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Substituent effects on the thioamide group in thiobenzanilides: simultaneous conformational and acid–base equilibria

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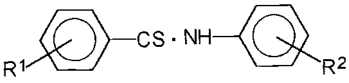
ABSTRACT: Substituent effects in substituted thiobenzanilides were investigated by the acid dissociation constants in water and the half-wave potentials of the anodic oxidation in acetonitrile; the substituents were chosen with respect to related pharmacological research. The p*K* values are well correlated by the Hammett equation, and the effects of substituents in the two benzene rings are additive. Since the acid–base equilibrium is combined with an equilibrium of conformers $Z \rightleftharpoons E$, the general mathematical consequences for a Hammett correlation were calculated. In the common case, a Hammett correlation is not obeyed for the apparent dissociation constants even when it is obeyed for all partial processes. In the present case, the effect of conformation is relatively slight and insufficient to disturb the overall Hammett correlation of the acidities. The half-wave potentials gave bad correlations, only an additive relationship is roughly valid. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: thioamides; thiobenzanilides; dissociation constants; conformation equilibrium; Hammett equation

INTRODUCTION

Our systematic investigation of thioamides has been proceeding along two lines. On the one hand, we followed their pharmacological activity as tuberculostatics[1] and antimycotics,[2] inhibition of photosynthesis[3] and hepatotoxicity.[4] On the other, we investigated their physico-chemical properties with particular respect to QSAR. In the latter case, the thioamide group may either act as a substituent[5–9] characterized by constants σ of a different kind, or as a functional group on which some observable properties are measured,[10,11] or ultimately as a connecting group characterized by its ability to transfer the substituent effects.[8,9]



The present paper may be classified in the second category. We are dealing with the dissociation constants of disubstituted thiobenzanilides **1–38** (Table 1) with substituents in both benzene rings. The choice of substituents in **1–30** was dictated by the intention to use the same compounds also in pharmacological studies;[2a] **31–38** have been used already in a study of the transmission through the thioamide group.[8] Here both sets are treated together. The range of substituents is thus somewhat restricted, in particular strong acceptors are lacking. However, the two substituents 3,4-Cl_2 are together almost as strong as any common acceptor, which would not be acceptable in studies of pharmacological activity. The dissociation constants have been fundamental quantities in the theory of substituent effects and may also be of importance for the mechanism of pharmacological activity. In addition, we have measured the half-wave potentials in voltammetric oxidation. In our previous studies,[7–11] all properties measured were compared with those of the corresponding amides. In the present case, we do not have this possibility. On the other hand, these compounds offer a rare opportunity of studying simultaneous ionization and conformation equilibria. Both thiobenzanilides and their anions exist in an equilibrium of two relatively stable conformations $Z \rightleftharpoons E$.[12,13] The abundance of the conformers was determined previously from the integrated intensity of the N—H bands in the infrared spectra.[13] With this knowledge, we might construct the complex depen-

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Table 1. Physico-chemical properties of substituted thiobenzanilides **1–38**

	Substituents					
Compound	X	Y	p*K*	$E_{1/2(V)}$	Population [*Z*]/[*E*][a]	LogK_C[a]
1	H	H	11.12	1.04	16	1.194
2	H	4-CH_3	—	1.01	15	1.170
3	H	4-OCH_3	11.72	0.95	18	1.263
4	H	4-Cl	10.85	1.08	26	1.411
5	H	3,4-Cl_2	9.96	1.14	41	1.616
6	H	4-Br	10.42	1.09	26	1.417
7	4-CH_3	H	11.50	—	14	1.161
8	4-CH_3	4-CH_3	—	1.03	14	1.131
9	4-CH_3	4-OCH_3	—	0.96	17	1.226
10	4-CH_3	4-Cl	10.80	1.13	22	1.349
11	4-CH_3	3,4-Cl_2	10.18	1.16	37	1.567
12	4-CH_3	4-Br	10.81	1.04	23	1.354
13	4-OCH_3	H	11.65	1.04	12	1.093
14	4-OCH_3	4-CH_3	11.81	0.99	12	1.070
15	4-OCH_3	4-OCH_3	11.85	—	13	1.118
16	4-OCH_3	4-Cl	10.93	1.02	20	1.293
17	4-OCH_3	3,4-Cl_2	10.14	1.03	32	1.504
18	4-OCH_3	4-Br	10.95	1.03	20	1.309
19	4-Cl	H	10.76	1.07	10	1.012
20	4-Cl	4-CH_3	11.18	1.05	9	0.943
21	4-Cl	4-OCH_3	11.26	0.97	11	1.057
22	4-Cl	4-Cl	10.25	1.13	18	1.245
23	4-Cl	3,4-Cl_2	9.51	1.15	28	1.454
24	4-Cl	4-Br	10.24	1.10	18	1.259
25	3-Br	H	10.49	1.01	20	1.307
26	3-Br	4-CH_3	10.89	1.09	20	1.300
27	3-Br	4-OCH_3	10.99	1.01	23	1.369
28	3-Br	4-Cl	10.10	1.15	41	1.608
29	3-Br	3,4-Cl_2	9.26	1.15	91	1.957
30	3-Br	4-Br	9.96	1.14	45	1.650
31	H	3-F	10.29	—	24	1.372
32	4-CH_3	3-F	10.63	—	21	1.316
33	4-Cl	3-F	10.16	—	17	1.226
34	3-Br	3-F	10.01	—	35	1.546
35	H	4-F	10.77	—	27	1.434
36	4-CH_3	4-F	10.97	—	24	1.388
37	4-Cl	4-F	10.41	—	19	1.280
38	3-Br	4-F	10.32	—	39	1.586

[a] Ref. 13; the values given are rounded off to 1% and were calculated by peak separation using a mixture of Gaussian and Lorentzian peak shapes; peak separation according to Voigt gave only insignificantly differing results.

dence of the apparent p*K* on substitution and even attempt to estimate separately the acidity of the *Z* and *E* conformers. As far as we know, a problem of this kind has not yet been encountered in correlation analysis: only the effect of conformation within a substituent has sometimes been mentioned.[7,14]

EXPERIMENTAL

Substituted thiobenzanilides **1–30**[2a] and **31–38**[15] have been described previously. Dissociation constants in water were measured by the spectrophotometric method: experimental details were given previously.[6] The p*K* values are listed in Table 1. Each measurement was repeated five times. Standard deviations from the mean were for individual compounds 0.01–0.04 p*K* units, hence the overall standard deviation of the mean values may be estimated as 0.015 p*K* units. Anodic oxidation on a platinum electrode in acetonitrile was carried out as described previously in the case of the unsubstituted benzanilide.[16] The values of $E_{1/2}$ are given in Table 1.

RESULTS AND DISCUSSION

Hammett correlation of the acidities

In the case of thiobenzanilides **1–38**, the Hammett equation can be applied in three ways:

(a) with a variable substituent X while Y is fixed,

Table 2. Statistics of the correlations of p*K* and $E_{1/2}$ of substituted thiobenzanilides **1–38**

Line	Quantity	Eqn	Regression coefficients[a] ρ_X	ρ_Y	R[b]	SD[b]	f[b]	ψ[c]
1	p*K*	(1)	1.39(11)		0.912	0.15	30	0.42
2	p*K*	(2)		2.03(10)	0.964	0.15	33	0.26
3	p*K*	(3)	1.41(8)	2.00(8)	0.983	0.12	32	0.18
4	p*K*	(8)	1.55(8)	2.15(7)	0.987	0.10	32	0.16
5	p*K*	(10)				0.10	23	0.16
6	$E_{1/2}$	(11)	0.12(3)[d]	0.16(2)[d]	0.863	0.033[d]	25	0.52
7	$E_{1/2}$	(12)				0.023[d]	18	0.37

[a] Standard deviation in parentheses.
[b] *R* = Correlation coefficient, SD = standard deviation from the regression and *f* = degrees of freedom; no 'outliers' were eliminated.
[c] Statistic measuring the fit in a general case including also the linear regression;[20] ψ <0.1 means a good fit, ψ > 0.5 means no correlation existing.
[d] In volts.

according to Eqn. (1):

$$\log K_{X,Y} = \log K_{H,Y} + \rho_X\sigma_X + \varepsilon \tag{1}$$

(b) with a variable Y and fixed X, Eqn. (2):

$$\log K_{X,Y} = \log K_{X,H} + \rho_Y\sigma_Y + \varepsilon \tag{2}$$

(c) with both X and Y variable. In this case the Hammett equation takes the form of Eqn. (3):

$$\log K_{X,Y} = \log K_{H,H} + \rho_X\sigma_X + \rho_Y\sigma_Y + \varepsilon \tag{3}$$

with σ_X and σ_Y belonging to the two sides of the molecule. This extension of the validity range[17] is not self-evident and assumes simultaneous validity of two independent relationships: the Hammett equation and the principle of additivity.[18,19] In all the equations, ϵ represents a random variable (fitting error): the sum of squares $\sum\epsilon^2$ is minimized in the fitting procedure.

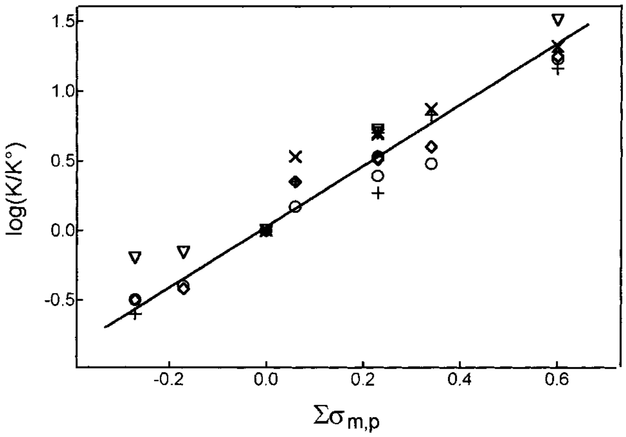


Figure 1. Hammett plot of relative acidities of thiobenzanilides $XC_6H_4CSNHC_6H_4$ vs constants $\sigma_{m,p}$ of the substituent Y, Eqn. (2): X = (+) H; (×) 4-CH_3; (▽) 4-OCH_3; (◊) 4-Cl; (○) 3-Br

The results of the correlations are given in Table 2, lines 1–3. In all cases, the correlations are satisfactory and the standard deviations are near to the estimated experimental uncertainty. Equation (2) is worth a graphical representation: Fig. 1 reveals no specific deviations of certain substituents, no outliers and only a marked scatter. The constants ρ are equal (within their uncertainty) in the different equations: ρ_X in Eqns (1) and (3), ρ_Y in Eqns (2) and (3). The ρ values are also comparable to those for other reactions; e.g. ρ_Y is equal to that in the same, position of substituted *N*-phenylbenzenesulfonamides.[21] As expected, ρ_Y is greater than ρ_X owing to the shorter distance of the substituent even when the system is conjugated. For the substituents Y, conjugation through the benzene ring should require merely the modified constants σ^- but our set is insufficient for a decision.

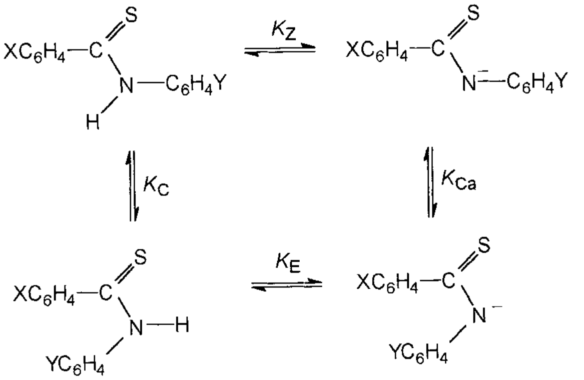
Acidities of conformationally non-uniform compounds

Correlation of our apparent p*K* values with the σ constants (or with any other parameters) is in principle a complex problem since both the thioanilides and their anions exist in an equilibrium of two conformers, *Z* and *E*, with the former prevailing.[12] Let us treat this problem in some detail since it may be encountered also with other compounds. In Scheme 1, the equilibrium constant of the conformational equilibrium $K_C = [E]/[Z]$ is known from previous IR measurements[13] in carbon tetrachloride; with some approximations discussed later, it can be used even in water solution. The remaining constants K_E, K_Z and K_{Ca} are not directly accessible and should be estimated from the correlation of p*K*.

The effective experimental ionization constant K_{exp} is related to the 'partial' ionization constants K_E and K_z by

$$K_{exp} = (K_Z + K_C K_E)/(1 + K_C) \tag{4}$$

For our compounds, we may suppose that these partial



Scheme 1.

equilibrium constants K_Z and K_E are controlled by the Hammett equation:

$$\log K_{Z,E} = \log K_{Z,E}{}^{o} + \rho_{Z,E}\sigma \tag{5}$$

where the parameters ρ_Z and ρ_E, and also $K_Z°$ and $K_E°$, are in principle unequal. For K_C, it was found[13] that it does not depend on σ constants of any kind. By introducing K_Z and K_E from Eqn. (5) into Eqn. (4) we obtain

$$K_{\mathrm{exp}}(1 + K_C) = K_Z{}^{o}10^{\rho_Z\sigma} + K_C K_E{}^{o}10^{\rho_E\sigma} \tag{6}$$

It follows that the dependence of K_{exp} on σ is curvilinear even when K_Z and K_E depend linearly on σ. It may become linear only in trivial cases such as for $K_C = 0$, or for $\rho_Z = \rho_E$ and simultaneously $K_Z° = K_E°$: it will be nearly linear when these conditions are only approached. When K_C is known from a direct determination, it would be still necessary to obtain four parameters, $K_Z°$, $K_E°$, ρ_Z and ρ_E, by an optimization procedure (non-linear regression) on the basis of experimental K_{exp}. This number can be reduced by means of two constraints: one is Eqn. (4) applied for $K_C°$, $K_Z°$, $K_E°$ and $K_{\mathrm{exp}}°$ and the second constraint is obtained by calculating the tangent to the curve of Eqn. (6) in one point, say at $\sigma = 0$. By differentiating Eqn. (6) with respect to σ we obtain

$$\begin{aligned}\lim_{\sigma\to 0}\frac{\partial K_{\mathrm{exp}}}{\partial\sigma} &= \rho_{\mathrm{exp}}\\ &= (K_Z°\rho_Z + K_C°K_E°\rho_E)/(1 + K_C°)K_{\mathrm{exp}}°\end{aligned} \tag{7}$$

The apparent reaction constant ρ_{exp} can be obtained by plotting K_{exp} vs σ as the slope of the tangent at $\sigma = 0$. There still remain two unknown parameters to be obtained by non-linear regression, Eqn. (6), and data of necessary accuracy and extent are not easy to obtain. In our case, it is mainly the low values of K_C which make Eqn. (6) hardly sensitive to both ρ_E and $K_E°$. The *Z* conformer prevails and the observed Hammett correlation describes approximately the behaviour of p*K* of this conformer. We used Eqn. (2) with $\rho_{\mathrm{exp}} = 2.03$ and tried different combinations of ρ_Z, ρ_E, $K_Z°$ and $K_E°$, satisfying the two constraints. It turned out that for $K_E° = K_Z°$, ρ_E can be varied from being equal to $0.5\rho_Z$ up to $2\rho_Z$ without affecting noticeably the fit with Eqn. (6). Similarly for $\rho_E = \rho_Z$, one can vary $K_E°$ from $0.5K_Z°$ up to $2K_Z°$. Since Eqn. (6) is so insensitive to both ρ_E and $K_E°$, there remains only the dependence on the experimental K_C which could possibly improve the fit over that of the simple linear Hammett correlation. With this idea, we corrected the experimental K_{exp} by the factor $(1 + K_C)$ with K_C taken from previous experiments,[13] and correlated the whole set of data by Eqn. (8), derived from Eqn. (6) by omitting the second term:

$$\begin{aligned}\log[K_{X,Y}(1 + K_{C,X,Y})] = \log[K_{H,H}(1 + K_{C,H,H})]\\ + \rho_X\sigma_X + \rho_Y\sigma_Y + \varepsilon\end{aligned} \tag{8}$$

Table 2, line 4 reveals that the improvement over Eqn. (3) is small, statistically insignificant (confidence level $\alpha = 0.15$, *F*-test). It is therefore possible that the Hammett correlation for one conformer would be better than that for the apparent values belonging to their mixture.

We conclude that the fairly close correlation of the acidity is only slightly disturbed by the conformation equilibrium. For this reason also the fundamental assumption appears to be less important, the extent to which the K_C values in carbon tetrachloride can be transferred into water. The *Z* $\rightleftharpoons$ *E* equilibrium is controlled partly by the steric hindrance in the *E* conformer and partly by the inner stability of the CS—N grouping in the *Z* conformation, similarly as in monoalkylamides, esters and other compounds with the structure —C(=X)—Y.[22] These effects would be relatively little affected by the solvent. A weak intramolecular bond between the sulphur atom and an *ortho* H atom in the *Z* conformer can be also taken into consideration (this possibility was kindly suggested by a referes). In this case, the dependence on solvent would be greater, but in our opinion this bond has a tour probability: the exact position of the benzene ring in **1** is not known but in benzanilide it is not coplanar with the CON plane.[23]

Additive relationship

Equation (3) presumes both the dependence on constants σ and the additivity of substituent effects. Since the two presumptions are independent,[19] the additivity can be tested in a separate test. Its simplest representation is Eqn. (9). However, this equation has the defect of giving more weight to mono-derivatives than to bis-derivatives. The statistically correct Eqn. (10) gives the same weight to all derivatives.[24] All the *de novo* constants, a_X and b_Y, are fitted at once in order to obtain the minimum sum of squares $\sum\epsilon^2$.

$$\log K_{\mathrm{X,Y}} = \log K_{\mathrm{X,H}} + \log K_{\mathrm{H,Y}} - \log K_{\mathrm{H,H}} + \varepsilon \qquad (9)$$

$$\log K_{\mathrm{X,Y}} = \log K_{\mathrm{H,H}} + a_{\mathrm{X}} + b_{\mathrm{Y}} + \varepsilon \qquad (10)$$

The pK values from Table 1 were processed according to the described program:[24] this program corresponds to the procedure called in QSAR the Free-Wilson treatment[25] and is applied here to only two substituents. The results are given in Table 2, line 5. They reveal that Eqn. (10) is fulfilled only with a slightly better precision (the confidence level $\alpha = 0.2$, F-test) than the corresponding Hammett relationship, Eqn. (3). The deviations from the latter may therefore be caused only slightly by the values of σ constants; mainly they are due to the experimental uncertainty or to unknown factors. For this reason, it is also not useful to tabulate or discuss the derived constants a_{X} and b_{Y}: they would be very nearly proportional to the customary σ in the proper position. This result is just the opposite of that in the correlations of the conformation equilibria of the same compounds.[13] In that case, the additivity relationship was much more precise than any Hammett correlation, showing that the experimental accuracy was good but the σ constants were not appropriate.

The additive behavior could be anticipated taking into account the distance of substituents situated in the two benzene rings. The accuracy of data and relatively small effects of substituents did not allow a test of the non-additive equation with a cross-term.[24,26] One must conclude that the effects are additive within the precision of the experiments.

Half-wave potentials

With the half-wave potentials of electrochemical oxidation, $E_{1/2}$, the same correlations were carried out as with the pK values. The results were similar but mostly less precise. It appears that the accuracy of $E_{1/2}$, in relation to the extent of values, is not sufficient for any more definite results. In Table 2, we give only the most significant figures. The Hammett equation, Eqn. (11), yielded a bad fit (Table 2, line 6) compared with Eqn. (3) (comparison according to the correlation coefficients or according to the ψ values[20]). Also the additive relationship, Eqn. (12), yielded a worse fit than the corresponding Eqn. (10) (comparison according to the ψ values[20]).

$$(E_{1/2})_{\mathrm{X,Y}} = (E_{1/2})_{\mathrm{H,H}} + \rho_{\mathrm{X}}\sigma_{\mathrm{X}} + \rho_{\mathrm{Y}}\sigma_{\mathrm{Y}} + \varepsilon \qquad (11)$$

$$(E_{1/2})_{\mathrm{X,Y}} = (E_{1/2})_{\mathrm{H,H}} + a_{\mathrm{X}} + b_{\mathrm{Y}} + \varepsilon \qquad (12)$$

In this case, however, the additive Eqn. (12) is valid with a higher precision than the Hammett equation, Eqn. (11): $\alpha = 0.005$, F-test. We must conclude that the common σ constants are not completely adequate for describing the reactivity in this reaction. Many deviations from the Hammett equation, both expected and unexpected, were observed on the half-wave potentials of electrochemical reduction or oxidation;[27] they are mostly attributed to adsorption phenomena. The only ‘chemical’ conclusion could concern the site of reaction. The assumed reaction mechanism[16] started with one-electron oxidation on the sulphur atom but was more complex, producing two products, 2-phenylbenzothiazole and benzanilide. Accordingly, one would expect in Eqn. (11) a greater value of ρ_{X} than ρ_{Y}. Actually, the two values are equal within their uncertainty and the precision of the correlation does not allow a decision.

CONCLUSIONS

Substituted thiobenzanilides offered an example of an ionization equilibrium connected with a conformation equilibrium. The mathematical analysis presented here is valid more generally, for any equilibrium of two arbitrary forms each of which is capable of ionization. This analysis revealed that the observed ionization constants need not depend regularly on substitution even when both the partial ionization constants and the conformation equilibrium constants do so. However, in practical examples a regular pattern of substitution effects (as expressed for instance by the Hammett equation) may be obtained when ionization depends strongly on substitution and only slightly on conformation. This pattern may be observed also whenever the conformation equilibrium is shifted strongly to one side. In such cases, the conformation equilibrium cannot be revealed from the ionization constants although it can be proven spectroscopically: this is the case described in this paper. It follows further that many systems might be more complex than one could guess from their simple control by substitution, e.g. from the validity of the Hammett equation.

Acknowledgements

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