CHEMOMETRICAL ANALYSIS OF SUBSTITUENT EFFECTS ON ^{13}C AND ^{15}N NMR CHEMICAL SHIFTS IN 1-AROYL-3- -SUBSTITUTED THIOUREAS

Oldřich PYTELA[a], Josef JIRMAN[b] and Antonín LYČKA[b]

[a] *Department of Organic Chemistry,*
Institute of Chemical Technology, 532 10 Pardubice and
[b] *Research Institute of Organic Syntheses, 532 18 Pardubice-Rybitví*

The methods of conjugated deviations and regression analysis have been used to study the substituent effects on ^{13}C and ^{15}N NMR chemical shifts of 12 derivatives of 1-aroyl-3-phenyl-thiourea and 1-aroyl-3-methylthiourea. The ^{13}C NMR chemical shifts can be described by two latent variables, one univocally correlated with the Hammett substituent constants ($r = 0.993$) and the other reflecting the increased shielding of the nuclei due to overlap of the adjacent bond electrons as a consequence of electron-donor or electron-acceptor character of the substituents. This effect is less pronounced with the ^{15}N nuclei. Application of dual substituent constants σ_R, σ_F with the additional constant σ_α describing the polarization has failed in giving sufficiently close correlations and explanation of the substituent effect found.
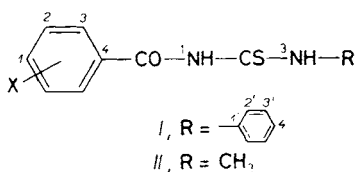
The substituent chemical shifts (SCS) represent a special phenomenon in NMR. The classical empirical description of substituent effects expressed by the ETR principle (LFER) is based upon the energy difference between two states of a molecule and is localized on bonds as the sites of increased electron density. However, the notion of chemical environment is more general in NMR: it not only describes the changes of magnetic field in the vicinity of the nucleus measured due to the local sterical distribution of bonding electrons, but it also reflects the changes of magnetic field due to the electron distribution over the molecule as a whole. Hence, it can be expected that the description of substituent effects on the NMR chemical shifts will be more complex as compared with the classical description and will need more than one parameter in the linear model postulated. Usually recommended are two parameters[1] most often in the parametrization according to Taft[1-5], Swain, Lupton[6,7] or other modifications[8-11]. The correlations carried out with the parametrization given usually are good in average but exhibit variable closeness of fit.

Another approach to substituent effects in NMR spectroscopy is based upon methods seeking latent variables (so far predominantly PCA and FA). A survey can be found e.g. in refs[12,13]. The number of latent variables found varies from two to six, which can be caused by both the selection of data and the criteria − so far not

univocal — for selection of the minimum necessary number of latent variables. In spite of doubtless advantages of application of the methods with latent variables (as compared with the regression analysis employing external empirical parameters), the contribution of these methods to understanding of the underlying principles of SCS has been small so far.

No systematic study of substituent effects on ^{13}C and ^{15}N NMR chemical shifts of the acylthioureas *I* and *II* has been carried out yet, although these substances were synthetized[14] and characterized by means of ^{1}H NMR spectroscopy[14,15]. Also published are spectra (^{15}N, ^{13}C, ^{1}H) of acylated ureas and thioureas[16] and the respective effects of acyl in some acetylated derivatives of 1-(4-substituted phenyl) thioureas[17].

The aim of this present communication is a chemometrical analysis of substituent effects on the ^{13}C and ^{15}N NMR chemical shifts in compounds *I* and *II* as well as determination of number and nature of independent substituent effects with a possible generalization.

EXPERIMENTAL

Syntheses of all the compounds studied, except the 4-tert. butyl derivative, have already been described[14]. The compounds *I* and *II* with the substituent X = 4-tert. butyl were prepared by the reaction of 4-tert. butylbenzoyl chloride with the corresponding amine in acetone in analogy to the procedure *B* in ref.[14]. The melting points after recrystallization from ethanol are 141— —142°C (*I*, X = C(CH$_3$)$_3$) and 125—127°C (*II*, X = C(CH$_3$)$_3$). The elemental analyses (H,C,N) agreed with the structures given with errors less than 0·3%.

Measurements of NMR Spectra

The ^{13}C and ^{15}N NMR spectra were measured with a JNM-FX 100 (JEOL) apparatus at 25·047 and 10·905 MHz, respectively, at 25°C. The substances were measured as saturated solutions in hexadeuteriodimethyl sulfoxide. The ^{13}C NMR chemical shifts are related to the solvent signal ($\delta = 39·60$) and were measured with a digital resolution of 1·46 Hz/point (0·06 ppm/point). The interpretation of spectra was based upon the proton-coupled spectra and SCS of the sub-stituents. The ^{15}N NMR chemical shifts are related to external nitromethane (25% ^{15}N, $\delta = = 0·00$) placed in a coaxial capillary. Negative values denote upfield shifts. The digital resolution 1·23 Hz/point (0·12 ppm/point). The measurement parameters for ^{15}N NMR: 5 000 Hz spectral width, 8 K, 45° pulse, 3·5 s pulse repetition, 1 000 to 3 000 pulses.

Reproducibility of NMR Spectral Measurements

The ^{13}C NMR spectra of compound I (X = H) were measured repeatedly (6×) within 2 h with one sample. The reproducibility of the ^{13}C NMR chemical shifts is better than 10^{-2} ppm. The effect of concentration change of the same substance within the limits of c_1 0·13 mol l^{-1} and c_2 0·52 mol l^{-1} (the saturated solution at 25°) was within the experimental accuracy. The change in the ^{15}N NMR chemical shifts accompanying the concentration change from c_1 (the minimum concentration of compound I (X = H) for the measurement of ^{15}N NMR without application of pulse sequence INEPT[18] or DEPT[19] at the magnetic field intensity of 2·35 T) to c_2 is 0·23 ppm, which is caused by the change of magnetic susceptibility of the sample with regard to the external standard. The ^{13}C and ^{15}N NMR chemical shifts measured, from which the differences $\Delta\delta$ ($\Delta\delta = \delta(X) - \delta(H)$) were calculated, are given in Table I.

Compound I (X = H) δ^{13}C: 133·20 (C—1), 128·76 (C—2), 128·52 (C—3), 132·21 (C—4), 168·36 (CO), 179·19 (CS), 138·06 (C—1'), 124·37 (C—2'), 128·76 (C—3'), 126·36 (C—4'). δ^{15}N: —221·40 (N—1), —232·89 (N—3; this value was verified by a measurement of the compound selectively labelled with ^{15}N isotope at the position 3).

Compound II (X = H) δ^{13}C: 132·97 (C—1), 128·46 (C—2), 128·58 (C—3), 132·38 (C—4), 167·84 (CO), 180·94 (CS), 32·17 (CH$_3$). $_9$ ^{15}N: —224·67 (N—1), —253·81 (N—3).

The experimental results were treated by the method of conjugated deviations[20,21] and by linear regression according to our own programs on an EC 1033 computer.

RESULTS AND DISCUSSION

Table I presents selected ^{13}C and ^{15}N NMR chemical shifts for twelve derivatives of compounds I and II related to the nonsubstituted derivative. The average values given on the last but one line of the same table indicate opposite substituent effects on ^{13}C and ^{15}N NMR chemical shifts along the chain, which is probably caused by different sensitivity of the two nuclei to the shielding factors operating. The scattering in the individual columns, which reflects the sensitivity of individual nuclei of chain to substitution, decreases roughly 5 times per each bond for carbon and roughly 1·5 times for nitrogen, as it is documented by the last line of Table II. Taking into account the interval of values of chemical shifts, we can see that the sensitivity of nitrogen nucleus is greater than that of carbon nucleus. However, it must not be forgotten that the C=S group shows a high transfer ability for electronic effects[16]. Surprisingly, the substituent effect is also felt on the most distant nitrogen atom, because the variance found is statistically significantly greater than that from both the repeated experiment $\left(s^2 < 10^{-4}\delta\right)$ and concentration change (see Experimental). The values of the mean and variance are comparable for both the parent structures, introduction of methyl group instead of phenyl group results in sensitivity lowering at the nuclei closer to the substituent X and sensitivity increase at the more distant nuclei.

In order to obtain the latent factors manifested in the chemical shifts, the data of Table I were treated by the method of conjugated deviations[20,21]. With respect to the above-shown similarity of results for both the basic skeletons I and II, the data

TABLE I

Selected ^{15}N and ^{13}C NMR substituent chemical shifts (SCS, δ) of the thiourea derivatives *I* and *II*

No.	Substituent X	I					II				
		C-4	C=O	N-1	C=S	N-3	C-4	C=O	N-1	C=S	N-3
1	H	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
2	4-N(CH$_3$)$_2$	+15·27	+0·70	−3·64	−0·17	−1·58	+14·97	+0·74	−3·51	−0·29	−1·94
3	4-OCH$_3$	+8·31	+0·58	−1·70	−0·11	−0·85	+8·19	+0·74	−1·57	−0·12	−0·61
4	4-CH$_3$	+2·99	+0·06	−0·73	−0·11	−0·25	+2·86	+0·12	−0·72	−0·12	−0·25
5	4-C(CH$_3$)$_3$	+2·93	−0·11	−0·6	−0·01	−0·61	+2·86	−0·30	−0·49	+0·06	−0·36
6	3-CH$_3$	+0·11	−0·12	+0·13	0·00	+0·25	+0·11	0·00	+0·12	−0·06	0·0
7	4-Cl	+1·11	+0·99	+0·12	+0·06	+0·36	+1·15	+0·98	+0·27	+0·10	+0·51
8	4-F	+3·46	+0·99	+0·13	+0·01	+0·12	+3·51	+1·06	+0·12	+0·06	−0·12
9	4-CO$_2$CH$_3$	−4·04	+0·82	+1·08	+0·24	+0·36	−4·10	+1·00	+1·69	+0·35	+0·84
10	3-NO$_2$	−1·46	+1·93	+0·43	+0·29	+0·12	−1·64	+1·88	+0·72	+0·17	+0·84
11	4-NO$_2$	−5·85	+1·69	+1·93	+0·41	+1·21	−5·86	+1·52	+1·81	+0·41	+1·21
12	3,5-(NO$_2$)$_2$	−3·28	+3·39	+2·29	+0·41	+1·93	−3·05	+3·98	+1·57	+0·64	+1·93
$\bar{x}$		+1·63	+0·91	−0·05	+0·09	+0·09	+1·58	+0·98	−0·0	+0·10	+0·17
s^2		33·10	1·06	2·50	0·04	0·83	32·15	1·32	2·25	0·07	0·98

were treated simultaneously. In the first phase, the minimum necessary number of latent variables was looked for. As the method of conjugated deviations is derived from the regression, it used the criterion testing the increase of explanation of variability by a further latent variable as compared with the non-explained variability[22]. This criterion has F distributions and is expressed by formula (1)

$$F(v_1, v_2) = \frac{S_k - S_{k+1}}{S_{k+1}} \cdot \frac{v_2}{v_1} , \qquad (1)$$

where S_k and S_{k+1} are residual sums of squares with k and $k + 1$ latent variables, v_1 is given by the difference in the number of degrees of freedom between the calculations with k and $k + 1$ latent variables, and v_2 is the number of degrees of freedom in the calculation with $k + 1$ latent variables. The results of application of the criterion (1) to the data of Table I including all the data, data concerning carbons, and those concerning nitrogens are given in Table II. From the table it follows that the whole data matrix is expressed by three latent variables, out of which two latent variables describe the substituent effect on the carbon chemical shifts and one latent variable describes the same effect for nitrogen. This result for carbons agrees with the results found in other types of compounds (vide supra). One latent variable for description of SCS at two nitrogen nuclei represents a very probable finding. It is also interesting that the first latent variable for the carbon nuclei includes only slightly more variability (43.6%) than the second latent variable (35.3%).

The values of statistically significant latent variables are given in Table III. The first latent variable determined from the carbon data shows a close correlation with the Hammett substituent constants (the values taken from ref.[23]) which is better with σ_p^- $(r = 0.993)$ than with σ_p $(r = 0.990)$. This is in accordance with the results expected for the compounds with possible conjugation between the substituent and reaction centre in the classical correlations of substituent effects. The relation between

TABLE II

Values of the criterion (1) depending on number of latent variables k calculated for the ^{13}C and ^{15}N NMR chemical shifts of all centres of Table I. The significance level $\alpha = 0.05$ was used for the test

k	$F^C(v_1, v_2)$	$F_{0,95}$	$F^N(v_1, v_2)$	$F_{0,95}$	$F^{C,N}(v_1, v_2)$	$F_{0,95}$
2	19·50(16, 32)	1·97	2·28(14, 14)	2·48	17·41(18, 70)	1·75
3	1·47(13, 19)	2·28			3·01(16, 54)	1·83
					1·62(20, 34)	1·89

the first and the second latent variables is given in Fig. 1. The pattern found is characteristic and similar to that obtained from chemometric studies of various substituent

TABLE III
Values of statistically significant latent variables (P) determined by the method of conjugated deviations from ^{13}C and ^{15}N NMR chemical shifts for the individual substituents

P	H	4-N(CH$_3$)$_2$	4-OCH$_3$	4-CH$_3$	4-C(CH$_3$)$_3$	3-CH$_3$
P_1^C	0·669	1·000	0·823	0·778	0·726	0·692
P_2^C	0·012	1·000	0·628	0·192	0·100	0·0
P_1^N	0·440	1·000	0·687	0·539	0·557	0·411

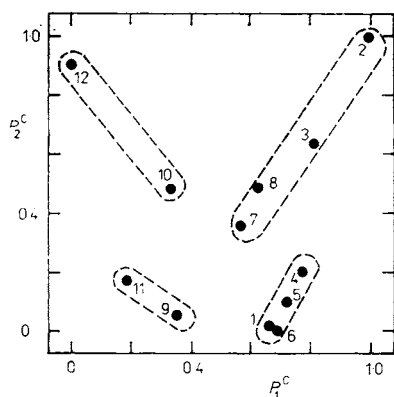| P	4-Cl	4-F	4-CO$_2$CH$_3$	3-NO$_2$	4-NO$_2$	3,5-(NO$_2$)$_2$
P_1^C	0·558	0·623	0·353	0·339	0·190	0·0
P_2^C	0·352	0·486	0·055	0·475	0·162	0·897
P_1^N	0·362	0·429	0·235	0·324	0·106	0·0

FIG. 1

Distribution of substituents in the space of first two latent variables P_1^C and P_2^C obtained by the method of conjugated deviations from the ^{13}C NMR chemical shifts. For numbers see Table I
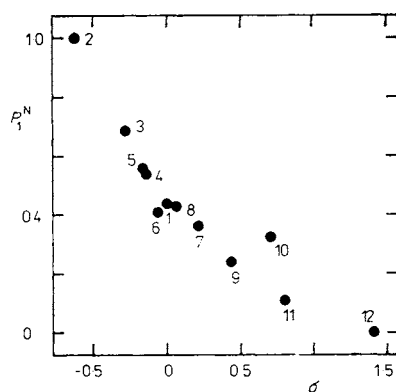

FIG. 2

Dependence of the first latent variable P_1^N obtained by the method of conjugated deviations from ^{15}N NMR chemical shifts on the Hammett substituent constants. For numbers see Table I

descriptors[24] or resonance effect[25]. The substituents attracting electrons either by their inductive effect (3-nitro, 3,5-dinitro) or combined inductive and mesomeric effects (4-nitro, 4-methoxycarbonyl) form independent clusters with a negative slope. An opposite behaviour is observed with the substituents exhibiting positive inductive effects (alkyls) or those exhibiting a combination of negative inductive and positive mesomeric effects (halogens, 4-methoxy, 4-dimethylamino). In the last group mentioned we can observe a change in relative importance of the two effects when going from halogens to 4-dimethylamino group. The pattern found can be interpreted in terms of an aditional polarization of the electron cloud of the molecule.The electron--donor substituents polarize the electron cloud of bonds towards the nucleus examined, increase the shielding and, hence, also the chemical shift of this nucleus. The electron-acceptor substituents polarize the electron cloud of bonds in the opposite direction, which — in the end — results in the same effect as in the first case. The greater is the electron-acceptor or -donor ability, the greater also is the respective chemical shift. The opposite effects are mutually compensated (e.g. halogens). Properties of the second latent variable cannot be satisfactorily explained in terms of the subtstituent constants for parametrization of the resonance (R) and field (F) effects extended — as the case may be — by the polarization parameter (P) in accordance with ref.[11]. These parameters provide a not very good correlation $(R = 0.907)$ in which the polarization parameter is statistically insignificant. The ratio of regression coefficients is $\varrho_R/\varrho_F = 1.25$, which does not indicate a predominance of some of the factors.

TABLE IV

Values of regression coefficients ϱ and statistical characteristics of the dependence of chemical shifts of the individual nuclei from Table I on the substituent constants σ_F and σ_R

Nucleus	ϱ_R	s_R	ϱ_F	s_F	R	$10^2 s$
I, C-4	−19·31	2·29	—	—	0·937	448
I, C=O	—	—	2·59	0·15	0·984	3·73
I, N-1	5·20	0·70	—	—	0·921	41·4
I, C=S	0·44	0·10	0·23	0·07	0·940	0·58
I, N-2	2·05	0·52	0·94	0·37	0·917	16·0
II, C-4	−19·03	2·26	—	—	0·936	437
II, C=O	—	—	2·87	0·21	0·975	7·27
II, N-1	4·90	0·70	—	—	0·912	41·6
II, C=S	0·55	0·12	0·31	0·09	0·947	0·86
II, N-2	2·64	0·37	0·85	0·26	0·967	7·90

Similar conclusions can be made from the latent variable determined from the chemical shifts of ^{15}N nuclei. However, the dependence on the Hammett constants is substantially less close (0.923) with an indication of break (Fig. 2). Hence, the additional effect of substituents also makes itself felt in the chemical shifts of nitrogen nuclei although this is not significant enough to allow it to manifest itself as an independent factor under the conditions of measurement. This fact indicates a greater rigidity of the free electron pair at the nitrogen with sp^3 hybridization and its less participation in conjugation. The regression of the latent varible on the substituent constants σ_R, σ_F, and σ_α (ref.[11]) is statistically significant only for the σ_R parameter, the correlation being little close $(r = 0.921)$ and the information volume being low.

Also the usual applications of the substituent constants σ_R, σ_F, and σ_α to the original chemical shifts from Table I give no close correlations, as it is seen in Table IV. Perhaps the only interesting facts are that (i) the substituent constant σ_α never is statistically significant and (ii) the ratio ϱ_R/ϱ_F always is greater than 1.

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