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Substituent Effects. 7.[1] Microscopic Dissociation Constants of 4-Amino- and 4-(Dimethylamino)benzoic Acid

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The thermodynamic microscopic dissociation constants of the title compounds have been determined from the two macroscopic constants K_1 and K_2 and K_A, the carboxylic acid dissociation constant of the cation. The latter were calculated by starting from the experimental value for 4-(trimethylammonio)benzoic acid and using our knowledge of the substituent effects of charged substituents. In water, the zwitterion equilibrium contains 10.5% zwitterion for 4-aminobenzoic acid and 19.4% for 4-(dimethylamino)benzoic acid. In 50% and 75% ethanol the zwitterion content is very low. Extended Hine equations are applied to show the contributions of the several substituent interactions in the individual species, and to predict the percent zwitterion in other acids. Glycine is also discussed. In water, σ-4-NH$_2$ = −0.62 and σ-4-NMe$_2$ = −0.69; the latter value is rather different from that commonly tabulated.

Introduction

The equilibria to be discussed in this paper have been exemplified in Scheme I for 4-aminobenzoic acid (I).[2] There are two composite "overall" or "macroscopic" constants, K_1 and K_2, and five "individual" or "microscopic" constants, K_A, K_B, K_C, K_D, and K_Z, related through the eq 1–3. Of these constants only K_1 and K_2 can be determined

$$K_1 = K_A + K_B \tag{1}$$

$$1/K_2 = 1/K_C + 1/K_D \tag{2}$$

$$K_Z = K_A/K_B = K_D/K_C \tag{3}$$

directly by the usual spectroscopic and/or potentiometric methods. The additional estimation of any one of the five microscopic constants then suffices to calculate the other four through eq 1–3.

As to 4-(dimethylamino)benzoic acid (II) in water, the literature gives only K_1 and K_2 as determined by Johnston.[3] No estimation of the microscopic constants has been reported.

For 4-aminobenzoic acid (I) in water, the literature abounds with determinations of either K_1 or K_2 or both, at various levels of sophistication. Some values that have been corrected for ionic strength effects and for the (small) overlap of K_1 and K_2 and that stem from the same series of experiments are given in Table I.

A calculation of the microscopic constants has been carried out by Robinson and Biggs[4] on the basis of their experimental values of K_1 and K_2, in combination with an estimation of K_B via their experimental values K_E of the dissociation constants of the conjugate acids of the related esters 4-COO(CH$_2$)$_n$H-aniline. The irregular behavior of K_E for n = 1–4 led them to two approaches: (a) equating K_B to K_E of the methyl ester, i.e., pK_B = 2.465; (b) extrapolating the pK_E values for n = 4, 3, and 2 linearly to n = 0, yielding pK_B = 2.528. The second approach, which disregards K_E of the methyl ester, had to be preferred since the first gave the anomalous result $K_C > K_A$.

Quite apart from the uncertainties inherent to the above extrapolation it should be emphasized that K_B is an unfortunate starting point in establishing the (other) microscopic constants in the present systems in which K_B is close to K_1, or, equivalently, in which the percentage zwitterion is low ($K_Z < 1$).[5] A small error in K_B causes an equally small error in pK_D but results in a much larger error in pK_A and pK_C, whereas pK_Z contains the sum of

Scheme I

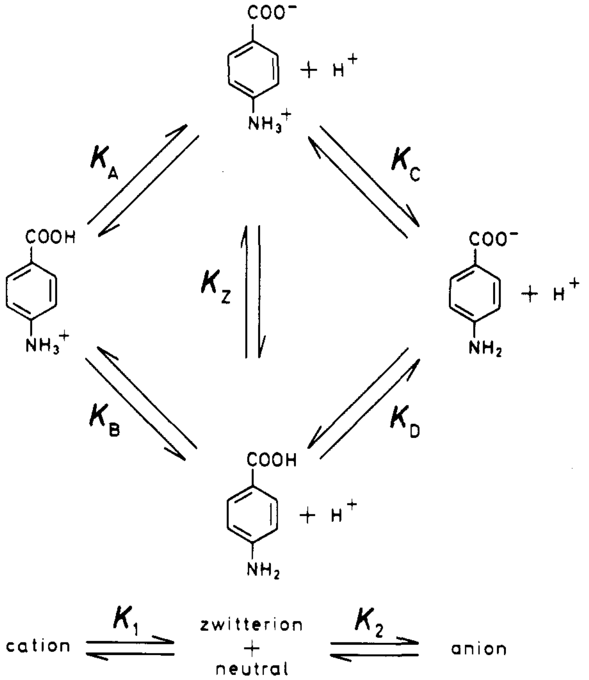

Table I. Some Values of pK_1 and pK_2 of 4-Aminobenzoic Acid, in Water, at 25 °C

ref	pK_1	pK_2
Kilpi et al.[a]	2.38	4.89
Robinson et al.[b]	2.45	4.85
Deviney et al.[c]	2.501	4.874
Lumme[d]	2.413	4.853
Schmid et al.[e]	2.20	4.68
Christensen et al.[f]	2.42	4.84
present work	2.419	4.877

[a] S. Kilpi and P. Harjanne, *Suom. Kemistil. B*, 21, 14 (1948). [b] Reference 4. [c] M. L. Deviney, Jr., R. C. Anderson, and W. A. Felsing, *J. Am. Chem. Soc.*, 79, 2371 (1957). [d] See ref 7. [e] H. Schmid, H. Sofer, and H. Pleschberger, *Monatsh. Chem.*, 98, 353 (1967). [f] See ref 6.

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[1] Part 6: A. J. Hoefnagel, M. A. Hoefnagel, and B. M. Wepster, *J. Org. Chem.*, **43**, 4720 (1978).

[2] See, e.g., E. Q. Adams, *J. Am. Chem. Soc.*, **38**, 1503 (1916); J. T. Edsall and M. H. Blanchard, *ibid.*, **55**, 2337 (1933); E. J. King, "Acid-Base Equilibria", Pergamon Press, Oxford, 1965.

[3] J. Johnston, *Proc. Roy. Soc., Ser. A*, **78**, 82 (1906); also *Z. Phys. Chem. Stoechiom. Verwandtschaftsl.*, **57**, 557 (1907).

[4] R. A. Robinson and A. I. Biggs, *Aust. J. Chem.*, **10**, 128 (1957).

[5] The most direct argument in favor of a small percentage zwitterion would seem to be the spectroscopic one. Thus, for II the plot of ϵ at 335 nm vs. pH shows a maximum value of 7340 at pH 3.87. At this wavelength ϵ = 0 for the cation and the zwitterionic compound 4-NMe$_3^+$-benzoate (a model for the zwitterion), ϵ = 241 for the anion, and ϵ = 10100 for methyl 4-NMe$_2$-benzoate (a model for the neutral acid).

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Table II. Macroscopic and Microscopic Thermodynamic Dissociation Constants of 4-Aminobenzoic Acid and 4-(Dimethylamino)benzoic Acid and Some of Their Esters in Water and 50% and 75% Ethanol-Water, at 25 °C

	pK_1	pK_2	pK_A	pK_B	pK_C	pK_D	pK_Z	K_Z	% zwitterion	pK of esters
				Water						
4-NH_2	2.419 ± 0.009[a]	4.877 ± 0.010[a]	3.40[b]	2.47	3.90	4.83	0.93	0.117	10.5	Me, 2.465,[c] 2.46,[d] 2.47[e]
	2.43[e]	4.88[e]								Et, 2.500,[c] 2.52[e]
4-NMe_2	2.568 ± 0.010[a]	4.996 ± 0.010[a]	3.28[b]	2.66	4.28	4.90	0.62	0.241	19.4	Me, 2.61[d]
				50% Ethanol[f]						
4-NH_2	1.69[g]	6.27[e]	4.26[b]	1.69	3.70	6.27	2.57	0.0027	0.27	Me, 1.52[g]
4-NMe_2	1.30[h]	6.40[e]	4.07[b]	1.30	3.63	6.40	2.77	0.0017	0.17	Me, 1.10[h]
				75% Ethanol[i]						
4-NH_2	1.0	7.19[e]	4.84[b]	1.0[j]	3.4	7.19	3.8	0.00015	0.015	
4-NMe_2	0.4	7.22[e]	4.65[b]	0.4[j]	3.0	7.22	4.3	0.00005	0.005	

[a] Standard deviation. [b] For estimation see text. [c] Reference 4. [d] A. G. N. Boers, unpublished; method of ref 4. [e] Potentiometric measurements; correction overlap K_1 and K_2 included where necessary. [f] 50 volumes of absolute ethanol in 100 volumes of final solution. [g] Based on an unpublished acidity function for $ArNH_3^+$ in 50% ethanol. [h] Based on an unpublished acidity function for $ArNMe_2H^+$ in 50% ethanol. [i] 75 volumes of absolute ethanol in 100 volumes of final solution. [j] Estimated by using σ-4-COOH = 0.7 (cf. Table IV); pK $PhNH_3^+$ 3.78, ρ-$ArNH_3^+$ 4; pK $PhNMe_2H^+$ 3.51, ρ-$ArNMe_2H^+$ 4.5 (cf. Table IV of ref 1).

these errors. Robinson and Biggs[4] were well aware of this[6] and from their tabulation we quote that an increase in pK_B of 0.063 pK units, from 2.465 to 2.528 (see above), led to a decrease of 0.06 in pK_D, of 0.61 in pK_A, of 0.67 in pK_Z, and an increase of 0.61 in pK_C.

Hence, a better starting point for our purposes is the estimation of K_A or K_C which shares the advantage that a small error leads to much smaller errors in K_B and K_D, as will be illustrated below. The best choice is K_A which can be estimated with confidence because: (a) through-resonance is not involved; (b) it can be based on the experimental value for 4-(trimethylammonio)benzoic acid,[1] our knowledge of the substituent effects of charged substituents,[1] and more detailed regularities to be given below. K_C will not be used since there is no good model compound and through-resonance is important.

The results of our approach follow; for reasons of consistency we have also carried out new determinations of the values of K_1 and K_2.

Results and Discussion

Thermodynamic values for K_1 and K_2 of either compound in water were obtained from spectroscopic measurements on (a) a solution in 1 M HCl (cation), (b) a solution in 0.01 M NaOH/0.03 M NaCl (anion), (c) 21 solutions of the same ionic strength ($I = 0.04$) at pH intervals of ca. 0.2 units, the pH being measured potentiometrically.[7] Two wavelengths were chosen for each compound: those of the maximum absorption of the neutral acid and the anion. The data were evaluated by an iterative least-squares method;[8] the values obtained are in Table II. For I very similar values could be obtained by direct potentiometry; II is not sufficiently soluble. Our values for I agree well with those of Kilpi and those of Lumme; the values of Schmid et al. must be in error.

The estimation of pK_A values in water is based on our experimental value for 4-NMe_3^+-benzoic acid, $pK = 3.23$, which, with our value for benzoic acid, $pK = 4.21$, gives the substituent effect of 4-NMe_3^+ as 4.21–3.23 = 0.98 pK units.[1] This value is in good agreement with that reported by Willi,[9] 0.96 units. Furthermore, we apply the equations which were shown to express effects of charged (and uncharged) substituents,[1] the extended Hammett equation (eq 4) and the extended Taft equation (eq 5), where Δ =

$$\Delta = \rho\sigma^L + \delta^B \qquad (4)$$

$$\Delta = \rho_I\sigma_I^L + \delta^B \qquad (5)$$

substituent effect, ρ and ρ_I are reaction constants, σ^L and σ_I^L are substituent constants ($\sigma^L \simeq \sigma^n$ and $\sigma_I^L \simeq \sigma_I$ for dipole substituents), δ^B is the electrostatic Bjerrum term ($\delta^B = 3.1/r$ pK units for charged groups in water at 25 °C where r is the distance from charge to dissociating proton in Å; in our cases $\delta^B = 0.43$). In this treatment, the substituent effect of 4-NMe_3^+ in ArCOOH ($\rho = 1$) appears as $\Delta = 0.98 = 1 \times 0.55 + 0.43$.

Our problem now is to estimate σ^L-NH_3^+ and σ^L-NMe_2H^+, starting from σ^L-$NMe_3^+ = 0.55$. In this connection we first note that experimental data invariably give the order of effects $NMe_3^+ > NMe_2H^+ > NMeH_2^+ > NH_3^+$, in a ratio of $(\Delta - \delta^B)$ values of approximately 100:90:80:70. In detail, the ratios $(\Delta - \delta^B)NH_3^+/(\Delta - \delta^B)NMe_3^+$, in water, are as follows: 0.68 in 4-N^+CH_2-benzoic acid;[1] 0.59 in 4-N^+-anilinium ion;[1] 0.71 in N^+CH_2COOH;[10] 0.72 in $N^+CH_2CH_2COOH$;[11] 0.72 in 4-N^+-bicyclooctanecarboxylic acid (in 50% ethanol).[12] The average of these ratios, 0.684, gives an estimated σ^L-NH_3^+ = 0.684 × 0.55 = 0.38, from which follows for 4-NH_3^+-benzoic acid, in water, $pK_A = 4.21 - 0.38 - 0.43 = 3.40$.

It is appropriate here to illustrate the (in)sensitivity of the other microscopic constants to an error in pK_A. The range of the above ratios, 0.59–0.72, corresponds with ranges in pK_A 3.46–3.38, pK_B 2.460–2.469, pK_C 3.84–3.92, pK_D 4.836–4.827, pK_Z 1.00–0.91 (9.1%–10.9% zwitterion).

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(6) Cf. also A. V. Willi and W. Meier, *Helv. Chim. Acta*, **39**, 318 (1956); J. J. Christensen, D. P. Wrathall, R. M. Izatt, and D. O. Tolman, *J. Phys. Chem.*, **71**, 3001 (1967).

(7) An illustration of the spectra at several pH values can be found in A. M. Liquori and A. Ripamonti, *Gazz. Chim. Ital.*, **85**, 578 (1955); also P. O. Lumme, *Suom. Kemistil. B*, **30**, 176 (1957).

(8) See W. C. Hamilton, "Statistics in Physical Science", Ronald Press, New York, 1964, Chapters 4 and 5.

(9) A. V. Willi, *Z. Phys. Chem. (Frankfurt/Main)*, **26**, 42 (1960).

(10) On the basis of our own measurements on NH_2CH_2COOH, pK = 2.35, $NHMeCH_2COOH$, pK = 2.11, NMe_2CH_2COOH, pK = 1.85, $NMe_3^+CH_2COOH$, pK = 1.72, CH_3COOH, pK = 4.76. These values are in excellent or good agreement with those reported in ref 1 (microfilm edition) by C. A. Grob, A. Kaiser, and T. Schweizer, *Helv. Chim. Acta*, **60**, 391 (1977), and by J. T. Edward, P. G. Farrell, J.-C. Hallé, J. Kirchnerova, R. Schaal, and F. Terrier, *J. Org. Chem.*, **44**, 615 (1979).

(11) C. A. Grob et al., ref 10.

(12) C. F. Wilcox, Jr., and J. S. McIntyre, *J. Org. Chem.*, **30**, 777 (1965).

The uncertainties in pK_B and pK_D are virtually determined by those in pK_1 or pK_2.

As for the ratios $(\Delta - \delta^B)NMe_2H^+/(\Delta - \delta^B)NMe_3^+$, in water, 0.91 is found in 4-N^+CH_2-benzoic acid,[1] 0.87 in 4-N^+-dimethylanilinium ions,[1] and 0.94 in N^+CH_2COOH.[10] The average, 0.907, gives σ^L-$NMe_2H^+ = 0.907 \times 0.55 = 0.50$, from which follows for 4-NMe_2H^+-benzoic acid, in water, $pK_A = 4.21 - 0.50 - 0.43 = 3.28$. In this case the extremes of the ratios, 0.87 and 0.94, correspond with $pK_A = 3.30$–3.26, $pK_B = 2.657$–2.667, $pK_C = 4.26$–4.30, $pK_D = 4.907$–4.897, $pK_Z = 0.64$–0.59 (18.5%–20.3% zwitterion).

Although we consider the above approach to the pK_A values as the best one available, we note that simpler approaches, such as a comparison of Δ values instead of $(\Delta - \delta^B)$ values, give largely the same results. The reason for this is that, in essence, we are making relatively small corrections to the experimental pK value of 4-NMe_3^+-benzoic acid.

Our values for the microscopic constants are in Table II. For 50% ethanol the procedure was as for water. For 75% ethanol only pK_2 was measured directly, pK_A was obtained as above, and pK_B was estimated by using the Hammett equation. In either solvent K_1 is virtually identical with K_B and K_2 with K_D.

It is of interest to take a closer look at the pK_Z values (Table III). If there were no interaction between the substituents, pK_Z would be given by $pK(PhCOOH) - pK(PhNH_3^+) = 4.21 - 4.62 = -0.41$ in water for I and by $pK(PhCOOH) - pK(PhNMe_2H^+) = 4.21 - 5.16 = -0.95$ for II. Hence, the difference between such a value and the actual pK_Z can be equated to the sum of the substituent interactions in zwitterion and neutral molecule. The interactions thus obtained, expressed in pK units, for the solvents H_2O and 50% and 75% ethanol (all in favor of the neutral molecule) are 1.34, 1.13, and 1.3 for I and 1.57, 1.45, and 1.5 for II, respectively. These values, which appear to be fairly constant, show that the strong variation of pK_Z with solvent is largely determined by the variation of pK values of the parent acids (see Table III) caused by their being of different charge type.

In a further analysis the substituent interactions can be dissected in contributions from (a) "normal" terms, corresponding to the $\rho\sigma$ terms of eq 4 or 5, (b) electrostatic terms, δ^B,[1] and (c) through-resonance terms. Table III lists these contributions to the individual species as calculated through the relevant extended Hine equations[13] written out below and using (average) constants from Parts 4[14] and 6[1] of this series. Thus, for I, in water, the zwitterion is calculated to be stabilized by $\delta^B = 0.43$ pK units and destabilized by $\tau^L \times \sigma^L(NH_3^+) \times \sigma^L(COO^-) = 5.5 \times 0.39 \times 0.26 = 0.56$ pK units, whereas the neutral molecule is stabilized by both the normal interaction, $-\tau^L \times \sigma^n(NH_2) \times \sigma^n(COOH) = 5.5 \times 0.25 \times 0.41 = 0.56$ pK units, and through-resonance, $-\omega_p \times \Delta\sigma_R^+(NH_2) \times \Delta\sigma_R^-(COOH) = 2.4 \times 1.23 \times 0.28 = 0.83$ pK units. In spite of the uncertainties in the several parameters used in the calculations, the sum of these four terms, 1.52 pK units in favor of the neutral molecule, is in satisfactory agreement with that mentioned above, 1.34 pK units, which depends only on $pK(PhCOOH)$, $pK(PhNH_3^+)$, pK_1, and an estimation of pK_A based on a small and sensible adjustment of the pK of 4-NMe_3^+-benzoic acid. Accordingly, the results of the calculations for the 4-NR_1R_2-benzoic acids listed in Table III can be expected to be good approximations of the widely varying pK_Z values. It is appropriate to note here that the $pK_Z = -2.55$, calculated for 4-NMe-*t*-Bu-benzoic acid in 10% ethanol, leaves no doubt that in Part 6[1] we have correctly equated pK_A to pK_1.

Glycine has been included in Table III to demonstrate the results for aliphatic amino acids (using appropriate τ^L values). Interestingly, the overwhelming predominance of the zwitterion appears not to be caused by a specific stabilization of this species but is mainly determined by the strengths of the parent acids. In fact, the small sum of the interactions is in favor of the neutral molecule; in our analysis this turns out to be due to a dominating *de*stabilization of the zwitterion caused by the "normal" interaction of NH_3^+ and COO^-, both of which have positive σ_I^L values.

Our values for σ and σ^L (for dipole and pole substituents, respectively) are listed in Table IV. For 4-NH_2, in water, $\sigma = -0.62$ is close to the one usually tabulated, $\sigma = -0.660$, taken from Hammett's original table[15] and stemming from Kindler's work[16] on alkaline hydrolysis of ethyl benzoates in 88% ethanol at 30 °C (our value,[17] $\sigma = -0.629$). The value $\sigma = -0.57$, which, as noted by Serjeant,[18] follows from the data of Robinson and Biggs[4] has to be considered as less reliable for reasons discussed above. The value $\sigma = -0.688$ derived by Willi[19] cannot be accepted since it was based on the assumption, shown to be erroneous,[1] that the substituent effects of charged substituents follow the Hammett equation.

As for 4-NMe_2, our value for water, $\sigma = -0.69$, differs rather widely from that commonly tabulated, $\sigma = -0.83$,[20] and obtained by using Johnston's measurement[3] of K_2 without correction for zwitterion. We shall not try to evaluate the consequences of the erroneous value for the several correlations. We only note that, ironically, the exaltation we calculate as $\sigma - \sigma^n = -0.69 - (-0.25) = -0.44$ is not far from the exaltation obtained when using Johnston's value in combination with Taft et al.'s[21] σ^0 value (leaning heavily on NMR data): $\sigma - \sigma^0 = -0.83 - (-0.44) = -0.39$.

The σ^L values of 4-COO^- differ slightly from those given previously,[1] as the result of a redetermination of K_1 and K_2 and a different way of evaluation of the data. These σ^L values, as also the σ values of COOH (and COOR), are exalted ones, defining σ^- and σ^{L-} values.

Comparison of the effects of COOH and COOMe shows that, although pK_E of the esters can be used as a good first approximation of pK_B, the generalizations by Bryson et al.[22] and Serjeant[18] of the Wegscheider rule do not hold well.

Finally, the observed variation of σ values with solvent deserves to be commented upon in relation to the through-resonance involved. In earlier papers[23] we have noted that the difference in through-resonance energies is given by eq 6. It follows that a change in solvent which

$$-\Delta\Delta G_p = \rho(\sigma - \sigma^n)2.3RT \qquad (6)$$

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(13) See B. M. Wepster, *J. Am. Chem. Soc.*, **95**, 102 (1973), eq 12; ref 1, eq 18 and 20.

(14) A. J. Hoefnagel and B. M. Wepster, *J. Am. Chem. Soc.*, **95**, 5357 (1973).

(15) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, 1940.

(16) K. Kindler, *Justus Liebigs Ann. Chem.*, **450**, 1 (1926).

(17) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

(18) E. P. Serjeant, *Aust. J. Chem.*, **22**, 1189 (1969).

(19) A. V. Willi and W. Meier, *Helv. Chim. Acta*, **39**, 318 (1956).

(20) E.g., D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(21) J. Bromilow, R. T. C. Brownlee, V. O. Lopez, and R. W. Taft, *J. Org. Chem.*, **44**, 4766 (1979).

(22) A. Bryson, N. R. Davies, and E. P. Serjeant, *J. Am. Chem. Soc.*, **85**, 1933 (1963); ref 18.

(23) References 17 and 13 and A. J. Hoefnagel, J. C. Monshouwer, E. C. G. Snorn, and B. M. Wepster, *J. Am. Chem. Soc.*, **95**, 5350 (1973).

Table III. Contributions to the Zwitterion Equilibria in 4-NR_1R_2-Benzoic Acids and Glycine According to the Extended Hine Equations, in p*K* Units, at 25 °C

substituent	solvent[a]	p*K* of parents[b]		*D*[c]	substituent interactions[d]				Σ[e]	pK_Z		% zwitterion	
					zwitterion		neutral						
					normal	δB	normal	through-resonance		calcd[f]	exptl[g]	calcd	exptl[g]
4-NH_2	H_2O	4.21	4.62	−0.41	0.56	−0.43	0.56	0.83	1.52	1.11	0.93	7.2	10.5
	50E	5.48	4.04	1.44		−0.63			1.32	2.76	2.57	0.17	0.27
	75E	6.29	3.78	2.51		−0.87			1.08	3.59	3.8	0.026	0.015
4-NMe_2	H_2O	4.21	5.16	−0.95	0.80	−0.43	0.56	0.96	1.89	0.94	0.62	10.3	19.4
	50E	5.48	4.16	1.32		−0.63			1.69	3.01	2.77	0.098	0.17
	75E	6.29	3.51	2.78		−0.87			1.45	4.23	4.3	0.0059	0.005
4-NEt_2[h]	H_2O	4.21	6.88	−2.67	0.80	−0.43	0.56	0.96	1.89	−0.78		85.8	
	50E[h]	5.48	5.64	−0.16		−0.63			1.69	1.53		2.9	
	75E	6.29	4.87	1.42		−0.87			1.45	2.87		0.13	
4-N-*i*-Pr_2[i]	H_2O	4.21	8.25	−4.04	0.80	−0.43	0.32[j]	0.55[j]	1.24	−2.80		99.8	
	50E[i]	5.48	7.11	−1.63		−0.63			1.04	−0.59		79.6	
	75E	6.29	6.39	−0.10		−0.87			0.80	0.70		16.7	
4-NMe-*t*-Bu[k]	H_2O	4.21	7.60	−3.39	0.80	−0.43	0.11[l]	0.18[l]	0.66	−2.73		99.8	
	10E	4.37	7.55	−3.18		−0.46			0.63	−2.55		99.7	
	50E	5.48	6.63	−1.15		−0.63			0.46	−0.69		83.0	
	75E	6.29	6.05	0.24		−0.87			0.22	0.46		25.7	
4-pyrrolidino[m]	50E	5.48	3.28	2.20	0.80	−0.63	0.56	0.96	1.69	3.89		0.013	
4-piperidino[n]	50E	5.48	4.97	0.51	0.80	−0.63	0.56	0.96	1.69	2.49		0.32	
glycine	H_2O	4.76[k]	10.62[k]	−5.86	2.38[o]	−0.84[k]	−0.98[o]	0	0.56	−5.30	−5.31[p]	99.9995	99.9995[p]

[a] 50E and 75E = 50% and 75% ethanol; see Table II. [b] Parents: PhCOOH and $PhNR_1R_2H^+$. [c] *D*: difference p*K* of parents = pK_Z in the absence of substituent interaction. [d] Positive values signify interactions which favor the neutral molecule. [e] Sum of figures in preceding four columns. [f] $D + \Sigma$. [g] Table II. [h] In 50E $pK_2 = 6.56$; with $pK_Z = 1.53$ this gives $pK_D = 6.55$ and σ-4-$NEt_2 = -0.71$. Cf. ref 25. [i] Cf. ref 25. [j] Based on reduced resonance contributions as indicated by $\epsilon_{max} = 10\,200$ for $PhNiPr_2$ as compared with 17 900 for $PhNBu_2$ in isooctane, and σ-$NiPr_2 = 0$ for 90° twist (cf. ref 1, p 4740). [k] Reference 1. [l] Based on reduced resonance contributions as indicated by $\epsilon_{max} = 3400$ for PhNMe-*t*-Bu and 17 900 for $PhNBu_2$ in isooctane, and σ-4-NMe-*t*-Bu = 0 for 90° twist (cf. ref 1, p 4740). [m] In 50E $pK_2 = 6.52 = pK_D$; σ-4-pyrrolidino = −0.69. Cf. ref 25. [n] In 50E $pK_2 = 6.10 = pK_D$; σ-4-piperidino = −0.41. Cf. ref 25. [o] $\tau_I^L = 3.95 \times 5.5 = 22$ for YCH_2COOH, obtained from $\rho(YCH_2COOH) = 3.95$ (M. Charton, *J. Org. Chem.*, 29, 1222 (1964)) and $\tau^L = 5.5$ for benzene derivatives (ref 1); σ_I-$NH_2 = 0.12$ (ref 21); σ_I-COOH = 0.37 = σ_m-COOH in water (ref 1, Table XIII). [p] From $pK_A = pK_1 = 2.35$ and pK_B = p*K*(methyl ester) = 7.66 (Edsall and Blanchard, ref 2).

Table IV. Calculated σ and σ^L Values[a]

	4-aminobenzoic acid					
	σ		σ^L		σ	
solvent	4-NH_2	4-COOH	4-NH_3^+	4-COO^-	4-CO-OMe	4-CO-OEt
H_2O	−0.62	0.73	0.38[b]	0.40	0.73	0.71
50E	−0.52	0.66	0.39[b]	0.29	0.72	
75E	−0.54	0.7[c]	0.35[b]	0.40		

	4-(dimethylamino)benzoic acid				
	σ		σ^L		σ
solvent	4-NMe_2	4-COOH	4-NMe_2H^+	4-COO^-	4-CO-OMe
H_2O	−0.69	0.70	0.50[b]	0.38	0.72
50E	−0.61	0.67	0.52[b]	0.28	0.71
75E	−0.56	0.7[c]	0.46[b]	0.32	

[a] $\sigma = (\Delta \log K)/\rho$; $\sigma^L = (\Delta \log K - \delta^B)/\rho$. Cf. ref 1, also for ρvalues. 50E and 75E, see Table II. [b] Used in calculating pK_A. [c] Used in calculating pK_B; cf. footnote *j* of Table II.

increases ρ leads to a decrease in the exaltation of σ if $-\Delta\Delta G_p$ and σ^n remain the same. From this point of view, the positive shift in the σ values of 4-NMe_2 and 4-NH_2 between water and 50%[24] and 75% ethanol, for example, can be rationalized. At the same time, the observed irregularities in these and other σ values suggest the variation of other factors as well; some of these will be discussed in future papers.

Experimental Section

Compounds. Solids were recrystallized to a constant melting point: 4-aminobenzoic acid (I), from water, 188.5–189.5 °C; methyl 4-aminobenzoate, aqueous methanol, 111–112 °C; ethyl 4-aminobenzoate, 50% ethanol–water, 89–90 °C; 4-(dimethylamino)benzoic acid (II), ethanol, 238–240 °C dec; methyl 4-(dimethylamino)benzoate, ethanol, 101–102 °C; aminoacetic acid (glycine), 30% ethanol–water, 229–230 °C dec; (methylamino)acetic acid (sarcosine), 90% ethanol–water, 211–212 °C dec; (dimethylamino)acetic acid hydrochloride,[26] ethanol, 189.5–191 °C (equiv wt 140.2, calcd 139.6); (trimethylammonio)acetic acid chloride, 80% ethanol–water, 229–230 °C dec (equiv wt 154.7, calcd 153.6).

Benzoic acid,[1] aniline,[27] *N*,*N*-dimethylaniline,[27] *N*,*N*-diethylaniline,[28] and *N*-*tert*-butyl-*N*-methylaniline[29] were prepared as described. *N*,*N*-Diisopropylaniline was prepared by refluxing aniline and isopropyl bromide in 2-propanol. The secondary amine is formed rapidly and the tertiary amine is obtained only after repeated alkylation for several days. Purification was effected via the picrate (from ethanol, mp 170–171 °C); the liberated amine has bp 103 °C (13 mm), $n^{25}{}_D$ 1.5165. *N*-Phenylpyrrolidine was purified as the picrate (from ethanol, mp 116.5–117.5 °C); the free amine had bp 122 °C (14 mm), $n^{25}{}_D$ 1.5799. *N*-Phenylpiperidine was purified as the β-naphthalenesulfonate (from ethanol, mp 166–167 °C); the free amine had bp 121 °C (13 mm), $n^{25}{}_D$ = 1.5596.

Spectroscopy. The spectroscopic measurements for the p*K* determinations of I and II were carried out with a Cary 15 instrument; 10-cm cuvettes were used as they were necessary for II because of its very low solubility (for the same reason the solutions of II were prepared from an ethanol–water stock solution, yielding 0.2% ethanol as the final solvent). In the pH range 6.3–3.6 the buffer solutions of ionic strength 0.04 were prepared by using acetic acid and sodium acetate solutions.[30] In the pH range 3.4–2.0 the ionic strength 0.04 was obtained by using hydrochloric acid and sodium chloride solutions. The pH of the measured solutions was determined with a Beckman G instrument with a GP glass electrode and type 270 calomel electrode (fiber). Corrections for the ionic strength (−0.077 for pK_1 and +0.077 for pK_2) were obtained in the usual way.[1]

Table V. Calculated (± Standard Deviation) and Experimental Molecular Extinction Coefficients for I, II, Their Methyl Esters, and 4-NMe_3^+-Benzoate in Aqueous Media

	4-NH_2		4-NMe_2	
	ϵ_{285}	ϵ_{265}	ϵ_{315}	$\epsilon_{287.5}$
cation, calcd	324 ± 119	1009 ± 87	202 ± 145	278 ± 99
exptl (1 M HCl)	207	831	32	156
zwitterion + neutral, calcd	14809 ± 38	9832 ± 31	18371 ± 62	9194 ± 46
anion, calcd	8326 ± 31	14460 ± 29	7670 ± 53	16277 ± 48
exptl (pH = 11)	8340	14500	7730	16300
neutral, calcd[a]	16500	10900	22800	11400
methyl ester, exptl (pH = 6)	17000[b]	11200[b]	22600[b]	11600[b]
4-NMe_3^+-benzoate, exptl (pH = 10)	0	660	0	0

[a] From ϵ(zwitterion + neutral) and % zwitterion, taking ϵ(zwitterion) = ϵ(4-NMe_3^+-benzoate). [b] From data in 4% and 2% ethanol.

For I the wavelengths 265 and 285 nm were chosen, for II 287.5 and 315 nm, i.e., the maxima of anion and neutral acid. The figures given in Table II were obtained by using 46 data points for each compound, without constraining any of the parameters; the spectral data obtained are in Table V along with some experimental values for comparison. The agreement is quite satisfactory; the discrepancies for the cations are possibly due to medium effects.

Potentiometry. The potentiometric measurements were carried out as described previously.[31] The aliphatic amino acids and the esters with the lower p*K* values had to be measured at higher concentrations, up to about 0.03 M, implying ionic strength corrections of about 0.06. For some of the amines the thermodynamic p*K* values of Table III replace apparent p*K* values given in earlier publications. The conclusions in the relevant papers are not affected.

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Registry No. I, 150-13-0; II, 619-84-1; methyl 4-aminobenzoate, 619-45-4; ethyl 4-aminobenzoate, 94-09-7; methyl 4-(dimethylamino)benzoate, 1202-25-1; glycine, 56-40-6; sarcosine, 107-97-1; (dimethylamino)acetic acid hydrochloride, 2491-06-7; (trimethylammonio)acetic acid chloride, 590-46-5; *N*,*N*-diisopropylaniline picrate, 23970-60-7; *N*,*N*-diisopropylaniline, 4107-98-6; *N*-phenylpyrrolidine picrate, 75420-84-7; *N*-phenylpyrrolidine, 4096-21-3; *N*-phenylpiperidine 3-naphthalenesulfonate, 75420-85-8; *N*-phenylpiperidine, 4096-20-2; 4-(diethylamino)benzoic acid, 5429-28-7; 4-(diisopropylamino)benzoic acid, 22090-23-9; *N*-*tert*-butyl-*N*-methyl-4-aminobenzoic acid, 67688-78-2; 4-pyrrolidinobenzoic acid, 22090-27-3; 4-piperidinobenzoic acid, 22090-24-0.

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(24) Our values in 50% ethanol confirm those obtained by W. G. Herkstroeter, *J. Am. Chem. Soc.*, **95**, 8686 (1973), σ-4-NH_2 = −0.52 and σ-4-NMe_2 = −0.63.

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