[CONTRIBUTION FROM THE DEPARTMENT OF PHYSICAL CHEMISTRY IN THE LABORATORIES OF PHYSIOLOGY, HARVARD MEDICAL SCHOOL, AND THE BIOLOGICAL LABORATORIES OF HARVARD UNIVERSITY]

Studies in the Physical Chemistry of Betaines and Related Substances. I. Studies of Dielectric Constants and Apparent Molal Volume[1]

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Introduction

The betaines and the amino acids occupy a distinctive place among organic substances. Both these classes of compounds are distinguished by their unusually high melting points, by their high solubility in water and insolubility in truly nonpolar solvents, and by the fact that in all cases their solutions have a dielectric constant greater than that of the solvent. All these properties find a natural explanation in terms of their structure as zwitterions.

In additon to these general resemblances, however, there are certain notable differences between the two classes of compounds. Instead of the $—^{+}NH_3$ group found in the amino acids, the betaines contain the group $—^{+}NR_1R_2R_3$, where the R's may be almost any organic radicals, but are generally methyl groups. This structure greatly increases both the volume and the basic strength of the nitrogenous radical, and results in important modifications in the properties of the molecules. Moreover, the betaines, unlike the amino acids, are soluble not only in water but in alcohol and in mixtures of alcohol with ether or benzene. Furthermore, their dissociation constants and other properties indicate that they remain as zwitterions, and do not pass over to the uncharged form, in all of these solvents. This has made possible the present study of their dielectric behavior in solvents both of very high and very low dielectric constant, which reveals certain new relationships between the dielectric effect of zwitterions and the properties of the solvent. One highly polar molecule closely related to the betaines, N-dimethylanthranilic acid, is very soluble in pure benzene, and its dipole moment in this solvent has been directly determined, as well as its dielectric increment in other solvents, and its dissociation constants.

Moreover, in the case of the betaines, in distinction from the amino acids, it is possible to obtain in pure form the uncharged molecule corresponding to a given zwitterion. Thus, to a betaine of the type $(CH_3)_3{}^{+}NRCOO^{-}$, there corresponds the uncharged ester $(CH_3)_2NRCOOCH_3$. We have made an experimental study of one such pair, namely, ortho benz betaine and its isomer, dimethylanthranilic acid methyl ester. The striking contrasts found between them throw considerable light on the relation of the electric charges to the properties of the molecule.

In one important class of these substances, namely, the benz betaines, the electric charges on the zwitterion are closely attached to the benzene ring. Owing to the rigid nature of this structure the moments of these compounds can then be calculated with greater reliability than has hitherto been possible in other cases, and considered in relation to their dielectric effects in polar solvents.

Zwitterions, like ions, produce electrostriction of the solvent, an effect which in theory should decrease as the radius of the charged group or ion increases. The increase in bulk of the charged nitrogenous group in the betaines as compared with amino acids should therefore lead to a decrease of electrostriction, and our density measurements confirm this conclusion. The electrostriction due to the betaines becomes much greater in media of low dielectric constant than in water. A fairly extensive study of this phenomenon has been carried out, and the results obtained are in general accord with theoretical expectations.

Preparation of Materials

Betaine [N-Trimethylglycine, $(CH_3)_3N^{+}CH_2COO^{-}$] was obtained from a pure sample of betaine hydrochloride (Eastman Kodak Co.) by the action of silver oxide, recrystallized four times from absolute alcohol by gradual addition of anhydrous ether, and dried forty-eight hours in a vacuum desiccator over phosphorus pentoxide; m. p. 293°.[2]

Other betaines described below were liberated from their halogen salts and purified by the same method.

Pyridine Betaine [$C_5H_5N^{+}CH_2COO^{-}$].—The hydrochloride was prepared by heating pyridine with chloroacetic acid.[3] Heating for five hours at about 60° gave a purer product than a shorter heating at a higher tempera-

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[1] A preliminary account of part of this work was published in *J. Biol. Chem.*, **105**, Proc. XXIV (1934).

[2] Willstätter, *Ber.*, **35**, 584 (1902).

[3] E. von Gerichten, *ibid.*, **15**, 1251 (1882).

ture. The hydrochloride was dissolved in alcohol and crystallized by addition of ether. The free betaine was liberated and purified as described above. Its behavior on heating was exactly as described by von Gerichten.

Dimethylphenyl Betaine [$C_6H_5(CH_3)_2N^+CH_2COO^-$].—The hydrochloride was prepared by heating dimethylaniline with chloroacetic acid.[4] The reaction proceeded much more slowly than for pyridine betaine: twelve to eighteen hours heating on the water-bath was required, and the yield even then was less good than for pyridine betaine. A considerable amount of an impurity with a deep blue color was present, which went into solution with the free betaine when the latter was liberated from the hydrochloride. The impurity, like the betaine, was soluble in water and alcohol and insoluble in ether; but it proved to be soluble in acetone, or in a mixture of 90% acetone and 10% alcohol, in which the betaine is insoluble, and the two substances were separated by this means. The purified betaine melted at 124–126° (in agreement with Willstätter and Kahn).

Dimethylanthranilic Acid Methyl Ester [ortho $(CH_3)_2N\text{-}C_6H_4COOCH_3$].—To a solution of 340 g. of anthranilic acid (2.5 moles) in 500 cc. of water containing just enough potassium hydroxide to allow a faintly alkaline solution, 1600 g. (12.7 moles) of dimethyl sulfate is added, with stirring, during two and a half hours; 40% potassium hydroxide is added simultaneously at such a rate as to maintain a faintly alkaline reaction. The temperature is held at about 10° during the addition of the first half; it is then gradually raised to 65°. The resulting oily ester is taken up in ether, dried over calcium chloride, and distilled under reduced pressure. The yield was 150 g. (33% of the theoretical amount); b. p. 139° at 16 mm.

Dr. W. D. Peterson, who developed this method in Professor E. P. Kohler's laboratory, obtained in one preparation a yield as high as 75%, using smaller quantities of material than those above given.

Dimethylanthranilic acid [ortho$(CH_3)_2NC_6H_4COOH$] was obtained almost quantitatively by heating its methyl ester with excess of water for eight hours in a reflux condenser.[5] It was purified by recrystallization from ether and melted at 68°.

Ortho Benz Betaine [$(CH_3)_3N^+C_6H_4COO^-$].—Methyl iodide was added to dimethylanthranilic acid methyl ester (1.5 moles of iodide per mole of ester) and the solution left to stand. The iodide of the methyl ester of ortho benz betaine slowly crystallized out. The yield after one week in the cold was 15–20%, in agreement with Willstätter and Kahn. A large additional yield was obtained when the reacting mixture was allowed to stand for several weeks longer.

The iodide of the betaine ester, after crystallization from alcohol, was treated with silver oxide, whereby the free betaine is liberated. Subsequent purification as described above; m. p. 223–224°.

Meta Benz Betaine.—The iodide was prepared from meta aminobenzoic acid and three moles of methyl iodide, following the method of Griess[6] as modified by Cumming,[7] and the free betaine liberated and purified as described above (m. p. 236–238°).

The betaine was also prepared by the action of dimethyl sulfate (4 moles) on *m*-aminobenzoic acid. When the reaction was complete, most of the salt in the system was precipitated by addition of alcohol; the filtrate was concentrated *in vacuo* until nearly all alcohol was removed; the betaine was then precipitated as the triiodide by addition of iodine dissolved in hydriodic acid. The triiodide was converted to the iodide, as described by Willstätter and Kahn for the triiodide of *p*-benz betaine.

Para Benz Betaine.[4,8]—The iodide was prepared from para aminobenzoic acid and methyl iodide, by essentially the same procedure as the meta compound. The melting point of the free betaine was 252–255°.

Methods and Experimental Results

Dielectric Constant.—The dielectric constant of solutions of the betaines and related compounds in various solvents was determined by a resonance method previously developed.[9] Measurements were made at 25°, at a variety of wave lengths between 3 and 26 meters. In no case was there any indication of variation of dielectric constant with frequency in this range. The settings were least sharp, indicating relatively greatest absorption, for solutions in alcohol and solvents containing a large proportion of alcohol. In all cases, excepting a few involving solvents of relatively low dielectric constant, the dielectric constant was found to be strictly linear in the concentration of solute in moles per liter, and the experimental results can be expressed in terms of a first degree equation involving the dielectric constant of the solvent ϵ_0 and the slope of the dielectric constant concentration curve δ. In the small number of cases where this was not so the deviation from linearity was generally slight and the limiting value of δ for infinite dilution could be estimated from a graph with considerable accuracy. In Table I the data in regard to dielectric constant are given on this basis in terms of ϵ_0 and δ. Cases in which the curves were not linear are marked with an asterisk and the limiting value of δ is followed by the value, enclosed in brackets, reckoned from the difference between the dielectric constant of the most concentrated solution and that of the solvent. In the right-hand column of Table I is given in each case the range of concentration studied. The contents of this table are shown graphically in Fig. 1.

Several of these substances have also been studied by Devoto, although only in aqueous

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[4] Reitzenstein, *Ann.*, **326**, 326 (1903); Willstätter and Kahn, *Ber.*, **37**, 401 (1904).

[5] Willstätter and Kahn, *ibid.*, **37**, 401 (1904).

[6] Griess, *ibid.*, **6**, 585 (1873).

[7] Cumming, *Proc. Roy. Soc.* (London), **78A**, 138 (1906–1907).

[8] Michael and Wing, *Am. Chem. J.*, **7**, 195 (1885).

[9] Wyman, *Phys. Rev.*, **35**, 623 (1930).

TABLE I

Substance	Solvent	ϵ_0	δ	Range of concentration
N-Dimethylanthranilic acid methyl ester	Benzene	2.275	+ 0.570 ± 0.002	0.18–0.39
	53.1% Benzene–ethanol	11.49	− 1.2 ± 0.1	.14–0.29
	Ethanol	24.50	− 4.21 ± 0.04	.15–0.25
	49.17% Ethanol–water	49.37	− 9.4 ± 0.1	.21–0.33
N-Dimethylanthranilic acid	*Benzene	2.273	+ 5.1 ± 0.1(5.55 ± 0.05)	.00038–0.43
	71.1% Benzene–ethanol	6.868	+10.7 ± 0.1	.12–0.17
	51.0% Benzene–ethanol	12.05	+12.1 ± 0.5	.049–0.12
	28.66% Benzene–ethanol	17.91	+11.2 ± 0.3	.026–0.16
	Ethanol	24.36	+10.3 ± 0.2	.041–0.23
	83.25% Ethanol–water	31.41	+14.9 ± 0.3	.080–0.12
	73.0% Ethanol–water	35.96	+16.2 ± 0.2	.14
	65.37% Ethanol–water	40.09	+16.5 ± 0.6	.055–0.13
	49.08% Ethanol–water	49.37	+16.2 ± 0.2	.082–0.16
	29.94% Ethanol–water	66.05	+13.6 ± 0.8	.048–0.12
	Water	78.54	+12.0 ± 0.3	.045–0.15
Betaine	89.95% Benzene–ethanol	3.205	+ 7.0 ± 0.7	.00089–0.0042
	*79.90% Benzene–ethanol	4.913	+12.5 ± 1.0 (8.9 ± 0.2)	.0016–0.017
	*68.9% Benzene–ethanol	7.427	+22 ± 2 (10.9 ± 0.1)	.0034–0.065
	*50.9% Benzene–ethanol	12.19	+19 ± 2 (13.5 ± 0.2)	.012–0.11
	*27.6% Benzene–ethanol	18.15	+17.3 ± 0.5 (16.0 ± 0.2)	.074–0.17
	*Ethanol	24.42	+19.3 ± 0.3 (17.1 ± 0.3)	.042–0.18
	44.3% Ethanol–water	52.29	+19.5 ± 0.2	.20–0.29
	Water	78.54	+18.2 ± 0.3	.034–0.16
Pyridine betaine	Water	78.54	+18.5 ± 0.2	.11–0.33
Ortho benz betaine	81.48% Benzene–ethanol	4.579	+10.7 ± 0.2	.020–0.046
	72.74% Benzene–ethanol	6.501	+13.1 ± 0.2	.039–0.077
	59.27% Benzene–ethanol	9.90	+17.0 ± 0.2	.054–0.11
	34.86% Benzene–ethanol	16.33	+20.3 ± 0.4	.054–0.12
	Ethanol	24.26	+22.4 ± 0.2	.17–0.40
	73.71% Ethanol–water	35.70	+23.6 ± 0.2	.12–0.24
	52.34% Ethanol–water	47.37	+23.2 ± 0.4	.10–0.22
	31.70% Ethanol–water	60.43	+21.3 ± 0.2	.082–0.20
	Water	78.54	+18.7 ± 0.2	.055–0.56
Meta benz betaine	90.11% Benzene–ethanol	3.191	+10.1 ± 0.5	.0015–0.0037
	83.2% Benzene–ethanol	4.234	+12.3 ± 1.0	.0065–0.017
	75.70% Benzene–ethanol	5.825	+24.2 ± 0.8	.012–0.048
	61.78% Benzene–ethanol	9.27	+40.5 ± 0.4	.042–0.073
	48.59% Benzene–ethanol	12.74	+47.9 ± 0.4	.048–0.089
	25.45% Benzene–ethanol	18.63	+54.0 ± 0.5	.057–0.30
	Ethanol	24.42	+52.3 ± 0.5	.062–0.094
	42.78% Ethanol–water	53.50	+57.2 ± 0.5	.062–0.089
	Water	78.54	+48.4 ± 0.4	.032–0.084
Para benz betaine	19.90% Benzene–ethanol	19.97	+83.4 ± 4.0	.00078–0.0031
	*Ethanol	24.41	+77.4 ± 2.5 (70.0 ± 0.7)	.0043–0.019
	67.80% Ethanol–water	38.71	+76.5 ± 0.7	.0054–0.023
	43.37% Ethanol–water	53.21	+76.1 ± 0.7	.021–0.039
	Water	78.54	+72.4 ± 0.7	.011–0.043

solution, and his δ values, which differ somewhat from ours, may be given for comparison: betaine, +25[10]; N-dimethylanthranilic acid, +16.7[11]; *o*-benz betaine, +20;[11] *m*-benz betaine, +58;[11] *p*-benz betaine, +68.[11]

Optical Polarizations

In the case of N-dimethylanthranilic acid and its methyl ester, values of the optical polarization were determined from measurements of the refractive index for sodium light made with a Pulfrich Zeiss refractometer. The index of refraction of the pure ester at 25° was found to be 1.55743 and the density was 1.0950. This gives a polarization of 52.69 cc. The polarization of the ester was also calculated from the index of refraction at 25° of a 0.3867 molar solution in

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[10] Devoto, *Gazz. chim. ital.*, **64**, 76 (1934).

[11] Devoto and Ardissone, *ibid.*, **64**, 371 (1934).

benzene and the value obtained was 52.3 cc.

The index of refraction of the pure acid, which melts at 68°, could not well be measured; the optical polarization was therefore calculated from measurements of the refractive index at 25° of aqueous solutions at three concentrations with the following results: 0.1631 molar, 45.9 cc.; 0.1295 molar, 46.4 cc.; 0.0925 molar, 45.6 cc. We may accept 45.9 cc. as a value correct to at least 1%.

Total Polarizations and Electric Moments

In the case of N-dimethylanthranilic acid and its ester it is possible on the basis of the foregoing data and that on the densities given in the following section to calculate the polarizations and electric moments in benzene. The results, extrapolated to infinite dilution, are as follows: for the acid, 879 cc. for the polarization and 6.31×10^{-18} e. s. u. for the moment; for the ester, 140 cc. for the polarization and 2.05×10^{-18} e. s. u. for the moment.

Densities and Apparent Molal Volumes

The density of N-dimethylanthranilic acid methyl ester, measured with a pycnometer at 25°, was found to be 1.0950. The densities of the solid *o*-, *m*-, and *p*-benz betaines were determined to an accuracy of about 0.2% by flotation in benzene–chloroform mixtures, in which they are insoluble, with the following results: *o*-benz betaine, 1.290; *m*-benz betaine, 1.299; *p*-benz betaine, 1.261.

The apparent molal volumes of the various substances studied were calculated in the usual way from the density of the solutions, together with the density of the solvents, measured with a pycnometer. Each substance was measured at two or three concentrations in each solvent studied (concentration of solute 1 to 4% by weight, generally from 2 to 3% by weight) and the apparent molal volumes listed in Table II are the averages of these individual determinations. There was no evidence of any significant change with concentration. The apparent molal volumes in water are probably reliable to within 1 cc. and the others to within 2 cc., except in the very volatile alcohol ether mixtures, where the error may be 4 or 5 cc.

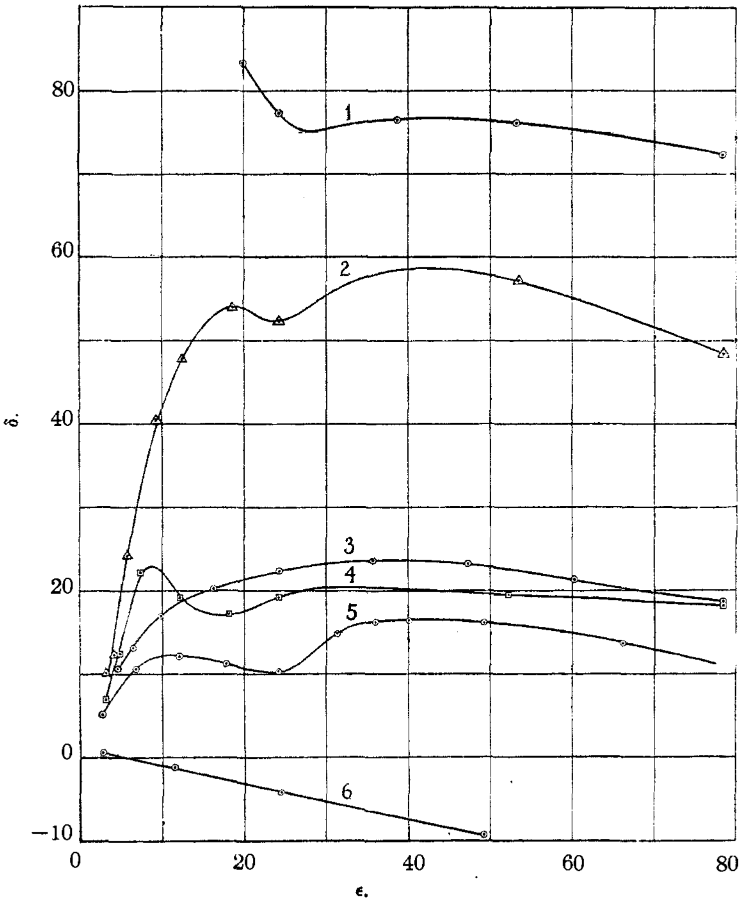

Fig. 1.—Dielectric increments in relation to dielectric constant of solvent: 1, *p*-benz betaine; 2, *m*-benz betaine; 3, *o*-benz betaine; 4, glycine betaine; 5, N-dimethylanthranilic acid; 6, N-dimethylanthranilic acid methyl ester.

Dissociation Constants of N-Dimethylanthranilic Acid and its Methyl Ester.—The dissociation constants were determined at 25° with the hydrogen electrode, using a bubbling electrode of the Simms type.[12] Before titration dimethylanthranilic acid methyl ester was converted into its hydrochloride (m. p. 145–146°, after recrystallization) which is readily soluble in water, and the hydrochloride was titrated with sodium hydroxide. The following values of the logarithmic dissociation constants (pK') were obtained (pK_1' and pK_2' refer to dimethylanthranilic acid, pK_E' to its methyl ester; concentration of substances titrated was 0.04 molar).

The acidity of the solution in 90% ethanol was

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[12] For details of method and calculation of pK' see Edsall and Blanchard, THIS JOURNAL, **55**, 2337 (1933).

TABLE II

APPARENT MOLAL VOLUMES (CC.) IN VARIOUS SOLVENTS AT 25°

		Apparent molal volume						
Solvent	Dielectric constant	Betaine	Dimethyl phenyl betaine	Ortho benz betaine	Meta benz betaine	Para benz betaine	Dimethyl-anthranilic acid
Water	78.54	97.7	146.8	146.5	145	141.3	134.6
70% Water–30% alcohol	60					135	
50% Water–50% alcohol	47					133	134
25% Water–75% alcohol	34				133	130	
Absolute ethyl alcohol	24.3	91.9	133	133	124	119	132
70% Alcohol–30% ether	17.2	93.0	122	124			
55% Alcohol–45% ether	13.7			121			
50% Alcohol–50% benzene	12.5	89.0	137	134			
30% Alcohol–70% benzene	7.0		131	132			
Benzene	2.275						137.2

Dimethylanthranilic acid methyl ester: apparent molal volume in alcohol 159.0 cc.; in benzene 159.6 cc.

TABLE III

Solvent	pK_1'	pK_2'	pK_E'
Water	1.4	8.42	5.55
90% Ethanol		8.15	2.4

so great that pK_1' could not be exactly determined. It probably lies between 1 and 2. From the earlier measurements of Cumming[13] (in aqueous solution at 25°) we calculate pK_1' as 1.36, pK_2' as 8.64, and pK_E' as 3.70. This last value diverges greatly from our own. We believe our value to be the more reliable of the two, as it is based on seven different sets of e. m. f. measurements, in which the ratio of ester to ester hydrochloride was varied from 7:1 to 1:7. The values of pK' calculated from these measurements all lay within 0.06 of the value given in Table III. On the other hand Cumming (who employed a catalytic method) obtained shifting values which he himself regarded as not altogether reliable.

Discussion

Dielectric Constant.—In the case of polar solutions the interpretation of the dielectric constant offers a very difficult problem, at the present time lacking a theoretical solution from general principles. Certainly the Clausius–Mosotti relation is inapplicable and indeed yields results probably many times too small for the polarizations. On the other hand consideration of a variety of experimental results in the light of our knowledge of molecular structure suggests that the dielectric constant itself is in a general way proportional to the volume polarization. An attempted rationalization of the situation has been given by one of us[14] which leads to the result that in the case of polar liquids the Clausius–Mosotti relation for the volume polarization p in terms of the dielectric constant ϵ is to be replaced by the expression

$$p = (\epsilon - 1)/3 \qquad (1)$$

This expression would afford a ready explanation of the additive character of the dielectric constant so apparent in the case of polar solutions and of the close correlation between δ, the dielectric increment per mole of solute, and the polarization of the solute in substances for which there is a basis for estimating the polarization, notably the aliphatic amino acids which exist as zwitterions. Hitherto, however, there has always been a considerable degree of uncertainty in such estimates of the polarizations arising principally from the possibility of free rotation of the carbon atoms in the aliphatic chains, involving a change in the distance between the oppositely charged groups of the zwitterionic molecule.

In the benz betaines the groups bearing the positive and negative charges are attached to the relatively rigid benzene ring, and the separation of the charges, and consequently the moments and polarizations, can be reckoned with considerably less uncertainty. We may in fact calculate the separation of the charged groups in *o*-, *m*- and *p*-benz betaine, assuming the molecules to be undistorted, quite simply from models based on data from recent x-ray and electron diffraction studies.[15] In each the positive charge of the zwitterion is assumed to be located at the center of the nitrogen atom, and the negative charge midway between the two oxygens of the carboxyl group, owing to the resonance involving these. The locus of the carboxyl carbon atom is taken to

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[13] Cumming, *Proc. Roy. Soc.* (London), **78A**, 138 (1906–1907).

[14] Wyman, THIS JOURNAL, **56**, 536 (1934). See also Greenstein, Wyman and Cohn, *ibid.*, **57**, 637 (1935).

[15] Pauling and Brockway, *Proc. Nat. Acad. Sci.*, **20**, 336 (1934), and *J. Chem. Physics*, **2**, 867 (1934); Hengstenberg and Lenel, *Z. Krist.*, **77**, 424 (1931); Pauling and Sherman, *Proc. Nat. Acad. Sci.*, **20**, 340 (1934).

be on the straight line passing through the corresponding carbon of the benzene ring and the center of the hexagon, the ring itself being regarded as plane; the same is assumed also for the nitrogen atom. The various interatomic distances (in Ångströms) are taken as follows: carbon to carbon in the ring, 1.39; carboxyl carbon to adjoining carbon in the ring, 1.54; nitrogen to adjoining carbon in the ring, 1.4; oxygen to carboxyl carbon, 1.29. The angle subtended by the two oxygens at the carboxyl carbon atom is taken as 125°. This gives $1.29 \cos (125°/2) = 0.6$ Å. for the distance from this carbon atom to the locus of the negative charge, and this distance, owing to symmetry, is in a direction radial to the ring. The dipole distances (*i. e.*, distances between the positive and negative charges of the zwitterions) calculated from these models are 3.23, 5.49, and 6.36 Å. for *o*-, *m*- and *p*-benz betaine, respectively.

In the case of *o*-benz betaine the distance calculated in this way would seem to be too small in view of the size of the carboxyl group and of the methyl groups attached to the nitrogen atom. If we take the carbon to hydrogen distance as 1.07, the radius of the hydrogen atom as half the hydrogen to hydrogen distance or 0.75/2, the distance from the nitrogen to the carbons of the methyl groups as 1.4,[16] and assume the tetrahedral arrangement for the four valences of the nitrogen atom, we may estimate the minimum dipole distance as in the neighborhood of 3.9 Å. This estimate[17] is based on the assumption that there is free rotation of both the carboxyl carbon and nitrogen atoms about the valences joining them with corresponding carbon atoms of the ring. It would seem, therefore, that the ortho compound must be somewhat deformed and exist in a state of strain involving a certain amount of potential energy.[18] This would be expected to give rise to an effect of "steric hindrance" to the introduction of the methyl groups into this molecule, and corresponds to the fact that it is indeed much more difficult to effect the complete methylation of the amino group in anthranilic acid than in *m*- and *p*-aminobenzoic acids.[19]

If we adopt for the dipole distances of the *o*-, *m*- and *p*-benz betaines the values 3.9, 5.49, and 6.36, respectively, the corresponding moments are 18.6, 26.2 and 30.4×10^{-18} e. s. u. The same moments calculated from the data on the dielectric constant in water by means of Eq. (1), taking the optical polarization in each case as 52.7 (*i. e.*, the value experimentally determined for the uncharged isomer N-dimethylanthranilic acid methyl ester) are 21.9, 31.0 and 36.4. The values are 18, 18, and 20% too high, respectively. It would seem therefore that the moments, or polarizations, calculated from Eq. 1, though probably somewhat too high, are closely proportional to the true values as far as we can estimate them.

The behavior of the benz betaines as we pass to solvents of lower dielectric constant consisting of alcohol–water mixtures, alcohol, and alcohol–benzene mixtures is apparent from Fig. 1. Unfortunately it is impossible to dissolve these substances in pure benzene itself. If we make use of Eq. (1) to calculate the polarizations from these data, we obtain the results shown graphically in Fig. 2. The polarizations of course follow the δ values quite closely and are fairly constant down to a dielectric constant of about 20. It is impossible to extend the measurements on the para compound below this point owing to its insolubility, but the polarizations of the ortho and meta compounds fall rapidly from here on with diminishing dielectric constant of the solvent. Indeed it is extraordinary that the δ values for both these compounds (and of glycine betaine) seem to be converging toward the value 5.1 actually observed in the case of dimethylanthranilic acid in benzene.

The results obtained for ortho and meta benz betaine in the solvents of lowest dielectric constant actually studied, are given in Table IV. Here we have tabulated, in addition to the dielectric constant of the solvent and the δ value, the molal polarizations (P) and the corresponding moments (μ), calculated first from the Clausius–Mosotti equation at infinite dilution and then from Equation 1. In these calculations the apparent molal volumes are taken to be the same as in alcohol, namely, 133 cc. and 124 cc. for the ortho and meta compounds, respectively (they contribute at most less than 10% to the calculated polarizations), and the optical polarizations are again taken as 52.7 cc. For comparison, the results of similar calculations for betaine are included, in which the volume is taken as 91.9 cc. and the optical polarization as 35 cc.

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[16] Mark, *Z. Elektrochem.*, **40**, 413 (1934).

[17] This would involve a 17° displacement of the valence bonds joining the carboxyl carbon and nitrogen atoms to the ring.

[18] See Weissberger, Sängewald and Hampson, *Trans. Faraday Soc.*, 887 (1934), and discussion by de Laszlo, p. 892, who states: "In the case of 1-8-diiodonaphthalene the I atoms are spread out at 18° from the vertical and in ortho diiodobenzene 4° from the direction joining the C atom to the center of the hexagon."

[19] Willstätter and Kahn, *Ber.*, **37**, 412 (1904).

TABLE IV

Compound	ε (Solvent)	δ	P, cc., Clausius–Mosotti	P, cc., Eq. 1	$\mu \times 10^{18}$ Clausius–Mosotti	$\mu \times 10^{1}$ Eq. 1
Ortho B B	4.579	10.7	813	3725	6.05	13.2
Meta B B	3.191	10.1	1177	3457	7.36	12.8
Betaine	3.205	7.0	814	2401	6.11	10.7

It should be noted that in this range the values calculated on any basis are changing rapidly with the dielectric constant of the solvent. Nevertheless, however, we interpret the dielectric constant in this doubtful region, it appears clear that the moments of the betaines in these solvents of very low dielectric constant are decidedly lower than in water. It might be supposed that this effect is due to association of dipoles. Hooper and Kraus[20] have recently shown for certain highly polar molecules dissolved in benzene that the δ value and molal polarization decrease rapidly with increasing concentration at concentrations in the neighborhood of 0.001 molar. Hence the apparent moments deduced from studies at concentrations greater than this are much lower than the true moments determined at very great dilutions. Kraus interprets these phenomena as being due to association of dipoles, with decrease in apparent moment, at the higher concentrations. It seems improbable that our data on the betaines can be explained on this basis. In N-dimethylanthranilic acid in benzene there is actually a slight increase of δ from the value 5.1 observed at the lowest concentration 38 × 10^{-5} to the value 5.5 obtained at a concentration of 0.43; in the case of *p*-benz betaine in 19.9% benzene–ethanol δ is constant in the range 78 × 10^{-5} to 31 × 10^{-4} molar. Only in the case of betaine (N-trimethylglycine) in certain solvents is there anything resembling the effect described by Hooper and Kraus, and for this compound we have based our calculations on the limiting value of δ for the lowest concentrations.

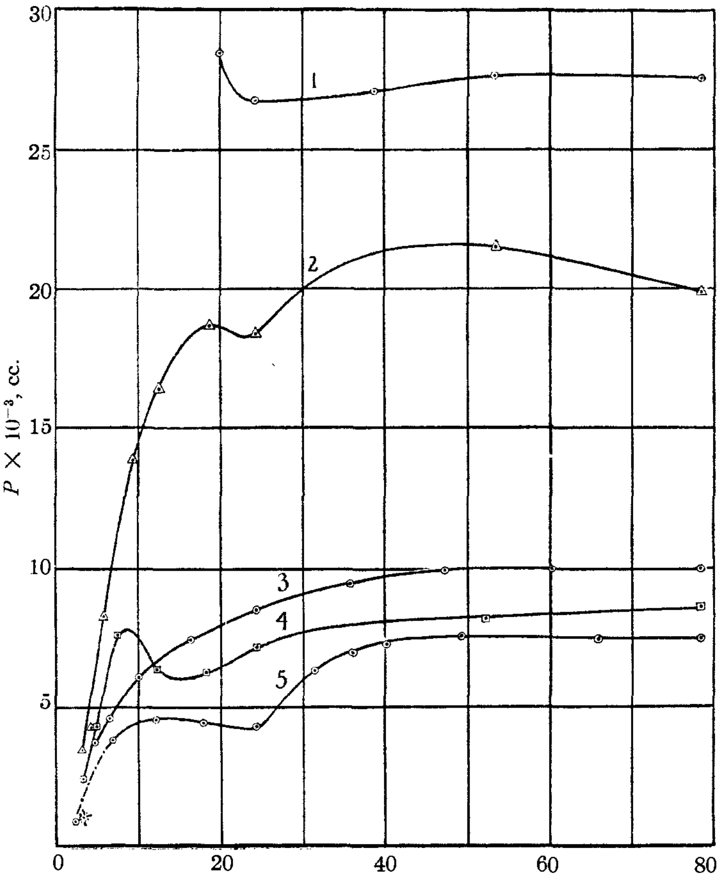

Fig. 2.—Polarizations calculated from Eq. 1, in relation to dielectric constant of solvent. The point marked by an asterisk, corresponding to pure benzene, is calculated by the Clausius-Mosotti relation: 1, *p*-benz betaine; 2, *m*-benz betaine; 3, *o*-benz betaine; 4, glycine betaine; 5, N-dimethylanthranilic acid.

If we accept the reality of the great reduction in moment indicated by the results in solvents of low dielectric constant and reject an explanation based on association, it remains to account for this in terms of a change in the individual molecules. The most natural explanation is probably in terms of a distortion of the valence bonds uniting the carboxyl carbon and the nitrogen atoms to the corresponding carbons of the ring. Such a distortion, involving a decrease in the dipole distance easily reckoned on the basis of simple geometrical considerations, would lead to a decrease of electrostatic energy inversely proportional to the dielectric constant of the solvent. If we regard this energy as that arising from two opposite elementary charges (±*e*) uniformly distributed over two equal spheres of radius *b* whose centers are separated by a distance *R*, we may apply the formula given by Scatchard[21] for the electrostatic energy *E* per mole.

$$E = \frac{Ne^2}{\epsilon}\left(\frac{1}{b} - \frac{1}{R}\right)$$

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[20] Hooper and Kraus, THIS JOURNAL, **56**, 2265 (1934).

[21] See Cohn, McMeekin, Edsall and Weare, *ibid.*, **56**, 2270 (1934).

In this expression ϵ denotes the dielectric constant of the medium and N is Avogadro's number. On the basis of this formula and the geometry of the molecule we can calculate the energy change $E_0 - E$ associated with a given angular distortion ω of both the valences uniting the nitrogen and carboxyl carbon atoms to the ring. In the ortho and meta compounds the distortion is assumed to take place in the plane of the ring, which makes it most effective; in the case of the para compound it makes no difference in what plane the bending occurs. The results of the calculation, expressed in calories per mole, for a medium of dielectric constant unity, are given in Fig. 3. This figure shows how much greater must be the tendency for a distortion of the valence bonds in the ortho compound than in the two others and how relatively small is the tendency in para benz betaine. The question then arises how such a decrease of electrostatic energy compares with the corresponding energy increase due to valence distortion itself. Stuart[22] has estimated that the distortion of a valence bond by 10° involves an increase of potential energy of the order of 1000 to 2000 calories per mole. Although we do not know how this varies with the angle, nevertheless it is clear that in solvents of low dielectric constant there will probably be a considerable distortion and corresponding reduction of moment of the ortho and meta molecules. In water, calculation shows that such an effect would be relatively insignificant. It may well be that the greater dipole moment and the smaller tendency for this to reduce itself in less polar solvents accounts for the very much smaller solubility of *p*-benz betaine in solvents of low dielectric constant. It would appear, however, at least in the case of the ortho compound, that this deformation would demand an approach of the charged groups to a distance actually less than that consistent with the bulk of these groups, discussed above. In regard to this, it is conceivable that when the forces become very great the interfering methyl groups are actually forced aside or that the carboxyl carbon atom is prevented from rotating, or both, with the result that the locus of the negative charge is brought into close proximity to the positively charged nitrogen atom; to this effect might be added the result of an actual polarization of the molecule under the influence of the strong field arising from the zwitterionic charges of the molecule itself in a medium of low dielectric constant.

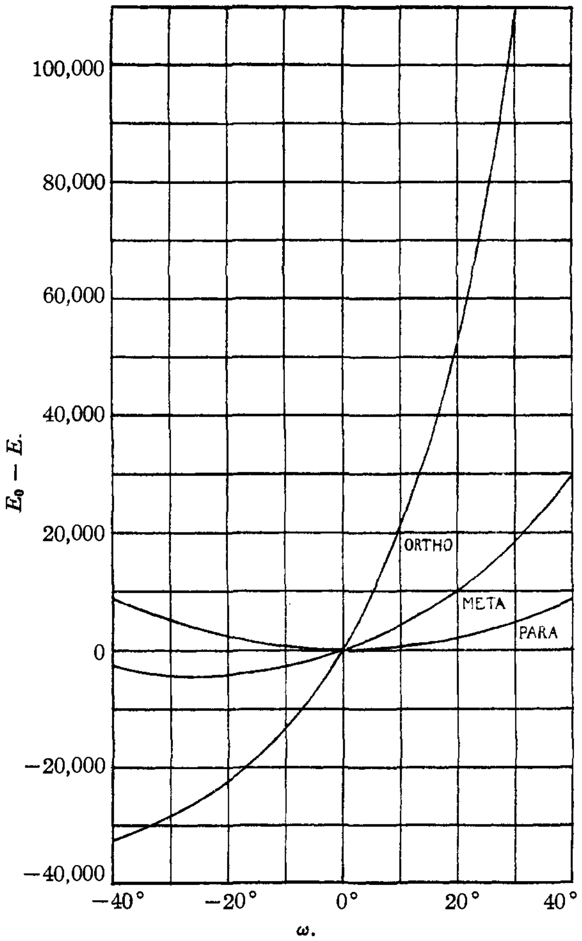

Fig. 3.—Energy change in relation to angular distortion, ω, of valence bonds for the benz betaines. Negative values of ω correspond to an increase of distance between the charges.

Of course the possibility remains of an intramolecular rearrangement of the betaines into their uncharged isomers, with a great resultant decrease in moment. At very high temperatures such a transformation does occur, as Willstätter[23] has shown. Under the conditions of our experiments, however, there has never been any sign of this. The uncharged isomers (*i. e.*, the methyl esters of the dimethylated aminobenzoic acids) are low melting substances, readily soluble in ether and benzene. When the betaines, dissolved in the solvents of lowest dielectric constant studied, were treated with ether, they were quantitatively precipitated, and no trace of ether-soluble material could be found. Furthermore,

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(22) Stuart, *Phys. Rev.*, **38**, 1372 (1931).

(23) Willstätter, *Ber.*, **35**, 584 (1902); Willstätter and Kahn, *ibid.*, **37**, 404 (1904).

the betaine so isolated showed no change of melting point from that of the substance as originally prepared.

For comparison with the betaines, we have studied the properties of one of these uncharged substances, namely, dimethylanthranilic acid methyl ester. This substance, dissolved in benzene, gives a δ value of +0.570 and has a moment of 2.05×10^{-18} e. s. u. In solvents of higher dielectric constant the δ value becomes negative. The results are included in Fig. 1 and show the striking contrast in behavior between this moderately polar molecule and the zwitterionic betaines.

The behavior of the ester is in marked contrast with that of N-dimethylanthranilic acid itself. This substance shows throughout a high δ value characteristic of zwitterionic structure, although in details it differs decidedly from glycine betaine, pyridine betaine, and ortho benz betaine in regard to δ. In pure benzene its moment is 6.31×10^{-18} e. s. u. or more than three times that of the ester. The detailed character of the variation both of δ and of the polarization (calculated from Eq. 1) with the dielectric constant of the solvent may be seen from Figs. 1 and 2. It would appear therefore that N-dimethylanthranilic acid remains largely in the zwitterion form even in pure benzene.

The study of its dissociation constants and that of its ester (Table III) further supports the view that this substance is a zwitterion, at least in water and in alcohol–water mixtures. According to the relations developed by Ebert[24] the ratio K_z of zwitterions to uncharged molecules in a solution of a simple ampholyte is given by the equation

$$K_z = (K_1/K_E) - 1$$

where K_1 is the first dissociation constant of the acid and K_E that of its ester, both being expressed as acid dissociation constants. On the basis of the data given in Table III this yields a value of approximately 12,000 for K_z in water and about 10 in 90% alcohol. There seems no doubt whatever therefore that in these solvents dimethylanthranilic acid exists predominantly in the zwitterion form. That a large proportion of zwitterions should remain in pure benzene is certainly surprising on the basis of our general knowledge of dissociation constants as a function of the dielectric constant of the solvent.[2]

It may be noted that N-dimethylanthranilic acid shows very unusual properties in other respects also.[26] Unlike most zwitterions it is very soluble not only in water but also in alcohol, acetone and benzene, and quite soluble even in ether and carbon tetrachloride. It melts at 70° to a clear liquid which solidifies on cooling and the solid so obtained shows all the properties of the original substance. In contrast with this, most zwitterionic acids melt between 200 and 300°, and decompose on melting. Likewise this compound shows markedly different properties from the other ortho, meta and para aminobenzoic acids, whether the nitrogen is unmethylated, monomethylated or dimethylated. These melt at temperatures from 140 to 180°; they are sparingly soluble in water, appreciably more soluble in alcohol or benzene; and their dissociation constants and those of their esters indicate values of K_z in water which are not far from unity.[27] Devoto[28] has indeed reported a δ value of about 40 for meta aminobenzoic acid in water, while that for dimethylanthranilic acid is only 12,[29] but there are no essential inconsistencies here since the charged zwitterions in the meta compound possess higher dipole moments than those in an ortho compound and hence even though they do not predominate so completely over the uncharged molecules they still have a much higher effect on the dielectric constant of the solvent.

It should be noted that the δ value and the polarization of dimethylanthranilic acid calculated from Eq. 1 are lower in all solvents studied than for ortho benz betaine (see Figs. 1 and 2). It seems not improbable that this is because of the substitution of a hydrogen atom for one of the methyl groups, which permits the positive and negative radicals to pack together more closely and results in a decrease of dipole moment. Indeed the moment in water calculated from Eq. 1 is 18.9×10^{-18} e. s. u., or about 14% less than that of ortho benz betaine. 3.23 Å., the dipole dis-

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(24) Ebert, *Z. physik. Chem.*, **121**, 385 (1926). See also Edsall and Blanchard, THIS JOURNAL, **55**, 2337 (1933).

(25) Professor Linus Pauling has suggested to us that the hydrogen atom of the carboxyl group in dimethylanthranilic acid may form a hydrogen bond with the nitrogen of the methylated amino group. Such a structure might account for the high moment and other peculiar properties of this substance.

(26) For previous discussions of this substance, see Cumming, *Proc. Roy. Soc.* (London), **78A**, 138 (1906–1907), and Devoto, *Gazz. chim. ital.*, **64**, 371 (1934).

(27) Ebert, *Z. physik. Chem.*, **121**, 385 (1926).

(28) Devoto, *Gazz. chim. ital.*, **63**, 247 (1933).

(29) Devoto and Ardissone [*Gazz. chim. ital.*, **64**, 371 (1934)] give the higher value, 16.7.

tance calculated from the model of the molecule in the undistorted condition is 17% less than 3.9, the dipole distance of the more bulky benz betaine. In any case the very remarkable properties of dimethylanthranilic acid clearly demand further study for they are unparalleled among all the ampholytes known to us.

Apparent Molal Volumes and Electrostriction of the Solvent

Betaines, possessing charged groups, produce electrostriction of the solvent, similar to that which has been shown to occur in solutions of amino acids.[30] The magnitude of the effect may be estimated by a comparison with similar uncharged substances, and with the aid of Traube's atomic volumes. In Table V are listed the apparent molal volumes in water calculated from Traube's theory for the substances studied, the observed volumes, and the estimated electrostriction, which is given by the difference between the observed and calculated volumes. Certain typical amino acids are also listed for comparison. In the last column is tabulated the value ΔE, which represents the difference in electrostriction between a given betaine and a corresponding amino acid (ortho, meta and para benz betaines are considered to correspond approximately to α, β and γ amino acids, respectively).

TABLE V

BETAINES IN WATER

Substance	Apparent molal vol., cc. Calcd.	Obs.	Electrostriction, cc./mole	ΔE
Betaine	105.9	97.7	8.2	5.1
Dimethyl phenyl betaine	151.4	146.8	4.6	8.7
Ortho benz betaine	151.4	146.5	4.9	8.4
Meta benz betaine	151.4	145.0	6.4	8.0
Para benz betaine	151.4	141.3	10.1	5.8
Pyridine betaine	108.8	99.6	9.2	4.1
Dimethylanthranilic acid	135.2	134.6	0.6	12.7
Glycine	57.0	43.5	13.5	..
α-Aminovaleric acid	105.9	92.7	13.2	..
β-Alanine	73.3	58.9	14.4	..
γ-Aminovaleric acid	105.9	90.0	15.9	..

It is apparent that when hydrogen atoms, surrounding a charged nitrogen, are replaced by the more bulky methyl or phenyl groups, the electrostriction diminishes. In betaine, with three methyl groups, the decrease is 5.1 cc. out of 13.3, an average value for an α-amino acid. Substitution of a phenyl for a methyl group, as in dimethylphenyl glycine, produces a further diminution of 3.6 cc. These results experimentally observed accord closely with what would be expected from the theory of electrostriction produced by ions in solution.[31] The smaller a given ion the more intense will be the electric field in its immediate neighborhood and the greater the orientation and compression effects producing electrostriction of the solvent.

These data suggest an approach to the solution of another problem. It has hitherto been impossible to decide whether most of the electrostriction produced by amino acids is due to the carboxyl or to the amino group since only the effect of the two groups in combination can be observed. In dimethyl phenyl betaine, however, the electrostriction produced is 8.7 cc. less than that characteristic of α amino acids. Almost all this diminution must be due to an effect on the charged nitrogen atom although the electrostriction produced by the carboxylic group may also be slightly diminished by the introduction of the large groups adjacent to it. It seems fair to assume, however, that at least 8.7 cc. of the total electrostriction (13.3 cc.) characteristic of α amino acids is due to the amino group and, therefore, not more than 4.6 cc. to the carboxyl group. Adopting tentatively the same ratio for the two groups when the charges are far apart and the total electrostriction is some 20 cc. per mole, we should assign approximately 13 cc. to the amino and 7 cc. to the carboxyl group. Utilizing the calculations of Vosburgh, Connell and Butler[32] for the relation between electrostriction and ionic radius, we may deduce an apparent radius of 2.25 Å. for the amino and 2.9 Å. for the carboxyl group.

In solvents of lower dielectric constant, the apparent molal volumes of the betaines are invariably smaller than in water. The same is true for salts, as was shown long ago by Carrara and Levi[33] and more recently by the careful and exact measurements of Vosburgh, Connell and Butler.[34] In the betaines the decrease in apparent molal volume is greater the greater the separation of the charged groups. Thus the value for

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(30) Cohn, McMeekin, Edsall and Blanchard, *J. Biol. Chem.*, **100**, Proc. XXVII (1933); THIS JOURNAL, **56**, 784 (1934). Reference may be made to these papers for the details of the calculation of electrostriction values.

(31) See Webb, *ibid.*, **48**, 2589 (1926).

(32) Vosburgh, Connell and Butler, *J. Chem. Soc.*, 933 (1933).

(33) Carrara and Levi, *Gazz. chim. ital.*, [II], **30**, 197 (1900).

(34) Vosburgh, Connell and Butler, *J. Chem. Soc.*, 933 (1933).

ortho benz betaine is 13 cc. per mole lower in absolute alcohol than in water; for para benz betaine, it is 22 cc. lower.

In solvents other than water, the electrostriction of the betaines cannot be calculated directly from Traube's atomic volumes, since the "Co-volume" of Traube varies with the solvent employed in a manner depending largely on the particular substance studied.

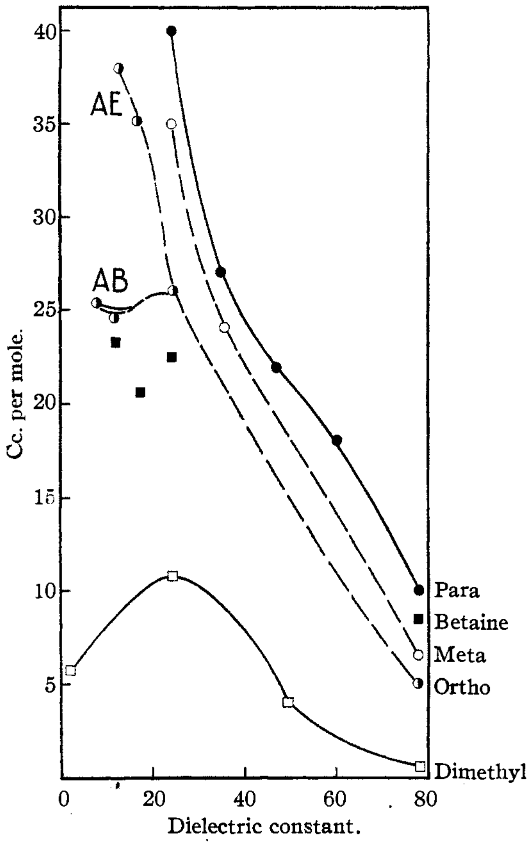

Fig. 4.—Electrostriction of betaines and dimethylanthranilic acid in various solvents: abscissa, dielectric constant of solvent; ordinate, electrostriction in cc. per mole; ◑, *o*-benz betaine; ○, *m*-benz betaine; ●, *p*-benz betaine; ■, betaine; □, dimethylanthranilic acid. The values for dimethylphenyl-betaine (not shown) are almost identical with these for *o*-benz betaine. The branch of the *o*-benz betaine curve marked AE refers to alcohol–ether mixtures; that marked AB, to alcohol–benzene mixtures.

We can, however, estimate the electrostriction directly by comparing a betaine in any given solvent with the isomeric uncharged ester *in the same solvent*. The difference between the two apparent molal volumes gives the contraction of the system due to the reaction $(CH_3)_2NRCOOCH_3 \longrightarrow (CH_3)_3N^+RCOO^-$; *i. e.*, by definition, the electrostriction.

We have taken dimethylanthranilic acid methyl ester as the uncharged isomer for comparison with all the benz betaines and with dimethylphenylglycine.[35] Its apparent molal volume in alcohol and in benzene is shown in Table II. It will be seen that the two volumes are almost identical, and that both are about 8 cc. higher than the value (151.4 cc.) calculated from Traube's theory for water.[36] (The ester is insoluble in water, so that this determination cannot be made directly.) For purposes of interpolation we have assumed the apparent molal volume of the ester in alcohol–water mixtures to vary linearly with the weight fraction of alcohol in the solvent, from 151.4 to 159.0 cc. In other organic solvents the value 159 cc. (identical with that in alcohol and benzene) has been taken.

In the case of betaine (trimethylglycine) we have no data on the uncharged isomer, dimethylglycine methyl ester. We have therefore calculated its volume in water from Traube's theory (see Table V) and have assumed the value in alcohol and other organic solvents to be 8 cc. greater than in water by analogy.

Dimethylanthranilic acid differs from its ester by one CH_2 group, whose contribution to the volume of the molecule is known to be nearly constant and equal to 16.3 cc. per mole in all solvents. To estimate the apparent molal volume of the acid in the uncharged form, therefore, we have subtracted 16.3 cc. from the volume of the ester in the same solvent. The difference between this value and the observed apparent molal volume of the acid yields the electrostriction. The electrostriction of the substances studied is plotted against the dielectric constant of the solvent in Fig. 4.

It may be seen from the figure that the electrostriction produced by the benz betaines is four or five times as great in ethyl alcohol (ϵ = 24.3) as in water (ϵ = 78.5) while that of trimethylglycine is nearly three times as great.

We may compare these experimental results with the effects to be expected theoretically from the calculations of Vosburgh, Connell and Butler for ions. Para benz betaine may be selected for comparison, since in this substance the charged groups are widely separated, and their mutual influence is small. The electrostriction in water is

[35] Traube [*Sammlung Chem. Vorträge*, **4**, 255 (1899) and references there given] has shown that the apparent molal volumes of uncharged ortho, meta and para isomers are identical within 1 or 2 cc.

[36] This is in harmony with the finding of Traube that apparent molal volumes of uncharged compounds are generally 8 to 13 cc. greater in organic solvents than in water.

10 cc. per mole, of which we may tentatively assign 6 cc. to the carboxyl and 4 cc. to the methylated amino group.[37] Groups producing this amount of electrostriction in water should from the tables of the above-named authors in ethanol produce 23 and 18 cc. of electrostriction respectively, or a total of 41 cc. The observed value in ethanol (Fig. 4) is 40 cc. The agreement is far better than we should have any right to expect, considering the approximations involved in the theory itself and in its application to such substances as the betaines.

The results in mixed solvents are more difficult to interpret. It should be noted, however, that the electrostriction produced by ortho benz betaine is markedly greater in alcohol–ether mixtures than in alcohol–benzene mixtures of the same dielectric constant. It seems probable that this difference is correlated with the fact that ether is much more compressible than benzene.

It will be noted from Fig. 4 that the electrostriction of dimethylanthranilic acid is almost zero in water, and in all solvents is much lower than that of any of the betaines. Qualitatively these low values appear to parallel the relatively low δ values of this substance, and suggest that its electrical constitution must differ in some significant respect from that of the betaines.

Summary

1. Dielectric constant increments and apparent molal volumes have been determined for various betaines, and for N-dimethylanthranilic acid and its methyl ester in a variety of solvents ranging from water to benzene.

2. For the relatively rigid benz betaines, approximate dipole moments have been calculated on the basis of known interatomic distances. These have been compared with the values calculated from the observed dielectric increments with the aid of theoretical considerations.

3. In solvents of low dielectric constant, the dielectric increments (and probably the moments) of all the betaines studied fall far below their values in water. This effect appears to be due to actual deformation of the molecules rather than to association.

4. N-Dimethylanthranilic acid appears to exist largely as a zwitterion, not only in water and alcohol, but also in pure benzene, in which its dipole moment is more than three times as great as that of its methyl ester.

5. The electrostriction of the solvent produced by betaines in water is less than that produced by similar amino acids, presumably due to the greater bulk of the positively charged group in the betaines.

6. The electrostriction due to the betaines is much greater in solvents of low dielectric constant than in water, and the magnitude of the effects observed is in good accord with theoretical predictions.

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RECEIVED JUNE 13, 1935

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[37] The results of the ensuing calculation would not be significantly altered if we assigned 5 cc. to each group, or 7 cc. to one group and 3 to the other.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

The "Salting-in" of Hydrogen Peroxide by Electrolytes

BY M. H. GORIN

Non-electrolytes are in general salted out of solution by the addition of electrolytes. The magnitude of this effect varies widely with the nature of the electrolyte and non-electrolyte, and in a few cases even changes in sign. However a search of the literature revealed that sodium chloride and sodium sulfate give relatively large salting-out effects with all non-electrolytes so far investigated, excepting hydrogen peroxide; Livingston[1] found the activity coefficient, $\gamma_{H_2O_2}$, of hydrogen peroxide to be less than unity in aqueous solutions of these salts. This is a "salting-in" effect of sodium chloride and sodium sulfate on hydrogen peroxide. On account of the exceptional nature of this result it was considered worth while to check Livingston's work with sodium chloride, and to study the behavior of hydrogen peroxide with several other electrolytes. The data are presented in Table I and plotted together with Livingston's in Fig. 1.

The experimental method used was the same as Livingston's; the distribution ratio of hydrogen peroxide between the salt solutions and iso-

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[1] Livingston, THIS JOURNAL, **50**, 3207 (1928).