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The U.V. Absorption Spectra of *p*-Aminosalicylic Acid and some Related Compounds—IV. The Ampholytic Forms of *p*-Aminosalicylic Acid and some Structurally Related Compounds and their Decarboxylation

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Introduction*

In a previous paper in this series,[1] we reported on the decarboxylation of *p*-aminosalicylic acid in aqueous solutions. As this decarboxylation was found to be strongest at the isoelectric point, we assumed that decarboxylation takes place through the ampholytic forms of the *p*-aminosalicylic acid molecule.

Studying the kinetics of the decarboxylation of *p*-aminosalicylic acid, Willi and Stocker[2] concluded that the diprotic acid formed from *p*-aminosalicylic acid by proton addition to the NH_2-group is also capable of decarboxylation.

According to these authors, the rates of decarboxylation follow the equation:

$$r = K_{HA}[HA] + K_{H_2A^+}[H_2A^+]$$

where K_{HA} and $K_{H_2A^+}$ represent rate constants of ampholytic and diprotic material respectively, $[HA]$ and $[H_2A^+]$ represent concentrations. From this equation a decomposition of 3 per cent in 24 h can be calculated for *p*-aminosalicylic acid dissolved in 2 N

* The study of the physical properties of important medicinal agents has become one of the main preoccupations of chemists and pharmacologists interested in relations between such properties and the fate of the drug in the organism.

The present paper presents U.V. spectra of *p*-aminosalicylic acid and some related compounds as the basic groundwork in such an investigation.

HCl. However, we found only negligibly small decarboxylation rates under these conditions. We were not able to detect any significant change in the optical density of these solutions at 300 mμ even if they were left standing for a week (decarboxylation is readily observable at 300 mμ as the *m*-aminopnenol formed is transparent at this wavelength).

Table I. Relation between pH, ampholyte concentration and decomposition of an aqueous solution of *p*-aminosalicylic acid

pH	Relative concentrations			Percentage decomposition in 24 h	$\beta = \frac{[\text{Amph.}]}{\text{fraction decomposed}}$
	D.P.A.	Amph.	D.P.B.		
0	0·984	0·016	—	0	
0·5	0·951	0·049	—	—	
1·0	0·858	0·142	—	—	
1·3	0·751	0·248	0·001	13·1	(1·90)
1·8	0·487	0·505	0·008	19·0	2·66
2·1	0·321	0·664	0·019	23·2	2·86
2·4	0·186	0·769	0·045	23·5	3·27
2·7	0·095	0·810	0·095	25·5	3·18
3·0	0·047	0·774	0·179	24·2	3·20
3·2	0·023	0·714	0·263	23·5	3·04
4·2	—	0·213	0·787	13·0	(1·65)
5·3	—	0·023	0·977	1·8	(1·28)
6·3	—	0·002	0·998	0	
7·2	—	—	1·000	0	
					Average: 3·03 ± 0·17

In order to obtain greater insight into the decarboxylation of *p*-aminosalicylic acid solutions, in particular into the question as to which of the two ampholytic forms decarboxylates preferentially, we decided to subject our experimental material to a renewed investigation and to extend our experiments to *p*-dimethylaminosalicylic acid, because a preliminary investigation had shown that this compound decarboxylates even more rapidly than *p*-aminosalicylic acid itself.

p-*Aminosalicylic acid*

In aqueous solutions of *p*-aminosalicylic acid, the following dissociations are involved:

$$^{+}NH_3(C_6H_3)OHCOOH \underset{K_{a_1}}{\rightleftharpoons} H^+ + NH_2(C_6H_3)OHCOOH$$

and

$$^{+}NH_3(C_6H_3)OHCOO^- \underset{K_{a_2}}{\rightleftharpoons} H^+ + NH_2(C_6H_3)OHCOO^-$$

where K_{a_1} and K_{a_2} represent the two ionization constants, for which reliable values have been reported by Willi and Stocker.[2] These constants are given in their negative logarithmic form (pK_a's), together with the pK_b's, in Table VII (columns 2 and 3). In Table I the relative concentrations of $^{+}NH_3(C_6H_3)OHCOOH$ (diprotic acid = D.P.A.), $NH_2(C_6H_3)OHCOO^-$ (diprotic base = D.P.B.) and the sum of $NH_2(C_6H_3)OHCOOH$ and $^{+}NH_3(C_6H_3)OHCOO^-$ (ampholyte = Amph.) are given for a series of pH-values ranging from 0–7·2.

These relative concentrations were calculated from*

$$\text{D.P.A.} = \frac{(H^+)^2}{K_{a_1}(H^+) + K_{a_1}K_{a_2} + (H^+)^2} \tag{1}$$

$$\text{D.P.B.} = \frac{K_{a_1}K_{a_2}}{K_{a_1}(H^+) + K_{a_1}K_{a_2} + (H^+)^2} \tag{2}$$

$$\text{Amph.} = \frac{K_{a_1}(H^+)}{K_{a_1}(H^+) + K_{a_1}K_{a_2} + (H^+)^2} \tag{3}$$

* These equations are most easily obtained by expressing D.P.A., D.P.B. and Amph. each as fractions of the total and then substituting the data from the above dissociation. For D.P.A. this derivation is as follows:

$$\begin{aligned}
\text{D.P.A.} &= \frac{\text{D.P.A.}}{\text{Amph.} + \text{D.P.B.} + \text{D.P.A.}} \\
&= \frac{1}{(\text{Amph.}/\text{D.P.A.}) + (\text{D.P.B.}/\text{D.P.A.}) + 1} \\
&= \frac{(H^+)^2}{(\text{Amph.}\ (H^+)^2/\text{D.P.A.}) + (\text{D.P.B.}\ (H^+)^2/\text{D.P.A.}) + (H^+)^2} \\
&= \frac{(H^+)^2}{K_{a_1}(H^+) + K_{a_1}K_{a_2} + (H^+)^2}
\end{aligned}$$

Comparison of columns 3 and 5 of Table I makes it clear that the 'one day decomposition' closely parallels the ampholyte concentration. These two quantities are connected via the parameter β which is given in column 6 and shows a rather good constancy

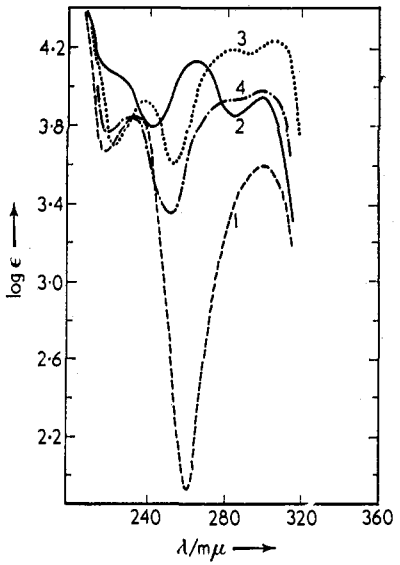


Fig. 1. Ultraviolet absorption of *p*-aminosalicylic acid
curve 1: diprotic acid (pH = 0)
curve 2: diprotic base (pH = 7)
curve 3: ampholytic NH_2—R—COOH (ethanolic solution)
curve 4: ampholyte NH_2—R—COOH + ampholyte $^+NH_3$—R—COO^-

($\beta_{av.} = 3 \cdot 03 \pm 0 \cdot 17$) over the main part of the pH-range investigated. From the paper of Willi and Stocker, a $\beta_{av.}$ of $3 \cdot 04 \pm 0 \cdot 14$ could be calculated, in excellent agreement with our own results.

From our previously published spectral data[3] and from the relative percentages given in Table I, we could calculate rather accurately the U.V. absorption curve of 100 per cent ampholytic material. This curve is shown in Fig. 1 (curve 4). The accuracy of this calculation is demonstrated in Table II which gives the molecular extinctions of the three U.V. maxima of the ampholyte.

Table II. Molecular extinctions of *p*-aminosalicylic acid ampholyte (NH_2—R—COOH + NH_3^+—R—COO′) derived from the absorption curves of this compound at varying pH-values

pH	$\lambda = 233$ mμ	$\lambda = 280$ mμ	$\lambda = 300$ mμ
1·8	7060	8100	8820
2·1	7020	8050	8810
2·4	6970	8130	8930
2·7	6900	8360	9000
3·0	6620	8350	9000
3·2	6500	8300	8970
4·2	6580	8400	9080
Average:	6810 ± 200	8240 ± 120	8940 ± 80

The ampholyte curve shows a good qualitative resemblance to the spectrum of the acid in ethanolic solution (Fig. 1, curve 3). The differences in wavelengths can be ascribed mainly to solvent effects, whereas the differences in extinction arise from the fact that zwitterionic material, although present in aqueous solutions, is absent in ethanolic solutions.

We were able to calculate the amounts of $NH_2(C_6H_3)OHCOOH$ and $^+NH_3(C_6H_3)OHCOO^-$, constituting the ampholyte, from the integrated C_2-band absorptions using the following equation:

$$a\int\{\text{D.P.A.}\} + bx\int\{NH_2(C_6H_3)OHCOOH\} + b(1-x)\int\{^+NH_3(C_6H_3)OHCOO^-\} + c\int\{\text{D.P.B.}\} = \int\{\text{solution of given pH}\} \qquad (4)$$

In this equation $\int\{\ \}$ represents integrated C_2-band absorptions, a, b and c the concentrations of D.P.A., Amph. and D.P.B. respectively, and x and $(1-x)$ the relative fractions of the ampholyte present as $NH_2(C_6H_3)OHCOOH$ and $^+NH_3(C_6H_3)OHCOO^-$ respectively.*

* For the calculation of x, use can also be made of molecular extinctions instead of integrated absorptions. As, however, the C_2-bands and B-bands are blurring one another, the method proposed here works much more accurately, the more so as it takes into account absorptions over a wide wavelength region.

Substituting in the above equation:

$$\int \{\text{D.P.A.}\} = \int \{^{+}NH_3(C_6H_3)OHCOO^{-}\} = 0,$$

and

$$\int \{\text{D.P.B.}\} = \int \{NH_2(C_6H_3)OHCOOH\},^{*}$$

we arrive at

$$(0\cdot 8x + 0\cdot 1) \int \{\text{D.P.B.}\} = \int \{\text{solution of pH} = 2\cdot 7\},$$

from which follows, after substitution of the two $\int\{\ \}$-values, that $x = 0\cdot 62$.

The same value for x is found at pH = 3·2. Performing the calculation for pH = 4·2, an erroneous value is obtained, mainly due to the fact that the steep fall in Amph. combined with the large increase in D.P.B. going from pH = 3·2 to pH = 4·2 no longer permits accurate calculations.

The integrated absorptions of some compounds under several conditions are collected in Table III. For the assignments of the absorption bands (C_2, C_1 and B) see ref. 3. The integrated absorptions expressed in the table as $10^{-7} \times \int \epsilon \, d\nu$ were obtained by measuring planimetrically the area under the different absorption bands reproduced on a frequency scale, after separating them graphically from their neighbours as consistently as possible. For a complete survey of the relative compositions of *p*-aminosalicylic acid at its isoelectric point, reference is made to Table VII (last column). The value of 0·62 found for the relative fraction of uncharged ampholyte agrees remarkably well with the results of Willi and Meier.[4] Via quite different methods (determinations

* The assumption is made here that absorption differences between D.P.A. and $^{+}NH_3(C_6H_3)OHCOO^{-}$ and between $NH_2(C_6H_3)OHCOOH$ and D.P.B. are negligible. This assumption surely holds for D.P.A.–$^{+}NH_3(C_6H_3)OHCOO^{-}$ as no C_2-band is present in the spectra of these species due to the absence of a free NH_2-group. For $NH_2(C_6H_3)OHCOOH$–D.P.B. we can state that slight differences may be expected: as a matter of fact $\int \{NH_2(C_6H_3)OHCOOH\}$ will be slightly greater than $\int \{\text{D.P.B.}\}$. The electron repulsion of carboxyl-OH is reduced when compared with carboxyl-O-, which means a stronger absorption in the C_2-band for $NH_2(C_6H_3)OHCOOH$ (bathochromic shift). Though these bathochromic shifts can frequently be observed, the differences in absorption are not so large, however, that the above assumption is invalidated, especially when integrated absorptions are used (reference is made to the spectra we published[3] for salicylic acid at pH = 3·2 and 8·0).

of ionisation constants of carefully selected compounds), the Hammett σ-value for NH_3^+ (*para*) could be calculated, which in turn enabled the calculation of the ratio zwitterion/uncharged ampholyte. This ratio amounted to 0·688 and gives 0·59 for the relative fraction of uncharged ampholyte.

Table III. Integrated absorptions of *p*-aminosalicylic acid and some related compounds

	Compound	Solvent	$10^{-7} \times \int \epsilon \, d\nu$		
			C_1	C_2	B
1	*p*-Aminosalicylic acid	buffer, pH = 7·2	1·41	2·59	1·00
2		4·2	1·41	2·22	1·00
3		3·2	1·39	1·82	1·04
4		2·7	1·32	1·55	0·90
5	„ 100 per cent ampholyte, calculated from ref. 4			1·61	
6	*p*-Aminosalicylic acid	buffer, pH = 0	1·37	—	0·65
7		ethanol	1·53	3·22	1·00
8	Salicylic acid		1·41	—	0·65
9	*p*-Aminobenzoic acid			4·15	(0·16)
10		buffer, pH = 7·0		3·31	(0·16)
11		3·6		3·22	(0·16)
12	„ 100 per cent ampholyte, calculated from ref. 11			3·37	
13	*p*-Aminobenzoic acid	buffer, pH = 3·1		2·69	(0·16)
14		1·1		—	0·16

p-*Aminobenzoic acid*

The decarboxylation of *p*-aminobenzoic acid is established as negligible,[5] and therefore it seemed interesting to treat the U.V. data of *p*-aminobenzoic acid[3] in an analogous way to that described above for *p*-aminosalicylic acid. The integrated absorptions are given in Table III and the acid's main constants[6] in Table VII. The C_2-band of *p*-aminobenzoic acid, if present, fully submerges the rather weak B-band; so we had to correct the integrated C_2-band absorptions with the estimated value of 0·16. This value represents the integrated absorption for the highest

wavelength (B-band) of p-aminobenzoic acid at a pH where the C_2-band is absent due to complete protonisation of the NH_2-group.

A comparison of the integrated absorptions of p-aminobenzoic acid at pH = 7 and at pH = 3·6 (isoelectric point) using an equation of the type of (4), clearly demonstrates the absence of

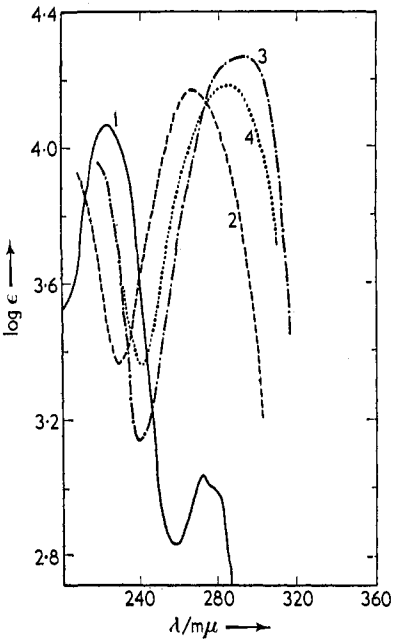


Fig. 2. Ultraviolet absorption of p-aminobenzoic acid

curve 1: diprotic acid (pH = 1)
curve 2: diprotic base (pH = 7)
curve 3: ampholyte NH_2—R—COOH (ethanolic solution)
curve 4: ampholyte NH_2—R—COOH

zwitterionic material in the ampholytic species of p-aminobenzoic acid.

For these reasons we strongly believe that the decarboxylating form of the investigated acids is the zwitterionic one. Only thus can it be explained why p-aminosalicylic acid shows rapid decarboxylation in aqueous solutions whereas an aqueous p-amino-

benzoic acid solution may be kept boiling for 6 h without more than 10 per cent decarboxylation.[5] In addition, it can now be explained why ethanolic solutions of *p*-aminosalicylic acid are stable towards decarboxylating influences since no appreciable amount of zwitterionic material is present in these solutions.

Our observations are not in agreement with the views of Bjerrum[7] and Willi and Meier[4] who suppose that the zwitterionic form of *p*-aminobenzoic acid constitutes at least 10 per cent of the total amount of ampholytic material.

By a different line of reasoning, it is indicated that the zwitterionic part of *p*-aminobenzoic acid ampholyte can be about 3 per cent maximally. In the equation $x(1-x) = nK_{a_2}/K_{a_1}$ (Bjerrum[7]) the substitution of $K_{a_1} = 10^{-1.79}$, $K_{a_2} = 10^{-3.63}$ and $x = 0.62$ yields the value of 16·2 for n, representing the ratio of the acid strengths of $^{+}NH_3(C_6H_3)OHCOOH$ and $NH_2(C_6H_3)OHCOOH$. This result can be used in the Hammett equation, $\log k/k_0 = \sigma\rho$, to find $\sigma_{NH_3^+}$ (*para*). A value of +0·435 is obtained, which is in good agreement with that of Willi and Meier (+0·485).*

Also $\sigma_{NH_3^+}$ (*para*) together with σ_{NH_2} (*para*) and $\rho_{\text{benzoic acid}}$ (electrolytic dissociation) were used in the calculation of $n = 10.7$ for the ratio of the acid strengths of $^{+}NH_3(C_6H_4)COOH$ and $NH_2(C_6H_4)COOH$. Finally substitution of $K_{a_1} = 10^{-2.37}$, $K_{a_2} = 10^{-4.94}$ and $n = 10.7$ in the above equation of Bjerrum yields $x = 0.03$, this being the amount of zwitterionic material present in *p*-aminobenzoic acid ampholyte. Taking into account that the Hammett σ-values used are not as accurately known as could be wished, we are justified in stating that the low value of $x = 0.03$ estimated via the Hammett method is in good agreement with the results obtained from comparison of integrated absorptions. This shows the absence of zwitterionic material.

* In fact the above calculation gives the relationship: $\sigma_{NH_3^+}$ (*para*) = 1·095 + σ_{NH_2} (*para*). In an analogous way, the results from the next paragraph (*p*-dimethylaminosalicylic acid) could be used to calculate: $\sigma_{N(CH_3)_2H^+}$ (*para*) = 0·795 + $\sigma_{N(CH_3)_2}$ (*para*). Using for σ_{NH_2} (*para*) and $\sigma_{N(CH_3)_2}$ (*para*) the values given by Jaffé[6] (−0·660 and −0·600 respectively) we find $\sigma_{NH_3^+}$ (*para*) = +0·435 and $\sigma_{N(CH_3)_2H^+}$ (*para*) = +0·195. In the calculation of the factors 1·095 and 0·795 use was made of $\rho_{\text{salicylic acid}} = 1.103$ (electrolytic dissociation). This latter value was also taken from Jaffé's review article. It is worth noting that recently H. van Bekkum c.s. gave a re-evaluation of the Hammett $\rho\sigma$ relation. [*Rec. Trav. chim. Pays-Bas*, 78, 815 (1959)].

p-*Dimethylaminosalicylic acid*

A preliminary investigation of *p*-dimethylaminosalicylic acid showed that this compound is rapidly decarboxylated in aqueous solutions below pH = 7; from the above discussion, it is reasonable to predict a certain amount of zwitterionic material.

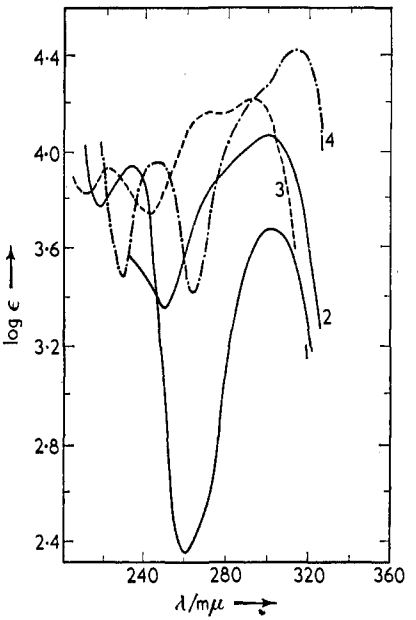


Fig. 3. Ultraviolet absorption of *p*-dimethylaminosalicylic acid
curve 1: aqueous solution, pH = 1·0
curve 2: ,, ,, pH = 3·0
curve 3: ,, ,, pH = 7·0
curve 4: ethanolic solution

(*a*) *U.V. absorption.* No ultraviolet data for *p*-dimethylaminosalicylic acid are available from the literature. Fig. 3 illustrates its changes in absorption due to pH variations. In Table IV, absorption data for a number of aqueous solutions with different pH-values ranging from 0–7 are given. The absorption data of a strongly alkaline solution (0·1 N NaOH) and an ethanolic solution were included for comparison.

Table IV. U.V. absorption of *p*-dimethylaminosalicylic acid

pH	λ_{C_1}	ϵ_{C_1}	λ_{C_2}	ϵ_{C_2}	λ_B	ϵ_B
0	2340	7800	—	—	3005	5000
1·0	2330	7850	—	—	3030	5300
1·8	2330	7900	—	—	3110	7800
2·2	a	a	—	—	3160	9700
2·7	a	a	—	—	3150	11200
3·0	a	a	—	—	3150	11400
3·3	a	a	2980	9300	3150	11800
3·7	a	a	2900	9500	3120	12600
4·2	a	a	2880	11000	3100	13700
5·0	a	a	2860	13000	3070	15000
5·2	2400	8100	2860	13500	3070	15200
6·0	2410	8170	2860	14000	3070	15500
6·5	2410	8220	2860	14200	3070	15600
7·0	2390	8740	2860	14500	3070	15500
(0·1 N NaOH)	2370	8950	2840	14500	3070	15600
(ethanol)	2450	9300	2950	16500	3140	25000

When the ultraviolet spectra of *p*-aminosalicylic acid and its *N*-dimethylderivative are compared, it is clear that the three absorption bands of the latter compound have to be interpreted as C_1, C_2 and B* in order of increasing wavelength. Fully in accordance with expectation is the good correspondence in C_1-absorption and the difference in C_2-absorption of the two compounds.

(*b*) *Decarboxylation.* The decarboxylation of *p*-dimethylaminosalicylic acid was studied at varying pH-values in aqueous solutions of this acid stored at constant temperature.

From spectral measurements carried out immediately after preparation of the solutions and after predetermined times of standing, the decomposition data compiled in Table V were obtained. In Fig. 4 (curve 1), the 'one day decomposition'—percentage of *p*-dimethylaminosalicylic acid, is plotted *versus* the pH of the solution. From a comparison with curve 2, showing

* For the meaning of these symbols see reference 3.

the decomposition of *p*-aminosalicylic acid, one may conclude that: (1) qualitatively both decarboxylations show an identical picture, (2) the decarboxylation rate of *p*-dimethylaminosalicylic acid is nearly twice that of *p*-aminosalicylic acid, and (3) for

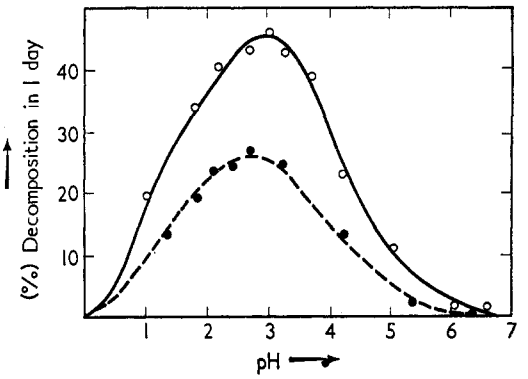


Fig. 4. The decarboxylation of *p*-dimethylaminosalicylic acid (curve 1) and of *p*-aminosalicylic acid (curve 2) *versus* pH

Table V. Decomposition of *p*-dimethylaminosalicylic acid

pH	% decomposition in 24 h	pH	% decomposition in 24 h
0	0	3·7	39·0
1·0	19·6	4·2	23·4
1·8	34·0	5·0	11·2
2·2	40·5	6·0	1·78
2·7	43·7	6·5	1·36
3·0	46·1	7·2	0
3·3	43·4		

p-dimethylaminosalicylic acid the decarboxylation is strongest at pH = 3·0, which means that the isoelectric point of this acid is at pH = 3·0.

The determination of K_{a_1} by means of a potentiometric titration yielded the value of $1{\cdot}78 \times 10^{-4}$. This value, together with the

pH of the isoelectric point, enabled us to complete Table VII for *p*-dimethylaminosalicylic acid. Comparison with *p*-aminosalicylic acid shows pK_{a_2} to be only slightly higher for the dimethyl-substituted compound than for the unsubstituted one, while pK_{a_1} shows a much stronger increase. These differences agree fairly well with the differences existing between *p*-aminobenzoic acid and its *N*-dimethyl-substituted derivative. To make comparison possible, the dissociation constants[9] of the latter compound are given in Table VII, together with its relative composition at the pH of the isoelectric point. Though no experiments were carried out by us on *p*-dimethylaminobenzoic acid, a comparison of the four compounds from Table VII justifies our supposition of the absence of observable amounts of zwitterionic material for *p*-dimethylaminobenzoic acid.

The evaluation of the integrated absorption of *p*-dimethylaminosalicylic acid (given in Table VI) as described under *p*-aminosalicylic acid shows the presence of 38 per cent of zwitterionic

Table VI. Integrated absorptions of *p*-dimethylaminosalicylic acid

	Solvent	$10^{-7} \times \int \epsilon \, d\nu$		
		C_1	C_2	B
1	buffer, pH = 7·0	1·50	2·96	1·22
2	3·0		1·74	1·06
3	0	1·15		0·73
4	ethanol	1·53	3·40	1·15
5	(100% ampholyte, calculated from 2)		1·84	

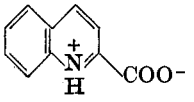
material in the ampholytic species of the acid. This means that at the isoelectric point the said acid has the composition given in column 6 of Table VII. As this composition does not differ greatly from that of *p*-aminosalicylic acid at its isoelectric point, it is obviously concluded that the grouping $(CH_3)_2NH^+$ is more active than NH_3^+ in promoting decarboxylation of $—COO^-$. We believe that the present paper gives sufficient support to the

Table VII. pK's of some aromatic amino acids and I.P.'s (isoelectric points) and relative compositions of their aqueous solutions at the I.P.

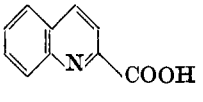
	Species	Dissociation constants pK$_a$'s	Dissociation constants pK$_b$'s	Character[10]	I.P.	Relative composition
1.	p-*aminosalicylic acid*				2·71	
	$^+NH_3$—C_6H_3(OH)COOH	1·79 (1)		diprotic acid		0·10
	NH_2—C_6H_3(OH)COOH	3·63 (2)	12·21 (1)	ampholyte		0·50
	$^+NH_3$—C_6H_3(OH)COO^-					0·30
	NH_2—C_6H_3(OH)COO^-		10·37 (2)	diprotic base		0·10
2.	p-*dimethylaminosalicylic acid*				3·0	
	$^+(CH_3)_2HN$—C_6H_3(OH)COOH	2·2[5] (1)		diprotic acid		0·13
	$(CH_3)_2N$—C_6H_3(OH)COOH	3·7[5] (2)	11·7[5] (1)	ampholyte		0·46
	$^+(CH_3)_2HN$—C_6H_3(OH)COO^-					0·28
	$(CH_3)_2N$—C_6H_3(OH)COO^-		10·2[5] (2)	diprotic base		0·13
3.	p-*aminobenzoic acid*				3·65	
	$^+NH_3$—C_6H_4—COOH	2·37 (1)		diprotic acid		0·04[5]
	NH_2—C_6H_4—COOH	4·94 (2)	11·63 (1)	ampholyte		0·91
	$^+NH_3$—C_6H_4—COO^-					—
	NH_2—C_6H_4—COO^-		9·06 (2)	diprotic base		0·04[5]
4.	p-*dimethylaminobenzoic acid*				3·8	
	$^+(CH_3)_2HN$—C_6H_4—COOH	2·51 (1)		diprotic acid		0·05
	$(CH_3)_2N$—C_6H_4—COOH	5·03 (2)	11·49 (1)	ampholyte		0·90
	$^+(CH_3)_2HN$—C_6H_4—COO^-					—
	$(CH_3)_2N$—C_6H_4—COO^-		8·97 (2)	diprotic base		0·05

idea that decarboxylation of aminobenzoic acids takes place via the zwitterionic state.

In this connection the kinetic study of Brown and Hammick[12] on quinaldinic acid might be mentioned. These authors concluded that it is the zwitterion (V) and not the undissociated acid (VI) which undergoes decarboxylation.



(V)



(VI)

Outside the amino acid field sufficient evidence is found in the literature to support the premise that decarboxylations generally take place via the anions[13] and are highly favoured by electron-withdrawing substituents.[14] As the electron-withdrawing power of the $(CH_3)_2\ NH^+$-group is more pronounced than that of the NH_3^+-group our results are far from surprising.

For the sake of completeness we want to mention that decarboxylations via a carbonium ion[15,16] have also been suggested; we hold the view that in our case such a mechanism need not be considered, nor a decarboxylation via the bimolecular electrophylic substitution mechanism suggested by Schenkel and Schenkel-Rudin:[17]

$$H^+ + R.COOH \longrightarrow RH^+.COOH \longrightarrow RH + CO_2 + H^+$$

Experimental

Preparation of p-*dimethylaminosalicylic acid* (*Dr. C.v.d. Stelt*)

Dimethyl sulphate (2 mole) was added slowly, with constant stirring, to aminosalicylic acid (10 g) dissolved in 25 per cent sodium hydroxide solution (4 mole). When addition was completed, the reaction product was kept at about 60° for half an hour. Addition of 2 N HCl until the pH reached a value of 3·0 yielded a precipitate which was filtered off and dissolved in 2 N HCl. After decoloration with charcoal, the pH was adjusted to 3·0 with NH_4OH and the resulting precipitate crystallized twice from methanol to yield *p*-dimethylaminosalicylic acid (0·5 g), m.p. 129° (d.).

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59·7; H, 6·1; N, 7·7. Found: C, 59·4; H, 5·9; N, 7·9. Upon resolidification the product (*m*-dimethylaminophenol) had m.p. 83–85°.

Decarboxylation studies of p-*dimethylaminosalicylic acid*

The solutions needed for these studies were prepared as follows: about 0·2 mmoles of accurately weighed *p*-dimethylaminosalicylic acid were transferred to a 250-ml volumetric flask and dissolved in the minimal amount of 0·1 N NaOH. The solution was diluted with distilled water up to the mark; this slightly alkaline solution can be stored in a refrigerator for several days without showing any decomposition. Portions (10 ml) of the above stock-solution were diluted with appropriate buffer solutions to 100 ml.

Buffer-solutions used:

pH < 3: diluted HCl-solutions
pH = 3–8: McIlvaine's citric acid–phosphate buffers.[11]

The buffered solutions were measured (1) immediately after preparation, and (2) after a predetermined time of standing.

During these experiments the temperature was kept at 20° ± 1°. The flasks were kept tightly closed between the measurements. The ultraviolet light absorption was measured at the wavelength of the *B*-band, varying from 3005–3160 Å, depending on the pH of the solution. At this wavelength, the absorption of *m*-aminophenol can be neglected,[1] which means that the extinction decrease of a *p*-dimethylaminosalicylic acid solution is directly proportional to the decarboxylation percentage. The instrument used in the absorption measurements was a Unicam SP 500.

Summary. From previously published spectral data on *p*-aminosalicylic acid and some related compounds, we calculated the ratio of the two amphotytic species of this acid present in aqueous solutions. It is suggested that decarboxylation can only take place via the *p*-ammonium-salicylate-zwitterion. At the pH of the isoelectric point, this species is present to an amount of *ca.* 30 per cent. For *p*-aminobenzoic acid solutions, we could make plausible the absence of determinable amounts of zwitterion, which is in agreement with its good stability towards decarboxylating influences. On the other hand, *p*-dimethylaminosalicylic acid decarboxylates rather rapidly; in fact at the pH of its isoelectric point *ca.* 28 per cent of zwitterion is present.

The Hammett σ-values for NH_3^+(*para*) and $N(CH_3)_2H^+$(*para*) could be derived.

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