

THE IONIZATION CONSTANTS OF SUBSTITUTED
SALICYLIC ACIDS AND THE HAMMETT RELATIONSHIP

by
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A Thesis Submitted to the
Faculty of Graduate Study and Research
of the University of Manitoba
in Partial Fulfillment of the Requirements
for the Degree of Master of Science

August 1964



ACKNOWLEDGEMENTS

I gratefully acknowledge the supervision, the assistance, and the patience of my research director, Dr. G.E. Dunn, who was a continual source of encouragement in this study. Special thanks are also due to M.A. Morello and I.E. Scheffler for their helpfulness during the course of the work. The financial assistance of the National Research Council and the University of Manitoba is very much appreciated.

TO MOM

ABSTRACT OF M.Sc.THESIS

Submitted by Fei-Lin Kung

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The ionization constants of 4- and 5-substituted salicylic acids were determined in aqueous solution at 25°C by an improved ultraviolet absorption spectrophotometric method. Their pK's were plotted against the Hammett substituents. A good correlation was obtained with the simple Hammett equation ($\log K/K_0 = \rho \sigma$) using σ_m for substituents in the 5-position and σ_p for substituents in the 4-position relative to the carboxyl group. The reaction constant, ρ , was calculated to be (+0.898±0.039). The results indicate that electronic effects are transmitted to the acid centre through the benzene ring and that virtually no transmission occurs through the phenolic hydrogen bond. At the isoelectric point 4-aminosalicylic acid is almost entirely in the neutral form whereas 5-aminosalicylic is almost completely zwitterion.

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INTRODUCTION

Ionization constants of aromatic acids, in particular salicylic acids, have been determined by a number of workers. The investigations of these authors (prior to 1930) were determined chiefly by conductimetric methods (34, 57, 13). However, potentiometric (40) and spectrophotometric (19, 43) methods have also been used.

Values obtained under different conditions vary considerably, and in order to establish any correlations for a series of compounds the same conditions must be used. The scope of the present investigation is to determine the ionization constants of a family of substituted salicylic acids by an improved spectrophotometric method (7, 8) and to correlate the experimental data, aided by an IBM 1620 Computer, with the intention of examining the electronic properties of various substituents in the benzene ring. The main advantages of spectrophotometric methods of determining acid dissociation constants are that optical measurements made at very low concentrations are relatively as accurate as those made at higher concentrations, and that even for very small dissociation constants quite reliable results can be obtained under favourable conditions (19).

An application of the Hammett equation (25, 29) to the ionization constants shows a satisfactory correlation with Hammett's sigma constants. A discussion of a two-

parameter Hammett relationship (31) is also given.

LITERATURE REVIEW

SPECTROPHOTOMETRIC DETERMINATION
OF IONIZATION CONSTANTS

The spectrophotometric determination of the ionization constants of aromatic acids is based on the fact that different ionic species have different ultraviolet absorption spectra.

The equation of the spectrophotometric determination of ionization constants is derived below. Beer's law (12) of light absorption states that the amount of light absorbed is proportional to the number of absorbing molecules through which the light passes. The absorption of the solution, if the absorbing substance is dissolved in a transparent medium, will be proportional to its concentration. The mathematical statement of Beer's law is as follows:

$$\frac{dP}{dn} = -kP \quad (1)$$

$$\int_{P_0}^P \frac{dP}{P} = -k \int_0^n dn$$

$$\ln \frac{P}{P_0} = -kn$$

$$\ln \frac{P_0}{P} = kn$$

$$\log \frac{P_0}{P} = k'n \quad (2)$$

where P_0 : power incident on sample.

P : power leaving the sample.

n : the number of absorbing centres in a volume of unit cross section.

Let

$$\log \frac{P_0}{P} = \log \frac{I_0}{I} = \log \frac{1}{T} = d \quad (3)$$

where I_0 : the intensity of incident light.

I : the intensity of light transmitted.

d : optical density (absorbance) which is actually measured with the spectrophotometer.

T : transmittance.

Then the relationship between absorbance and concentration will be given by

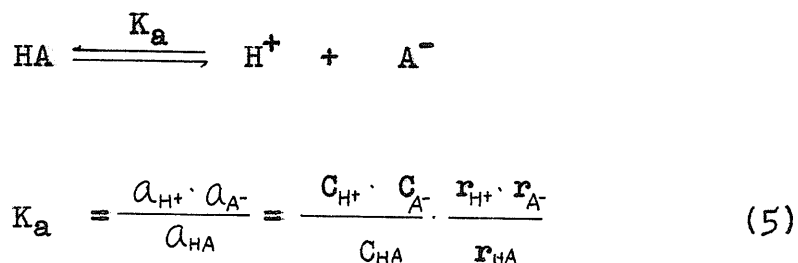
$$d = \log \frac{I_0}{I} = \epsilon \ell C \quad (4)$$

where ϵ : molar extinction coefficient.

ℓ : the thickness of the cell, cm.

C : molarity of the solution, moles per liter.

Consider now the monobasic acid equilibrium with an equilibrium constant K_a



where a : activity.

r : activity coefficient.

C : concentration.

In sufficiently dilute solution,

$$\frac{r_{H^+} \cdot r_{A^-}}{r_{HA}} \approx 1 \quad (6)$$

For spectrophotometric measurements on a partly ionized acid at a selected wavelength, Beer's law may be applied in the following form:

$$d_p = \epsilon_p l C_p \quad (7)$$

$$d_r = \epsilon_r l C_r \quad (8)$$

$$d_n = \epsilon_n l C_n \quad (9)$$

where d_p , d_r , d_n : optical densities of pure HA, pure A^- and of a mixture of HA and A^- , respectively.

ϵ_p , ϵ_r , ϵ_n : molar extinction coefficients of pure HA, pure A^- , and a mixture of HA and A^- ,

respectively.

C_p, C_r, C_n : concentration of pure HA, pure A^-
and a mixture of HA, and A^- ,
respectively.

l : the thickness of the cell.

When the two conjugate forms, HA and A^- , coexist in solution, the observed optical density for the solute at any wavelength is equal to the sum of optical density of HA and A^- or equal to the sum of the products of mole fraction and optical density of each pure form. Thus,

$$d_n = d_{HA} + d_{A^-}$$

$$\epsilon_n l C_n = \epsilon_{HA} l C_{HA} + \epsilon_{A^-} l C_{A^-}$$

since

$$C_n = C_{HA} + C_{A^-}$$

$$\epsilon_n l (C_{HA} + C_{A^-}) = (\epsilon_{HA} C_{HA} + \epsilon_{A^-} C_{A^-}) l$$

Dividing both sides by l and rearranging

$$\frac{C_{A^-}}{C_{HA}} = \frac{\epsilon_{HA} - \epsilon_n}{\epsilon_n - \epsilon_{A^-}}$$

or

$$\frac{[A^-]}{[HA]} = \frac{\epsilon_{HA} - \epsilon_n}{\epsilon_n - \epsilon_{A^-}}$$

Therefore,

$$K_a = \frac{[H^+][A^-]}{[HA]} = [H^+] \frac{\epsilon_{HA} - \epsilon_n}{\epsilon_n - \epsilon_{A^-}}$$

$$= [H^+] \frac{\frac{d_{HA}}{\ell C_{HA}} - \frac{d_n}{\ell C_n}}{\frac{d_n}{\ell C_n} - \frac{d_{A^-}}{\ell C_{A^-}}} \quad (10)$$

For a single solution of acid, measured successively under acidic (β), basic (γ), and intermediate (n) conditions, the three concentrations are equal,

$$C_\beta = C_\gamma = C_n$$

Therefore, Eq. 10 becomes

$$K_a = [H^+] \frac{d_{HA} - d_n}{d_n - d_{A^-}} \quad (11)$$

$$-\log K_a = -\log \left\{ [H^+] \frac{d_{HA} - d_n}{d_n - d_{A^-}} \right\}$$

$$pK_a = pH + \log \frac{d_n - d_{A^-}}{d_{HA} - d_n}$$

or

$$pK_a = pH + \log \frac{d_{A^-} - d_n}{d_n - d_{HA}} \quad (12)$$

One method (21,2) for calculating ionization constants from spectrophotometric data is to measure the optical densities of the pure HA(d_{HA}), pure A^- (d_{A^-}) and a solution containing both species at an intermediate

condition (d_n). These values are then substituted in equation 12, together with the pH at which d_n was determined, to give pK_a . This method involves only three determinations of optical densities, but two of these must be made with the pure conjugate forms.

Another approach (54) does not require pure conjugate forms. Any three solutions with sufficient differences in pH and optical density can give the ionization constant. Equation 11 can be written as follows:

$$d_n - d_{A^-} = \frac{[H^+](d_{HA} - d_n)}{K_a}$$

and

$$d_n - d_{A^-} = \frac{[H^+]d_{HA}}{K_a} - \frac{[H^+]d_n}{K_a}$$

Finally,

$$[H^+]d_n \left(\frac{1}{K_a} \right) - [H^+] \left(\frac{d_{HA}}{K_a} \right) - (d_{A^-}) = -d_n \quad (13)$$

Equation 13 is a linear equation in four terms and three unknowns (they are $\frac{1}{K_a}$, $\frac{d_{HA}}{K_a}$, and d_{A^-}), since d_n and $[H^+]$ are measurable quantities. Solution for the unknown K_a thus can be obtained from three simultaneous equations which may be solved with determinants, that is

$$K_a = \frac{\begin{vmatrix} H_1^+ d_1 & H_1^+ & 1 \\ H_2^+ d_2 & H_2^+ & 1 \\ H_3^+ d_3 & H_3^+ & 1 \end{vmatrix}}{\begin{vmatrix} H_1^+ & d_1 & 1 \\ H_2^+ & d_2 & 1 \\ H_3^+ & d_3 & 1 \end{vmatrix}} \quad (14)$$

In the present work, sixteen solutions were used and the ionization constants were calculated from the IBM 1620 Computer. These are discussed in the Experimental Section.

In the case of determining the overlapping ionization constants of aminosalicyclic acids, the ionic equilibria of the acids in aqueous solution is considered first. In aqueous solution four species are in equilibrium with each other and they are present in a proportion depending on the hydronium ion concentration. The equilibria may be represented as follows, where hydronium ion is omitted from the diagram for simplicity.

Species : HA \equiv Neutral molecule.

H_2A^+ \equiv Diprotic acid.

HA^+ \equiv Zwitterion.

A^- \equiv Anion.

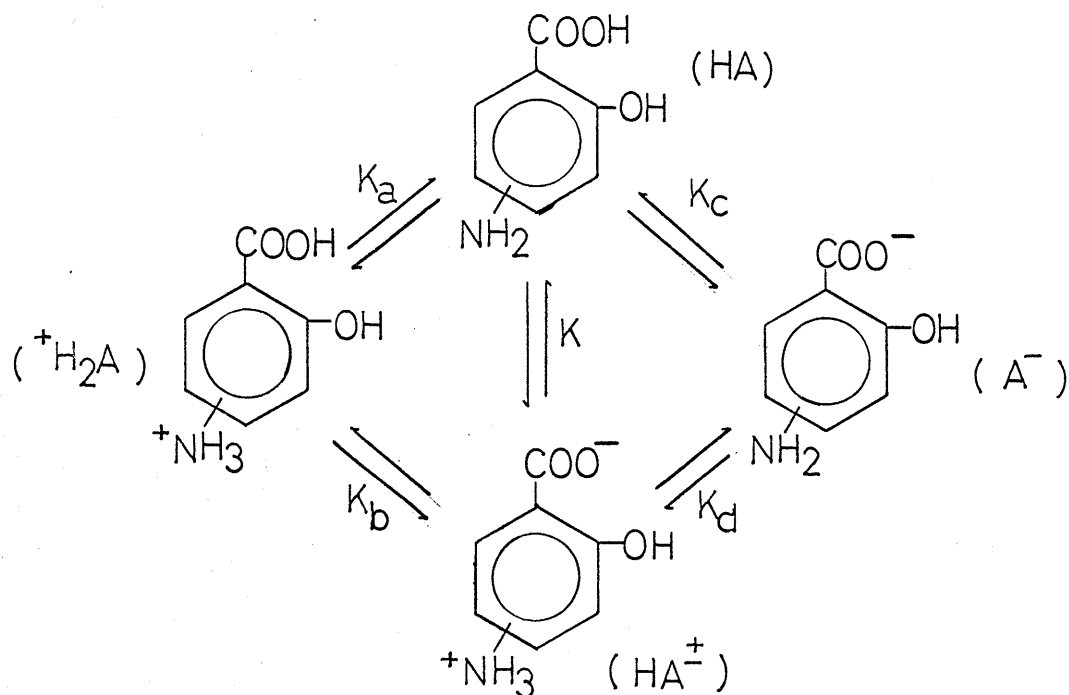


Fig. 1. Schematic Representation of Species and Ionic Equilibria of 4-Amino and 5-Aminosalicylic Acids in Aqueous Solution.

If $\{N\}$ refers to the total concentration of ampholyte, i.e.

$$\{HA\} + \{HA^{\pm}\} = \{N\}$$

Then,

$$\{H_2A^+\} \xrightleftharpoons{K_1} \{N\} \xrightleftharpoons{K_2} \{A^-\}$$

where

$$K_1 = \frac{\{N\} \{H^+\}}{\{H_2A^+\}} \quad (15a)$$

$$K_2 = \frac{\{A^-\} \{H^+\}}{\{N\}} \quad (15b)$$

From Figure 2 the ionization of individual species

are:

$$K_a = \frac{\{HA\} \{H^+\}}{\{H_2A^+\}} \quad (16a)$$

$$K_b = \frac{\{HA^+\} \{H^+\}}{\{H_2A^+\}} \quad (16b)$$

$$K_c = \frac{\{A^-\} \{H^+\}}{\{HA\}} \quad (16c)$$

$$K_d = \frac{\{A^-\} \{H^+\}}{\{HA^+\}} \quad (16d)$$

It follows that

$$\frac{K_c}{K_d} = \frac{K_b}{K_a} = \frac{\{HA^+\}}{\{HA\}} = K \quad (16e)$$

$$K_a K_c = K_b K_d \quad (16f)$$

$$K_a + K_b = K_1 \quad (17a)$$

$$\frac{1}{K_c} + \frac{1}{K_d} = \frac{1}{K_2} \quad (17b)$$

Let C be the total concentration of acid in solution;

$$C = \{H_2A^+\} + \{N\} + \{A^-\} \quad (18)$$

From Eq. 16,

$$C = \frac{\{HA\}\{H^+\}}{K_a} + \{HA\} + \frac{K_c}{K_d}\{HA\} + K_c \frac{\{HA\}}{\{H^+\}} \quad (19)$$

Therefore

$$\{HA\} = C / \left\{ \frac{(H^+)}{K_a} + 1 + \frac{K_c}{K_d} + \frac{K_c}{(H^+)} \right\} \quad (20a)$$

Similarly

$$\{HA^+\} = C / \left\{ \frac{(H^+)}{K_b} + 1 + \frac{K_d}{K_c} + \frac{K_d}{(H^+)} \right\} \quad (20b)$$

$$\{H_2A^+\} = C / \left\{ 1 + \frac{K_a + K_b}{(H^+)} + \frac{K_a K_c}{(H^+)^2} \right\} \quad (20c)$$

$$\{A^-\} = C / \left\{ \frac{(H^+)^2}{K_a K_c} + (H^+) \left(\frac{1}{K_c} + \frac{1}{K_d} \right) + 1 \right\} \quad (20d)$$

$$[N] = c / \left\{ \frac{(H^+)}{K_1} + 1 + \frac{K_2}{(H^+)} \right\} \quad (20e)$$

The concentration of HA reaches a maximum when

$$\frac{\partial [HA]}{\partial [H^+]} = \frac{\partial f(K_a, K_c, K_d, H^+)}{\partial [H^+]} = 0 \quad (21)$$

Thus

$$[HA]_{\max.} \text{ when } [H^+] = (K_c K_d)^{\frac{1}{2}}$$

Similarly

$$[HA]_{\max.} \text{ when } [H^+] = (K_b K_d)^{\frac{1}{2}} \\ = (K_a K_c)^{\frac{1}{2}}$$

From the relationship of Eq. 16f,

$$K_a = \frac{K_b K_d}{K_c} = \frac{(K_1 - K_a) K_d}{K_c} \quad (22)$$

From Eqs. 17a and 16f,

$$K_a = \frac{K_1 K_d}{K_c + K_d} \quad (23)$$

and

$$K_a K_c = K_1 K_2 \quad (24)$$

Therefore, $[HA^{\pm}]$, $[HA]$, and $[N]$ have a maximum concentration at

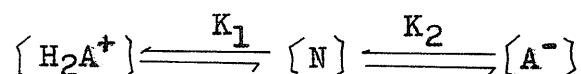
$$H^+ = (K_1 K_2)^{\frac{1}{2}}$$

or

$$pH = \frac{1}{2} (pK_1 + pK_2) \quad (25)$$

This particular pH is called the isoelectric point. The above general expressions of equilibria have been applied to 4-methoxyanthranilic acid by Scheffler (55).

Thamer and Voigt (19) first described the determination of the overlapping ionization constants of dibasic acids by using the spectrophotometric method. This method was modified by Kok-Peng Ang (37) and further by Dunn and Leggate (18). The ionization of aminosalicyclic acid (omitting $[H^+]$) may be expressed by



If d_1 , d_2 , d_3 are the optical densities ^{of 1M solutions} of the pure species H_2A^+ , N and A^- respectively, then, at a fixed wavelength, the optical density d of a solution containing a mixture of these species in a cell of one centimetre length is given by

$$d = d_1 [H_2A^+] + d_2 [N] + d_3 [A^-] \quad (26)$$

where the total concentration is assumed to be 1M, i.e.

$\{H_2A^+\} + \{N\} + \{A^-\} = 1$. From Eqs. 15 and 26, the optical density, d , of a solution of the acid may be expressed in the form,

$$\{H^+\}^2 (d - d_1) + \{H^+\} K_1 (d - d_2) + K_1 K_2 (d - d_3) = 0 \quad \text{----- (27)}$$

A value of d determines two values of pH, pH_1 and pH_2 (See Fig. 2) and hence two values, $\{H^+\}_1$ and $\{H^+\}_2$. These may be substituted in turn into Eq. 27 and a combination of the two resulting equations yields the following expression :

$$d = \frac{d_2 + K_2 d_3 A}{1 + K_2 A} \quad (28)$$

where

$$A = \frac{1}{\{H^+\}_1} + \frac{1}{\{H^+\}_2}$$

and

$$d = \frac{d_1 + K_1 d_2 B}{1 + K_1 B} \quad (29)$$

where

$$B = \frac{1}{\{H^+\}_1 + \{H^+\}_2}$$

The general form of Eqs. 28 and 29 is

$$Y = \frac{A + BCX}{1 + BX} \quad (30)$$

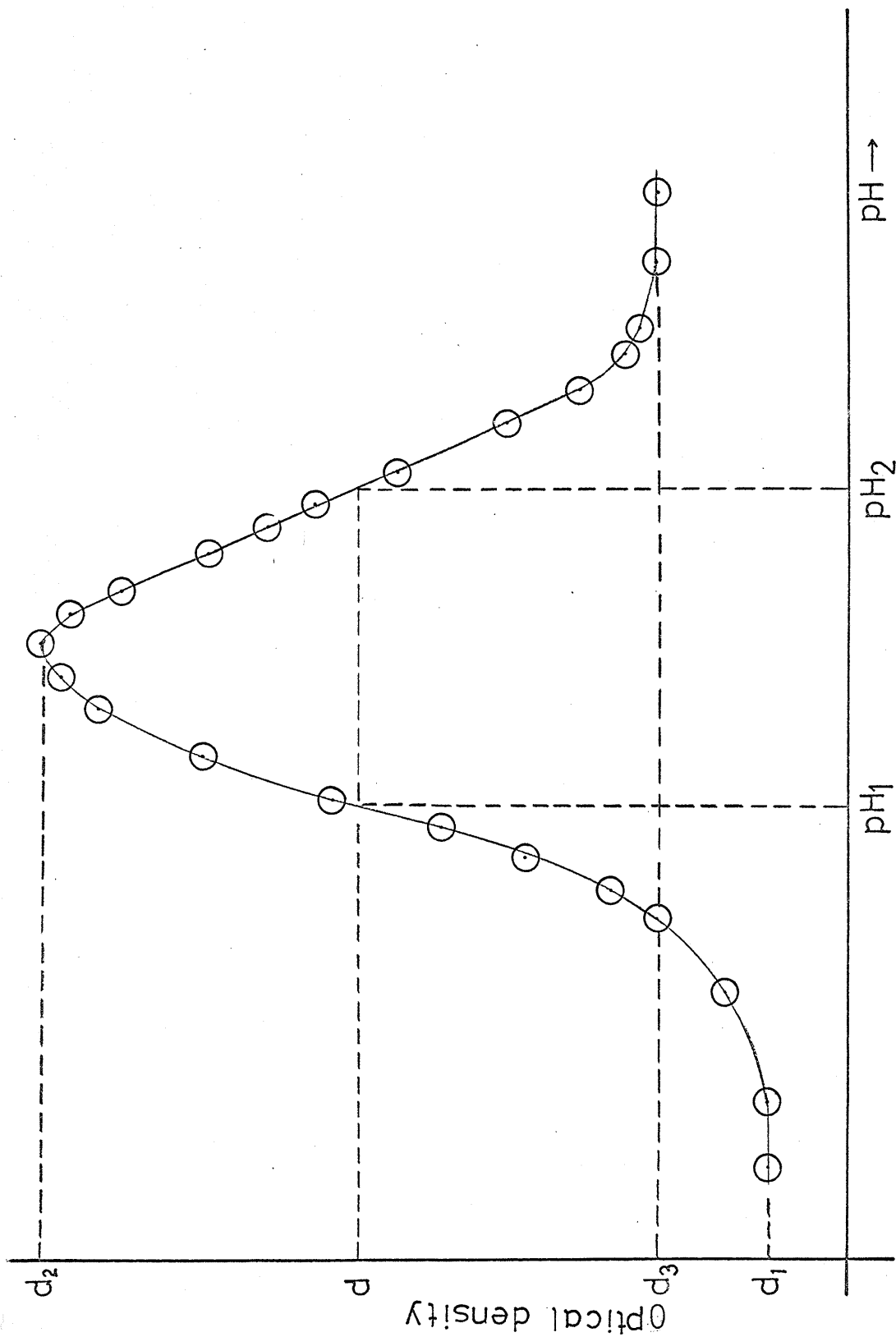


Fig. 2. A hypothetical plot of pH vs. d showing the variation of the optical densities of (buffered) aqueous solutions of a diprotic acid at a suitable wavelength.

where X and Y are variables and A, B and C are constant parameters.

Equation 30 was solved on the IBM 1620 Computer by using the method of Dunn and Leggate (18) and Scheffler (55) as briefly outlined below. A plot shown in Figure 2 was constructed. Experimental points (d, pH_1) were used together with interpolated values for pH_2 (corresponding to d) for the calculation of K_1 , and similarly, for the calculation of K_2 experimental d's and pH_2 's were used together with the corresponding interpolated pH_1 's. The best curve through the given points was obtained from the Computer. In each case the interpolated value of the pH appeared in the least significant term in Eq. 28 or 29. The Fortran Program is shown in Appendix II.

THE HAMMETT RELATIONSHIP

The quantitative relationship between the structure of organic compounds and their chemical reactivity has been of major interest to physical-organic chemists. Hammett (26, 25) first related structure to both equilibrium

constants and rate constants for the reactions of meta- and para-substituted benzene derivatives by the mid-1930's. This relation is known as the Hammett equation.

$$\text{or} \quad \log \frac{K}{K_0} = \rho \sigma \quad (31)$$

$$\log \frac{k}{k_0} = \rho \sigma$$

The first parameter, sigma (σ), is characteristic only of the substituent and represents the ability of the group to attract or repel electrons by a combination of its inductive and resonance effects. The second parameter, rho (ρ), characteristic of the reaction series at hand, is a measure of the sensitivity of this type of reaction series to ring substitution. K and K_0 are the ionization constants of the substituted and unsubstituted compound, respectively; k and k_0 are the rate constants for reaction of the substituted and unsubstituted compound, respectively. $\log K/K_0$ is proportional to the difference in standard free energy between the reaction of the substituted compound and the unsubstituted compound; $\log k/k_0$ is proportional to the difference in standard free energy of activation when the transition state theory is assumed.

Hammett chose the dissociation of substituted benzoic acids as the standard reaction for which rho was

set arbitrarily equal to one. The sigma value for a substituent was obtained by measuring the effect of that substituent on the ionization constant of benzoic acid in water at 25°C and defining it through the relationship,

$$\delta = \log \frac{K_{R-C_6H_4COOH}}{K_{C_6H_5COOH}} \quad (32)$$

where $K_{R-C_6H_4COOH}$ and $K_{C_6H_5COOH}$ are the ionization constants for the substituted and the unsubstituted benzoic acid, respectively. A large series of reactions with various groups on the benzene nucleus have been very well correlated with equation 31 using Hammett's sigma constants.

The direct resonance interaction between the substituent group and the reaction centre has led to the modification of the Hammett equation by using alternate sets of sigma constants (25). The ordinary sigma for electron withdrawing groups through resonance in the para position (c.f. p-nitro, p-cyano) caused large deviations when used in conjunction with strong electron donating groups (c.f. -NH₂, -O⁻) which were present at the reaction centre. Large deviations were also found with substituents capable of electron donating by resonance when the reaction centre is one of strong electron withdrawal. Sigma minus (δ^-) constants (21) refer to those para substituents capable of

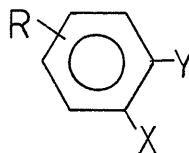
strong electron withdrawal through resonance and have been used in reactions of aniline and phenol derivatives. In a corresponding manner sigma plus (δ^+) constants (11) were used for strong electron donating para substituents in such reactions as aromatic nitration.

Extensions of the Hammett equation to more complicated types of compounds have been reported by Jaffe (30, 29). The effects of several substituents in the 3, 4 and 5 positions relative to the reacting side chain have been observed to be additive, that is

$$\log \frac{K}{K_0} = \rho \sum \delta \quad (33)$$

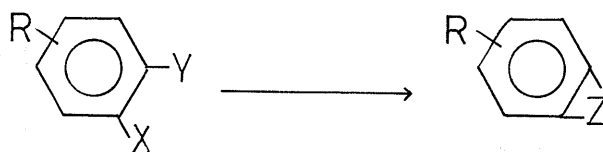
Equation 33 is a good approximation to the effect of multiple substituents. However, substituents which interact strongly with each other must be excepted from this generalization.

Compounds of the type



have been measured on a few reaction series (23, 24, 7) where R is a substituent in the 4- or 5-position, X is the same throughout the series. Two situations may be possible. The first case is that Y and X do not react with each other.

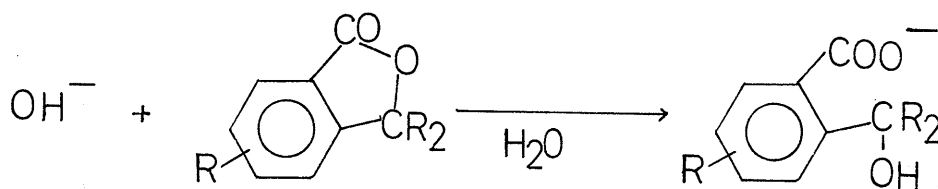
The reaction constants are reported almost always equal within experimental error when comparing several groups X which may include X=H. The second case is that in which Y and X will react with each other as shown below:



The reacting side chain are now attached in two places to the ring bearing the substituent. The substituent effect is transmitted to the reaction site by two paths, and separate reaction constants are required. The general form of the modified Hammett equation (31) is

$$\log \frac{K}{K_0} = \sigma_1 \rho_1 + \sigma_2 \rho_2 \quad (34)$$

This situation is encountered in the alkaline hydrolyses of ^{the substituted} phthalide and its derivatives.



This two-parameter Hammett equation has been proposed also by Jaffe (11) to be applicable to fused ring systems. Compounds in which the reacting group is hydrogen bonded to a vicinal substituent are classified of this type and proposed to fit the two-parameter rather than the one-parameter Hammett equation. Among the examples to have been considered were the pK 's of the *o*-(hydroxymethyl)-benzoic acids and the catechols.

If a reaction series is considered of the type



where X is the changing substituent, the

following equation may be expressed:

$$\log \frac{K}{K_0} = \rho \sigma + \chi \quad (35)$$

Where χ is the effect the substituent X in the ortho position exerts on the reactivity of unsubstituted compound C_6H_5Y , i.e. $\chi = \log K_X/K_0$. The applicability of this equation is subject to the limitation that the substituent X does not affect the mechanism of the reaction. Equation 35 can be applied to nuclear chlorinations of benzyl phenyl ethers (33) where X represents the cumulative effect of the several substituents in the phenyl group.

When several aromatic rings are in nonequivalent positions relative to the reaction site, the following

equation is proposed:

$$\log \frac{K}{K_0} = \rho_1 \sigma_1 + \rho_2 \sigma_2 + \dots + \quad (36)$$

where ρ_1, ρ_2, \dots measure the susceptibility of the reaction to the effect of substituents in rings 1, 2, ... and $\sigma_1, \sigma_2, \dots$ refer to the substituents in the respective rings. The relative rates of decomposition of the potassium salts of certain meta- and para-substituted dibenzhydroxamic acids (53) have been reported to fit equation (36).

Numerous detailed reviews have been published with regard to the applicability of Hammett's equation in its many modifications as well as other related linear free energy relationships (29, 30, 49, 64).

Para- and meta-substituted salicylic acids have been reported by Jaffe (29) not to fit equation 34. However, he had data for only six substituted salicylic acids. The purpose of this investigation is to examine the correlation of the effect of substituents on the ionization equilibria of para- and meta-substituted salicylic acids with the nature of the substituents.

EXPERIMENTAL

MATERIALS

Table 1 lists the substituted salicylic acids used in this investigation together with their source of preparation. Most acids were recrystallized from water unless otherwise noted. All melting points were determined by using the conventional short Anschutz enclosed-scale thermometers in a Hershberg melting point apparatus. Methods for synthesis of the substituted salicylic acids prepared in this laboratory are described below.

4-Methylsalicylic acid was prepared by treating 4-methylanthranilic acid with nitrous acid. A solution of 7.6 gm. (0.05 mole) 4-methylanthranilic acid (Aldrich Chemical) in 33 ml. concentrated sulfuric acid and 45 ml. water was cooled to 0 - 5°C and stirred with a magnetic stirrer. A solution of 4 gm. sodium nitrite in 10 ml. water was added dropwise over a period of eight to ten minutes. After stirring the solution for another ten to fifteen minutes, it was poured into 200 ml. of boiling water. The solution was boiled briskly and cooled. 4-methylsalicylic acid precipitated on cooling, and after two recrystallizations from water 1.1 gm. was recovered (14.5% of theoretical) with melting point 177.0 - 177.8° C (lit. 172° C (63)).

Table 1

Substituted Salicylic Acids

Substituent	Source	Melting Point, °C	
		Observed	Literature Value
4-Methoxy	Prepared	159-160.5	155.9-156.3(32)
5-Methoxy	Prepared	144.5-146.0	145.7-146.2(32)
4-Methyl	Prepared	177.0-177.8	172(63)
5-Methyl	Matheson, Coleman & Bell	147.0-148.0	149.6-150.6(32)
4-Nitro	L. Light & Co.LTD(England)	231.0-231.8	234.8-235.3(32)
5-Nitro	Eastman Organic Chemicals	231.8-232.2	227-228(46)
4-Hydroxy	Eastman Organic Chemicals	229.0-230.0d	226d(32)
5-Hydroxy	Eastman Organic Chemicals	206.2-207.0d	201(7)
4-Amino	Matheson, Coleman & Bell	153.5-154.0d*	146-147(56)
5-Amino	Matheson, Coleman & Bell#	286.0-286.6d	280(23)
4-Bromo	Prepared by W. Rodewald	208.0-209.0	212(28)
5-Bromo	Matheson, Coleman & Bell	167.8-169.0 [ⓐ]	166.5-167.5(44)
4-Cyano	Prepared	228.0-229.0	227-229(10)
4-Ethoxy	Eastman Organic Chemicals	152.0-153.0 [ⓐ]	148-150(41)

Table 1
(continued)

5-Chloro	Matheson, Coleman & Bell	175.0-176.4 [@]	172(42)
5-Iodo	Aldrich Chemicals	196.0-197.5	195(52)
3-Methyl	Matheson, Coleman & Bell	166.8-168.0	164(64)
Salicylic Acid	May & Baker (Bulk)	158.0-159.0	156-158(36)

: Practical grade

* : Ethylacetate and toluene used for recrystallization

@ : Aqueous ethyl alcohol used for recrystallization

d : Decomposition

4-Methoxysalicylic acid was prepared by methylating 4-hydroxysalicylic acid (12). A solution of 7.1 gm. (0.052 mole) 4-hydroxysalicylic acid (Eastman Organic Chemical) in 40 ml. 10% sodium hydroxide solution (0.1 mole) was brought to reflux with 9 ml. dimethylsulfate (12.1 gm., 0.1 mole). Another 40 ml. 10% sodium hydroxide solution was added dropwise to the refluxing solution over a period of four hours. Impure 4-methoxysalicylic acid precipitated from the cooled solution on acidification with hydrochloric acid. This acid was filtered and refluxed with 10% sodium hydroxide solution to hydrolyse ester impurities. The acid was recovered by acidification and after recrystallization from water the yield was 4.0 gm. (46% of theoretical) with melting point 159.0 - 160.5°C (lit. 155.9 - 156.3°C (32), 157°C (12)).

5-Methoxysalicylic acid was prepared by the same method used in the preparation of 4-methoxysalicylic acid. The starting material, 5-hydroxysalicylic acid, was an Eastman Organic Chemical. The yield was 2.1 gm. (24% of theoretical) with melting point 144.5 - 146.0°C (lit. 145.7 - 146.2°C (32), 143.5°C (22)).

4-Cyanosalicylic acid was prepared by diazotizing p-aminosalicylic acid and subsequently treating the diazonium solution with potassium cyanide and cuprous cyanide. A solution of 10.0 gm. (0.065 mole) p-aminosalicylic acid (Matheson Coleman & Bell) in 30 ml. of concentrated sulfuric acid and 60 ml. water was cooled to 0 - 5°C with stirring. A solution of 20 gm. sodium nitrite in 100 ml. water was added slowly until the mixture gave a positive test with potassium iodide starch test paper. The latter was poured into another solution which contained 14.5 gm. (0.164 mole) cuprous cyanide, 200 ml. water and as much potassium cyanide as needed to aid dissolution. The resulting mixture was warmed on a water bath at 60°C with stirring for half an hour. The solid was filtered and extracted with ether three times (200 ml. each) from which 4-cyanosalicylic acid was recovered by evaporation of the ether. After recrystallisation from water, the yield was 0.2 gm. (1.9% of theoretical) with melting point 228.0 - 229.0°C (lit. 227 - 229°C (10)).

3-Methylsalicylic acid : The acid obtained from and labelled by the Matheson Coleman & Bell as 2,4-cresotic acid was identified as 3-methylsalicylic acid(2,3-cresotic acid).

A number of solid derivatives were made from the

acid. The p-bromophenacyl ester, the p-nitrobenzyl ester and the dinitro derivative were prepared according to Shriner (56B). Treatment of the acid with acetic anhydride and a small amount of phosphoric acid secured the acetyl derivative (1B).

Conclusive evidence was obtained by decarboxylating the acid in quinoline assisted by the presence of copper powder (26B). The resulting cresol was treated with bromine (56B) to form the dibromo derivative. A mixed melting point with the dibromo derivative of an authentic sample of o-cresol gave no depression.

Pertinent information on the melting points of the substances described is summarized in Table 2A.

Table 2A Melting points of methylsalicylic acids(64), cresols(56B) and the unknown acid, including the corresponding derivatives.

<u>Name of Compound</u>	<u>M.P.(°C)</u>	<u>p-Bromo-phenacyl Ester</u>	<u>p-Nitro-benzyl Ester</u>	<u>Acetyl</u>	<u>Dinitro</u>	<u>Bromo Derivative</u>
3-Methyl-salicylic acid	164		99	113		
4-Methyl-salicylic acid	177	162	175	139		
5-Methyl-salicylic acid	153		147	153		
6-Methyl-salicylic acid	168			123-4*	155*	
Unknown acid	166.8-168.0	138.0-139.5	106.0-107.5	118.0-119.0	93.0-94.0	
<hr/>						
o-Cresol	31					56
m-Cresol	3					84
p-Cresol	36					49
Decarboxylated unknown acid						55.0-56.0

* : Data taken from Reference (3B)

SPECTROPHOTOMETRIC STUDIES

The spectrophotometric method was utilized in this investigation for determining overlapping ionization constants of 4- and 5-aminosalicylic acids as well as the first ionization constants of other substituted salicylic acids.

Theoretical

One method of determination of the first ionization constants has been to make a series of determinations of optical densities at a particular wavelength and at various hydronium ion concentrations. The hydronium ion concentration corresponding to the point midway between the maximum and minimum values for the optical density is then equivalent to the ionization^{constant} (see Fig. 3). This method was first suggested by Bjerrum (8) in 1915. A significant improvement to the procedure is made possible by the use of an electronic computer. Working within the Debye-Huckel concentration range optical densities are measured at varying pH but a constant ionic strength. The experimental points of optical density and corresponding pH are inserted into equation 37 which is derived as follows.

From equation 11, the following expression can be written:

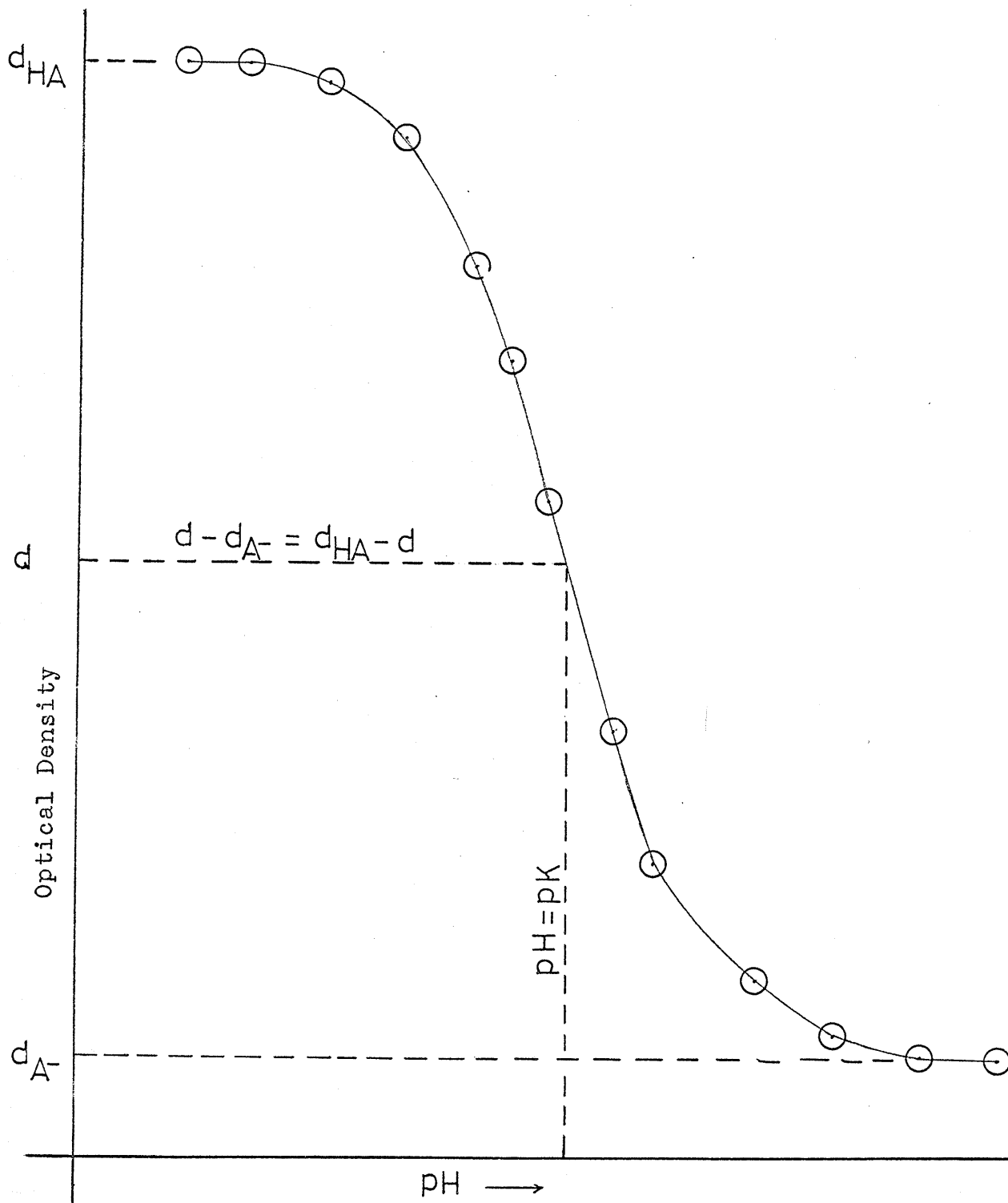


Fig. 3. A hypothetical plot of optical density versus pH showing the inflection point between the maximum and minimum values of the optical density to be equal to the ionization constant.

$$\begin{aligned}
 (d_n - d_{A^-}) K_a &= \{H^+\} (d_{HA} - d_n) \\
 d_n K_a - d_{A^-} K_a &= \{H^+\} d_{HA} - \{H^+\} d_n \\
 d_n (K_a + \{H^+\}) &= d_{A^-} K_a + \{H^+\} d_{HA}
 \end{aligned}$$

$$d_n = \frac{d_{HA} \{H^+\} + d_{A^-} K_a}{K_a + \{H^+\}} \quad (37)$$

The general form of the above equation is

$$Y = \frac{AX + BC}{C + X} \quad (38)$$

where X and Y are the variables and A, B and C are constant parameters which can be obtained by fitting a curve to the experimental points ($d_n, \{H^+\}$). Equation 38 was actually fitted on the computer by Dolittle's method (14), weighting the values of d_n and $\{H^+\}$ inversely as the estimated experimental error (see Appendix I).

This method of calculation has the advantages over previous methods that d_{HA} and d_{A^-} , as disposable parameters, are not subject to experimental error and that the curve-fitting procedure permits a reliable estimation of the standard error in K_a to be made. In Dolittle's method an estimation of the approximate values of A, B and C is necessary in order to compute their best values. The esti-

mated value of A (optical density of pure HA) is the optical density measured in acidic media (pH=0) in which only neutral molecules of HA can exist. The estimated value of B is the optical density measured in alkaline media (pH=9) in which only the anion A⁻ can exist. Figure 1 outlines the manner in which the value C may be estimated. It is equivalent to the pH corresponding to the inflection point of the pH versus optical density curve. The mean optical density at this point represents a condition where the two forms, HA and A⁻, are present in the solution in equal concentrations. Since from equation 12; when HA and A⁻ are present in equal concentration, d_n will be half of the sum of d_{A^-} and d_{HA} , and therefore $d_{A^-} - d_n = d_n - d_{HA}$, thus

$$pK_a = pH + \log \frac{d_{A^-} - d_n}{d_n - d_{HA}} = pH + 0 = pH$$

Buffer Solutions

A series of buffer solutions of various pH values were first prepared. Buffer solutions used to determine first ionization constants ranged from pH= 2.0 to pH=4.0 with intervals of 0.2 pH units. Each buffer solution was kept to a constant ionic strength of 0.01. In the case of the aminosalicyclic acids, buffers ranged from pH=1.0 to pH=6.0 with constant ionic strength of 0.1.

Up to pH=2.4, the buffer solutions were prepared from hydrochloric acid and potassium chloride. An example of making this kind of solution is shown in Appendix IV.

Monochloroacetate, formate and acetate buffers, used for the pH values above 2.4, were made according to the suggestions of Bates (5). An example of the preparation of a buffer solution of pH= 3.6 with ionic strength of 0.01 is shown in Appendix V.

Acid Stock Solutions

Stock solutions of most of the substituted salicylic acids were prepared by warming a sufficient quantity of the acid in approximately 300 ml. of distilled water for one minute. Decarboxylation of the acid was assumed to be negligible at this temperature (about 80°C). The solution was diluted to 500 ml. in order to make the concentration of the acid about 1.0×10^{-3} to 3.0×10^{-3} M and transferred to the reservoir of a 10 ml. automatic burette. Some of the acid solutions were prepared by dissolving the acid in 0.005N sodium hydroxide solution.

Optical Densities and pH Measurements

Measurements of optical density were made with a Beckman Model DK Spectrophotometer. Matched silica cells

of 1cm. length were used throughout. The temperature of the cell compartment being kept at $25 \pm 1^\circ\text{C}$ by balancing of the heater adjustment and the flow of cooling water. The change of absorbance line due to the deviation of 1°C was so small that it could be neglected.

In order to secure a suitable wavelength for study, complete ultraviolet absorption spectra of each of the acids were obtained at pH values approximating strongly acidic, intermediate and strongly alkaline conditions in the region of 200 -400 m μ . The spectra of the acids that were recorded are given in Fig. 5 through 21. A suitable wavelength was chosen where the optical density differences between the three absorption curves were the largest. Once selected, the wavelength drum was set at the chosen value throughout all the measurements of one particular acid.

A series of determinations of optical densities at this wavelength and at various hydronium ion concentrations were made in the following manner. Five milliliter portions of the acid stock solution were delivered into 50 ml. volumetric flasks and diluted to the mark with the buffer solutions previously prepared. Without undue delay the absorbance of each resulting solution was recorded and its pH immediately measured by using a Radiometer (pH M4C

Kopenhagen) equipped with a glass (0.202 B) and a Calomel electrode (K100). The solution to be measured was contained in a U-tube suspended in a constant temperature ($25 \pm 0.1^{\circ}\text{C}$) water bath. NBS (National Bureau of Standards) potassium tetroxalate buffer (pH=1.68 at 25°C) was used as a standard for measurements below pH=2.80. For the measurements of higher pH the meter was standardized with NBS potassium hydrogen phthalate buffer (pH=4.01 at 25°C).

RESULTS

The results of the determination of ionization constants of substituted salicylic acids at 25°C are shown in this section.

The ultraviolet absorption spectra of substituted salicylic acids in aqueous solution in various buffers are given in Figures 5 through 21.

In Table 2 through Table 16 the pH and corresponding absorbance of the various buffered solutions are given together with a symbol denoting the kind of buffer used; ClA, F, Ac and NH₃ refer to chloroacetate, formate, acetate and ammonia buffers, respectively. For aminosalicic acids the interpolated pH values from Figure 22 and Figure 23 are also recorded. The pH versus absorbance of aminosalicic acids plots constructed from the experimental data are shown in Figure 22 and Figure 23.

The ionization constants computed from Equation 38 by the Fortran Program of Appendix I are listed in Table 19. A consideration of the values of pK shows that electron withdrawing substituents aid in the ionization of the salicylic acids. Further appraisal will be given in the Discussion.

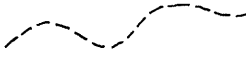


The overlapping ionization constants of the 4- and

5-aminosalicylic acids computed by the method of Dunn and Leggate (Appendix II) from Equations 28 and 29 are listed in Table 20.

As far as the uncertainty in the computation of ionization constants is concerned, a probable error of ± 0.01 was taken for all values of the measured absorbance (d) and of the measured pH. Errors in the data of absorbance were due to the fluctuation in the performance of the instrument, the reading of a "noisy" line on graph paper or the 0 - 100% adjustments. Errors in the data of pH arose from the calibration of the instrument. The squares of the reciprocals of these uncertainties were used as weighting factors for d and pH in solving Equations 28, 29 and 38 for K_a . It was observed that changing the uncertainty from ± 0.005 to ± 0.02 for both optical density and pH produced no significant change in the computed values of the ionization constants. The uncertainties shown for K and pK in Tables 19 and 20 are the standard errors in the solution of Equation 38, 28 or 29 as appropriate.

Figures 5 through 21

Ultraviolet absorption spectra of aqueous solutions of substituted salicylic acids at 25°C.

- (1) 1.0N HCl (pH=0), 
- (2) Formate buffer (pH=3), 
- (3) Ammonia buffer (pH=9), 

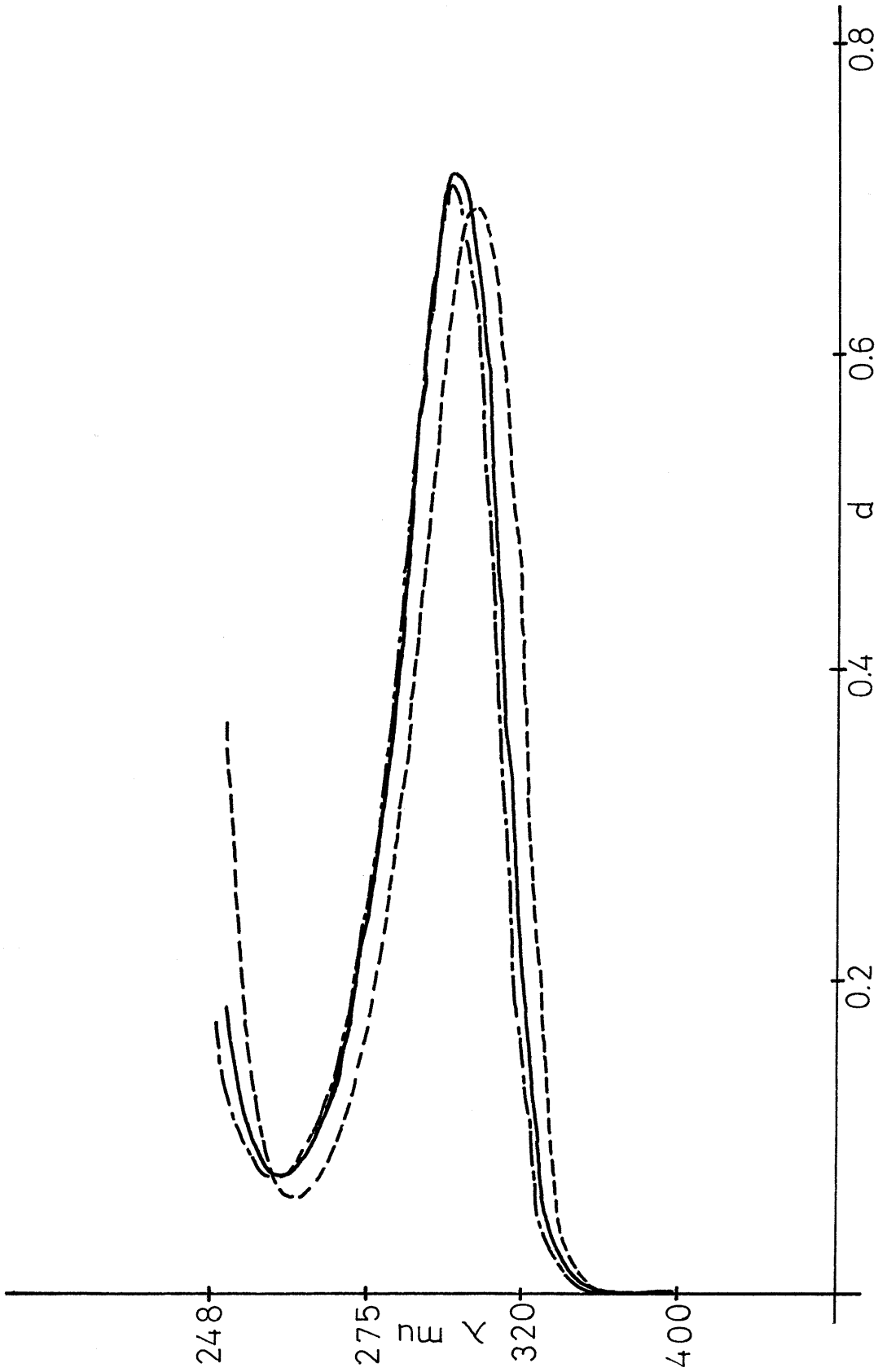


Fig. 5. Salicylic Acid
 $c = 2.0 \times 10^{-4} \text{ M}$



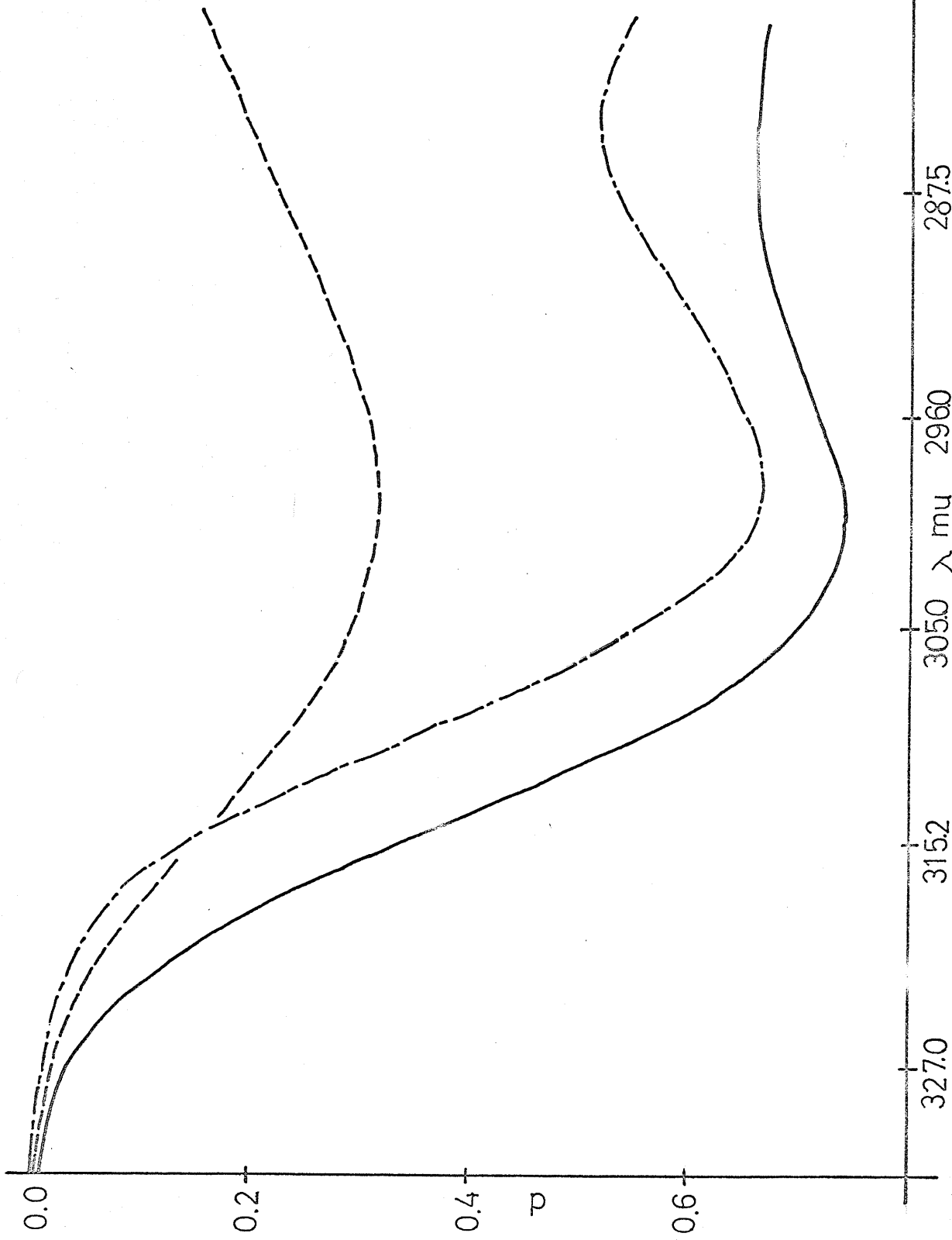


Fig. 6. 4-Aminosalicylic Acid
 $c=0.8 \times 10^{-4} M$

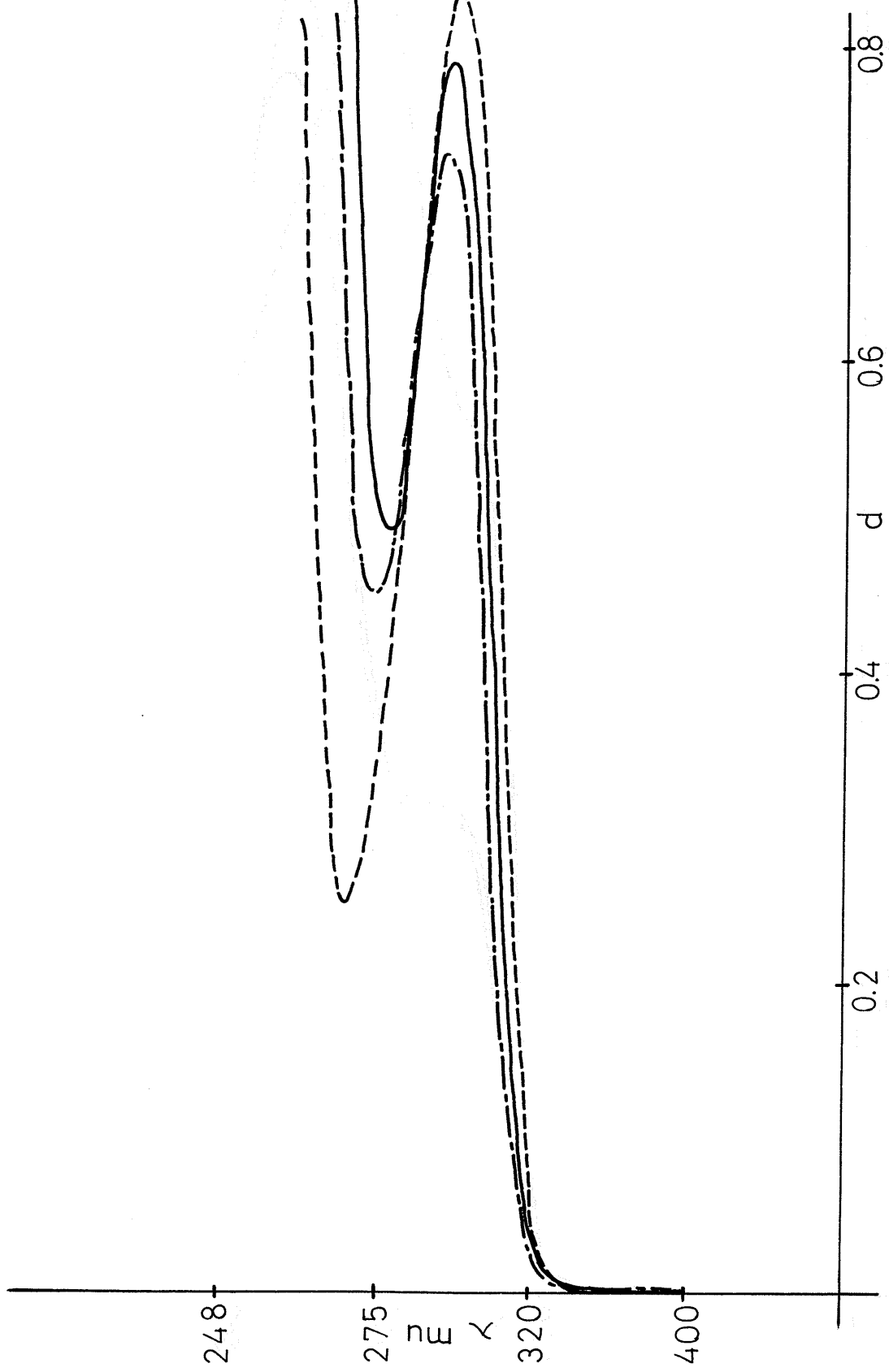


Fig. 7. 4-Methoxysalicylic Acid

$c=1.4 \times 10^{-4} M$

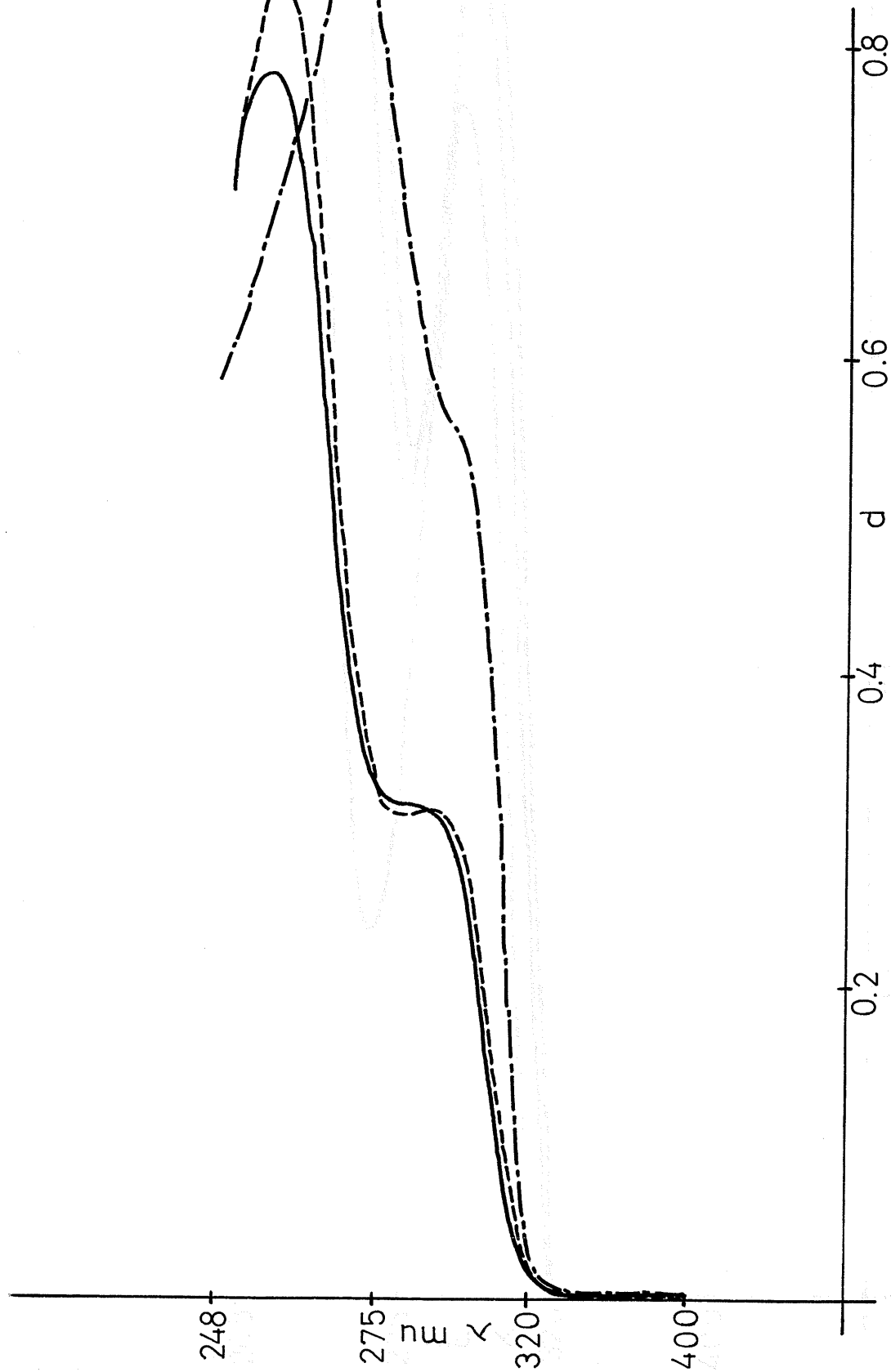


Fig. 8. 4-Hydroxysalicylic Acid

$c = 0.5 \times 10^{-4} \text{ M}$

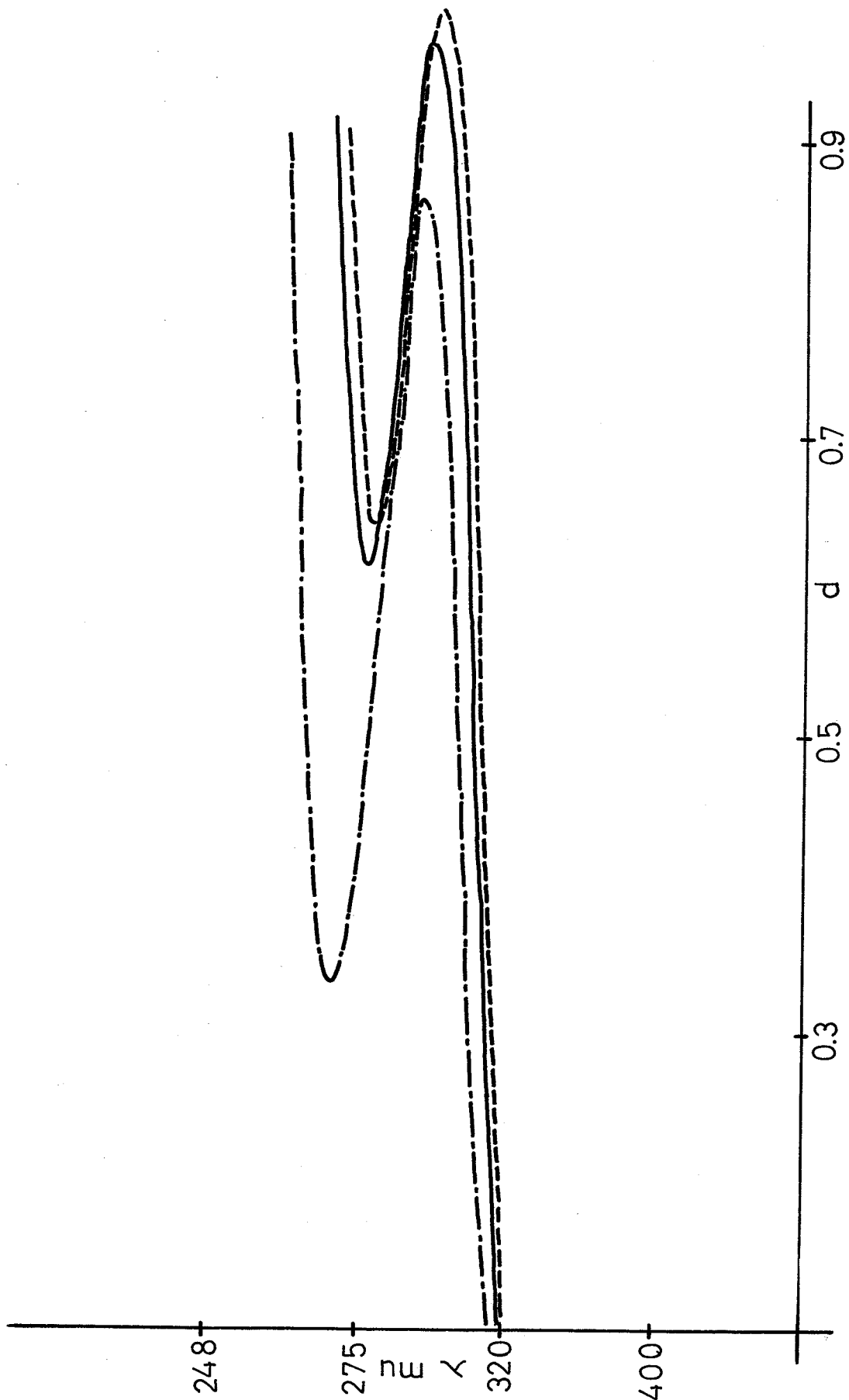


Fig. 9. 4-Ethoxysalicylic Acid
 $c=1.6 \times 10^{-4} M$

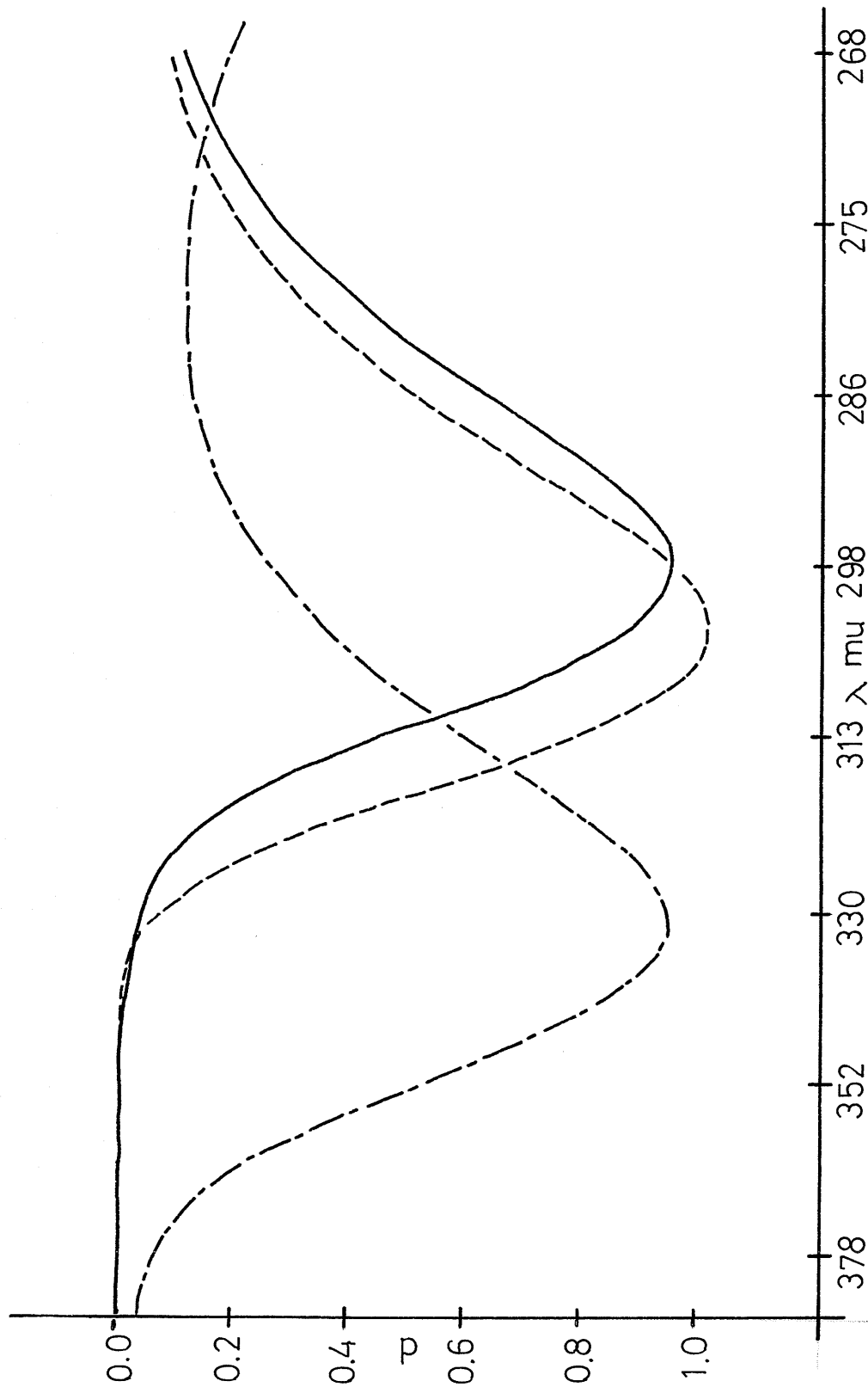


Fig. 10. 5-Aminosalicylic Acid
 $c=2.3 \times 10^{-4}M$

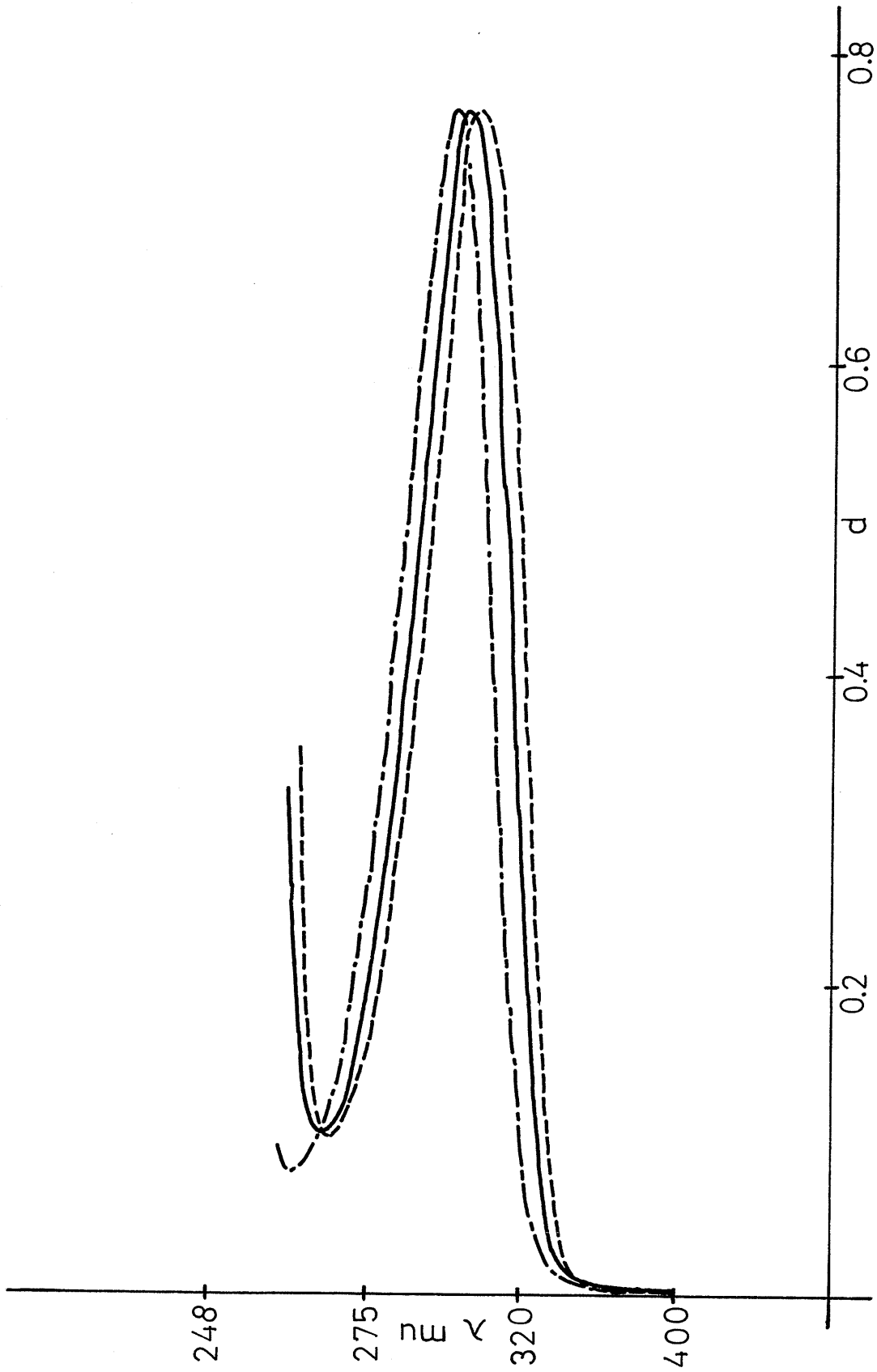


Fig. 11. 4-Methylsalicylic Acid

$c=1.6 \times 10^{-4} M$

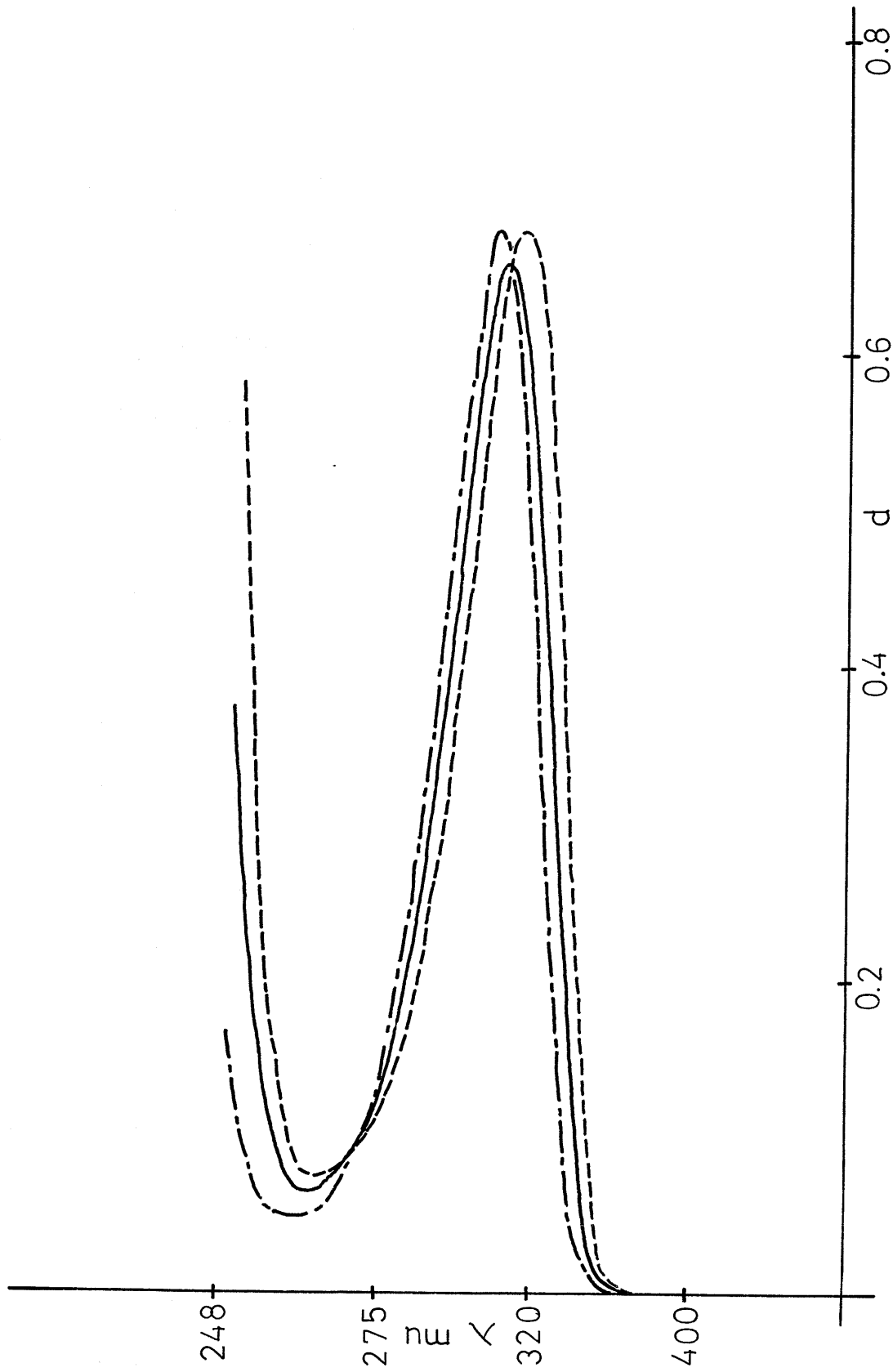


Fig. 12. 5-Methylsalicylic Acid
 $c = 2.0 \times 10^{-4} M$

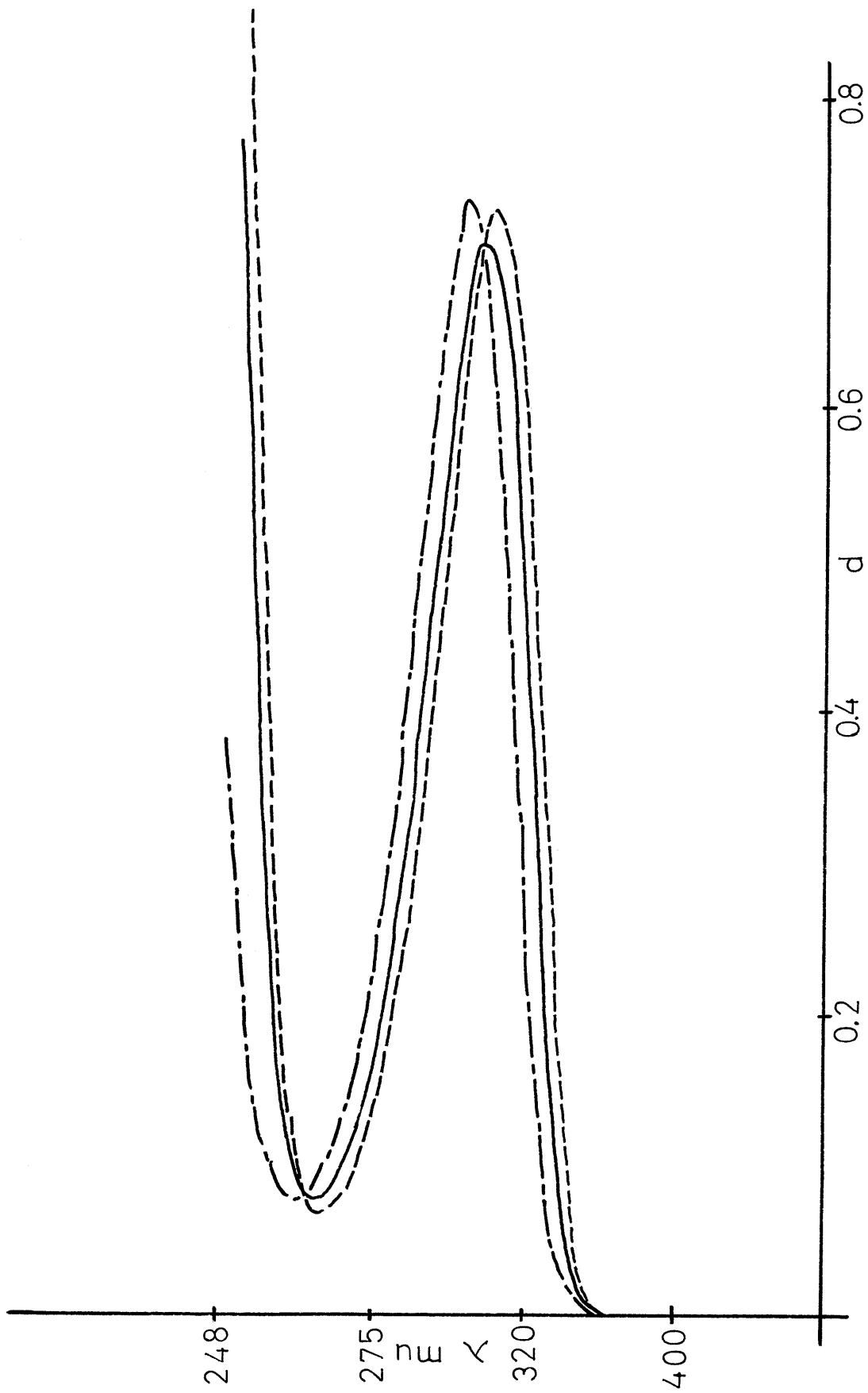


Fig. 12B. 3-Methylsalicylic Acid
 $c = 2.0 \times 10^{-4} M$

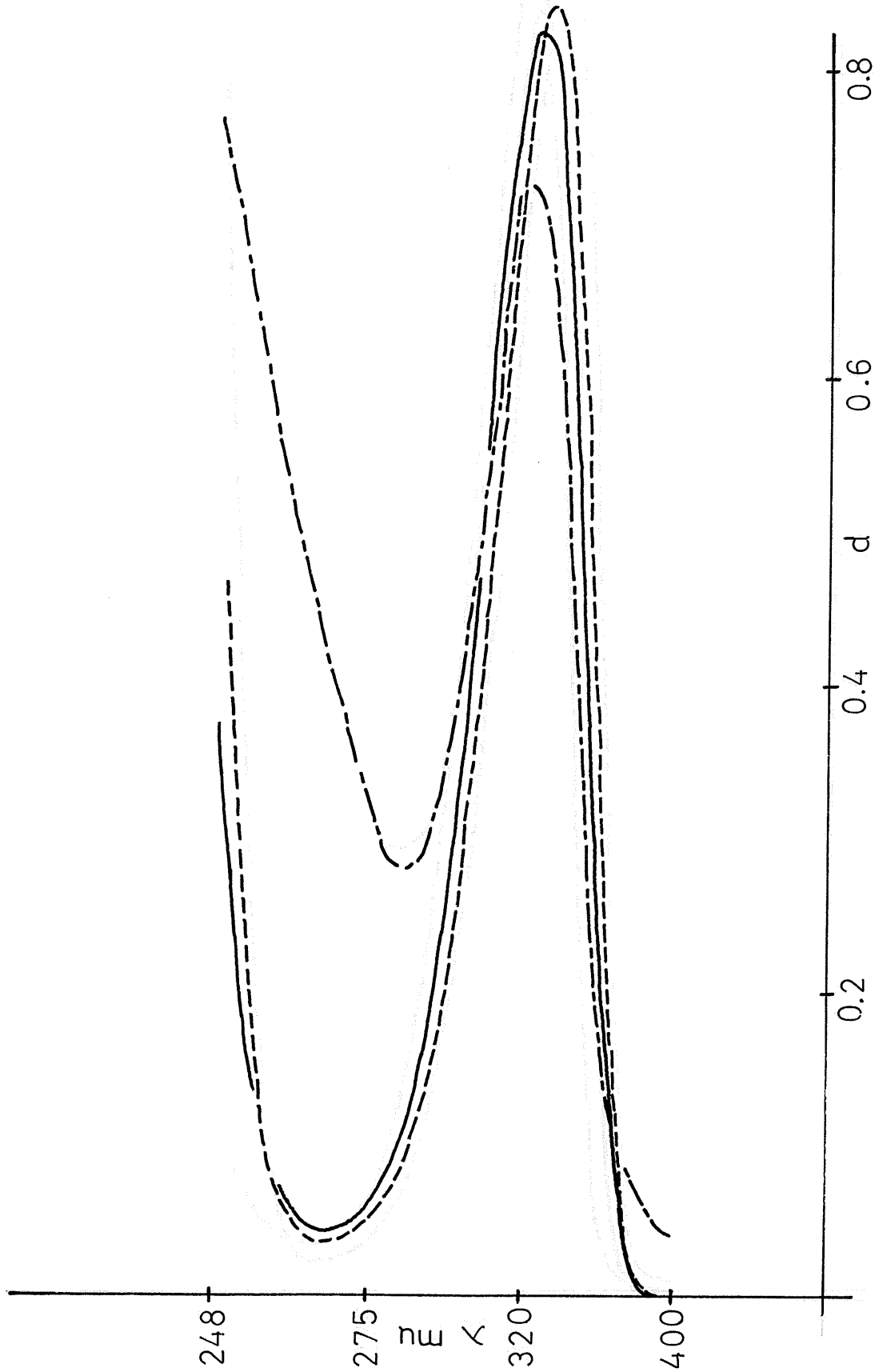


Fig. 13. 5-Hydroxysalicylic Acid

$c = 2.2 \times 10^{-4} \text{ M}$

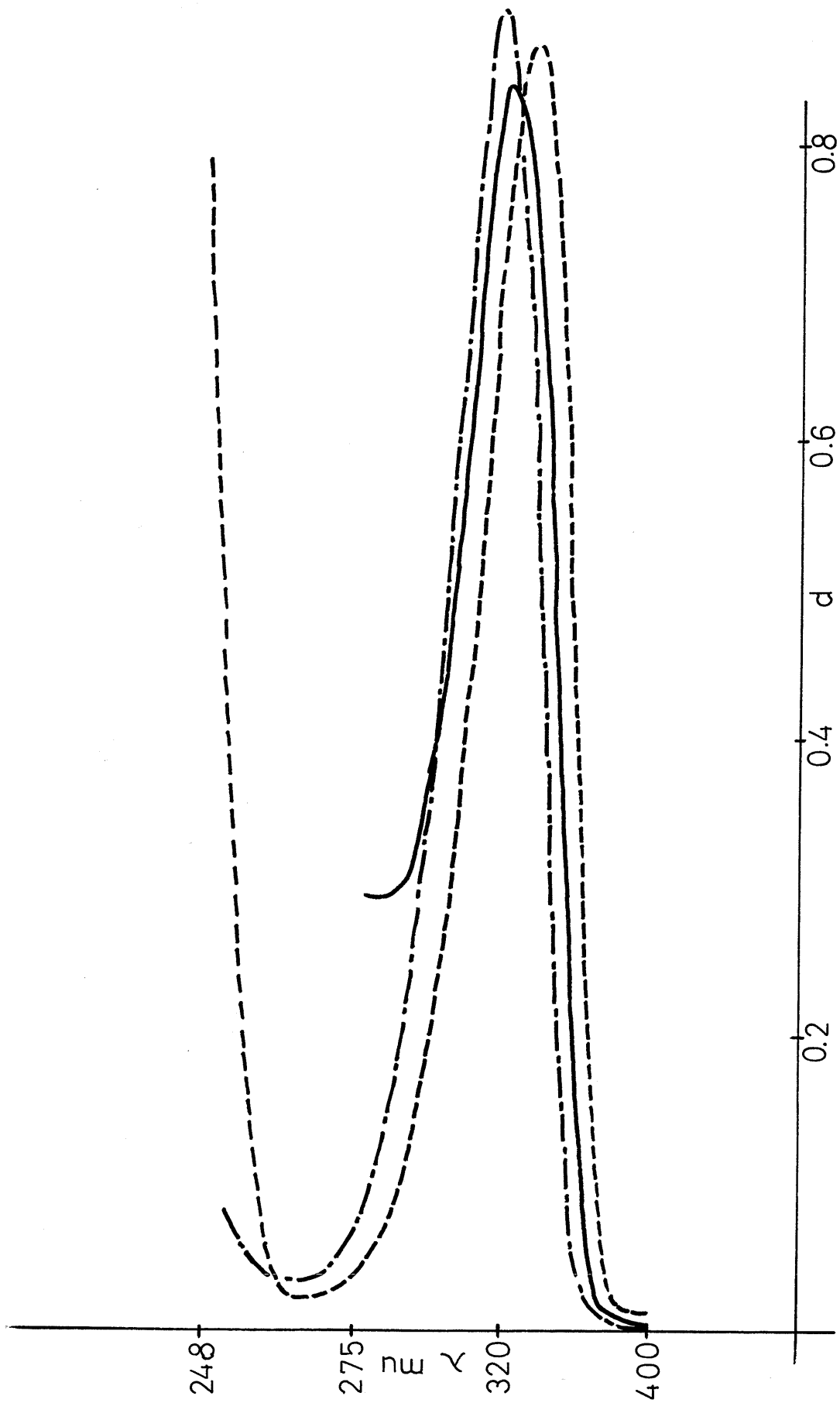


Fig. 14. 5-Methoxysalicylic Acid
 $c=2.0 \times 10^{-4} M$

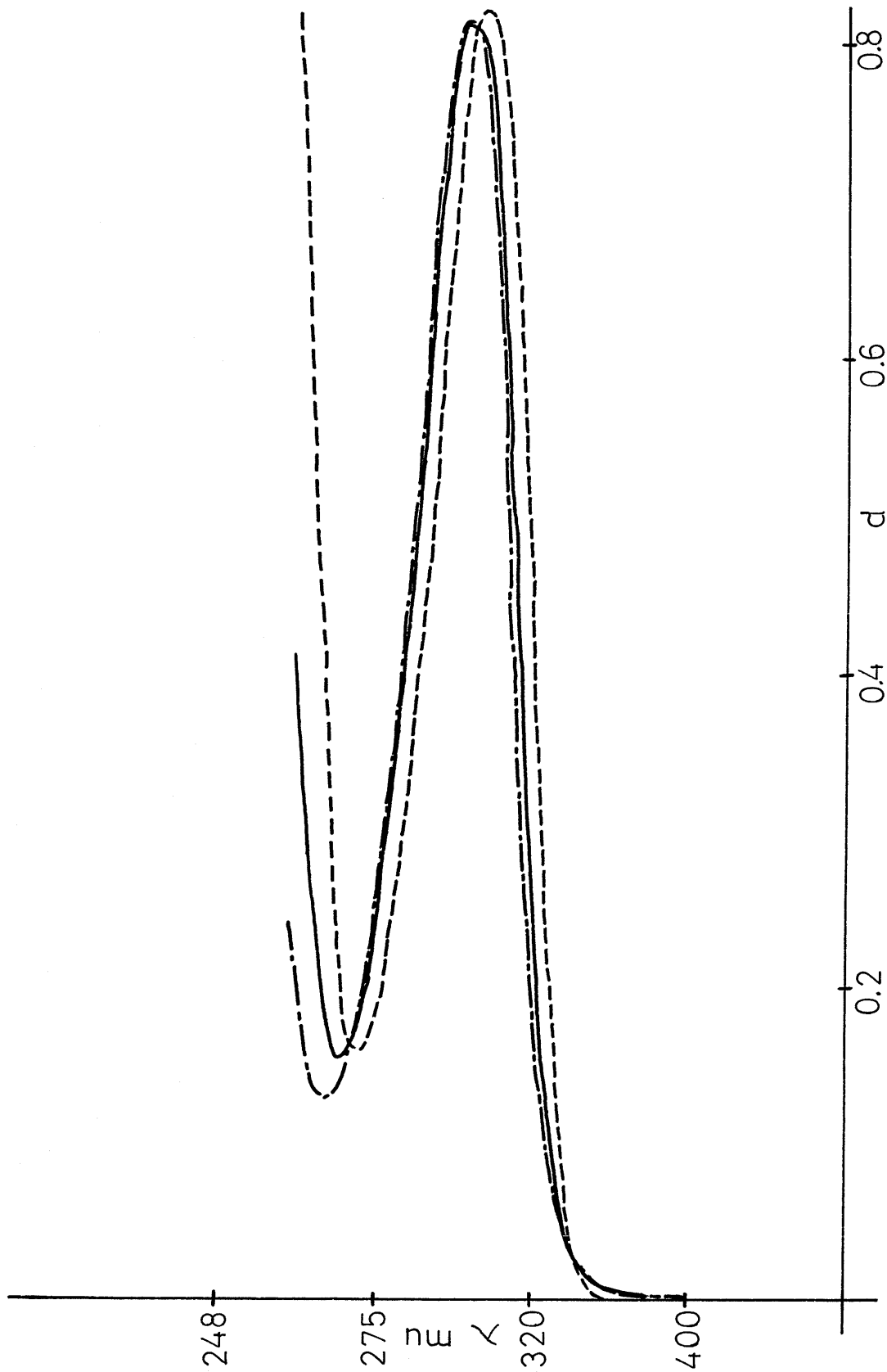


Fig. 15. 4-Bromosalicylic Acid
 $c = 2.0 \times 10^{-4} \text{ M}$

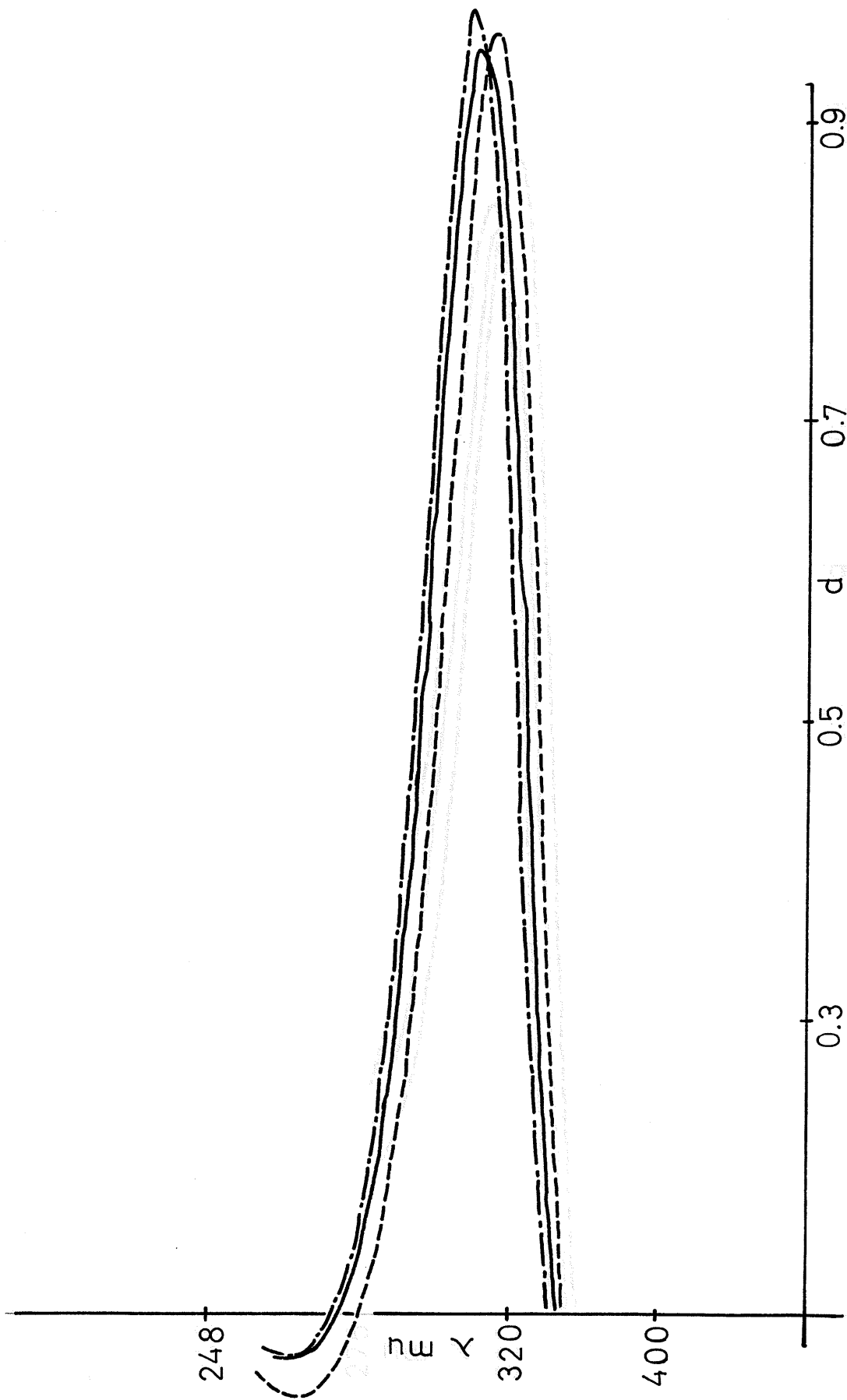


Fig. 16. 5-Chlorosalicylic Acid

$c = 3.0 \times 10^{-4} \text{ M}$

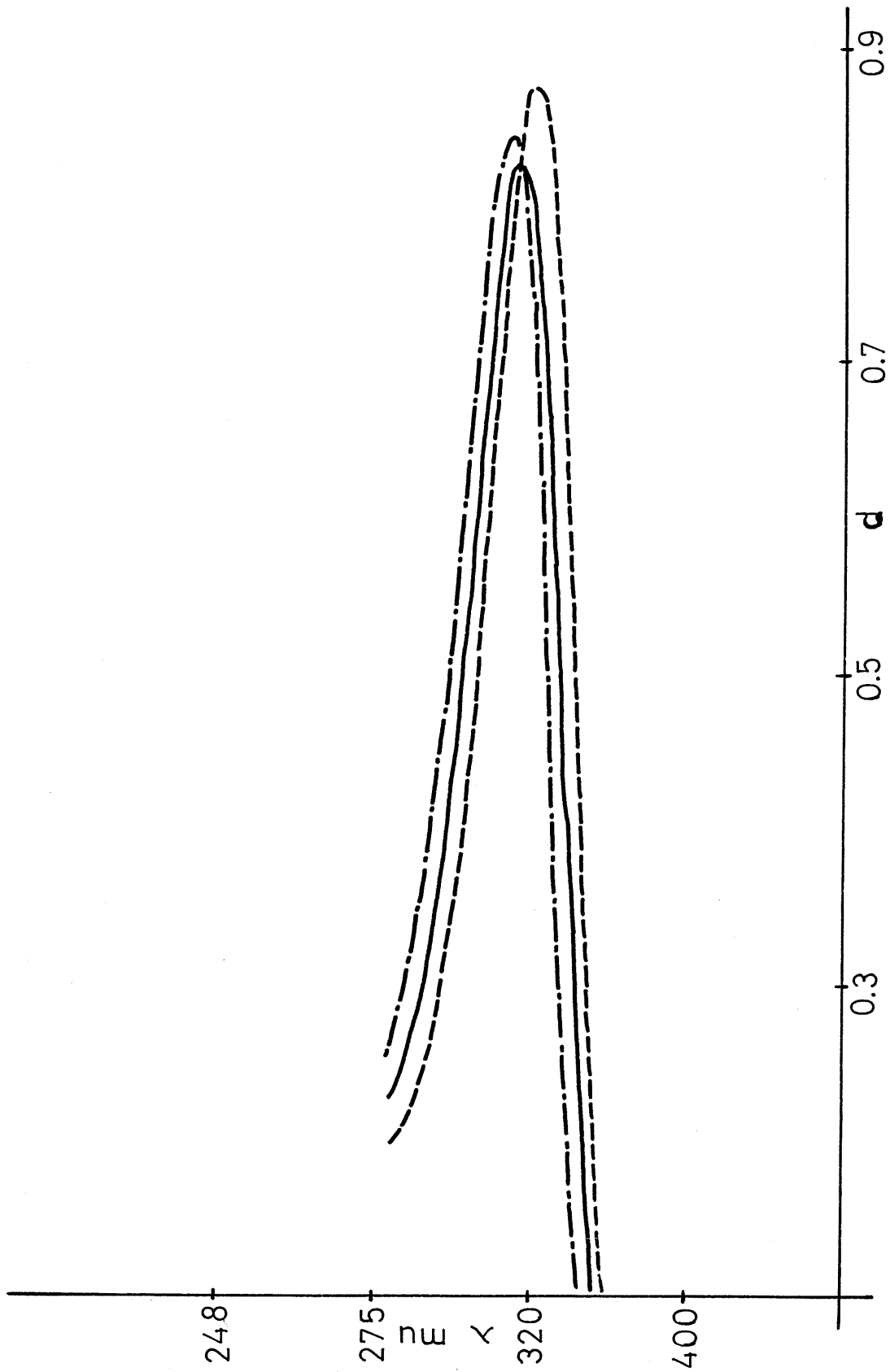


Fig. 17. 5-Iodosalicylic Acid
 $c=3.0 \times 10^{-4} M$

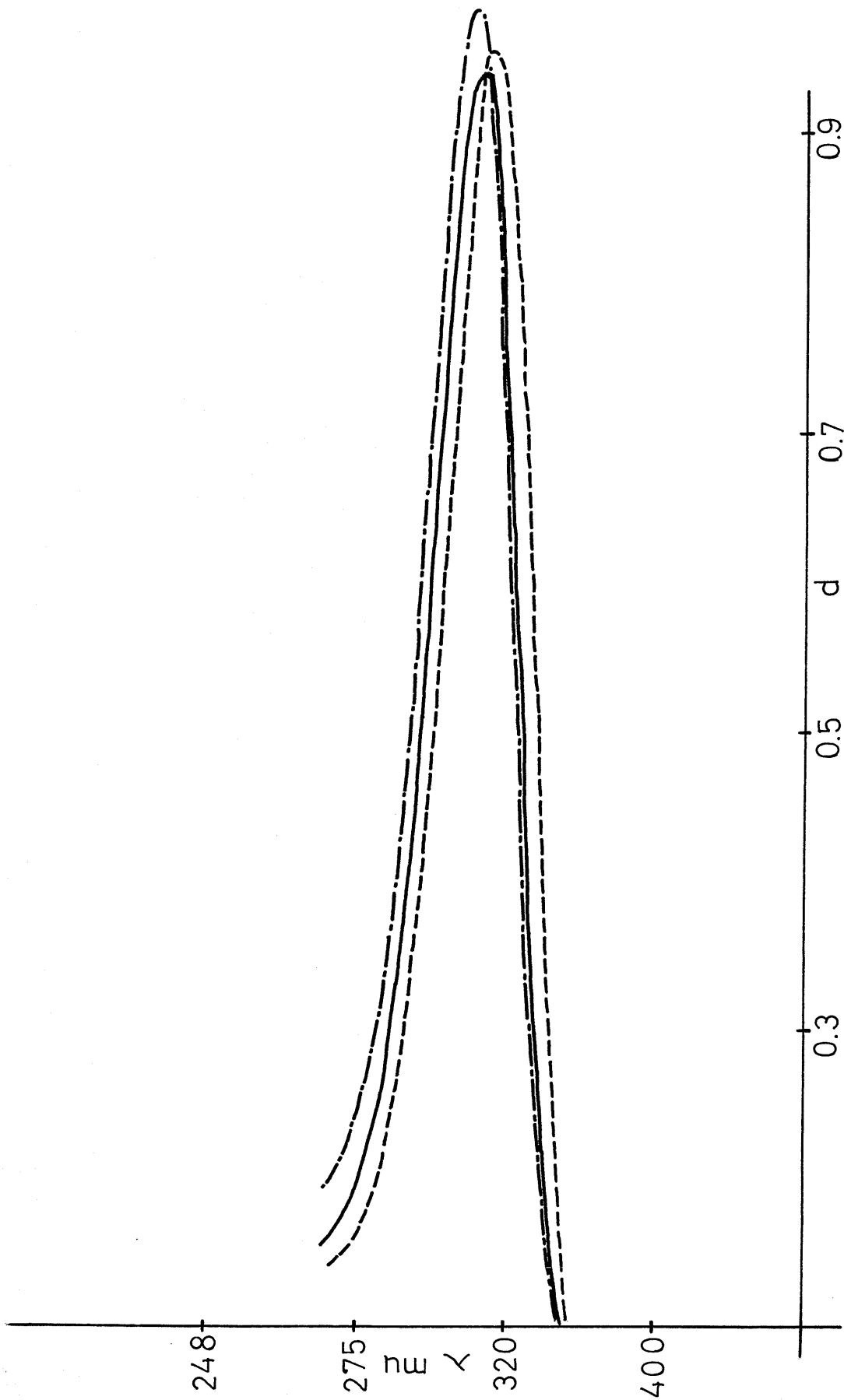


Fig. 18. 5-Bromosalicylic Acid

$c = 2.9 \times 10^{-4} \text{ M}$

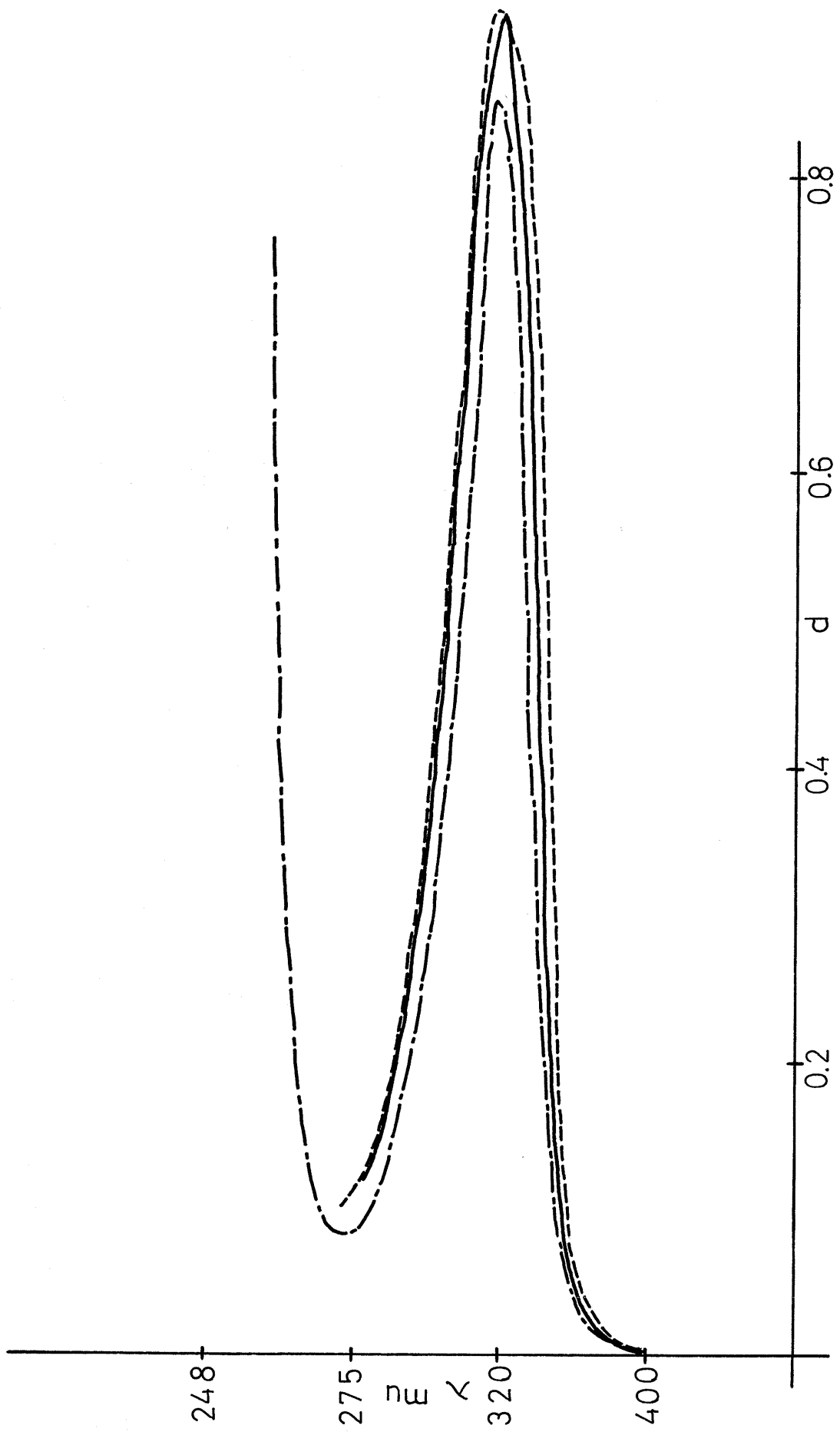


Fig. 19. 4-Cyanosalicylic Acid
 $c=2.0 \times 10^{-4} M$

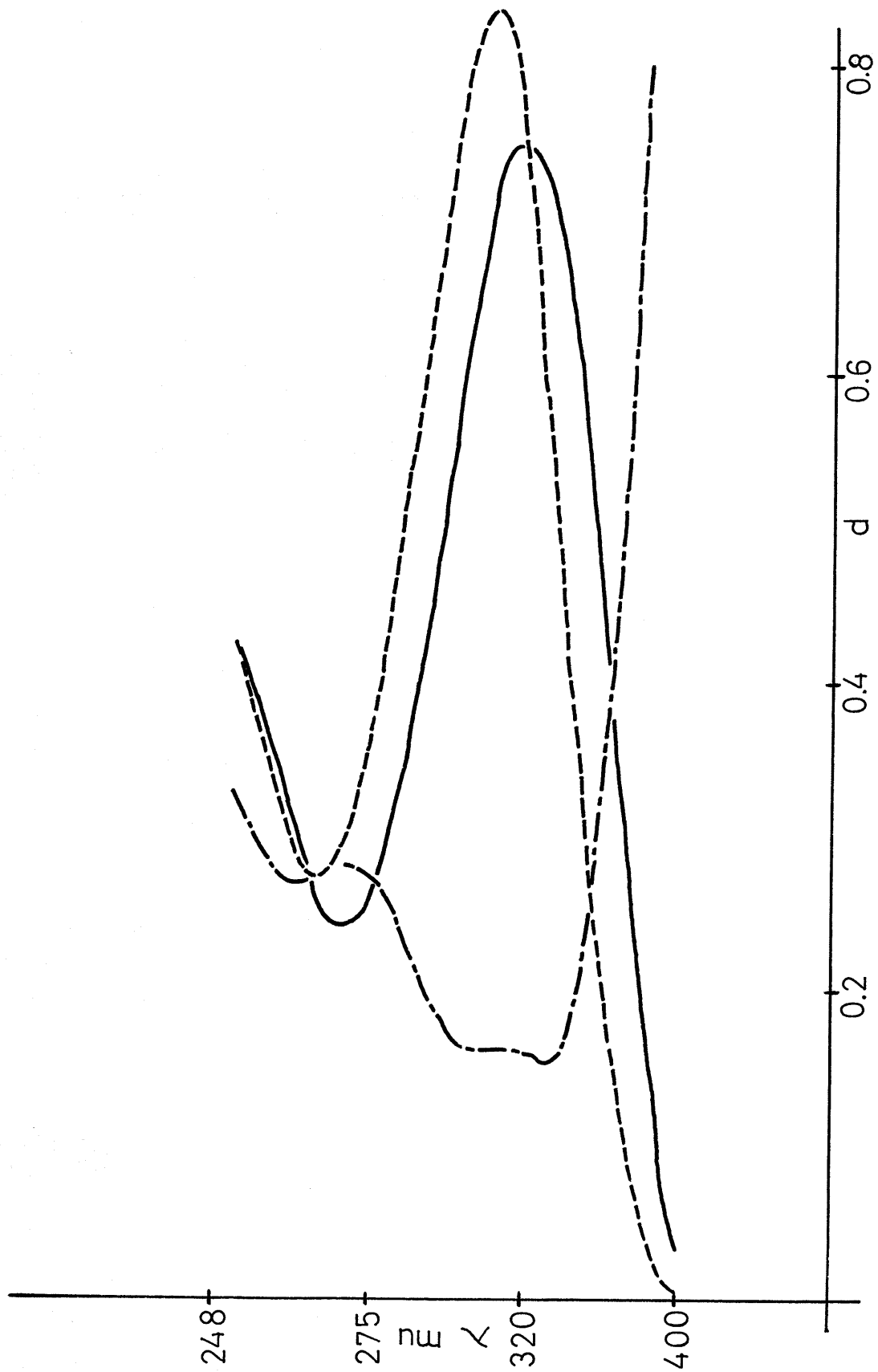


Fig. 20. 5-Nitrosalicylic Acid
 $c=0.8 \times 10^{-4}M$

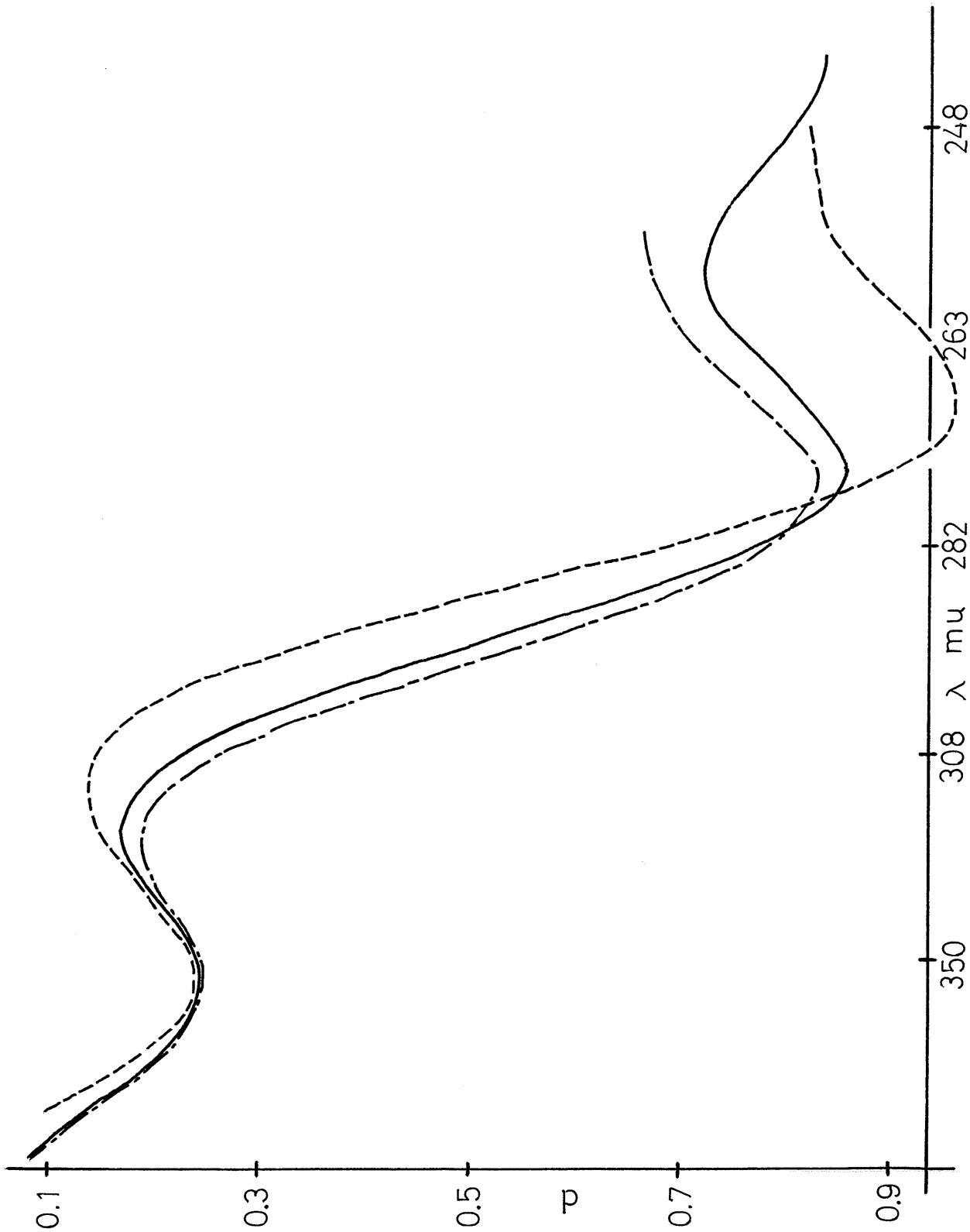


Fig. 21. 4-Nitrosalicylic Acid
 $c=0.96 \times 10^{-4} M$

Tables 2 through 16

Experimental data of pH and corresponding absorbance of the various buffered solutions.

μ : ionic strength

c : concentration

t : temperature

λ : wavelength

d : optical density (absorbance, $\log \frac{I_0}{I}$)

ClA : monochloroacetate buffer

F : formate buffer

Ac : acetate buffer

NH₃ : ammonia buffer

TABLE 2
SALICYLIC ACID

$u=0.01$

$t=25^{\circ}\text{C}$

$c=2.5 \times 10^{-4} \text{M}$

$\lambda = 313 \text{ m}\mu$

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.653
1	HCl	0.649 ± 0.010	0.652 ± 0.010
2	HCl	1.115	0.648
3	HCl	1.538	0.639
4	HCl	2.065	0.617
5	HCl	2.291	0.593
6	HCl	2.489	0.570
7	ClA	2.702	0.533
8	ClA	2.897	0.500
9	ClA	3.075	0.470
10	ClA	3.276	0.432
11	ClA	3.482	0.405
12	F	3.628	0.387
13	F	3.817	0.369
14	F	3.999	0.357
15	Ac	4.970	0.328
16	Ac	5.832	0.328
B	NH ₃	9	0.328

TABLE 3

4-METHOXY-SALICYLIC ACID

u=0.01

t=25°C

c=1.4x10⁻⁴_M

λ=305mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~0	0.575
1	HCl	0.630±0.010	0.575±0.010
2	HCl	1.153	0.566
3	HCl	1.650	0.561
4	HCl	2.108	0.550
5	HCl	2.332	0.540
6	ClA	2.552	0.522
7	ClA	2.763	0.505
8	ClA	2.978	0.475
9	ClA	3.112	0.456
10	ClA	3.341	0.425
11	F	3.564	0.385
12	F	3.818	0.347
13	F	4.056	0.325
14	Ac	4.365	0.308
15	Ac	5.029	0.299
16	Ac	5.854	0.291
B	NH ₃	9	0.289

TABLE 4

4-HYDROXYSALICYLIC ACID

u=0.01

t=25°C

c=0.4x10⁻⁴M

λ=255mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.542
1	HCl	0.636±0.010	0.542±0.010
2	HCl	1.143	0.542
3	HCl	1.624	0.539
4	HCl	2.068	0.527
5	HCl	2.275	0.521
6	HCl	2.467	0.510
7	ClA	2.614	0.500
8	ClA	2.855	0.476
9	ClA	3.000	0.460
10	ClA	3.145	0.441
11	ClA	3.400	0.411
12	F	3.605	0.388
13	F	3.794	0.371
14	F	3.991	0.355
15	Ac	4.982	0.330
16	Ac	6.556	0.329
B	NH ₃	9	0.328

TABLE 5

4-ETHOXY-SALICYLIC ACID

u=0.01

t=25°C

c=1.6x10⁻⁴M

λ=305mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.698
1	HCl	0.659±0.010	0.698±0.010
2	HCl	1.148	0.697
3	HCl	1.566	0.696
4	HCl	2.085	0.665
5	HCl	2.303	0.653
6	ClA	2.511	0.638
7	ClA	2.725	0.609
8	ClA	2.882	0.575
9	ClA	3.098	0.541
10	ClA	3.308	0.498
11	F	3.548	0.458
12	F	3.752	0.423
13	F	3.982	0.399
14	Ac	4.236	0.385
15	Ac	4.983	0.353
16	Ac	5.834	0.353
B	NH ₃	9	0.353

TABLE 6

4-METHYLSALICYLIC ACID

u=0.01

t=25°C

c=1.8x10⁻⁴M

λ = 308mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~0	0.763
1	HCl	0.627±0.010	0.763±0.010
2	HCl	1.092	0.760
3	HCl	1.630	0.758
4	HCl	2.081	0.730
5	HCl	2.297	0.720
6	HCl	2.481	0.701
7	ClA	2.634	0.682
8	ClA	2.893	0.655
9	ClA	3.056	0.625
10	ClA	3.202	0.603
11	ClA	3.487	0.565
12	F	3.678	0.544
13	F	3.863	0.524
14	F	4.071	0.515
15	Ac	5.053	0.483
16	Ac	6.028	0.478
B	NH ₃	9	0.478

TABLE 6B

5-METHYLSALICYLIC ACID

u=0.01

t=25°C

c=2.5x10⁻⁴M

λ =325mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.681
1	HCl	0.680±0.010	0.678±0.010
2	HCl	1.174	0.666
3	HCl	1.642	0.659
4	HCl	2.135	0.632
5	HCl	2.345	0.613
6	ClA	2.555	0.585
7	ClA	2.759	0.547
8	ClA	2.913	0.507
9	ClA	3.126	0.464
10	ClA	3.337	0.424
11	F	3.578	0.388
12	F	3.774	0.365
13	F	4.024	0.342
14	Ac	4.294	0.327
15	Ac	4.993	0.307
16	Ac	5.855	0.306
B	NH ₃	9	0.306

TABLE 7

3-METHYLSALICYLIC ACID

u=0.01

t=25°C

c=2.4x10⁻⁴M

λ =318mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.720
1	HCl	0.659±0.010	0.716±0.010
2	HCl	1.148	0.717
3	HCl	1.568	0.711
4	HCl	2.076	0.683
5	HCl	2.300	0.660
6	ClA	2.500	0.633
7	ClA	2.732	0.595
8	ClA	2.882	0.550
9	ClA	3.081	0.508
10	ClA	3.298	0.470
11	ClA	3.495	0.436
12	F	3.634	0.410
13	F	3.832	0.392
14	F	4.016	0.382
15	Ac	4.981	0.346
16	Ac	5.845	0.346
B	NH ₃	9	0.345

TABLE 8

5-HYDROXYSALICYLIC ACID

u=0.01

t=25°C

c=2.2x10⁻⁴M

λ=337mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.819
1	HCl	0.624±0.010	0.818±0.010
2	HCl	1.113	0.817
3	HCl	1.558	0.804
4	HCl	2.060	0.786
5	HCl	2.278	0.770
6	HCl	2.472	0.746
7	ClA	2.680	0.714
8	ClA	2.883	0.683
9	ClA	3.074	0.647
10	ClA	3.278	0.618
11	ClA	3.488	0.585
12	ClA	3.500	0.583
13	F	3.651	0.569
14	F	3.826	0.557
15	F	3.982	0.549
16	Ac	4.983	0.522
17	Ac	5.852	0.522
B	NH ₃	9	0.521

TABLE 9

5-METHOXYSALICYLIC ACID

u=0.01

t=25° C

c=2.0x10⁻⁴ M

λ=342mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.598
1	HCl	0.616±0.010	0.598±0.010
2	HCl	1.130	0.596
3	HCl	1.621	0.582
4	HCl	2.073	0.560
5	HCl	2.302	0.532
6	ClA	2.513	0.504
7	ClA	2.714	0.465
8	ClA	2.926	0.426
9	ClA	3.110	0.388
10	ClA	3.335	0.362
11	ClA	3.553	0.327
12	F	3.822	0.300
13	F	4.043	0.285
14	F	4.351	0.275
15	Ac	5.025	0.262
16	Ac	5.842	0.262
B	NH ₃	9	0.262

TABLE 10

4-BROMOSALICYLIC ACID

u=0.01

t=25°C

c=2.0x10⁻⁴M

λ=315mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.583
1	HCl	0.616±0.010	0.583±0.010
2	HCl	1.140	0.578
3	HCl	1.640	0.564
4	HCl	2.106	0.531
5	HCl	2.348	0.506
6	ClA	2.594	0.470
7	ClA	2.804	0.447
8	ClA	3.047	0.411
9	ClA	3.266	0.376
10	ClA	3.400	0.369
11	F	3.998	0.348
12	F	4.105	0.340
13	Ac	4.428	0.331
14	Ac	5.043	0.329
15	Ac	5.365	0.329
16	Ac	5.840	0.329
B	NH ₃	9	0.329

TABLE 11

5-CHLOROSALICYLIC ACID

u=0.01

t=25°C

c=3.0x10⁻⁴M

λ=325mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.817
1	HCl	0.651±0.010	0.817±0.010
2	HCl	1.147	0.803
3	HCl	1.624	0.780
4	HCl	2.140	0.729
5	HCl	2.277	0.712
6	HCl	2.446	0.693
7	ClA	2.702	0.615
8	ClA	2.892	0.578
9	ClA	3.033	0.549
10	ClA	3.227	0.520
11	ClA	3.469	0.491
12	F	3.552	0.482
13	F	3.696	0.471
14	F	3.865	0.465
15	Ac	5.019	0.447
16	Ac	5.813	0.441
B	NH ₃	9	0.441

TABLE 12

5-IODOSALICYLIC ACID

u=0.01

t=25°C

c=3.0x10⁻⁴M

λ=325mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.805
1	HCl	0.616±0.010	0.804±0.010
2	HCl	1.149	0.797
3	HCl	1.652	0.782
4	HCl	2.095	0.745
5	HCl	2.310	0.721
6	ClA	2.521	0.689
7	ClA	2.673	0.660
8	ClA	2.861	0.630
9	ClA	3.064	0.604
10	ClA	3.273	0.585
11	ClA	3.488	0.567
12	F	3.872	0.545
13	F	4.062	0.540
14	Ac	5.020	0.520
15	Ac	5.840	0.517
B	NH ₃	9	0.517

TABLE 13
5-BROMOSALICYLIC ACID

$u=0.01$ $t=25^{\circ}\text{C}$
 $c=3.0 \times 10^{-4}\text{M}$ $\lambda=328\text{m}\mu$

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~0	0.670
1	HCl	0.645 ± 0.010	0.670 ± 0.010
2	HCl	1.143	0.660
3	HCl	1.600	0.638
4	HCl	2.091	0.591
5	HCl	2.294	0.552
6	ClA	2.500	0.512
7	ClA	2.702	0.469
8	ClA	2.845	0.429
9	ClA	3.051	0.393
10	ClA	3.264	0.372
11	ClA	3.478	0.352
12	F	3.705	0.334
13	F	3.965	0.323
14	F	4.213	0.319
15	Ac	4.986	0.308
16	Ac	5.840	0.308
B	NH ₃	9	0.308

TABLE 14

4-CYANOSALICYLIC ACID

u=0.01

t=25°C

c=2.0x10⁻⁴M

λ=334mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.645
1	HCl	0.658±0.010	0.640±0.010
2	HCl	1.150	0.632
3	HCl	1.627	0.607
4	HCl	2.080	0.561
5	HCl	2.278	0.540
6	HCl	2.471	0.520
7	ClA	2.604	0.501
8	ClA	2.841	0.483
9	ClA	3.065	0.464
10	ClA	3.115	0.458
11	ClA	3.351	0.450
12	F	3.566	0.437
13	F	3.760	0.434
14	F	3.946	0.431
15	Ac	4.930	0.430
16	Ac	6.080	0.430
B	NH ₃	9	0.430

TABLE 15

5-NITROSALICYLIC ACID

u=0.01

t=25°C

c=0.9x10⁻⁴M

λ=310mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.0NHCl	~ 0	0.946
1	HCl	0.652±0.010	0.938±0.010
2	HCl	1.145	0.933
3	HCl	1.562	0.924
4	HCl	2.082	0.902
5	HCl	2.285	0.890
6	HCl	2.474	0.880
7	ClA	2.691	0.869
8	ClA	2.884	0.858
9	ClA	3.060	0.854
10	ClA	3.276	0.850
11	ClA	3.497	0.846
12	F	3.658	0.845
13	F	3.860	0.844
14	F	4.130	0.843
15	Ac	4.995	0.840
16	Ac	5.815	0.840
B	NH ₃	9	0.840

TABLE 16

4-NITROSALICYLIC ACID

u=0.01

t=25°C

c=0.8x10⁻⁴M

λ=288mμ

	<u>Buffer</u>	<u>pH</u>	<u>d</u>
A	1.ONHCl	~ 0	0.405
1	HCl	0.641±0.010	0.425±0.010
2	HCl	1.138	0.439
3	HCl	1.610	0.457
4	HCl	2.065	0.481
5	HCl	2.269	0.493
6	HCl	2.457	0.508
7	ClA	2.603	0.519
8	ClA	2.851	0.528
9	ClA	3.033	0.538
10	ClA	3.150	0.543
11	ClA	3.400	0.549
12	F	3.606	0.554
13	F	3.798	0.558
14	F	4.000	0.560
15	Ac	4.980	0.566
16	Ac	5.800	0.570
B	NH ₃	9	0.570

Tables 17 and 18

Experimental and interpolated data of pH and corresponding absorbance of buffered solutions of aminosalicyclic acids for the calculation of the first ionization constants (Tables 17A and 18A) and for the calculation of the second ionization constants (Table 17B and 18B).

TABLE 17A

4-AMINOSALICYLIC ACID

u=0.1

t=25°C

c=1.6x10⁻⁴M

λ =314μ

	Experimental			Interpolated
	Buffer	pH ₁	d	pH ₂
A	1.0NHCl	~0	0.280	
1	HCl	1.150±0.010	0.323±0.010	5.00
2	HCl	1.327	0.340	4.63
3	HCl	1.533	0.372	4.31
4	HCl	1.736	0.405	4.08
5	HCl	1.914	0.445	3.80
6	HCl	2.021	0.470	3.63
7	HCl	2.160	0.494	3.44
8	HCl	2.260	0.512	3.30
9	HCl	2.358	0.514	3.29
10	ClA	2.570	0.533	3.12
11	ClA	2.474	0.533	3.12
12	ClA	2.637	0.545	

TABLE 17B

4-AMINOSALICYLIC ACID

u=0.1

t=25°C

c=1.6x10⁻⁴M

λ =314mμ

	<u>Experimental</u>			<u>Interpolated</u>
	<u>Buffer</u>	<u>pH₂</u>	<u>d</u>	<u>pH₁</u>
13	CLA	3.200±0.010	0.525±0.010	2.41
14	CLA	3.445	0.491	2.14
15	F	3.634	0.470	2.02
16	F	3.744	0.453	1.95
17	F	3.840	0.437	1.88
18	F	3.934	0.425	1.82
19	F	3.966	0.422	1.81
20	Ac	4.265	0.379	1.58
21	Ac	4.480	0.352	1.42
22	Ac	4.690	0.336	1.28
23	Ac	4.861	0.328	1.20
B	NH ₃	9	0.297	

TABLE 18A

5-AMINOSALICYLIC ACID

u=0.1

t=25°C

c=2.3x10⁻⁴M

λ =315mμ

	<u>Experimental</u>			<u>Interpolated</u>
	<u>Buffer</u>	<u>pH₁</u>	<u>d</u>	<u>pH₂</u>
A	1.0NHCl	~0	0.580	
1	HCl	1.534±0.010	0.530±0.010	6.34
2	HCl	1.754	0.506	6.06
3	HCl	1.908	0.478	5.84
4	HCl	2.016	0.466	5.76
5	HCl	2.166	0.439	5.61
6	HCl	2.260	0.425	5.54
7	HCl	2.349	0.413	5.47
8	HCl	2.475	0.390	5.32
9	ClA	2.570	0.378	5.24
10	ClA	2.630	0.370	5.18
11	ClA	2.858	0.348	4.99
12	ClA	3.005	0.333	4.81
13	ClA	3.189	0.322	4.63
14	ClA	3.438	0.311	4.40

TABLE 18B

5-AMINOSALICYLIC ACID

u=0.1

t=25°C

c=2.3x10⁻⁴M

λ =315mμ

<u>Experimental</u>			<u>Interpolated</u>	
	<u>Buffer</u>	<u>pH₂</u>	<u>d</u>	
			<u>pH₁</u>	
15	Ac	4.257±0.010	0.304±0.010	3.63
16	Ac	4.482	0.316	3.31
17	Ac	4.686	0.323	3.17
18	Ac	4.860	0.337	2.95
19	Ac	5.080	0.360	2.71
20	Ac	5.150	0.365	2.66
21	Ac	5.233	0.377	2.57
22	Ac	5.353	0.394	2.45
23	Ac	5.547	0.424	2.25
24	Ac	5.685	0.455	2.05
25	Ac	5.983	0.496	1.77
26	Ac	6.254	0.525	1.57
B	NH ₃	9	0.590	

Figures 22 and 23

Plotted experimental data of
Tables 17 and 18 of amino-
salicylic acids.

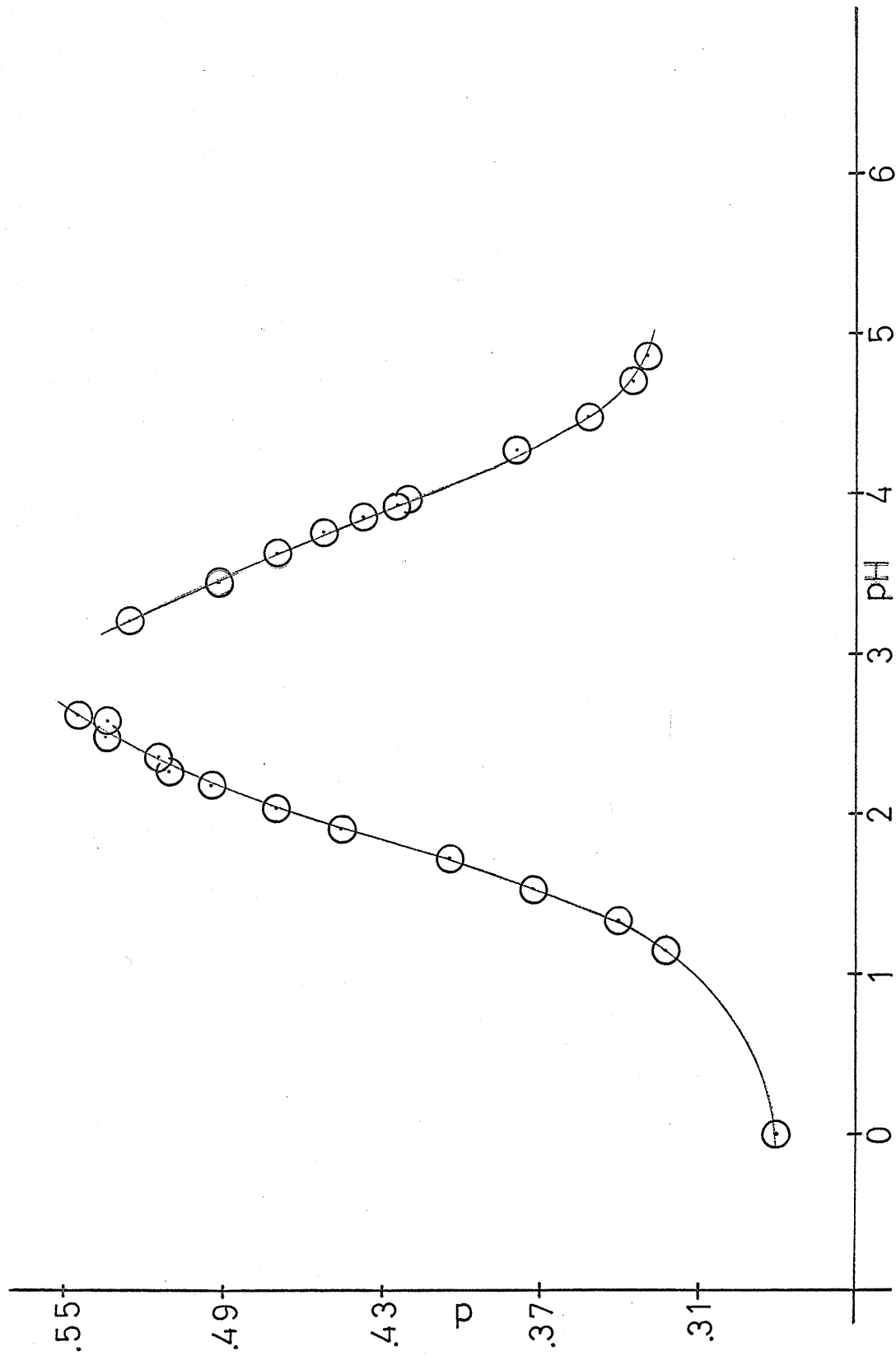


Fig. 22. 4-Aminosalicylic Acid

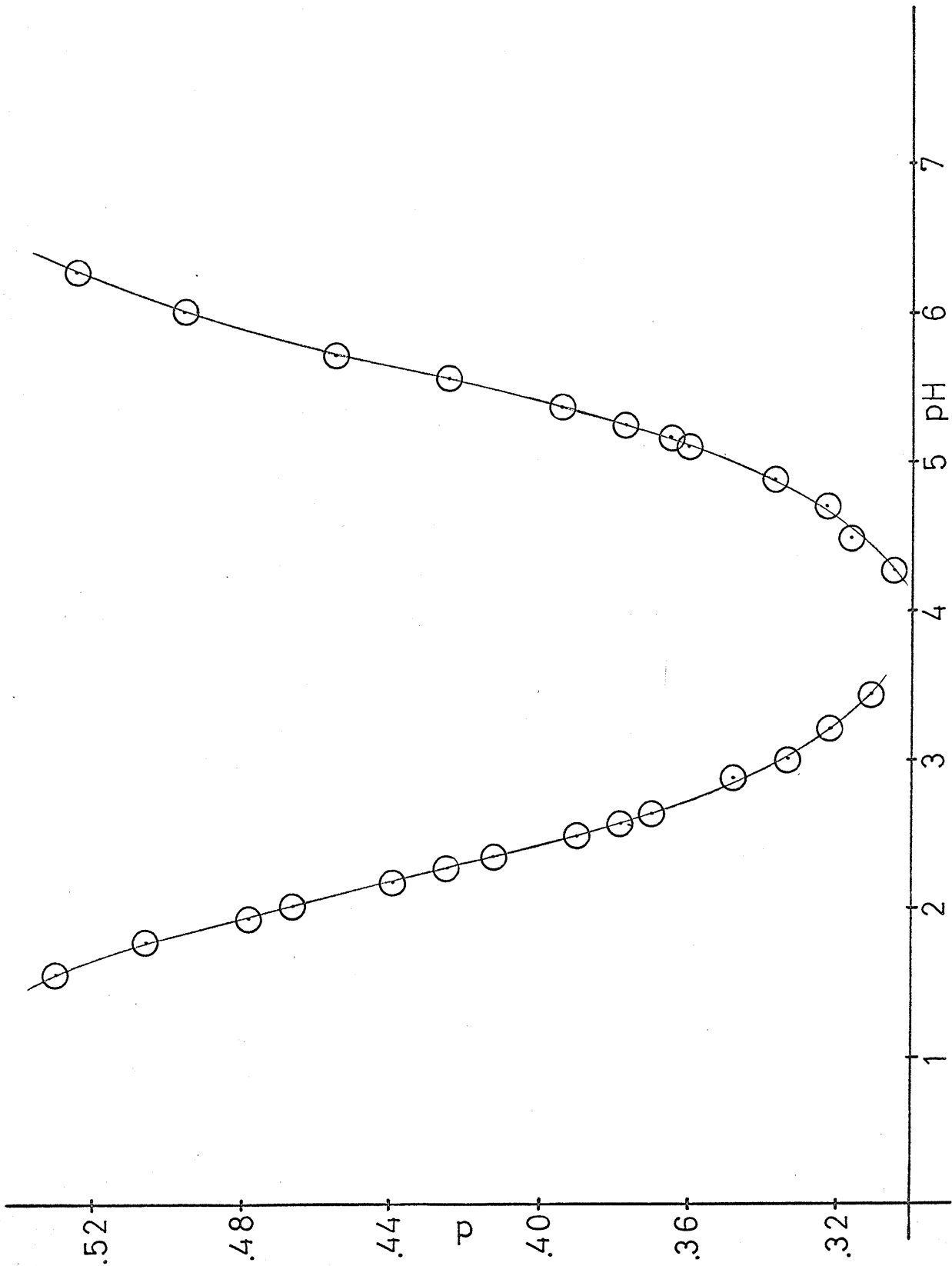


Fig. 23. 5-Aminosalicyclic Acid

Table 19

Computed first ionization constants of substituted salicylic acids.

<u>Substituent</u>	<u>pK</u>
4-CH ₃ O	3.274 ± 0.015
4-OH	3.197 ± 0.006
4-C ₂ H ₅ O	3.168 ± 0.014
4-CH ₃	3.081 ± 0.019
5-CH ₃	2.999 ± 0.014
3-CH ₃	2.986 ± 0.013
Salicylic acid	2.956 ± 0.012
5-OH	2.952 ± 0.010
5-CH ₃ O	2.907 ± 0.011
4-Br	2.701 ± 0.017
5-Cl	2.668 ± 0.022
5-I	2.667 ± 0.019
5-Br	2.582 ± 0.014
4-CN	2.318 ± 0.016
5-NO ₂	2.285 ± 0.014
4-NO ₂	2.275 ± 0.032

Table 20

Computed overlapping ionization
constants of aminosalicyclic acids

<u>Substituent</u>	<u>pK₁</u>	<u>K₁</u>	<u>pK₂</u>	<u>K₂</u>
4-NH ₂	2.022	(9.503±0.110)×10 ⁻³	3.344	(4.523±0.927)×10 ⁻⁴
5-NH ₂	2.158	(6.937±0.822)×10 ⁻³	5.609	(2.457±0.150)×10 ⁻⁶

DISCUSSION

The apparent ionization constants of substituted salicylic acids computed from the IBM 1620 Computer were corrected according to Kielland (35) to give thermodynamic ionization constants.

$$K_{\text{therm.}} = \frac{a_{\text{H}^+} \cdot a_{\text{A}^-}}{a_{\text{HA}}} = \frac{C_{\text{H}^+} f_{\text{H}^+} \cdot C_{\text{A}^-} f_{\text{A}^-}}{C_{\text{HA}} f_{\text{HA}}} \quad (42)$$

where a : activity.

C : concentration.

f : activity coefficient.

$K_{\text{therm.}}$: thermodynamic ionization constant.

The value of $C_{\text{H}^+} f_{\text{H}^+}$ was determined from the pH of the solution. The activity coefficient of neutral molecule, f_{HA} , was assumed to be unity. Therefore, Equation 42 becomes

$$K_{\text{therm.}} = \frac{C_{\text{H}^+} f_{\text{H}^+} C_{\text{A}^-}}{C_{\text{HA}}} f_{\text{A}^-} = K_{\text{obs.}} f_{\text{A}^-} \quad (43)$$

and
$$pK_{\text{therm.}} = pK_{\text{obs.}} - \log f_{\text{A}^-} \quad (44)$$

where $K_{\text{obs.}}$: observed (apparent) ionization constant.

Since no data are available for the activity coefficients for each of the substituted salicylate anions, all corrections were based on the activity coefficient of the salicylate anion ($C_6H_4OHCOO^-$). For the solution ionic strength 0.01, $f_{A^-}=0.929$ and $\log f_{A^-}=-0.032$; for ionic strength 0.1, $f_{A^-}=0.835$ and $\log f_{A^-}=-0.080$ (35). These were substituted into Equation 44.

Table 21 shows the thermodynamic ionization constants determined in this laboratory together with those from previous papers. The Table was arranged according to the order of increasing acid strength.

Comparing present work with previous data, a fairly good agreement is evident with the exception of the nitrosalicylic acids. The stronger acidity of 4-nitrosalicylic acid compared to that of the 5-nitrosalicylic acid observed in the present work agrees with the general observation that a nitro group at the para-position with respect to the carboxyl in an aromatic acid enhances the strength more than when it occupies the meta-position.

The previous values of K 's of nitrosalicylic acids were obtained from conductivity data (17,15,16) and it is probable that they are too large because the nitro group increases the acidity of the phenolic $-OH$ to such an extent that it contributes significantly to the conductivity.

Table 21

Thermodynamic ionization constants of substituted salicylic acids in aqueous solution at 25°C.

Substituent	Hammett's ρ (27)	This Investigation		Earlier Values
		pK	10^3K	
4-Amino	-0.66	3.583±0.039	0.264±0.024	
4-Methoxy	-0.268	3.306±0.015	0.494±0.017	
4-Hydroxy	-0.370	3.229±0.006	0.591±0.008	0.505(34) ; 0.605(1)
4-Ethoxy	-0.240	3.200±0.014	0.630±0.020	
5-Amino	-0.16	3.136±0.016	0.731±0.033	
4-Methyl	-0.170	3.113±0.019	0.770±0.034	0.72(57)
5-Methyl	-0.069	3.031±0.014	0.931±0.030	0.86(57)
3-Methyl		3.018±0.013	0.962±0.029	1.018(57) ; 1.00(58)
Salicylic Acid	0	2.988±0.012	1.02 ± 0.03	1.05(47) ; 1.06(19)
5-Hydroxy	+0.121	2.982±0.010	1.04 ± 0.02	1.08(34) ;
5-Methoxy	+0.115	2.939±0.011	1.15 ± 0.03	
4-Bromo	+0.232	2.733±0.017	1.85 ± 0.07	
5-Chloro	+0.373	2.700±0.022	1.99 ± 0.10	1.97(13) ; 2.35(9) 2.23(19)
5-Iodo	+0.352	2.699±0.019	2.00 ± 0.09	

Table 21
(continued)

<u>Substituent</u>	<u>Hammett's σ (27)</u>	<u>This Investigation</u>		<u>Earlier Values</u>
		<u>pK</u>	<u>10³K</u>	
5-Bromo	+0.391	2.614±0.014	2.43±0.08	2.44(9) ; 2.40(34) 2.20(19)
4-Cyano	+0.660	2.350±0.016	4.46±0.16	
5-Nitro	+0.710	2.317±0.014	4.82±0.16	7.57(9) ; 8.00(45)
4-Nitro	+0.778	2.307±0.032	4.93±0.36	5.88(9)

The possible existence of hydrogen bonding between the carboxyl group and ortho-hydroxy group of para- or meta-substituted salicylic acid has led Jaffe (31) to suggest that the effect of the 4- or 5-substituent on the ionization constant of salicylic acid may be exerted through two paths ; one path is through to the phenolic hydrogen bond ; the other one is centered on the carboxyl group. According to this theory the pK's of those acids should fit the two-parameter Hammett equation.

$$\log \frac{K}{K_0} = \rho_1 \sigma_1 + \rho_2 \sigma_2 \quad (48)$$

where σ_1 and σ_2 refer to the substituent constants of the substituent (5- and 4-) relative to the points of attachments 1 and 2 of the side chain, respectively. ρ_1 and ρ_2 are their respective reaction constants.

Jaffe (31) found that the data of Shorter et al. (58) for six substituted salicylic acids fit the simple Hammett relationship, Equation 31, better than the two-parameter one, Equation 48. He attributed this to the fact that, for his six acids, σ_1 and σ_2 were linearly related with a correlation coefficient $\rho_{\sigma_1, \sigma_2}$ of 0.918. He proposed that $r_{12} > 0.9$ is the limit of usefulness of Equation 48, i.e. if $r_{12} > 0.9$, Equation 48 can not be distinguished from Equation 31.

This is because σ_1 and σ_2 are linearly related when $\gamma_{\sigma_1, \sigma_2} > 0.9$

Hence,

$$\sigma_1 = c \sigma_2 \quad (50)$$

where c is a constant. It follows that

$$\begin{aligned} \log \frac{K}{K_0} &= \rho_1 \sigma_1 + \rho_2 \sigma_2 \\ &= \rho_1 c \sigma_2 + \rho_2 \sigma_2 \\ &= (\rho_1 c + \rho_2) \sigma_2 \end{aligned} \quad (51)$$

The above equation is obviously a type of one-parameter Hammett equation.

Sigma 1's (σ_1 's) and sigma 2's (σ_2 's) (27) for the fifteen substituted salicylic acids of the present investigation are listed in Table 22. The correlation coefficient,

$\gamma_{\sigma_1, \sigma_2}$, between σ_1 and σ_2 was calculated according to Deming (14).

$$\gamma_{\sigma_1, \sigma_2} = \frac{\sum (\sigma_1 - \bar{\sigma}_1)(\sigma_2 - \bar{\sigma}_2)}{\sqrt{(\sum \sigma_1^2 - n \bar{\sigma}_1^2)(\sum \sigma_2^2 - n \bar{\sigma}_2^2)}} \quad (49)$$

The data in Table 22 were substituted into Equation 49 and the correlation coefficient $\gamma_{\sigma_1, \sigma_2}$ was calculated to be 0.674. A graph of σ_1 versus σ_2 in the present study is shown in Figure 24.

Table 22

Substituent constants of substituted salicylic acids used in the two-parameter Hammett equation.

<u>Substituent</u>	<u>σ_1</u>	<u>σ_2</u>
Salicylic Acid	0	0
4-Methoxy	-0.268	+0.115
4-Bromo	+0.232	+0.391
4-Ethoxy	-0.24	+0.1
4-Cyano	+0.66	+0.56
4-Nitro	+0.778	+0.710
4-Hydroxy	-0.37	+0.121
4-Methyl	-0.170	-0.069
5-Methoxy	+0.115	-0.268
5-Chloro	+0.373	+0.227
5-Bromo	+0.391	+0.232
5-Nitro	+0.710	+1.27
5-Iodo	+0.352	+0.276
5-Methyl	-0.069	-0.170
5-Hydroxy	+0.121	-0.37

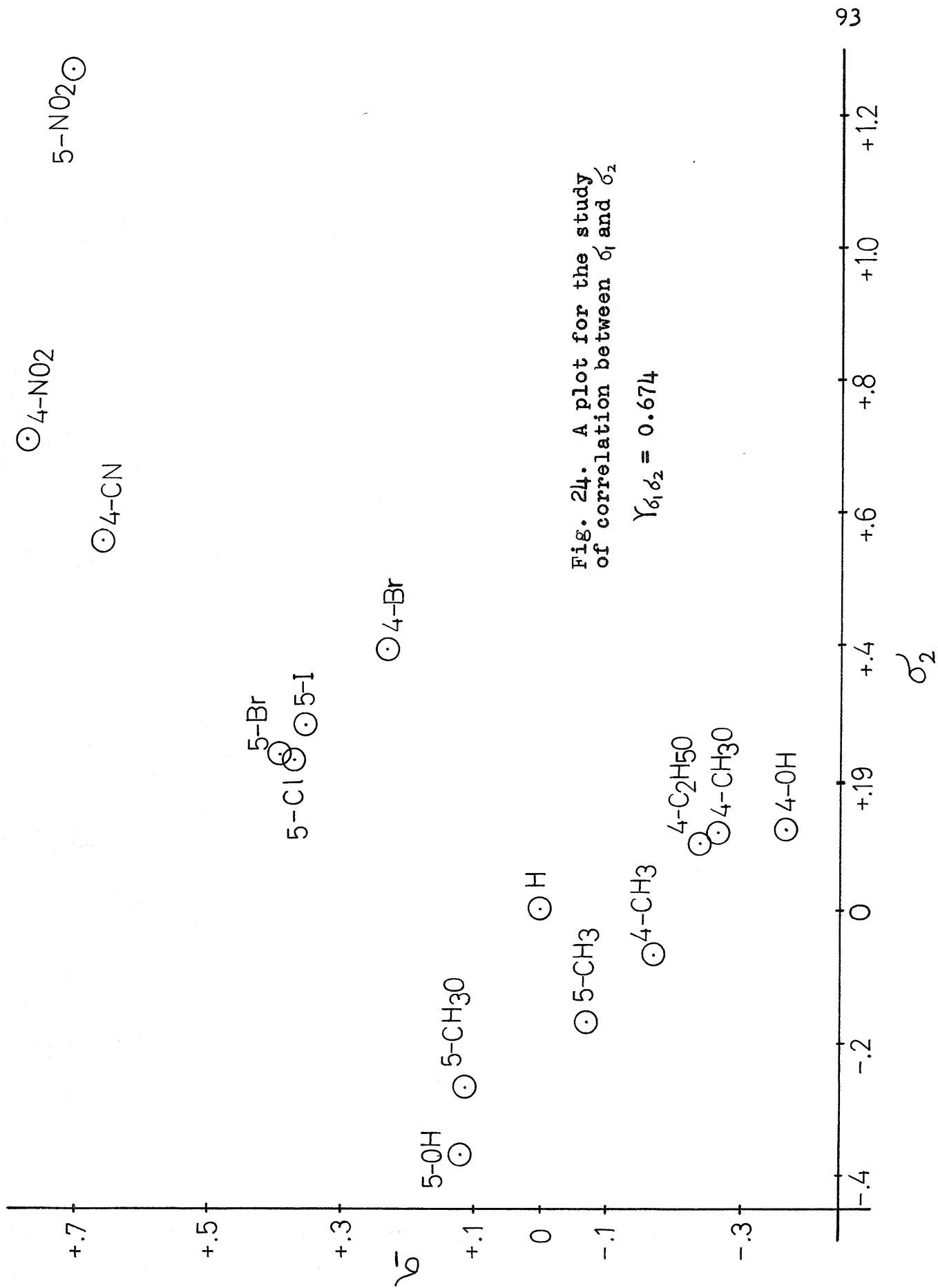


Fig. 24. A plot for the study of correlation between σ_1 and σ_2

$$r_{\sigma_1\sigma_2} = 0.674$$

Because the $\gamma_{\sigma_1, \sigma_2}$ was calculated to be much less than 0.9 our data can be thus used to test the relative fits of Equation 48 and Equation 31 to the ionization constants of substituted salicylic acids.

Equation 48 was tested by rearranging it into the form

$$\frac{\log K - \log K_0}{\sigma_1} = \rho_2 \left(\frac{\sigma_2}{\sigma_1} \right) + \rho_1 \quad (52)$$

The general form of Equation 52 is $y=ax+b$ which is a straight line. If a plot of y versus x corresponding to each substituted salicylic acid is constructed, the slope of the line gives ρ_2 and the distance between the origin and the intersect of the line on the y axis gives ρ_1 . The calculated y 's and x 's are listed in Table 23. These values are plotted in Figure 25. If Equation 52 should be applicable to correlate the pK 's of substituted salicylic acids, all points in Figure 25 would be on a single straight line. The randomness of those points disproves the usefulness of Equation 48.

Having proved that Equation 48 does not fit the pK 's of substituted salicylic acids, a simple Hammett equation

$$\log \frac{K}{K_0} = \rho \sigma \quad (31)$$

Table 23

Values of y and x for testing
Equation 52.

<u>Substituted salicylic Acid</u>	$y = \frac{\log K/k_0}{\delta_1}$	$x = \frac{\delta_2}{\delta_1}$
4-Methoxy	1.187	-0.429
4-Bromo	1.099	1.685
4-Ethoxy	0.883	-0.417
4-Cyano	0.966	0.848
4-Nitro	0.875	0.913
4-Hydroxy	0.651	-0.327
4-Methyl	0.735	0.406
5-Methoxy	0.426	-2.330
5-Chloro	0.772	0.609
5-Bromo	0.956	0.593
5-Nitro	0.945	1.789
5-Iodo	0.821	0.784
5-Methyl	0.623	2.464
5-Hydroxy	0.050	-3.058

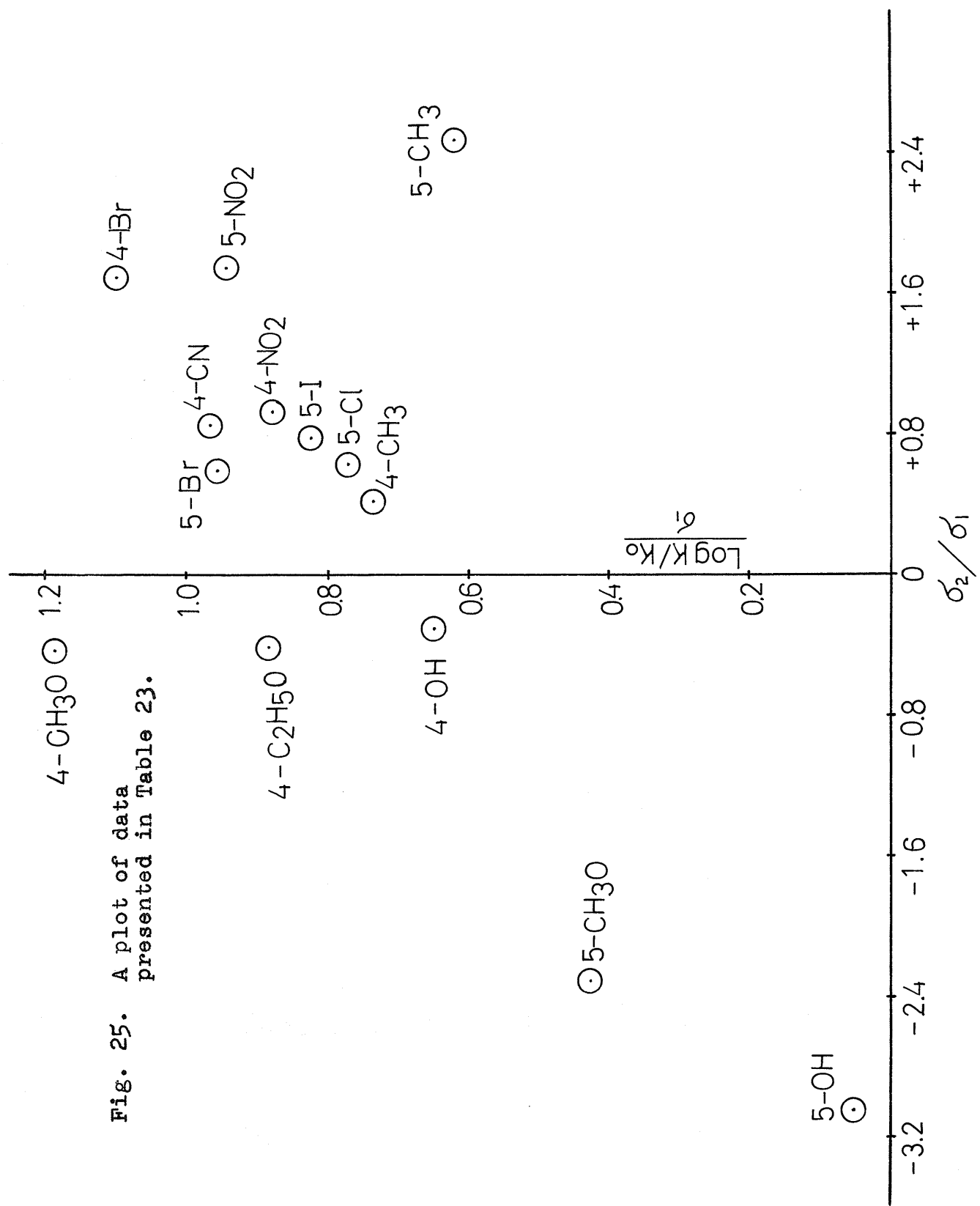


Fig. 25. A plot of data presented in Table 23.

was tested and the plot of Hammett sigma versus log K shown in Figure 26 gives a very good correlation. The correlation coefficient between log K and σ , $\gamma_{\log K, \sigma}$, was calculated to be 0.984 as compared to Jaffe's value of 0.978 (29) which was estimated by using data from the work of Shorter et al. (58).

The least squares method (Appendix III) was used to compute the slope of the line (ρ) through the given points and this eliminates a certain arbitrariness with which the same line might be drawn visually. The rho was computed to be $+0.898 \pm 0.039$. This agrees fairly well with Jaffe's requirement that ρ for ortho-substituted benzoic acids is equal to 1. A rho of 1.103 was reported from the information obtained from Shorter's six substituted salicylic acids (58) by Jaffe (29).

Before consideration can be given to the question why the pK's of substituted salicylic acids fit the one-parameter Hammett equation, one should examine the evidence for intramolecular hydrogen bonding of salicylic acid between the hydroxy group and the carboxylic oxygen atom (4, 39, 51). Table 24 presents data from Reference (51). The abnormal acid strengths of ortho-hydroxy benzoic acids can not be predicted solely from a consideration of the electronic effects of the substituents and steric factors; intramolecular

Fig. 26. Hammett-equation plot of the ionization constants of substituted salicylic acids.

$$\rho = +0.898 \pm 0.039$$

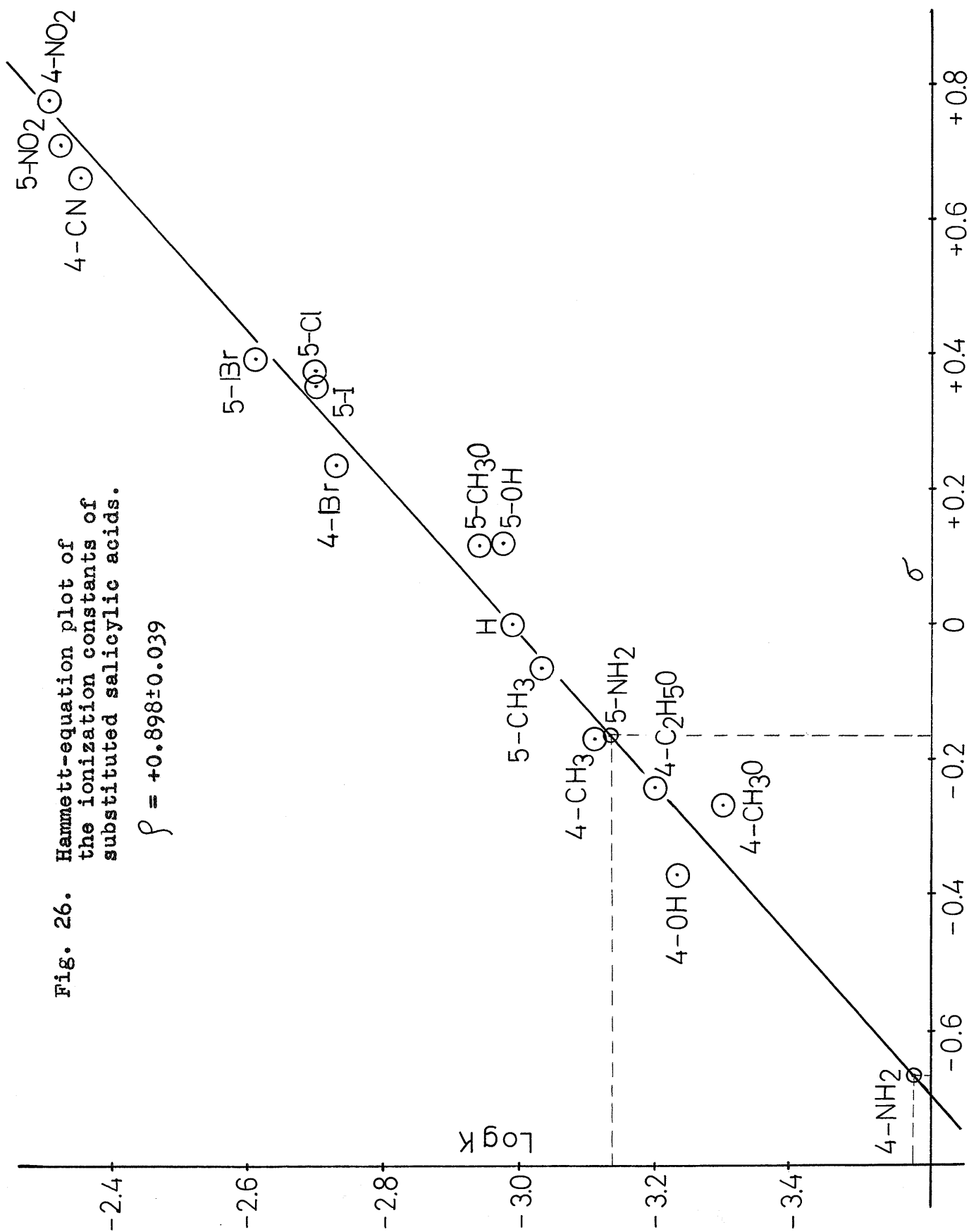


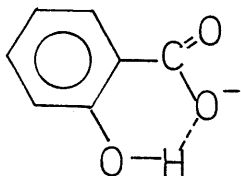
Table 24

Ionization constants of hydroxybenzoic acids as compared to the parent acid (51).

<u>Substituent</u>	<u>10^5K</u>	<u>$K/K(\text{benzoic})$</u>
Benzoic Acid	6.27	1
o-Hydroxy	101	16.1
m-Hydroxy	8.33*	1.33
p-Hydroxy	2.95	0.47
2,6-Dihydroxy	5200	830

* Data taken from Reference (39).

hydrogen bonding between the hydroxy group and the carboxylic oxygen atom was postulated to stabilize the carboxylate anion (4).



The recent evidence of intramolecular hydrogen bonding of salicylic acid is due to Shigorin (24). He showed the IR spectroscopic characteristics of the hydrogen bond between 3200 and 3600 cm^{-1} of salicylic acid and similar compounds. This kind of characteristic intramolecular hydrogen bonding of salicylic acid is also shown by Korobkov (38) in organic solvents, such as CCl_4 , dioxane and ether.

There are at least two possible ways to explain why the dissociation of substituted salicylic acids can be correlated with Equation 31.

One way to interpret the data is to assume that no hydrogen bond exists between the hydroxy group and the carboxylic oxygen atom. The effect of the ortho-hydroxy group on the acid strength is then considered to be through normal electronic displacement. Therefore, the following relationship could be expressed :

$$\log \frac{K}{K_0} = \rho (\sigma + \sigma_{OH}) \quad (53)$$

where σ is the substituent constant of para- or meta-substituent relative to the reacting site and σ_{OH} represents the effect of OH group on the reacting site. σ_{OH} is a constant because it is same throughout the reaction series. Equation 53 may be also written

$$\log K = \rho \sigma + (\rho \sigma_{OH} + \log K_0) \quad (54)$$

Since the last term, $\rho \sigma_{OH} + \log K_0$, in Equation 54 is a constant, the whole expression belongs to the type of one-parameter Hammett equation. However, if this interpretation is correct it is very difficult to explain the data of Table 24 previously referred to.

The second interpretation of our results is to assume that the hydrogen bonding between the hydroxy group and the carboxylic-oxygen atom is so strong that the effect of para- or meta-substituents on the ionization equilibrium through the path of hydrogen bond is constant. This might be the case if the influence of the hydrogen bond on acid strength is the result of it holding the carboxyl group in

the plane of the ring and thus enhancing mesomeric effects. Then the effect of the ortho-hydroxyl group would be constant so long as the hydrogen bond is strong enough to maintain co-planarity. Consequently, the pK 's of substituted salicylic acids would give a good correlation with Equation (31).

However, the carboxylate anion of benzoic acid would have more freedom than that of salicylic acid to assume any spatial arrangement relative to the benzene ring. Thus in the case of benzoic acid mesomeric effects at the carboxyl center would be expected to be less pronounced than in the case of salicylic acid which is a stabilized hydrogen bonded species. This interpretation would predict that ρ should be larger for salicylic acids than that for benzoic acids so that the second interpretation can hardly be correct.

No single interpretation is available at present which can include both the previous evidence for chelation in salicylic acids and our evidence against it.

With regard to the 4- and 5-aminosalicylic acids, the ionization constants of the free acids (K_c (Fig.26)) are obtained by interpolation in the Hammett plot using the known σ_m and σ_p of aminosalicylic acids as shown in Figure 26. The ionization constants of the individual species, the isoelectric points and the percentage of zwitterions at the isoelectric points were calculated from the relationships given in Equation 15 through Equation 21 and shown in Table 25 together with standard deviations as calculated according to Topping (62). The literature values of pK's of aminosalicylic acids are also given in Table 25. The ionization constants determined in the present work are probably more reliable than previous values because the computer enables one to take account of the unobtainable experimental data for the overlapping portions of the first and second ionization constants. The thermodynamic ionization constants, K_b , K_d , and K , of 4-aminosalicylic acid were calculated to be negative with errors larger than the corresponding values. Since the ionization constant can not be negative in reality its value must lie between zero and the maximum value which is obtained by subtraction of the calculated ionization constant from the positive value of the error. These are also listed in parentheses in Table 25.

Table 25 reveals the interesting and previously unknown fact that at the isoelectric point 4-aminosalicylic acid is almost entirely in the neutral form whereas 5-aminosalicylic acid is almost completely zwitterion.

Table 25

The thermodynamic ionization constants, the isoelectric points and the percentage of zwitterions of aminosalicyclic acids.

	<u>4-NH₂</u>	<u>5-NH₂</u>
$10^4 K_1$	79.5 ± 1.1	57.5 ± 8.2
pK_1	2.10 ± 0.01 $1.99(43)$ $1.7 (20)$	2.24 ± 0.05 $2.74(20)$
$10^4 K_2$	3.80 ± 0.93	0.0204 ± 0.0015
pK_2	3.42 ± 0.09 $3.92(43)$ $3.9 (20)$	5.69 ± 0.03 $5.84(20)$
$10^4 K_a$	114.5 ± 43.2	0.100 ± 0.027
$10^4 K_b$	-35.0 ± 44.3 (0 - 8.3)	57.4 ± 8.2
$10^4 K_c$	2.64 ± 0.24	7.31 ± 0.33
$10^4 K_d$	-8.63 ± 10.05 (0 - 1.42)	0.0204 ± 0.0015
K	$(-0.305 \pm 0.495) \times 10^{-4}$ (0 - 0.19×10^{-4})	$(3.58 \pm 0.31) \times 10^2$
$pH_{isoe.}$	2.76	3.92
$\%HA_{isoe.}$	(0 - 0.0019)	96.15 ± 3.70

SUMMARY

1. The first ionization constants of sixteen substituted salicylic acids have been determined in aqueous solution at 25°C using an improved ultraviolet absorption spectrophotometric method.

2. The first and second ionization constants of 4- and 5-aminosalicylic acids have also been determined by using the method of Dunn and Leggate (18).

3. The first ionization constants of sixteen substituted salicylic acids were well correlated with the simple Hammett equation better than the two-parameter equation.

4. Calculations of the zwitterion concentration of aminosalicylic acids pointed out that, whereas 4-aminosalicylic acid is almost entirely in the neutral form, 5-aminosalicylic acid is almost completely in the zwitterion form.

APPENDIX

APPENDIX I

THE 1620 IBM FORTRAN PROGRAM FOR
 SOLVING THE GENERAL EQUATION: $Y=(AX+BC)/(C+X)$
 FOR THE FIRST IONIZATION CONSTANT OF A
 SUBSTITUTED SALICYLIC ACID

```

DIMENSION PH(20),D(20)
1 READ 2,N,EDHA,EDA,EPK,JA,UPH,UD
2 FORMAT (I3,F6.3,F6.3,F6.3,I4,F7.3,F7.3)
  IF (SENSE SWITCH 1)3,4
3 ACCEPT 2,N,EDHA,EDA,EPK,JA,UPH,UD
4 C=EXP(-2.303*EPK)
  DO 5 J=1,JA
5 READ 6,PH(J),D(J)
6 FORMAT (F6.3,F6.3)
7 AA=0.
  AB=0.
  AC=0.
  AO=0.
  BB=0.
  BC=0.
  BO=0.
  CC=0.
  CO=0.
  OO=0.
  DO 8 J=1,JA
  X=EXP(-2.303*PH(J))
  UX=X-(EXP(-2.303*(PH(J)+UPH)))
  CX=C+X
  FA=-X/CX
  FB=-C/CX
  FC=X*(EDHA-EDA)/(CX**2)
  FX=C*(EDA-EDHA)/(CX**2)
  FY=1.
  FO=D(J)-(EDHA*X+(EDA*C))/CX
  FL=1./(((FX**2)*(UX**2))+((FY**2)*(UD**2)))
  AA=AA+(FA*FA*FL)
  AB=AB+(FA*FB*FL)
  AC=AC+(FA*FC*FL)
  AO=AO+(FA*FO*FL)
  BB=BB+(FB*FB*FL)
  BC=BC+(FB*FC*FL)
  BO=BO+(FB*FO*FL)

```

APPENDIX I
(continued)

```

CC=CC+(FC*FC*FL)
CO=CO+(FC*FO*FL)
OO=OO+(FO*FO*FL)
8 CONTINUE
P1=-AB/AA
P2=-AC/AA
P3=BB+(P1*AB)
P4=BC+(P1*AC)
P5=BO+(P1*AO)
P6=-P4/P3
P7=CC+(P2*AC)+(P6*P4)
P8=CO+P2*AO)+(P6*P5)
P9=P2+(P1*P6)
VC=P8/P7
VB=(P5-(P4*VC))/P3
VA=(AO-(AC*VC)-(AB*VB))/AA
A=EDHA-VA
B=EDA-VB
C=C-VC
IF (C**2-VC**2)9,9,11
9 PRINT 10,N
10 FORMAT (12HNO SOLUTION I3)
GO TO 18
11 IF (SENSE SWITCH 2)12,13
12 IF (VC**2-.000025*(C**2))13,13,7
13 C31=P9/P7
C21=(P1-(P4*C31))/P3
C11=(1.-(AC*C31)-(AB*C21))/AA
C32=P6/P7
C22=(1.-(P4*C32))/P3
C12=-((AB*C22)+(AC*C32))/AA
C33=1./P7
C23=- (P4*C33)/P3
C13=-((AB*C23)+(AC*C33))/AA
S=OO-((AO*AO)/AA)-((P5*P5)/P3)-((P8*P8)/P7)
AJ=JA
EXT=S/(AJ-3.0)
SEA=SQRT(C11*EXT)
SEB=SQRT(C22*EXT)
SEC=SQRT(C33*EXT)
PK=-LOG(C)/2.303
SEPK=PK+(LOG(C+SEC)/2.303)
PRINT 14,N,JA
14 FORMAT (6HRUN NO I3,13H NO POINTS I3)
PRINT 15,EDHA,EDA,EPK

```


APPENDIX I
(continued)

```
15 FORMAT (5HEDHA=F5.3,4HEDA=F5.3,4HEPK=F5.3)
   PRINT 16,A,B,PK
16 FORMAT (4HDHA=F6.4,7H    DA=F6.4,7H    PK=F6.4)
   PRINT 17,SEA,SEB,SEPK
17 FORMAT (6HSEDHA=F6.4,9H    SEDA=F6.4,9H    SEPK=F6.4)
18 PAUSE
   GO TO 1
   END
```

APPENDIX II

THE 1620 IBM FORTRAN PROGRAM FOR
 SOLVING THE GENERAL EQUATION: $Y=(A+BCX)/(1+BX)$
 FOR THE OVERLAPPING IONIZATION CONSTANTS OF
 AN AMINOSALICYLIC ACID

```

DIMENSION PH1(20),PH2(20),D(20)
1 IF (SENSE SWITCH 1)2,4
2 READ 3,ED1,ED2,EPK1,UPH,UD,JA,N
3 FORMAT (F7.2,F7.2,F6.2,F6.2,F5.1,I3,I3)
  A=ED1
  B=ED2
  C=EXP(-2.303*EPK1)
  GO TO 5
4 READ 28,ED2,ED3,EPK2,UPH,UD,JA,N
28 FORMAT (F7.2,F7.2,F6.2,F6.2,F5.1,I3,I3)
  A=ED2
  B=ED3
  C=EXP(-2.303*EPK2)
5 AJ=JA
  DO 6 J=1,JA
6 READ 7,PH1(J),PH2(J),D(J)
7 FORMAT (F5.3,F5.3,F6.3)
8 AA=0.0
  AB=0.0
  AC=0.0
  AO=0.0
  BB=0.0
  BC=0.0
  BO=0.0
  CC=0.0
  CO=0.0
  OO=0.0
  DO 12 J=1,JA
  IF (SENSE SWITCH 1)9,10
9 X=1.0/(EXP(-2.303*PH1(J))+EXP(-2.303*PH2(J)))
  IF (SENSE SWITCH 4)30,31
30 UX=(1.0/(EXP(-2.303*(PH1(J)+UPH))+EXP(-2.303*(PH2(J)+UPH))))-X
  GO TO 11
31 UX=X-1.0/(EXP(-2.303*(PH1(J)-UPH))+EXP(-2.303*(PH2(J)-UPH)))
  GO TO 11

```

APPENDIX II
(continued)

```

10 X=EXP(2.303*PH1(J))+EXP(2.303*PH2(J))
   IF (SENSE SWITCH 4)32,33
32 UX=(EXP(2.303*(PH1(J)+UPH))+EXP(2.303*(PH2(J)+UPH)))-X
   GO TO 11
33 UX=X-(EXP(2.303*(PH1(J)-UPH))+EXP(2.303*(PH2(J)-UPH)))
11 FA=-1.0/(1.0+(X*C))
   FB=FA*X*C
   FC=X*(A-B)*(FA**2)
   FD=1.0
   FX=C*(A-B)/(FA**2)
   FO=D(J)+(FA*(A+(B*C*X)))
   FL=1.0/((FX**2)*UX+(FD**2)*UD)
   AA=AA+(FA*FA*FL)
   AB=AB+(FA*FB*FL)
   AC=AC+(FA*FC*FL)
   AO=AO+(FA*FO*FL)
   BB=BB+(FB*FB*FL)
   BC=BC+(FB*FC*FL)
   BO=BO+(FB*FO*FL)
   CC=CC+(FC*FC*FL)
   CO=CO+(FC*FO*FL)
   OO=OO+(FO*FO*FL)
12 CONTINUE
   P1=-AB/AA
   P2=-AC/AA
   P3=BB+(P1*AB)
   P4=BC+(P1*AC)
   P5=BO+(P1*AO)
   P6=-P4/P3
   P7=CC+(P2*AC)+(P6*P4)
   P8=CO+(P2*AO)+(P6*P5)
   P9=P2+(P1*P6)
   VC=P8/P7
   VB=(P5-(P4*VC))/P3
   VA=(AO-(AC*VC)-(AB*VB))/AA
   A=A-VA
   B=B-VB
   C=C-VC
   IF (C**2-VC**2)13,13,15
13 PRINT 14,N
14 FORMAT (12HNO SOLUTION I3)
   GO TO 26
15 IF (SENSE SWITCH 2)16,17
16 IF (VC**2-1.E-06*(C**2))17,17,8

```

APPENDIX II
(continued)

```

17 C31=P9/P7
   C21=(P1-(P4*C31))/P3
   C11=(1.0-(AC*C31)-(AB*C21))/AA
   C32=P6/P7
   C22=(1.0-(P4*C32))/P3
   C12=-((AB*C22)+(AC*C32))/AA
   C33=1.0/P7
   C23=-(P4*C33)/P3
   C13=-((AB*C23)+(AC*C33))/AA
   S=00-((A0*A0)/AA)-((P5*P5)/P3)-((P8*P8)/P7)
   EXT=S/(AJ-3.0)
   SEA=SQRT(C11*EXT)
   SEB=SQRT(C22*EXT)
   SEC=SQRT(C33*EXT)
   PK=-LOG(C)/2.303
   PRINT 18,N,JA
18 FORMAT (6HRUN NO I3,13H      NO POINTS I3)
   IF (SENSE SWITCH 1)20,23
20 PRINT 19,ED1,ED2,EPK1
19 FORMAT (4HED1=F4.0,7H      ED2=F4.0,8H      EPK1=F4.2)
   PRINT 21,A,B,C,PK
21 FORMAT (3HD1=F6.0,6H      D2=F6.0,6H      K1=E10.4,7H      PK1=F6.4)
   PRINT 22,SEA,SEB,SEC
22 FORMAT (5HSED1=F6.4,8H      SED2=F6.4,8H      SEK1=E10.4)
   GO TO 26
23 PRINT 27,ED2,ED3,EPK2
27 FORMAT (4HED2=F4.2,7H      ED3=F4.2,8H      EPK2=F4.2)
   PRINT 24,A,B,C,PK
24 FORMAT (3HD2=F6.4,6H      D3=F6.4,6H      K2=E10.4,7H      PK2=F6.4)
   PRINT 25,SEA,SEB,SEC
25 FORMAT (5HSED2=F6.4,8H      SED3=F6.4,8H      SEK2=E10.4)
26 PAUSE
   GO TO 1
   END

```

APPENDIX III

THE 1620 IBM FORTRAN PROGRAM FOR
 SOLVING THE GENERAL EQUATION: $Y=AX+B$ FOR THE
 REACTION CONSTANT, ρ , IN THE IONIZATION OF
 SUBSTITUTED SALICYLIC ACIDS

```

DIMENSION X(40), Y(40)
1 READ 2, N, JA
2 FORMAT (I3, I4)
  AJ=JA
  DO 3 J=1,JA
3 READ 4, X(J), Y(J)
4 FORMAT (E11.4, E11.4)
  X1=0.
  Y1=0.
  X2=0.
  Y2=0.
  XY=0.
  DO 5 J=1,JA
  X1=X1+X(J)
  Y1=Y1+Y(J)
  X2=X2+X(J)**2
  Y2=Y2+Y(J)**2
5 XY=XY+X(J)*Y(J)
  XM=X1/AJ
  YM=Y1/AJ
  XS=X2-AJ*(XM**2)
  YS=Y2-AJ*(YM**2)
  XYS=XY-AJ*XM*YM
  A=XYS/XS
  B=YM-A*XM
  SEA=SQRT((YS/XS-A**2)/(AJ-2.))
  SEB=SEA*SQRT(X2/AJ)
  PRINT 6, N, JA
6 FORMAT (///8HRUN NO =I3, 15H NO POINTS =I3)
  PRINT 7, A, SEA
7 FORMAT (/2HA=E11.4,7H SEA=E11.4)
  PRINT 8, B, SEB
8 FORMAT (2HB=E11.4,7H SEB=E11.4)
  IF (SENSE SWITCH 1)9,11
9 DO 12 J=1,JA
  YC=A*X(J)+B
12 PRINT 10, X(J), Y(J), YC
10 FORMAT (E11.4, E11.4, E11.4)
11 PAUSE
  GO TO 1
  END

```

APPENDIX IV

PREPARATION OF HCl BUFFERS

As an example, consider that a 400 ml. solution of pH=2.4 with ionic strength 0.01 was required.

$$\text{pH}=2.4$$

$$[\text{H}^+]=4.0 \times 10^{-3} \text{N}$$

Calculating the volume (ml.) of HCl stock solution (0.1000N) needed:

$$0.1000 \frac{X}{400} = 4.0 \times 10^{-3}$$

$$X=16 \text{ ml.}$$

The concentration of KCl required in order to keep ionic strength of the buffer solution at 0.01 was

$$0.01 - 0.004 = 0.006 \text{ M}$$

Calculating the volume (ml.) of KCl stock solution (0.1000N) needed:

$$0.1000 \frac{Y}{400} = 0.006$$

$$Y=24 \text{ ml.}$$

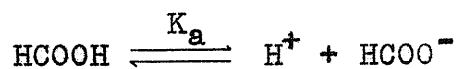
Therefore, a 400 ml. buffer solution with pH=2.4 and ionic strength 0.01 could be made from

16 ml. 0.1000N HCl
 24 ml. 0.1000N KCl
 Diluted to 400 ml. with distilled water.

APPENDIX V

PREPARATION OF CARBOXYLATE BUFFERS

A buffer solution of pH=3.6 with ionic strength 0.01 was prepared by mixing 100 ml. of a solution A (0.005N HCOONa and 0.005N KCl) and the required volume of a solution B (0.02N HCl and 0.01N KCl) which is calculated as follows:



$$K_a = \frac{[\text{H}^+][\text{HCOO}^-]}{[\text{HCOOH}]}$$

$$\log K_a = \log [\text{H}^+] + \log \frac{[\text{HCOO}^-]}{[\text{HCOOH}]}$$

$$\text{p}K_a = \text{pH} - \log \frac{[\text{HCOO}^-]}{[\text{HCOOH}]}$$

Since

$$\text{p}K_{\text{HCOOH}} = 3.75$$

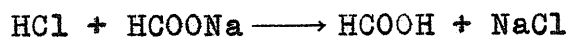
$$\text{pH} = 3.6$$

Then

$$\log \frac{[\text{HCOO}^-]}{[\text{HCOOH}]} = 3.6 - 3.75 = -0.15$$

$$\frac{[\text{HCOOH}]}{[\text{HCOO}^-]} = 1.41 \quad (40)$$

Since



and

$$\text{HCOO}^- + \text{HCOOH} = 5 \times 10^{-4} \text{ moles}$$

$$\text{HCOO}^- = 5 \times 10^{-4} - \text{HCOOH} \quad (41)$$

Substituting Eq. 41 into Eq. 40,

$$\frac{\text{HCOOH}}{5 \times 10^{-4} - \text{HCOOH}} = 1.41$$

$$\text{HCOOH} = 2.92 \times 10^{-4}$$

Therefore, 2.92×10^{-4} moles HCl was needed and the volume (ml.) of 0.02N HCl required was

$$\frac{0.02}{1000} X = 2.92 \times 10^{-4}$$

$$X = 14.6 \text{ ml.}$$

A buffer solution with pH = 3.6 and ionic strength 0.01 was, therefore, made from

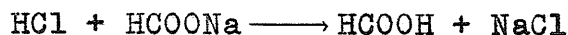
$$\text{Solution A : 100 ml. } \left\{ \begin{array}{l} 0.005\text{N HCOONa} \\ 0.005\text{N KCl} \end{array} \right.$$

$$\text{Solution B : 14.6 ml. } \left\{ \begin{array}{l} 0.02\text{N HCl} \\ 0.01\text{N KCl} \end{array} \right.$$

The ionic strength 0.01 of the above buffer solution with pH = 3.6 was checked as follows:

The contribution to the ionic strength due to the ionization of formic acid was negligible so long as less than 25 ml. of Solution B was used per 100 ml. of Solution A.

The equation for the reaction in solution was represented as follows:



The concentration of each component in that solution was

$$\text{HCOONa} : 5 \times 10^{-4} - 2.92 \times 10^{-4}$$

$$\text{NaCl} : 2.92 \times 10^{-4}$$

$$\text{KCl} : 5 \times 10^{-4}$$

$$\text{KCl} : (2.92/2) \times 10^{-4}$$

The total concentration was 11.45×10^{-4} moles by adding up the above four. Since the total volume of the buffer solution was 114.6 ml. , the ionic strength was obtained as follows:

$$\frac{11.46 \times 10^{-4}}{114.6} \times 1000 = 0.01$$

Two values of pH and their corresponding volumes of Solution B were then calculated for the monochloroacetate, formate and acetate buffer, respectively. These data were plotted on a graph of pH versus volume of Solution B with constant volume of Solution A. By connecting the two points for each buffer, three straight lines were obtained as shown in Fig. 4. These calculated values were compared with measured values of pH. Because the values of the concentration of Solutions A and B may not have been exactly as those noted in Fig. 4, corrected lines using the measured pH were constructed.

Fig. 4. A plot from which the volume of Solution B can be read which must be added to a 100 ml. of Solution A to give the desired pH.

- (1) Monochloroacetate Buffer, -----
- (2) Formate Buffer, -----
- (3) Acetate Buffer, -----

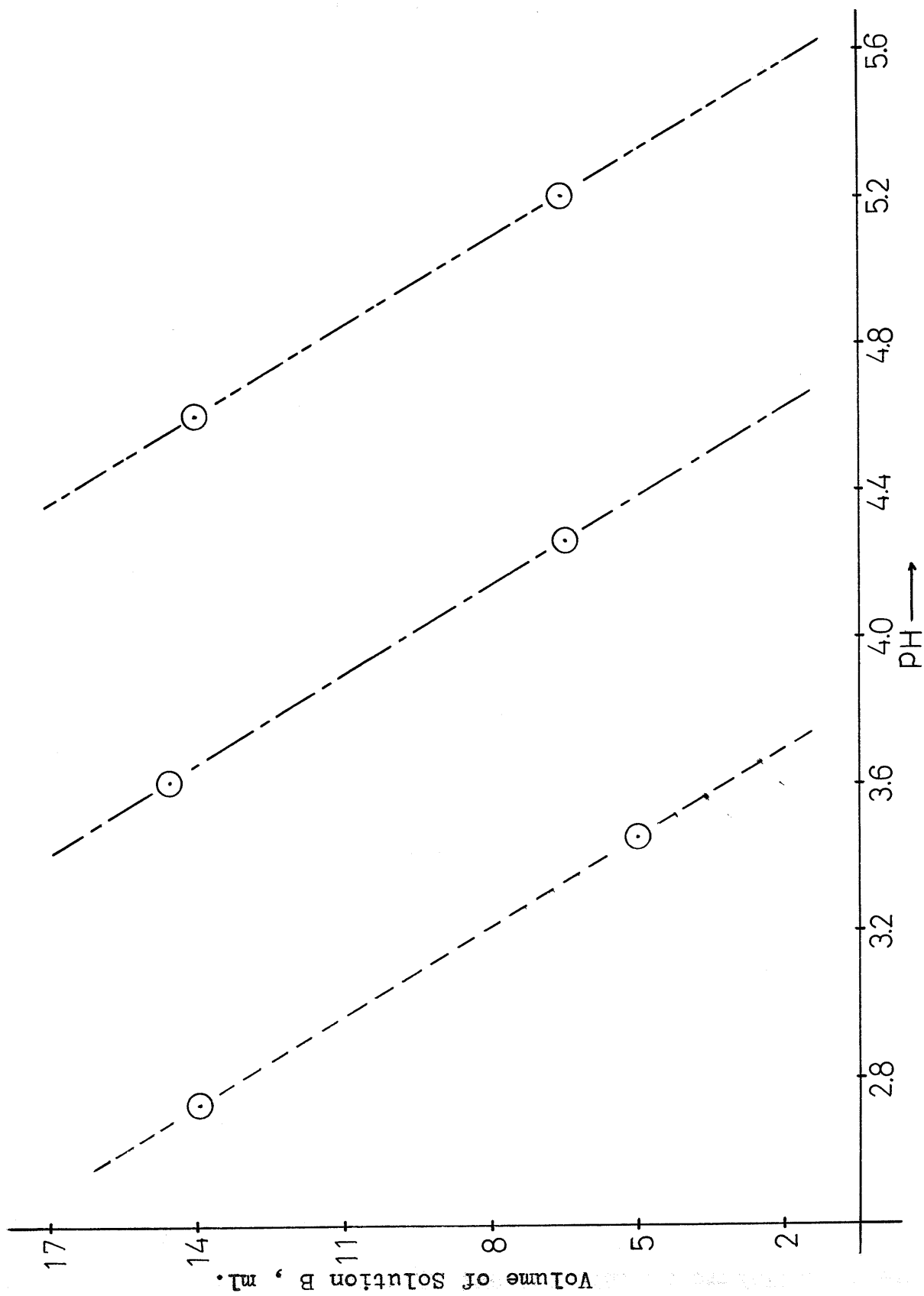


Fig. 4.

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