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Tautomerism studies of 3-(ω-sulphoalkylamino)benzoic acids. Substituent effects

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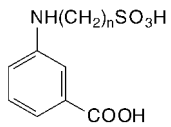
ABSTRACT: Two SAABA [3- and 4-(ω-sulphoalkylamino)benzoic acid] derivatives, 3-(3-sulphopropylamino)-benzoic acid and 3-(4-sulphobutylamino)benzoic acid, were studied by a potentiometric method to determine two macroscopic constants (K_{a_2} and K_{a_3}) for each derivative. The combination of these values with ^{13}C NMR spectroscopic titration data was used to determine their tautomeric (K_T) microscopic constants at 25.0 °C and ionic strength 1.00 mol dm^{-3} (KCl). From these results, it was possible to estimate the other microscopic constants and consequently the Hammett substituent constants (σ_m) for two *m*-aminoalkylsulphonates and the electronic effects of two alkylsulphonate substituents separately. For the *m*-aminoalkylsulphonate substituents the σ_m values are −0.12 for *m*-aminopropylsulphonate and −0.27 for *m*-aminobutylsulphonate, and therefore the electron-donating effect prevails when three methylene units are present. On the other hand, in alkylsulphonate substituents, this effect prevails only for four methylene units. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: macroscopic constants; microscopic constants; electronic effects; ^{13}C NMR spectroscopic titration; potentiometric titration; tautomerism; 3-(ω-sulphoalkylamino)benzoic acids

INTRODUCTION

3- and 4-(ω-sulphoalkylamino)benzoic acids and their salts, **I** (**SAABA** derivatives), are interesting model compounds owing to the presence of ammonium alkanesulphonate groups (substituent with acid and basic groups), which make them similar to essential amino acids.[1,2] Also, these compounds contain sulphoalkyl groups and some of them look like substituted anilinomethanesulphonates[3] as in sodium *p*-ethoxyanilinomethanosulphonate, which is pharmacologically active.



(n=3 and 4)

I

Reported pK_a values of the anilinium groups for some compounds (**II–V**) are given in Table 1. It is important to note that the media used for the pK_a determination of compounds **III** and **V** are very different from the media used for **II** and **IV**, because the acidities of these compounds differ appreciably. Comparison of these pK_a values for compounds **II** and **III** and compounds **IV** and **V** indicates an intense electron-withdrawing effect[9] caused by the additional methylsulphonate substituent.

The evaluation of the electronic effects for the aminoalkylsulphonate substituents [—$NH(CH_2)_nSO_3^-$] and even alkylsulphonates [$-(CH_2)_nSO_3^-$] in **SAABA** can be done by comparing, respectively, the acid dissociation constants of their carboxylic and ammonium groups (anilinium) with the acidity constants of benzoic acid and aminobenzoic acids.[10,11]

Note that for the **SAABA** derivatives we used the established convention: the pK_{a_1} value refers to the strongest group (—SO_3H), pK_{a_2} to the amino groups ($-NH_2^+-$) and pK_{a_3} to the carboxylic groups (—COOH)

However, some of the *meta*-substituted **SAABA** derivatives can be involved in a branched acid–base equilibrium system in aqueous medium[8,12–15] (Scheme 1), making the evaluation of electronic effects difficult. When the difference in the pK_a values between the ammonium group and the carboxylic group is high, as in the *para*-substituted **SAABA** and **MBMS**[8] [3-(sulphomethylamino)benzoic acid, **V** in Table 1], the tautomeric equilibrium (between AH^- and AH^{-+}) is negligible (consequently the equilibria represented by K_A and K_C are not significant and $K_{a_2} = K_B$ and $K_{a_3} = K_D$) and the pK_a

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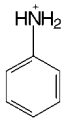
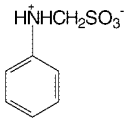
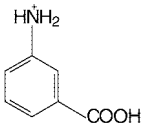
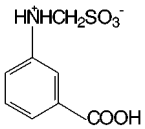
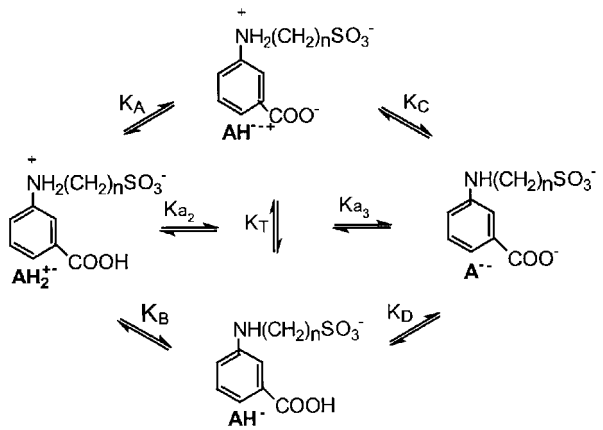
Table 1. pK_a values of the anilinium groups for different compounds

Compound	pK_a
 **(II)**	4.60[a]
 **(III)**	0.92[b]
 **(IV)**	3.08[c]
 **(V)**	−1.06[d]

[a] Ref. 4.
[b] Ref. 5 (at 20.0 °C in H_2O–H_2SO_4 medium.[6] H_0 acid function conceived by Hammett and Deyrup).
[c] Ref. 7 (at 25.0 °C in aqueous medium and constant ionic strength of 1.6×10^{-2} mol dm^{-3}).
[d] Ref. 8 (at 25.0 °C in H_2O–H_2SO_4 medium.[6] H_0 acid function conceived by Hammett and Deyrup).

values of the acid macroscopic constants (K_{a_2} and K_{a_3}) can be determined by a standard spectrophotometric titration method. When the pK_a values of the ammonium and carboxylic groups are close, all the related acid microscopic constants are relevant. However, they cannot be obtained directly by any single experimental method and an alternative experimental procedure is necessary to evaluate the system illustrated in Scheme 1.



Scheme 1

A complete elucidation of the thermodynamic cycle in Scheme 1 can be achieved by the experimental determination of the acid macroscopic constants and by the estimation of any one of the acid microscopic constants.

The determination of the acid macroscopic constants (K_{a_2} and K_{a_3}) comprises the following equilibria, when the tautomeric forms AH^- and $AH^{-\,+}$ (Scheme 1) are treated collectively as a single species AH.

$$AH_2^{+-} \underset{}{\overset{K_{a_2}}{\rightleftharpoons}} AH + H^+ \qquad (1)$$

$$AH \underset{}{\overset{K_{a_3}}{\rightleftharpoons}} A^{--} + H^+ \qquad (2)$$

However, the acid microscopic constants are related to the macroscopic constants by the following relationships:[14,15]

$$K_{a_2} = K_A + K_B \qquad (3a)$$

$${K_{a_3}}^{-1} = {K_C}^{-1} + {K_D}^{-1} \qquad (3b)$$

$$K_T = \frac{K_A}{K_B} = \frac{K_D}{K_C} \qquad (3c)$$

Many experimental methods have been used to estimate the microscopic constants of various compounds, e.g. for several amino acid analogues, aminobenzoic acids and a great variety of others, which have two or more dissociable groups involved in protolysis equilibria.[16–22] The estimated acid microscopic constants along with the macroscopic ones allow the elucidation of the cycle.

In the present work, the investigation of the thermodynamic cycle (Scheme 1) for two *meta*-substituted **SAABA**, 3-(3-sulphopropylamino)benzoic acid (**MBPSH**) and 3-(4-sulphobutylamino)benzoic acid (**MBBSH**), was carried out by potentiometric and ^{13}C NMR measurements using benzoic acid as a model compound.[18] From these acid constants, mainly K_D and K_B, a real evaluation of the electronic effects of *m*-aminoalkylsulphonate and alkylsulphonate substituents in **SAABA** derivatives, for $n = 3$ and 4 methylene groups, was obtained.

EXPERIMENTAL

Materials. Reagent-grade chemicals (Aldrich) were used without purification. IR spectra were recorded on a Bomem, Hartmann & Braun-MB100 FT-IR spectro-

photometer as KBr pellets. Melting-points were determined on a Biosystems APF-301 melting-point apparatus. ^{1}H NMR (in D_2O and TMS as internal standard) and ^{13}C NMR (in H_2O and TMSP (sodium 3-(trimethylsilyl)propanesulphonate) in D_2O as external standard) spectra were recorded on a Varian Gemini 2000 (300 MHz) FT spectrometer. Chemical shifts are reported in ppm. Thin-layer chromatography (TLC) was performed on precoated silica gel GF_{254} plates (Merck) using *n*-butanol–water (11.5:1) as eluent. Elemental analyses of the sodium salts[8] were carried out at the Microanalysis Laboratory of the Institute of Chemistry at São Paulo University on a Perkin-Elmer 2400 CHN instrument.

MBPSH and **MBBSH** were prepared by reaction between *m*-aminobenzoic acid and 1,3-propanesultone and 1,4-butanesultone, respectively, using the method described by Zeid and Ismail.[23]

MBPSH (yield 57%): m.p. 267–269 °C (decomp.) (lit. 267–269 °C[8] and 270 °C[23]); TLC; $R_f = 0.28$. Anal.:calcd for $C_{10}H_{12}NO_5SNa$: C, 42.70; H, 4.30; N, 4.98%. Found: C, 42.75; H, 4.30; N, 4.66%. IR: $\nu_{charact}$ (cm^{-1}), 3440 (N—H), 3300–2500 (dimeric OH), 2934 and 2829 (CH_2), 1712 (C=O), 1191 (S=O_{asymm}), 1040 (S=O_{symm}). ^{1}H NMR: δ (D_2O), 2.02 (2H, q, 2-H_{aliph}), 2.87 (2H, t, 3-H_{aliph}), 3.42 (2H, t, 1-H_{aliph}), 7.45–7.84 (4H, 2-, 4-, 5- and 6-$H_{arom\ m-subst}$). ^{13}C NMR: δ (H_2O–TMSP in D_2O), 24.6 (2-C_{aliph}), 51.0 (3-C_{aliph}), 51.9 (1-C_{aliph}), 124.9 (5-C_{arom}), 128.5 (6-C_{arom}), 133.8 (4-C_{arom}), 136.5 (2-C_{arom}), 137.7 (1-C_{arom}), 140.6 (3-C_{arom}), 173.4 (C_α).

MBBSH (yield 60%): m.p. 279–282 °C (decomp.) (lit. 280 °C[8]); TLC: $R_f = 0.30$. Anal.:calcd for $C_{11}H_{14}NO_5SNa.H_2O$: C, 42.17; H, 5.15; N, 4.47%. Found: C, 41.92; H, 5.22; N, 4.20%. IR: $\nu_{charact}$ (cm^{-1}), 3452 (N—H sp OH), 3300–2500 (dimeric OH), 2924 and 2811 (CH_2), 1718 (C=O), 1177 (S=O_{asymm}), 1042 (S=O_{symm}). ^{1}H NMR: δ (D_2O), 1.87 (4H, m, 2 and 3-H_{aliph}), 2.94 (2H, t, 4-H_{aliph}), 3.50 (2H, t, 1-H_{aliph}) 7.66–8.07 (4H, 2-, 4-, 5- and 6-$H_{arom\ m-subst}$). ^{13}C NMR: δ (H_2O–TMSP in D_2O), 24.3 (3-C_{aliph}), 27.4 (2-C_{aliph}), 53.2 (4-C_{aliph}), 53.7 (1-C_{aliph}), 125.9 (5-C_{arom}), 129.3 (6-C_{arom}), 133.0 (4-C_{arom}), 133.8 (2-C_{arom}), 137.0 (1-C_{arom}), 139.3 (3-C_{arom}), 173.5 (C_α).

Determination of the macroscopic constants (K_{a_2} and K_{a_3}). For the experimental measurement of the macroscopic constants, a Radiometer PHM240 pHmeter equipped with a PHC 2401-8 combined electrode was employed. The electrode calibration was carried out by a procedure based on the Bierdermann and Sillen[24] method with solutions of HCl and NaOH, where the potential readings were converted into hydrogen ion concentrations.[25] A Gilmont GS-1200A microsyringe of 2.000 ± 0.002 cm^3 was employed to add the NaOH solutions (ca 0.2 mol dm^{-3}) to 20 cm^3 of the samples (ca 4.0×10^{-2} mol dm^{-3}) prepared in aqueous solutions of KCl (1.00 mol dm^{-3}). All measurements (in triplicate) were performed at 25.0 ± 0.1 °C using a Microquímica MQBTC 99-20 thermostatic bath. The acid dissociation constant of benzoic acid (sample concentration 1.18×10^{-2} mol dm^{-3}) was obtained under the same conditions.

Linear functions for the treatment of the titration data developed by Aleixo *et al.*[25] were applied to the potentiometric data to calculate the macroscopic constants (K_{a_2} and K_{a_3}).

Determination of the microscopic constants. The microscopic constants were determined using a tautomeric constant (K_T) estimated from ^{13}C NMR spectra. About 0.5 cm^3 aliquots of samples, titrated in the same pH range, temperature, concentrations and ionic strength, were withdrawn and analysed[18] as for the potentiometric titration. The reference compound was benzoic acid in basic and acidic media.

The Statistica[26] computer program was used to calculate the intrinsic chemical shifts of species with non-equivalent carbon atoms.

RESULTS AND DISCUSSION

The observed chemical shifts (δ_{obs}) of the carbonyl and phenyl ring carbons for the **MBPSH** and **MBBSH** derivatives as a function of pH are shown in Fig. 1. The

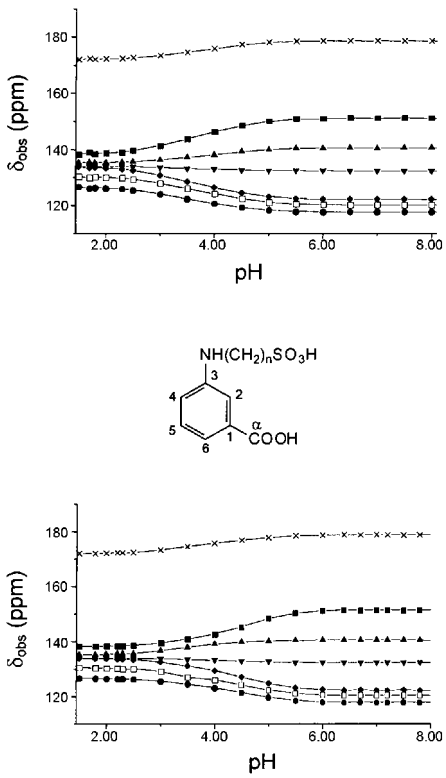


Figure 1. ^{13}C NMR chemical shifts for the carbons of the **MBPSH** (top) and **MBBSH** (bottom) derivatives (x, ■, ▲, ▼, ◆, □ and ● refer to C_α, C_3, C_2, C_1, C_4, C_6 and C_5, respectively) as a function of pH at 25.0 °C

Table 2. Macroscopic and microscopic constants of SAABA derivatives at 25.0 °C

Derivative	pK_{a_2}	pK_{a_3}	K_T	pK_A	pK_B	pK_C	pK_D
MBPSH	2.93 ± 0.04	4.22 ± 0.02	0.89 ± 0.02	3.26 ± 0.03	3.21 ± 0.04	3.89 ± 0.02	3.94 ± 0.03
MBBSH	3.21 ± 0.03	4.61 ± 0.04	2.33 ± 0.06	3.36 ± 0.05	3.73 ± 0.04	4.46 ± 0.07	4.09 ± 0.05

chemical shift changes at low pH are slightly larger for **MBPSH** than for **MBBSH**. For the C_α, C_1 and C_3 carbon atoms the signal changed to low field whereas for C_2 (slight change), C_4, C_5 and C_6 it changed to high field. The chemical shift profiles were similar for all the carbons analysed as the pH was increased.

From the acid macroscopic constants and the chemical shift values shown in Fig. 1, the tautomeric microscopic constants ($K_T = X_{AH^{-+}}/X_{AH^-}$) were estimated using the molar fractions of $\mathbf{AH}^-$ species in the tautomeric equilibria by[18]

$$X_{AH^-} = \frac{\delta_{AH} - \delta_{AH^{-+}}}{\delta_{AH^-} - \delta_{AH^{-+}}} \quad (4)$$

where the δs are intrinsic chemical shifts of a certain carbon atom of subscripted species[18] (note that AH represents collectively AH^- and AH^{-+}).

The δ_{AH}, $\delta_{AH_2^{+-}}$ and $\delta_{A^{--}}$ values were determined by a multiple linear regression procedure[26] on the $\delta_{A^{--}}$ at each pH value that was regarded as a mole fraction-weighted average:

$$\delta_{obs} = \{[AH_2^{+-}]\delta_{AH_2^{+-}} + [AH]\delta_{AH} + [A^{--}]\delta_{A^{--}}\}/F \quad (5)$$

where F is the analytical concentration of the **SAABA** derivatives (same value at all pH).

Otherwise δ_{AH}, as in aminobenzoic acids,[18] was regarded as a mole fraction-weighted average of intrinsic chemical shifts of the species present in the tautomeric equilibria:

$$\delta_{AH} = X_{AH^-}\delta_{AH^-} + X_{AH^{-+}}\delta_{AH^{-+}} \quad (6)$$

The δ_{AH^-} and $\delta_{AH^{-+}}$ values were estimated by adding to $\delta_{A^{--}}$ and subtracting from $\delta_{AH_{2+-}}$ the change in the chemical shifts $[\Delta(C_6H_5COOH) = \delta_{C_6H_5CO_2H} - \delta_{C_6H_5CO_2^-}]$, at the corresponding carbon atom due to proton transfer of benzoic acid, which was used as a modelling system.

From the estimated K_T values and the macroscopic constants (obtained by the potentiometric method) the other microscopic constants were calculated according to Eqns 3(a)–(c). These results are given in Table 2. The concentrations at each pH for the four species in Scheme 1 were estimated from these results. The distribution curves for **MBPSH** and **MBBSH** are illustrated in Fig. 2. For **MBPSH** and **MBBSH** at low pH (<3), the solution presented AH_2^{--} as the major species and at high pH (>5) a preponderance of the A^{--} form. At intermediate pHs, the AH^{-+} (zwitterionic form) prevailed for **MBBSH** whereas AH^- slightly prevailed for **MBPSH**.

The K_T values presented by the **SAABA** derivatives show that in **MBPSH** the proton transfers occur approximately in the same proportions for the two ionizing groups, ca 53% for the $-NH_2^+-$ group and ca 47% for the —COOH group, corresponding to $K_T = 0.89$ ($\Delta G° = 289$ J mol^{-1}) and predominantly for the —COOH group, ca 70%, corresponding to $K_T = 2.33$ ($\Delta G° = -2097$ J mol^{-1}) in **MBBSH** (Table 2).

Furthermore, the K_B values (which involve only the proton transfer of the anilinium group obtained from estimated K_T values) indicate that the substitution of one hydrogen atom by a propylsulphonate group (**MBPSH**) in the 3-aminobenzoic acid, whose K_T value is 1.49[18] and $K_B = 3.34 \times 10^{-4}$ ($pK_B = 3.48$), increases the acid constant of the anilinium group ($pK_B = 3.21$) by ca 1.8-fold, indicating an electron-withdrawing effect for this substituent. However the replacement of the hydrogen atom by a butylsulphonate group (**MBBSH**) decreases the acidity constant of the anilinium group ($pK_B = 3.73$) by ca 0.56-fold, conferring an electron-donating effect on this substituent.

Interestingly, the methylsulphonate group in sodium 3-sulphonatemethylaminobenzoic acid,[8] yielded a pK_{a_2} (amino group) of -1.06, which corresponds to an increase (ca 3×10^4-fold) in the acid constant of the anilinium group, showing a strong electron-withdrawing effect.

From these real electronic effects, it can be concluded that the electron-withdrawing effect is preponderant when the sulphonate $(-SO_3^-)$ is moved one to three

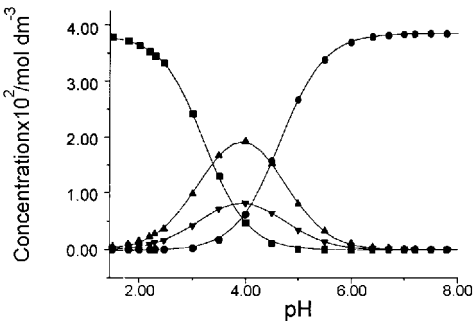


Figure 2. Concentration distribution curves of the four species (■, ▲, ▼ and ● refer to AH_2^{+-}, AH^{-+}, AH^- and A^{--} species, respectively) in Scheme 1 as a function of pH for **MBBSH** derivative at 25.0 °C

methylene units from the reaction center ($-NH_2^+-$). On the other hand, the electron-donating feature of the alkylsulphonate substituents prevails when the sulphonate group is separated by four methylene units.

Comparison of the pK_D values (which involves only the proton transfer of the carboxylic group in 1.00 mol dm^{-3} KCl) for the two **SAABA** with the pK_a of benzoic acid (3.82 at 25 °C in 1.00 mol dm^{-3} KCl) indicated a difference of −0.12 for **MBPSH** and −0.27 for **MBBSH**. These values correspond to the substituent constants (σ_m) in the Hammett equation[10] of *m*-aminopropylsulphonate (-0.12 ± 0.03) and *m*-aminobutylsulphonate (-0.27 ± 0.05), in a medium where the ionic strength is 1.00 mol dm^{-3} (KCl). Hence the real electronic effects of these two aminoalkylsulphonate substituents are essentially electron donation in aqueous medium with an ionic strength of 1.00 mol dm^{-3}.

This dichotomy between electron withdrawal and electron donation presented by the two alkylsulphonate substituents and the increase in the electron-donation effect of the aminoalkylsulphonate substituents are inherent features of ionic substituents and one or other effect will prevail depending on the distance between the reaction centre and the charged group.

Extended Hammett equations for substituents in the *meta* position and an extended Taft equation for aliphatic series were proposed by Hoefnagel *et al.*[27] These equations stated that the pK_a difference (ΔpK_a) of 3-aminobenzoic acid and the derivative (e.g. *meta*-substituted **SAABA**) is a sum of two factors: the inductive effect and the field effect (or electrostatic, δ^B). To estimate the field effect for **SAABA** derivatives[7] the distance (r) from the reaction centre ($-NH_2^+-$) to the sulphonate group, based on geometries[28,29] of aniliniummethanesulphonate derivatives in the solid state (obtained by crystallographic data), resulted in 2.74 Å (methylsulphonate) and 6.60 Å (butylsulphonate). Taking this distance (r), the electron-donation field effect (δ^B) was calculated with the equation[27] $\delta^B = 3.1/r$, resulting in −1.15 and −0.47 for methyl- and butyl-**SAABA**, respectively. Using the ΔpK_a value (pK_{a_2} for **SAABA**) and the calculated field effect (δ^B) for these compounds, the electron-withdrawing inductive effect changed from 5.68 to 0.68, showing the expected decrease when the methylene chain groups increase from 1 to 4 units. These data indicate that the electron-withdrawing effect underwent drastic attenuation. On introducing another methylene group ($n = 5$) the distance increases to 7.60 Å and the electron-donation effect must overcome the electron-withdrawing effect. All these calculations are valid for the solid state, once the distances considered were estimated from the crystallographic data. In solution, our data showed that this effect occurs when the number of methylene groups changed from three to four units, reflecting the molecular conformations differences (in the solid state and in solution).

According to this calculation, the electron-withdrawing inductive effect of the sulphonate group dominates for shorter distances, whereas the electron-donation field effect dominates at longer distances. When the substituent is an alkylsulphonate group the reaction centre is the anilinium group ($-NH_2^+-$), which in **SAABA** derivatives is closer to the sulphonate group and therefore the electron-withdrawing effect is preponderant. This effect remains when the sulphonate is separated from anilinium by three methylene units. When the substituent is an aminoalkylsulphonate group the reaction centre is the carboxylic group (—COOH), which in **SAABA** derivatives is far away from the sulphonate group. In this case the electron-donation effect already dominates even when the substituent has three methylene units.

Thus, for the alkylsulphonate substituents with three methylene units, the electron-withdrawing inductive effect of the sulphonate group is greater than its electron-donation field effect, whereas for the aminoalkylsulphonate substituents, with the same number of methylene units, the electron-donation field effect is greater than the inductive effect.

Acknowledgements

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