Determination of the Hammett constant σ_p for the thioamide group

[a]J. GABRIEL, [a]I. NĚMEC, [a]N. ZIMOVÁ, and [b]K. WAISSER

[a]*Department of Analytical Chemistry, Faculty of Natural Sciences,*
Charles University, CS-128 40 Prague

[b]*Department of Inorganic and Organic Chemistry, Faculty of Pharmacy,*
Charles University, CS-500 27 Hradec Králové

The value of the Hammett substituent constant $\sigma_p = 0.40$ has been obtained for the thioamide group from potentiometric determination of the dissociation constants for benzoic acid derivatives. Because of insolubility of 4-thiocarbamoylbenzoic acid in water, the series of pK_a measurements on seven derivatives of benzoic acid had to be carried out in diluted methanol and the σ_p value was obtained from the $pK_a(50\ \%\ CH_3OH, 25\ °C)$ *vs.* σ_p dependence.

На основании потенциометрического определения констант диссоциации производных бензойной кислоты определена величина Гамметтовой константы заместителя, $\sigma_p = 0{,}40$, для тиоамидной группы. Вследствие нерастворимости 4-тиокарбамоилбензойной кислоты в воде, ряд измерений $pK_a(50\ \%\ метанол, 25\ °C)$ семи производных бензойной кислоты пришлось проводить в 50 % метаноле, и величины σ_p были получены из зависимости $pK_a(50\ \%\ метанол, 25\ °C)$ от σ_p.

The reactivity of benzene derivatives with the reaction centre located in a side chain and a substituent in the *para* or *meta* position is described by the empirical Hammett equation

$$\log (k/k°) = \varrho\sigma$$

where k is an equilibrium or rate constant, $k°$ under standard conditions, ϱ is a function of the reaction conditions and σ describes the substituent effect [1]. Constant σ is very important, as a numerical quantity describing a certain substituent, and transcends the field of validity of the Hammett equation; it yields a quantitative scale for substitution effects that have previously been evaluated only qualitatively. In addition to the field of theoretical organic chemistry, substituent constants find use *e.g.* in correlations between the chemical structure and biological activity in pharmacy, which permits more effective research of new chemotherapeuticals [2—4]. This work was also stimulated by research of aromatic thioamides from the point of view of their tuberculostatic activity [5, 6]. The Hammett constant σ_p for the thioamide group cannot be found in the reviews and thus this quantity has not yet been described [7, 8].

Experimental

Prior to use, benzoic acid was purified by sublimation and its derivatives, except 4-thiocarbamoylbenzoic acid, by recrystallization from methanol. 4-Thiocarbamoylbenzoic acid was synthesized (at the Faculty of Pharmacy, Charles University, Hradec Králové) by the action of hydrogen sulfide on p-cyanobenzoic acid and was purified by multiple recrystallization from hot water [9]. All the substances were dried prior to measurement for 20 h over phosphorus pentaoxide at a pressure of 2.5 kPa and a temperature of 60 °C. Substances of anal. grade purity (Lachema, Brno) were used, the melting points of which were in a good agreement with the literature values. The pH measurements were performed with a combined glass-calomel electrode and a pH-meter 26, both from Radiometer, Denmark. The electrode was calibrated by aqueous buffers of pH 4.01 and 7.00.

Stock solutions of 0.002 M benzoic, p-amino-, p-nitro-, p-chloro-, p-bromo-, p-acetyl-, p-methoxy-, and p-thiocarbamoylbenzoic acid were prepared in 50 vol. % methanol. A volume of 10 cm³ of a stock solution was diluted to 50 cm³ in a titration vessel; the ionic strength was adjusted to $I = 0.1$ mol dm^{-3} by NaClO$_4$. The titration vessel was wrapped in an aluminium foil to prevent absorption of light. The temperature was adjusted to 25 °C and the solution was titrated by adding small portions of 0.2 M-NaOH, prepared by dilution of a 50 % solution. In the equivalence point, the volume of the hydroxide added amounted to 0.1 cm³, which caused only a minimal effect on the relative permittivity of the medium. Purified and dried nitrogen was passed through the solution during the titration.

To calculate a_{H^+} in water, the activity coefficient for the H$^+$ ion, 0.83, according to *Kielland* [10] was used, for 50 % methanol, the value 0.70, according to *Hulshoff* and *Perrin* [11] was employed (Table 1). For the calculation of pK_a(50 % CH$_3$OH, 25 °C) of the studied substances from the experimental points on the titration curve, the *Briggs* and *Stuehr* [12] version of the computer program was modified for the Video-Genie computer. It is based on the solution of the equations

$$V = V_e + a_{H^+}(V + R - \Delta V)/(K_i - R + \Delta V)$$

where

$$R = (c_{H^+} - c_{OH^-})\, V_t/c_B$$

$$1/K_i = (V_e - V - R + \Delta V)/(V + R - \Delta V)\, a_{H^+}$$

where the solution volume and the concentrations are related by

$$Vc_B c_{H^+} = V_e + K_S(V_0 + V)$$

V_0 is the solution volume in the beginning of the titration, V is the volume of the titrant added, c_B is the titrant concentration, V_t is the total volume of the solution, K_i, K_S are the dissociation constants of the studied compound and of

Table 1

Some properties of CH₃OH—H₂O mixtures according to *Hulshoff* and *Perrin* [11]

Quantity	$\varphi(CH_3OH)/\%$				
	0	30	40	50	60
ε_r	78.48	65.55	60.94	56.28	51.67
pK_S	14.00	14.07	14.08	14.11	14.14
γ_{H^+}	0.79	0.74	0.72	0.70	0.67
γ_{OH^-}	0.75	0.70	0.68	0.65	0.62

Table 2

pK_a' Values for benzoic acid at 25 °C

pK_a'	0.1 M solution	Ref.
3.997	KCl	[17]
3.998	NaCl	[17]
4.01	NaClO₄	[18]
4.116	(C₂H₅)₄NBr	[12]

the solvent, V_e is the theoretical volume of the hydroxide in the equivalence point and ΔV is the hydroxide volume required to neutralize acidic impurities; the initial estimates are iteratively refined. The program treats the titration curve points in the almost linear region in the beginning of titration. These points are in the region of rapid stabilization of equilibrium potential and thus are subject to the smallest experimental error. As the literature does not give* the dissociation constants for benzoic acid (derivatives) in 50 % methanol, the method was tested on an analogous determination of pK_a' of benzoic acid in water. The value found, $pK_a' = 4.04 \pm 0.05$ (4 measurements), is in a good agreement with the values found under analogous conditions (Table 2).

Results and discussion

For the correlations, the Hammett constant values according to *Exner* [19] and *Hansch* [7] were used. The pK_a experimental values (50 % CH₃OH, 25 °C) are means of five measurements (Table 3). The correlation with the Hansch

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* The dissociation constants for benzoic acid derivatives have been given *e.g.* for 50 % C₂H₅OH by *Mollin et al.* [13], for 100 % CH₃OH by *Exner* and *Kalfus* [14], *Ludwig et al.* [15]; for recent data in 70 % CH₃OH see *Kenndler* and *Jenner* [16].

Table 3

Dissociation and Hammett constants of the measured substances

Substituent	pK_a(50 % CH_3OH, 25 °C)	σ_p According to Hansch	σ_p According to Exner
H	5.11 ± 0.06	0	0
p-NH_2	5.78 ± 0.02	−0.66	−0.57
p-NO_2	4.26 ± 0.04	0.78	0.81
p-Cl	4.85 ± 0.08	0.23	0.22
p-Br	4.90 ± 0.06	0.23	0.22
p-CH_3CO	4.67 ± 0.02	0.50	0.47
p-CH_3O	5.45 ± 0.03	−0.27	−0.28
p-NH_2SC	4.70 ± 0.04	—	—

values yields the equation

$$pK_a(50\text{ \% }CH_3OH,\ 25\text{ °C}) = 5.1215 - 1.0430 \cdot \sigma_p$$

and gives the Hammett constant for the *p*-thioamide group

$$\sigma_p = 0.404\ (r = 0.9961,\ F = 635.66,\ s = 0.0485)$$

A closer correlation was obtained when using the Exner Hammett constant values. The equation

$$pK_a(50\text{ \% }CH_3OH,\ 25\text{ °C}) = 5.1383 - 1.0895\ \sigma_p$$

gives the value of the Hammett constant for the *p*-thioamide group

$$\sigma_p = 0.401\ (r = 0.9982,\ F = 1347.59,\ s = 0.0334)$$

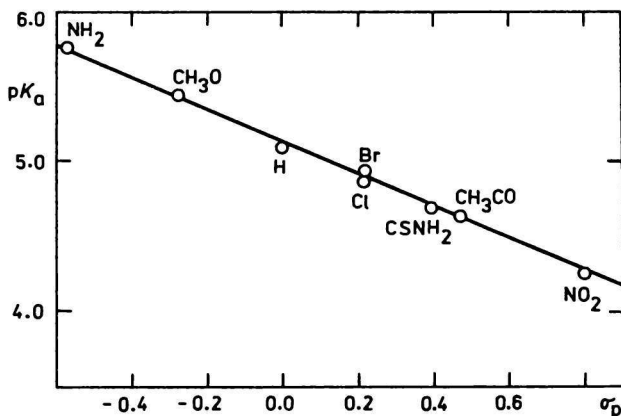This dependence is plotted in Fig. 1.

Fig. 1. Dependence of pK_a values in 50 % methanol on Hammett constants σ_p.

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