

**SUBSTITUENT EFFECTS ON CONFORMATIONAL EQUILIBRIA:
SUBSTITUTED THIOBENZANILIDES**Karel WAISSER^{a1,*}, Karel PALÁT, Jr.^a and Otto EXNER^{b,*}^a Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University,
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Infrared absorption spectra of 38 thiobenzanilides in tetrachloromethane solutions were recorded in the $\nu(\text{N-H})$ region. From the integrated absorption intensity of the computer-resolved N-H bands, the abundance of the *Z* and *E* conformations was calculated. The values of pertinent $\log K_C$ depend on substitution in an unexpected way which cannot be described by the Hammett equation or by any other known type of modified constants σ . The only regularity observed is that the substituent effects from the two benzene rings of thioanilide are additive with a remarkable precision. The $\nu(\text{N-H})$ frequencies are not much sensitive to substitution and the dependence is not simple: only $\nu(\text{N-H})$ of the *E* conformer depend on substitution in a regular way.

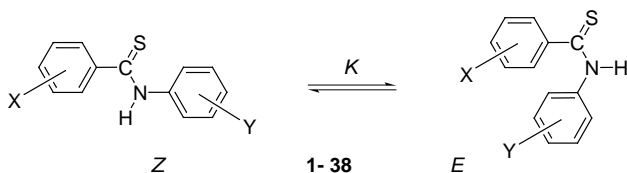
Key words: Thiobenzanilides; Thioamides; Conformation equilibrium; Infrared spectroscopy; Hammett equation; Substituent effects; Transmission effects.

Substituted thioamides have received our attention as potential tuberculostatics^{1,2} and antimycotics^{3,4}; at the same time, their physico-chemical properties have been investigated⁵ with a particular respect to QSAR. In quantitative correlations, the thioamide group may act either as a substituent⁶⁻¹⁰, or as a functional group^{11,12}, or finally as a linking group transferring the substituent effects^{9,10}. In N-substituted thioamides, a conformation equilibrium $E \rightleftharpoons Z$ on the C-N bond is possible^{13,14}, affecting all the quantities measured. For instance, the calculated constants σ of the groups $-\text{C}(=\text{S})\text{NH-X}$ change rather strongly with conformation⁸, the effective value then depending on the abundance of conformers. The conformation equilibrium of thiobenzanilide was estimated in the pioneer work of Walter and Kubersky¹³ by infrared spectroscopy from the intensities of the two $\nu(\text{N-H})$ bands, using the technique available in 1972. Several substituted thiobenzanilides were also investigated¹³ but the dependence of K_C

on substitution was not evident. In our opinion, this dependence could be important for several reasons. On one hand, it was argued that validity of the Hammett equation is conditioned by the presence of an ion or a polar transition state in the process and that for reactions between nonpolar species, this equation often does not hold with a sufficient accuracy¹⁵. On the other hand, relative independence of conformation on substitution was a presumption in determining conformations from dipole moments¹⁶ or from the Kerr constant¹⁷ but later on, slight dependence was found using the more sensitive NMR approach¹⁸.

In this work, we determined conformation equilibria of a series of thiobenzanilides. We believed that more reliable results would be obtained than in previous work¹³ when using a larger series of compounds and a contemporary IR technique: evaluation from the integrated absorption intensities A instead from absorption coefficients ϵ , a Fourier spectrometer, computer program for separating bands using the Gaussian-Lorentzian band shape or Voigt band shape¹⁹. Instead of the assumption of equal values of ϵ_Z and ϵ_E of the two conformers, we must assume now equal A_Z and A_E .

We investigated the thiobenzanilides **1-38** (Table I) bearing 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 studies³, compounds **31-38** were already used when measuring the transmission through the thioamide group^{10,20}. Both sets of compounds were treated here together.



EXPERIMENTAL

The compounds **1-30** (ref.³) and **31-38** (ref.²⁰) were already described.

Infrared absorption spectra were recorded on a Nicolet Impact 400FTIR spectrometer (512 scans, resolution 1 cm⁻¹, detector DTGS KBr) in 1 cm quartz cells in tetrachloromethane. The concentrations used were between 6 · 10⁻⁴–1 · 10⁻³ mol l⁻¹, except for the sparingly soluble compounds **7** and **24** which were measured in saturated solutions; the results for these compounds did not show any irregularity within the series. Separation of the N-H bands was achieved by the standard program¹⁹ which offers two possible procedures: either using mixed Gaussian-Lorentzian bands or the Voigt band shape. In Table I, we give the

TABLE I
Infrared spectral data and conformer population of substituted thioanilides 1-38

	Substituents		ν_{N-H} (cm ⁻¹)		$\Delta\nu_{1/2}$ (cm ⁻¹)		A^a (cm ⁻¹ mol ⁻¹)		$[Z]/[E]^a$	log K_C^a				
	X	Y	Z	E	Z	E	Z	E						
1	H	H	3 391.9	3 364.9	16.67	11.72	2.55	(2.53)	0.16	(0.17)	15.6 ^b	(14.8)	1.194	(1.171)
2	H	4-CH ₃	3 391.7	3 364.2	16.71	11.87	1.87	(1.86)	0.13	(0.12)	14.8 ^b	(15.1)	1.170	(1.179)
3	H	4-OCH ₃	3 391.7	3 362.7	16.98	11.84	3.17	(3.15)	0.17	(0.18)	18.3 ^b	(17.8)	1.263	(1.251)
4	H	4-Cl	3 391.6	3 363.8	17.26	11.68	3.00	(2.98)	0.12	(0.12)	25.8 ^b	(25.6)	1.411	(1.409)
5	H	3,4-Cl ₂	3 391.3	3 363.1	17.08	11.41	3.11	(3.06)	0.075	(0.082)	41.3	(37.5)	1.616	(1.575)
6	H	4-Br	3 391.4	3 363.8	17.51	11.81	2.93	(2.91)	0.11	(0.11)	26.1	(25.7)	1.417	(1.410)
7	4-CH ₃	H	3 393.2	3 365.6	17.15	11.33	1.46	(1.44)	0.10	(0.10)	14.5 ^c	(14.0)	1.161	(1.146)
8	4-CH ₃	4-CH ₃	3 393.0	3 364.8	17.38	11.42	2.79	(2.77)	0.21	(0.20)	13.5	(13.7)	1.131	(1.135)
9	4-CH ₃	4-OCH ₃	3 392.9	3 363.3	17.58	11.49	2.87	(2.84)	0.17	(0.17)	16.8	(16.3)	1.226	(1.212)
10	4-CH ₃	4-Cl	3 393.1	3 364.5	17.87	11.52	2.89	(2.86)	0.13	(0.13)	22.4	(21.7)	1.349	(1.337)
11	4-CH ₃	3,4-Cl ₂	3 392.7	3 363.6	18.51	11.50	3.49	(3.43)	0.094	(0.10)	36.9	(33.5)	1.567	(1.525)
12	4-CH ₃	4-Br	3 392.9	3 364.5	18.11	11.61	3.01	(2.98)	0.13	(0.13)	22.6	(22.0)	1.354	(1.343)
13	4-OCH ₃	H	3 395.2	3 366.5	18.01	11.09	2.40	(2.36)	0.19	(0.20)	12.4 ^d	(12.0)	1.093	(1.077)
14	4-OCH ₃	4-CH ₃	3 395.0	3 365.7	18.29	11.19	2.58	(2.55)	0.22	(0.22)	11.8 ^d	(11.5)	1.070	(1.060)
15	4-OCH ₃	4-OCH ₃	3 395.0	3 364.1	18.59	11.49	3.28	(3.20)	0.23	(0.24)	13.1 ^d	(13.1)	1.118	(1.118)
16	4-OCH ₃	4-Cl	3 395.2	3 365.5	18.67	11.36	2.79	(2.73)	0.14	(0.15)	19.6 ^d	(18.2)	1.293	(1.260)
17	4-OCH ₃	3,4-Cl ₂	3 394.9	3 364.6	19.30	11.31	3.02	(2.92)	0.094	(0.11)	31.9	(27.1)	1.504	(1.433)
18	4-OCH ₃	4-Br	3 394.9	3 365.4	18.84	11.16	2.66	(2.60)	0.13	(0.14)	20.4	(18.8)	1.309	(1.272)
19	4-Cl	H	3 391.9	3 364.1	17.67	12.26	2.21	(2.20)	0.22	(0.22)	10.3	(10.0)	1.012	(1.002)

TABLE I
(Continued)

Substituents		$\nu_{\text{N-H}}$ (cm^{-1})		$\nu_{1/2}$ (cm^{-1})		A^a ($\text{cm}^{-1} \text{mol}^{-1}$)		$[Z]/[E]^a$	$\log K_C^a$				
X	Y	Z	E	Z	E	Z	E						
20	4-Cl	4-CH ₃	3 391.8	3 363.3	17.91	12.35	2.46	(2.45)	0.28	8.8	(8.5)	0.943	(0.929)
21	4-Cl	4-OCH ₃	3 391.7	3 361.8	18.07	12.53	2.70	(2.69)	0.24	11.4	(10.7)	1.057	(1.031)
22	4-Cl	4-Cl	3 391.8	3 362.9	18.41	12.53	2.68	(2.66)	0.15	17.6	(17.2)	1.245	(1.234)
23	4-Cl	3,4-Cl ₂	3 391.4	3 362.0	19.13	12.78	3.05	(3.02)	0.11	28.5	(26.9)	1.454	(1.430)
24	4-Cl	4-Br	3 391.6	3 362.7	18.66	12.49	2.11	(2.08)	0.12	18.2	(16.4)	1.259	(1.215)
25	3-Br	H	3 389.4	3 363.3	17.26	11.19	2.91	(2.88)	0.14	20.3	(19.5)	1.307	(1.289)
26	3-Br	4-CH ₃	3 389.1	3 362.5	17.14	11.30	4.04	(4.02)	0.20	20.0	(19.4)	1.300	(1.287)
27	3-Br	4-OCH ₃	3 389.0	3 361.0	17.35	11.41	4.08	(4.02)	0.17	23.4	(21.7)	1.369	(1.337)
28	3-Br	4-Cl	3 389.2	3 362.1	17.86	10.60	3.60	(3.55)	0.089	40.5	(37.2)	1.608	(1.571)
29	3-Br	3,4-Cl ₂	3 388.6	3 360.7	18.51	9.61	2.77	(2.72)	0.031	90.7	(74.1)	1.957	(1.870)
30	3-Br	4-Br	3 388.8	3 361.8	17.99	10.37	3.49	(3.44)	0.078	44.7	(40.8)	1.650	(1.611)
31	H	3-F	3 393.0	3 365.4	17.33	11.92	2.70	(2.68)	0.12	23.5	(23.1)	1.372	(1.364)
32	4-CH ₃	3-F	3 394.4	3 366.0	17.79	12.01	2.87	(2.84)	0.14	20.7	(20.2)	1.316	(1.306)
33	4-Cl	3-F	3 393.2	3 364.3	18.52	12.82	2.92	(2.90)	0.17	16.8	(16.5)	1.226	(1.217)
34	3-Br	3-F	3 390.4	3 363.3	18.03	11.00	3.34	(3.29)	0.10	35.1	(32.5)	1.546	(1.512)
35	H	4-F	3 393.0	3 364.2	17.21	11.60	3.23	(3.21)	0.12	27.2	(27.1)	1.434	(1.432)
36	4-CH ₃	4-F	3 394.4	3 364.7	17.80	11.16	3.02	(2.98)	0.12	24.4	(23.5)	1.388	(1.370)
37	4-Cl	4-F	3 393.0	3 363.0	18.37	11.94	3.24	(3.20)	0.17	19.0	(18.0)	1.280	(1.254)
38	3-Br	4-F	3 390.3	3 362.3	17.61	10.64	3.56	(3.50)	0.092	38.6	(34.9)	1.586	(1.543)

^a Calculated by peak separation using a mixture of Gaussian and Lorentzian peak shapes (in parentheses – by peak separation according to Voigt¹⁹). ^b Ref.¹³ gives the values of 8.1, 7.7, 8.5 and 12.3 for compounds **1**, **2**, **3** and **4**, respectively. ^c Ref.¹³ gives the value of 6.1. ^d Ref.¹³ gives the values of 5.5, 5.5, 6.1 and 7.3 for compounds **13**, **14**, **15** and **16**, respectively.

wavenumbers ν , integrated absorption intensities A obtained from both procedures, and the band half-widths $\Delta\nu_{1/2}$ only from the Gaussian-Lorentzian bands. (Those from the Voigt bands are not directly comparable.) Note particularly that the values $\nu(\text{N-H})$ are those from the separation procedure not from the direct reading. Assignment of the bands to the E and Z conformers¹³ was accepted.

RESULTS AND DISCUSSION

Substituent Effects on the Conformation Equilibrium

Populations of the two conformers of **1-38** are given in Table I as the ratio $[Z]/[E] = K_C$ and as $\log K_C$. Values obtained with mixed Gaussian-Lorentzian bands or with the Voigt band shape¹⁹ are very near: $\log K_C$ from the former method is in average greater by 0.022, root-mean-square difference between the methods is 0.029. These differences, although systematic, are virtually within the experimental error; in any case, they are insignificant for the purpose of the correlation analysis. In the following, we shall refer to the separation with Gaussian-Lorentzian bands.

In the case of seven compounds, our results can be compared directly with those determined by Walter and Kubersky¹³. The difference is striking: according to our measurements, the abundance of the minor conformer E is to be reduced about to one half. In our opinion, the previous results were in error and tended to overestimate this value mainly for the reason that they were based on molar absorption coefficients ϵ_{\max} instead of on the integrated absorption intensities A . This is evident from the half-widths $\Delta\nu_{1/2}$ which are always smaller for the less abundant conformer E . When we calculated the apparent K_C from ϵ_{\max} of the separated bands, we obtained actually the figures virtually equal to those of Walter and Kubersky¹³.

The dependence of $\log K_C$ on substituent constants σ can be followed either separately for substitution in one benzene ring or for substitution in both rings simultaneously. In the former case, we use the Hammett equation either in the form of Eq. (1) or (2) for the substituents X and Y , respectively: note the difference in defining the unsubstituted compound. The random variable ϵ represents the difference between the statistical intercept and the experimental value of $\log K_{H,Y}$ or $\log K_{X,H}$. In the latter case, substitution in both rings, the correlation equation takes the form of Eq. (3) based both on the Hammett equation and on the additivity principle²¹.

$$\log K_{X,Y} = \log K_{H,Y} + \rho_X \sigma_X + \epsilon \quad (1)$$

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

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

We tried first a correlation of all substituent effects together, Eq. (3); when this was unsuccessful (Table II, line 3), we analyzed the effects from both sides separately according to Eqs (1) and (2) (lines 1 and 2). No significant correlation was found. The reason for the failure may be sought: (i) in the experimental uncertainty, possibly greater than in standard kinetic or pK measurements, (ii) in the assumption of equal integrated absorptivities, A_Z and A_E , which need not be valid, (iii) in a failure of Hammett equation

TABLE II
Statistics for the correlations of the properties of substituted thiobenzanilides 1-38

No.	Quantity	Equation	Regression coefficients, ρ^a		R^b	SD^b	f^b	ψ^c
			at X	at Y				
1	$\log K_C$	(1)	0.26(8)		0.466	0.12	36	1.03
2	$\log K_C$	(2)		0.52(6)	0.841	0.090	36	0.55
2a	$\log K_C^d$	(2)		0.47(5)	0.835	0.081	35	0.57
3	$\log K_C$	(3)	0.25(9)	0.51(8)	0.732	0.14	35	0.73
4	$\log K_C$	(5)				0.032	26	0.16
4a	$\log K_C^d$	(5)				0.021	25	0.12
5	$\nu(\text{N-H})_Z$	(7)	-7.7(5)	^e	0.929	0.72	36	0.38
6	$\nu(\text{N-H})_Z$	(9)				0.065	26	0.034
7	$\nu(\text{N-H})_E$	(7)	-5.06(11)	^e	0.990	0.17	36	0.14
8	$\nu(\text{N-H})_E$	(9)				0.11	26	0.076
9	$\nu(\text{N-H})_E$	(10)	0.63(7)		0.846	0.77	36	0.55

^a Standard deviation in parentheses. ^b Correlation coefficient R , standard deviation from the regression SD , and degrees of freedom f , respectively. ^c Statistic measuring the fit in a general case including also the linear regression, ref.²⁴; ψ 0.1 means good fit, ψ 0.5 no correlation existing. ^d With the compound 29 excluded; improvement with respect to the line 2 or 4 is significant at the level $\alpha = 0.005$. ^e Correlations with Eq. (8), for substituents Y, are insignificant.

as already observed in the absence of ions or strongly polar transition states in the reaction¹⁵, (iv) in some special features of the structures *E* and *Z* of **1-38** which would possibly need some special values of constants σ .

The explanation sub (i) can be rejected since the effect of a substituent *X* is constant at variable substituent *Y*. This is expressed most clearly by the additivity relationship, see the next section. We consider also the explanation sub (ii) as less probable. Even when the ratio A_Z/A_E is not unity, it should be nearly constant within a series of such similar compounds, or at least it should depend regularly on substitution. The validity of correlation would thus not be impaired. Concerning the possibility sub (iv), some attention should be given to the proper choice of constant σ for substituents *Y* which should be free of any resonance effect (so-called²² σ°). However, the available values²³ do not improve the correlation. Figure 1 reveals first that both electron-attracting and electron-releasing substituents *Y* tend to suppress the amount of the conformer *E*: the dependence on σ can be viewed as a curve with a minimum between the substituents H and 4-CH₃. However, this dependence is disturbed by the substituents 3-F and 4-F which deviate quite unexpectedly in the sense that they would require greater values of σ . For this purpose, even the value derived for 4-F from the dissociation of phenols^{23b} would not be sufficient, and for 3-F, no such possibility is available. Concerning the explanation sub (iii), several conformational equilibria furnished linear dependence on the constant σ

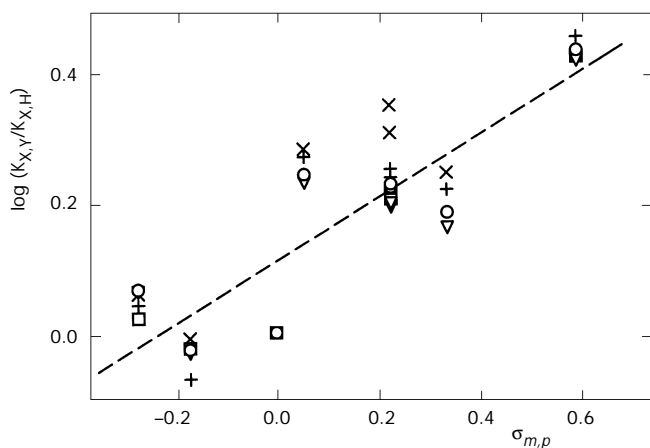


FIG. 1

Plot of $\log K_C$ for the conformational equilibrium of **1-38** vs the constants $\sigma_{m,p}$ of the variable substituent *Y*, Eq. (2); substituents *X* are held constant: H (○), 4-CH₃ (▽), 4-OCH₃ (□), 4-Cl (+), 3-Br (×)

(refs^{25,26}) but sometimes with a great scatter^{25d} or with an insufficient number of points^{25c}. The example, most similar to our case, is the equilibrium of substituted thioacetanilides²⁶ where the correlation is remarkably good. As far as we know, a scatter similar to Fig. 1 has not been observed. We can only suggest that the reason could be sought in a particular structure of the conformer *Z* in which the proximity of the two benzene rings can raise some interactions.

We do not report explicitly all unsuccessfully attempted correlations with various parameters. The most popular is the Dual Substituent Parameter (DSP) treatment²⁷, using multiple linear regression with inductive and resonance constants, σ_F and σ_R . With one explanatory variable more and applied separately to *para* and *meta* derivatives, this treatment could be attempted only to four substituent *Y* in the position *para*: no correlation was observed. It is evident even from Fig. 1 that the deviations cannot be explained in terms of inductive and resonance effects.

Effects of substituents *X* according to Eq. (1) need not be represented graphically due to the restricted number of substituents. A characteristic feature is the strong deviation of the substituent 4-Cl which behaves as a donor. We have no explanation of this fact: one cannot imagine such strong conjugation with the CSNH group that the resonance effect of Cl would outweigh its inductive effect.

Additive Behaviour

Equation (3) is based both on the Hammett equation and on the additive behaviour but these two assumptions are independent²⁸ and their validity can be tested separately. Whereas the Hammett relationship, Eq. (1) or (2), was already found not to hold in our case, the additive character can be tested now. Its simplest representation is Eq. (4). However, it has the defect of predicting bisderivatives on the basis of monoderivatives which are thus given more weight. Equation (5), statistically correct²⁹, gives the same weight to all derivatives by introducing *de novo* constants a_X and b_Y which are defined by the least-squares condition.

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

$$\log K_{X,Y} = \log K_{H,H} + a_X + b_Y + \varepsilon \quad (5)$$

Correlation according to Eq. (5), Table II, line 4, is much closer than any correlation with constants σ . It is still improved when the compound **29** with the highest value of $\log K_C$ (and probably with a greater uncertainty) is omitted (line 4a): then the general experimental uncertainty may be approached in the value of the standard deviation. This proves any kind of regularity in substituent effects and excludes that the correlations with σ could be disturbed by experimental errors. We must conclude that these substituent effects are regular but are not controlled by the electron-attracting or electron-releasing power.

Possible deviations from additivity could be tested by means of Eq. (6) in which the *de novo* constants are denoted as c_X and d_Y (ref.²⁹). The additivity remains the best expression since the correlation with Eq. (6) is not better than with Eq. (5).

$$\log K_{X,Y} = \log K_{H,H} + c_X d_Y + \varepsilon \quad (6)$$

Substituent Effects on the $\nu(N-H)$ Frequencies

The measured wavenumbers of the two conformers, $\nu(N-H)_Z$ and $\nu(N-H)_E$ offered an opportunity to explore also their control by substitution. The question was whether the irregularity observed on $\log K_C$ would re-appear with these quantities. Correlations of the wavenumbers with the σ constants are rather numerous in the literature³⁰ but a more exact analysis showed that a curvilinear dependence should be generally observed³¹. The Hammett correlation holds only as an approximation within a limited range; however, its accuracy is usually sufficient. In our case, the Hammett correlations have the form of Eq. (7) or (8).

$$\nu_{X,Y} = \nu_{H,Y} + \rho_X \sigma_X + \varepsilon \quad (7)$$

$$\nu_{X,Y} = \nu_{X,H} + \rho_Y \sigma_Y + \varepsilon \quad (8)$$

We obtained reasonable correlations only with Eq. (7); with $\nu(N-H)_E$ it was much better than with $\nu(N-H)_Z$ (Table II, lines 7 and 5, respectively). The problem may be seen in a relatively small sensitivity to substituent effects

but a smaller span of values (6 cm^{-1}) is not so bad compared with their experimental uncertainty (say 0.3 cm^{-1}). This ratio is worse when only substituents Y in the aniline moiety are considered; they affect $\nu(\text{N-H})$ only slightly and quite irregularly (statistics not given). Of the correlations reported in the literature, most similar to our compounds are substituted acetanilides³¹⁻³³ which exist only in one observable conformation. The sensitivity to substitution was very small: these compounds were just in the middle³² between those with a positive and a negative proportionality constant ρ , or an evident effect was observed³² only for the 4- NO_2 substituent which is absent in our set. The small sensitivity is in accord with the theory³¹ predicting generally a curvilinear dependence on σ with a maximum.

On the other hand, the additive character according to Eq. (9) is fulfilled with great accuracy, virtually within the experimental error (Table II, lines 6 and 8). The *de novo* constants a_X and b_Y cannot be given much importance since they have been determined only on a particular set of compounds. Nevertheless, one can ask whether there is any similarity between a_X and b_Y determined from the wavenumbers and those determined from K_C . The similarity is small. Even two sets of a_X (or b_Y), both derived from wavenumbers, one from the *Z* conformers and the other from the *E* conformers, showed only a restricted similarity. No correlation was found even directly between the values of $\nu(\text{N-H})_Z$ and $\nu(\text{N-H})_E$, see Eq. (10) and Table II, line 9, or between these wavenumbers and $\log K_C$ (not shown).

$$\nu_{X,Y} = \nu_{H,H} + a_X + b_Y + \varepsilon \quad (9)$$

$$\nu(\text{N-H})_E = A + B \nu(\text{N-H})_Z \quad (10)$$

CONCLUSIONS

Observed substituent effects on vibrational frequencies, not always compatible with the Hammett equation, are not quite uncommon and are explicable³¹. In contrast, effects on conformational equilibrium are quite unexpected and show that even the Hammett equation can have its limitation when applied to equilibria between little polar molecules; possibly certain folded conformations are particularly unfavourable. These cases might be more common than one could guess from the literature. On one hand, it

is probable that all unsuccessful correlations have not been published: an unsuccessful correlation is often viewed as a failure and such reports are not accepted by the reviewers and editors. On the other hand, discovering such cases needs a detailed analysis and a more extensive data set than it is usual.

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