with pH, for most purposes the ampholyte may be treated as a single species.

The equilibrium constants which relate the four organic species are difficult to evaluate (60), but they can be related to the measurable ionization constants, K_1 and K_2, of the equilibria:

$$H_2A^+ \xrightleftharpoons{K_1} H^+ + N$$

$$N \xrightleftharpoons{K_2} H^+ + A^-$$

and $$K_1 = \frac{[H^+][N]}{[H_2A^+]} = \frac{[H^+]([HA] + [Z])}{[H_2A^+]}$$

$$K_2 = \frac{[H^+][A^-]}{[N]} = \frac{[H^+][A^-]}{([HA] + [Z])}$$

The equilibrium constants K_A , K_B , K_C , and K_D can also be expressed in terms of the four organic species as:

$$K_A = \frac{[HA][H^+]}{[H_2A^+]} \qquad \text{or} \quad [HA] = \frac{K_A[H_2A^+]}{[H^+]}$$

$$K_B = \frac{[Z][H^+]}{[H_2A^+]} \qquad \text{or} \quad [Z] = \frac{K_B[H_2A^+]}{[H^+]}$$

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

$$K_D = \frac{[A^-][H^+]}{[Z]}$$

and $$K_Z = \frac{[Z]}{[HA]} = \frac{K_B}{K_A} = \frac{K_C}{K_D}$$

$$K_AK_C = K_BK_D$$

Substitution for $[HA]$ and $[Z]$ leads to the relationships:

$$K_1 = K_A + K_B$$

$$\frac{1}{K_2} = \frac{1}{K_C} + \frac{1}{K_D}$$

When the total concentration of amino acid is $[C]$, i.e.,

$$[C] = [H_2A^+] + [HA] + [Z] + [A^-]$$

then, from the above relationships, the concentrations of the individual Bjerrum species are given by the equations:

$$[H_2A^+] = \frac{[C]}{K_1K_2/[H^+]^2 + K_1/[H^+] + 1}$$

$$[N] = \frac{[C]}{[H^+]/K_1 + 1 + K_2/[H^+]}$$

$$[A^-] = \frac{[C]}{[H^+]^2/K_1K_2 + [H^+]/K_2 + 1}$$

In a solution of concentration $[C]$ with respect to total amino acid, $[H_2A^+]$ and $[A^-]$ approach $[C]$ at low and high pH respectively, and $[N]$ reaches a maximum when $[H^+]$ lies between K_1 and K_2. By setting $d[N]/d[H^+] = 0$, it is found that $[N]$ reaches a maximum when $[H^+] = \sqrt{K_1K_2}$; that is, at the isoelectric point, where $pH = 1/2 (pK_1 + pK_2)$. Since $[Z]$ and $[HA]$ are both proportional to $[N]$, and the proportionality is independent of pH, it follows that both $[HA]$ and $[Z]$ will also have their maximum values at the isoelectric point.

In principle, any of the four forms of amino acids can decarboxylate, and the rate of decarboxylation should be greatest at the pH where the concentration of that form is greatest. The same will be true, of course, for any other

(non-Bjerrum) species in equilibrium with one of the Bjerrum species, or with one of these and water, so long as the equilibrium does not involve gain or loss of protons.

The aromatic amino acid for which the effect of pH upon rate of decarboxylation in aqueous solution has been most thoroughly examined is p-aminosalicylic acid. Willi and Stocker (92) found that the overall rate of disappearance of acid was first order with respect to total acid in solution, and the pseudo first order rate constant was a function of the pH of the solution. Rate of decarboxylation was observed to reach a maximum at the isoelectric point, and it was concluded that the rate-controlling step involves the protonation of p-aminosalicylate anion, A^-, at the 1-position of the aromatic ring. However, it was also found that, although the rate decreases as the pH is decreased below the isoelectric point, it does not decrease as fast as does the calculated value of $[H^+][A^-]$. Therefore, the zwitterion may also be subject to decarboxylation by proton attack at the 1-carbon, so that the overall rate expression becomes

$$-\frac{d[C]}{dt} = k'[H^+][A^-] + k''[H^+][N] \qquad .....(1)$$

with k' larger than k'' by a factor of about 10.

Slightly different conclusions were drawn by Rekker and Nauta (74), who investigated the UV absorption spectra of p-aminosalicylic acid and related compounds and their rates of decarboxylation. They found that the protonated species did not decompose, but that the rate at various hydrogen ion concentrations was proportional to the amount of free acid or zwitterion present, as calculated from the known dissociation constants of the acid (94). In agreement with Willi's findings (92), they also observed a maximum in the rate of decarboxylation of p-aminosalicylic acid in aqueous solution at the isoelectric point, but did not find any decarboxylation in strong acid where Willi's kinetic expression shows it should be appreciable. The reaction was concluded to be a first-order decarboxylation of the zwitterion.

The decarboxylation of p-aminosalicylic acid in aqueous solution was also investigated by Liquori and Ripamonte (61). They too, observed the rate-maximum at the isoelectric point at 25°C, but concluded that the rate-controlling step is a first-order decomposition of the molecular acid HA.

In order to determine whether a slow proton transfer or a rupture of a carbon-carbon bond was involved in the

rate-determining step, Stevens and co-workers (82) looked for an isotope effect in the decarboxylation of anthranilic acid both in melt and in aqueous solution with varying pH. None was found in either case. A relatively broad maximum in the rate was observed in 0.75N sulfuric acid (without using buffered solutions or constant ionic strength) at the temperature of boiling water. Unfortunately, no pH measurements were made, and the effect of acidity on the ionization equilibria was considered only qualitatively. However, they concluded that the rate controlling step is protonation of the zwitterion at the 1-carbon.

The pH dependence of rate of decarboxylation using p-aminobenzoic acid was carefully investigated by Willi (95). He found that the rate of decarboxylation increases with increasing hydrogen-ion concentration, but does not reach a maximum at the isoelectric point (pH = 3) nor even at pH = 1.7, the highest acidity studied. He showed that, as with p-aminosalicylic acid, his data can be accommodated by equation (1) with $k'' = 25k'$.

Dunn, Leggate and Scheffler (27) studied the effect of changing pH upon the rate and mechanism of decarboxylation of 4-methyl- and 4-methoxyanthranilic acids. The decar-

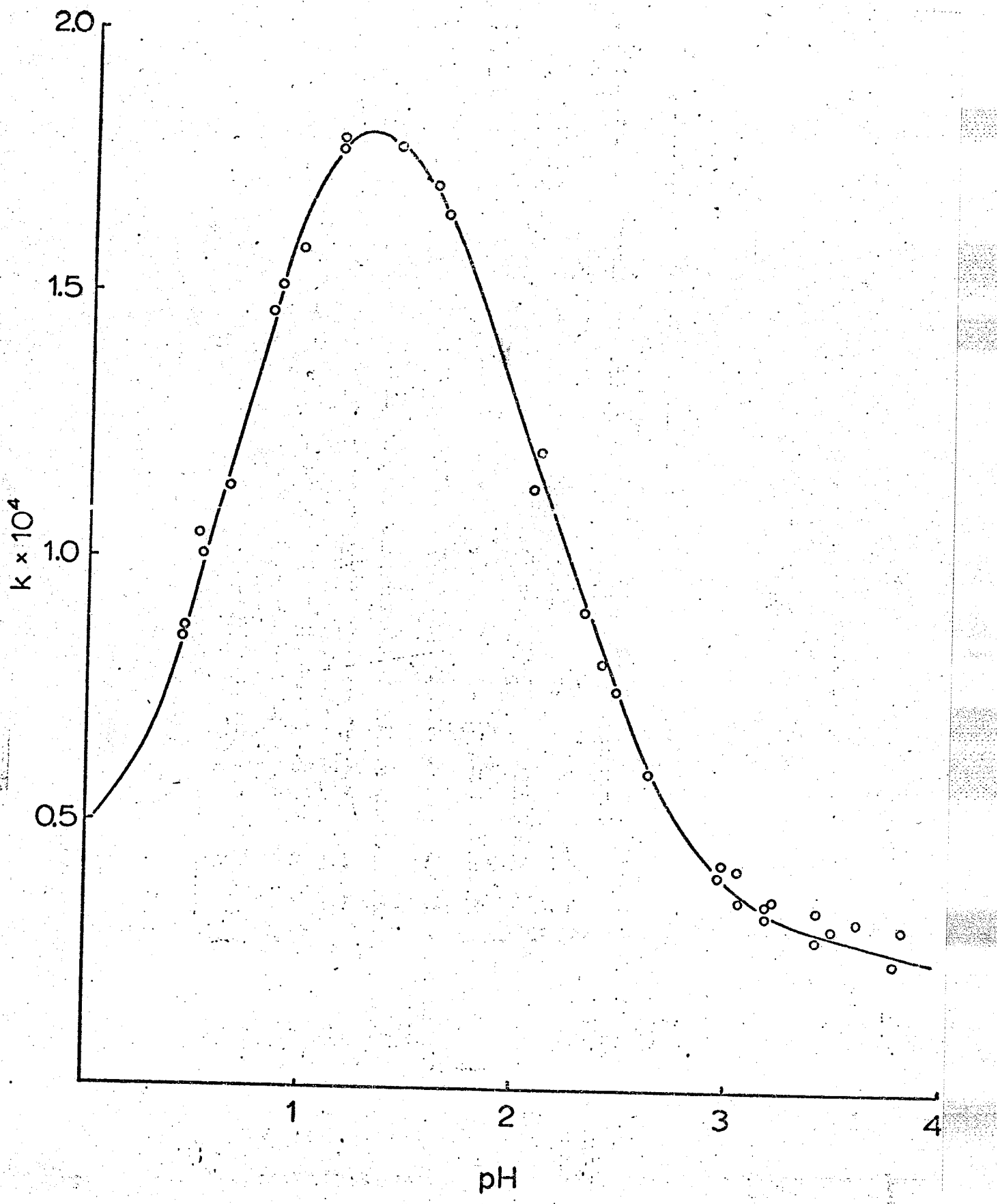
boxylation was followed by noting the change in concentration of substituted anthranilic acid with time spectrophotometrically by measurements made in alkaline solution where all the acid was in anionic form. Although the effect of acidity upon the rate of decomposition of anthranilic acid in aqueous solution had been investigated earlier by Stevens and co-workers (82), no buffered or constant ionic strength solutions were used. It was on rather qualitative evidence that they concluded that the rate-determining step was protonation of the zwitterion at carbon 1.

Dunn and co-workers (27) found that both 4-methoxy- and 4-methylanthranilic acids decarboxylated by a first-order process at a constant pH. They showed that the rate is a maximum at a pH of about 1.1 - 1.4, whereas the isoelectric pH was found to be 3.3, and decreases at both higher and lower pH values. The observed dependence of the rate constant, k, upon pH obtained by these authors is shown graphically in Figure 1. Since the pH dependence of the rate constant could not by accounted for by reaction of any combination of Bjerrum species, it was concluded that decarboxylation must take place via some intermediate which is not part of the Bjerrum system.

Dunn et. al. (27) have proposed a mechanism for

FIGURE 1

The observed pH dependence of the rate constant for the decarboxylation of 4-methoxyanthranilic acid at 60°C and ionic strength of 0.5 .


2.0
1.5
1.0
0.5
k x 10⁴
1
2
3
4
pH

the reaction in which the non-Bjerrum intermediates H_2A^*, HA^*, and HZ^* are formed by protonation of the α-carbon of HA, A^- and Z respectively. This mechanism is shown in Equation (2).

Assuming that all three non-Bjerrum intermediates decarboxylate, the following expression was derived (27) for the rate of decarboxylation:

$$\frac{-d[C]}{dt} = [N]\left\{k_A K_2 + \left(k_{HA}K_B/K_1 + k_Z K_A/K_1\right)[H^+]\right\} \times \frac{k^* + \left(k^+/K_C^* + k^{\ddagger}/K_D^*\right)[H^+]}{k^* + k_{-A} + \left\{(k^+ + k_{-HA})/K_C^* + (k^{\ddagger} + k_{-Z})/K_D^*\right\}[H^+]} \quad \ldots\ldots(3)$$

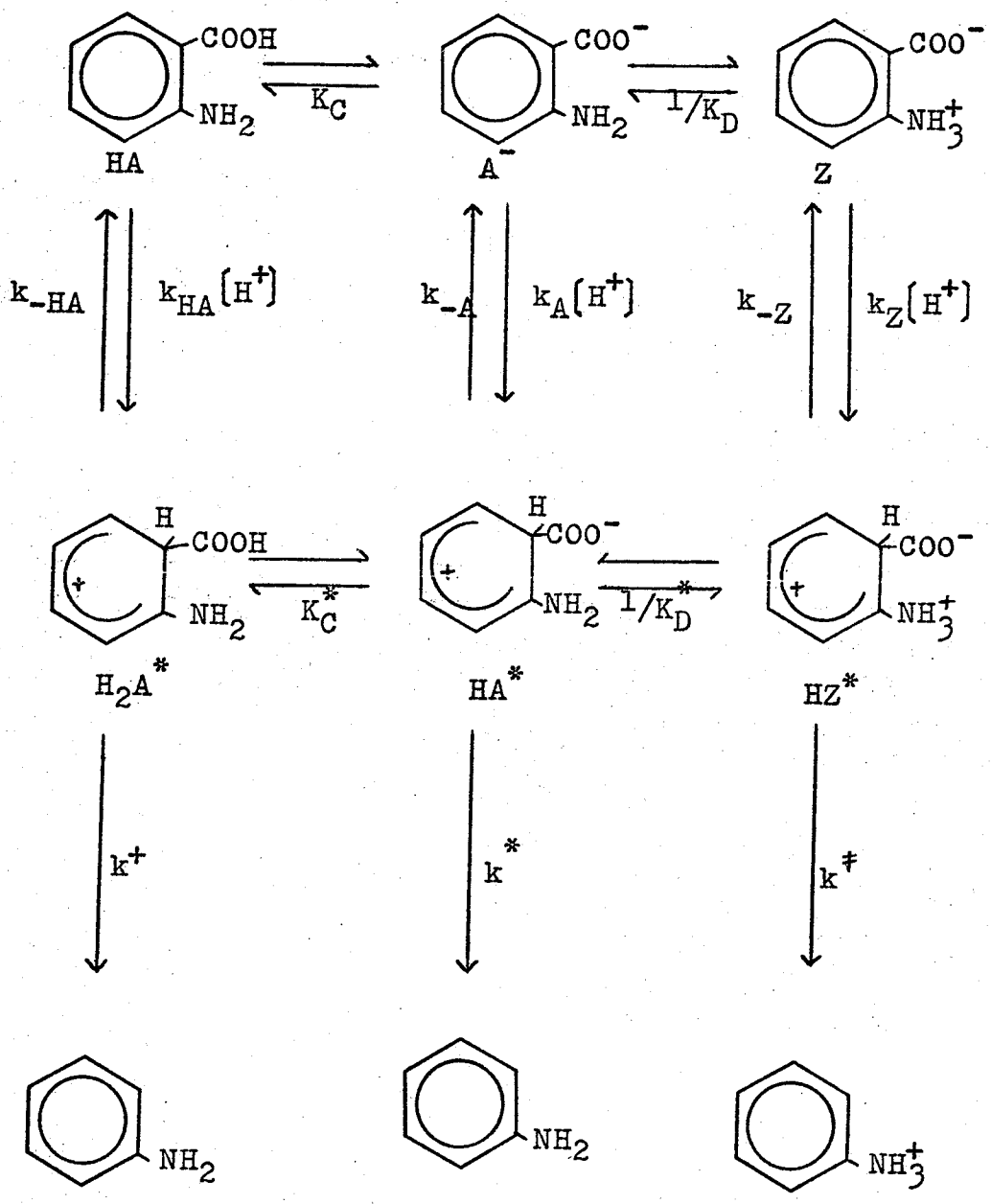
where $[N] = [HA] + [Z]$

and K_1 and K_2 are defined as

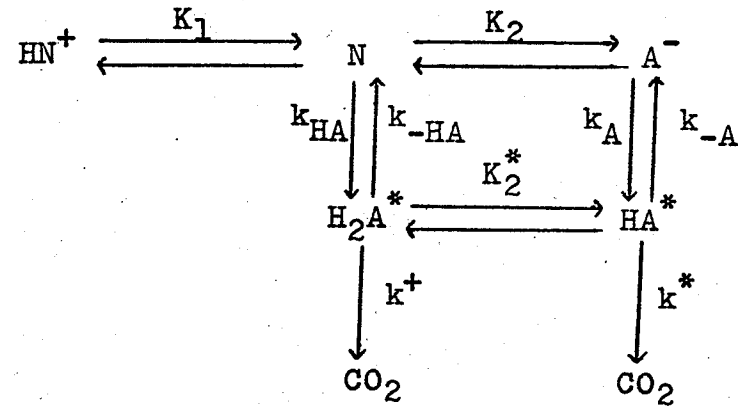
$$H_2A^+ \underset{\longleftarrow}{\xrightarrow{K_1}} H^+ + N \quad \ldots\ldots(4)$$

$$N \underset{\longleftarrow}{\xrightarrow{K_2}} H^+ + A^- \quad \ldots\ldots(5)$$

Since the ratio $[HA]/[Z]$ is independent of pH, HA and Z may be combined under the single symbol N. Equation (2) may then be simplified to


COOH
NH2
HA
K_C
COO⁻
NH2
A⁻
1/K_D
COO⁻
NH3⁺
Z
k_-HA
k_HA[H⁺]
k_-A
k_A[H⁺]
k_-Z
k_Z[H⁺]
H
COOH
NH2
H2A*
K_C*
H
COO⁻
NH2
HA*
1/K_D*
H
COO⁻
NH3⁺
HZ*
k⁺
k*
k≠
NH2
NH2
NH3⁺

.....(2)



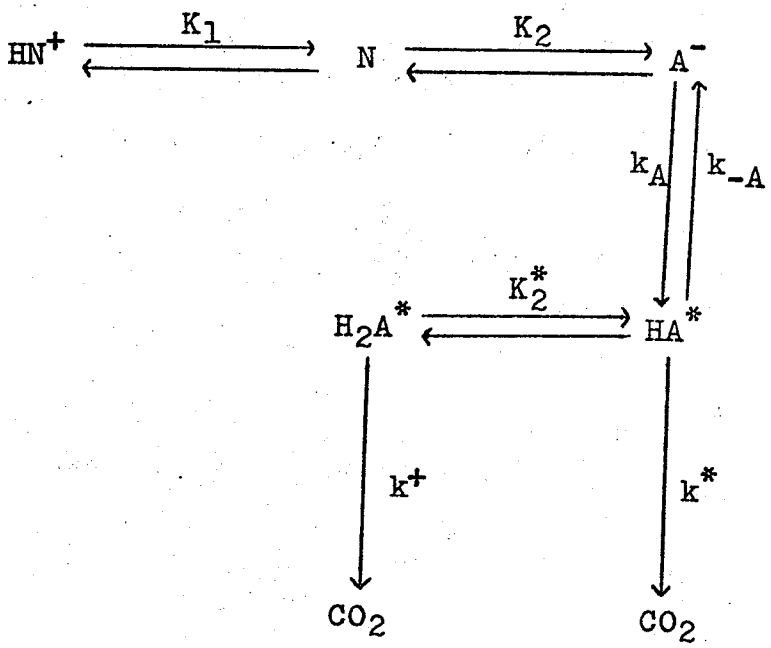
.....(6)

The rate expression then simplifies to:

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

.....(7)

As it stands, equation (7) does not fit the data, because the $[H^+]^2$ terms of the numerator prevent the rate from becoming small at low pH. For the rate to decrease at low pH, it will require either that $k_{HA} = 0$ or that $k^+ = 0$, but not both. That is, in order for equation (2) to represent the mechanism, H_2A^* must participate, but either it is not formed directly by protonation of HA and Z ($k_{HA} = 0$), or it does not decarboxylate ($k^+ = 0$). In the former case, the mechanism becomes:

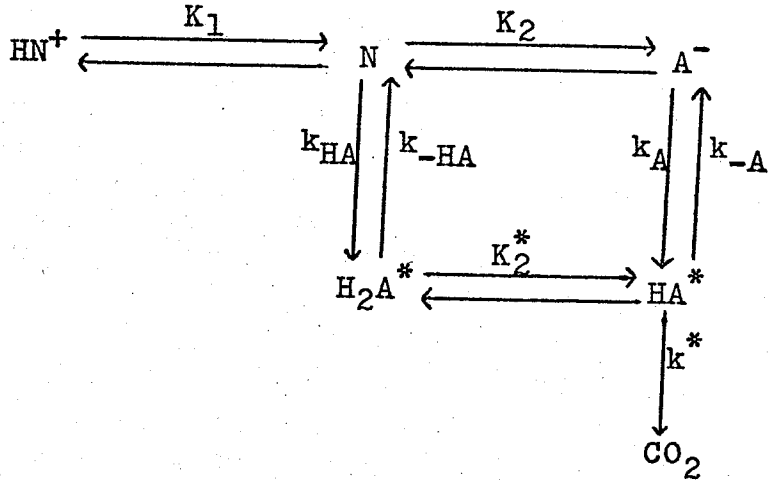


and

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

.....(8)

and in the latter case:



and

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

.....(9)

Dunn et. al. concluded that mechanism (8) requires a kinetic isotope effect at both low and high pH values, whereas mechanism (9) requires an isotope effect at low pH but can accommodate an effect or none at high pH.

Dunn and Buccini (29) solved the problem by measuring the carboxyl-C^{13}-kinetic isotope effect for 4-methoxyanthranilic acid at 60°C in aqueous solutions of different pH and constant ionic strength. The kinetic isotope effects are summarized below:

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

Thus, a large effect of 4.2% was found at low pH, and no isotope effect was found at high pH. Therefore, the reaction proceeds via mechanism (9), in which both of HA and Z may be protonated to form H_2A^* and HZ^*, but neither H_2A^* nor HZ^* decarboxylate directly.

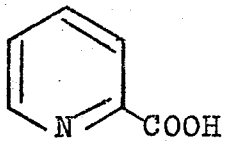
Since there is no C^{13}-carboxyl kinetic isotope effect at low acidity, so k_{-A} is small compared to k^*, and because there is such an isotope effect at high acidity, k^+ is small compared to k_{-HA}. Hence, equation (9) can be reduced to:

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H^+]}{K_1 + [H^+]} \times \frac{k^* K_2^*}{k^* K_2^* + k_{-HA} [H^+]} \qquad \text{.....(10)}$$

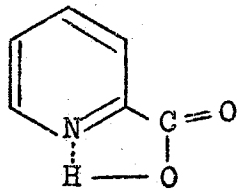
E. PYRIDINE-CARBOXYLIC ACIDS

The ready decarboxylation of pyridine-carboxylic acids was early appreciated. Historically, the reaction played an important role in the studies of orientation of quinoline, isoquinoline, and the benzoquinolines (58). Decarboxylation occurs more readily than with benzene-carboxylic acids, and in the sequence $2 \gg 4 > 3$. The decarboxylation temperatures of solid pyridine-dicarboxylic acids depend roughly on their strengths as acids - the stronger the acid, the lower the temperature (48). At 185°-190°C, pyridine-2,3,4 -tricarboxylic acid gives pyridine-3,4-dicarboxylic acid, which above its m.p. produces mainly nicotinic with some isonicotinic acid (47). The easier removal of an α- than of a β-carboxyl group has important practical consequences, for the oxidation of quinoline at 150°- 190°C with sulphuric and nitric acid and a catalyst gives quinolinic acid, but at temperature higher than 210°C nicotinic acid results (97). For the same reason, "aldehyde collidine" (5-ethyl-2-methylpyridine) is also a valuable source of nicotinic acid (51).

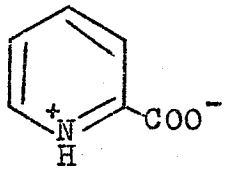
Three reactive forms which could possibly be the initial reactants in the decarboxylation of picolinic acid were postulated in the literature. They are the un-ionized acid (XIV), the chelated form (XV) and the zwitterion form (XVI).



XIV



XV

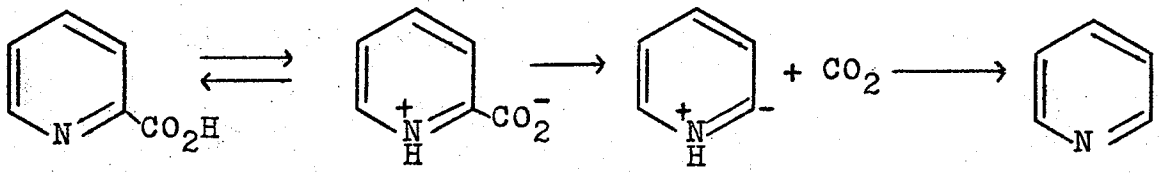


XVI

Reactive form (XIV) was not considered as a possibility (65;70;85) for it has been fairly well established in the literature on decarboxylation of other acids that the initial reactant is an anionic or intramolecularly hydrogen bonded structure rather than the free acid except in the case of the dibasic acids oxalic and malonic (4). Both forms (XV) and (XVI) increase the positive potential of the ring nitrogen and reduce the electron density on the α-carbon which could then exert an attraction on the carbon to carboxyl pair of electrons, drawing them toward the ring and favouring release of carbon dioxide.

The form (XV) was suggested in the work of Doering and Pasternak on α- pyridylacetic acids (25). Similar cyclic intermediates have been proposed by Wiig (91) and Muus (66) in their work on β- keto acids. Hammick (44), on the basis of his work with quinaldinic acid in quinoline, suggested that the heterocyclic α- amino acids, picolinic, quinaldinic, and isoquinaldinic acids, probably decarboxylate in the form of their zwitterions (from XVI).

The decarboxylation of picolinic acid with the carboxylate group α to a quaternary ammonium function was suggested by Brown (14) to proceed at an accelerated rate presumably attributed to inductive stabilization of the carbanion in the form of an ylid intermediate (XVII):



XVII

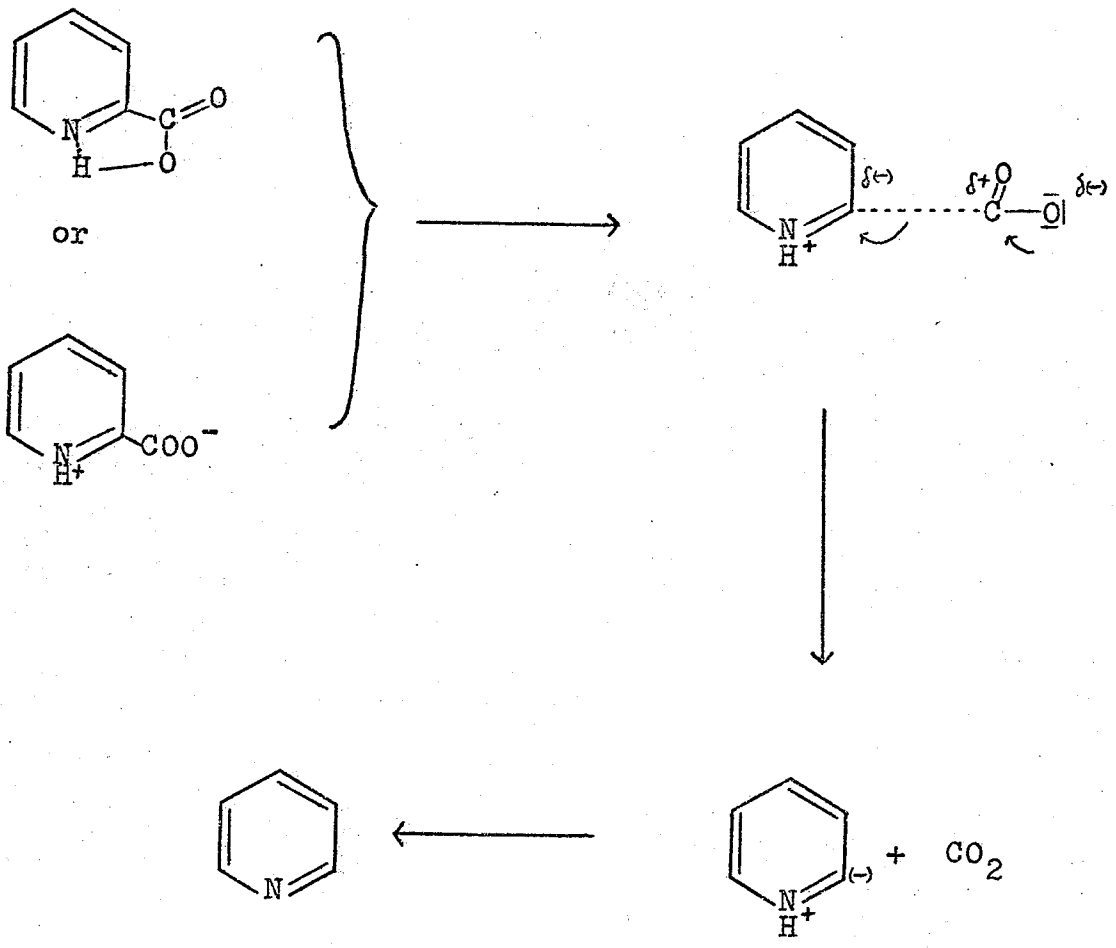
In an attempt to decide between the hydrogen-bonded structure (XV) or the zwitterionic structure (XVI) for picolinic acid as the species undergoing decarboxylation, the uncatalyzed reaction rates of picolinic acid and some of its methyl derivatives were determined by Cantwell and Brown (15). Kinetic data for the decarboxylation of picolinic and methylpicolinic acids in p-dimethoxybenzene are shown in Table II.

On the basis of the data obtained, they could not decide whether form (XV), the cyclic form, or form (XVI), the zwitterion form, is the predominant initial reactant since both can take part in the mechanism proposed by these authors:

TABLE II

DECARBOXYLATION OF PICOLINIC ACIDS IN P-DIMETHOXYBENZENE (15)

Substituent	E, kcalmole^{-1}	$\log_{10}A$	k, sec^{-1} x 10^4(°C)
-	31.1	15.63	2.155 (171.5)
3-Me	32.1	16.66	8.471 (171.2)
4-Me	34.6	17.35	1.858 (169.6)
5-Me	40.0	20.66	1.510 (175.4)
6-Me	35.0	17.41	1.439 (170.0)
$4,6\text{-Me}_2$	38.7	19.27	1.547 (171.0)



Methyl substitution of the pyridine ring has a pronounced effect on the rate as well as the activation energy of decarboxylation. However, from these studies, no definite conclusion could be reached as to the nature of the initial reactant in the decarboxylation process.

In Cantwell and Browns' subsequent studies on the decarboxylation mechanism of picolinic acid (16), the rates of decarboxylation of this acid were determined in acidic,

basic and polar neutral solvents. The observed rates were found to be first order in all cases, and in the order of neutral solvent > basic solvent > acidic solvent. The rate constants in neutral, acidic and basic solvents are quoted from the work of Cantwell and Brown (16), and are shown in Table III.

The data obtained indicated that the rate of decarboxylation of picolinic acid is lowered and the activation energy raised by both acidic and basic solvents. Neutral polar solvents also have a pronounced but varied effect. The suppression of the rate by acidic solvents was believed to be caused by competition between the acidic hydrogen of picolinic acid and the acidic hydrogen of the solvent (phenol, AOH) for the nitrogen of the pyridine ring.

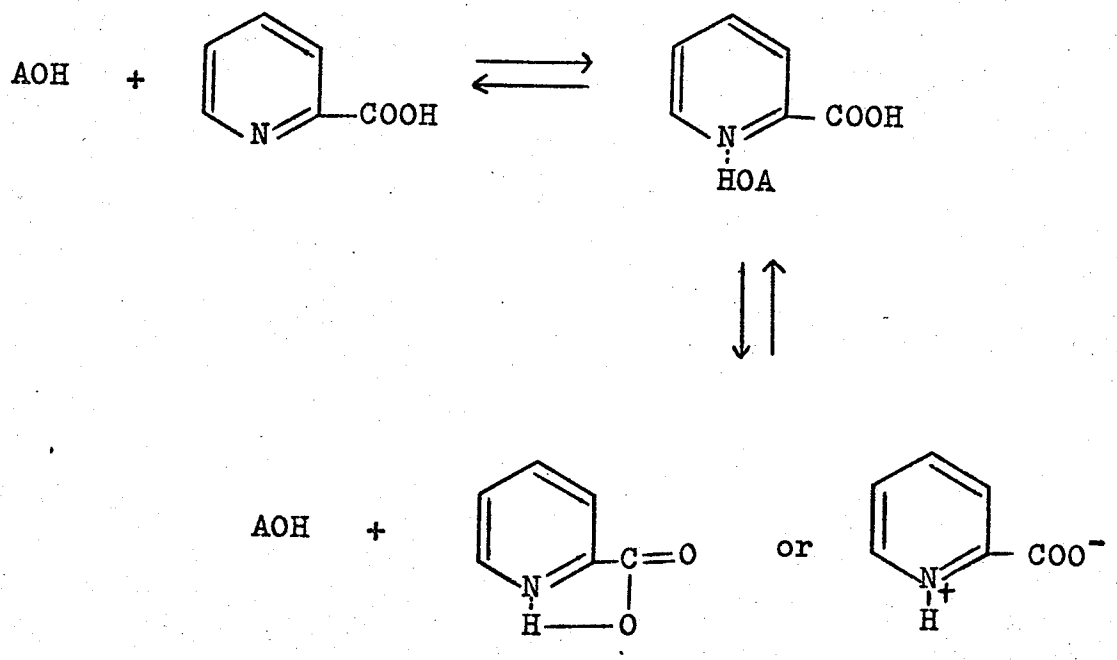


TABLE III

FIRST-ORDER RATE CONSTANTS FOR THE DECARBOXYLATION OF PICOLINIC ACID IN NEUTRAL, ACIDIC AND BASIC SOLVENTS (16)

NEUTRAL SOLVENTS

Temp., °C.	$k \times 10^4$, sec.
p-Dimethoxybenzene	
171.5	2.16
179.0	3.94
184.5	5.87
190.5	9.18
p-Bromoanisole	
174.2	2.60
178.8	3.91
183.0	5.39
Nitrobenzene	
169.0	1.75
174.6	3.06
179.0	4.71
183.0	5.82

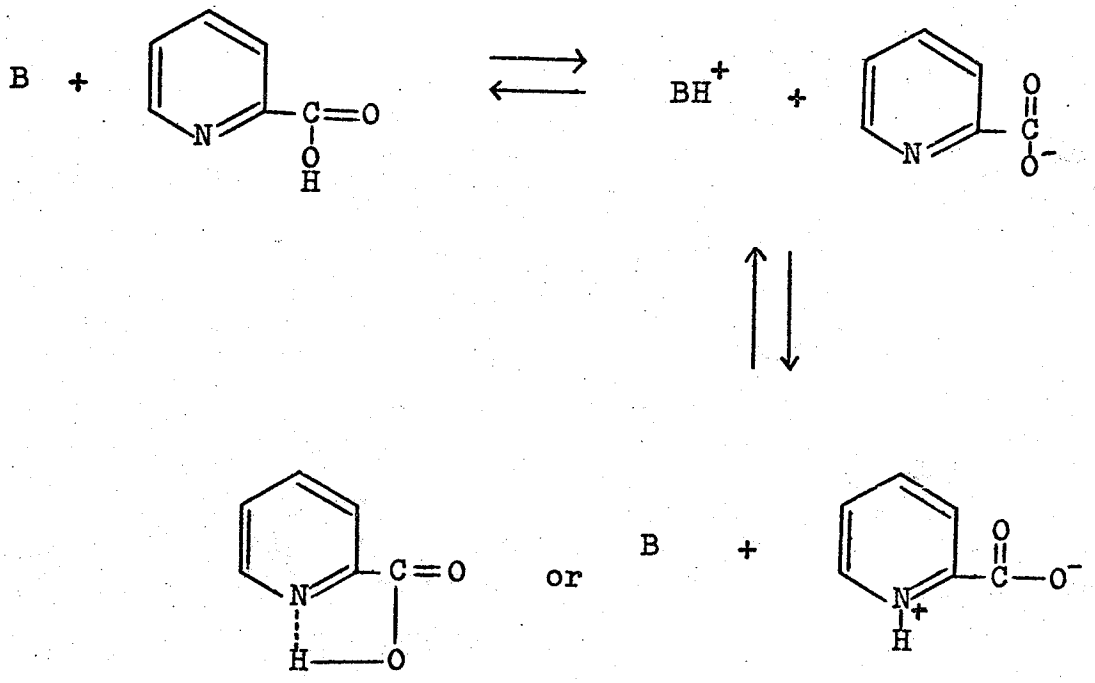
BASIC SOLVENTS

Temp., °C.	$k \times 10^4$, sec.
Aniline	
168.5	1.21
173.6	1.89
177.0	2.43
Quinoline	
169.2	1.04
173.5	1.67
178.5	2.56
Tributylamine	
168.5	0.92
173.5	1.79
179.0	3.17
182.5	4.87

ACIDIC SOLVENTS

Temp., °C.	$k \times 10^4$, sec.
Phenol	
170.0	0.60
174.0	1.03
p-Nitrophenol	
169.0	0.22
173.5	0.34
179.2	0.75
182.6	1.04

In the case of basic solvents (aniline, quinoline, tributylamine), a probable acid-base equilibrium between the acid in question and the base, B, to form the anion could have helped to reduce the reactivity.



From a consideration of the over-all observed effect of solvents on the activation energy of decarboxylation and an analysis of the effect of solvation on the potential energies of the two forms, the chelated form (XV) and the zwitterion form (XVI), Cantwell and Brown favored the zwitterion as the initial reacting form.

Clark added to the investigation by studying the decarboxylation of picolinic acid in the molten state and in p-cresol, aniline, phenetole, β-chlorophenetole, p-dimethoxybenzene and nitrobenzene (18). The first-order rate constants are quoted from his work and presented in Table IV. He, in this and subsequent studies in 12 more polar solvents (21), found that the rate was in the order of basic solvents > neutral solvents > acidic solvents, which is not in agreement with Cantwell and Browns' findings. He also found that the results in different solvents conformed very closely to a single isokinetic-temperature line in an enthalpy-entropy plot which was parallel to a similar line obtained previously for the decarboxylation of oxamic acid and its derivatives in the molten state and in a variety of solvents (20). On this evidence and on information presented earlier by Fraenkel et al. (36) that the decarboxylation of oxamic acid in quinoline involved the formation of an activated complex between unionized acid and the nucleophilic solvent, Clark, in a different view from Cantwell and Brown, favoured the hydrogen-bond form of picolinic acid (XV) over the zwitterion (XVI).

TABLE IV

FIRST-ORDER RATE CONSTANTS FOR THE DECARBOXYLATION OF MOLTEN PICOLINIC ACID, AND OF PICOLINIC ACID IN SEVERAL SOLVENTS (18)

System	Temp. (^{o}C)	$k \times 10^{4}$ (sec^{-1})	Av. dev.
Molten picolinic acid	167.47	1.28	0.02
	173.67	2.46	0.02
	180.61	3.73	0.02
	184.22	7.05	0.04
	188.35	10.57	0.04
Picolinic acid + p-dimethoxybenzene	170.56	1.64	0.02
	180.61	3.74	0.03
	191.20	8.71	0.02
Picolinic acid + β-chlorophenetole	172.46	1.75	0.03
	182.72	4.15	0.02
	192.89	11.13	0.04
Picolinic acid + phenetole	150.71	0.37	0.01
	159.60	0.665	0.005
	165.47	1.18	0.01
	168.2	1.53	0.04
Picolinic acid + nitrobenzene	172.36	1.73	0.01
	180.50	3.52	0.01
	189.61	6.69	0.03
Picolinic acid + aniline	160.37	1.20	0.02
	168.35	3.98	0.02
	178.90	3.98	0.02
Picolinic acid + p-cresol	170.45	1.19	0.02
	179.70	2.79	0.02
	189.61	6.69	0.03

However, it is the author's opinion that, in changing solvents Cantwell and Brown had changed solvent polarity as well as solvent acidity, and that the rate differences in different solvents were small enough to be caused by the polarity changes alone. Clark had added to the investigation by increasing the number of solvents studied, and in his results, differences in rates obtained in different solvents were even smaller. Therefore, it is felt that the effect of acidity on rates as reported by these authors is not too reliable.

Kinetic ^{14}carbon-isotope effects on decarboxylating picolinic acid in the fused state as well as in quinoline and phenols were studied by Zlotowski and Zielinski experimentally and compared to a theoretical model (98). The kinetic isotope effect is quoted from their work and presented in Table V.

These results show that the C-C bond is broken in or before the rate-determining step of the decarboxylation, which agrees with the ylid type of mechanism proposed by the workers previously quoted. It is interesting to note that the isotope effect is noticeably larger in acidic solvents than in basic ones. However, the authors did not comment on this point.

TABLE V

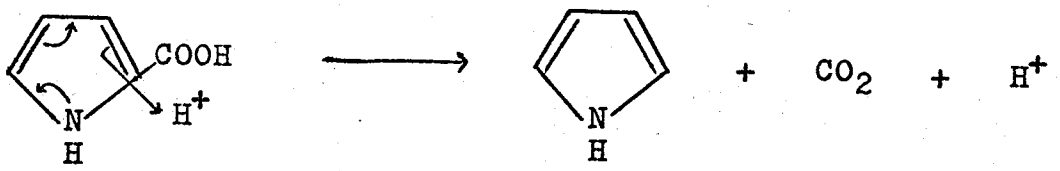
THE KINETIC ISOTOPE EFFECT IN THE DECARBOXYLATION OF PICOLINIC ACID AT 186°C (98)

Solvent	$\left[\left(k_{C^{12}}/k_{C^{14}} \right) - 1 \right]$ in %
Melt	4.6
Quinoline	4.7
o-Nitrophenol	5.0
Phenol	5.4
o-Methylphenol	5.4
Hydroquinone	5.6

F. PYRROLE-CARBOXYLIC ACIDS

The most striking properties of pyrrole-carboxylic acids having the carboxyl group directly attached to the nucleus is their ready decarboxylation. This occurs when the acids are heated under a variety of conditions; the ease varies with the character of other substituents present. Melting is usually accompanied by decarboxylation, and preparative procedures have used decarboxylation by heating at reduced pressure (40), by heating in glycerol, 2-aminoethanol and alkali, and distillation from weakly acid solution (17;35).

No quantitative data are available to permit an assessment of the effect of substituents or carboxyl group orientation upon ease of decarboxylation. It is believed that in the pyrrole series, the behaviour observed is similar to that of hydroxybenzoic acids having one or more hydroxyl groups ortho and para to the carboxyl group (13). In these cases of decarboxylation facilitated by electron-



releasing groups (13), it is likely that the mechanism involved is that denoted (14) S_E2; but whether the acid or its anion is involved is not known. Rough qualitative comparisons suggest that pyrrole-2- and -3-carboxylic acids are decarboxylated about as readily as the resorcylic acids (23; 24).

III. OBJECT OF THE PRESENT WORK

Since mechanisms proposed in the literature for the decarboxylations of pyridine- and pyrrole-carboxylic acids are based entirely on qualitative evidence, and arguments by analogy with the substituted benzoic acids, it was thought that it may be desirable to study these decarboxylations in aqueous solution. In this case, quantitative measurements of the effect of acidity on rates are possible.

The mechanism of the decarboxylation of pyrrole-carboxylic acids have not previously been examined. Pyrrole is generally thought to resemble aniline and phenol, so the decarboxylation might be expected to resemble that of anthranilic or salicylic acid. It was therefore an object of the present work to find out if the acid dependence of pyrrole-carboxylic acid decarboxylation resembles that of anthranilic or salicylic acid previously described.

IV. RESULTS AND DISCUSSIONS

A. PYRIDINE-CARBOXYLIC ACIDS

1. Picolinic acid

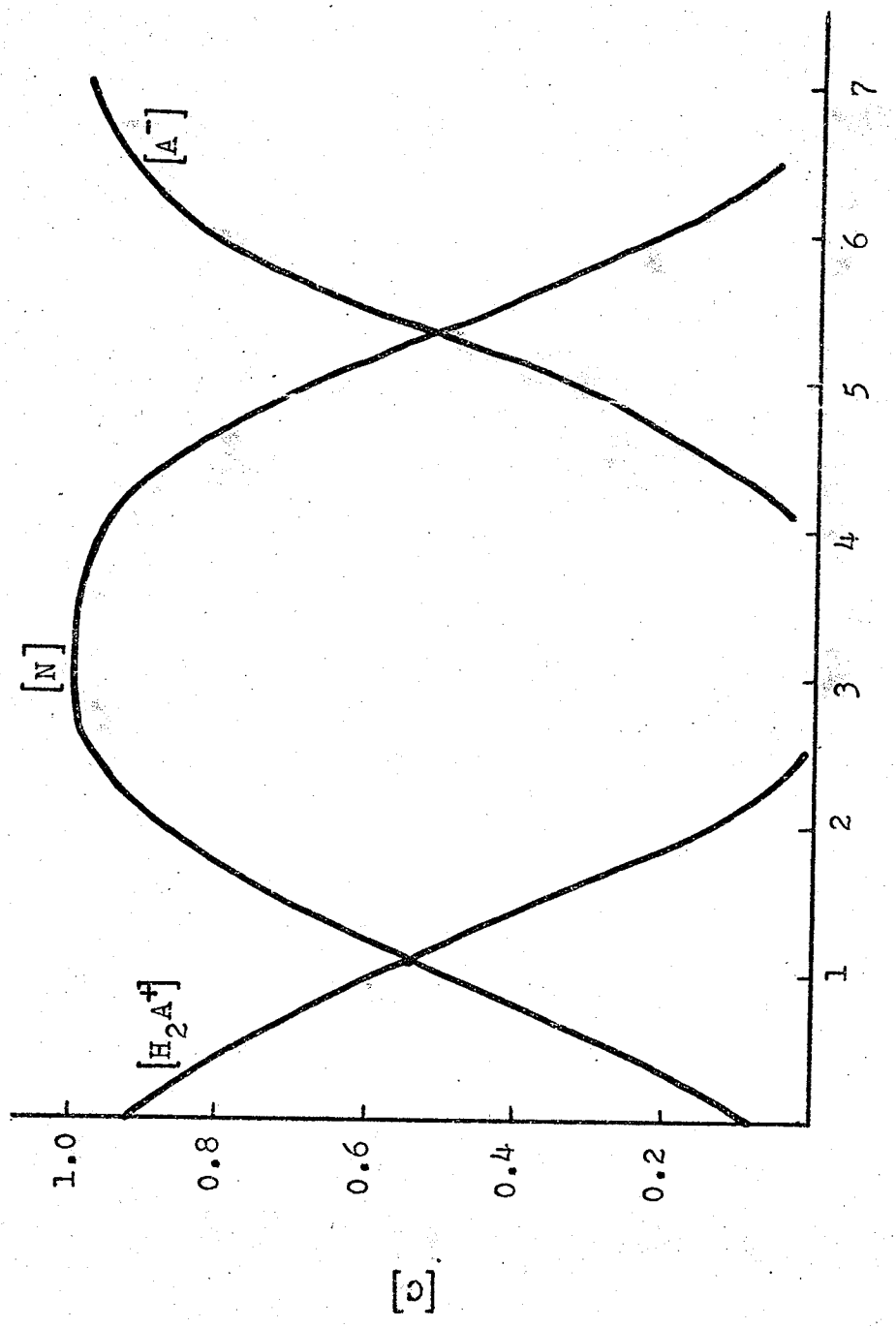
It was shown earlier in the Thesis that for an amino acid if the concentrations (or, at high ionic strengths, the activities) of HA and Z are represented by $[HA]$ and $[Z]$, then the concentration of total ampholyte is $[N] = [HA] + [Z]$, and that $[N]$ reaches a maximum when $pH = 1/2\ (pK_1 + pK_2)$; that is, at the isoelectric point. Since $[Z]$ and $[HA]$ are both proportional to $[N]$ and the proportionality is independent of pH, it follows that both $[HA]$ and $[Z]$ will also have their maximum values at the isoelectric point. If the rate-controlling step in the decarboxylation of picolinic acid is the first-order or pseudo-first-order decomposition of any of the Bjerrum species, H_2A^+, HA, Z, A^-, a plot of the rate constant against pH should show the same inflections as the concentration versus pH plot for the corresponding species as shown in Figure 2.

In other words, if the literature mechanism for the decarboxylation of picolinic acid (via neutral species)

FIGURE 2

pH dependence of substrate concentration of picolinic acid in aqueous solution at 25°C

(K_1 and K_2 were taken to be 8.32×10^{-2}, and 4.79×10^{-6} respectively (33))


[c]
1.0
0.8
0.6
0.4
0.2
[H2A+]
[N]
[A-]
1
2
3
4
5
6
7
pH

is correct, the rate of decarboxylation should be a maximum at the isoelectric pH. The investigation therefore began with an attempt to test this requirement of the literature mechanism.

A statement in Sidgwick's well-known book on nitrogen compounds reads (79):

"The pyridine-α-carboxylic acids are decarboxylated very easily by heating with hydrochloric acid ....."

In order to confirm this statement, attempts were made to decarboxylate picolinic acid in aqueous solution. A stock solution was made up by dissolving 2 gm of picolinic acid in one liter of distilled water. Two ml aliquots of the stock solution were then withdrawn and injected into seven flasks each containing 100 ml of buffered solutions of pH = 2; pH = 5; 1N NaOH; 5N NaOH; 1N H_2SO_4; 2N H_2SO_4 and 5N H_2SO_4. These solutions were kept refluxing and the evaporation losses were minimized by using water condensers. The UV spectra of these solutions were taken in approximately one-day intervals, and it was found that the UV spectra remained unchanged after two weeks, indicating no decomposition had occurred in any of these solutions. Therefore, Sidgwick's statement seemed to be invalid.

In some subsequent experiments on the decarboxylation of picolinic acid, it was found that it did not decarboxylate at a measurable rate until the temperature reached 150°C. Numerous difficulties were encountered in trying to study the effect of changing pH upon the rate at such high temperature. The reaction vessels used by Dunn et. al. (27) at 60°C cannot be used when the temperature of the solution is above 100°C due to evaporation. However, it was found that sealed ampoules of 2 ml capacities can stand such high temperature, and the ampoule technique was therefore used for the rate measurements.

In order to test the hypothesis that the rate should be a maximum at the isoelectric pH, rates will have to be measured in buffered solutions at constant ionic strength. The following buffered solutions as suggested by Bates (3) were tested separately for their stabilities at high temperature:

Acidic component	Basic component	pH Range
HCl	Glycine	1.0-3.7
HCl	Na_2H citrate	1.0-5.0
Citric acid	NaOH	2.2-6.5
Citric acid	Na_2HPO_4	2.2-8.0
Formic acid	NaOH	2.8-4.6

Nine ampoules, each containing the same buffered solutions, were kept in the oil bath at 150°C for one week, and three ampoules were withdrawn at the beginning, the middle and the end of the experiment. These were cooled down to 25°C for pH measurements. It was found that for all the buffered solutions mentioned above, the pH's before and after the experiment had a difference of between 1 to 2 pH units, probably due to the decomposition of the organic components of these buffered solutions at 150°C.

In subsequent experiments, it was found that the pH of phosphate buffer remained unchanged after being kept for 500 hours at 150° C, and the following buffered solutions were therefore used for the rate measurements in this investigation:

Buffer	pH region
HCl	0-2.2
$HCl-NaH_2PO_4$	1.8-4.2
$NaH_2PO_4-Na_2HPO_4$	4.0-6.4

The rates of decarboxylation of picolinic acid were measured by using the above buffers for different pH regions, and ampoules as reaction vessels. The rates were obtained

spectrophotometrically by following the change in concentration of the acid with time. The absorbance measurements were made in alkaline solution where all the acid is in the anionic form, and at wavelength where the absorbance of the reaction product, pyridine, is negligible. The UV spectra of picolinic acid and pyridine are shown in Figure 3. As shown in the Figure, 275 mμ was chosen as the wavelength for the rate measurements.

First-order plots of the logarithm of absorbance against time gave excellent fits up to more than 90% conversion. A typical plot of log. absorbance versus time for the decarboxylation of picolinic acid at 150°C , and $\mu = 1.0$ is shown in Figure 4.

Table VI records the rates obtained on the decarboxylation of picolinic acid at 150°C in buffered solutions with pH measured at 25°C, and ionic strength, μ , of 1.0. Enough data are available to show that the rate is a maximum at an intermediate pH and decreases at both high and low pH. The pH at the maximum cannot be determined precisely because the pH's were measured at 25°C instead of 150°C. However, it will be shown in the subsequent studies on quinolinic acid that the pH's of buffers similar to these

FIGURE 3

The UV spectra of picolinic acid and pyridine in 1N NaOH

——— Picolinic acid, C = 2.8×10^{-4} M

····· Pyridine, C = 2.8×10^{-4} M

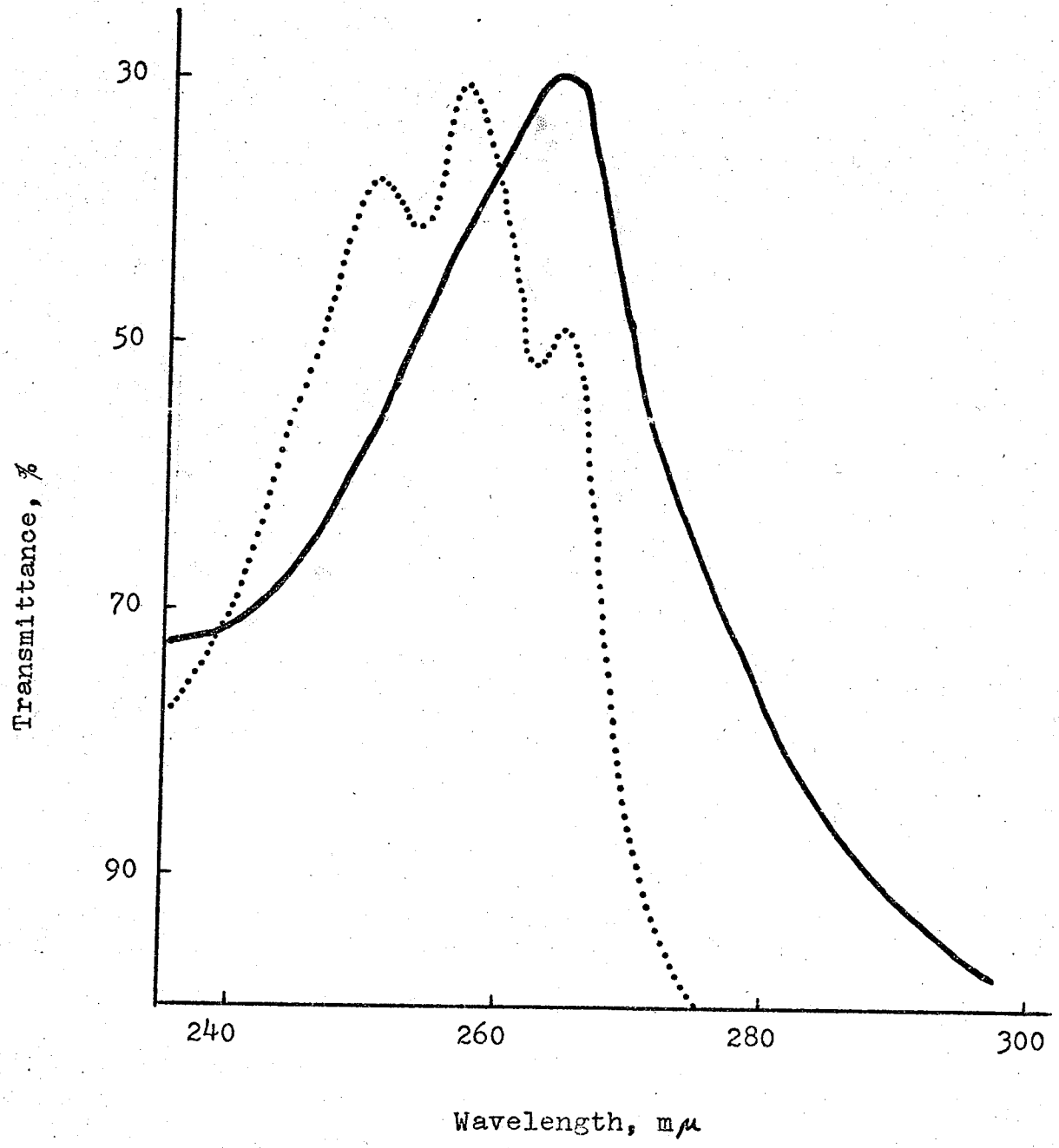

30
50
70
90
Transmittance, %
240
260
280
300
Wavelength, mμ

FIGURE 4

A typical plot of log. absorbance versus time for the decarboxylation of picolinic acid at 150°C, $\mu = 1.0$.

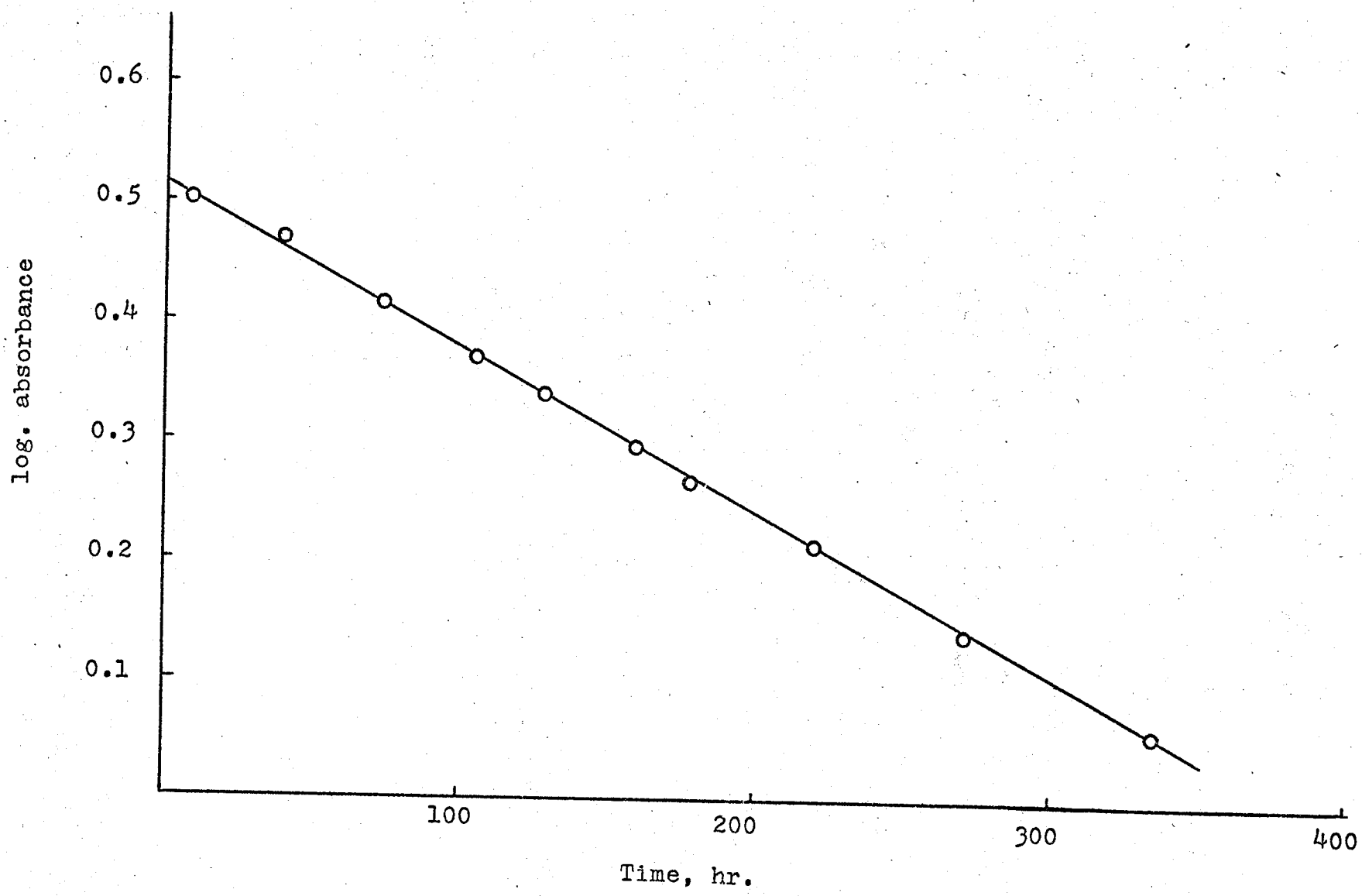

log. absorbance
0.6
0.5
0.4
0.3
0.2
0.1
100
200
300
400
Time, hr.

TABLE VI

RATES OF DECARBOXYLATION OF PICOLINIC ACID AT 150°C, μ = 1.0

(WITH pH AT 25°C)

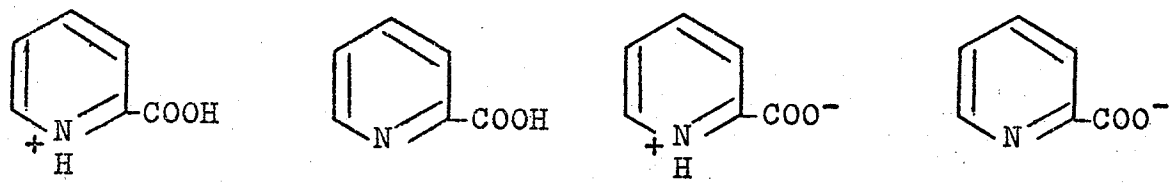
Buffer*	pH at 25°C	k x 10^7, s^{-1}
A	0.124	1.61
A	0.252	2.19
A	0.411	2.92
A	0.598	3.78
A	0.735	4.57
A	0.832	5.54
A	0.984	6.22
A	1.11	7.07
A	1.38	8.20
A	1.53	9.21
A	1.68	9.84
A	1.75	9.81
A	1.78	10.1
A	2.01	10.4
A	2.16	10.5
B	1.78	10.0
B	1.88	10.0
B	2.01	10.2
B	2.24	10.4
B	2.29	10.7
B	2.38	10.6
B	2.61	10.4
B	2.92	10.1
B	3.09	9.52
B	3.25	8.99
B	3.41	8.55
B	3.64	7.63
B	3.81	7.02
B	3.88	6.80
B	4.05	6.49
C	4.02	6.50
C	4.53	5.62
C	5.03	5.10
C	5.45	5.14
C	5.74	5.17
C	6.24	5.01

* The symbols A, B and C refer to HCl; HCl-NaH_2PO_4 ; and NaH_2PO_4-Na_2HPO_4 buffers respectively.

were found to increase in pH by less than 0.1 unit on changing temperature from 25°C to 95°C, therefore, it may be safe to assume that the pH's may increase about 0.2 unit on changing from 25°C to 150°C. The results appeared in Table VI are reproduced in Table VII with the assumption that pH's increase 0.2 unit on changing from 25°C to 150°C.

As shown in Table VII, the rate maximum appears to occur at about pH of 2.4 at 150°C. The rates of decarboxylation of picolinic acid at 150°C and μ = 1.0 as shown in Table VII are plotted in Figure 5. The most noticeable feature of the rate vs pH profile as seen in Figure 5 is its unsymmetrical shape. This alone tells us that the decarboxylation is not the decomposition of a single species, because the concentration profile of the neutral acid would be symmetrical about the isoelectric pH as shown in Figure 2.

As suggested by Evans et al. (33), the three molecular species which occur in aqueous solution of picolinic acid can be represented by the structural formulae XVIII, XIX and XX.



(a) (b)

XVIII XIX XX

TABLE VII ♯

RATES OF DECARBOXYLATION OF PICOLINIC ACID AT 150°C, μ = 1.0

(WITH pH AT 150°C)

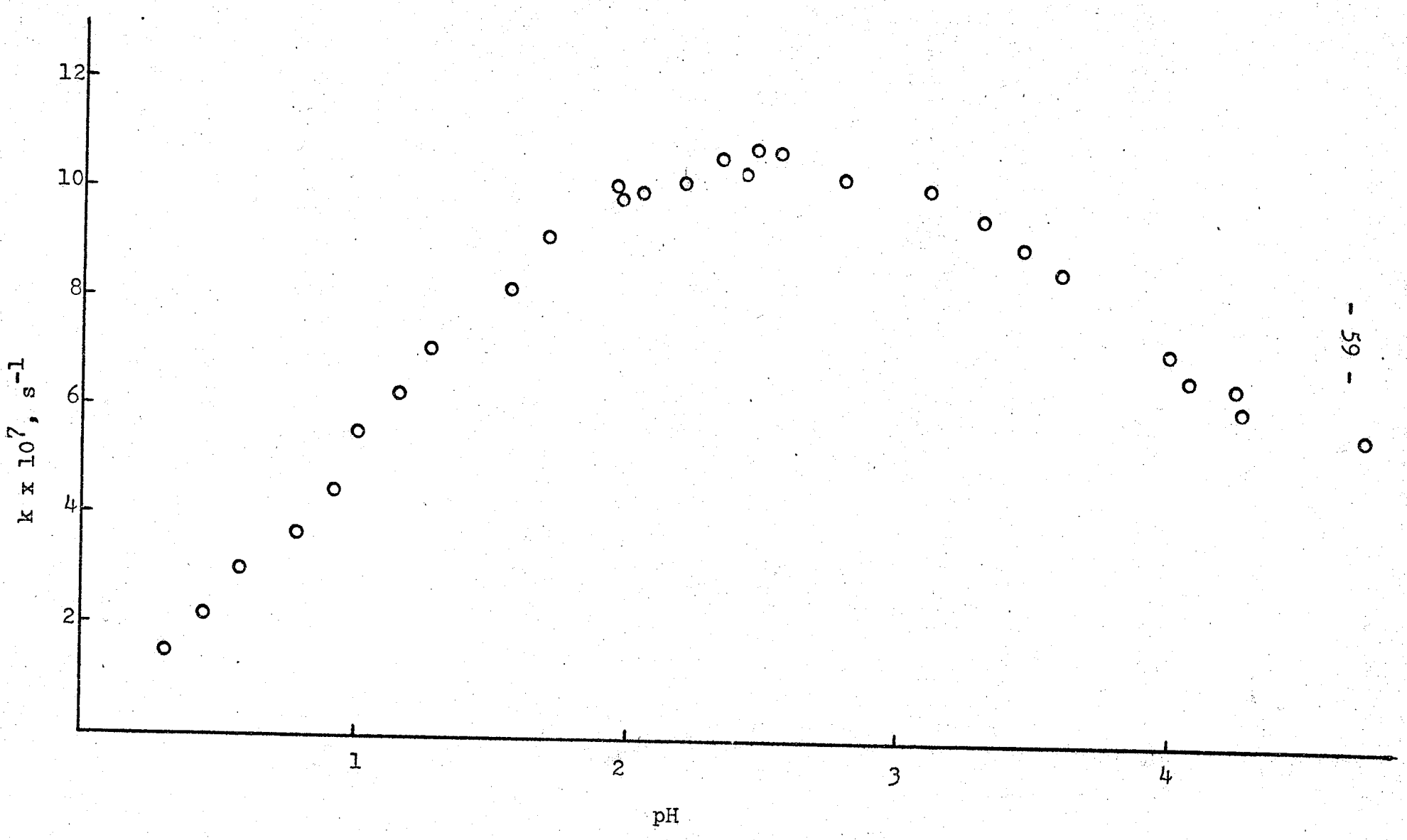
Buffer*	pH at 150°C	k x 10^7, s^{-1}
A	0.324	1.61
A	0.452	2.19
A	0.611	2.92
A	0.798	3.78
A	0.935	4.57
A	1.03	5.54
A	1.18	6.22
A	1.31	7.07
A	1.58	8.20
A	1.73	9.21
A	1.88	9.84
A	1.95	9.81
A	1.98	10.1
A	2.21	10.4
A	2.36	10.5
B	1.98	10.0
B	2.08	10.0
B	2.21	10.2
B	2.44	10.4
B	2.49	10.7
B	2.58	10.6
B	2.81	10.4
B	3.12	10.1
B	3.29	9.52
B	3.45	8.99
B	3.61	8.55
B	3.84	7.63
B	4.01	7.02
B	4.08	6.80
B	4.25	6.49
C	4.22	6.50
C	4.73	5.62
C	5.23	5.10
C	5.65	5.14
C	5.94	5.17
C	6.44	5.01

♯ Data from Table VI; pH's at 150°C are from those measured at 25°C, and an increase of 0.2 unit from 25°C to 150°C is assumed.

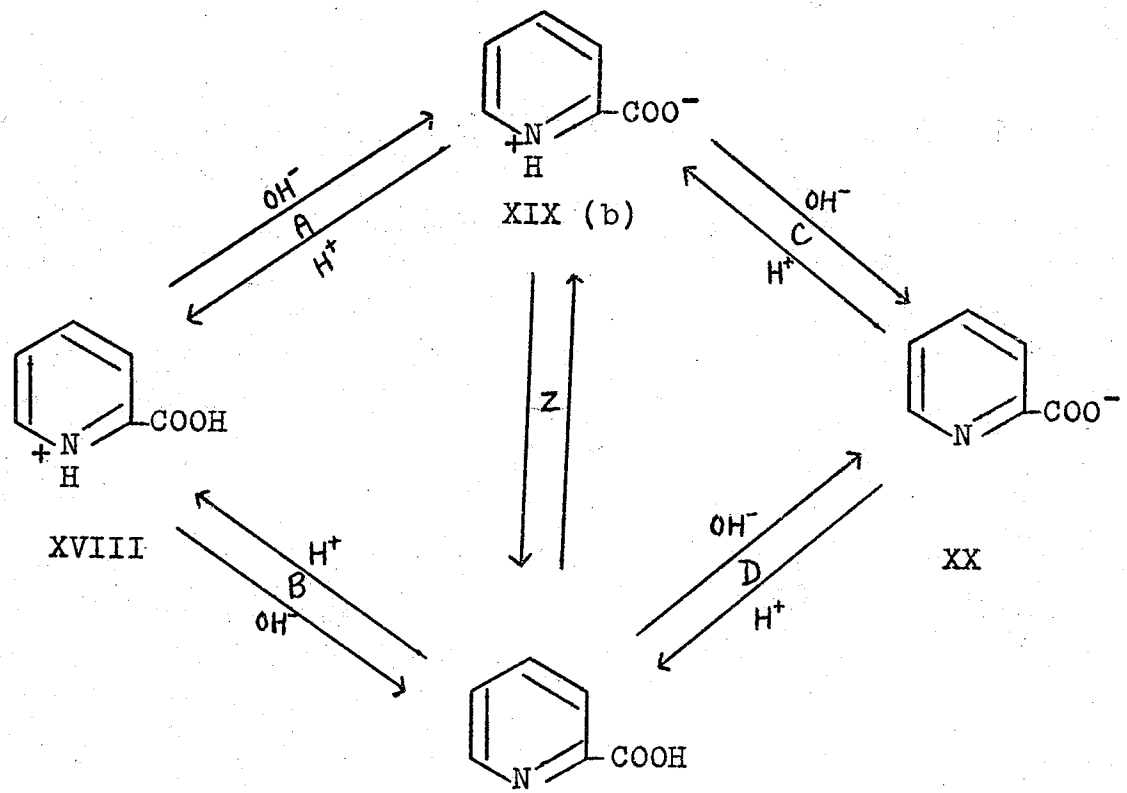
* The symbols A, B and C refer to HCl; HCl-NaH_2PO_4 ; and NaH_2PO_4-Na_2HPO_4 buffers respectively.

FIGURE 5

pH dependence of experimental rate constants for the decarboxylation of picolinic acid at 150°C, μ = 1.0 .


12
10
8
6
4
2
k x 10^7, s^-1
1
2
3
4
pH

In an aqueous solution of picolinic acid, the following equilibria, analogous to aminobenzoic acids, can be considered (39):



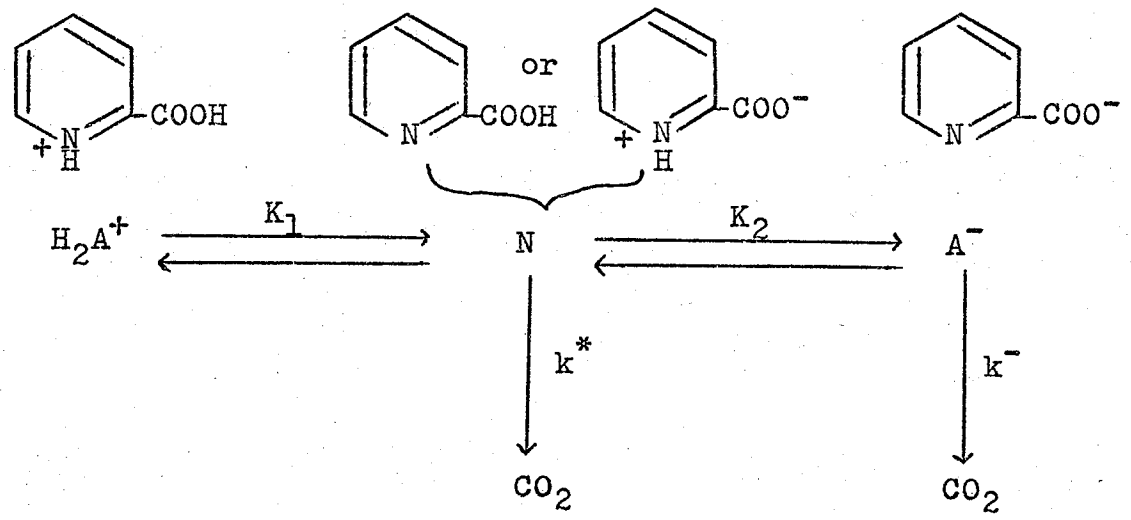
The cationic species behaves as a dibasic acid for which two thermodynamic dissociation constants K_1 and K_2 can be measured by the usual methods. These are related to the constants of the above equilibria by

$$K_1 = K_A + K_B$$

$$1/K_2 = 1/K_C + 1/K_D$$

$$K_Z = K_A/K_B = K_D/K_C$$

The unsymmetrical shape of the rate vs. pH curve for picolinic acid as shown in Figure 5 suggests that the decarboxylation of this acid is not the decomposition of a single species. The reaction may involve simultaneous decarboxylation of two or more of species XVIII to XX. Since the left hand side of the maximum approaches zero at lower pH, whereas the right hand side seems to level off at higher pH, the reaction, besides involving the decarboxylation of the neutral species, XIX, may also involve the decarboxylation of the anion. XX. This can be represented in the following scheme:



where $K_1 = \dfrac{[N][H^+]}{[H_2A^+]}$ $\qquad [H_2A^+] = \dfrac{[N][H^+]}{K_1}$

$K_2 = \dfrac{[A^-][H^+]}{[N]}$ $\qquad [A^-] = \dfrac{K_2[N]}{[H^+]}$

and $[H_2A^+] + [N] + [A^-] = [C]$

$$\frac{[N][H^+]}{K_1} + [N] + \frac{K_2[N]}{[H^+]} = [C]$$

$$[N] = \frac{[C]}{\frac{[H^+]}{K_1} + 1 + \frac{K_2}{[H^+]}}$$

For $N \xrightarrow{k^*} CO_2$

the rate expression is:

$$-\frac{d[C]}{dt} = k[C] = k^*[N]$$

$$= \frac{k^*[C]}{[H^+]/K_1 + 1 + K_2/[H^+]}$$

or $$k = \frac{k^*}{[H^+]/K_1 + 1 + K_2/[H^+]} \qquad \text{.....(11)}$$

For $A^- \xrightarrow{k^-} CO_2$

the rate expression is:

$$\frac{-d[C]}{dt} = k[C] = k^-[A^-]$$

$$= \frac{k^- K_2 [C]}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)}$$

$$\text{or} \quad k = \frac{k^- K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \qquad \text{.....(12)}$$

and the overall rate constant for the reaction is the addition of equations (11) and (12):

$$k = \frac{k^*[H^+] + k^- K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \qquad \text{.....(13)}$$

In order to obtain k^* and k^- in equation (13), and eventually to calculate the rate constants at various hydrogen ion concentrations, it is necessary to know the values of K_1 and K_2 at 150 °C and μ= 1.0. According to Evans, Herington, and Kynaston (33), the pK_1 and pK_2 of picolinic acid are 1.08 and 5.32 respectively. These were measured at 25 °C and at ionic strength of 0.03. Since K_1 and K_2 were not measured at μ= 1.0, the ionic strength

of our experiment, it will be necessary to estimate them by an extrapolation of the Debye-Hückel theory to this range of ionic strengths. If it is assumed that ionic strength will have little effect on the activity of the neutral species, N, then it follows that:

$$(K_1)_{1.0} = (K_1)_{0.03} \times \frac{\left(f_{H_2A^+}\right)_{1.0}}{\left(f_{H_2A^+}\right)_{0.03}}$$

and

$$(K_2)_{1.0} = (K_2)_{0.03} \times \frac{\left(f_{A^-}\right)_{0.03}}{\left(f_{A^-}\right)_{1.0}}$$

where K represents observed ionization constant, f represents activity coefficient, and the subscripts outside parentheses refer to ionic strengths. Introducing the simple Debye-Hückel relationship for activity coefficient in aqueous solution

$$-\log f = \frac{\sqrt{0.5\mu}}{1 + 1.6\sqrt{\mu}}$$

gives $(K_1)_{1.0} = 5.55 \times 10^{-2}$ and $(K_2)_{1.0} = 7.18 \times 10^{-6}$ or $pK_1 = 1.25$ and $pK_2 = 5.14$ at $\mu = 1.0$.

The pK's mentioned above were measured at 25°C, whereas our rate measurements were carried out at 150°C.

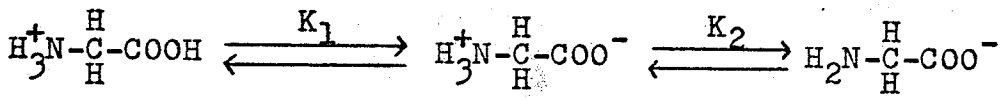
Unfortunately, measurement of ionization constants at 150°C proved to be impossible. However, although no work has been published on the temperature effect of ionizations of picolinic acid in the literature, temperature dependence of glycine, an amino acid, has been reported (54) from 10°C to 50°C, and the results are summarized in Table VIII.

TABLE VIII

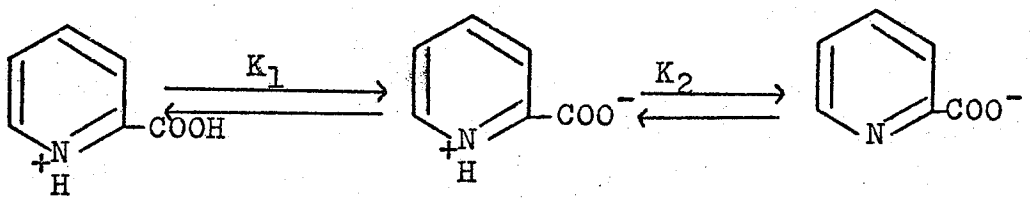
TEMPERATURE DEPENDENCE OF GLYCINE IN AQUEOUS SOLUTION

Temp. °C	pK_1	pK_2
10	2.3971	10.1928
15	2.3800	10.0493
20	2.3640	9.9103
25	2.3503	9.7796
30	2.3394	9.6517
35	2.3312	9.5300
40	2.3266	9.4124
45	2.3242	9.2988
50	2.3200	9.1887

The equilibrium constants which relate the organic species of glycine in aqueous solution may be represented in the following equilibria (57):



Stephenson and Sponer (81) studied the near ultraviolet absorption spectra of the pyridine monocarboxylic acids in water and ethanol solutions, and concluded that picolinic acid exists primarily in the zwitterion form in water. This view is also in agreement with the findings of Green and Tong (39). Therefore, as analogous to glycine, we can relate the equilibrium constants, K_1 and K_2, of picolinic acid to its organic species in aqueous solution as follows:



As shown in Table VIII, the temperature seems to have a drastic influence on pK_2 of glycine, which decreases one whole pK unit, from 10.2 to 9.19; whereas pK_1 does not seem to change very much in the temperature range of 10°C to 50°C. By analogy to glycine, we may assume that the pK_2 of picolinic acid probably decreases to a very large extent from 25°C to 150°C, but pK_1 only slightly decreases. Since the pK_1 and pK_2 were calculated to be 1.25 and 5.14 respectively at 25°C, we can further estimate

that the value of pK_2 probably would be between 3 to 4, and pK_1 probably would be slightly less than 1.2 at 150°C.

The general rate expression (equation (13)) can be simplified if we consider when pH < 2, the $K_2/[H^+]$ term in the denominator may be neglected, and equation (13) becomes:

$$k = \frac{k^*[H^+] + k^-K_2}{[H^+]\left([H^+]/K_1 + 1\right)} \qquad \text{.....(14)}$$

Also, if we assume that k^* would have a value at least as great as k^-, and since $K_2 \ll H^+$, then $k^*[H^+] \gg k^-K_2$, and equation (14) thus becomes:

$$k = \frac{k^*K_1}{[H^+] + K_1}$$

$$\text{or} \quad 1/k = [H^+]/k^*K_1 + 1/k^* \qquad \text{.....(15)}$$

From the linear plot of 1/k vs. $[H^+]$, the slope should give the value of $1/k^*K_1$, whereas the intercept should give the value of $1/k^*$.

The data (pH of 0 to 2) from Table VII were used to plot 1/k vs. $[H^+]$. The calculations are shown in Table IX,

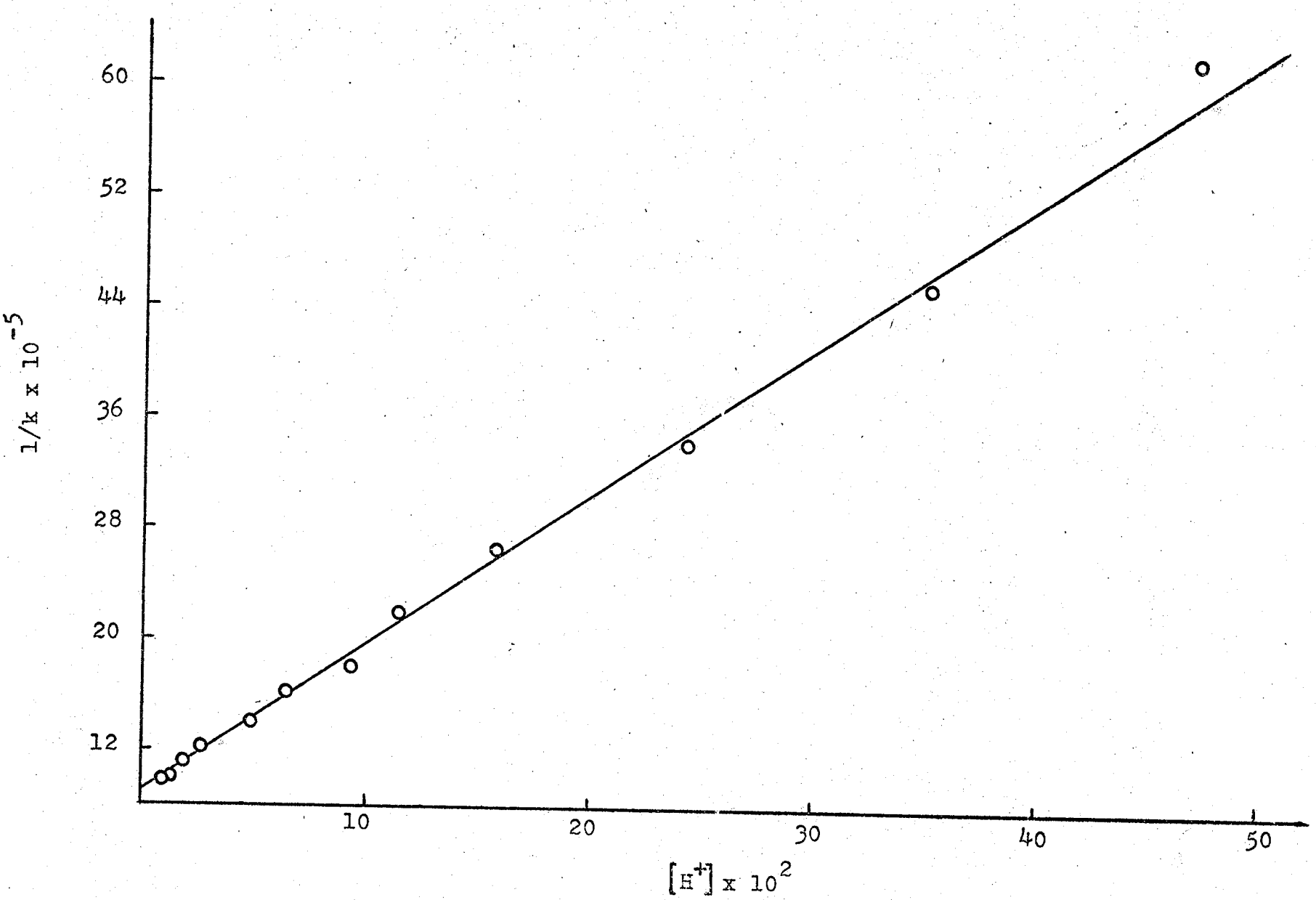
TABLE IX

CALCULATIONS FOR THE PLOT OF 1/k VS. $[H^+]$ FOR PICOLINIC ACID

pH	$[H^+] \times 10^2$	$k \times 10^7$	$1/k \times 10^{-5}$
0.324	47.4	1.61	62.1
0.452	35.3	2.19	45.7
0.611	24.5	2.92	34.3
0.798	15.9	3.78	26.5
0.935	11.6	4.57	21.9
1.03	9.33	5.54	18.1
1.18	6.61	6.22	16.1
1.31	4.90	7.07	14.1
1.58	2.63	8.20	12.2
1.73	1.86	9.21	10.9
1.88	1.32	9.84	10.2
1.95	1.12	9.81	10.2
1.98	1.05	10.1	9.90

FIGURE 6

Plot of 1/k versus $[H^+]$ for picolinic acid


60
52
44
36
28
20
12
1/k x 10^-5
10
20
30
40
50
[H+] x 10^2

and are plotted in Figure 6. A good linear plot was obtained, and from this we get:

$$k^* = 1.20 \times 10^{-6} \text{ sec}^{-1}$$

$$k^* K_1 = 9.65 \times 10^{-8}$$

$$\text{or } K_1 = 8.05 \times 10^{-2} \quad (pK_1 = 1.09)$$

The pK_1 of 1.09 obtained from the plot is quite agreeable with our previous assumption that pK_1 would be slightly less than 1.2.

Equation (13) can also be simplified if we consider when pH $>$ 2, i.e., $[H^+]$ less than 10^{-2}, Since the pK_1 obtained from the plot of 1/k vs. $[H^+]$ is 1.09, the term $[H^+]/K_1$ in equation (13) will be negligible, and the equation thus becomes:

$$k = \frac{k^*[H^+] + k^- K_2}{[H^+] + K_2} \qquad \ldots\ldots(16)$$

$$\text{or} \quad k\left([H^+] + K_2\right) = k^*[H^+] + k^- K_2 \qquad \ldots\ldots(17)$$

From the linear plot of $k\left([H^+] + K_2\right)$ vs. $[H^+]$, the slope should give the value of k^*, and the intercept should give the value of $k^- K_2$.

It was assumed earlier that pK_2 would be between

3 and 4, and pK_1 was found to be 1.09 from the previous plot. In order to have a best fit into the experimental rates vs. pH profile, we further assume that pK_2 would be about 3.7, or $K_2 = 1.99 \times 10^{-4}$. This value of K_2 was used to plot $k\left([H^+] + K_2\right)$ vs. $[H^+]$. The calculations are shown in Table X, and are plotted in Figure 7. From the linear plot, the following values were obtained:

$$k^* = 1.08 \times 10^{-6} \text{ sec}^{-1}$$

$$k^- K_2 = 9.9 \times 10^{-11}$$

$$\text{or} \quad k^- = 4.96 \times 10^{-7} \text{ sec}^{-1}$$

The values of k^* obtained from Figure 6 and Figure 7 are quite agreeable, and the average value of k^* would be 1.14×10^{-6} sec^{-1}.

Substituting the values of k^*, k^-, K_1 and K_2 into the general rate expression (equation (13)) gives:

$$k = \frac{1.14 \times 10^{-6}[H^+] + 9.9 \times 10^{-11}}{[H^+]\left(\frac{[H^+]}{8.05 \times 10^{-2}} + 1 + \frac{1.99 \times 10^{-4}}{[H^+]}\right)} \quad \ldots.(18)$$

With varying hydrogen ion concentrations substituted in equation (18), different values of k were obtained, and the construction of a theoretical rate vs. pH profile

TABLE X

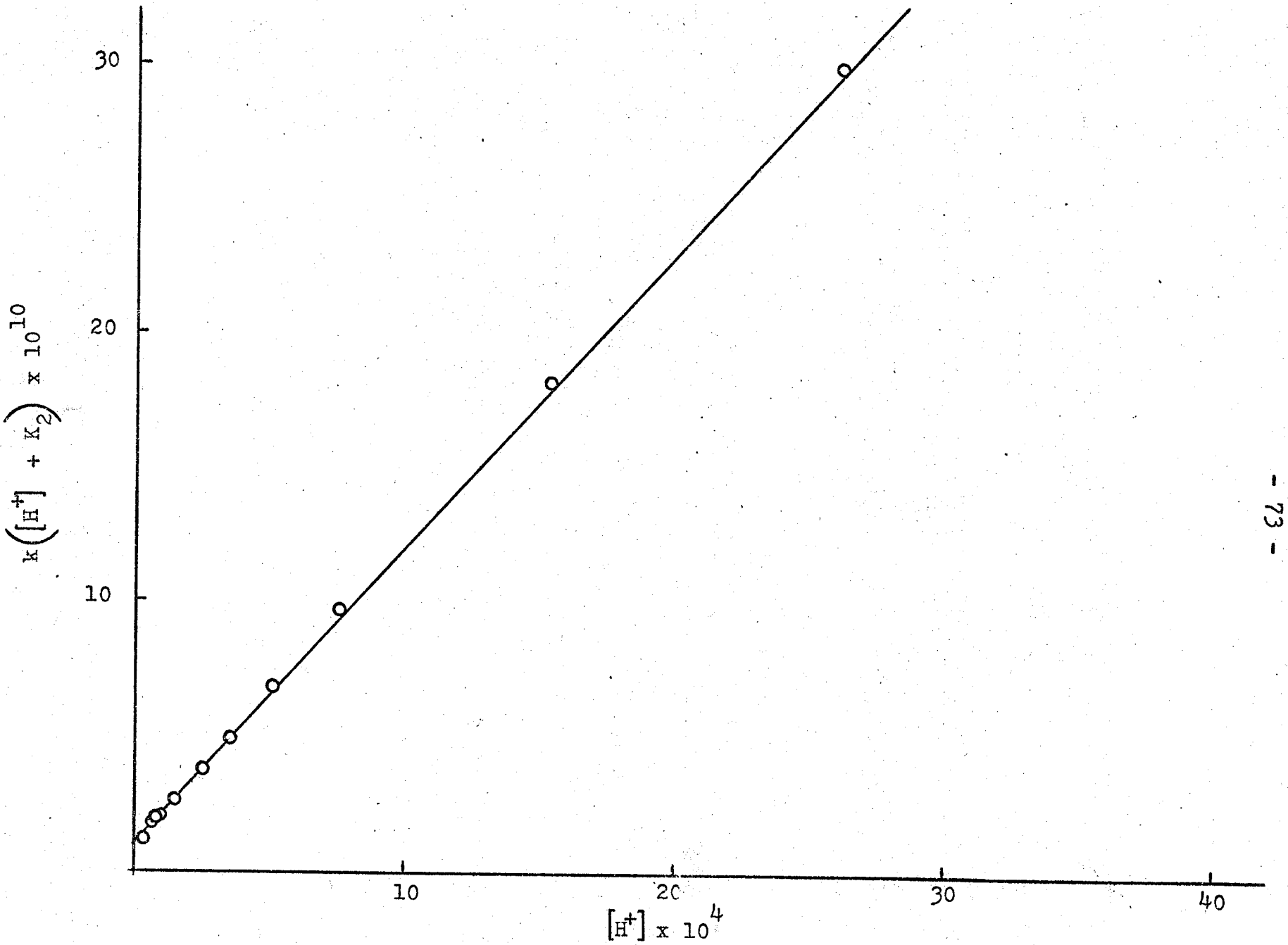
CALCULATIONS FOR THE PLOT OF $k\left([H^+] + K_2\right)$ VS. $[H^+]$ FOR PICOLINIC ACID

pH	$[H^+] \times 10^4$	$\left([H^+] + K_2\right) \times 10^{4*}$	$k \times 10^7$	$k\left([H^+] + K_2\right) \times 10^{10}$
2.58	26.3	28.3	10.6	30.0
2.81	15.5	17.5	10.4	18.2
3.12	7.59	9.58	10.1	9.68
3.29	5.13	7.12	9.52	6.78
3.45	3.55	5.54	8.99	4.98
3.61	2.46	4.45	8.55	3.80
3.84	1.45	3.44	7.63	2.62
4.01	0.977	2.97	7.02	2.08
4.08	0.832	2.82	6.80	1.92
4.22	0.603	2.59	6.50	1.68
4.73	0.186	2.18	5.62	1.23

* $K_2 = 1.99 \times 10^{-4}$

FIGURE 7

Plot of $k\left([H^+] + K_2\right)$ versus $[H^+]$ for picolinic acid


30
20
10
$k\left([H^+] + K_2\right) \times 10^{10}$
10
20
30
40
$[H^+] \times 10^4$

was possible. Rate constants calculated from equation (18) are presented in Table XI, and are plotted in Figure 8. In Figure 8, the experimental rate constants with varying pH values were also included. As shown in the figure, the theoretical values have an excellent fit into the experimental results. Therefore, we may be able to assume that our proposed mechanism agrees with the kinetics of the decarboxylation of picolinic acid in aqueous solution.

In order to compare the decarboxylation of picolinic acid with that of anthranilic acid, the C^{13}-kinetic isotope effect of picolinic acid at 150°C and μ=1.0 were determined, and the results are shown in Table XII.

If the ylid mechanism is correct, with only one species decarboxylating, the C^{13}-kinetic isotope effect should be independent of pH, but the results shown in Table XII seem to have a small dependence on pH. This could be explained if the species decarboxylating at high pH is different from the one decarboxylating at lower pH as postulated on page 61. However, the C^{13}-kinetic isotope effect on pyridine-carboxylic acids will be discussed later when work on quinolinic acid has been covered.

TABLE XI

RATE CONSTANTS CALCULATED FROM EQUATION (18) FOR THE DECARBOXYLATION OF PICOLINIC ACID AT 150°C, $\mu = 1.0$

pH	$[H^+] \times 10^3$	$k \times 10^7$, s^{-1}
0	1000	0.851
0.2	631	1.29
0.4	398	1.92
0.6	251	2.76
0.8	159	3.84
1.0	100	5.07
1.2	63.1	6.37
1.4	39.8	7.61
1.6	25.1	8.62
1.8	15.9	9.42
2.0	10.0	10.1
2.2	6.31	10.4
2.4	3.98	10.6
2.6	2.51	10.6
2.8	1.59	10.5
3.0	1.00	10.3
3.2	0.631	9.82
3.4	0.398	9.27
3.6	0.251	8.59
3.8	0.159	7.87
4.0	0.100	7.13
4.2	0.0631	6.55
4.4	0.0398	6.08
4.6	0.0251	5.73
4.8	0.0159	5.47
5.0	0.001	5.31
6.2	6.31×10^{-4}	5.04
7.2	6.31×10^{-5}	4.99

FIGURE 8

Plot of calculated rate constants versus pH for the decarboxylation of picolinic acid at 150°C, μ = 1.0

— Rate constants calculated from Equation (18)

o Experimental rate constants

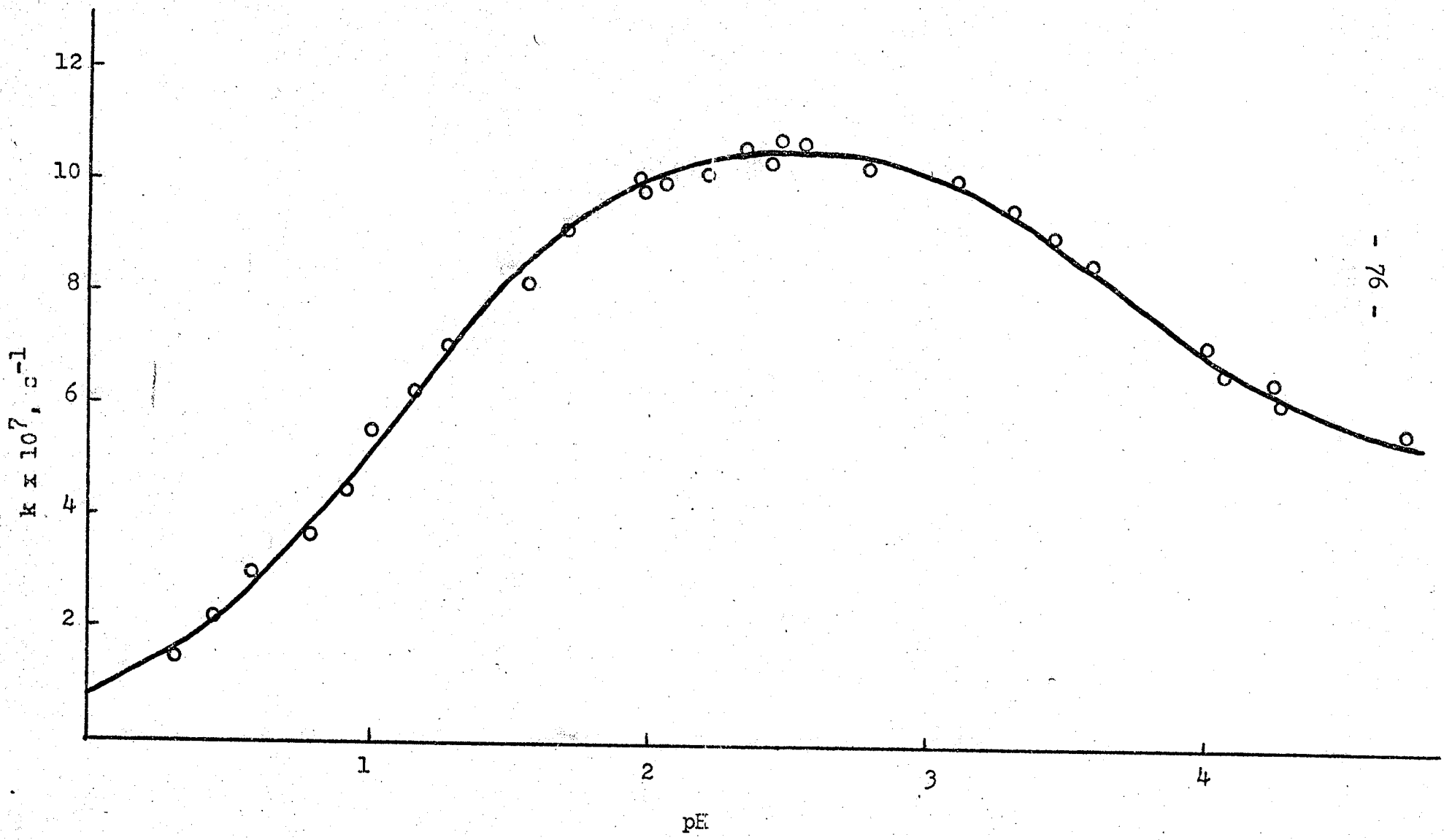

12
10
8
6
4
2
k x 10^7, c^-1
1
2
3
4
pE

TABLE XII

C^{13}-KINETIC ISOTOPE EFFECTS ON THE DECARBOXYLATION OF PICOLINIC ACID AT 150°C and μ= 1.0

Buffer*	pH at 25°C	% Reaction	$^{13}CO_2/^{12}CO_2$	$100(k_{12}/k_{13} - 1)$
B	2.41	100.0	0.010362	
B	2.41	100.0	0.010357	
B	2.41	100.0	0.010356	
A	1.13	15.61	0.010148	2.25
A	1.13	15.61	0.010149	2.23
A	1.13	15.61	0.010147	2.26
B	3.95	14.76	0.010165	2.06
B	3.95	14.76	0.010162	2.09
B	3.95	14.76	0.010164	2.08

* The symbols A and B refer to $HClO_4$ and $HClO_4$-NaH_2PO_4 buffers respectively.

2. 6-Methylpicolinic acid

In the preceding section, a mechanism has been proposed for the decarboxylation of picolinic acid. The mechanism fits the experimental results very well if we assume that the dissociation constants of picolinic acid both increase (pK's decrease) with temperature. It was further assumed that pK_2 decreases to quite a large extent, whereas pK_1 only changes slightly in going from 25°C to 150°C. However, the proposed mechanism is not conclusive, since the pK's were not actually measured at 150°C. It was thought that with either electron-donating or electron-attracting substituents in picolinic acid, we may be able to find a substituted picolinic acid which can decarboxylate conveniently below 100°C where the dissociation constants can be measured experimentally.

It was therefore decided to continue our study on the decarboxylation mechanism of picolinic acid with picolinic acids having electron-donating and electron-attracting substituents. 6-Methylpicolinic acid is commercially available and was tried while 5-nitropicolinic acid was being synthesized.

The UV spectra of 6-methylpicolinic acid and its decarboxylation product, 2-picoline (2-methylpyridine),

are shown in Figure 9; and 280 mμ was chosen as the wavelength for rate measurement.

Unfortunately, it was found that the rate of decarboxylation of 6-methylpicolinic acid in aqueous solution at 150°C was slower than that of picolinic acid itself. The decomposition was also found to be first-order, and the plot of logarithm of absorbance versus time gave excellent fits up to more than 90% conversion. A typical plot of log. absorbance versus time is shown in Figure 10, and the rates obtained on buffered solutions are recorded in Table XIII.

Although the dissociation constants, K_1 and K_2, of 6-methylpicolinic acid could not be measured experimentally at 150°C, it is very interesting to note that its rate versus pH profile seemed to be quite similar to that of picolinic acid. The rate is a maximum at an intermediate pH and decreases at both high and low pH. The unsymmetrical shape of the rate versus pH curve can be seen in Figure 11.

The dissociation constants of 6-methylpicolinic acid were reported in the literature by Homes and Crimmin (46), and have the following values:

$pK_1 = 0.9$ ($\mu = 0.5$ and at 18°C)
$pK_2 = 5.83$ ($\mu = 0.02$ and at 25°C)

FIGURE 9

The UV spectra of 6-methylpicolinic acid and 2-picoline in 1N NaOH

——— 6-Methylpicolinic acid, C = 3.0×10^{-4} M

····· 2-Picoline, C = 3.0×10^{-4} M

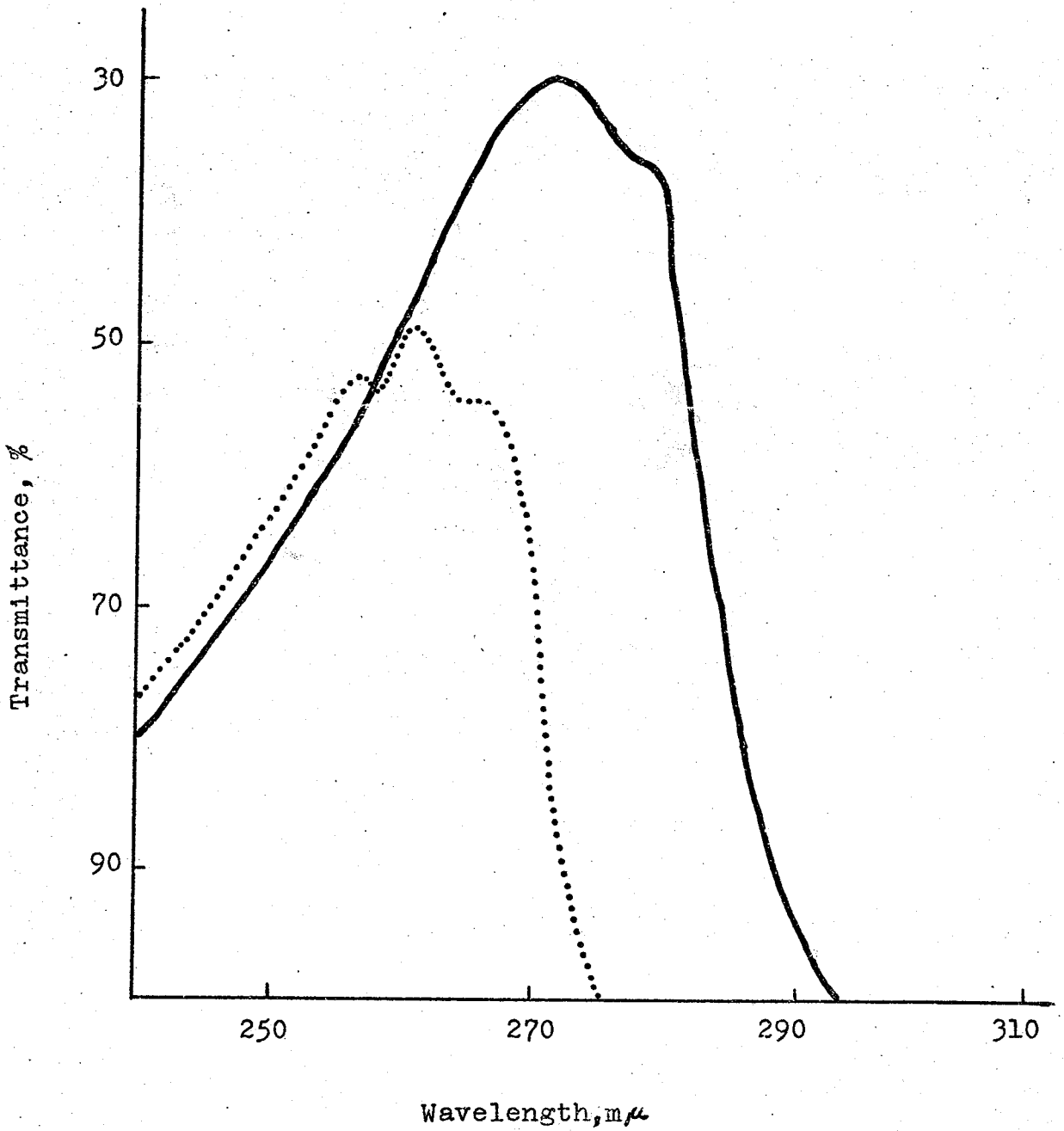

30
50
70
90
Transmittance, %
250
270
290
310
Wavelength, mμ

FIGURE 10

A typical plot of log. absorbance versus time for the decarboxylation of 6-methylpicolinic acid at 150°C, μ = 1.0 .

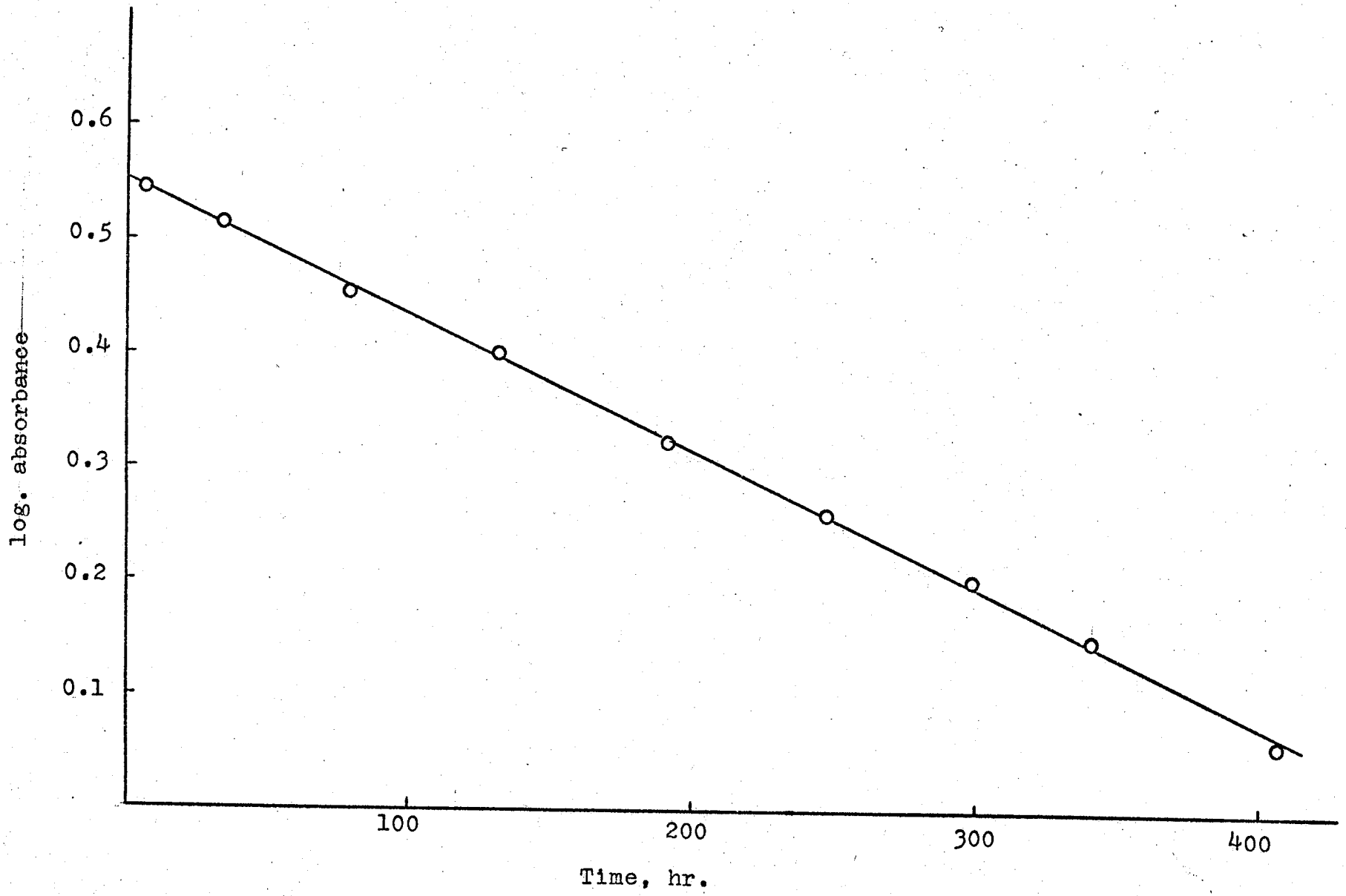

0.6
0.5
0.4
0.3
0.2
0.1
log. absorbance
100
200
300
400
Time, hr.

TABLE XIII

RATES OF DECARBOXYLATION OF 6-METHYLPICOLINIC ACID AT 150°C, μ = 1.0

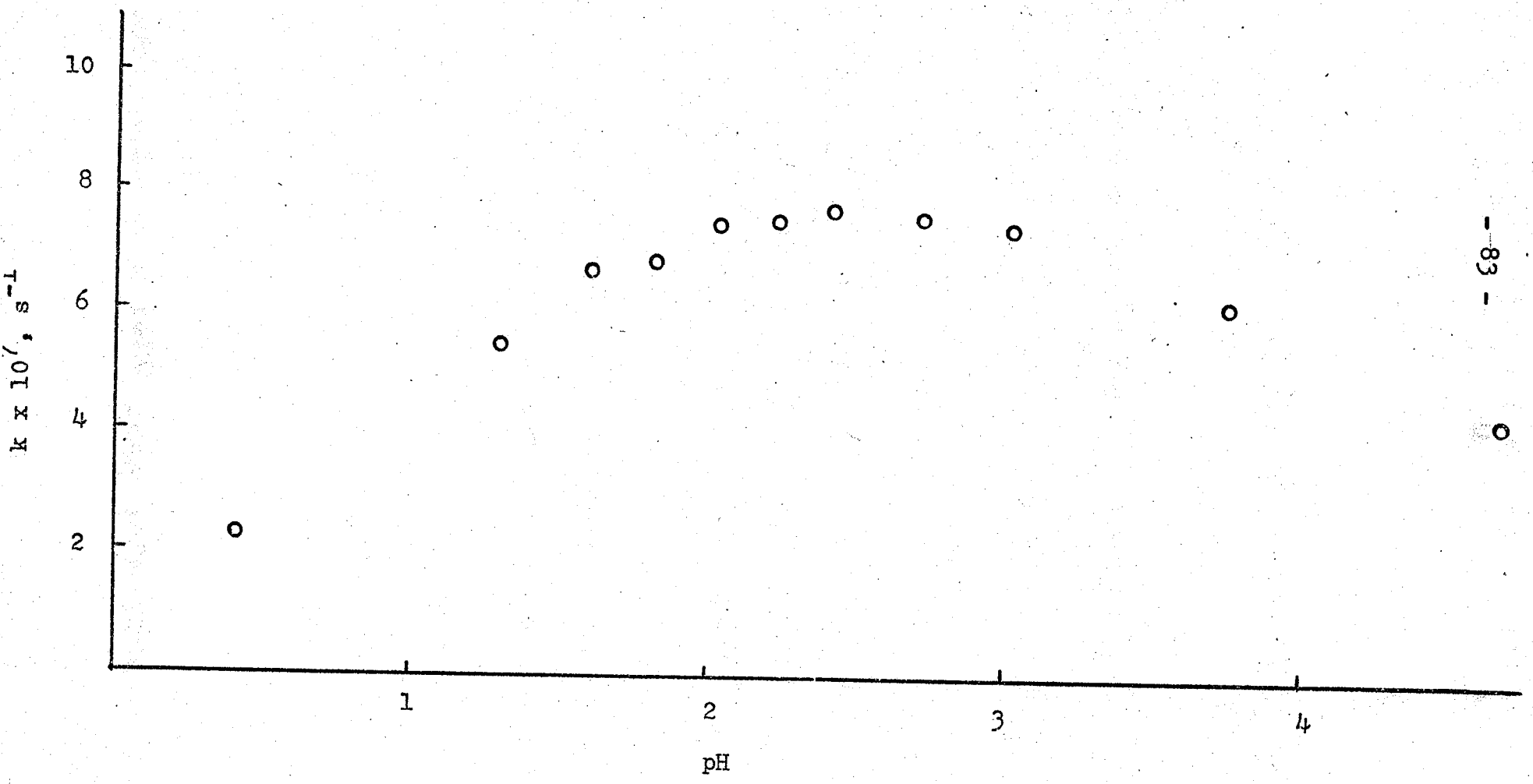
	pH of the solution		
Buffer*	At 25°C	At 150°C ‡	$k \times 10^7$, s^{-1}
A	0.225	0.425	2.19
A	1.09	1.29	5.48
A	1.41	1.61	6.67
A	1.64	1.84	6.96
A	1.85	2.05	7.42
A	2.05	2.25	7.53
B	2.21	2.41	7.81
B	2.50	2.70	7.57
B	2.79	2.99	7.40
B	3.53	3.73	6.25
C	4.46	4.66	4.48

* The symbols A, B and C refer to HCl; HCl-NaH_2PO_4 ; and NaH_2PO_4-Na_2HPO_4 buffers respectively.

‡ Data from those measured at 25°C, and an increase of 0.2 unit from 25°C to 150°C is assumed.

FIGURE 11

pH dependence of experimental rate constants for the decarboxylation of 6-methylpicolinic acid at 150°C, μ = 1.0 .


10
8
6
4
2
k x 10⁷, s⁻¹
1
2
3
4
pH

Since these values were not obtained at the ionic strength of our experiment ($\mu = 1.0$), an extrapolation of the Debye-Hückel theory will be necessary. The calculation is similar to that of picolinic acid, and the following values were obtained at $\mu = 1.0$:

$$pK_1 = 0.94 \quad \text{at } 18^\circ C$$
$$pK_2 = 5.64 \quad \text{at } 25^\circ C$$

or

$$K_1 = 1.15 \times 10^{-1} \quad \text{at } 18^\circ C$$
$$K_2 = 2.29 \times 10^{-6} \quad \text{at } 25^\circ C$$

As previously mentioned, the general rate expression (equation 13) for the mechanism proposed for picolinic acid is:

$$k = \frac{k^* [H^+] + k^- K_2}{[H^+]\left(\frac{[H^+]}{K_1} + 1 + \frac{K_2}{[H^+]}\right)} \qquad \ldots(13)$$

If the same mechanism applies to 6-methylpicolinic acid, the calculated rate constants should agree with our experimental values.

At pH $<$ 2, the term $K_2 / [H^+]$ in the denominator can be neglected. If we assume $k^* [H^+] \gg k^- K_2$, then:

$$k = \frac{k^*[H^+]}{[H^+]\left(\frac{[H^+]}{K_1} + 1\right)} = \frac{k^*K_1}{[H^+] + K_1}$$

or $1/k = [H^+]/k^*K_1 + 1/k^*$

A plot of $1/k$ versus $[H^+]$ is shown in Figure 12, and the calculations are shown in Table XIV.

From the linear plot, the following values are obtained:

$k^* = 7.93 \times 10^{-7}$ sec^{-1}

$k^*K_1 = 1.02 \times 10^{-6}$

or $K_1 = 1.29 \times 10^{-1}$ ($pK_1 = 0.89$)

At pH > 2, $[H^+]/K_1$ term will be neglected, and this leads to

$$k = \frac{k^*[H^+] + k^-K_2}{[H^+] + K_2}$$

or $k([H^+] + K_2) = k^*[H^+] + k^-K_2$

Again, if we assume that pK_2 changes drastically from 25°C to 150°C, and a value of 3.95 is used, a linear plot of $k([H^+] + K_2)$ versus $[H^+]$ is obtained as shown in Figure 13. Calculations are shown in Table XV. A value of 3.9×10^{-7} sec^{-1} was obtained for k^- and 7.69×10^{-7} sec^{-1} for k^*. Inserting all the values of K_1, K_2, k^-, k^* to equation (13), the general rate expression becomes:

$$k = \frac{7.81 \times 10^{-7}[H^+] + 4.37 \times 10^{-11}}{[H^+]\left(\frac{[H^+]}{1.29 \times 10^{-1}} + 1 + \frac{1.12 \times 10^{-4}}{[H^+]}\right)} \quad \text{.....(19)}$$

FIGURE 12

Plot of 1/k versus $[H^+]$ for 6-methylpicolinic acid

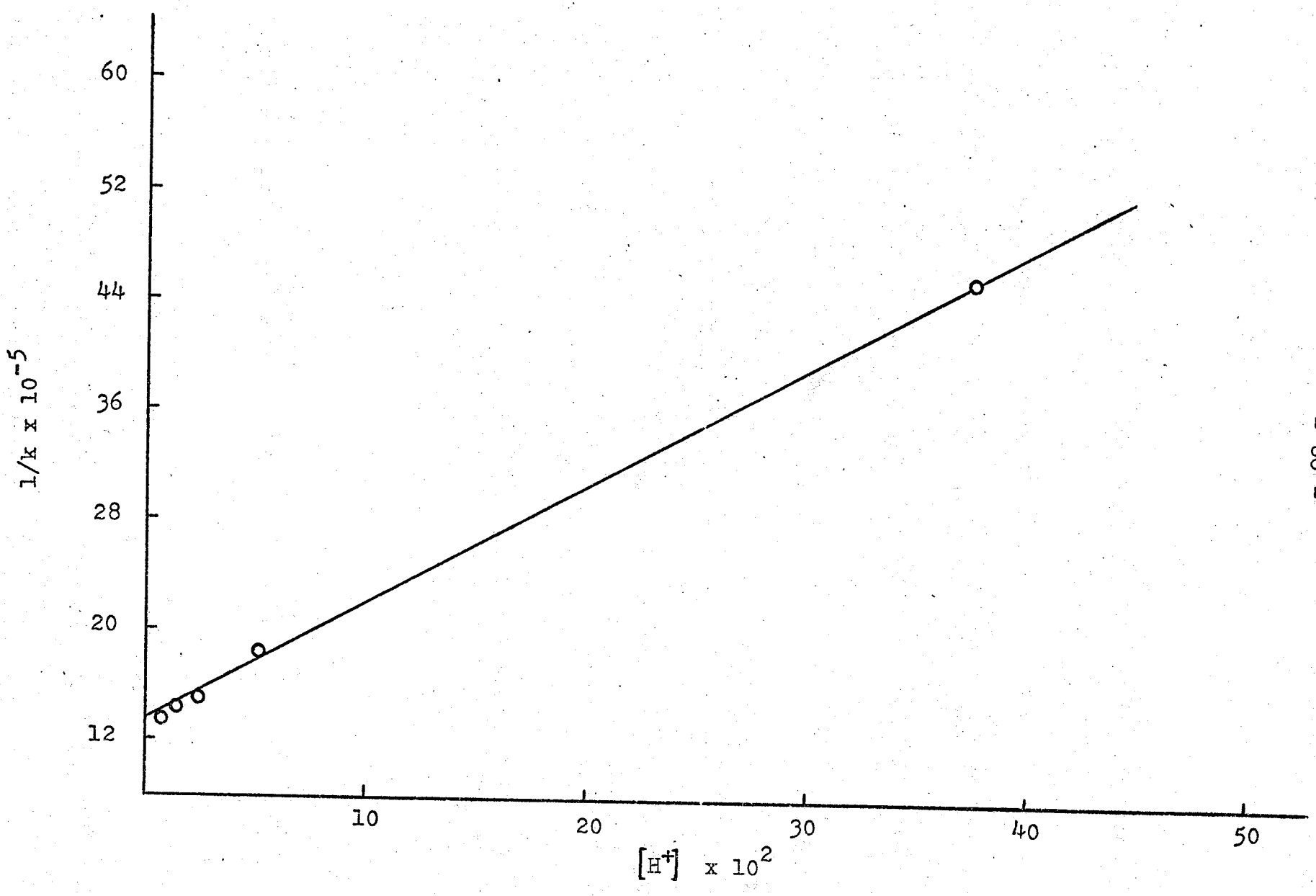

60
52
44
36
28
20
12
1/k x 10^-5
10
20
30
40
50
[H+] x 10^2

TABLE XIV

CALCULATIONS FOR THE PLOT OF 1/k VS. $[H^+]$ FOR 6-METHYL-PICOLINIC ACID

pH	$[H^+] \times 10^2$	$k \times 10^7$	$1/k \times 10^{-5}$
0.425	37.6	2.19	45.7
1.29	5.13	5.48	18.3
1.61	2.46	6.67	15.0
1.84	1.45	6.96	14.4
2.05	0.891	7.42	13.5

FIGURE 13

Plot of $k\left([H^+] + K_2\right)$ versus $[H^+]$ for 6-methylpicolinic acid

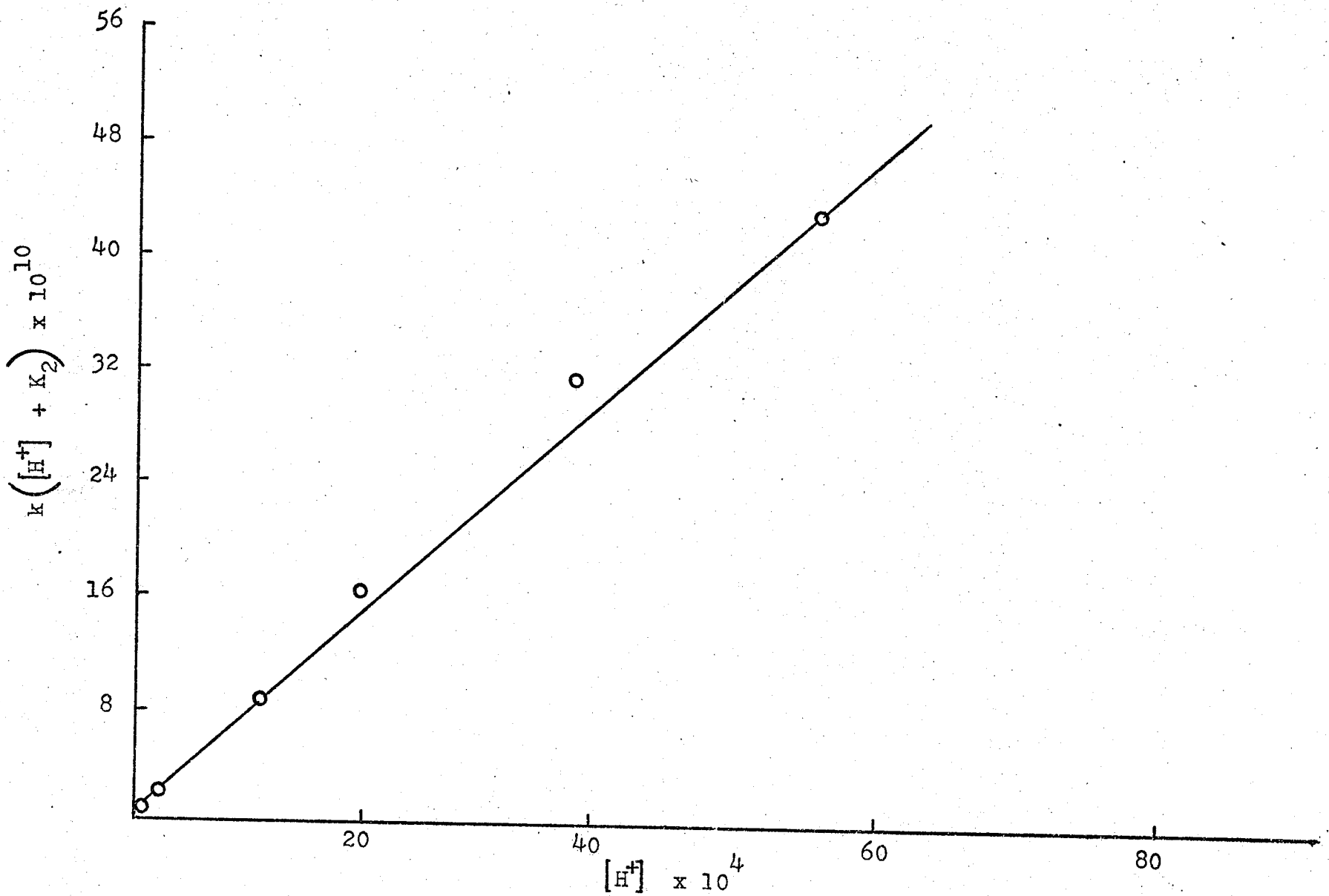

56
48
40
32
24
16
8
$k\left([H^+] + K_2\right) \times 10^{10}$
20
40
60
80
$[H^+] \times 10^4$

TABLE XV

CALCULATIONS FOR THE PLOT OF $k\left([H^+] + K_2\right)$ VS. $[H^+]$ FOR 6-METHYLPICOLINIC ACID

pH	$[H^+] \times 10^4$	$\left([H^+] + K_2\right) \times 10^{4*}$	$k \times 10^7$	$k\left([H^+] + K_2\right) \times 10^{10}$
2.25	56.2	57.3	7.53	43.2
2.41	38.9	40.0	7.81	31.2
2.70	20.0	21.1	7.57	16.0
2.99	10.2	11.3	7.40	8.36
3.73	1.86	2.98	6.25	1.86
4.66	0.219	1.34	4.48	0.601

* $K_2 = 1.12 \times 10^{-4}$

Rate constants with varying hydrogen ion concentrations calculated from equation (19) are presented in Table XVI, and are plotted in Figure 14. As shown in Figure 14, the experimental results fit very well with the theoretical rate constants, and the results obtained from 6-methyl-picolinic acid seem to agree with our proposed mechanism for picolinic acid.

TABLE XVI

RATE CONSTANTS CALCULATED FROM EQUATION (19) FOR THE DECARBOXYLATION OF 6-METHYLPICOLINIC ACID AT 150°C, $\mu = 1.0$

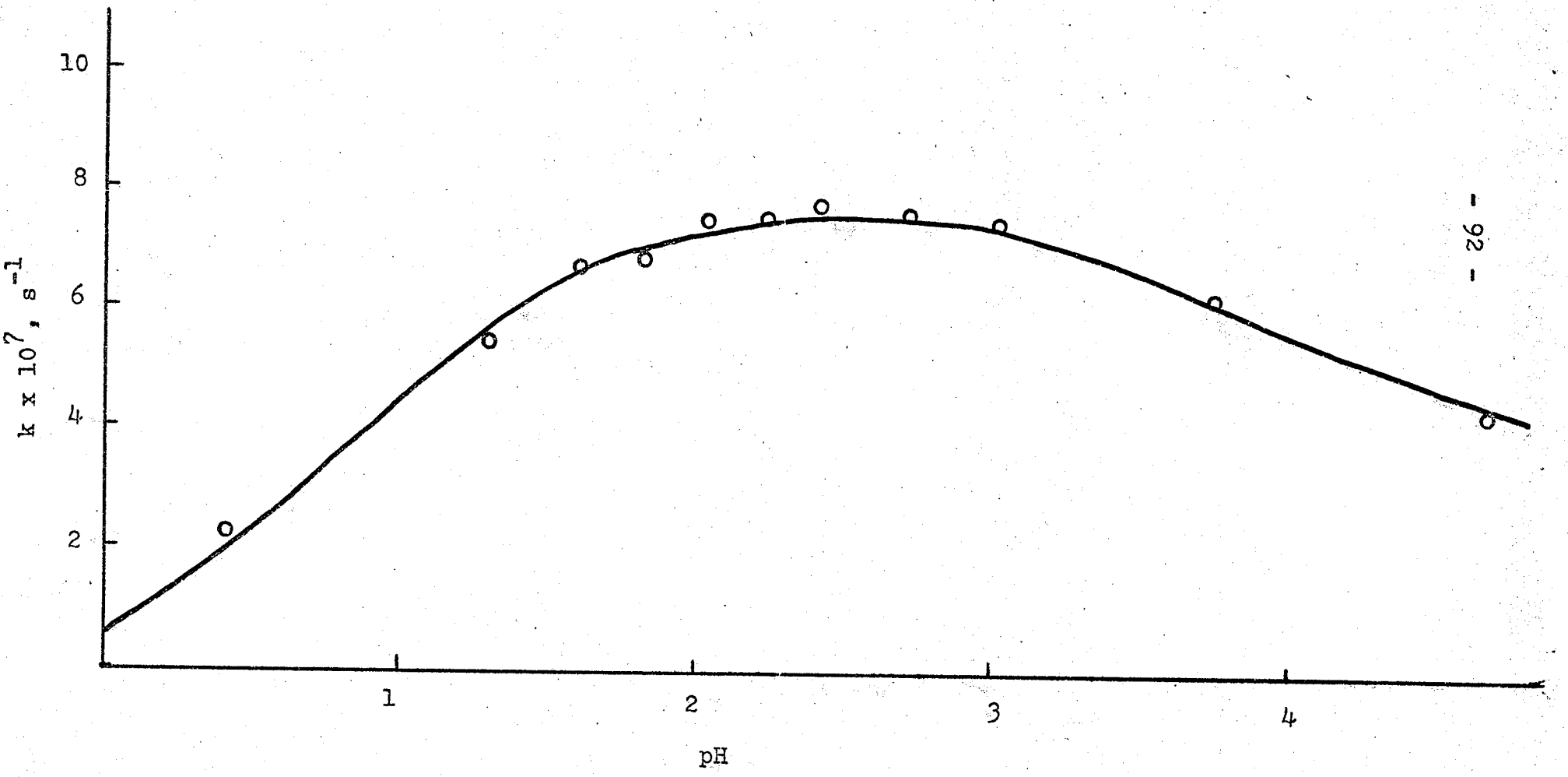
pH	$[H^+] \times 10^3$	$k \times 10^7$, s^{-1}
0.2	631	1.23
0.4	398	1.91
0.6	251	2.66
0.8	159	3.52
1.2	63.1	5.26
1.6	25.1	6.55
2.0	10.0	7.21
2.4	3.98	7.49
2.8	1.59	7.52
3.2	0.631	7.20
3.6	0.251	6.41
4.0	0.100	5.75
4.4	0.0398	4.95
4.8	0.0159	4.39

FIGURE 14

Plot of calculated rate constants versus pH for the decarboxylation of 6-methylpicolinic acid at 150°C, $\mu = 1.0$

— Rate constants calculated from Equation (19)

o Experimental rate constants


10
8
6
4
2
k x 10^7, s^-1
1
2
3
4
pH

3. 5-Nitropicolinic acid

In the preceding section, 6-methylpicolinic acid was found to decarboxylate at a slower rate than its parent acid at 150°C, and consequently, the determination of its dissociation constants at a temperature corresponding to its decarboxylation temperature was not possible. It was therefore decided to continue the search for a substituted picolinic acid which can decarboxylate at a temperature below 100°C.

5-Nitropicolinic acid was chosen because nitro, in contrast to methyl which is electron-donating, is considered to be a strong electron-withdrawing group. Since the electron-donating substituent was found to inhibit the rate, the electron-withdrawing substituent might be expected to enchance the rate.

The UV spectra of 5-nitropicolinic acid and its decarboxylation product, 3-nitropyridine, are shown in Figure 15, and 285 mμ was chosen as the wavelength for rate measurement.

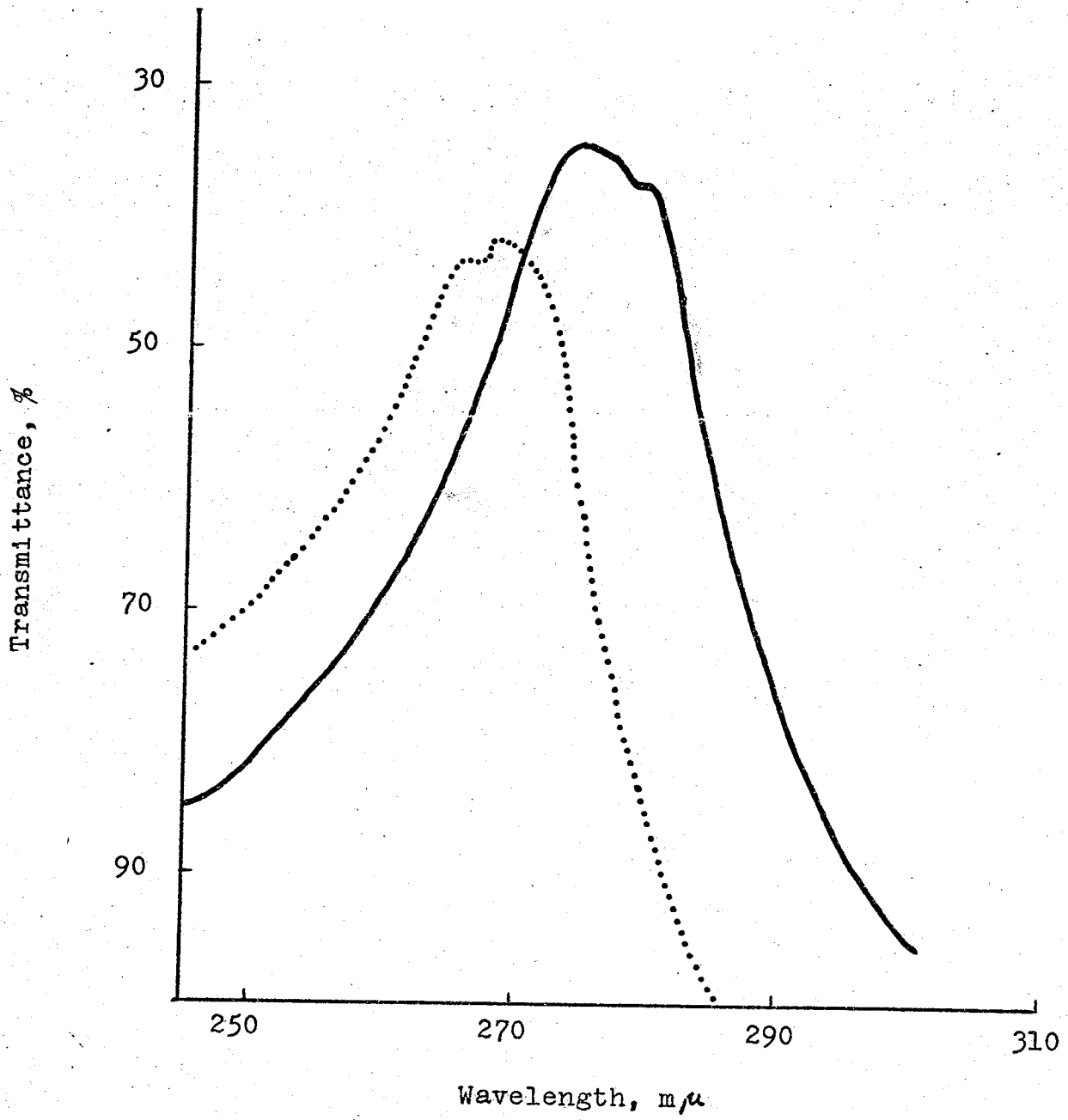
The decomposition was found to be first-order, and

FIGURE 15

The UV spectra of 5-nitropicolinic acid and 3-nitropyridine in 1N NaOH

——— 5-Nitropicolinic acid, C = 2.5×10^{-4} M

····· 3-Nitropyridine, C = 2.5×10^{-4} M


30
50
70
90
Transmittance, %
250
270
290
310
Wavelength, mμ

the plot of logarithm of absorbance against time gave excellent fits up to 90% conversion. A typical plot of log. absorbance versus time is shown in Figure 16, and the rates obtained at 150°C on the buffered solutions with pH measured at 25°C and μ= 1.0 are recorded in Table XVII. As shown in Table XVII, the rate of decarboxylation of 5-nitropicolinic acid is, as expected, faster than its parent acid. However, it is not fast enough to decarboxylate at a temperature below 100°C where the dissociation constants can be measured. Similar to picolinic and 6-methylpicolinic acids, a maximum can also be observed in the rate vs. pH profile for 5-nitropicolinic acid; but, since the dissociation constants of this acid were not reported in the literature at any temperature, a detailed investigation of the pH dependence of this acid was felt not to be useful. However, more detailed discussion of the decarboxylation mechanism of picolinic acid will be found in the next section on the studies on quinolinic acid.

FIGURE 16

A typical plot of log. absorbance versus time for the decarboxylation of 5-nitropicolinic acid at 150°C, μ = 1.0 .

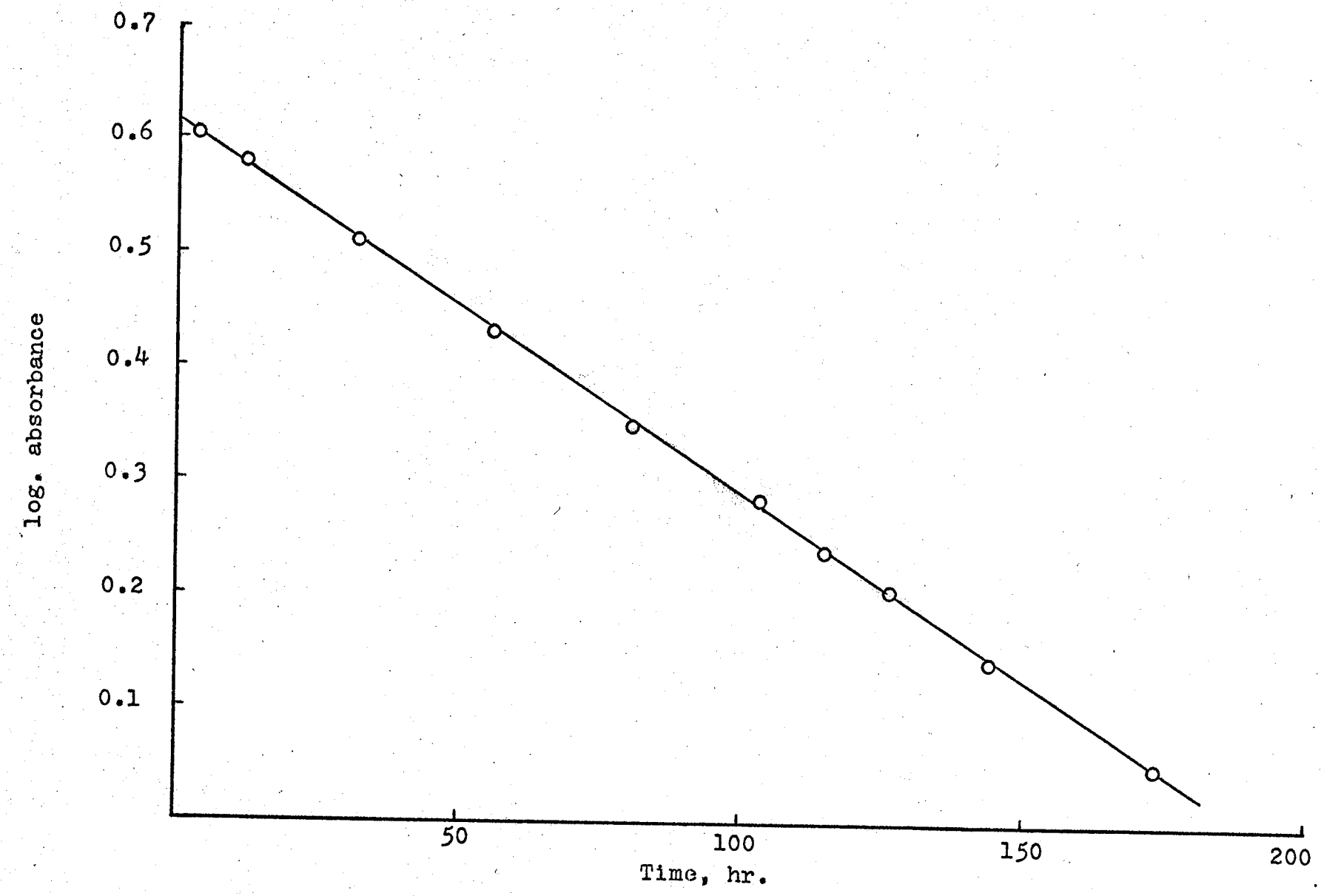

0.7
0.6
0.5
0.4
0.3
0.2
0.1
log. absorbance
50
100
150
200
Time, hr.

TABLE XVII

RATES OF DECARBOXYLATION OF 5-NITROPICOLINIC ACID AT 150°C, $\mu = 1.0$

Buffer*	pH at 25°C	$k \times 10^6$, s^{-1}
A	0.122	1.73
A	0.752	2.09
A	1.50	2.18
B	2.47	1.92

* The symbols A and B refer to HCl and HCl-NaH_2PO_4 buffers respectively.

4. Quinolinic acid

Since it was found in the preceding sections that 6-methyl- and 5-nitropicolinic acids decarboxylate too slowly at a temperature below 100°C, the search for another substituted picolinic acid which can decarboxylate conveniently below 100°C was continued.

A paper on the chromatographic determination of quinolinic acid (pyridine-2,3-dicarboxylic acid) among other pyridine derivatives was reported by Pallini et. al. (69), and the most striking aspect of this paper was its comments about the decarboxylation of quinolinic acid to nicotinic acid (3-pyridinecarboxylic acid). It was reported by these authors that quinolinic acid could be decarboxylated quantitatively in aqueous solution to nicotinic acid when heated for 21 hours at 120°C in a sealed tube. Quinolinic acid can also be regarded as a substituted picolinic acid, and since it can decarboxylate quantitatively to nicotinic acid in only 21 hours at 120°C, it will be very likely that it can also decarboxylate at a measurable rate at a temperature below 100°C.

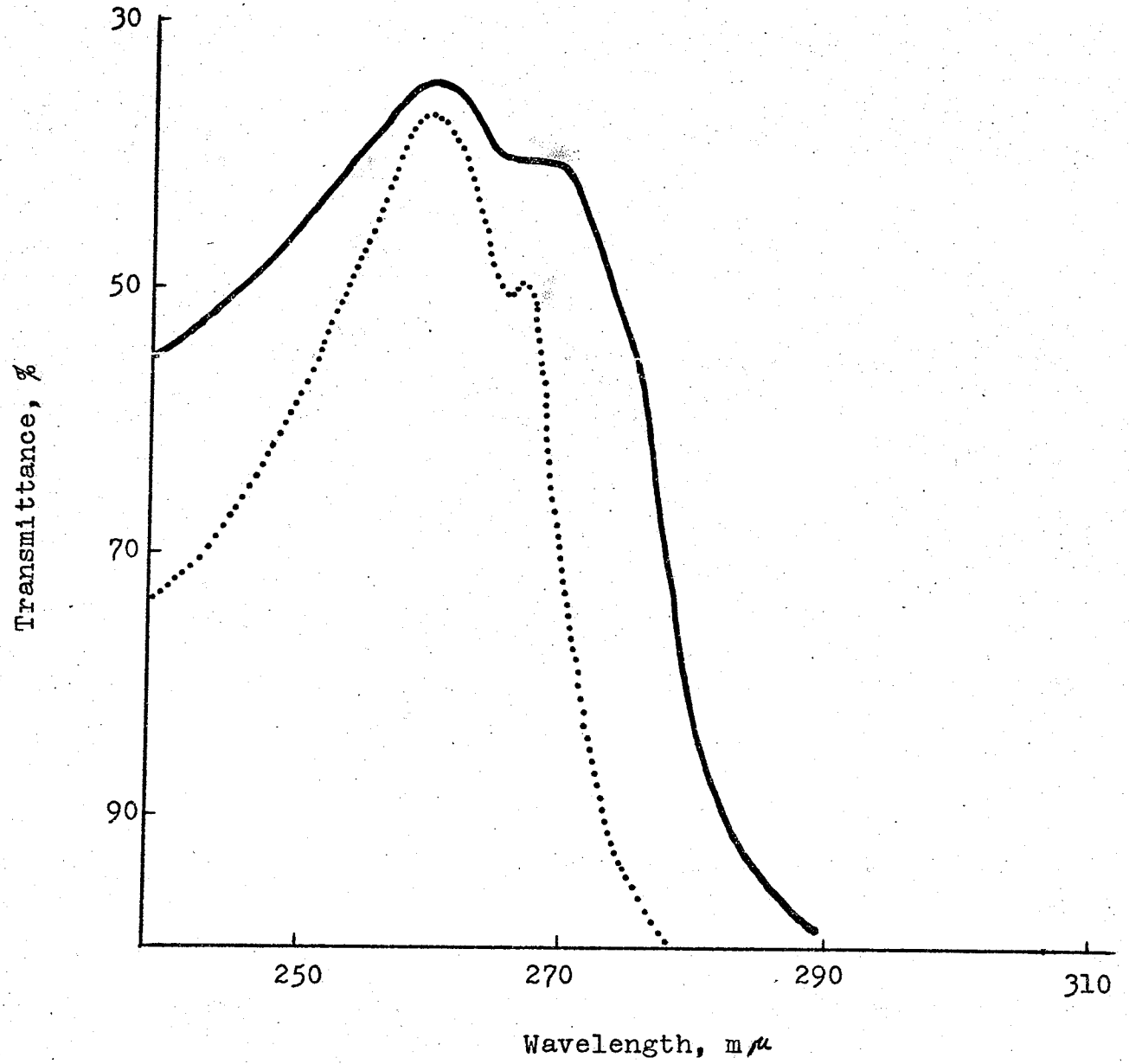
The UV spectra of quinolinic acid and its decarboxylation product, nicotinic acid, are shown in Figure 17,

FIGURE 17

The UV spectra of quinolinic and nicotinic acids in 1N NaOH

——— Quinolinic acid, C = 2.5×10^{-4} M

····· Nicotinic acid, C = 2.5×10^{-4} M


30
50
70
90
Transmittance, %
250
270
290
310
Wavelength, mμ

and 280 mμ was chosen as the wavelength for rate measurement.

It was found that quinolinic acid, as expected, can decarboxylate at a measurable rate at 95°C, and its decarboxylation product, nicotinic acid, is very stable at this temperature. First-order plots of the logarithm of absorbance against time gave excellent fits up to more than 90% conversion. A typical plot of log. absorbance versus time for the decarboxylation of quinolinic acid at 95°C, and $\mu = 1.0$ is shown in Figure 18.

Since the decarboxylation of quinolinic acid was carried out at 95°C and the determination of pH at that temperature is possible, the pH measurements were made at both 25°C and 95°C on the same series of buffer solutions covering the range of each buffer compound and having the same composition as those used for rate determinations. The effect of temperature on buffered solutions is shown in Table XVIII.

By plotting pH at 95°C against pH at 25°C, linear calibration curves were obtained which could be used to calculate from measurements made at 25°C the pH of solutions to be used for rate determinations at 95°C. Differences in

FIGURE 18

A typical plot of log. absorbance versus time for the decarboxylation of quinolinic acid at 95°C, $\mu = 1.0$.

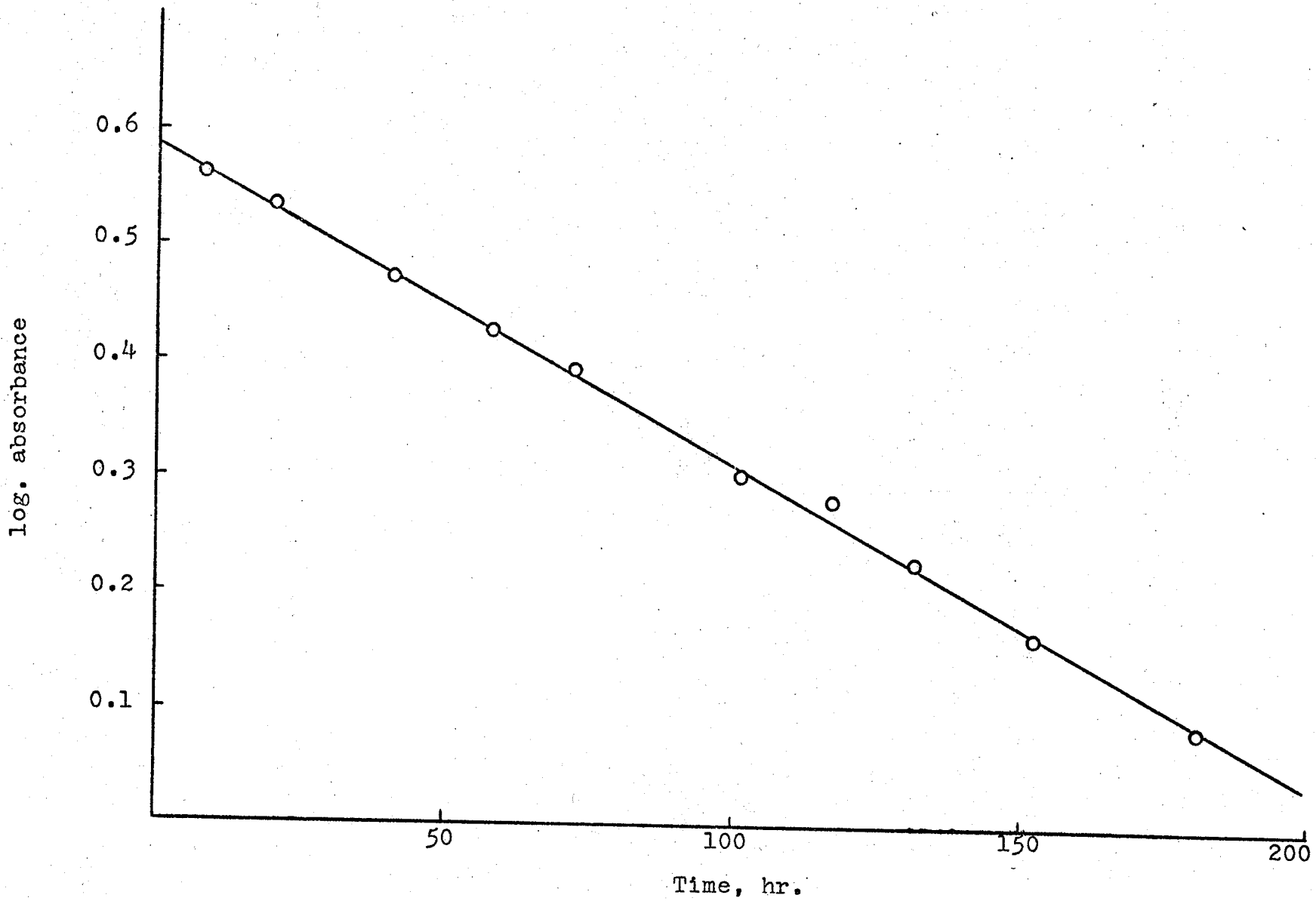

log. absorbance
0.6
0.5
0.4
0.3
0.2
0.1
50
100
150
200
Time, hr.

TABLE XVIII

THE EFFECT OF TEMPERATURE ON THE pH's OF THE BUFFER SOLUTIONS

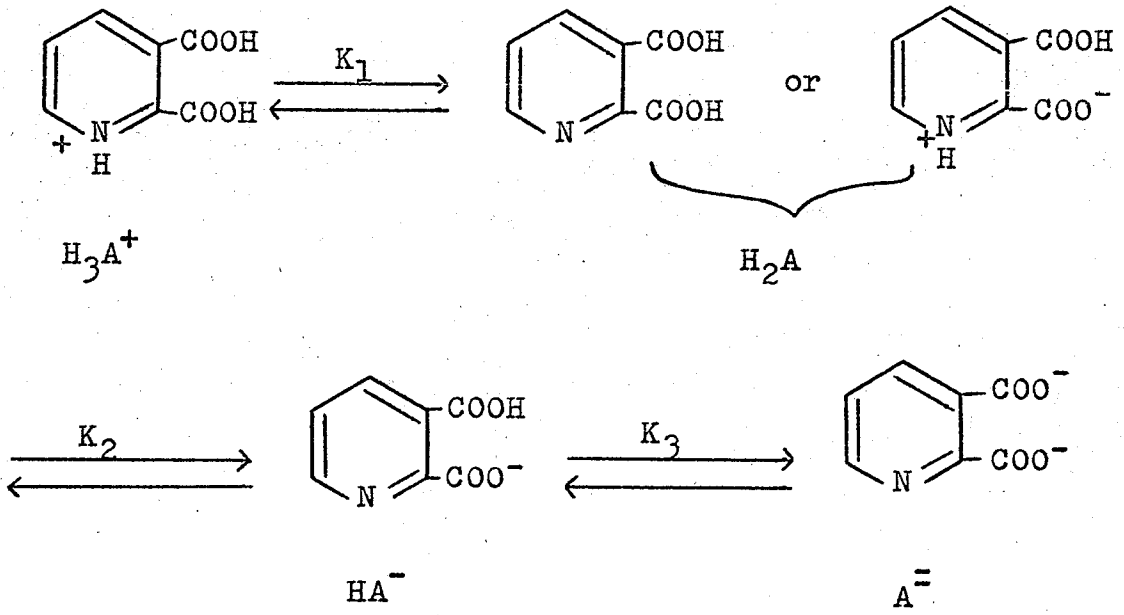
Buffer*	pH at 25°C	pH at 95°C
A	0.115	0.163
A	1.25	1.31
A	2.00	2.06
B	2.39	2.46
B	2.88	2.95
B	3.92	3.98
C	5.03	5.11
C	6.21	6.27

* The symbols A, B and C refer to HCl; HCl-NaH_2PO_4 ; and NaH_2PO_4-Na_2HPO_4 buffers respectively.

pH at the two temperatures were usually less than 0.1 pH unit.

Table XIX shows the variation with pH in the rate of decarboxylation of quinolinic acid at 95°C in buffered solutions of ionic strength 1.0.

In an aqueous solution of quinolinic acid, the following equilibria were suggested by Lecco and Saper (59):



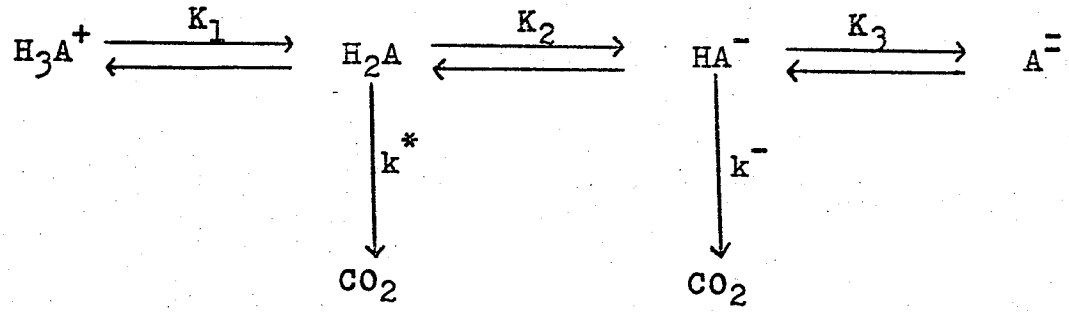
If the mechanism proposed for picolinic acid also applies to quinolinic acid, i.e., the reaction, besides involving the decarboxylation of the neutral species, H_2A, may also involve the decarboxylation of the monoanion, HA^-, then, it can be represented in the following scheme:

TABLE XIX

RATES OF DECARBOXYLATION OF QUINOLINIC ACID AT 95°C, μ = 1.0

Buffer*	pH at 95°C	k x 10^6, s^{-1}
A	0.079	1.69
A	0.189	1.92
A	0.373	2.24
A	0.418	2.26
A	0.464	2.34
A	0.570	2.50
A	0.702	2.57
A	0.781	2.66
A	0.907	2.71
A	0.971	2.76
A	1.11	2.76
A	1.35	2.67
A	1.52	2.56
A	1.61	2.42
A	1.90	2.14
B	2.19	1.84
B	2.87	1.25
B	3.41	1.08
B	3.98	1.06

* The symbols A and B refer to HCl and HCl-NaH_2PO_4 buffers respectively.



where $$K_1 = \frac{[H_2A][H^+]}{[H_3A^+]} \qquad [H_3A^+] = \frac{[H_2A][H^+]}{K_1}$$

$$K_2 = \frac{[H^+][HA^-]}{[H_2A]} \qquad [HA^-] = \frac{K_2[H_2A]}{[H^+]}$$

and $$[H_3A^+] + [H_2A] + [HA^-] + [A^=] = [C]$$

Since it was reported by Lecco and Saper (59) that pK_2 and pK_3 of quinolinic acid at 25°C were 2.43 and 5.06 respectively, the concentration of $A^=$ in the pH region where our rate measurements were made is very small, and therefore

$$[H_3A^+] + [H_2A] + [HA^-] = [C]$$

$$\frac{[H_2A][H^+]}{K_1} + [H_2A] + \frac{K_2[H_2A]}{[H^+]} = [C]$$

$$[H_2A] = \frac{[C]}{[H^+]/K_1 + 1 + K_2/[H^+]}$$

For $H_2A \xrightarrow{k^*} CO_2$

the rate expression is:

$$\frac{-d[C]}{dt} = k[C] = k^*[H_2A]$$

$$= \frac{k^*[C]}{[H^+]/K_1 + 1 + K_2/[H^+]}$$

or $$k = \frac{k^*}{[H^+]/K_1 + 1 + K_2/[H^+]} \quad \text{.....(20)}$$

For $HA^- \xrightarrow{k^-} CO_2$

the rate expression is:

$$\frac{-d[C]}{dt} = k[C] = k^-[HA^-]$$

$$= \frac{k^- K_2[C]}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)}$$

or $$k = \frac{k^- K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \quad \text{.....(21)}$$

and the overall rate for the reaction is the addition of equations (20) and (21):

$$k = \frac{k^{*}[H^{+}] + k^{-}K_2}{[H^{+}]\left([H^{+}]/K_1 + 1 + K_2/[H^{+}]\right)} \qquad \text{.....(22)}$$

Since the rates of decarboxylation of quinolinic acid were determined at 95°C, and the measurement of dissociation constants at this temperature is possible, K_2 of this acid was determined spectrophotometrically at 95°C and ionic strength of 1.0 by the method of Dunn and Kung (28). The absorbance measurements of various buffered solutions of this acid were carried out at 262 mμ. At this wavelength, the absorbance due to free acid, H_2A, is much more significant than due to the monoanion, HA^{-}. The data are shown in Table XX.

For the dissociation of quinolinic acid in water,

$$H_2A \xrightleftharpoons{K_2} HA^{-} + H^{+}$$

the dissociation constant, K_2, may be expressed by

$$K_2 = \frac{[HA^{-}][H^{+}]}{[H_2A]}$$

TABLE XX

EXPERIMENTAL DATA OF pH AND CORRESPONDING ABSORBANCE OF THE VARIOUS BUFFERED SOLUTIONS OF QUINOLINIC ACID AT 95°C

μ = 1.0 t = 95°C

C = 1.5×10^{-4} M λ = 262 mμ

Buffer*	pH at 95°C	Absorbance
A	0.301	0.335
A	0.840	0.331
A	1.29	0.322
A	1.68	0.298
B	2.15	0.273
B	2.42	0.257
B	2.70	0.245
B	2.99	0.239
B	3.18	0.237
B	3.65	0.237
B	4.09	0.237

* The symbols A and B refer to HCl and HCl-NaH_2PO_4 buffers respectively.

where the quantities in brackets represent molar concentrations. If the total concentration of acid (ionized plus un-ionized) is C, i.e., $C = [H_2A] + [HA^-]$, then

$$K_2 = \frac{[HA^-][H^+]}{C - [HA^-]} = \frac{[H^+]\left(C - [H_2A]\right)}{[H_2A]}$$

so that $$K_2C - K_2[HA^-] = [HA^-][H^+]$$

$$K_2C = [HA^-][H^+] + K_2[HA^-]$$

$$= [HA^-]\left([H^+] + K_2\right)$$

$$[HA^-] = \frac{K_2C}{[H^+] + K_2}$$

Similarly $$[H_2A] = \frac{C[H^+]}{[H^+] + K_2}$$

Since hydronium ion does not absorb in the visible or ultraviolet regions, the total absorbance, A, of the equilibrium solution of $H_2A \rightleftarrows HA^-$ is given by

$$A = A_{H_2A} + A_{HA^-}$$

where A_{H_2A} is the absorbance of the equilibrium concentration of un-ionized acid, H_2A, and A_{HA^-} is the absorbance of the equilibrium concentration of monoanion HA^-. For a

1cm cell, the Beer-Lambert relationship converts the preceding equation into

$$A = \varepsilon_{H_2A}[H_2A] + \varepsilon_{HA^-}[HA^-]$$

where ε = molar absorptivity.

When the expressions for $[H_2A]$ and $[HA^-]$ derived above are introduced, this becomes

$$A = C \times \left(\frac{\varepsilon_{H_2A}[H^+] + \varepsilon_{HA^-}K_2}{[H^+] + K_2} \right)$$

Since A, $[H^+]$, and C are observable quantities, the above equation contains only three unknowns : K_2, ε_{H_2A} and ε_{HA^-}. The computer program prepared by Leggate and Dunn (60) was used to calculate K_2. The pK_2 obtained by the computer was 1.90 ± 0.03, and the values of $C\varepsilon_{H_2A}$ and $C\varepsilon_{HA^-}$ were 0.339 ± 0.002 and 0.233 ± 0.001 respectively. The calculated curve and experimental points are shown in Figure 19.

If we consider the general rate expression, equation (22), i.e.,

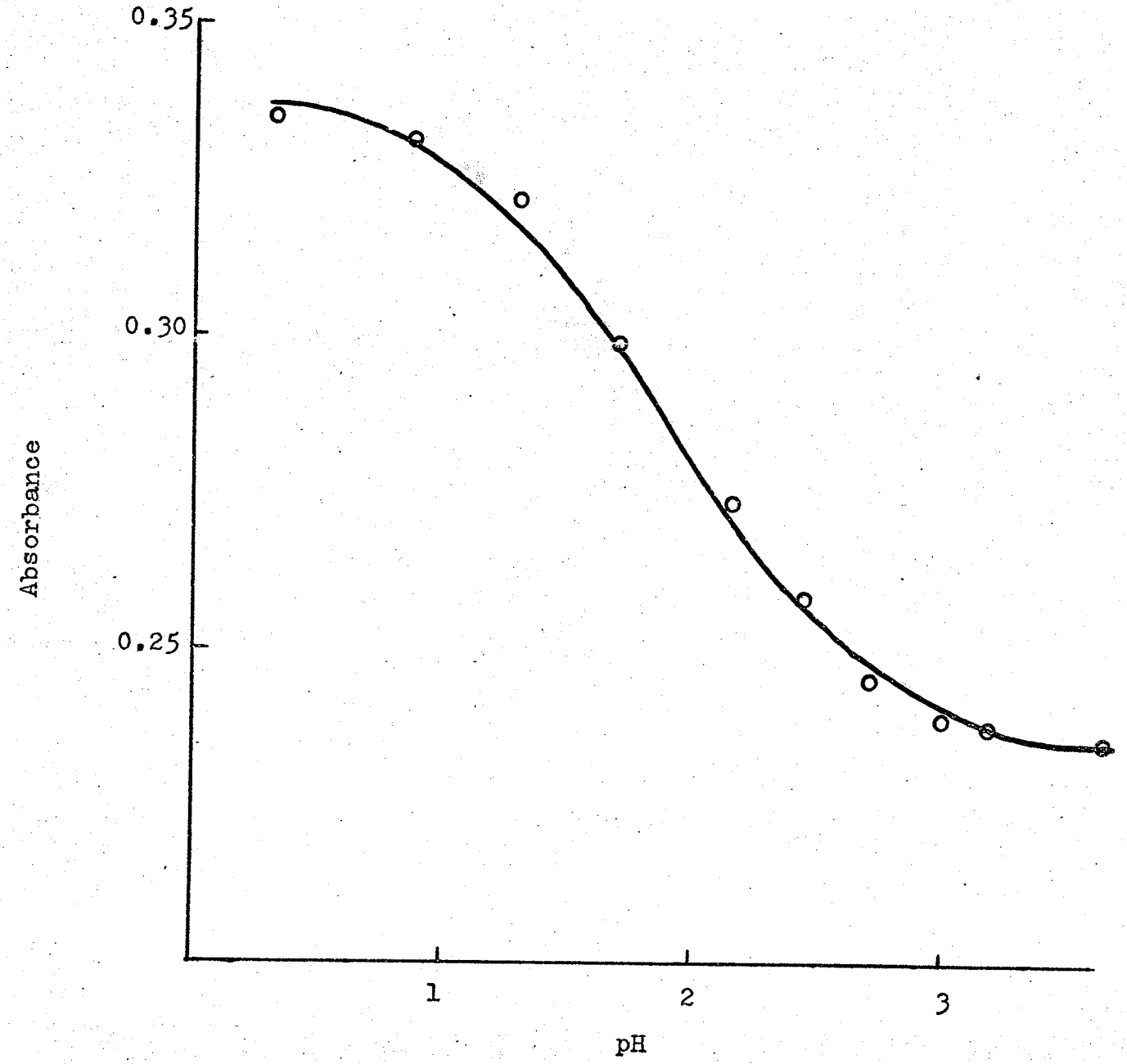
$$k = \frac{k^*[H^+] + k^-K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \qquad \ldots\ldots(22)$$

FIGURE 19

Plot of pH and corresponding absorbance of the various buffered solutions of quinolinic acid at $95^{\circ}C$, $\mu = 1.0$

—— Curve obtained from the computer

o Experimental points


0.35
0.30
0.25
Absorbance
1
2
3
pH

it can be simplified at the region where pH < 0.9. Since pK_2 of quinolinic acid was determined to be 1.90 at 95°C, the term $K_2/[H^+]$ is not important in this region, and

$$k = \frac{k^*[H^+] + k^-K_2}{[H^+]\left([H^+]/K_1 + 1\right)} \qquad \text{.....(23)}$$

If we further assume that k^* would have a value at least as great as k^-, and since $K_2 \ll [H^+]$, then $k^*[H^+] \gg k^-K_2$, and equation (23) thus becomes

$$k = \frac{k^*K_1}{[H^+] + K_1}$$

$$\text{or} \quad 1/k = [H^+]/k^*K_1 + 1/k^* \qquad \text{.....(24)}$$

The data (pH < 0.9) from Table XIX were used to plot $1/k$ vs. $[H^+]$. The calculations are shown in Table XXI, and are plotted in Figure 20.

From the linear plot, the following values were obtained:

$$k^* = 3.18 \times 10^{-6} \text{ sec}^{-1}$$

$$k^*K_1 = 2.99 \times 10^{-6}$$

$$\text{or} \quad K_1 = 9.55 \times 10^{-1}$$

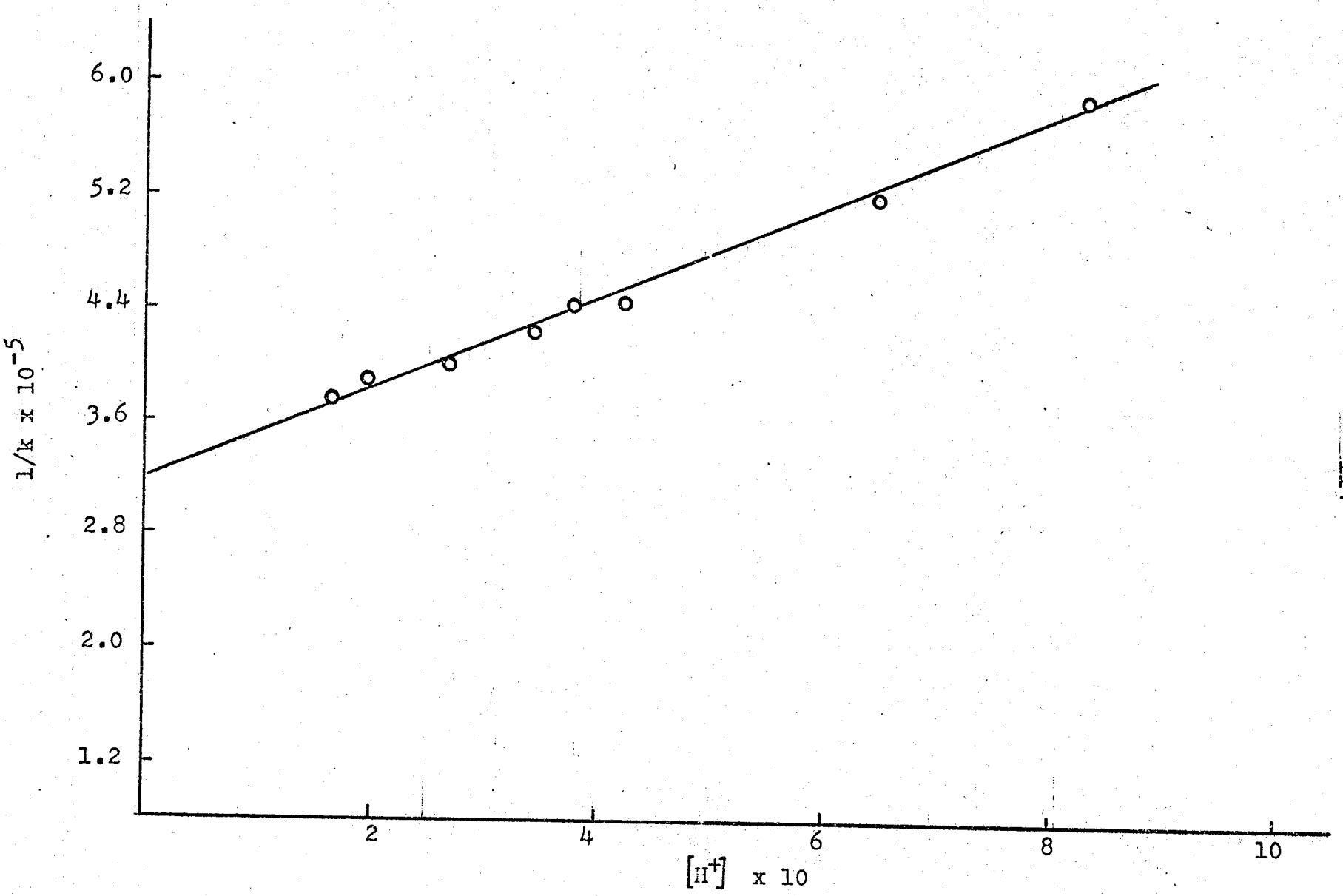
TABLE XXI

CALCULATIONS FOR THE PLOT OF 1/k VS. $[H^+]$ FOR QUINOLINIC ACID

pH	$[H^+] \times 10^1$	$k \times 10^6$	$1/k \times 10^{-5}$
0.079	8.34	1.69	5.92
0.189	6.47	1.92	5.21
0.373	4.24	2.24	4.46
0.418	3.82	2.26	4.43
0.464	3.44	2.34	4.27
0.570	2.69	2.50	4.00
0.702	1.99	2.57	3.89
0.781	1.66	2.66	3.76

FIGURE 20

Plot of 1/k versus $[H^+]$ for quinolinic acid


6.0
5.2
4.4
3.6
2.8
2.0
1.2
1/k x 10^-5
2
4
6
8
10
[H+] x 10

The general rate expression, equation (22), can also be simplified if we consider the region where pH $>$ 1.5. Since the K_1 obtained from the previous plot was 9.55×10^{-1}, the term $[H^+]/K_1$ will be negligible and the equation becomes

$$k = \frac{k^*[H^+] + k^-K_2}{[H^+] + K_2}$$

or $$k\left([H^+] + K_2\right) = k^*[H^+] + k^-K_2$$

The plot of $k\left([H^+] + K_2\right)$ vs. $[H^+]$ is shown in Figure 21, and the calculations are shown in Table XXII. From the linear plot, the values of k^* and k^- are:

$$k^* = 3.32 \times 10^{-6} \text{ sec}^{-1}$$

$$k^- = 1.02 \times 10^{-6} \text{ sec}^{-1}$$

The values of k^* obtained from Figures 20 and 21 are quite agreeable, and the average value would be $3.25 \times 10^{-6} \text{sec}^{-1}$.

Substituting the values of k^*, k^-, K_1 and K_2 into the general rate expression gives:

$$k = \frac{3.25 \times 10^{-6}[H^+] + 1.29 \times 10^{-8}}{[H^+]\left(\frac{[H^+]}{9.55 \times 10^{-1}} + 1 + \frac{1.26 \times 10^{-2}}{[H^+]}\right)} \qquad \ldots\ldots(25)$$

FIGURE 21

Plot of $k\left([H^+] + K_2\right)$ versus $[H^+]$ for quinolinic acid

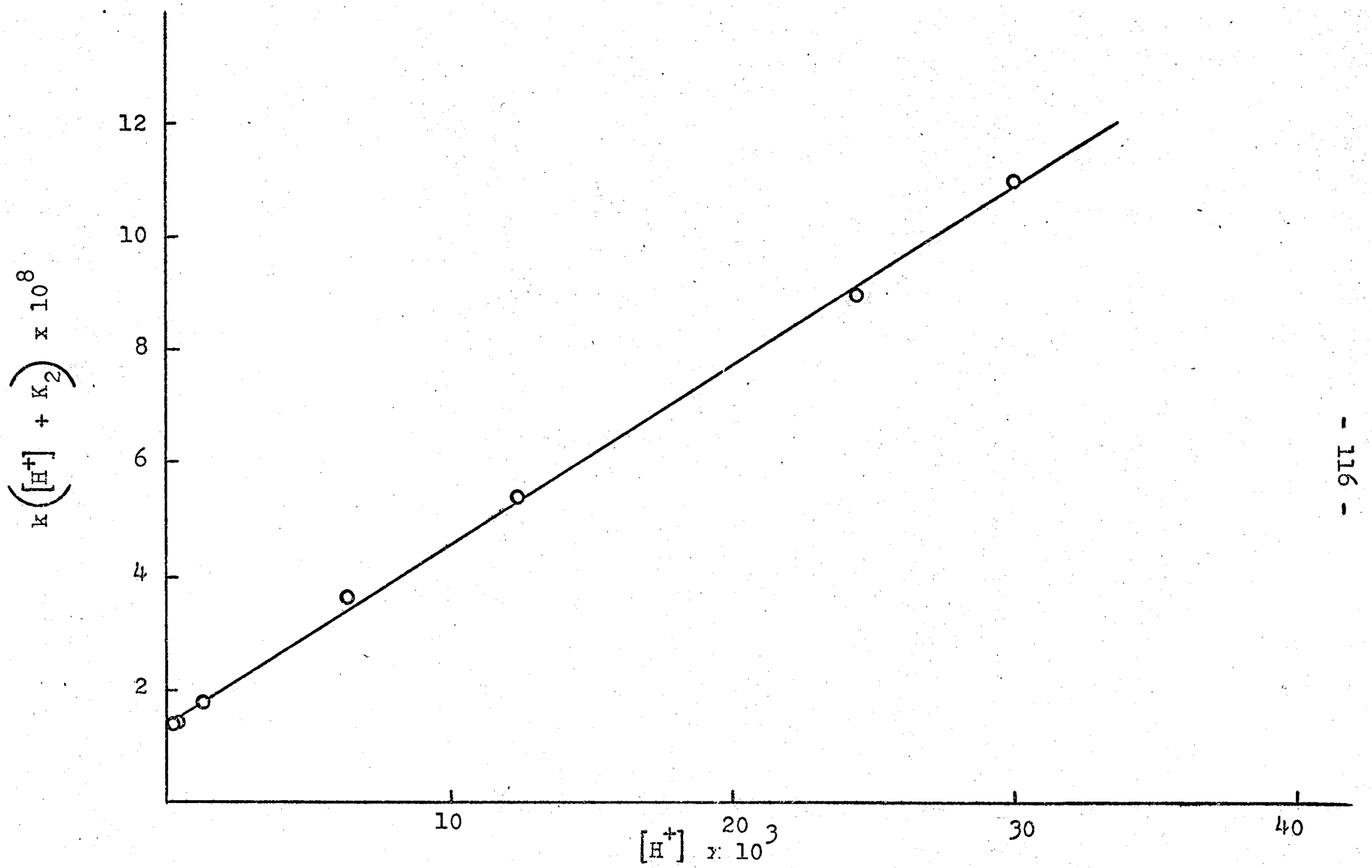

12
10
8
6
4
2
$k\left([H^+] + K_2\right) \times 10^8$
10
20
30
40
$[H^+] \times 10^3$

TABLE XXII

CALCULATIONS FOR THE PLOT OF $k\left([H^+] + K_2\right)$ VS. $[H^+]$ FOR QUINOLINIC ACID

pH	$[H^+] \times 10^3$	$\left([H^+] + K_2\right) \times 10^{2*}$	$k \times 10^6$	$k\left([H^+] + K_2\right) \times 10^8$
1.52	30.2	4.28	2.56	11.0
1.61	24.6	3.72	2.42	9.00
1.90	12.6	2.52	2.14	5.39
2.19	6.46	1.91	1.84	3.52
2.87	1.35	1.40	1.25	1.75
3.41	0.389	1.30	1.08	1.40
3.98	0.105	1.27	1.06	1.35

* $K_2 = 1.26 \times 10^{-2}$

Equation (25) was used to calculate k at varying hydrogen ion concentrations. The theoretical rate vs. pH curve for quinolinic acid, together with the experimental results, are shown in Figure 22 and the calculations are shown in Table XXIII. As shown in Figure 22, the experimental results give excellent fits to the calculated values.

In order to obtain more information about the decarboxylation mechanism, the C^{13}-kinetic isotope effect of quinolinic acid at 95°C and $\mu = 1.0$ was determined, and the results are shown in Table XXIV.

The general rate expression, equation (22), can be rewritten for the individual isotopes as:

$$k_{12} = \frac{k^*_{12}[H^+] + k^-_{12}K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \qquad .....(26)$$

$$k_{13} = \frac{k^*_{13}[H^+] + k^-_{13}K_2}{[H^+]\left([H^+]/K_1 + 1 + K_2/[H^+]\right)} \qquad .....(27)$$

$$\frac{k_{12}}{k_{13}} = \frac{k^*_{12}[H^+] + k^-_{12}K_2}{k^*_{13}[H^+] + k^-_{13}K_2} \qquad .....(28)$$

FIGURE 22

Plot of calculated rate constants versus pH for the decarboxylation of quinolinic acid at 95°C, $\mu = 1.0$

— Rate constants calculated from Equation (25)

o Experimental rate constants

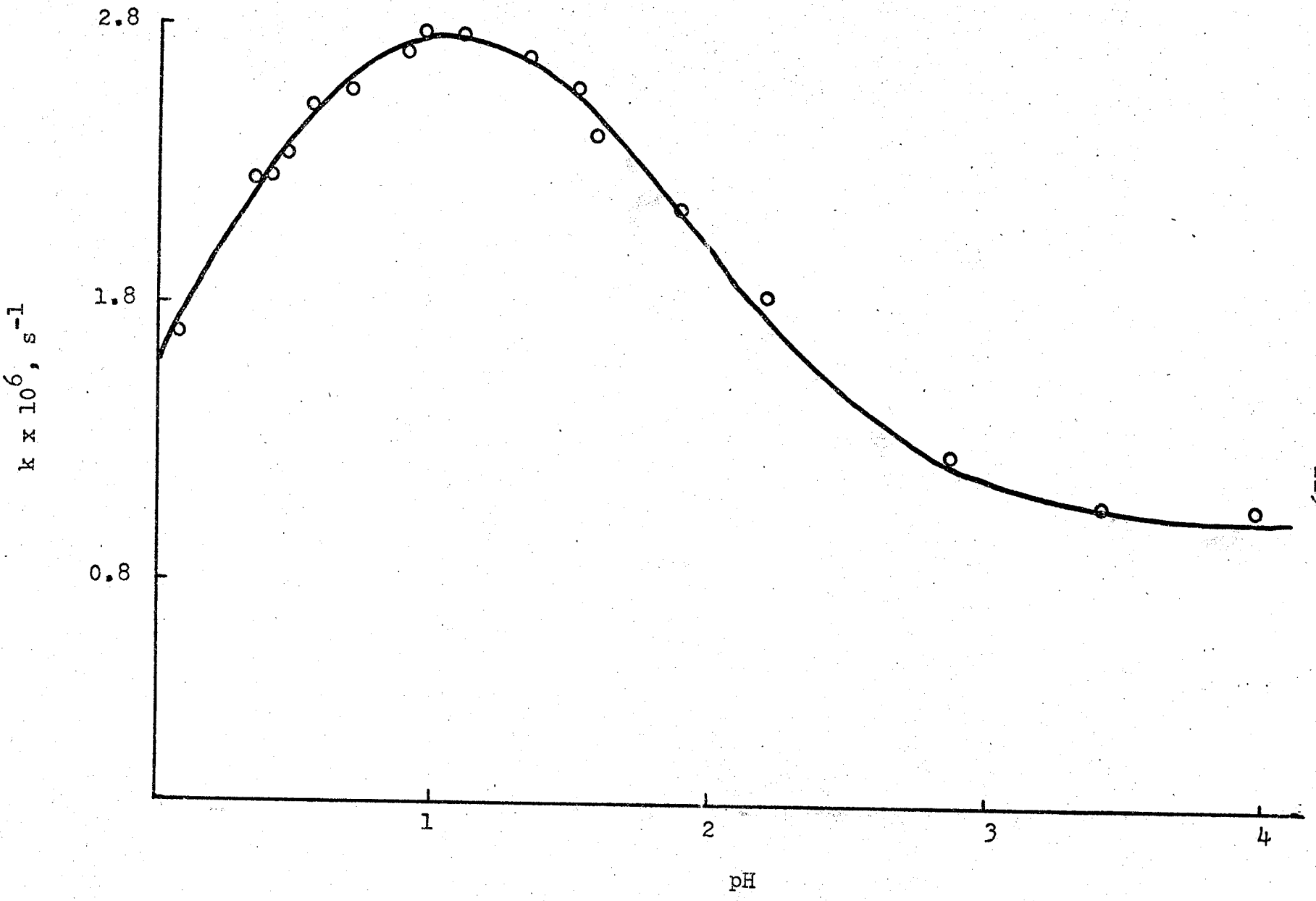

2.8
1.8
0.8
k x 10^6, s^-1
1
2
3
4
pH

TABLE XXIII

RATE CONSTANTS CALCULATED FROM EQUATION (25) FOR THE DECARBOXYLATION OF QUINOLINIC ACID AT 95°C, $\mu = 1.0$

pH	$[H^+] \times 10^3$	$k \times 10^6$, s^{-1}
0	1000	1.58
0.2	631	1.95
0.4	398	2.27
0.6	251	2.51
0.8	159	2.67
1.0	100	2.73
1.2	63.1	2.73
1.4	39.8	2.64
1.6	25.1	2.46
1.8	15.9	2.24
2.0	10.0	2.00
2.2	6.31	1.77
2.4	3.98	1.56
2.6	2.51	1.40
2.8	1.59	1.27
3.0	1.00	1.19
3.2	0.631	1.14
3.4	0.398	1.09
3.6	0.251	1.07
4.0	0.100	1.04
4.6	0.0251	1.03

TABLE XXIV

C^{13}-KINETIC ISOTOPE EFFECTS ON THE DECARBOXYLATION OF QUINOLINIC ACID AT 95°C and $\mu = 1.0$

Buffer*	pH at 95°C	% Reaction	$^{13}CO_2/^{12}CO_2$	$100(k_{12}/k_{13} - 1)$
A	1.04	100.0	0.010424	
A	1.04	100.0	0.010419	
A	1.04	100.0	0.010420	
A	0	38.31	0.010197	2.82
A	0	6.686	0.010144	2.84
A	0	6.919	0.010140	2.87
B	2.63	6.422	0.010152	2.74
B	2.63	6.758	0.010154	2.74
B	2.63	6.420	0.010157	2.70
B	3.95	9.445	0.010163	2.67
B	3.95	9.075	0.010165	2.66
B	3.95	6.764	0.010161	2.67

* The symbols A and B refer to $HClO_4$ and $HClO_4$-NaH_2PO_4 buffers respectively.

From equation (28)

$$\frac{k_{12}}{k_{13}} = \frac{\frac{k^*_{12}}{k^-_{12}}[H^+] + K_2}{\frac{k^*_{13}}{k^-_{13}}[H^+] + K_2} \times \frac{k^-_{12}}{k^-_{13}}$$

$$= \frac{\frac{k^*_{12}}{k^-_{12}}[H^+] + K_2}{\left(\frac{k^*_{13}}{k^*_{12}} \times \frac{k^*_{12}}{k^-_{12}} \times \frac{k^-_{12}}{k^-_{13}}\right)[H^+] + K_2} \times \frac{k^-_{12}}{k^-_{13}}$$

.....(29)

At pH = 0 or $[H^+] = 1$

$$k^*_{12}[H^+] \gg k^-_{12}K_2$$

$$k^*_{13}[H^+] \gg k^-_{13}K_2$$

and equation (28) becomes

$$\frac{k_{12}}{k_{13}} = \frac{k^*_{12}}{k^*_{13}}$$

and k_{12}/k_{13} at pH = 0 was found to be 1.0284,

therefore $k^*_{12}/k^*_{13} = 1.0284$ .....(30)

At pH = 3.948

$$k^-_{12}K_2 \gg k^*_{12}[H^+]$$

$$k^-_{13}K_2 \gg k^*_{13}[H^+]$$

and equation (28) becomes

$$k_{12}/k_{13} = k^-_{12}/k^-_{13} = 1.0267 \quad .....(31)$$

k^*_{12}/k^-_{12} was previously found to be 3.19 .....(32)

The values of k^*_{12}/k^*_{13}, k^-_{12}/k^-_{13}, k^*_{12}/k^-_{12} of equations (30), (31), (32) are substituted to equation (29), and at pH = 2.632, the calculated value of k_{12}/k_{13} is 1.0273 which is in excellent agreement with the experimental result.

From the results on the C^{13}-kinetic isotope effect of quinolinic acid, it is interesting to note that the isotope effect is slightly smaller in the anion than in the neutral species. Though the difference is small, it is outside the experimental error. In picolinic acid, the same trend was observed. This further agrees with the report by Zlotowski and Zielinski (98) who found that the C^{14}-isotope effect of picolinic acid is larger in acidic solvents than in basic ones (their results were quoted in page 44 of this Thesis).

5. Discussions on the decarboxylation mechanism of pyridine-carboxylic acids

In the preceding sections, a decarboxylation mechanism for picolinic and substituted picolinic acids has been proposed. This mechanism fits the experimental data for picolinic and 6-methylpicolinic acids very well if the pK_2's were assumed to change drastically from 25°C to 150°C, whereas pK_1's only change slightly. The work on the subsequent determination of the pK_2 of quinolinic acid at 95°C agrees very well with this assumption. Lecco and Saper (59) had reported that the pK_2 of quinolinic acid was 2.43 at 25°C and $\mu = 1.0$, but the pK_2 obtained in this work at 95°C and $\mu = 1.0$ was 1.90. That is, a change of more than 0.5 pK units was observed from 25°C to 95°C, and it would not be surprising if the pK_2's for both picolinic and 6-methylpicolinic would change more than one pK unit from 25°C to 150°C.

The pK_1 of quinolinic acid was not measured in this work, mainly because the pK_1 is so small (near zero) that when determining it spectrophotometrically, some UV spectra have to be measured at ionic strength of

greater than 1, whereas the ionic strengths of all the decarboxylation experiments performed on the pyridine-carboxylic acids were kept at a constant value of 1.0. Also, no work has been reported on the pK_1 of quinolinic acid at any temperature, and hence no comparison can be made with the pK_1 of 0.02 at 95°C obtained from the plot of 1/k vs. $[H^+]$. However, it is believed that the pK_1 obtained from the plot is reasonable since the pK_1 for pyridine-2,5-dicarboxylic acid at 25°C was reported to be 0.5 (69).

It is interesting to note that the ratio for the values k^* (rate constant of neutral species decarboxylation) and k^- (rate constant of anion decarboxylation) for quinolinic acid is about 3 to 1. Since the pH's and pK_2 of this acid were measured at the same temperature and same ionic strength in which the rate measurements were carried out, with the only assumption being the value of pK_1 which is believed to be quite reasonable, the values of k^* and k^- obtained would seem to be quite reliable. This further confirms the small ratio of k^* to k^- obtained earlier for picolinic and 6-methylpicolinic acids.

It must be remembered, however, that k^* is the rate constant for decarboxylation of the total of neutral species, unionized acid plus zwitterion.

$$[N] = [HA] + [Z]$$

Earlier workers have postulated that only zwitterion decarboxylates (14; 44), and this seems to be a reasonable assumption in view of the great advantage of CO_2 over $COOH^+$ as leaving group in the decarboxylation of anthranilic (27) and salicylic acid (92) in aqueous solution. If only Z decarboxylates, then the rate constant k_Z^* for decarboxylation of Z could be much larger than the overall rate constant for decarboxylation, k^*, which is based on $[N]$.

Recalling (page 20) that $[Z]/[HA] = K_Z$, it follows that

$$[Z] = \frac{[N]K_Z}{K_Z + 1}$$

Then, if only Z decarboxylates,

$$\frac{d(CO_2)}{dt} = k^*[N] = k_Z^*[Z]$$

so that

$$k^* = \frac{k_Z^* K_Z}{K_Z + 1} \qquad \text{.....(33)}$$

It was reported (39) that the K_Z for picolinic, nicotinic and isonicotinic acids are 15, 10 and 25 respectively, and it is believed that the K_Z probably would be also large for quinolinic acid. Therefore, the k^* obtained in our experiments are approximately equal to k_Z^* (rate constant for the zwitterion decarboxylation).

It is perhaps surprising to note that the rate constant for the zwitterion decarboxylation (k_Z^*) is not much larger than the rate constant for the anion decarboxylation (k^-) in the pyridine-carboxylic acids. It might have been expected that the unit positive charge on the nitrogen of the zwitterion would have exerted a large stabilizing effect on the carbanion (ylid) product by loss of CO_2 and, presumably, therefore on the transition state leading to it. However, it may be noted that calculations suggest that the positive charge on the nitrogen of pyridinium ion does not much increase the already large electron deficiency at the α-carbon of pyridine in the ground state (32). The same calculations show that the electron attraction of the ring nitrogen, whether charged or uncharged, is exerted largely through the σ-bond skeleton of the ring rather than through the π bonds. If it is assumed that electronic effects in the

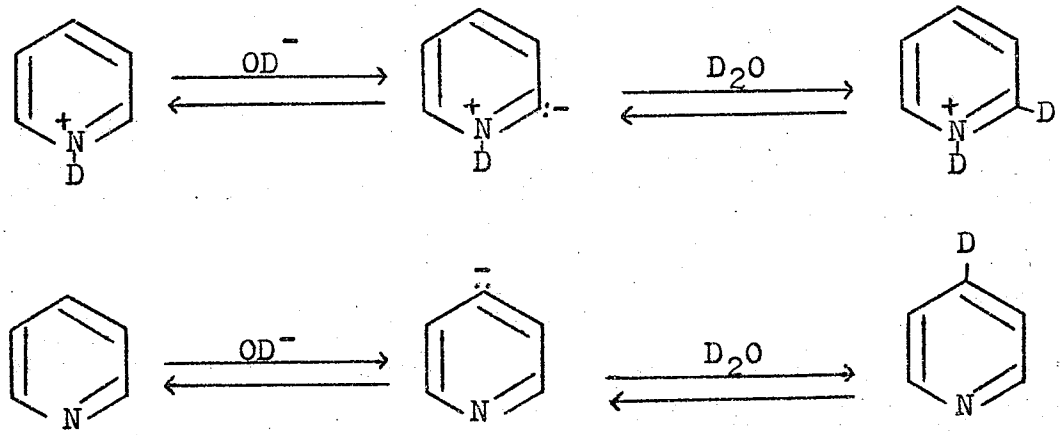
transition state are similar to those in the ground state, these calculations will agree with the report that picolinic acid decarboxylates much faster than nicotinic or isonicotinic acid (97), and our observation that nitro and methyl substituents in the 5 and 6 positions of picolinic acid have much less effect on the rate of decarboxylation than does the carboxyl group in the 3 position (quinolinic acid).

It is possible, however, that the accelerating effect of the ortho-carboxyl group in quinolinic acid could be at least partly steric. By forcing the 2-carboxyl group out of coplanarity with the ring, a 3-substituent would decrease conjugation of the 2-carboxyl group with the ring and so weaken the carbon-carbon bond to be broken in decarboxylation. It may be noted that 3-alkyl substituents have been found to increase the rate of decarboxylation of picolinic acid in non-aqueous solvents (15), although alkyl substituents elsewhere decrease the rate (15).

It is also possible, of course, that the 3-carboxyl group of quinolinic acid has some kind of neighbouring-group interaction with the departing CO_2 or the developing carbanion. This would be an interesting subject for future work.

Our mechanism proposed for the decarboxylation of picolinic acid involves anion decarboxylation, and in basic solution, this would be predominant. Carbanions can also be generated by other methods, and it is interesting to compare the ease of carbanion formation by decarboxylation and by other methods.

Kawazoe et al. (52) reported that pyridine exchanges hydrogen exclusively at the 2,6 positions at 220°C in D_2O -NaOD. However, Zoltewicz and Smith (99), in their study on the hydrogen-deuterium exchange for pyridine, reported that in D_2O-NaOD at 198°C, the pyridine protons at all positions exchange, and in the order of $4 \gg 3,5 \gg 2,6$. They suggested that the mechanism for exchange in basic solution most likely involved removal of a proton from pyridine by deuterioxide. The resultant pyridyl carbanion then abstracted a deuteron from solvent to form exchanged product. This can be shown as below:



If the order of reactivity reported by Zoltewicz and Smith (i.e., $4 \gg 3,5 \gg 2,6$) is correct, then in basic solution, 4-pyridinecarboxylic acid (isonicotinic acid) might be expected to decompose faster than 2-pyridine-carboxylic acid (picolinic acid). In order to test this hypothesis, the decarboxylation of isonicotinic acid was carried out in basic solution.

The UV spectra of isonicotinic acid and pyridine are shown in Figure 23, and 280 mμ was chosen for rate measurement.

The rate of decarboxylation of isonicotinic acid was measured spectrophotometrically as previously described for the other pyridine-carboxylic acids. However, no decarboxylation of isonicotinic acid was observed in 1N NaOH after 20 days (so that $k < 4 \times 10^{-9} sec^{-1}$), whereas the rate of decarboxylation of picolinic acid in 1N NaOH at the same temperature was found to be about $5 \times 10^{-7} sec^{-1}$. In other words, the rate of decarboxylation is in the order of $2 > 4$, even when it is the carboxylate salt rather than the carboxylic acid which is decarboxylating.

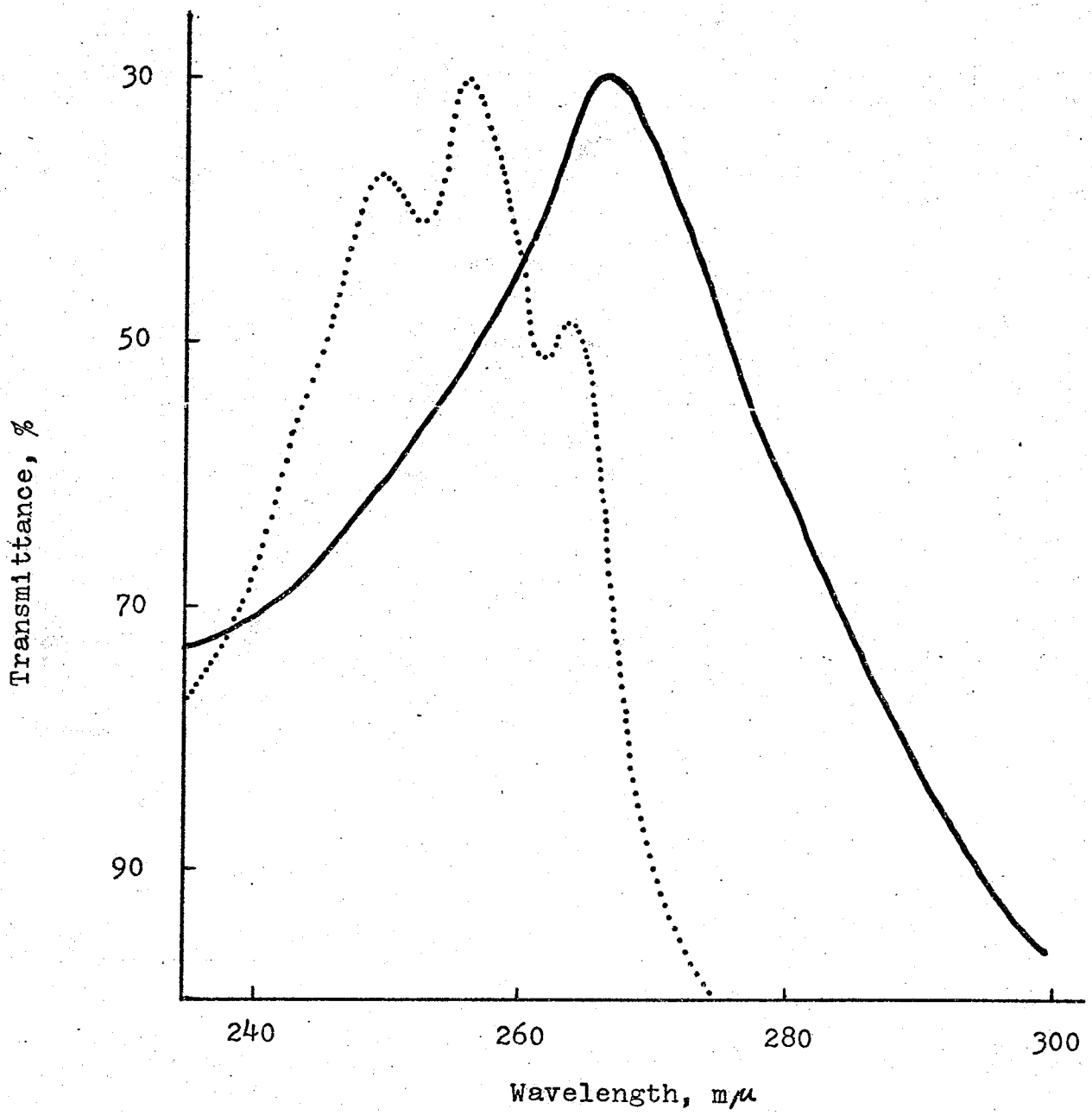
The order seems to contradict Zoltewicz and Smiths' (99) findings and is in agreement with the results

FIGURE 23

The UV spectra of isonicotinic acid and pyridine in 1N NaOH

——— Isonicotinic acid, C = 3.0×10^{-4} M

····· Pyridine, C = 3.0×10^{-4} M


30
50
70
90
Transmittance, %
240
260
280
300
Wavelength, mμ

of Kawazoe et. al. (52). However, it is quite possible that the transition state leading to carbon-carbon bond breaking would be different from that leading to C-H bond breaking, and thus the order of carbanion formation may be different for pyridine and pyridine-carboxylic acids.

Finally, the C^{13} isotope effect may be considered. In anthranilic (27) and salicylic acids (92), where protonation of the α-carbon precedes CO_2 cleavages, the former is rate-controlling at low acidity and the latter at high acidity. Consequently, there is a C^{13}-kinetic isotope effect at high acidity but not at low. We have shown that for picolinic and quinolinic acids there is a C^{13}-kinetic isotope effect at both low and high acidities. This shows that C-C bond breaking is always rate-controlling in picolinic acids and agrees with the carbanion mechanism proposed for these acids.

However, it was found that the C^{13} isotope effect is slightly less in the decarboxylation of the carboxylate anion than in that of the acid (zwitterion). The difference is not much outside the experimental error, but appears to be real. If so, it shows that C-C bond breaking has

proceeded further in the transition state derived from the zwitterion than in that for the anion. This is interesting and perhaps unexpected. It would show that the energy maximum (transition state) comes sooner in the bond-breaking process for the stronger bond (if bond strength can be related to rate of bond breaking). If one uses the simple model of a stretched spring for the C-C bond, then it would be expected that a stiffer spring (stronger bond) would reach its elastic limit (transition state) at a smaller extension than would a soft spring (weaker bond). This, however, is undoubtly a too naive model.

A slightly more sophisticated model can be obtained from the Hammond postulate (44A). It proposes that transition states for endothermic reactions (such as decarboxylations) resemble products more than reactants. It might be expected from this that the transition state for a more endothermic C-C bond breaking would occur later in the breaking process than would the transition state of a less endothermic C-C bond breaking. If it is assumed that the slower C-C bond breaking (that of the picolinate anion) is more endothermic than the faster one (zwitterion), then the transition state for the anion should resemble products more than that for the zwitterion, and should therefore have a larger C^{13} isotope effect. This is the

opposite of what is observed, so some of the assumptions involved in the argument must be unjustified. It is unfortunate that the difference in isotope effects is so small as to be uncertain and therefore unsafe to base any conclusion upon.

B. PYRROLE-2-CARBOXYLIC ACID

In the previous section, a mechanism has been proposed for the decarboxylation of picolinic acid in aqueous solution, which is quite different from that found for other aromatic amino acids such as anthranilic and p-aminobenzoic acids. Since pyrrole is generally believed to resemble aniline or phenol more than pyridine, it was of interest to find out if the decarboxylation of pyrrole-carboxylic acids resembles that of heterocyclic pyridine-carboxylic acids or the aminobenzoic acids; and pyrrole-2-carboxylic acid was chosen for this purpose.

The UV spectra of pyrrole-2-carboxylic acid and its decarboxylation product, pyrrole, are shown in Figure 24, and 250 mμ was chosen as the wavelength for rate measurements.

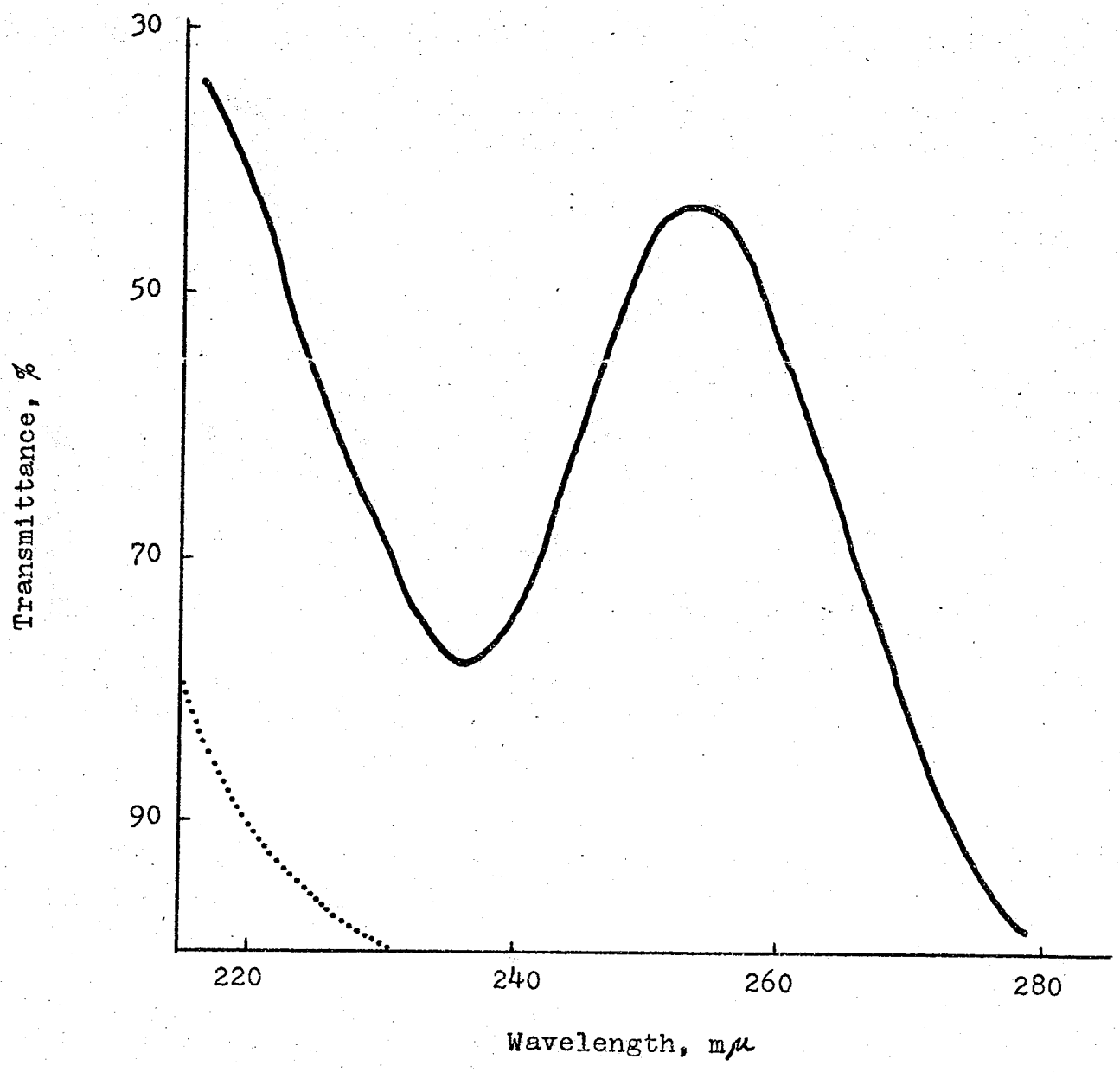
Pyrrole-2-carboxylic acid was found to decarboxylate very readily even at low temperature, and the rates of decarboxylation of this acid were obtained spectrophotometrically at 50°C by following the change in concentration of the acid with time. First-order plots of the logarithm of absorbance against time gave excellent fits up to more than 90% conversion. A typical plot of

FIGURE 24

The UV spectra of pyrrole-2-carboxylic acid and pyrrole in 1N NaOH

——— Pyrrole-2-carboxylic acid, C = 1.1×10^{-4} M

····· Pyrrole, C = 1.1×10^{-4} M


30
50
70
90
Transmittance, %
220
240
260
280
Wavelength, mμ

log. absorbance versus time for the decarboxylation of this acid at 50°C is shown in Figure 25.

Table XXV records the rates obtained on the decarboxylation of pyrrole-2-carboxylic acid at 50°C in buffered solutions with pH measured at the same temperature and ionic strength of 1.0. Some rates obtained at high acidities (where $\mu > 1.0$) are also included.

In order to gain more information about the decarboxylation mechanism of pyrrole-2-carboxylic acid, the C^{13}-carboxyl kinetic isotope effects were also determined. The results are shown in Table XXVI.

In order to interpret the rates as a function of pH, it is necessary to know the ionization constants of pyrrole-2-carboxylic acid. McCay and Schmidt (63) had reported that the pK_1 and pK_2 for pyrrole-2-carboxylic acid were 1.5 and 4.4 respectively. The main purpose of these authors was to determine the dissociation constants of proline by titration. The titration curves for proline and pyrrole-2-carboxylic acid reproduced from McCay and Schmidt are shown in Figure 26. As shown in the figure, only one point was obtained in each titration curve for

FIGURE 25

A typical plot of log. absorbance versus time for the decarboxylation of pyrrole-2-carboxylic acid at 50°C, μ = 1.0 .

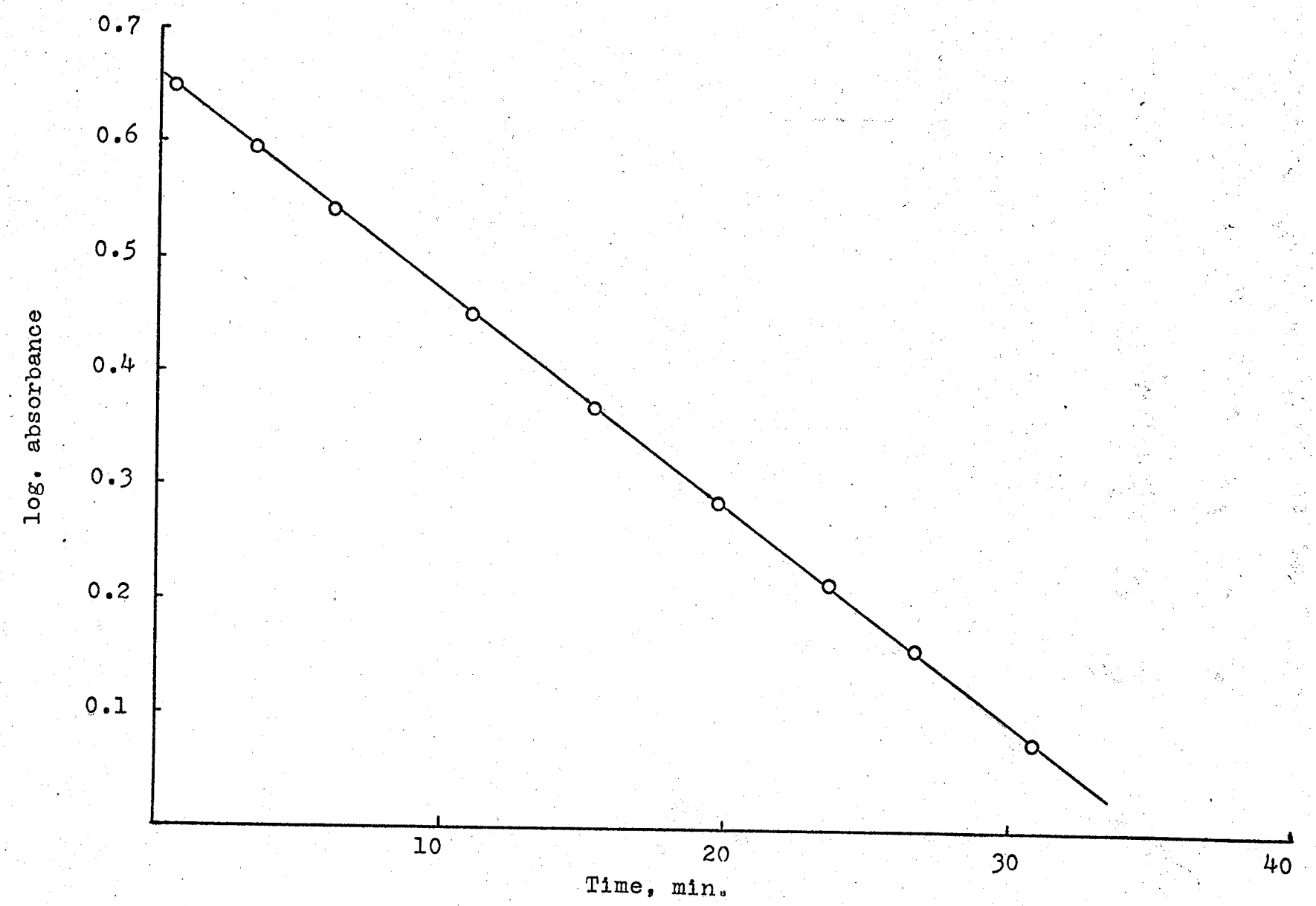

0.7
0.6
0.5
0.4
0.3
0.2
0.1
log. absorbance
10
20
30
40
Time, min.

TABLE XXV

RATES OF DECARBOXYLATION OF PYRROLE-2-CARBOXYLIC ACID AT 50°C, μ = 1.0

Buffer*	pH at 50°C	k x 10^5, s^{-1}
C	7.32	2.73
B	3.41	2.80
B	2.93	3.21
B	2.66	3.45
B	2.19	4.22
A	1.82	6.01
A	1.51	9.13
A	1.32	12.3
A	0.992	24.2
A	0.795	34.8
A	0.603	49.0
A	0.443	69.9
A	0.399	72.0
A	0.332	84.1
A	0.181	105
A	0.079	126
A	-0.161 (1.45N)#	168
A	-0.396 (2.49N)#	208
A	-0.822 (6.64N)#	318
A	-1.01 (10.3N)#	357

* The symbols A, B and C refer to HCl; HCl-NaH_2PO_4 ; and NaH_2PO_4-Na_2HPO_4 buffers respectively.

Ionic strength $>$ 1.0 .

TABLE XXVI

C^{13}-KINETIC ISOTOPE EFFECTS ON THE DECARBOXYLATION OF PYRROLE-2-CARBOXYLIC ACID AT 50°C, μ = 1.0

Buffer*	pH at 50°C	% Reaction	$^{13}CO_2/^{12}CO_2$	$100(k_{12}/k_{13} - 1)$
A	0.102	100.0	0.010301	
A	0.102	100.0	0.010301	
A	0.102	100.0	0.010300	
B	2.63	10.05	0.010296	0.043
B	2.63	9.945	0.010292	0.088
B	2.63	13.33	0.010300	0.016
C	-0.602	23.31	0.010052	2.83
C	-0.602	22.96	0.010056	2.79
C	-0.602	22.74	0.010053	2.81

* The symbols A, B and C refer to $HClO_4$; $HClO_4$-NaH_2PO_4 and 4N $HClO_4$ buffers respectively.

FIGURE 26

The titration curves for proline and pyrrole-2-carboxylic acid (63)

O Proline

X Pyrrole-2-carboxylic acid

Dissociation (%)
80
60
40
20
2
4
6
8
10
12
pH

pyrrole-2-carboxylic acid, and these authors estimated the dissociation constants of pyrrole-2-carboxylic acid by analogy to proline. Therefore, it is believed that the reported values of pK_1 and pK_2 for pyrrole-2-carboxylic acid are not too reliable.

It was therefore decided to determine the pK_1 of pyrrole-2-carboxylic acid spectrophotometrically at 50°C and at constant ionic strength of 1.0. However, it was found that the UV spectra remained unchanged in the region of pH = 3 up to 10N HCl (as shown in Figure 27). Therefore, it would appear that the pK_1 is actually negative, which is not in agreement with McCay and Schmidts' rough estimation.

Isotope effects for pyrrole-2-carboxylic acid as shown in Table XXVI resemble those of anthranilic acid (29), which suggests that the decarboxylation mechanism of this acid may be similar to that of anthranilic acid previously described in page 32 of this Thesis. Equation (10) is reproduced here for convenient reference:

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H^+]}{K_1 + [H^+]} \times \frac{k^* K_2^*}{k^* K_2^* + k_{-HA} [H^+]} \qquad \text{.....(10)}$$

FIGURE 27

The UV spectra of pyrrole-2-carboxylic acid at various acidities

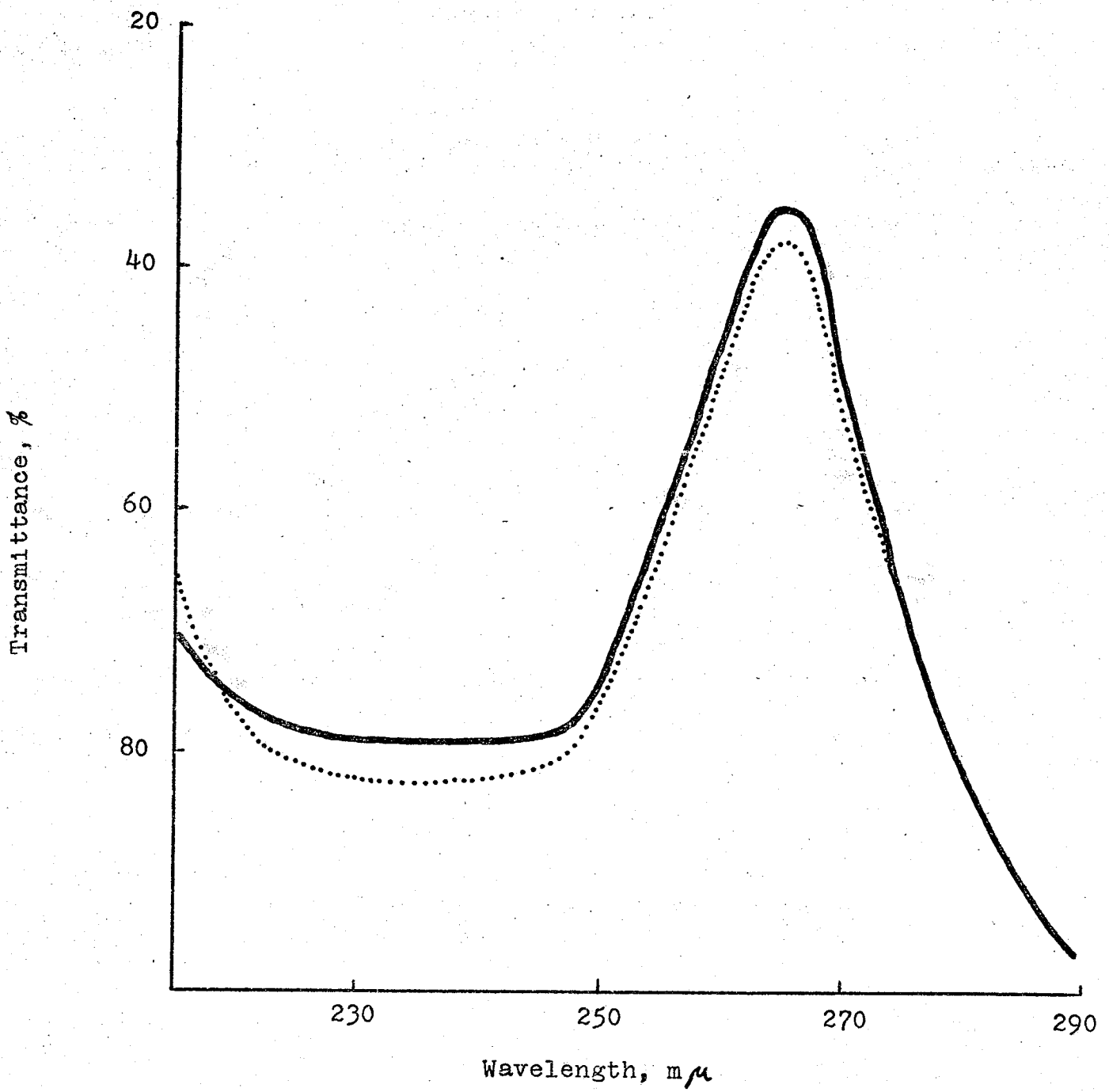
Temperature = 50°C

Ionic strength = 1.0

Concentration = 1.0×10^{-4}

——— The spectra in buffered solutions of pH = 2.98; 2.01; 1.56; and 1N, 2N, 4N and 8N HCl

····· The spectrum in 10N HCl


20
40
60
80
Transmittance, %
230
250
270
290
Wavelength, mμ

Since pK_1 is more negative than the lowest pH we studied (pH = -1.01 or 10.3N HCl), $[H^+]$ will be negligible with respect to K_1 at the pH region where the rates of decarboxylation were obtained.

In a region where there is no C^{13}-carboxyl kinetic isotope effect, the right hand fraction of the general rate expression (equation (10)) must equal to unity, since the rate constant for carbon-carbon bond breaking, k^*, appear only in this fraction. Under this condition, equation (10) can be reduced to

$$k = \frac{k_A K_1 K_2 + k_{HA} K_1 [H^+]}{K_1 + [H^+]} \times 1 \quad .....(34)$$

Since $K_1 \gg [H^+]$ as previously assumed, equation (34) will become

$$k = k_A K_2 + k_{HA} [H^+] \quad .....(35)$$

A plot of k versus $[H^+]$ is shown in Figure 28 and the calculations in Table XXVII. From the linear plot, the following values were obtained:

FIGURE 28

Plot of k vs. $[H^+]$ for pyrrole-2-carboxylic acid

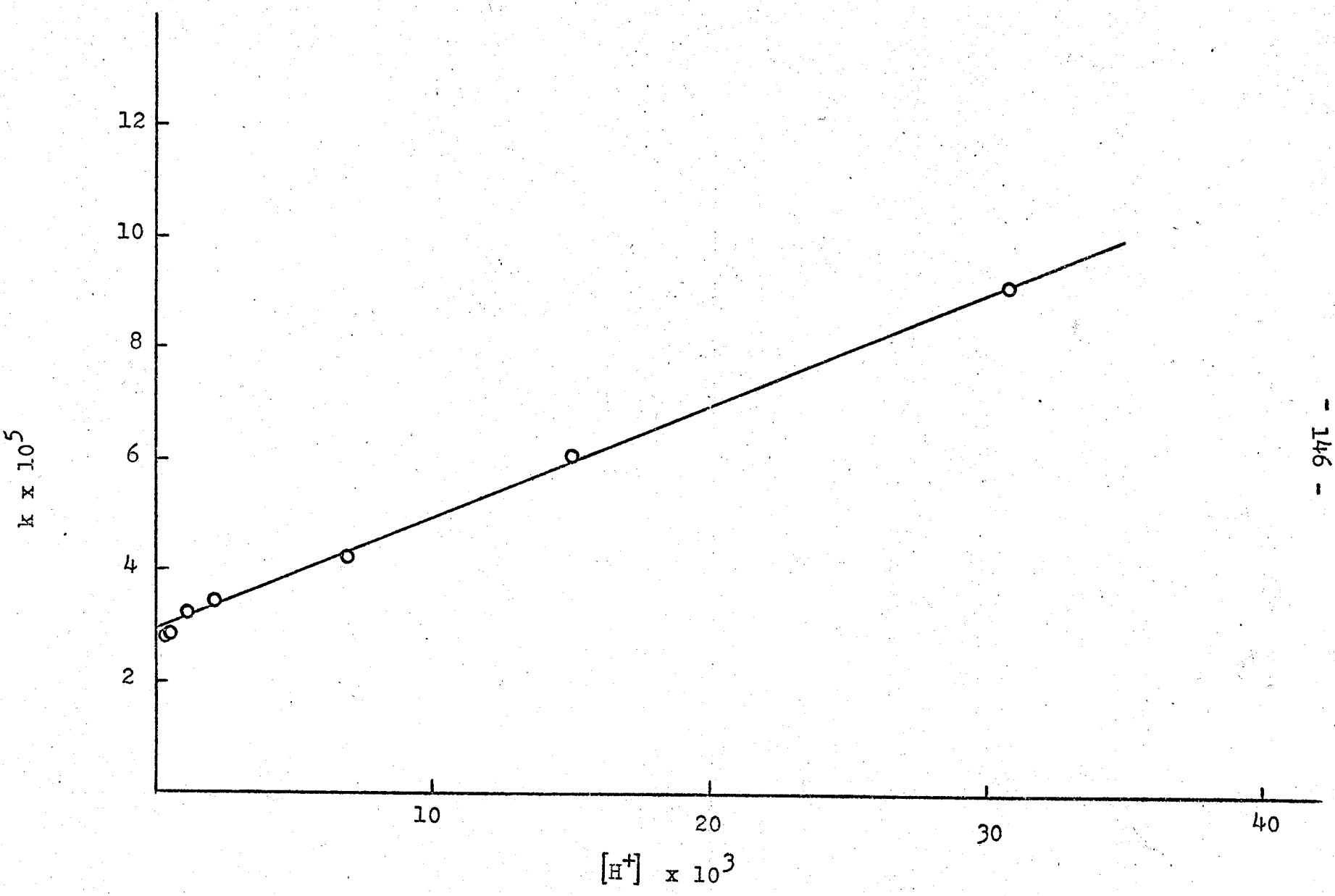

12
10
8
6
4
2
k x 10^5
10
20
30
40
[H+] x 10^3

TABLE XXVII

CALCULATIONS FOR THE PLOT OF k VS. $[H^+]$ FOR PYRROLE-2-CARBOXYLIC ACID

pH	$[H^+] \times 10^3$	$k \times 10^5$
7.32	~ 0	2.73
3.41	0.389	2.80
2.93	1.18	3.21
2.66	2.19	3.45
2.19	6.46	4.22
1.82	15.1	6.01
1.51	30.9	9.13

$$k_{HA} = 2.10 \times 10^{-3} \text{ sec}^{-1}$$
$$k_A K_2 = 2.9 \times 10^{-5} \text{ sec}^{-1}$$

In a region where there is C^{13}-carboxyl kinetic isotope effect, the right hand fraction of equation (10) does not equal unity, and since $K_1 \gg [H^+]$, the equation thus becomes

$$k = \left(k_A K_2 + k_{HA}[H^+]\right) \times \frac{1}{1 + \frac{k_{-HA}[H^+]}{k^* K_2^*}} \qquad \ldots\ldots(36)$$

From the previous plot, $k_{HA} \gg k_A K_2$, and therefore $k_{HA}[H^+] \gg k_A K_2$, and equation (36) becomes

$$k = \frac{k_{HA}[H^+]}{1 + \frac{k_{-HA}[H^+]}{k^* K_2^*}} \qquad \ldots(37)$$

or
$$\frac{1}{k} = \frac{1}{k_{HA}[H^+]} + \frac{k_{-HA}}{k^* K_2^* k_{HA}} \qquad \ldots\ldots(38)$$

A plot of $1/k$ versus $1/[H^+]$ is shown in Figure 29 and the calculations in Table XXVIII. From the linear plot, the following values were obtained:

$$k_{HA} = 2.26 \times 10^{-3} \text{ sec}^{-1}$$

$$k_{-HA}/k^*K_2^* = 5.83 \times 10^{-1}$$

The values of k_{HA} obtained from Figures 28 and 29 are quite agreeable, and the average value for k_{HA} is 2.18×10^{-3} sec^{-1}.

Substituting the values of k_AK_2, k_{HA}, $k_{-HA}/k^*K_2^*$ into the general rate expression governing the rate constants in the pH regions we studied (equation (36)), then

$$k = \left(2.9 \times 10^{-5} + 2.18 \times 10^{-3}[H^+]\right) \times \frac{1}{1 + 5.83 \times 10^{-1}[H^+]} \qquad \ldots\ldots(39)$$

With varying hydrogen ion concentrations substituted in equation (39), different values of k are obtained. The calculations are shown in Table XXIX, and the plot is shown in Figure 30. As shown in the figure, the experimental results have excellent fits into the calculated values (except at high acidities where ionic strength is not constant).

FIGURE 29

Plot of $1/k$ vs. $1/[H^+]$ for pyrrole-2-carboxylic acid

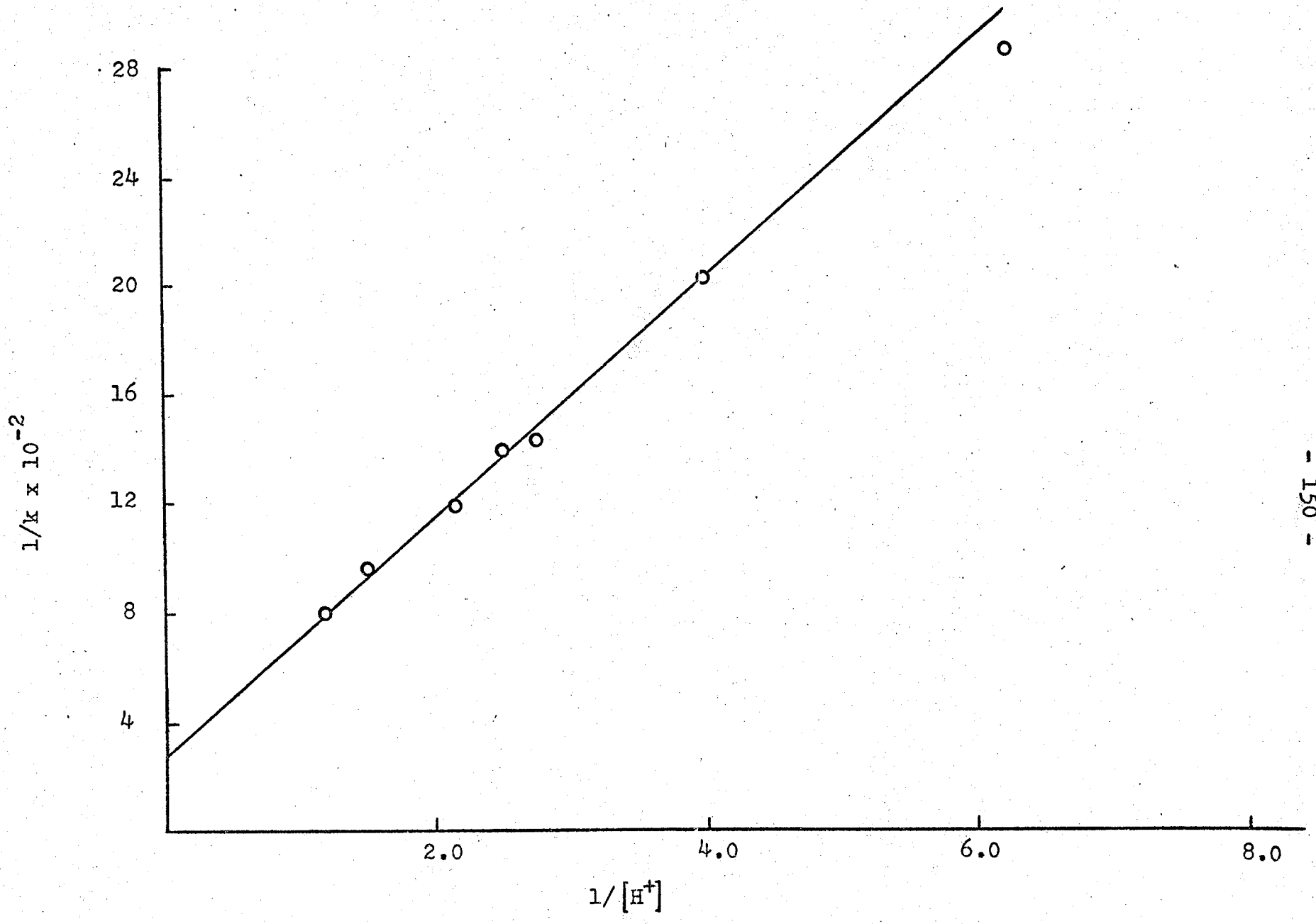

28
24
20
16
12
8
4
1/k x 10^-2
2.0
4.0
6.0
8.0
1/[H+]

TABLE XXVIII

CALCULATIONS FOR THE PLOT OF $1/k$ VS. $1/[H^+]$ FOR PYRROLE-2-CARBOXYLIC ACID

pH	$[H^+] \times 10^1$	$1/[H^+]$	$k \times 10^5$	$1/k \times 10^{-2}$
0.795	1.60	6.25	34.8	28.7
0.603	2.50	4.00	49.0	20.4
0.443	3.61	2.77	69.9	14.3
0.399	3.99	2.51	72.0	13.9
0.332	4.66	2.15	84.1	11.9
0.181	6.59	1.52	105	9.52
0.079	8.34	1.20	126	7.94

TABLE XXIX

RATE CONSTANTS CALCULATED FROM EQUATION (39) FOR THE DECARBOXYLATION OF PYRROLE-2-CARBOXYLIC ACID AT 50°C, $\mu = 1.0$

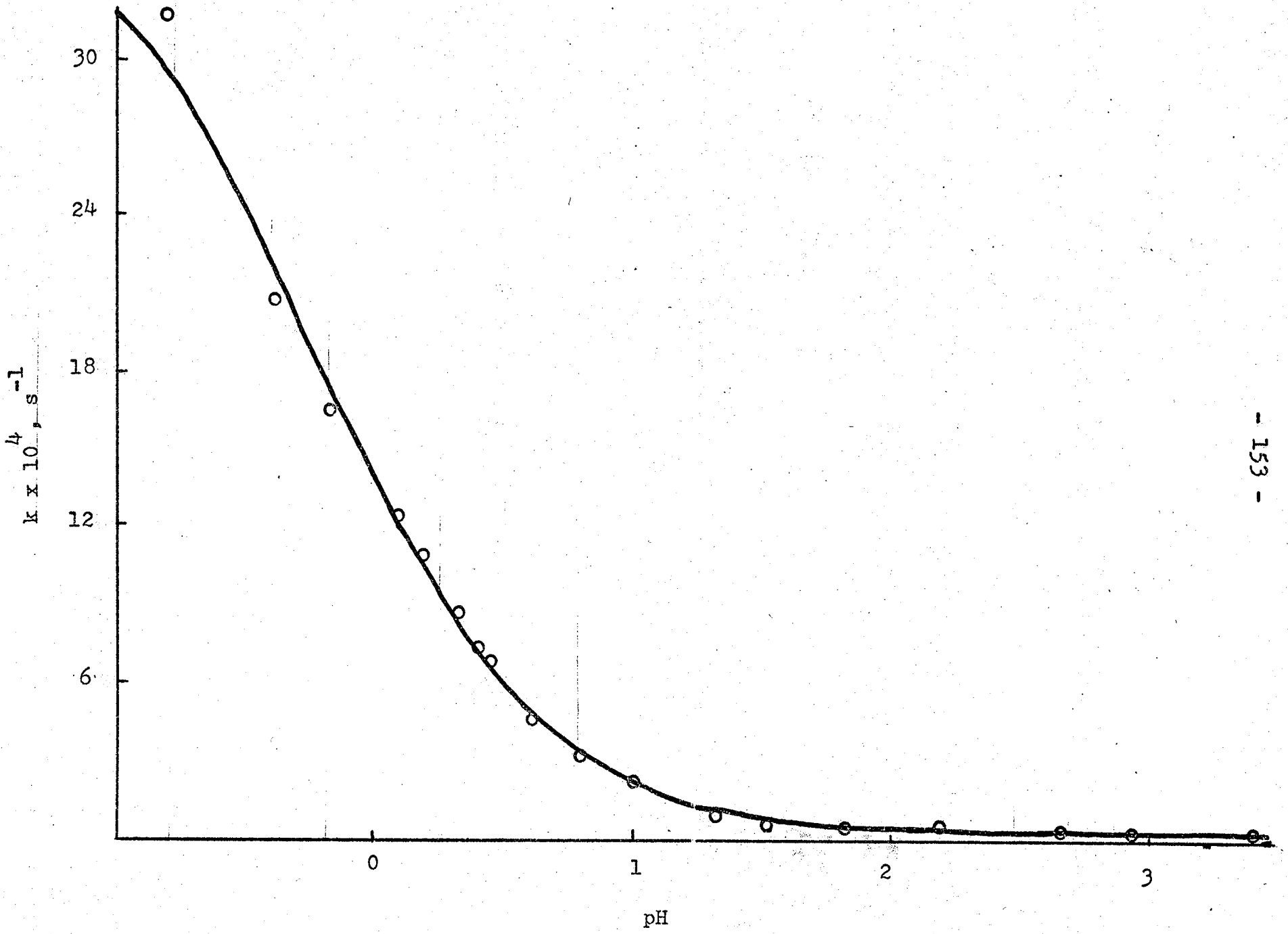
pH	$[H^+] \times 10^2$	$k \times 10^5$, s^{-1}
7.32	4.79×10^{-6}	2.90
3.41	0.0389	2.98
2.93	0.118	3.16
2.66	0.219	3.38
2.19	0.646	4.31
1.82	1.51	6.13
1.51	3.09	9.45
1.32	4.79	12.9
0.992	10.2	23.7
0.795	16.0	34.7
0.603	25.0	49.9
0.443	36.1	67.5
0.399	39.9	73.1
0.332	46.6	82.6
0.181	65.9	107
0.079	83.4	124
-0.161	145	173
-0.396	249	223
-0.822	664	298
-1.01	1030	320

FIGURE 30

Plot of calculated rate constants versus pH for the decarboxylation of pyrrole-2-carboxylic acid at 50°C, μ = 1.0

— Rate constants calculated from Equation (39)

o Experimental rate constants


30
24
18
12
6
k x 10^4 s^-1
0
1
2
3
pH

Equation (39) shows that a full C^{13}-kinetic isotope effect will not be observed until $[H^+] \geqslant 20$. The magnitude of the full isotope effect can be calculated from the data of Table XXVI as follows:

Equation (37) can be rewritten for the individual isotopes as:

$$k_{12} = \frac{k_{HA}[H^+]}{1 + \frac{k_{-HA}[H^+]}{k_{12}^* K_2^*}} \qquad \text{.....(40)}$$

and

$$k_{13} = \frac{k_{HA}[H^+]}{1 + \frac{k_{-HA}[H^+]}{k_{13}^* K_2^*}} \qquad \text{.....(41)}$$

$$\frac{k_{12}}{k_{13}} = \frac{1 + \frac{k_{-HA}[H^+]}{k_{13}^* K_2^*}}{1 + \frac{k_{-HA}[H^+]}{k_{12}^* K_2^*}} \qquad \text{.....(42)}$$

If i = full isotope effect = k^*_{12}/k^*_{13}

then $k^*_{13} = k^*_{12}/i$

and introducing the value of k^*_{13} to equation (42):

$$\frac{k_{12}}{k_{13}} = \frac{1 + \dfrac{ik_{-HA}[H^+]}{k^*_{12}K^*_2}}{1 + \dfrac{k_{-HA}[H^+]}{k^*_{12}K^*_2}} \qquad \text{.....(43)}$$

In 4N perchloric acid, the isotope effect obtained was 2.81%, therefore equation (43) becomes

$$1.0281\left(1 + \frac{4\,k_{-HA}}{k^*_{12}K^*_2}\right) = 1 + \frac{4i\,k_{-HA}}{k^*_{12}K^*_2} \qquad \text{.....(44)}$$

where $k_{-HA}/k^*_{12}K^*_2$ was previously found to be 5.83×10^{-1}. Equation (44) can be solved to give $i = 1.040$.

Dunn and Buccini (29) obtained a full isotope effect of 4.2% for the decarboxylation of 4-methoxyanthranilic acid at 60°C, therefore a full isotope effect of 4.0% for pyrrole-2-carboxylic acid would seem to be quite reasonable.

In conclusion, it is believed that the decarboxylation mechanism of pyrrole-2-carboxylic acid seems to resemble that of anthranilic acid previously proposed by Dunn and co-workers (27; 29); with the only major difference being that pyrrole-2-carboxylic acid is such a weak base that it is not protonated in the acid concentrations studied, so that the rate does not decrease at high acidity.

V. EXPERIMENTAL

A. MATERIALS

1. Pyridine and its derivatives

The pyridine-carboxylic acids and some substituted pyridines used in this investigation are listed in Table XXX, along with an indication of the source and melting or boiling point of the particular compound. The pyridine and substituted pyridines were freshly distilled before used, and all the acids were purified by one or more recrystallization from anhydrous benzene (except 5-nitropicolinic acid which was recrystallized from water). The melting points given are for the recrystallized acids determined with a Fisher-Johns melting point apparatus. The rate of heating within 10°C of the melting point was maintained at 1°C per 2 minutes.

Preparation of 5-nitropicolinic acid

The method reported by Thome and Goebel (83) for the preparation of this acid was closely followed.

Diphenyl (24 gm), 17 gm of 2-bromo-5-nitropyridine (K & K Laboratories, Inc.), and 9 gm of cuprous cyanide were melted in a 100 ml wide mouth flask, heated

TABLE XXX

PYRIDINE AND ITS DERIVATIVES

Pyridine	Source	Melting Point, °C. Observed	Literature
Parent	Matheson, Coleman and Bell	114 (b. p.)	115.25 (55)
2-Me	Aldrich Chemical Co.	130 (b. p.)	129.4 (55)
3-NO_2	Aldrich Chemical Co.	217 (b. p.)	216 (55)
2-CO_2H	Aldrich Chemical Co.	137 - 138	136.5 - 138 (7)
3-CO_2H	Aldrich Chemical Co.	236 - 238	234.5-235.5 (7)
4-CO_2H	Aldrich Chemical Co.	323 - 325	323 - 325 (7)
2-CO_2H-6-Me	J. T. Baker Chemical Co.	128 -129	129 (15)
2-CO_2H-5-NO_2	Synthesized in this work	210 - 212	211 - 212 (83)
2,3-$(CO_2H)_2$	Aldrich Chemical Co.	191 - 192	190 (55)

with stirring for two hours at 205 - 10°C. The melt was then poured into a mortar and ground. The residue in the flask was pulverized and extracted with 200 ml of acetone to which the original powder melt was added. The solution was added to 300 ml 6N HCl, precipitating the diphenyl, while the 2-cyano-5-nitropyridine remained in solution. The precipitated diphenyl was extracted with 150 ml 0.1N HCl, which was combined with the original acid extract, and the acid solution was distilled in vacuo, giving more diphenyl in the distillate, and leaving a residue of 5-nitropyridine-2-carboxamide (I). From the mother liquid, more (I) was obtained and the total yield was 4.8 gm, which on recrystallization from acetic acid gave yellow leaves, m.p. 244 - 5°C (lit., 246 - 7°C (83)).

4.6 gm of (I) were heated at 90°C in 100 ml conc. HCl for two hours. The solution was then diluted with water, and 5-nitropicolinic acid crystallized out at once. From the mother liquid, more of this acid was obtained, and the yield, after being recrystallized from water, was 1.2 gm. The acid was in the form of pale yellow leaves, and had the m.p. of 210 - 12°C (lit., 211 - 12°C (83)).

2. Pyrrole and its derivative

Pyrrole

Pyrrole (K & K Laboratories, Inc.) was distilled and the fraction boiling at 128 - 30°C was collected (lit., 132°C (24)).

Pyrrole-2-carboxylic acid

Pyrrole-2-carboxylic acid (K & K Laboratories, Inc.) was recrystallized twice with anhydrous benzene, vacuum dried and finally sublimed under vacuum. The product had a melting poing of 204 - 5°C (lit., 206°C (24)).

B. BUFFER AND STANDARD SOLUTIONS

Hydrochloric acid (in the pH region 0 - 2.2), hydrochloric acid-sodium dihydrogen phosphate (in the pH region 1.8 - 4.2), and sodium dihydrogen phosphate-disodium hydrogen phosphate (in the pH region 4.0 - 6.4) buffers were used for the rate measurements. All buffers were adjusted to ionic strength of 1.0 by addition of potassium chloride.

The phosphate buffer was chosen because it was found in some preliminary experiments that the pH of this buffer remained unchanged after being kept for 500 hours at 150°C. Also, the phosphate buffer showed no absorbance in the wavelengths where the rate measurements were made. In the pH region 1.8 - 2.2, some rates of decarboxylation at a particular pH were measured in both hydrochloric acid and hydrochloric acid-sodium dihydrogen phosphate buffers, and the rates in these two different buffers were found to be the same.

In those experiments where carbon dioxide was to be collected for isotopic ratio measurements, perchloric acid was substituted for hydrochloric acid because of the volatility of the latter.

Standard solutions of perchloric and hydrochloric acids were made by dilution of the bottle acids. These solutions were further standarized by titration with standard sodium hydroxide solution using a micro burette.

C. PH MEASUREMENTS

All pH measurements were made with a Radiometer model 4C pH meter with shielded glass and calomel electrodes in cells thermostatted to ± 0.1°C. At 25°C the electrodes were Radiometer G202B (glass) and K100 (calomel); at 95°C they were Radiometer G302BH (glass) and K4016 (calomel). The meter was calibrated against National Bureau of Standards (N. B. S.) tetroxalate and hydrogen phthalate buffers at the appropriate temperatures. Measured pH's were reproducible to ±0.003 pH unit and are assumed to be accurate to ±0.01 unit.

D. ABSORPTION SPECTRA AND ABSORBANCE MEASUREMENTS

Absorption spectra were measured on a Beckman DK-1 spectrophotometer. A Beckman DU spectrophotometer was used with matched cells for the absorbance measurements. The appropriate buffer solution was used as a standard in the reference cell. For the rate determination, the instrument was set at the predetermined optimum wavelength throughout the determination. Measurements were reproducible within ±0.01 unit of absorbance.

E. DETERMINATION OF THE IONIZATION CONSTANT OF QUINOLINIC ACID AT 95°C

Stock solution of quinolinic acid was prepared by dissolving 0.25 gm of the acid in a slight excess of 0.1N sodium hydroxide solution (about 1.5 ml) and then diluting to one liter with distilled water containing sufficient potassium chloride to give an ionic strength of 1.0. Aliquots (5 ml) of this stock solution, delivered from an automatic burette, were diluted to 50 ml with the appropriate buffer to give the solutions on which pH and absorbance determinations were made.

The spectrophotometric work was carried out on a Beckman Model DK-1 spectrophotometer. The instrument was equipped with a Beckman 92527 Temperature Regulated Cell Holder which was thermostatted at 95.0 ± 1.0°C. In order to secure a suitable wavelength for study, several complete UV absorption spectra of quinolinic acid were obtained at 95°C at pH of 0.2 to 4.2 and in the wavelength region of 200 - 400 mμ. A suitable wavelength of 262 mμ was chosen where the absorbance differences between these absorption curves were the largest.

In the actual ionization constant determination, the instrument was set at a fixed wavelength of 262 mμ throughout the determination. A series of determinations of absorbance at various hydrogen ion concentrations were then made. For each solution, a record was made of the absorbance over a period of several minutes during which the temperature of the cell oscillated between 94°C and 96°C several times. This temperature variation produced changes in the absorbance of not more than 0.002 absorbance units.

F. RATE MEASUREMENTS

1. Pyridine-carboxylic acids

The change in concentration of pyridine-carboxylic acid with time was followed spectrophotometrically by measurements made in alkaline solution where all the acid is in the anionic form, and at wavelengths where the absorbance of the reaction product is negligible. The wavelengths chosen for the acids studied were recorded individually in the Chapter of Results and Discussions in this dissertation.

The rate measurements were carried out at 95.0 ± 0.1°C and 150.0 ± 0.1°C. At these high temperatures the evaporation losses were found to be considerable, so the ampoule method was used. About twenty to thirty mg of the pyridine-carboxylic acid was dissolved in 50 ml of the buffered solution. Eighteen ampoules (2 ml capacity) each containing about 1.5 ml of the stock solution were sealed and kept in the thermostatted bath. After ten minutes, two ampoules were withdrawn and cooled to 25°C for pH measurement. Two more samples of two ampoules each were withdrawn for pH measurements, one at the middle and one at the end of the run. The three samples had the same

pH within 0.008 unit in all the runs reported in this Thesis.

One ampoule was withdrawn each time at approximately equal time intervals, and the reaction was quenched by placing the ampoule in water. Approximately one ml of the solution was then withdrawn from each ampoule and injected into weighed 25 ml volumetric flasks containing 15 ml of 1N sodium hydroxide solution each. The flasks were reweighed and the weights of the aliquots were calculated as a difference in weight. After dilution to the mark with 1N NaOH, the solutions were ready for the spectrophotometric determination of the concentration of the anion. The absorbance per gram of the aliquots was calculated.

2. Pyrrole-2-carboxylic acid

As with pyridine-carboxylic acids, the change in concentration of pyrrole-2-carboxylic acid with time was followed spectrophotometrically by measurements made in alkaline solution where all the acid is in the anionic form, and at a wavelength of 265 mμ where the absorbance of the reaction product, pyrrole, is negligible.

A 250 ml round-bottom flask immersed to the neck in an oil bath at 50.0 ± 0.1°C served as the reaction vessel. The flask with 200 ml of buffered solution was allowed to come to the bath temperature, then 50 mg of pyrrole-2-carboxylic acid dissolved in about 2 ml of 0.1N sodium hydroxide solution was added. The flask was shaken, and three samples of about 20 ml each were withdrawn at the beginning, the middle and the end of the run, and were cooled to 25°C for pH measurements. The three samples had the same pH in all the runs reported. At approximately equal time intervals, 2 ml aliquots were withdrawn for absorbance measurements and immediately injected into weighed 25 ml volumetric flasks containing about 15 ml of 1N sodium hydroxide solution each. It had been found experimentally that this stops the reaction since pyrrole-2-carboxylic acid in 1N NaOH did not change concentration on being kept at room temperature for two weeks. The volumetric flasks were reweighed, then filled to the mark with 1N sodium hydroxide and set aside for spectrophotometric measurements. Absorbances were corrected to correspond to a constant weight of aliquot.

G. C^{13}-CARBOXYL KINETIC ISOTOPE EFFECT

1. The high vacuum system

The high vacuum system was of a conventional design and is shown schematically in Figure 31. It was used to collect and purify the carbon dioxide produced in the decarboxylation. The two-way stopcocks (I - VII) were greased with Apiezon "M" stopcock grease. A rotary oil pump and a mercury diffusion pump were used to attain the high vacuum. A McLeod gauge was also connected into the system in order to measure the vacuum.

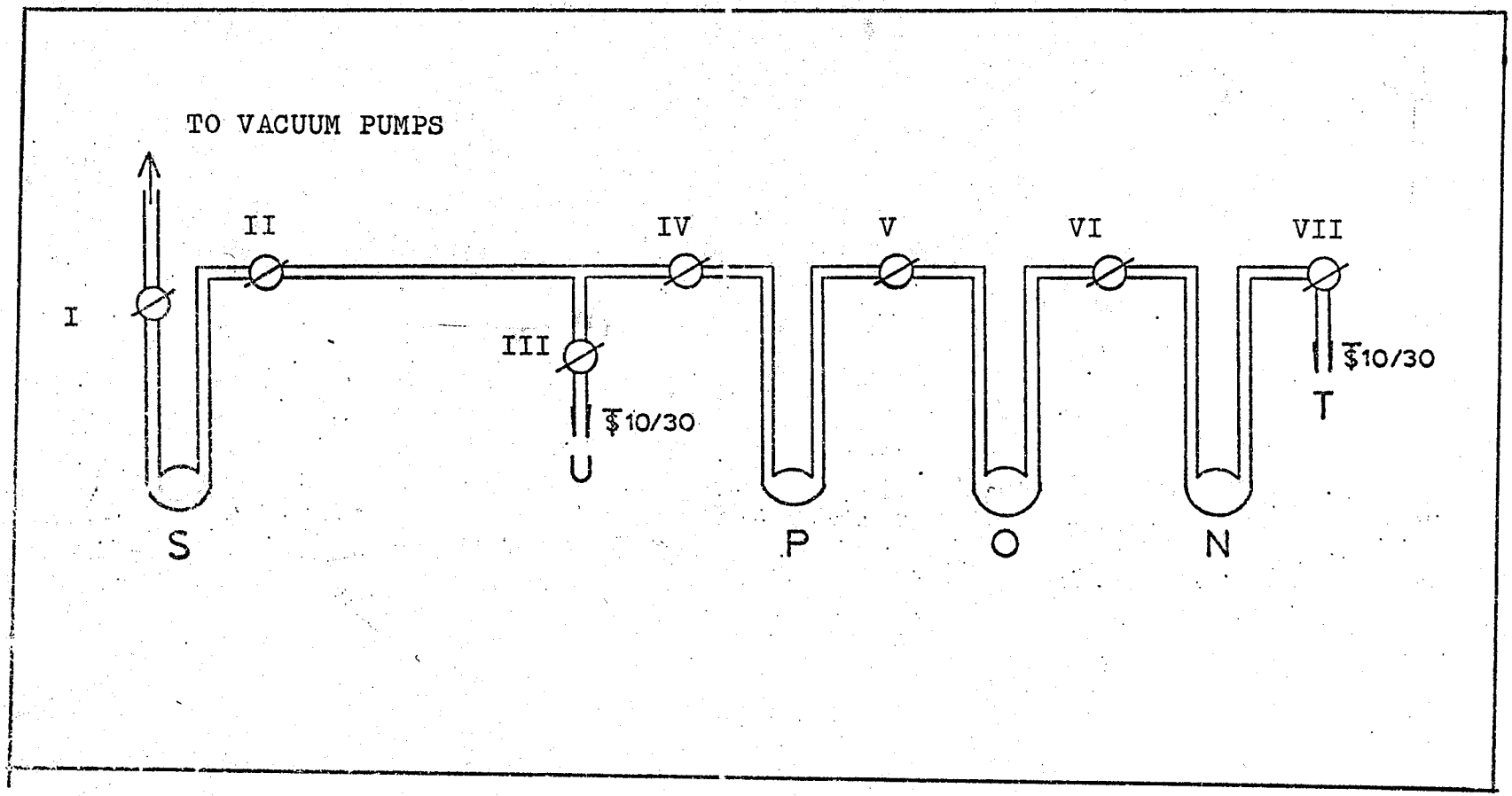
2. Determination of the extent of reaction in the decarboxylation

In this work, the extent of reaction was measured spectrophotometrically. This procedure was found to be simpler than the earlier method reported by Dunn and Buccini (29), who determined the extent of reaction by measuring the amount of carbon dioxide evolved in the decarboxylation.

About 200 mg of the acid studied was dissolved

FIGURE 31

The high vacuum system


TO VACUUM PUMPS
I
II
III
IV
V
VI
VII
S
U
P
O
N
T
$\overline{\$}$10/30
$\overline{\$}$10/30

in 100 ml of the buffered solution, and in order to determine the extent of reaction, three samples of exactly one ml each were pipetted out before the decarboxylation and after the decarboxylation was stopped. These samples were injected into 50 ml volumetric flasks containing about 30 ml of 1N NaOH each, then filled to the mark with 1N sodium hydroxide solution. The absorbances of these solutions were measured in Beckman DU spectrophotometer at a fixed wavelength. The absorbances of the different samples withdrawn at the same time were different from each other by not more than 0.005 absorbance units.

3. Procedure

(a) Quinolinic and pyrrole-2-carboxylic acids

For complete decarboxylation, four samples were prepared by dissolving 30 mg of the carboxylic acid in 50 ml of buffered solution each. The reaction vessel was a 250 ml flask containing a ground glass joint (B/24) and a stopcock A. The reaction vessel was attached to the high vacuum system at U keeping the stopcock IV closed. The reaction mixture was frozen in dry ice-acetone bath and was degassed till a high vacuum was obtained. The

stopcock A was then closed and the reaction vessel was allowed to come to the room temperature. The mixture was frozen again and was degassed. This process was repeated four to five times to ensure that all the dissolved carbon dioxide and oxygen had been removed from the reaction mixture.

All the four samples so prepared were kept together in the oil bath at 50.0 ± 0.1°C (pyrrole-2-carboxylic acid) or 95.0 ± 0.1°C (quinolinic acid) for three weeks to ensure complete decarboxylation. The samples were then taken out from the bath and the reaction was chilled in water. The vacuum line was flamed thoroughly to ensure that there were no organic impurities in the system. The sample (carbon dioxide) collecting bulb was attached at T and the reaction vessel at U to the vacuum line keeping the stopcock A closed. The whole system was evacuated till a high vacuum was indicated by the McLeod gauge. The stopcocks II, V, VI, and VII were then closed. Bulb P was immersed in liquid nitrogen bath and stopcock A was opened keeping the reaction vessel in ice cooled water. The reaction mixture was stirred by means of a magnetic stirrer for one hour. Assuming that all the carbon dioxide had been transferred by this time quantitatively into the bulb P, the stopcocks A and IV

were closed. Bulb P was brought to the room temperature and then it was cooled in dry ice-acetone bath whereas bulb O was immersed in methanol-liquid nitrogen bath. After fifteen minutes, the stopcock V was opened, thereby transferring the carbon dioxide from bulb P to O. Water and other high boiling impurities were trapped in bulb P. The carbon dioxide collected in the bulb O was further purified by distillation under high vacuum through the bulbs O and N and was eventually collected in the sample bulb immersed in liquid nitrogen.

Samples for partial decarboxylations were prepared by dissolving 200 mg of the organic acid in 100 ml of the buffered solution. After evacuation, they were kept in the oil bath for the length of time estimated from the known rate constants to give the desired percent reaction, and then were taken out. The extent of reaction was determined spectrophotometrically, and the carbon dioxide so produced was purified and collected as described above.

Mass-spectrometric analyses of the $^{13}CO_2/^{12}CO_2$ ratio were carried out with an Altas MAT mass spectrometer GD 150 with dual collectors. Prior to each analysis,

the samples were scanned and no interfering impurities were found to be present.

The isotope effect, $100 \left(\frac{k_{12}}{k_{13}} - 1 \right)$, was calculated (4) from the equation

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

where R_f is the ratio $^{13}CO_2/^{12}CO_2$ when the fraction of acid decarboxylated is f, and R_o is the same ratio when decarboxylation is complete.

(b) Picolinic acid

Since it was intended to measure the C^{13}-kinetic isotope effect for picolinic acid in aqueous solution at 150°C, the reaction vessels used for quinolinic and pyrrole-2-carboxylic acids would be required to withstand pressures up to about 10 atmospheres. In this case, ampoules of 50 ml capacities with long narrow necks and ground glass joints were made. For complete decarboxylation, 30 mg of picolinic acid was

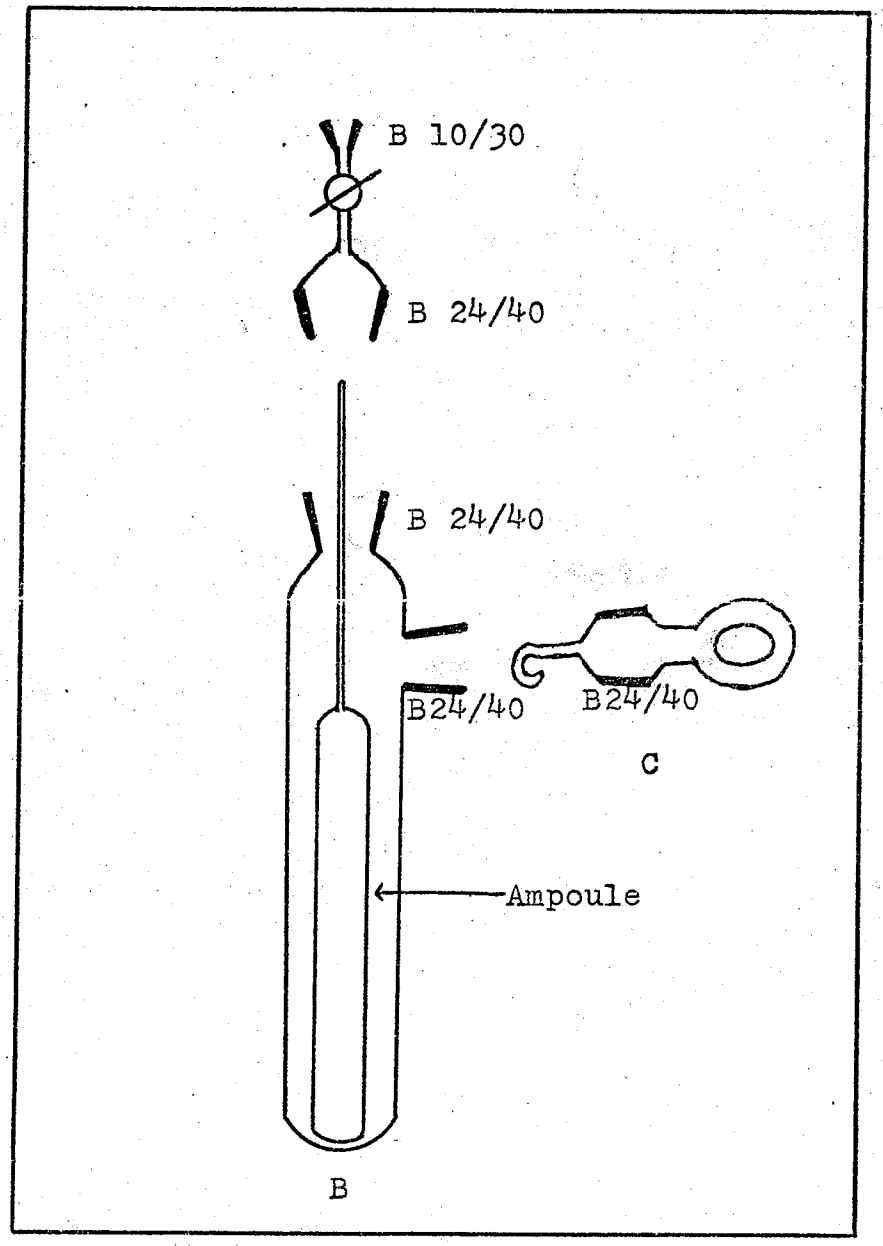
dissolved in 30 ml buffered solution and transferred into the ampoule. The ampoule was then attached to the high vacuum line and degassed several times in the same way as described before. The narrow neck was then sealed off with a torch under vacuum. Four samples were prepared in this manner, and were placed in the oil bath at 150.0 ± 0.1°C for one month to ensure complete decarboxylation.

The samples were taken out from the bath and cooled in water. Each ampoule was placed into a long tube B with a ground glass joint on the side as shown in Figure 32. A device C was then attached to B through the side arm so that the hook of C engaged the neck of the ampoule, and the tube B was then attached to the high vacuum line at U. The whole system was evacuated till a high vacuum was indicated by the McLeod gauge. With III of the high vacuum line closed, C was then turned 360° and the neck of the ampoule was thus broken, allowing the carbon dioxide generated from the decarboxylation to escape. From then on, the collection and purification of carbon dioxide was the same as described before.

Samples for partial decarboxylation were prepared by dissolving 200 mg of picolinic acid in 100 ml

FIGURE 32

A device for breaking ampoule under high vacuum


B 10/30
B 24/40
B 24/40
B24/40
B24/40
C
Ampoule
B

of the buffered solution, and they were transferred to ampoules of 125 ml capacities with long narrow necks and ground glass joints. After being evacuated and vacuum sealed, they were kept in the oil bath at 150°C for the calculated length of time, and then were taken out. The carbon dioxide so produced was collected and purified in the same way as the complete decarboxylation.

Mass-spectrometric analyses and calculations were carried out as previously described.

VI. SUMMARY

1. The variation in rate of decarboxylation with varying pH at constant ionic strength of 1.0 has been measured at 150 ± 0.1°C with picolinic, 6-methylpicolinic and 5-nitropicolinic acids; and at 95 ± 0.1°C with quinolinic acid. The results show that both the zwitterion and the anion of these acids decarboxylate. The rate of decomposition of the zwitterion is about 2 to 3 times as great as that of the anion.

2. The C^{13}-carboxyl kinetic isotope effects on the decarboxylation of picolinic and quinolinic acids have been determined in aqueous solutions of ionic strength 1.0 at 150 ± 0.1°C and 95 ± 0.1°C respectively. For picolinic acid, the isotope effect, $100(k_{12}/k_{13} - 1)$, is found to be 2.25% at pH 1.13 and 2.08% at pH 3.95; whereas for quinolinic acid, the isotope effect is found to be 2.84% at pH 0; 2.73% at pH 2.63 and 2.67% pH 3.95.

3. The first ionization constant of quinolinic acid (K_2) has been determined spectrophotometrically in water at 95°C and ionic strength of 1.0. The value of pK_2 is found to be 1.90 ± 0.03.

4. A mechanism is proposed for the decarboxylation of pyridine-carboxylic acids in which both the zwitterion and the anion lose carbon dioxide to produce carbanions which then abstract protons from solvent. It has been shown that this mechanism can account for the variation of rates with varying pH and also the C^{13}-carboxyl kinetic isotope effects.

5. The rates of decarboxylation of pyrrole-2-carboxylic acid have been measured at 50 $\pm$ 0.1°C in aqueous solution with varying pH and constant ionic strength of 1.0. It has been shown that the pK_1 of this acid is negative. The C^{13}-carboxyl kinetic isotope effect on the decarboxylation of this acid has also been determined in aqueous solutions of ionic strength 1.0 at 50°C. The isotope effect is found to be zero at pH 2.63 and 2.81% at pH -0.602. It is concluded that the decarboxylation mechanism of pyrrole-2-carboxylic acid resembles that of anthranilic acid in which the anion is first protonated at the alpha-carbon and then loses carbon dioxide.

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