Studies of the Protonation Equilibria of Sulphamates using ^{13}C and ^{1}H Nuclear Magnetic Resonance Spectroscopic, Potentiometric, and Conductimetric Methods

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pK_a Values are determined for the ionization $R\overset{+}{N}H_2SO_3 \rightleftharpoons RNHSO_3^- + H^+$ for sulphamates with R = Bu^n, Pr^n, Bu^s, and cyclohexyl using ^{13}C and ^{1}H n.m.r. spectroscopic, potentiometric, and conductimetric methods. These compounds have pK_a values in the range 1—1.9 and they are thus less acidic than sulphamic acid. Intramolecular standards were used in the n.m.r. measurements. The similarity in the pK_a values determined by the two n.m.r. methods suggests that solvation effects are small.

THE pK_a of sulphamic acid, $\overset{+}{N}H_3SO_3^-$, has been determined in aqueous solution using conductimetric,[1,2] potentiometric,[3] and electromotive force measurements [4] and in dimethylformamide by a spectrophotometric method.[5] The more weakly basic aromatic sulphamates (pK_a *ca.* -2 ± 0.5) protonate in strong acid and have been found to follow the H_0 acidity function approximately. Measurements have been made on phenyl-,[6,7] *p*-methoxyphenyl-,[8] and 1-naphthyl-sulphamates.[9] Apart from two somewhat divergent literature values [10,11] for the pK_a of cyclohexylsulphamic acid there appear to be no reports of studies of the basicities of alicyclic or aliphatic sulphamates, despite the utility of such compounds as sulphonating,[12] sulphating,[13,14] and sweetening agents,[15,16] and the fact that their free acids, like sul-

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phamic acid,[17] will exist in a zwitterionic or dipolar form, $R\overset{+}{N}H_2SO_3^-$.[18,19] In the present paper, we have determined pK_a values for several such sulphamates using ^{1}H and ^{13}C n.m.r. spectroscopic, potentiometric, and conductimetric methods.

EXPERIMENTAL

Materials.—Sodium cyclohexylsulphamate (Fluka), cyclohexylsulphamic acid (Fluka), and sulphamic acid (B.D.H.; analytical grade) were used as obtained. The sodium salts of n-propyl- and s-butyl-sulphamic acid, the potassium and barium salts of n-butylsulphamic acid, and the free acid were prepared as previously reported.[12,19] All the sulphamates gave satisfactory elemental analyses. Hydrochloric and sulphuric acid solutions were prepared from Volucon (M and B) standards and 1M-perchloric acid was prepared from 60% perchloric acid (B.D.H.). Deuteriated HCl (*ca.* 6M), deuteriated NaOH (*ca.* 7.5M), and deuterium oxide were obtained from Koch-Light. The strengths of all acid solutions were checked by titration with standard sodium hydroxide.

^{1}H *N.m.r. Measurements*.—The following represents the conditions of a typical run. A 0.03M solution of compound (1) (barium salt) in DCl was prepared by dissolving 66.2 mg in 1.26M-DCl (5 ml). The solution was added to a special three-necked reaction vessel in a dry box under nitrogen. The glass electrode of a pH meter (Pye–Unicam 290 Mk 2) which was standardized with buffers of pH 4.0, 6.5, and 9.3 was inserted through a tight-fitting rubber bung attached to the flask. The other two necks were sealed with Suba seals through which syringes could remove (and return) samples for n.m.r. and add sodium deuterioxide. The design of the reaction vessel was such that a small magnetic stirring pellet could be included and that the acid solution covered the glass electrode. The initial pH was determined, a suitable portion was withdrawn and the positions of the hydrogens attached to the C-4(-δ) and -1(-α) in the n.m.r. spectrum were noted. The addition of small volumes of sodium deuterioxide (4 and 1M) then allowed a progressive alteration in the pH, while maintaining the ionic strength constant and increasing the total solution volume by no more than 1 ml. After each addition of base the solution was stirred, the pH redetermined, and the chemical shifts measured. 12 Measurements were made over the pH range *ca.* 0—*ca.* 11. ^{1}H Spectra were measured on a JEOL MH-100 spectrometer at 28 °C at 100 MHz with a sweep width of 270 Hz. Resolution was 0.5 Hz. In order to avoid interference from H_2O bands, deuteriated acids in D_2O were used with compounds (1) and (3).

^{13}C *N.m.r. Measurements*.—^{13}C Spectra were measured on JEOL PFT-100 P spectrometer in 10 mm tubes at 21.5 °C at 25 MHz with proton decoupling. Chemical shifts (Hz) were determined relative to D_2O (internal lock). Resolution was 0.24 Hz. pH Readings were taken with a Beckmann model G pH meter, which was standardized with three buffers.

The following represents the conditions of a typical run. A *ca.* 0.1M solution of compound (4) (sodium salt) was made up by dissolving the salt (100 mg) in 1.46M-hydrochloric acid (5 ml) and adding D_2O (0.2 ml). The initial pH and the chemical shifts of the four carbon atoms were measured. The addition of small volumes of sodium hydroxide (4M, 1M, and 0.5M) changed the pH and the chemical shifts. After each addition of base the pH was redetermined, a portion was withdrawn (and later returned) and the chemical shifts measured.

Potentiometric Measurements.—A Pye–Unicam model 290 Mk 2 pH meter (standardized with buffers of pH 4.0, 6.5, and 9.3) was used. The following represents the conditions of a typical run. The procedure recommended by Albert and Serjeant[20] was followed. Compound (4) (acid) (0.089 5 g) was dissolved in distilled water (47.5 ml) in a 100 ml titration flask, which was placed in a water-bath maintained at 28 °C. A magnetic stirring pellet and a glass electrode were placed in the flask. After recording the initial pH, 1.0M-NaOH (5 ml) was added in 0.5 ml portions from a 5 ml microburette, the pH being recorded after the addition of each portion of base. The concentration of substrate is such that at half-neutralization it corresponds to a 0.1M solution. In the calculation of the pK_a values allowance was made for varying hydrogen and hydroxide ion concentrations. A correction for the dilution of the substrate was not applied since the revised pK_a values obtained were within the experimental error. In runs using compound (1) (acid) 0.076 5 g in 47.5 ml and 0.229 g in 47.5 ml were used. These represented 0.01M and 0.03M concentration respectively at half-neutralization. The standard bases used in the titration of these solutions were hence 0.1M and 0.33M respectively.

Conductimetric Measurements.—Measurements were made with a Beckmann conductivity bridge model RC-18A using a Beckman conductivity cell, CEL-Kl, cell constant, k = 1.00 cm^{-1}. The conductance of the deionized water used was 12×10^{-7} ohm^{-1}. In a typical run compound (4) (acid) (0.118 2 g, 0.013 2M) was dissolved in deionized water (50 ml) and placed in the conductance cell which was immersed in a water-bath at 25 °C. The conductance was read and 3 ml of the solution was withdrawn with an automatic pipette which was rinsed out twice, dried, and used again to transfer 3 ml of deionized water into the solution in the conductance cell. After thorough stirring the conductance was read again. After removal and addition of 20 portions in this manner the conductance had fallen from $32\,830 \times 10^{-7}$ to $11\,899 \times 10^{-7}$ ohm^{-1} and the concentration of substrate from the initial value to 0.003 87M. In a separate experiment, (4) (sodium salt) (0.101 g, 0.01M) was dissolved in deionized water (50 ml). Portions (25 ml) were withdrawn and replaced by portions (25 ml) of deionized water. The conductance was measured after each operation.

RESULTS AND DISCUSSION

Albert and Sergeant[21] consider the equilibria (1) for the zwitterionic amino-acid, glycine, and refer to step a

$$H_3\overset{+}{N}CH_2CO_2H \overset{a}{\rightleftharpoons} H_3\overset{+}{N}CH_2CO_2^- \overset{b}{\rightleftharpoons} H_2NCH_2CO_2^- \quad (1)$$

as ' proton gained ' and step b as ' proton lost '. Generally with amino-acids both equilibria can be observed in the pH region but, because of the strength of aliphatic

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[17] See F. L. Scott and W. J. Spillane, *Mech. React. Sulfur Compounds*, 1968, **2**, 133; 1970, **5**, 59.

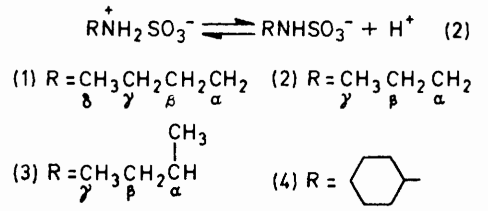
[18] C. D. Hurd and N. Kharasch, *J. Amer. Chem. Soc.*, 1947, **69**, 2113.

[19] W. J. Spillane, F. L. Scott, and C. B. Goggin, *Internat. J. Sulfur Chem.* (*A*), 1971, **1**, 223.

[20] A. Albert and E. P. Sergeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971, ch. 2.

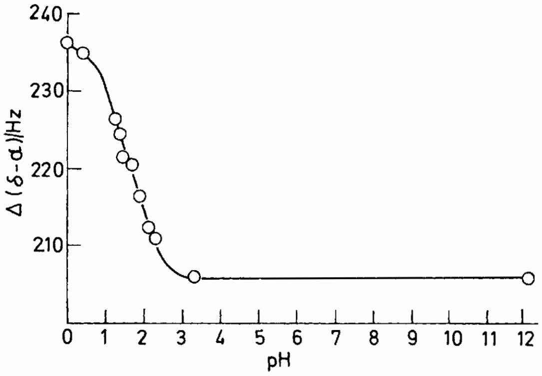
[21] Ref. 20, p. 76.

sulphonic acids (pK_a[22] < -1) the equilibrium corresponding to step a would be observable only in strong acids. The equilibria examined in the present study are of type (2) (' proton lost ').



^{1}H *Measurements*.—^{1}H N.m.r. has been extensively used for the determination of pK_a values of a large number of compounds.[23,24] The technique depends on the fact that protonation of a basic molecule leads to a downfield chemical shift in the spectral lines nearest to the protonation site because of a lowering of electron density at the basic centre. The extent of the chemical shift is a measure of the degree of protonation of the molecule and usually plots of change in chemical shift against pH (or against an acidity function, if a weak base is involved) give sigmoidal ' titration type ' curves.

For compound (1) shifts were measured from the centre peaks of the triplets due to the α- and δ-hydrogens. The pK_a could be calculated using the δ-hydrogens as an intramolecular standard and utilising a difference in chemical shift of 30 Hz between these and the α-hydrogens in acid (pH *ca.* 0) and alkaline solutions (pH *ca.* 12) (Figure). The chemical shift difference Δ(4 − 1) in the starting deuteriated acid was ascribed to (1) (zwitterionic form) and this was confirmed by measuring the spectrum of n-butylsulphamic acid (which should exist as a zwitterion) in pure D_2O which was identical with that of (1) in acid. The use of an intramolecular standard, which is said to minimise medium effects,[25] was convenient here because all the typical standards used have been shown to display shifts with changes in the acid strength of the medium.[22b,26] The use of the δ-hydrogens as an intramolecular standard was supported by the fact that the chemical shift differences of the peaks of added Me_3N and δ-hydrogen was constant in acid solutions ranging from 2 to 0.2M-DCl. For compound (2) shifts were measured from the centre peaks of the α- and γ-hydrogen triplets and the chemical shift difference Δ(3 − 1) was used to calculate pK_a. The use of the γ-hydrogens as an intramolecular standard was considered satisfactory because the chemical shift difference of the peaks of added Me_3N and the triplet due to these hydrogens was almost constant from 0.2 to 7.89M-HCl. For (3) shifts were measured for the α-, β-, and γ-protons. The chemical shift differences Δ(3 − 1) measured from the highest peak of the α- and the lowest downfield line of the ' γ '-triplet were used in subsequent calculations of the pK_a. The chemical shift difference, Δ(CH_3 − 1) could not be used since Δ(3 − CH_3) varied over the pH range employed in the study. The chemical shifts due to other protons in (1)—(3) could not be used because of their poor definition at some pH values. The complexity of its ^{1}H n.m.r. spectrum and the lack of readily discernible shifts on protonation precluded the use of this technique for determining the pK_a of (4). pK_a Values were calculated from the equation, $pK_a = \log(\Delta\nu - \Delta\nu_B)/(\nu_{BH^+} - \Delta\nu) + pH$, where $\Delta\nu_{BH^+}$ was the apropriate chemical shift difference measured at pH *ca.* 0 and $\Delta\nu_B$ was the chemical shift difference for the same hydrogen atoms at pH *ca.* 10.



Variation of Δ(δ − α) with pH for compound (1)

^{13}C *Measurements*.—The potential of ^{13}C n.m.r. has been mentioned[27] and recently demonstrated[28] when the pK_a of benzenesulphonic acid was determined and found to be in excellent agreement with the previously determined u.v. value. The kinetic acidities of some fluorine compounds have been measured from ^{19}F chemical shifts.[29a] Taft and Levins[29b] have found that pK_a values determined from chemical shifts are in good agreement with u.v. determined value. ^{31}P N.m.r. measurements have been used to study the protonation equilibria of aliphatic and aromatic phosphine oxides.[30]

^{13}C N.m.r. would appear to offer two advantages over ^{1}H n.m.r. for pK_a measurements. First, the magnitude of the observed shifts are greater[27,31] (the direction of the shifts[32] may also be both up- and down-field) and

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[22] (*a*) Ref. 20, p. 88; (*b*) A. Koeberg-Telder and H. Cerfontain, *J.C.S. Perkin II*, 1975, 226.

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[26] J. T. Edward, *Canad. J. Chem.*, 1971, **49**, 2364.

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[28] H. Cerfontain, A. Koeberg-Telder, and C. Kruk, *Tetrahedron Letters*, 1975, 3639.

[29] (*a*) K. J. Klabunde and D. J. Burton, *J. Amer Chem. Soc.*, 1972, **94**, 820; (*b*) R. W. Taft and P. L. Levins, *Analyt. Chem.*, 1962, **34**, 436.

[30] N. K. Skvortsov, A. V. Dogadina, G. F. Tereshchenko, N. V. Morkovin, B. I. Ionin, and A. H. Petrov, *Zhur. obshchei Khim.*, 1971, **41**, 2807.

[31] R. J. Pugmire and D. M. Grant, *J. Amer. Chem. Soc.*, 1968, **90**, 697.

[32] See I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa, and K. Goto, *J. Amer. Chem. Soc.*, 1973, **95**, 165; J. E. Sarneski, H. L. Surprenant, F. K. Molen, and C. N. Reilley, *Analyt. Chem.*, 1975, **47**, 2116.

secondly, uncertainty about the extent of medium effects, which are often a problem[23,24] in ^1H n.m.r. protonation studies are generally considered to be less.[28] A limiting factor (as with other forms of n.m.r.) may of course be poor solubility of the substrate under study.

The chemical shifts of the four different types of carbon atoms in (1) and (4) have been measured as a function of pH at *ca.* 12 values between *ca.* 0 and *ca.* 10. The shifts at pH *ca.* 0 and at *ca.* 10 were taken to represent the protonated (zwitterionic) form and the unprotonated form respectively. Chemical shift differences (in Hz) are given for (1) and (4) in Table 1. It is seen that the chemical shift difference between C-3 and -4, Δ(3 — 4), is almost constant over the whole pH range. Using these carbons as intramolecular standards, pK_a values could then be calculated in four ways utilising the differences Δ(4 — 1), Δ(4 — 2), Δ(3 — 1) and Δ(3 — 2) and using the equation, $pK_a = \log\ (\Delta\partial - \Delta\partial_B)/(\Delta\partial_{BH^+} - \Delta\partial) + pH$, where $\Delta\partial_{BH^+}$ was the appropriate chemical shift difference measured at pH *ca.* 0 and $\Delta\partial_B$ was the chemical shift difference for the same pair of carbon atoms at pH *ca.* 10. For compound (1) the four pK_a values obtained were 1.43 ± 0.07, 1.53 ± 0.07, 1.46 ± 0.03, and 1.51 ± 0.01 and for compound (4) the values were 1.42 ± 0.03, 1.43 ± 0.04, 1.43 ± 0.04, and 1.44 ± 0.03.

TABLE 1

^1H and ^{13}C Chemical shift differences (Hz) of unprotonated ($\Delta\nu_B$) and protonated ($\Delta\nu_{BH^+}$) sulphamates

Compound		Δ(4 — 1)		Δ(4 — 2)		Δ(3 — 1)		Δ(3 — 2)		Δ(4 — 3)	
		$\Delta\nu_B$	$\Delta\nu_{BH^+}$	$\Delta\nu_B$	$\Delta\nu_{BH^+}$	$\Delta\nu_B$	$\Delta\nu_{BH^+}$	$\Delta\nu_B$	$\Delta\nu_{BH^+}$	$\Delta\nu_B$	$\Delta\nu_{BH^+}$
(1)	Ba^{+2} [a]	206.0	236.0								
(2)	Na^+ [a]					200.0	227.0				
(3)	Na^+ [a]					227.0	261.5				
(1)	K^+ [b]	760.7	808.4	446.3	378.2	599.6	645.6	285.2	215.4	161.1	162.8
(4)	Na^+ [b]	712.1	828.7	208.0	138.6	721.7	835.8	217.5	145.8	9.5	7.1

[a] ^1H shifts. See Experimental shifts for details. [b] ^{13}C Shifts. See Experimental shifts for details.

TABLE 2

Conductances of (1)(acid) and (4)(acid) and of (1)K^+ and (4)Na^+ in water at 25 °C [a]

10^4[(1)(acid)]/M [a]	Λ	10^4[(1)K^+]/M	Λ	10^4[(4)(acid)]/M [b]	Λ	10^4[(4)Na^+]/M	Λ
100	247.7	10	45.47	132	248.7	100	71.96
88.5	252.7	9	45.49	116.6	256.2	50	73.42
78.3	258.1	8.1	45.43	103.1	263.2	25	74.6
72.1	261.7	7.3	45.50	91.1	270.3	12.5	75.7
63.8	266.7	6.6	45.59	80.5	276.8	6.25	75.4
56.5	271.3	5.9	45.63	71.1	282.6	3.13	76.5
48.0	276.7	4.7	45.70	59.1	291.6	1.56	77.8
44.2	279.2	1.8	45.81	52.2	297.7	0.78	72.7
39.1	282.8	1.1	46.78	46.1	303.0	0.39	74.0
36.0	284.7	0.68	50.03	38.3	310.7	0.20	*c*

[a] 25 readings were taken. A representative set of 10 readings including the first and the last are given. [b] 20 readings taken. A representative set including the first and the last are given. [c] Could not be determined.

Potentiometric Measurements.—The pK_a value was calculated at each pH from the equation: $pK_a = pH + \log\ (1 - \alpha)/\alpha$,$\alpha$ being calculated at each pH from the equation: $\alpha = c^{-1}\ ([Na^+] + [H^+] - K_W/[H^+])$ where c, the concentration of the substrate, $[Na^+]$, and $[H^+]$ were computed after each addition of base. The last term was generally negligible. In a test run, the pK_a of sulphamic acid was measured by this method using an aqueous solution of the anhydrous acid, which was 0.1M at 50 ml dilution. A pK_a of 1.15 ± 0.06 in excellent agreement with the value of Hargreaves[3] (1.19) was obtained. pK_a Values for compounds (1) and (4) are given in Table 3.

Conductance Measurements.—The conductance readings are given in Table 2. The equivalent conductance at infinite dilution (Λ_0) was obtained either from a plot of equivalent conductances (Λ) against $c^{\frac{1}{2}}$ or from equation (3) where HSul is the appropriate sulphamic acid, MSul is a suitable metallic sulphamate, and the

$$\Lambda_0(\mathrm{HSul}) = \Lambda_0(\mathrm{Sul}) - \lambda_0(M^+) + \lambda_0(H^+) \qquad (3)$$

remaining terms are the ionic conductances of the metal ion and hydrogen respectively. From measurements on (4)(sodium salt)$^+$, Λ_0 was taken as 77.8 which gives a value of 377.5 for the equivalent conductance at infinite dilution of (4) (acid) after substitution of the ionic conductances of sodium (50.1) and hydrogen (349.8) in the above equation. This is very close to the value obtained (381.0) from a plot of Λ *versus* $c^{\frac{1}{2}}$. The pK_a value was calculated from the equation $pK_a = -\log\ [c\ \alpha^2/(1 - \alpha)]$, where $\alpha - \Lambda/\Lambda_0$. The p$K_a$ values obtained by this method for compounds (1) and (4) are given in Table 3.

Conclusions.—All the pK_a values determined by the various methods are brought together in Table 3. If runs 1—6 for compound (1) are averaged a pK_a of 1.70 ±

0.22 is obtained. Considering that four quite independent methods were used in obtaining this value, the spread of 13% is small. For compound (4) the average value (runs 12—14) is 1.71 ± 0.29 (spread *ca.* 17%) which indicates that the literature value of 2.28 [11] is too high. For compound (2) the value obtained in perchloric acid (run 7) appears to be anomalous. The three values for the other acids are close and if averaged gave a value of 1.40 ± 0.05. Compound (3) has been determined only by ^1H n.m.r. and in deuterium chloride.

TABLE 3

pK_a Values for sulphamates and conditions and method of determination

Run no.	Compound	Concentration (M)	T/K	Medium [a]	pK_a	Spread (±)	Method [b]
1	(1)Ba^{+2}	0.03	301	1.26M-DCl	1.57	0.07	A
2	(1)Ba^{+2}	0.03	301	0.58M-DCl	1.59	0.09	A
3	(1)K^+	0.122	294.5	1.33M-HCl	1.48	0.05	B
4	(1)H^+	0.03	294.5	H_2O	1.92	0.10	C
5	(1)H^+	0.01	294.5	H_2O	1.84	0.12	C
6	(1)H^+	0.01	298	H_2O	1.64	0.02	D
7	(2)Na^+	0.05	301	1.0M-$HClO_4$	0.98	0.06	A
8	(2)Na^+	0.05	301	1.0M-HCl	1.43	0.07	A
9	(2)Na^+	0.05	301	1.0M-H_2SO_4	1.41	0.05	A
10	(2)Na^+	0.05	301	1.0M-DCl	1.35	0.08	A
11	(3)Na^+	0.10	301	1.0M-DCl	1.52	0.04	A
12	(4)Na^+	0.10	294.5	1.46M-HCl	1.42	0.03	B
13	(4)H^+	0.10	301	H_2O	1.77	0.05	C
14	(4)H^+	0.0132	298	H_2O	1.80	0.03	D

[a] In the case of the various acidic media, the stated molarity is the initial value prior to the addition of portions of base. [b] A, ^1H N.m.r.; B, ^{13}C n.m.r.; C, potentiometric; D, conductimetric.

It is of interest that ^{13}C and ^1H n.m.r. methods for measuring pK_a give approximately the same values of protonation constant and this suggests that the ^{13}C and ^1H chemical shifts observed reflect the extent of charge formation on nitrogen and that the contribution of processes such as solvation and changes in the magnetic anistropy of neighbouring bonds are small. Substantial differences in the values of protonation constants obtained for various phosphine oxides from ^{31}P and ^1H n.m.r. shifts have been found,[30] and it has been suggested that the ^{31}P chemical shifts reflect direct protonation more so than the ^1H shifts which the authors describe as ' depending on the state of the molecule in the solution as a whole '. The present work appears to be the first attempt to compare ^{13}C and ^1H n.m.r. methods for determining pK_a.

The ^1H n.m.r. and potentiometric determinations were made at 28 °C, the ^{13}C n.m.r. measurements at 21.5 °C and the conductance experiments at 25 °C. These temperatures should not affect the measured pK_a values by more than 0.013 which is within the experimental error.[33]

The acid-strengthening effect of the adjacent sulphonate group, well illustrated in the series $NH_3^+[CH_2]_nSO_3^-$, p$K_a = 1.1$ ($n = 0$), 5.75 ($n = 1$), and 9.20 ($n = 2$), *etc.*,[34] is the dominant feature in the acidity of the four sulphamates examined. Thus the nature of R in compounds (1)—(4) affects the acidity only slightly. However in aminomethanesulphonic acids, $RNH_2^+CH_2SO_3^-$, where the sulphamate group is one carbon atom removed from the amino-function, the group R plays a great role since for R = H, pK_a = 5.75 but, with R = Bu^n, pK_a = 7.1.[35]

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[33] Using the formula given in ref. 20, p. 7.

[34] R. P. Bell, ' The Proton in Chemistry,' Chapman and Hall, London, 1963, 2nd edn.

[35] F. H. McMillan and I. C. Pattison, *J. Pharm. Sci.*, 1969, **58**, 730.