DETERMINATION OF THE SUBSTITUENT CONSTANT σ_p^- FOR THE THIOAMIDE GROUP $-CSNH_2$ FROM THE IONIZATION OF ANILINES AND PHENOLS

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Thermodynamic ionization constants pK_a 2·62 ± 0·01 for the primary aromatic amino group of 4-aminothiobenzamide and pK_a 8·28 ± 0·01 for the phenolic hydroxy group of 4-hydroxythiobenzamide have been determined by ultra-violet spectrophotometry at 25°C. By using these pK_a values and the Hammett equations ($\log K_a$ vs σ) for the ionization of fourteen 3- or 4-substituted phenols and thirteen 3- or 4-substituted anilines the substituent constant $\sigma_p^- = 0{\cdot}68$ (from the ionization of anilines) or $\sigma_p^- = 0{\cdot}73$ (from the ionization of phenols) of the thioamide group $-CSNH_2$ was calculated.

Thiobenzamides rank among biologically active compounds that have been studied extensively in a number of laboratories. The relations between chemical structure of thiobenzamides and their biological activity were reviewed earlier[1,2]. The physicochemical properties of thiobenzamides have been discussed by Walter and Voss in a monograph dealing with the chemistry of amides[3]. In spite of these facts the values of Hammett substituent constants σ_p and σ_m of the thioamide group could not be found in the literature until recently[4,5]. The $-CSNH_2$ group belongs to electron-withdrawing substituents that are capable of conjugation with a reaction centre attached directly to the benzene ring in the *para*-position. For such a kind of substituents the Hammett equation (*1*) involving conventional σ_p constants does not hold and therefore another type of substituent constant, σ_p^-, is defined[6,7].

$$\log K_a = \log K_a^0 + \varrho\sigma \qquad (1)$$

The aim of this work is to determine the σ_p^- constant of the thioamide group which has not yet been published in the literature. For this purpose the equation (*1*) correlating the ionization of anilines or phenols with substituent constants is employed.

The parameters $\log K_a^0$ and ϱ in the straight line (*1*) needed for the calculation of the σ_p^- of the thioamide group are determined by linear regression of input data based on a series of literature pK_a values of 3- and 4-substituted anilines[8] or phenols[9] and σ_m, σ_p (or σ_p^- where appropriate) values of corresponding substituents compiled earlier[6,7]. With the $\log K_a^0$ and ϱ computed the σ_p^- of the $-CSNH_2$ group can be calculated from the pK_a values of 4-aminothiobenzamide and 4-hydroxythiobenzamide.

EXPERIMENTAL

Materials. The 4-aminothiobenzamide (*I*) was synthesized and purified as described elsewhere[10]. The 4-hydroxythiobenzamide (*II*) was prepared by introducing pre-dried hydrogen sulphide into 1 g of 4-hydroxybenzonitrile in 5 ml of 1 : 1 pyridine–triethylamine mixture at room temperature for 24 h (TLC test). The reaction mixture was poured onto ice and the product precipitated was purified by crystallization (water); yield 38%, m.p. 206—208°C (ref.[11] m.p. 199°C), for C_7H_7NOS (153·2) calculated: 20·93% S; found: 20·91% S. Aniline, phenol and 4-methylphenol were purified by distillation; 4-methylaniline, 4-bromoaniline and 4-nitrophenol were recrystallized from methanol, ethanol and water respectively. All other chemicals were of analytical grade. Distilled water deaerated by bubbling with nitrogen was used throughout.

Apparatus and measurements. A Radiometer PHM-64 pH meter with a GK-2401-B combined glass electrode calibrated with standard buffers (hydrogen phthalate pH 4·01, phosphate 6·87 and borate 9·18) was used for the pH measurements. The spectrophotometric measurements were carried out in fused silica cells (volume 100 cm^3, path length 35 mm). The Pye-Unicam SP-1700 spectrophotometer used was equipped with a thermostatted cell holder (25°C). Solutions of *I* ($c = 2-2·5 . 10^{-5}$ mol l^{-1}), *II* ($1·3-1·5 . 10^{-5}$ mol l^{-1}), aniline, 4-methylaniline and 4-bromoaniline ($3-4 . 10^{-5}$ mol l^{-1}), phenol and 4-methylphenol ($1-1·2 . 10^{-4}$ mol l^{-1}) and 4-nitrophenol ($1·5-2 . 10^{-5}$ mol l^{-1}) were titrated with small volumes of 0·1—2M-HCl (for anilines) or 0·1—2M-NaOH (for phenols) directly in the spectrophotometric cell at selected wavelenghts and the absorbance (*A*) and pH of the solutions were measured simultaneously as described earlier[12]. For the selection of optimum wavelengths the absorption curves of the above compounds were measured at various pH of the test solutions. The starting ionic strength $I = 0·02$ was adjusted with KCl. Pure aqueous solutions of the phenols were titrated whilst the solutions of anilines contained 0·5% of ethanol (because of problems with the solubility of *I* in water the stock solutions of the anilines were prepared in 50% ethanol).

Calculations. The data of the *A* vs pH curves obtained involving typically 25 to 30 experimental points and covering the pH range within ±0·8 pH units around the inflection point were used to compute[13] the molar absorption coefficients of the protonized and deprotonized species (ε_{HL} and ε_L, respectively) and the mixed ionization constants pK_a^M of the compounds under study by non-linear regression. The pK_a^M constants were converted to thermodynamic constants pK_a by using corrections for the actual ionic strength according to Albert and Serjeant[14]. All the *A*–pH curves were measured in quadruplicate and the final pK_a were calculated as the arithmetic mean of the four individual results. The parameters ϱ and pK_a^0 in equation (*1*) were calculted by a linear regression program which forms a part of the CHEMSTAT package[13].

RESULTS AND DISCUSSION

The non-ionized form of *I* exhibits an absorption maximum at 328 nm (the mean molar absorption coefficient $\varepsilon_L = 13\,516 \pm 128\,\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$) and the proto-

TABLE I

Thermodynamic ionization constants (25°C) of anilines and phenols and substituent constants σ_m, σ_p or σ_p^- of the substituents

Substituent	σ^x ref.[6]/ref.[7]	pK_a (ArOH) ref.[9]	pK_a ($ArNH_3^+$) ref.[8]
H	0·00/0·00	9·994; 9·996[a]	4·596; 4·600[a]
4-Br	0·26/0·23	9·366	3·888; 3·872[a]
4-Cl	0·24/0·23	9·406	3·982
4-CN	0·99/0·88	7·967	—
4-I	0·28/0·18	9·327	3·812
4-OCH_3	−0·12/−0·27	—	5·357
4-CH_3	−0·14/−0·17	10·276; 10·260[a]	5·084; 5·074[a]
4-NO_2	1·25/1·24	7·151; 7·142[a]	1·019
3-Br	0·37/0·39	9·031	3·527
3-Cl	0·37/0·37	9·119	3·521
3-CN	0·62/0·56	8·608	—
3-I	0·34/0·35	9·033	3·583
3-OCH_3	0·10/0·12	9·652	4·204
3-CH_3	−0·07/−0·07	—	4·712
3-C_2H_5	−0·08/−0·07	10·069	—
3-NO_2	0·71/0·71	8·360	2·460
4-$CSNH_2$	0·73[c]; 0·68[b]	8·280 ± 0·006[a]	2·604 ± 0·008[a]

[a] This communication; [b] this communication, σ_p^- from the ionization of anilines; [c] this communication, σ_p^- from the ionization of phenols; [x] σ_m, σ_p or σ_p^- as appropriate.

TABLE II

Parameters of Hammett equations (*1*) for anilines and phenols and calculated values of σ_p^- ($CSNH_2$). (*n* number of points processed; ϱ reaction constant; log K_a^0 intercept for $\sigma = 0$; *r* correlation coefficient; standard deviations are shown in parentheses)

Compounds	σ	*n*	log K_a^0	ϱ	*r*	σ_p^-
Ar-NH_2	ref.[6]	13	−4·654(0·048)	2·989(0·11)	0·9932	0·69 ± 0·022
Ar-NH_2	ref.[7]	13	−4·557(0·028)	2·868(0·06)	0·9975	0·68 ± 0·018
Ar-OH	ref.[6]	14	−9·912(0·031)	2·148(0·06)	0·9956	0·76 ± 0·023
Ar-OH	ref.[7]	14	−9·892(0·025)	2·217(0·02)	0·9972	0·73 ± 0·015

nized form at 290 nm ($\varepsilon_{HL} = 6\,720 \pm 70\,dm^3\,mol^{-1}\,cm^{-1}$); the A–pH curves were measured at 328 nm, where the $\varepsilon_{HL} = 2\,800 \pm 43\,dm^3\,mol^{-1}\,cm^{-1}$. The non-ionized form of *II* has an absorption maximum at 302 nm ($\varepsilon_{HL} = 12\,018 \pm 130\,dm^3\,.\,mol^{-1}\,cm^{-1}$) and its conjugated base at 356 nm ($\varepsilon_L = 18\,637 \pm 175\,dm^3\,mol^{-1}\,.\,cm^{-1}$); the A–pH curves of *II* were measured at 356 nm where the $\varepsilon_{HL} = 964 \pm 23\,dm^3\,mol^{-1}\,cm^{-1}$. The computed pK_a of *I* and *II* are shown in Table I together with the pK_a values of other substituted anilines and phenols selected from critical tables[8,9] and used for computing $\log K_a^0$ and ϱ in equation (*1*). The selection is based on the following criteria: only the thermodynamic pK_a determined by spectrophotometry at 25°C and assesed by the authors of the compilations[8,9] as reliable are accepted. The Table I involves also data for aniline, 4-bromoaniline, 4-methylaniline, phenol, 4-methylphenol and 4-nitrophenol determined by us to check the reliability of our measurements and compatibility of our results with the literature pK_a. It is clearly seen that our pK_a values agree well with those published earlier and that, as might be expected, the presence of 0·5% of ethanol in the titrated solutions (for anilines) has negligible effect on the pK_a values determined. Since somewhat different values of σ (σ_m, σ_p or σ_p^-) constants for the same substituents can be found in the literature, the σ constants from two sources[6,7] are employed as input data for the $\log K_a$–σ correlations (see Table I). The computed $\log K_a^0$ and ϱ for anilines and phenols with the two different sets of the σ constants together with the calculated σ_p^- for the $-CSNH_2$ group are presented in Table II. As closer correlations are obtained when using the σ constants from Kuchař and Rejholec monograph[7] (and even the ϱ values for the anilines and phenols compare well with those published by Exner[6], cf. 2·889 and 2·229, respectively) the corresponding σ_p^- ($CSNH_2$) calculated from those correlations should be more accurate. Though, theoretically, the σ_p^- determined from the ionization of different types of compounds ought to give the same value, quite often considerable differences between such σ_p^- are observed[15] (and usually explained in terms of difference, between the ionized and non-ionized forms, in resonance interaction of substituent with the reaction centre, on passing from one group of compounds to another). In view of those facts the difference between the σ_p^- ($CSNH_2$) determined in our case from the ionization of anilines and phenols and amounting to 0·05σ units does not seem to be critical. It should be noted that our σ_p^- ($CSNH_2$) of 0·68 or 0·73 is consistent with the $\sigma_p^- = 0{\cdot}61$ (ref.[7]) or 0·62 (ref.[6]) of the related $-CONH_2$ group.

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