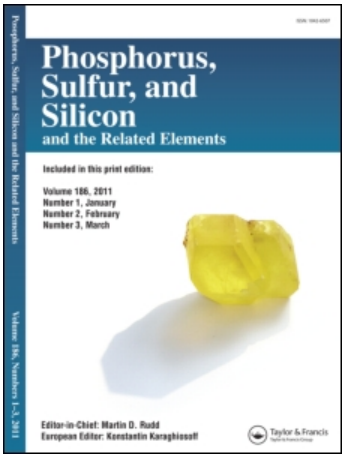

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TRANSMISSION OF SUBSTITUENT EFFECTS THROUGH THE CARBOXAMIDE AND THIOCARBOXAMIDE GROUPS

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TRANSMISSION OF SUBSTITUENT EFFECTS THROUGH THE CARBOXAMIDE AND THIOCARBOXAMIDE GROUPS

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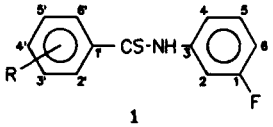
Dedicated to Prof. Wolfgang Walter on the occasion of his 75th birthday.

Substituted 3-fluorothiobenzanilides (**1**) and 4-fluorothiobenzanilides (**2**) were used as model compounds for evaluating the transmission of substituent effects through the thiocarboxamide group: in addition to ^{19}F substituent chemical shifts the ^{13}C and ^{1}H shifts were also monitored. The transmitted effect was always weaker than when transmitted through the carboxamide group in analogous carboxamides (**3**) and (**4**), the ratio of 0.76 was estimated conformably from ^{19}F, $^{13}C(1)$ and $^{13}C(4)$ substituent induced shifts. The interpretation may refer to the greater polarizability of the C=S bond which allows the greater part of the charge to be accommodated on sulphur and a relatively smaller part is transmitted further along the chain. This simplified picture is corroborated by substituent effects on the thiocarboxamide group itself (on the $^{13}C(S)$ and $^{1}H(N)$ substituent shifts) which are greater than in the case of carboxamides. This interpretation seems to us more probable than reference to the conformational equilibrium, observable in the solution of thioanilides but shifted in anilides to one side.

Key words: 3-Fluorothiobenzanilides, 4-fluorothiobenzanilides, thiocarboxamides, transmission of substituent effects.

INTRODUCTION

Physico chemical properties of thiocarboxamides were excellently reviewed[1] in 1976 but have been relatively little investigated by more modern methods,[2–10] in spite of the importance in pharmacology and bioorganic chemistry.[11] Our interest in this field is connected with Quantitative Structure Activity Relationships[11] and with Correlation Analysis[12] in general. Within the framework of these disciplines the thiocarboxamide group can be considered: a) as a substituent characterized in terms of various constants σ,[5–7] b) as a functional group whose basic physical properties can be investigated,[4,8–10] c) as a chain connecting the substituent with the functional group and transferring the substituent effects.[12] In this paper we are dealing mainly with the last aspect which has not yet received attention. Transmission of the electronic substituent effects is followed on model compounds: thiocarboxamides **1** and **2** which are compared to the corresponding carboxamides **3** and **4**.



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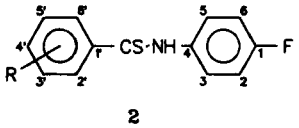

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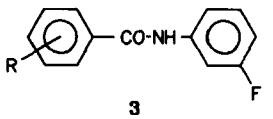

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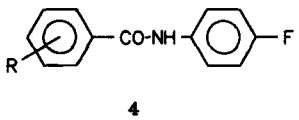
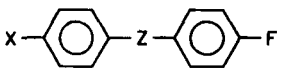


4

a R = H
b R = 3-Cl
c R = 3-NO_2
d R = 4-Cl
e R = 4-CH_3
f R = 4-NO_2
g R = 4-OCH_3
h R = 4-$N(CH_3)_2$

In **1–4** the fluorine atom serves as a probe and its ^{19}F NMR shift is monitored. Due to its sensitivity to substituent effects[13] this quantity seems more advantageous than some alternatives: the C≡N vibration of a cyano group,[14] the rate constant of acylation on an amino group,[15] or even the dissociation constant of a carboxyl group.[16] Note that the results of these approaches are well comparable.[15] Model compounds with two benzene rings, general formula **5**, were often used,[15,17–19] once even with Z = —CONH-[18]; the natural reference system[19] are biphenyl derivatives **6** in which Z is reduced to a bond. Comparison of thiocarboxamides to carboxamides is a common procedure.[4–6,8,9]



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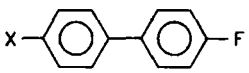


6

EXPERIMENTAL AND RESULTS

Compounds **1–4** were prepared by the standard procedure,[21] some physico chemical properties are given elsewhere.[22]

The NMR spectra were measured on a FT NMR spectrometer Varian UNITY 500 (^1H at 500 MHz, ^{13}C at 125.7 MHz and ^{19}F at 470.3 MHz, resp.). All spectra (see Tables I–V) were run with the same solution of compounds **1–4** (about 10 mg in 0.5 ml $CDCl_3$) at 30°C and referenced to internal tetramethylsilane (^1H and ^{13}C) or $CFCl_3$ (^{19}F). Carbon-13 NMR spectra were accumulated with a broad-band proton decoupling. The structure assignment of carbon signals was done on the basis of chemical shifts (C=O, C=S, CH_3 signals), signal intensities, molecular symmetry, characteristic fluorine-carbon coupling constants and known substituent effects in benzene ring (aromatic carbons). While all carbon atoms of benzanilides **3** and **4** give sharp lines, in thiobenzanilides the signals of C(S) and the neighbouring

TABLE I

Fluorine-19 NMR chemical shifts δ(F) and substituent effects Δδ(F) in thiobenzanilides 1, 2 and benzanilides 3, 4 in $CDCl_3$

	1		2		3		4	
R	δ(F)	Δδ(F)	δ(F)	Δδ(F)	δ(F)	Δδ(F)	δ(F)	Δδ(F)
H	-111.30		-114.27		-111.84		-118.18	
3-Cl	-111.04	0.26	-113.76	0.51	-111.58	0.26	-117.59	0.59
3-NO_2	-110.85	0.45	-113.37	0.90	-111.33	0.51	-116.99	1.19
4-Cl	-111.11	0.19	-113.95	0.32	-111.64	0.20	-117.77	0.41
4-Me	-111.41	-0.11	-114.47	-0.20	-111.94	-0.10	-118.42	-0.24
4-NO_2	-110.76	0.54	-113.27	1.00	-111.26	0.58	-116.86	1.32
4-OMe	-111.46	-0.16	-114.59	-0.32	-111.95	-0.11	-118.56	-0.38
4-NMe_2	-111.83	-0.53	-115.36	-1.09	-112.25	-0.41	-119.31	-1.13

TABLE II

Carbon-13 NMR chemical shifts of thiobenzanilides 1 and 2 in $CDCl_3$

	Chemical shifts (ppm) [a]													
R	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(S)	C(1')	C(2')	C(3')	C(4')	C(5')	C(6')	R
	thiobenzanilides 1													
H	140.43	110.78	162.68	113.67	130.17	118.91	198.67	143.08	126.69	128.67	131.37	128.67	126.69	–
3-Cl	140.11	110.79	162.65	113.93	130.26	118.94	196.72	144.46	126.99	134.75	131.20	129.88	124.72	–
3-NO_2	139.94	110.89	162.70	114.26	130.41	121.04	195.21	144.17	119.03	148.02	125.53	133.13	129.81	–
4-Cl	140.27	110.85	162.72	113.88	130.28	118.96	197.20	b	128.09	128.85	137.72	128.85	128.09	–
4-Me	140.53	110.94	162.67	113.54	130.11	118.97	198.49	140.19	126.75	129.27	142.10	129.27	126.75	21.34
4-NO_2	139.90	110.75	162.75	114.29	130.38	118.85	195.70	148.10	127.70	123.92	149.07	123.92	127.70	–
4-OMe	140.66	110.98	162.70	113.49	130.12	119.09	197.85	135.15	128.73	113.83	162.53	113.83	128.73	55.53
4-NMe_2	141.11	111.06	162.70	113.01	129.96	119.19	197.40	129.25	128.81	110.91	152.88	110.91	128.81	40.09
	thiobenzanilides 2													
H	135.03	125.92	115.92	160.89	115.92	125.99	198.96	142.85	126.67	128.67	131.38	128.67	126.67	–
3-Cl	134.72	125.97	115.96	160.96	115.96	125.97	197.00	144.22	126.95	134.72	131.18	129.87	124.74	–
3-NO_2	134.57	126.04	116.15	161.14	116.15	126.04	195.53	143.96	120.92	148.07	125.55	133.23	129.82	–
4-Cl	134.86	126.02	116.02	160.98	116.02	126.02	197.38	137.72	128.84	128.04	141.03	128.04	128.84	–
4-Me	135.12	126.06	115.87	160.84	115.87	126.06	198.71	140.02	126.70	129.26	142.06	129.26	126.70	21.35
4-NO_2	134.51	125.87	116.17	161.13	116.17	125.87	196.80	147.87	127.68	123.94	149.12	123.94	127.68	–
4-OMe	135.26	126.18	115.91	160.85	115.91	126.18	197.80	135.26	128.68	113.88	153.86	113.83	128.68	55.53
4-NMe_2	135.53	126.31	115.75	160.67	115.75	126.31	197.80	b	128.81	110.92	152.85	110.92	128.81	40.10

[a] The signals of carbon atoms C(1) to C(6) are split into doublets with following coupling constants: J(C(1),F) = 9.8-10.8 Hz, J(C(2),F) = 25.4-26.4 Hz, J(C(3),F) = 246.1-247.1 Hz, J(C(4),F) = 20.5-21.5 Hz, J(C(5),F) = 8.8-9.8 Hz, J(C(6),F) = 3.0 Hz in thiobenzanilides 1 and J(C(1),F) = 3.0 Hz, J(C(2),F) = J(C(6),F) = 7.8-8.8 Hz, J(C(3),F) = J(C(5),F) = 22.5-23.4 Hz, J(C(4),F) = 247.1-249.0 Hz in thiobenzanilides 2.

[b] The signal was not detected.

TABLE III
Carbon-13 NMR chemical shifts of benzanilides 3 and 4 in $CDCl_3$

R	Chemical shifts (ppm) [a]												
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(O)	C(1')	C(2')	C(3')	C(4')	C(5')	C(6')	R
	benzanilides 3													
H	139.49	107.69	163.10	111.27	130.13	115.36	165.72	134.66	128.85	127.00	132.06	127.00	128.85	–
3-Cl	139.11	107.83	163.06	111.62	130.21	115.50	164.40	136.41	127.38	135.11	132.08	130.15	125.09	–
3-NO_2	138.77	108.03	163.08	112.05	130.35	115.67	163.25	136.25	121.77	148.38	126.59	130.24	133.34	–
4-Cl	139.22	107.78	163.08	111.53	130.21	115.42	164.63	132.99	129.15	128.47	138.47	128.47	129.15	–
4-Me	139.63	107.65	163.09	110.92	130.07	115.34	165.98	131.77	129.48	127.04	142.64	127.04	142.64	21.46
4-NO_2	138.74	107.96	163.09	112.11	130.38	115.56	163.61	140.14	128.77	124.11	149.98	124.11	128.27	–
4-OMe	139.70	107.59	163.11	111.01	130.08	115.25	165.15	126.80	128.92	114.09	162.73	114.09	128.92	55.48
4-NMe_2	140.17	107.40	163.12	110.48	129.94	115.11	165.17	120.97	128.64	111.17	152.85	111.17	128.64	40.05
	benzanilides 4													
H	133.92	122.09	115.77	159.60	115.77	122.09	165.66	134.80	128.84	126.98	131.94	126.98	128.84	–
3-Cl	133.57	122.27	115.84	159.76	115.84	122.27	164.38	136.54	127.37	135.07	131.95	130.13	125.09	–
3-NO_2	133.21	122.49	115.97	159.98	115.97	122.49	163.25	136.36	121.73	148.35	126.46	130.17	133.33	–
4-Cl	133.64	122.23	115.81	159.71	115.81	122.23	164.65	133.10	129.09	128.43	138.29	128.43	129.09	–
4-Me	134.05	122.05	115.72	159.53	115.72	122.05	165.61	131.91	129.47	127.00	142.50	127.00	129.47	21.46
4-NO_2	133.19	122.40	116.00	159.99	116.00	122.40	163.63	140.27	128.24	124.05	149.88	124.05	128.24	–
4-OMe	134.11	122.04	115.72	159.49	115.72	122.04	165.16	126.94	128.87	114.06	162.62	114.06	128.87	55.48
4-NMe_2	134.54	121.86	115.56	159.22	115.56	121.86	165.56	121.15	128.58	111.18	152.77	111.18	128.58	40.06

[a] The signals of carbon atoms C(1) to C(6) are split into doublets with following coupling constants: J(C(1),F) = 9.8-10.8 Hz, J(C(2),F) = 26.4 Hz, J(C(3),F) = 244.2-246.1 Hz, J(C(4),F) = 20.5-21.6 Hz, J(C(5),F) = 8.8-9.8 Hz, J(C(6),F) = 2.9-3.0 Hz in benzanilides 3 and J(C(1),F) = 2.5-3.3 Hz, J(C(2),F) = J(C(6),F) = 7.4-8.2 Hz, J(C(3),F) = J(C(5),F) = 22.2-23.0 Hz, J(C(4),F) = 244.2-246.1 Hz in benzanilides 4.

carbon atom C(1') are broadened with halfwidths of 30–50 Hz and those of carbon atoms C(2') and C(6') with halfwidths of 10 Hz. Fluorine-19 NMR spectra of benzanilides showed generally multiplets due to J(F, H) with aromatic protons (except nitro derivatives **4c** and **4f** where splitting was not resolved). Thiobenzanilides showed typically broad unresolved peak (J(F, H) splitting was partly resolved in compounds **1a**, **1e**, **1h** and **2b** only). Similar systematic difference in linewidths was observed also in proton NMR spectra.

DISCUSSION

Transmission of Substituent Effects

The transmission efficiency was often evaluated[14–17] within the framework of the Hammett equation: ratio of the two reaction constants ρ was called the transmission

TABLE IV

Proton NMR chemical shifts of thiobenzanilides **1** and **2** in $CDCl_3$

	Chemical shifts (ppm)											
R	H(2)	H(3)	H(4)	H(5)	H(6)	H(N)	H(2′)	H(3′)	H(4′)	H(5′)	H(6′)	R
	thiobenzanilides **1**											
H	7.797	–	6.976	7.361	~7.40	9.022	7.796	7.414	7.493	7.414	7.796	–
3-Cl	~7.76	–	6.993	~7.36	~7.36	9.034	~7.76	–	7.454	~7.36	7.646	–
3-NO_2	7.771	–	7.021	7.400	~7.42	9.167	8.567	–	8.313	7.614	8.177	–
4-Cl	7.740	–	6.992	7.372	~7.39	8.880	7.744	7.390	–	7.390	7.744	–
4-Me	~7.74	–	6.962	7.347	~7.37	8.998	7.706	7.207	–	7.207	7.706	2.338
4-NO_2	~7.82	–	~7.04	~7.42	~7.44	~9.09	~7.94	~8.27	–	~8.27	~7.94	–
4-OMe	7.690	–	6.964	7.350	7.360	8.938	7.817	6.907	–	6.907	7.817	3.858
4-NMe_2	7.671	–	6.932	7.332	7.350	8.850	7.824	6.639	–	6.639	7.824	3.042
	thiobenzanilides **2**											
H	7.696	7.120	–	7.120	7.696	8.945	7.839	7.429	7.503	7.429	7.839	–
3-Cl	7.656	7.116	–	7.116	7.656	9.000	7.790	–	7.458	7.347	7.673	–
3-NO_2	7.710	7.154	–	7.154	7.710	9.083	8.611	–	8.333	7.631	8.230	–
4-Cl	7.674	7.126	–	7.126	7.674	8.897	7.787	7.401	–	7.401	7.787	–
4-Me	7.679	7.107	–	7.107	7.679	8.918	7.756	7.222	–	7.222	7.756	2.396
4-NO_2	7.723	7.160	–	7.160	7.723	8.981	7.965	8.279	–	8.279	7.965	–
4-OMe	7.662	7.113	–	7.113	7.662	8.860	7.863	6.923	–	6.923	7.863	3.870
4-NMe_2	7.603	7.091	–	7.091	7.603	8.802	7.850	6.650	–	6.650	7.850	3.047

TABLE V

Proton NMR chemical shifts of benzanilides **3** and **4** in $CDCl_3$

	Chemical shifts (ppm)											
R	H-2	H-3	H-4	H-5	H-6	NH	H-2′	H-3′	H-4′	H-5′	H-6′	R
	benzanilides **3**											
H	7.617	–	6.845	7.299	7.268	7.890	7.850	7.479	7.553	7.479	7.850	–
3-Cl	7.596	–	6.867	7.308	7.266	7.940	7.825	–	7.522	7.415	7.715	–
3-NO_2	7.621	–	6.904	7.345	7.299	7.963	8.685	–	8.418	7.718	8.250	–
4-Cl	7.593	–	6.862	7.309	7.253	7.810	7.794	7.462	–	7.462	7.794	–
4-Me	7.609	–	6.828	7.283	~7.26	7.889	7.742	7.267	–	7.267	7.742	2.414
4-NO_2	7.613	–	6.918	7.347	7.273	7.835	8.032	8.354	–	8.354	8.032	–
4-OMe	7.608	–	6.831	7.294	7.249	7.762	7.827	6.976	–	6.976	7.827	3.875
4-NMe_2	7.615	–	6.791	7.267	7.243	7.759	7.759	6.695	–	6.695	7.759	3.040
	benzanilides **4**											
H	7.596	7.065	–	7.065	7.596	7.767	7.862	7.491	7.557	7.491	7.862	–
3-Cl	7.580	7.064	–	7.064	7.580	7.840	7.836	–	7.522	7.419	7.723	–
3-NO_2	7.614	7.094	–	7.094	7.614	7.897	8.685	–	8.411	7.712	8.251	–
4-Cl	7.572	7.063	–	7.063	7.572	7.750	7.796	7.458	–	7.458	7.796	–
4-Me	7.584	7.048	–	7.048	7.584	7.778	7.752	7.276	–	7.276	7.752	2.421
4-NO_2	7.600	7.095	–	7.095	7.600	7.811	8.028	8.340	–	8.340	8.028	–
4-OMe	7.577	7.055	–	7.055	7.577	7.685	7.829	6.975	–	6.975	7.829	3.876
4-NMe_2	7.556	7.027	–	7.027	7.556	7.700	7.762	6.696	–	6.696	7.762	3.045

factor π. It is assumed that π is determined by the character of the transmitting chain and independent of the system and of the functional group within the accuracy of the correlation equations.[12] However, as a ratio of two regression coefficients, π is loaded with a considerable statistical error. Whenever possible (viz. when there is a sufficient number of common substituents in the two series) we prefer a direct plot of the observed quantities,[18,19] in our case of chemical shifts. A plot of fluorine-19 shifts (Figure 1) reveals a close linear dependence, with 3-fluoro and 4-fluoro derivatives lying nearly on the same straight line. The standard deivation of 0.07 ppm is reduced to 0.045 ppm when two deviating points for the substituent $N(CH_3)_2$ are omitted: the correlation coefficient is 0.994. The slope of the line (0.80) is obtained with a standard deviation of 0.02. The traditional treatment[5,17,23,24] of substituent shifts proceeds in terms of Dual Substituent Parameters[23] (DSP) σ_I and σ_R: *meta* and *para* derivatives are to be treated separately. In our case we would get for compounds **2** and **4** the equations (1) and (2), respectively. The transmission coefficient would be 0.79 ± 0.22 for the inductive component and 0.87 ± 0.20 for the resonance component. These values are concordant with our value from the direct treatment but much less reliable: one cannot even decide whether they differ

$$\delta_F(2) = 1.34(\pm 0.32)\sigma_I + 1.79(\pm 0.34)\sigma_R - 0.016 \quad R = 0.978 \quad (1)$$

$$\delta_F(4) = 1.70(\pm 0.23)\sigma_I + 2.05(\pm 0.25)\sigma_R - 0.003 \quad R = 0.992 \quad (2)$$

from each other. Results of similar calculations[17] must be accepted with precaution. The DSP treatment was criticized generally that it is in many cases overparametrized and results in a loss of information.[25]

Of the ^{13}C shifts only those in the positions C(1) and C(4) come into consideration for estimating transmission of electronic effects: the C(2) and C(3) are known to

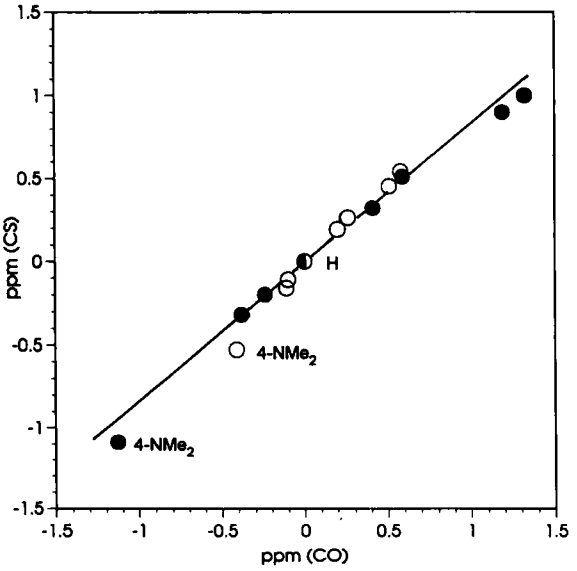


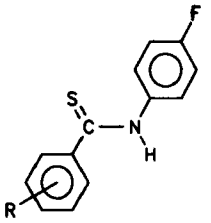
FIGURE 1 Plot of ^{19}F NMR substituent induced shifts, benzanilides **3** and **4** (x-axis) vs. thiobenzanilides **1** and **2** (y-axis): ○ = *meta* derivatives **1** and **3**, ● = *para* derivatives **2** and **4**.

be controlled by other, not exactly specified factors.[25] In Figure 2 not only 3-F and 4-F derivatives are situated on the same straight line but also the points for C(1) and C(4). Again the $N(CH_3)_2$ substituent deviates. The slope of the line in Figure 2 (0.74 ± 0.02) does not differ significantly from that in Figure 1, also the scatter is similar (s.d. = 0.039 ppm, R = 0.993).

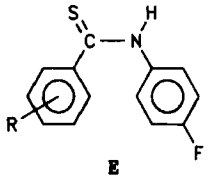
Of the ^1H shifts we have examined only that in the position H(5) which is present in all derivatives **1–4**. Since all the shifts are in an interval of 0.08 ppm, the signal to noise ratio is unfavourable and the plot (not shown) is more scattered. The slope does not seem to differ significantly from unity.

When the —CH=CH— chain in substituted stilbenes is used as standard,[19] the transmission through —CONH— is given by 0.72 and through —CSNH— by 0.54. These figures are little accurate since they are based on rather scattered plots. From the data of Pews[18] one gets 0.60 for —CONH— while Ager[19] gives 0.47 for the reversed group —NHCO—. Our ratio of thiocarboxamides to amides is based on homogeneous data and on plots with a better fit, and is much more accurate: the transmission through the thiocarboxamide group is distinctly weaker. This fact can be explained in two ways as follows.

When discussing the acidity of thiocarboxamides and carboxamides in the gas phase[9] or in dioxan,[4] the deciding factor is greater polarizability of the C=S bond, or in somewhat different terms, the ability of sulphur to accommodate a negative charge. For the transmission of electronic effects this means that the greater part of the electronic demand (or electron supply) is balanced on the sulphur atom and a smaller part transmitted to nitrogen and to further atoms. This simplified picture is supported by the greater substituent effect on the thiocarboxamide group itself,



Z



E

vide infra. The second explanation would operate with the conformational equilibrium Z ⇌ E which is assumed from the broad signals in our ^{13}C and ^1H NMR spectra, and which has been proven from the IR spectrum of unsubstituted thiobenzanilide.[2] Note that benzanilide is practically in the conformation Z.[26] In our opinion, this explanation is less probable. The equilibrium Z:E was determined[2] to be 89:11 for **1a** and cannot depend too much on remote substitution: hence even a transmission factor in E equal to zero would not be sufficient to account for the whole effect. A strong dependence of the substituent effect on conformation was calculated[27] for —$NHCOCH_3$, but the dependence experimentally found for —NHCHO was less dramatic[28] (Table VI).

The Thiocarboxamide Group as Substituent

As mentioned in the Introduction, the thiocarboxamide group can be considered either as a transmitting group, substituent, or a functional group (reaction centre).

TABLE VI

Inductive and resonance constants of thioacylamino and acylamino groups[a]

Substituent	σ_I E	σ_I Z	σ_R E	σ_R Z	Reference
-NHCS-C_6H_5	0.33		-0.10		this work
-NHCS-CH_3	0.30[b]		-0.18[b]		32
-NHCO-C_6H_5	0.26		-0.21		this work
-NHCO-CH_3	0.34		-0.21		30
	0.30[b]		-0.31[b]		30
			-0.41[c]		33
	0.41[d]	0.08[d]			27
-NHCHO	0.29	0.34	-0.22	-0.34	28
	0.33[d]				35

[a] From ^{19}F NMR shifts unless otherwise indicated.
[b] Determined indirectly from the constants σ_m and σ_p.
[c] From IR intensities.
[d] From quantum chemical calculations, empirically correlated.

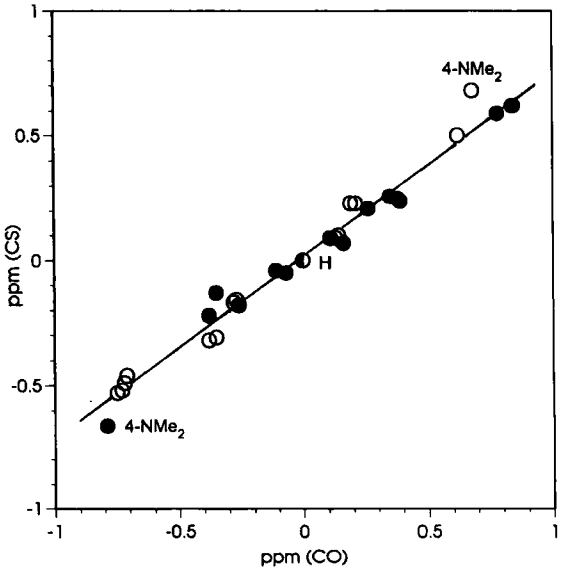


FIGURE 2 Plot of ^{13}C NMR substituent induced shifts, benzanilides **3** and **4** (x-axis) vs. thiobenzanilides **1** and **2** (y-axis): ○ = C(1) atom, ● = C(4) atom.

The first aspect was the goal of our investigation, the two remaining will be dealt with now as secondary results. The compounds **1–4** may represent models for determining the inductive constant σ_I and resonance constant σ_R of the Taft's classical DSP model,[13,23] when the whole group —NH—CX—C_6H_4R is taken as substituent. The defining relationships[29] are equations (3) and (4).

$$\sigma_I = (0.60 + \delta_m)/7.1 \quad (3)$$

$$\sigma_R = (\delta_p - \delta_m)/29.5 \quad (4)$$

The ^{19}F NMR shifts, δ_m and δ_p, in these equations are related to fluorobenzene. The calculated values of σ_I and σ_R are given in Table VI and compared with literature data concerning some similar substituents. The reduced resonance effect of the thiobenzamido group, compared to benzamido group, can be understood in terms of crossed resonance: stronger resonance of C═S with the NH nitrogen reduces the resonance of nitrogen with the benzene ring. The crossed resonance, when too strong, may be also responsible for the deviations of the substituent $N(CH_3)_2$ in Figures 1 and 2. In general, the DSP parameters σ_I and σ_R are acceptable when defined in an unambigous way[31] as in equations (3) and (4): they can be then considered essentially as experimental quantities. However, their physical meaning need not be always unambiguous, and a DSP treatment of arbitrary data may be criticized.[25]

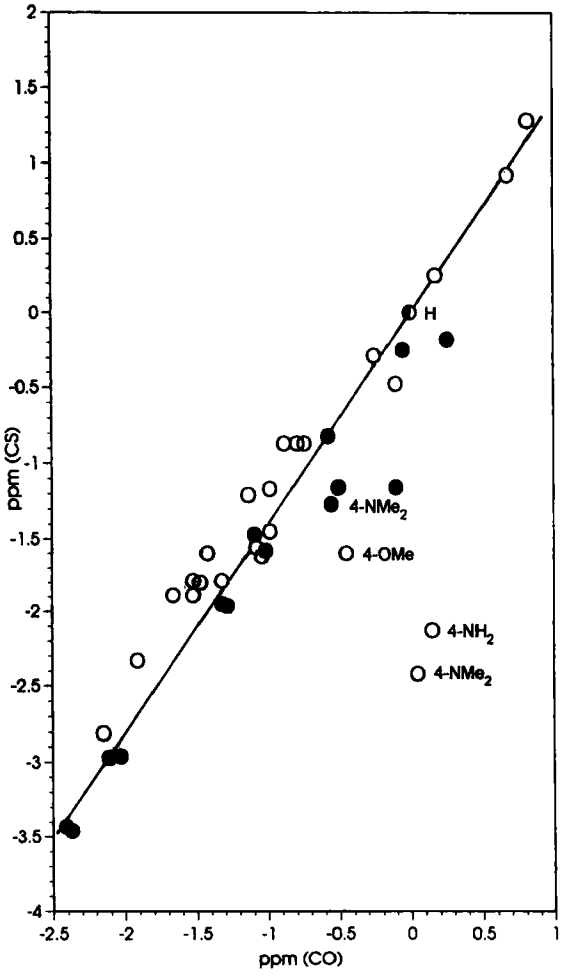


FIGURE 3 Plot of ^{13}C NMR substituent induced shifts, $^{13}C(C═O)$ of carboxamides (x-axis) vs. $^{13}C(C═S)$ of thiocarboxamides (y-axis): ● = benzanilides and thiobenzanilides **1–4**, ○ = benzamides and thiobenzamides from Reference 24.

The Thiocarboxamide Group as a Reaction Centre

The effect of variable substituents on a thiocarboxamide group, acting as reaction centre, can be estimated from the $^{13}C(S)$ and $^{1}H(N)$ chemical shifts. In either case the carboxamido group will be the reference. Figure 3 is a plot of $^{13}C(S)$ shifts in **1** and **2** vs. $^{13}C(O)$ in **3** and **4**. Some points concerning simpler compounds[24] $RC_6H_4CSNH_2$ and $RC_6H_4CONH_2$ were added for comparison. In spite of the deviations, it is evident that thiocarboxamides are more sensitive to substitution (slope approximately 1.3). This fact is consistent with its less efficiency in transmitting as interpreted in the first section. We may say in simple terms that in thiocarboxamides a greater part of the whole electronic substituent effect is neutralized on sulphur and a smaller part transmitted further along the chain. On the other hand, there would be little consistency with an explanation in terms of conformational equilibrium. Note that chemical shifts in the α-position of a conjugated chain (carbonyl, thiocarbonyl, vinyl) are not simple[25] and a linear plot as in Figure 3 can be obtained only for very similar compounds. A general explanation was advanced in terms of "localized" and "extended" polarization[24] but a DSP treatment was not convincing and was challenged.[25] One could possibly understand that σ_R are reversed in sign for carboxamides and thiocarboxamides, but they are also reversed for *meta* and *para* thiocarboxamides.[24] What is still less understandable *meta* derivatives of carboxamides should be stronger conjugated than *para*.[24] All the problems are due to donor substituents in the *para* position. An alternative treatment, based on principal component analysis, gave an additional factor to these substituents, treating the others together.[25]

A plot of $^{1}H(N)$ shifts (not shown), thiocarboxamides vs. carboxamides, is still more scattered than Figure 3 but no doubt the effects are greater for thiocarboxamides (slope approximately 1.6). This is consistent with the whole picture.

CONCLUSIONS

The weaker transmission of substituent effects through the thiocarboxamide group and its greater sensitivity as a probe can be understood in terms of the larger volume of sulphur and greater polarizability of its electrons. The difference in the conformational equilibrium is in our opinion not decisive. A definite proof could be obtained with a frozen equilibrium by determining the transmission coefficients for each conformer separately. Our preliminary experiments in this direction have not yet met with success, although in the case of fluorinated formanilides this was achieved already at room temperature.[28]

ACKNOWLEDGEMENTS

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