

Reaction series not obeying the Hammett equation: conformational equilibria of substituted thiobenzanilides

Karel Palát Jr.,^a Stanislav Böhm,^b Gabriela Braunerová,^a Karel Waisser*^a and Otto Exner*^c

^a Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, 501 65 Hradec Králové, Czech Republic

^b Department of Organic Chemistry, Prague Institute of Chemical Technology, 166 28 Praha 6, Czech Republic

^c Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, 166 10 Praha 6, Czech Republic

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The conformation of the C–N bond of 4,4′-disubstituted thiobenzanilides and the equilibrium $Z \rightleftharpoons E$ were investigated by infrared spectroscopy and by the density functional theory (DFT) at the B3LYP/6-311+G(d,p) level. Together with previous work, 54 derivatives were examined spectroscopically and the conformational equilibrium was determined from the intensities of the $\nu(\text{N–H})$ bands. It was confirmed that the substituent effects on $\log K$ are not governed by the Hammett equation. This failure is neither due to experimental errors nor to specific shortcomings of the IR method, since the results agree with the DFT calculations and also fulfil the additive relationship. The constant shift of the DFT energies with respect to the experimental Gibbs energies can be explained by entropy factors. The most probable explanation of the failure is as a result of strong resonance effects and, in addition, a π – π interaction between the two substituted benzene rings in the E conformation.

Introduction

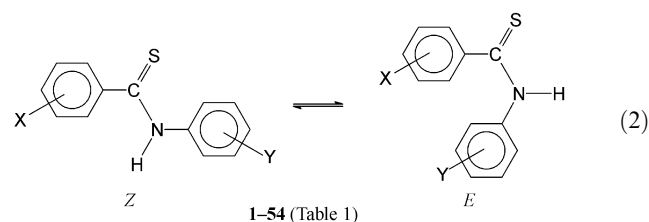
The Hammett equation,¹ eqn. (1) has been very successful in rationalizing rates and equilibria of *meta*- and *para*-substituted benzene derivatives in terms of empirical substituent constants, σ , and reaction constants, ρ . The symbol k can stand either for a rate constant or for an equilibrium constant.

$$\log k = \log k^\circ + \rho\sigma_{\text{m,p}} \quad (1)$$

This success was so great that recently an opinion was offered that a contingent failure should deserve more attention than the cases when the equation is obeyed.² The failures were observed mostly as a curvilinear graph or as single deviations of some substituents, and were discussed in terms of the reaction mechanism: as its gradual changes or individual peculiarities.^{1,2} Nevertheless, several cases appeared in the past when eqn. (1) fails more completely; they were explained differently, mostly again by a complex reaction mechanism.³ More recently, attention was drawn to the fact that the most typical and most important reactions obeying the Hammett equation involve either an ionic final state (in equilibrium processes) or a strongly polar transition state (in kinetics).⁴ Interaction of this charge with strongly polar substituents may be deciding for the success of the empirical relationship. In agreement with this, correlations of ground-state properties of neutral molecules were generally less successful.^{4,5}

We recently encountered a case where a failure of the Hammett equation was well proven on a number of derivatives.⁶ The conformational equilibrium $Z \rightleftharpoons E$ of substituted thiobenzanilides, eqn. (2), was determined from the integrated absorptivities of the $\nu(\text{N–H})$ bands and the Hammett equation was not fulfilled either for the X substituents or for the Y substituents. Nevertheless, there was a shortcoming in that the substi-

tuents investigated were selected with respect to the importance of these compounds in pharmacology as possible antimycotic and tuberculostatic compounds.⁷ Strongly polar substituents considered to be central to the Hammett equation⁴ were not included due to their supposed toxicity. Moreover, there was a possibility of a fundamental shortcoming in the infrared method. Determination of the equilibrium constants assumes equal integrated absorptivities, A_Z and A_E , of the two conformers and this approximation need not hold with sufficient precision.



X = H, 4-CH₃, 4-OCH₃, 3-F, 4-F, 4-Cl, 3-Br, 3-NO₂, 4-NO₂, 4-N(CH₃)₂
Y = H, 4′-CH₃, 4′-OCH₃, 3′-F, 4′-F, 4′-Cl, 4′-Br, 3′-NO₂, 4′-NO₂, 4′-N(CH₃)₂, 3′,4′-Cl₂

We consider this example to be important for the general theory of the Hammett equation and return to it in this contribution. Firstly, we have extended the experimental material by including strongly polar substituents, particularly NO₂ and N(CH₃)₂, now without regard to their utility in pharmacological studies. Secondly, we have calculated the energies of some representative compounds using density functional theory (DFT) with the reasonably large B3LYP/6-311+G(d,p) basis set. By these means, we are able to show that the substituent effects are exceptional and failure of the Hammett equation is not caused by shortcomings of the method or by experimental errors.

Experimental

The substituted thiobenzanilides **1–54** (Table 1) were prepared by standard methods.¹¹ Most of them have been characterized previously,⁷ however, compounds **9**, **10**, **25–32** and **49–52** are new and will be characterized later in connection with their biological activity.

The infrared absorption spectra were recorded on a Nicolet Impact 400 FTIR spectrometer in tetrachloromethane solu-

tion, the conditions used for the previous measurements⁶ were maintained as far as possible. Since the low solubility of some derivatives did not allow measurement of all compounds at the same concentration, determination of integrated absorption intensities was abandoned and only their ratios were evaluated, corresponding to the ratio of concentrations $[E]/[Z] = K_C$. Separation of bands was achieved by the standard program.⁸ Of the two possible procedures, separation with mixed Gaussian–Lorentzian bands was chosen (as previously); separation

Table 1 IR spectral data for substituted thiobenzanilides **1–54** and populations of conformers calculated therefrom^a

Compound	Substituents		$\nu(\text{N-H})/\text{cm}^{-1}$		$[Z]/[E]$	$-\log K_C$
	X	Y	Z	E		
1^b	H	H	3391.9	3364.9	15.6	1.194
2^b	H	4'-CH ₃	3391.7	3364.2	14.8	1.170
3^b	H	4'-OCH ₃	3391.7	3362.7	18.3	1.263
4^b	H	3'-F	3393.0	3365.4	23.5	1.372
5^b	H	4'-F	3393.0	3364.2	27.2	1.434
6^b	H	4'-Cl	3391.6	3363.8	25.8	1.411
7^b	H	3',4'-Cl ₂	3391.3	3363.1	41.3	1.616
8^b	H	4'-Br	3391.4	3363.8	26.1	1.417
9	H	4'-N(CH ₃) ₂	3389.2	3359.9	13.5	1.129
10	H	4'-NO ₂	3388.7	3362.5	32.3	1.509
11^b	4-CH ₃	H	3393.2	3365.6	14.5	1.161
12^b	4-CH ₃	4'-CH ₃	3393.0	3364.8	13.5	1.131
13^b	4-CH ₃	4'-OCH ₃	3392.9	3363.3	16.8	1.226
14^b	4-CH ₃	4'-Cl	3393.1	3364.5	22.4	1.349
15^b	4-CH ₃	3'-F	3394.4	3366.0	20.7	1.316
16^b	4-CH ₃	4'-F	3394.4	3364.7	24.4	1.388
17^b	4-CH ₃	3',4'-Cl ₂	3392.7	3363.6	36.9	1.567
18^b	4-CH ₃	4'-Br	3392.9	3364.5	22.6	1.354
19^b	4-OCH ₃	H	3395.2	3366.5	12.4	1.093
20^b	4-OCH ₃	4'-CH ₃	3395.0	3365.7	11.8	1.070
21^b	4-OCH ₃	4'-OCH ₃	3395.0	3364.1	13.1	1.118
22^b	4-OCH ₃	4'-Cl	3395.2	3365.5	19.6	1.293
23^b	4-OCH ₃	3',4'-Cl ₂	3394.9	3364.6	31.9	1.504
24^b	4-OCH ₃	4'-Br	3394.9	3365.4	20.4	1.309
25	3-F	4'-Br	3389.6	3361.8	33.2	1.521
26	3-F	4'-N(CH ₃) ₂	3387.7	3358.4	13.8	1.141
27	3-F	3'-NO ₂	3388.8	3360.7	68.9	1.838
28	3-F	4'-NO ₂	3387.2	3361.2	40.9	1.612
29	4-F	4'-Br	3392.5	3363.3	19.2	1.284
30	4-F	4'-N(CH ₃) ₂	3390.2	3359.5	8.2	0.911
31	4-F	3'-NO ₂	3391.6	3362.5	35.9	1.555
32	4-F	4'-NO ₂	3390.1	3362.7	25.7	1.411
33^b	4-Cl	H	3391.9	3364.1	10.3	1.012
34^b	4-Cl	4'-CH ₃	3391.8	3363.3	8.8	0.943
35^b	4-Cl	4'-OCH ₃	3391.7	3361.8	11.4	1.057
36^b	4-Cl	3'-F	3393.2	3364.3	16.8	1.226
37^b	4-Cl	4'-F	3393.0	3363.0	19.0	1.280
38^b	4-Cl	4'-Cl	3391.8	3362.9	17.6	1.245
39^b	4-Cl	3',4'-Cl ₂	3391.4	3362.0	28.5	1.454
40^b	4-Cl	4'-Br	3391.6	3362.7	18.2	1.259
41^b	3-Br	H	3389.4	3363.3	20.3	1.307
42^b	3-Br	4'-CH ₃	3389.1	3362.5	20.0	1.300
43^b	3-Br	4'-OCH ₃	3389.0	3361.0	23.4	1.369
44^b	3-Br	3'-F	3390.4	3363.3	35.1	1.546
45^b	3-Br	4'-F	3390.3	3362.3	38.6	1.586
46^b	3-Br	4'-Cl	3389.2	3362.1	40.5	1.608
47^b	3-Br	3',4'-Cl ₂	3388.6	3360.7	90.7	1.957
48^b	3-Br	4'-Br	3388.8	3361.8	44.7	1.650
49	4-N(CH ₃) ₂	3'-F	3399.5	3369.2	12.1	1.084
50	4-N(CH ₃) ₂	4'-F	3399.9	3367.8	13.5	1.131
51	3-NO ₂	3'-F	3389.4	3361.5	24.5	1.389
52	3-NO ₂	4'-F	3389.1	3361.3	19.7	1.295
53	4-NO ₂	H	3388.6	3361.1	6.0	0.779
54	4-NO ₂	4'-F	3389.5	3360.0	12.8	1.109

^a Separation of bands carried out using a mixture of Gaussian and Lorentzian peak shapes. ^b Data from ref. 6.

according to Voigt⁸ gives in this case essentially identical results.⁶ The new and old results are summarized in Table 1. The uncertainty of K_C in repeated experiments is estimated to be less than ± 0.02 .

Calculations

DFT calculations were carried out according to the original proposal⁹ exploiting the standard program.¹⁰ The starting conformation was preliminarily estimated by an AM1 calculation, the exact geometry and energy was calculated at the B3LYP/6-311+G(d,p) level. In particular cases, further possible conformations were assumed and their energies calculated at the same level. All conformations represented local energy minima according to the vibrational analysis. The population of conformers in an equilibrium mixture and the effective energy at 298 K were calculated using the energy difference $\Delta E(\text{DFT})$ instead of $\Delta G^\circ(298)$. With the same approximation, the equilibrium constant, K_C , of the conformational equilibrium and the corresponding Gibbs energy, $\Delta G^\circ(298)$, were also calculated. In some cases, this Gibbs energy $\Delta G^\circ(298)$ was calculated independently by statistical thermodynamics using the same program¹⁰ as above. The sums of the electronic and thermal enthalpies, $\Delta H^\circ(298)$, were calculated in the same way. The results of the calculations are summarized in Table 2.

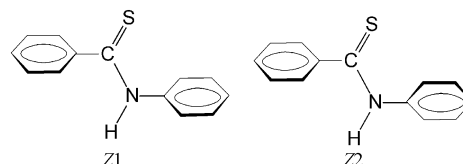
Results and discussion

Conformation

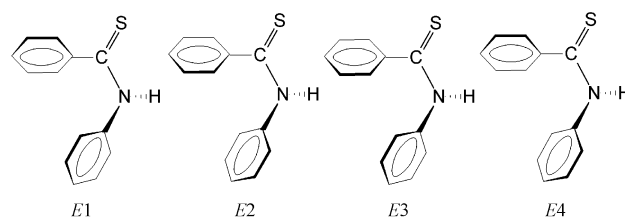
The molecule of thiobenzanilide contains three single bonds allowing more or less hindered rotation. Rotation around the C–N partially double bond leads to two conformations, denoted *Z* and *E* here, which are stable.¹² They were originally considered as planar,^{6,12} but, according to our calculations, this is an acceptable approximation for *Z* only. Their abundance is the main subject of this investigation. This goal is made more complex by the simultaneous occurrence of the conformations around the bonds $\text{C}_{\text{ar}}\text{--N}$ and $\text{C}_{\text{ar}}\text{--C}$, and by the non-planar configuration on N. These conformations are expected to be much less stable and have not been observed in the experimental studies,^{6,12} but they cannot be neglected in the calculations.

Let us first consider the unsubstituted thiobenzanilide **1**; the conclusions drawn will also be valid for all *para* derivatives. In the conformation *Z*, the functional group deviates very slightly from planarity. We calculate the dihedral angle $\text{C}_{\text{ar}}\text{--C--N--C}_{\text{ar}}$ to be 176° , and this value is only slightly changed with substitution. In the formulae *Z1* and *Z2*, this group is pictured as planar. However, the benzene rings are not coplanar, as

already observed on the parent thiobenzamide.¹³ For the conformation around the $\text{C}_{\text{ar}}\text{--C}$ bond, we calculated the torsion angle $\phi_1 = 41^\circ$; for the conformation around the $\text{C}_{\text{ar}}\text{--N}$ bond, $\phi_2 = 5^\circ$. Even these values are changed only slightly with substitution. The small value of ϕ_2 is remarkable in comparison with the greater values estimated for benzanilide.¹⁴ When positive and negative values of ϕ_1 and ϕ_2 are combined, two forms of the *Z* conformer can arise, *Z1* and *Z2*. Since ϕ_2 is small, their energies differ little. In the case of 4-nitrothiobenzanilide **53**, ϕ_2 is somewhat larger (11°), nevertheless the calculated energy difference between *Z1* and *Z2* is only 0.04 kJ mol^{-1} . The approximation that the rotamers *Z1* and *Z2* are equally populated is thus acceptable for all derivatives.



In the *E* conformation, the functional group is not planar due to strong steric hindrance. For **1**, we calculate the dihedral angle $\text{C}_{\text{ar}}\text{--C--N--C}_{\text{ar}} = 23^\circ$, $\phi_1 = 44^\circ$ and $\phi_2 = 28^\circ$. By combining the rotations in two senses, we may derive four forms which are possible in principle, *E1–E4*. However, they cannot be populated equally since the forms *E3* and *E4* are strongly sterically hindered (interaction of the two *ortho* hydrogen atoms). We were not able to calculate their energies: for the example of compound **53** we obtained no minimum at the potential energy surface. The form *E1* was the most stable, *E2* was destabilized by 8.30 kJ mol^{-1} . Hence, the approximation that the conformer *E* is represented only by the form *E1* is acceptable (see also Fig. 3). Note still that all forms, *Z1*, *Z2*, *E1–E4*, are racemates, but this does not influence their relative populations.



In *meta* derivatives, the picture is more complex due to the two possible positions of the *meta* substituent. Even in this case, one can assume that their populations are approximately equal, as confirmed by calculations on 3'-fluorothiobenzanilide, **4**. The two forms of *Z1* differ by 0.94 kJ mol^{-1} , the position of the fluorine atom near the sulfur is preferred. For the two forms of *E1*, the energy difference is 0.36 kJ mol^{-1} , the

Table 2 Calculated energies and populations of conformers for the substituted thiobenzanilides

Compound ^a	Substituents		$E(\text{DFT})/\text{a.u.}$		$\Delta_2 E /$ kJ mol^{-1}	$\log K_C \text{ calc.}$	$\log K_C \text{ corr.}^b$	$\log K_C \text{ exper.}$	$\Delta_8 E /$ kJ mol^{-1}	$\Delta_9 E /$ kJ mol^{-1}
	X	Y	<i>Z</i>	<i>E</i>						
1	H	H	−955.122998	−955.121511	3.91 ^c	−0.68 ^c	−0.98	−1.194 ^d	0	0
4	H	3'-F	−1054.390911	−1054.389289	4.26	−0.75	−1.05	−1.372 ^d	2.5	2.9
6	H	4'-Cl	−1414.745145	−1414.743275	4.91	−0.86	−1.16	−1.411 ^d	2.1	3.1
9	H	4'-N(CH ₃) ₂	−1089.126130	−1089.124856	3.35	−0.59	−0.89	−1.129	−0.8	−1.4
10	H	4'-NO ₂	−1159.686761	−1159.684610	5.65	−0.99	−1.29	−1.509	−1.0	0.7
33	4-Cl	H	−1414.745328	−1414.744157	3.07	−0.54	−0.84	−1.012 ^d	1.6	0.8
41	3-Br	H	−3528.664643	−3528.663146	3.93	−0.69	−0.99	−1.307 ^d	2.6	2.7
53	4-NO ₂	H	−1159.684599	−1159.683654	2.48	−0.43	−0.74	−0.779	4.6	3.2

^a See Table 1. ^b Corrected by $-\log 2$ to account for the possible symmetry entropy; see Discussion. ^c The calculated difference of the sums of the electronic and thermal enthalpies is 3.44 , the difference in the Gibbs energies is 4.13 kJ mol^{-1} ; the corresponding values of calculated $\log K$ would be -0.60 and -0.72 , respectively. ^d Ref. 6.

Table 3 Correlations of conformational equilibria of substituted thiobenzanilides **1–54**

	Response function	Explanatory variables	Regression coefficients ^a	<i>R</i> ^b	<i>SD</i> ^b	<i>f</i> ^b
1	log <i>K</i> _C (exp)	log <i>K</i> _C (calc)	1.17(15)	0.950	0.080	6
2	log <i>K</i> _C (exp)	σ _{m,p} (X) σ _{m,p} (Y)	−0.11(7) −0.44(7)	0.691	0.167	51
3	log <i>K</i> _C (exp)	eqn. (4)	—	—	0.041	34
4	log <i>K</i> _C (exp)	σ _{m,p} (Y)	−0.33(7)	0.864	0.084	8
5	log <i>K</i> _C (exp)	σ _{m,p} (X)	0.35(10)	0.898	0.086	3 ^c
6	log <i>K</i> _C (exp)	σ _{m,p} (X) Δσ _p ⁺ (X)	0.49(9) −0.20(7)	0.991	0.031	2 ^c
7	log <i>K</i> _C (exp)	σ _{m,p} (Y) Δσ _p [−] (Y)	−0.44(6) 0.24(15)	0.944	0.059	7
8	log <i>K</i> _C (exp)	σ _I (Y) σ _R [°] (Y)	−0.51(6) −0.17(6)	0.974	0.038	5 ^d
9	log <i>K</i> _C (exp)	σ _I (Y) σ _d (Y) σ _e (Y)	−0.50(2) −0.087(17) −0.41(6)	0.9980	0.012	4 ^d
10	Δ ₈ <i>E</i>	σ _{m,p} (X)	5.7(4)	0.9956	0.22	4
11	Δ ₉ <i>E</i>	σ _{m,p} (X)	4.2(12)	0.929	0.69	4

^a Standard deviation in parentheses. ^b Correlation coefficient *R*, standard deviation from the regression *SD* and degrees of freedom *f*, respectively.

^c Substituent 3-Br eliminated as outlier. ^d Only *para* substituents.

preferred position of fluorine is nearer to the second benzene ring. Even with compound **41**, with the sterically demanding bromine atom, this energy difference is the same (0.36 kJ mol^{−1}); the preferred position of bromine is again nearer to the second benzene ring (Fig. 3, left). In summary, the number of possible rotamers is doubled in *meta* derivatives, both in the *Z* and *E* conformations.

Calculated and experimental equilibria

For calculations, we selected 8 derivatives with the most characteristic substituents. The DFT energies of the *Z* and *E* conformers are given in Table 2, columns 4 and 5, their difference in column 6 and the logarithm of the calculated equilibrium constant, *K*_C = [*E*]/[*Z*], in column 7. Comparison with the experimental values is carried out in terms of log *K*_C, as required by the Hammett equation. There is an apparent disagreement in the absolute values of the calculated and experimental log *K*_C (column 9), but the relative values are reproduced well (Table 3, line 1); the experimental uncertainty is only slightly exceeded. This is also evident from Fig. 1. As expected, there is no observable solvent effect in tetrachloromethane as compared with the calculations on isolated molecules. The systematic, almost constant deviation can be explained in two ways: by a defect in the infrared method (*i.e.* mainly by unequal extinction coefficients) or by uniform differences between the electronic energy, *E*(DFT), and experimental Gibbs energy, Δ*G*[°](298). Attempting to explain this difference, we calculated first the sums of the electronic and thermal enthalpies, Δ*H*[°](298), but the improvement was negli-

gible [Table 2, footnote (c)]. Calculations of this quantity within the framework of DFT theory were, in general, not encouraging;^{13,15} in one series, the agreement with experiment was even distinctly worse with Δ*H*[°](298) than with *E*(DFT).^{15b} Calculation of Δ*G*[°](298) was less successful still [Table 2, footnote (c)]. Nevertheless, we suggest a possible explanation that the disagreement is due to a statistical factor which is not included into the standard calculations.¹⁰ In the preceding paragraph, we suggested an approximation that the *Z* conformer consists of two forms of equal energy while the *E* conformer virtually consists of one form. When this is accepted, it is understandable that the *Z* conformer will be populated twice as much and a −log 2 term must be included into log *K*_C (Table 2, column 8). This is only a tentative suggestion, but a correction of this magnitude significantly improves the agreement of calculations and experiment (Fig. 1). The small remaining difference may be attributed to inequality of extinction coefficients. Note that this not fully resolved problem does not affect the main subject of the present work, violation of the Hammett equation, since this equation concerns only relative values.

Hammett correlations

In the case of substitution on two sides of the molecule, the Hammett equation takes the form shown in eqn. (3), which is based on two independent presumptions:¹⁷ the validity of the simple Hammett equation, eqn. (1), and of the additivity principle.

$$\log K_{X,Y} = \log K_{H,H} + \rho_X \sigma_X + \rho_Y \sigma_Y \quad (3)$$

The statistics given in Table 3, line 2 reveal that eqn. (3) is not fulfilled. The fit is similar, even slightly worse, than previously for a smaller set.⁶ It was not improved by including further, strongly polar substituents. Of the two presumptions mentioned, the additivity principle can be tested separately using eqn. (4), in which the constants *a*_X and *b*_Y are to be determined *de novo* according to the least-squares principle.¹⁸

$$\log K_{X,Y} = \log K_{H,H} + a_X + b_Y \quad (4)$$

According to Table 3, line 3, additivity is valid with a much better precision than the Hammett equation: the standard deviation is reduced to one quarter.

The failure of the Hammett equation is also evident from simple plots (Fig. 2) based on substitution from one side according to eqn. (1), although these plots have less statistical weight. *Y* substituents give rise to a very approximate Hammett dependence (Fig. 2), which would be classified as invalid according to common statistics (Table 3, line 4). A relatively better fit was obtained with the normal constant σ_p for the substituent NO₂, instead of the constant σ_p[−], expressing an exalted conjugation. Among the *X* substituents, there is a big

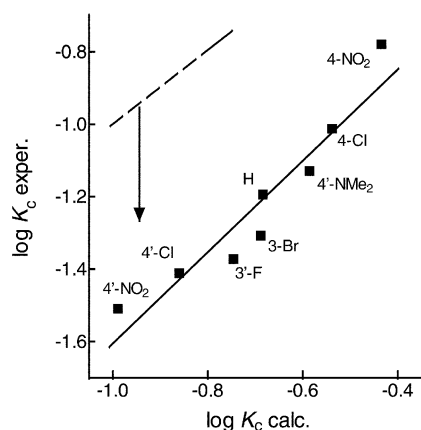


Fig. 1 Comparison of calculated and experimental equilibrium constants, log *K*_C, of substituted thiobenzanilides; the full line is a regression line, the broken line represents the relation *y* = *x*, the arrow has the length −log 2.

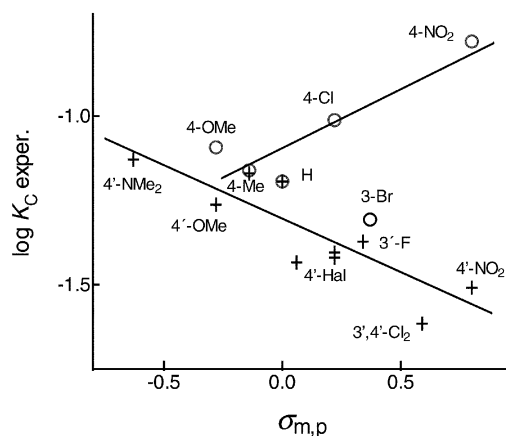


Fig. 2 Hammett plot of the conformational equilibrium constants, $\log K_C$, of monosubstituted thiobenzanilides: (O) X substituents in the thiobenzoic moiety (Y = H), (+) Y substituents in the aniline moiety (X = H).

deviation with the substituent 3-Br. Even when this is eliminated as an outlier, the fit is as bad (Table 3, line 5) as in the preceding case.

Extending our previous reasoning,⁶ we can consider the following reasons for a failure of the Hammett equation:

(a) The experimental uncertainty in the spectral measurements may be greater than in standard kinetics or pK measurements. For instance, some bands might be coupled or not well resolved. (b) There could be a systematic error in the spectral data, in particular, the assumption of equal integrated absorptivities A_Z and A_E need not be valid. (c) The correlation would need some special substituent constants (for instance, the exalted value σ_p^+ or σ_p^-) or a more sophisticated correlation equation with two or more parameters.^{3d,19} (d) As already observed,⁴ the Hammett equation need not hold for reaction of nonpolar species in which an ion or a polar transition state is not involved. (e) When the main principle of the Hammett equation is in the given structure eliminating direct steric effects, this principle may be flawed in the *E* conformer, in which the two benzene rings are relatively near to each other and a π - π interaction may occur.

First, we can reject the hypotheses (a) and (b): (a) is incompatible with the accuracy of the additive relationship, eqn. (4), both (a) and (b) are disproved by the close agreement of calculated and experimental equilibria. On the eight compounds in Table 3, it is possible to show that calculated and experimental equilibrium constants give the same low precision in Hammett correlations (statistics not given). The hypothesis (c) must be taken into consideration, but the bad fit is caused mainly by the difference between the *meta* and *para* derivatives, rather than by systematic operation of the resonance effect. The deviation with the substituent 3-Br is striking, that involving 3',4'-Cl₂ is smaller, but also evident (Fig. 2). Of the many-parameter equations,¹⁹ the Yukawa-Tsuno treatment,^{19a} eqn. (5), is most important, since it treats the *meta* and *para* substituents together.

$$\log K_X = \log K_H + \rho_X(\sigma_{m,p} + r^+ \Delta\sigma_p^+) \quad (5)$$

The constants $\Delta\sigma_p^+$ account for an exalted resonance and apparently improve the fit (Table 3, line 6, as compared to line 5). However, the substituent 3-Br must be eliminated as an outlier and the result is little significant due to the small number of the degrees of freedom. Moreover, the coefficient $r^+ = -0.20/0.49$ is negative and has no physical meaning (reduced resonance when donors are conjugated with an acceptor reaction centre). With the Y substituents, eqn. (5) should be applied in the alternative form²¹ with the constants $\Delta\sigma_p^-$ instead of $\Delta\sigma_p^+$, and with the coefficient r^- . Apparently, an

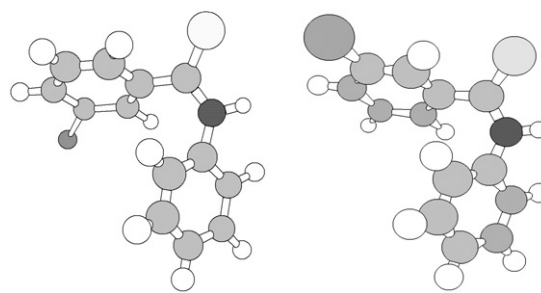


Fig. 3 3-Bromothiobenzanilide **41** in the conformation *E1*; the two forms differ by the position of the bromine atom, the form on the left is slightly preferred (by 0.36 kJ mol⁻¹).

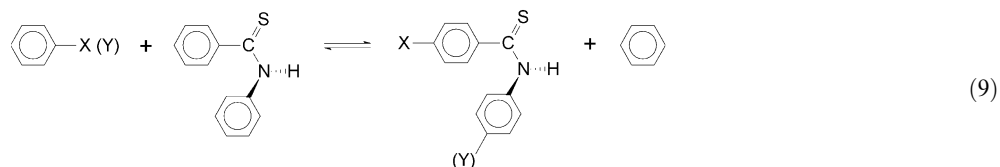
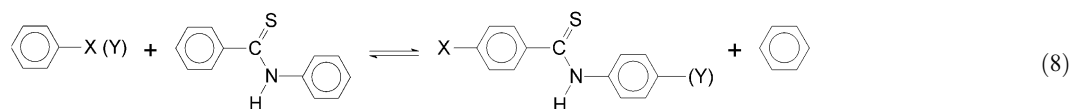
improvement is obtained, see Table 3, line 7 as compared with line 4. However, the negative coefficient r^- would mean a decreased resonance and this term is of little significance.

$$\log K_X = \log K_H + \rho_I\sigma_I + \rho_R\sigma_R \quad (6)$$

$$\log K_X = \log K_H + L\sigma_I + D\sigma_d + R\sigma_e \quad (7)$$

In the dual substituent parameter (DSP) treatment,^{19b} eqn. (6), and in the Charton three-parameter equation,^{19c} eqn. (7), the *meta* and *para* substituents must be treated separately;²⁰ this is in some cases hindered by the insufficient number of data. Significant correlations were obtained only with *para* Y derivatives. The DSP treatment,^{19b} eqn. 6, and particularly the Charton equation,^{19c} eqn. (7) give apparently good fits (Table 3, lines 8 and 9, respectively) but the improvement has been reached mainly by separating the *meta* and *para* series, as in many other cases,²⁰ and the degrees of freedom are not sufficient. We conclude that many-parameter equations improve the fit in the subseries of *para* derivatives† but cannot account for the main problem, deviation of *meta* derivatives. The failure of the Hammett equation is thus caused, at least partly, by exceeding its range of validity, hypotheses (d) or (e) or both. Of these, hypothesis (e) attributes the effect mainly to the *E* conformation. We tried a test by separately calculating the substituent effects in *Z* and *E* by means of isodesmic reactions.^{13,15,22} The reaction energies of eqn. (8) and (9), $\Delta_8E(\text{DFT})$ and $\Delta_9E(\text{DFT})$, were calculated from the DFT energies of thiobenzanilides (Table 2) and of mono derivatives of benzene,¹³ and are listed in Table 2 in the last two columns. They reveal that the substituent effects in both *Z* and *E* forms are nearly equal; the effect on the equilibrium is then given by the small difference between them: $\Delta_2E = \Delta_9E - \Delta_8E$. As far as only X substituents are concerned, Δ_8E for the *Z* conformer depends closely on $\sigma_{m,p}$ (Table 3, line 10), including the 3-Br substituent. The values of Δ_9E for the *E* conformer depend much less on $\sigma_{m,p}(X)$ and it is just the 3-Br substituent which deviates very strongly. With the Y substituents, there is no dependence on $\sigma_{m,p}$. These results were obtained on small sets; nevertheless, they suggest that the Hammett equation is violated mainly by the energy of the *E* conformer. A π - π interaction of the two benzene rings in the *E* conformer does not seem to be excluded. In **41**, the distance between the atoms C2 and C2' is 3.32 and 3.95 Å in the two forms shown in Fig. 3, respectively, and depends rather strongly on substitution. A π - π interaction may also be corroborated by the fact that in the conformational equi-

† We thank a referee for drawing our attention to this possibility, particularly to the Charton equation. However, we do not accept the suggested correlation of all 4,4'-derivatives (31 items) with eqn. (7) extended to three terms for X substituents plus three terms for Y substituents. This correlation gave an apparently good fit with $R = 0.985$, but this was essentially due to the additivity of substituent effects. In order to evaluate the fit due purely to eqn. (7), one must restrict the correlation to substituents in one moiety.



bria of substituted thioacetanilides, no irregularities were encountered and there were no deviations from the simple Hammett equation.²³ We are thus of the opinion that exalted conjugation is responsible only for a part of the deviations from the Hammett equation, the rest may be attributed to π - π interaction.

Note that even the bad Hammett correlation does not prevent a qualitative conclusion that the prevailing conformer *Z* is made still more stable by electron-releasing *X* substituents or by electron-attracting *Y* substituents (Fig. 2), both conjugated with the C(S)NH group. The most probable interpretation is that this conjugation is stronger in the more nearly planar *Z* conformer. Alternatively, one might imagine that there is a stabilization of the *E* conformer due to attraction of an electron-poor and an electron-rich benzene ring: it is stronger when the former is richer in electrons and the latter more electron poor. In this interpretation, the substituent effect on conformation would depend more on the energy of the *E* conformer than on the *Z* conformer but this was not confirmed (Table 3, lines 10 and 11).

Conclusions

Absence of direct (steric) interaction between the variable substituent and the constant functional group was pointed out² as the main principle of the Hammett equation and a precondition of its general validity. When this equation is applied to conformational equilibria, the concept of functional group loses its exact significance. It may then happen that interactions between apparently distant parts of the molecule disturb the otherwise regular substituent effects. In general, the Hammett equation may be valid even for conformational equilibria. On the other hand, deviations from it may indicate that some non-bonded interactions occur.

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