AN ANALYSIS OF SUBSTITUENT EFFECTS ON THE PROTON AND CARBON-13 CHEMICAL SHIFTS OF 2-SUBSTITUTED 9-ISOTHIOCYANATOACRIDINES

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Proton and ^{13}C NMR chemical shifts and coupling constants J(H,H) of a series of 2-substituted 9-isothiocyanatoacridines and their 4-methyl and 4-methoxy analogs were determined. The obtained values were utilized in analysis of substituent effects using empirical equations based on two- and three-parameter linear correlations. It was found that short-range interactions (positions *ipso*, *ortho* and *meta*) are well described by the three-parameter model of Reynolds whereas long-range effects are satisfactorily compatible with the two-parameter model. The dominant direction of conjugation in the acridine skeleton was derived from changes in chemical shifts due to substitution (SCS).

Isothiocyanatoacridine derivatives represent polybiovalent type of compounds which not only contain the biologically active –NCS group[1], but also are capable of intercalation effects, as manifested by nonbonding interactions with DNA (refs[2–4]).

There are several ^{1}H and ^{13}C NMR studies[5–8] dealing with the relation between structure and physicochemical properties of acridine derivatives with the aim to determine active centers in the molecule and thus to elucidate the mechanism of action. The authors of the cited papers investigated the transmission of substituent effects in 9-substituted and 3,9-disubstituted acridines. The obtained data contribute to construction of a theoretical model suitable for description of possible interactions of such compounds with biological material.

As a continuation of our previous investigation[9], we turned our attention to a complex analysis of substituent effects in 2-substituted 9-isothiocyanatoacridines by means of ^{1}H and ^{13}C NMR chemical shifts and ^{1}H–^{1}H coupling constants.

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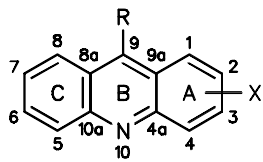
The relationship between the ^1H and ^{13}C chemical shifts and the character of substituents was studied by multilinear correlation method. For positions more distant from the substituent, i.e. other than *ipso*, *ortho* or *meta*, the correlations in similar series are usually satisfactorily described by two-parameter equations. The corresponding long-range interactions are mostly well compatible with an empirical model based on correlation of chemical shifts with substitution parameters of Taft[10] (σ_I and σ_R^0) or Swain and Lupton[11] (*F* and *R*). For short-range interactions (positions *ipso*, *ortho* and *meta*) some authors[12–14] recommend empirical equations based on three-parameter linear correlations. For description of the *ortho* effect, Smith and Proulx[12] include substitution parameters *Q* (*F*, *R* and *Q* or σ_I, σ_R^0 and *Q*) determined by Schaefer[13]. On the basis of factor analysis, Reynolds[14] determined empirical substitution parameters suitable for analogous correlations involving the "*ortho* effect" as well as the positions *ipso* and *meta* (models: *F*, *R* and $S_{i,o,m}$ or σ_I, σ_R^0 and $S_{i,o,m}$, where indices *i*, *o*, and *m* relate to the *ipso*, *ortho* and *meta* positions, respectively). In the present study, all these empirical equations have been subjected to statistical analysis using SCS values for the series of 2-substituted 9-isothiocyanatoacridines.



	X	R
I	2-OMe	NCS
II	2-Me	NCS
III	H	NCS
IV	2-Cl	NCS
V	2-NO_2	NCS
VI	4-OMe	NCS
VII	4-Me	NCS

	X	R
VIII	2-OMe	Cl
IX	H	Cl
X	2-Cl	Cl

EXPERIMENTAL

Synthesis of the compounds is described in ref.[9]. Proton and ^{13}C NMR spectra were measured on Varian VXR-300 and Bruker AMX 300 instruments (300 MHz for ^1H and 75 MHz for ^{13}C) at room temperature. The chemical shifts (δ, ppm) are referenced to tetramethylsilane. In addition to the ^1H and ^{13}C NMR spectra (broad band proton decoupled NMR by pulse sequence WALTZ16), we used the following 1D and 2D methods: DEPT-135, DEPT-90, inversion HC-correlated and inversion

COLOC spectra (Bruker, 5 mm cell), as well as DQCOSY, HETCOR and NOE differential spectra and selective 1D INEPT; the selective excitation was realized by DANTE pulse of selectivity 25 Hz and evolution period optimized for J(H,C) = 7 and 3.5 Hz (Varian, 5 mm cell).

RESULTS AND DISCUSSION

The ^{1}H and ^{13}C chemical shifts and coupling constants ^nJ(H,H) of 2- and 4-substituted 9-isothiocyanatoacridines *I* – *VII* are given in Tables I, II and III. For comparison, we also measured the corresponding values for 9-chloroacridines *VIII* – *X* (Table IV). As the result of electron accepting effect of the heterocyclic nitrogen atom, the carbon atom of the NCS group in 9-isothiocyanatoacridine is much more deshielded (140.45 ppm) than that in phenyl isothiocyanate[15] (135.20 ppm). This fact is also reflected by the higher reactivity of 9-isothiocyanatoacridines *I* – *VII* with nucleophilic reagents as compared with the corresponding phenyl isothiocyanates[9]. On the other hand, the effect of substituents on the ^{13}C chemical shift of the NCS group is less marked for 2-substituted 9-isothiocyanatoacridines *I* – *V* than for 4-substituted phenyl isothiocyanates[9].

Apart from changes in chemical shifts of carbon atom C-8 and C-1, C-2 and C-3, which in derivatives *I* – *V* are influenced by direct polar and steric effects of the substituent in position 2, we see that the electronic interactions of X with the other acridine carbon atoms are alternating and are transmitted also into the unsubstituted benzene ring. For the carbon atoms separated by an even number of bonds from substituent X (C-9, C-4a, C-10a, C-6) the maximum differences in ^{13}C chemical shifts are 3 – 5 times greater (3.3 – 6.7 ppm) than those for carbon atoms separated by an odd number of bonds (0.5 – 1.2 ppm for C-4, C-8a, C-5 and C-7).

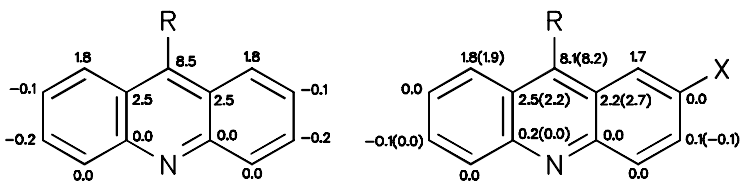
TABLE I
Chemical shifts (δ, ppm) in ^{1}H NMR spectra of 2- and 4-substituted 9-isothiocyanatoacridines *I* – *VII*

Hydrogen	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*
H-1	7.13	7.79	8.03	7.97	9.21	7.76	8.10
H-2	–	–	7.49	–	–	7.49	7.52
H-3	7.37	7.55	7.69	7.60	8.49	7.03	7.65
H-4	7.98	8.01	8.06	8.00	8.30	–	–
H-5	8.09	8.12	8.06	8.07	8.25	8.38	8.28
H-6	7.67	7.72	7.69	7.74	7.94	7.78	7.80
H-7	7.52	7.53	7.49	7.56	7.73	7.61	7.63
H-8	8.04	8.10	8.03	8.04	8.31	8.19	8.23
OCH_3	3.95	–	–	–	–	4.14	–
CH_3	–	2.50	–	–	–	–	2.91

It is interesting to compare the SCS values for carbon atoms of the rings B and C in the 2-methoxy derivative *I* and in the 4-methoxy derivative *VI*. The spectrum of compound *I* shows a greater shielding effect of the 2-substituent in positions C-5 (–2.32 ppm), C-10a (–1.80 ppm), C-6 (–1.08 ppm) and C-8 (–0.38 ppm) that are separated from the substituent by even number of bonds. In derivative *VI* the shielding effects in the mentioned positions are negligible, on the other hand, the deshielding effects in

TABLE II
Chemical shifts (δ, ppm) in ^{13}C NMR spectra of 2- and 4-substituted 9-isothiocyanatoacridines *I* – *VII*

Carbon	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*
C-1	98.06	120.91	122.68	121.34	121.06	114.59	120.76
C-2	158.20	137.28	126.81	133.08	145.31	127.15	126.86
C-3	125.82	133.47	130.48	131.85	123.55	107.09	129.97
C-4	131.50	129.59	129.80	131.44	131.97	155.48	137.95
C-4a	146.08	148.02	148.86	147.02	149.59	142.20	148.51
C-5	129.83	129.91	129.80	129.99	130.45	130.70	130.46
C-6	129.40	130.10	130.48	130.83	132.75	130.36	130.11
C-7	127.05	126.83	126.81	127.51	128.23	127.43	126.88
C-8	122.30	122.69	122.68	122.60	123.09	122.64	122.66
C-8a	121.98	122.00	121.70	122.17	122.98	122.28	121.68
C-9	130.07	131.26	132.39	131.73	136.73	132.62	132.40
C-9a	123.07	121.83	121.70	121.74	119.84	123.16	121.91
C-10a	147.06	148.37	148.86	148.85	151.28	147.99	148.15
NCS	140.97	140.19	140.45	141.04	142.87	140.56	140.20
OCH_3	55.69	–	–	–	–	56.34	–
CH_3	–	22.17	–	–	–	–	18.48



SCHEME 1

positions separated by an odd number of bonds predominate (C-8a: 0.58 ppm, C-5: 0.90 ppm, C-7: 0.62 ppm).

Comparison of ^{13}C chemical shifts in the spectra of 9-isothiocyanatoacridines *I*, *III* and *IV* (Table II) with those of 9-chloroacridines *VIII*, *IX* and *X* (Table IV) shows that in positions C-1, C-9a, C-8, C-8a and C-9 the 9-chloro substituent has a higher electron accepting effect than the 9-NCS group (Scheme 1).

For 9-isothiocyanatoacridine the coupling constants ^nJ(H,H), given in Table III, are higher for spin–spin interactions between the α- and β-protons (^3J(1,2), ^3J(5,6) and ^3J(7,8) = 8.60 – 8.84 Hz) than for interactions between the β-protons (^3J(2,3), ^3J(6,7) = 6.60 – 6.70 Hz). A substituent in position 2 or 4 increases the value of the neighbouring *ortho* constant (^3J(3,4) = 0.48 – 0.76 Hz, ^3J(2,3) = 0.20 – 1.00 Hz). At the same time, in 2-substituted derivatives *I* and *IV* the *meta* constant ^4J(1,3) increases by 0.92 – 1.35 Hz in comparison with the analogous constant ^4J(6,8).

We followed the effects of substituents on NMR chemical shifts in the individual positions of 2-substituted 9-isothiocyanatoacridines using empirical models based on linear correlations of the shifts with the substitution parameters. As follows from previous correlations between chemical shifts and substitution parameters[12,14], for atoms farther away from the substituent X (other than in the *ipso*, *ortho* or *meta* positions), we can write empirical equation (*1*)

$$\delta^{13}C_j = aS_I + bS_R + c \,, \qquad (1)$$

TABLE III
Coupling constants (*J*(H,H), Hz) of 2- and 4-substituted 9-isothiocyanatoacridines *I*, *III* – *VII*

J(H,H)	*I*	*III*	*IV*	*V*	*VI*	*VII*
J(1,2)	–	8.60	–	–	8.73	8.65
J(1,3)	2.75	1.40	2.32	2.47	1.05	[a]
J(1,4)	<0.30	0.70	0.58	[a]	–	–
J(2,3)	–	6.60	–	–	7.60	6.80
J(2,4)	–	1.20	–	–	–	–
J(3,4)	9.45	8.80	9.28	9.56	–	–
J(5,6)	8.73	8.80	8.73	8.84	8.68	8.70
J(5,7)	1.19	1.20	1.21	1.19	1.16	1.19
J(5,8)	0.68	0.70	0.70	0.62	0.71	0.68
J(6,7)	6.63	6.60	6.62	6.68	6.70	6.68
J(6,8)	1.42	1.40	1.42	1.38	1.40	1.42
J(7,8)	8.58	8.60	8.61	8.66	8.63	8.66

[a] The value was not determined.

where the subscript *j* denotes a position other than *ipso*, *ortho* or *meta*, and *S* are substitution parameters expressing essentially the inductive and resonance effects of the substituent[10,11] (σ_I or *F*, and σ_R^0 or *R*, respectively). For atoms in the immediate vicinity of the substituent X (*ipso*, *ortho* or *meta*) the above-mentioned equation is not valid and therefore further substitution parameters were introduced[12–14] that take into account short-range interactions of substituent with the given atom. The corresponding empirical equations are then

$$\delta^{13}C_o = aS_I + bS_R + cQ + d \,, \qquad (2)$$

where the subscript *o* denotes the *ortho* position and *Q* is a substitution parameter defined by Schaefer[13], and

$$\delta^{13}C_{i,o,m} = aS_I + bS_R + cS_{i,o,m} + d \,, \qquad (3)$$

TABLE IV
Chemical shifts (δ, ppm) in ^{1}H and ^{13}C NMR spectra of 2-methoxy-9-chloroacridine (*VIII*), 9-chloroacridine (*IX*) and 2-chloro-9-chloroacridine (*X*)

Position	^{1}H			^{13}C		
	VIII	*IX*	*X*	*VIII*	*IX*	*X*
1	7.48	8.43	8.31	99.77	124.45	123.04
2	–	7.61	–	158.16	126.73	133.05
3	7.47	7.81	7.66	125.92	130.31	131.78
4	8.09	8.24	8.10	131.50	129.79	131.48
4a	–	–	–	146.12	148.86	147.00
5	8.18	8.24	8.15	129.79	129.79	129.84
6	7.74	7.81	7.78	129.34	130.31	130.80
7	7.61	7.61	7.61	127.03	126.73	127.53
8	8.36	8.43	8.32	124.14	124.45	124.50
8a	–	–	–	124.43	124.15	124.38
9	–	–	–	138.17	140.87	139.89
9a	–	–	–	125.24	124.15	124.45
10a	–	–	–	147.21	148.86	148.85
CH_3O	–	–	–	55.71	–	–

where indices *i*, *o*, and *m* denote the respective *ipso*, *ortho* and *meta* positions relative to the substituent X, and S_i, S_o, and S_m are the corresponding substitution parameters. Statistical treatment of data from Tables I – III has shown that slightly more significant correlations were obtained with the Taft parameters[10] σ_I and σ_R^0 than with the parameters *F* and *R*. In order to avoid presentation of data of similar meaning, we included into Table V only the results of correlations obtained with the Taft substitution parameters[10]; for the positions *ipso*, *ortho* and *meta* we give the results obtained with the better fitting model of Reynolds[14].

Our observation that the conjugation effects, manifested by the SCS values at the carbon atoms of the acridine skeleton, alternate, is also supported by the results of the correlations, particularly the relation between the coefficients *b*, characterizing the resonance increments, and the differences between ^{13}C chemical shifts of the individual carbon atoms, Δ_C. These intercorrelation relationships show that the resonance transmission effect of substituents is stronger for carbon atoms separated by an even number of bonds from the substituent X ($b = 1.46\ \Delta_C - 0.58$; $r = 0.9860$) than for those separated by an odd number of bonds ($b = 1.18\ \Delta_C - 0.89$; $r = 0.9292$). As expected, no analogous correlations were found for the transmission of inductive effects. As seen

TABLE V
Results of correlations $\delta^{13}C_{i,o,m} = a\sigma_I + b\sigma_R^0 + cS_{i,o,m} + d$ (Eq. (*3*)) and $\delta^{13}C_j = a\sigma_I + b\sigma_R^0 + c$ (Eq. (*1*))

Position	Equation	*a*	*b*	*c*	*d*	r^a
1	3[b]	–0.92	45.85	1.26	122.49	0.9999
2	3	12.24	–40.21	0.94	127.42	0.9991
3	3[c]	–5.48	1.95	0.69	130.78	0.9982
4	3	3.90	–1.69	0.18	129.60	0.9704
4a	1	–0.74	6.84	148.92	–	0.9886
5	1	0.67	0.58	129.88	–	0.9514
6	1	2.42	4.16	130.54	–	0.9989
7	1	1.92	0.71	126.84	–	0.9962
8	1	0.21	1.20	122.76	–	0.9738
8a	1	1.39	0.69	121.86	–	0.9327
9	1	3.95	9.19	132.44	–	0.9778
9a	3	–1.66	–4.19	0.91	121.63	0.9971
10a	1	2.18	5.85	148.97	–	0.9979
NCS	1	3.12	1.31	140.40	–	0.9416

[a] Significance level of the correlation 0.01. For Eq. (*3*) values: [b] $a = -3.71$, $b = 22.70$, $c = 7.70$, $d = 125.13$, $r = 0.9839$; [c] $a = -12.66$, $b = -21.03$, $c = 6.56$, $d = 132.13$, $r = 0.9440$. $Q' = Q_X - Q_H = Q_X - 2.28$, see ref.[7].

from Table V, there is a great difference between the values of *b* for the *ortho* carbon atoms C-1 and C-3 (45.85 and 1.95, respectively). The mean value of this dissymmetry (23.9) is close to that found by Reynolds[14] (23.6) for the benzene ring and that obtained by Faure[7] (23.5) for 3-substituted 9-amino/chloro acridines. This finding can be related to a different localization of the π-system in the *ortho* positions. This is in accord with our above-mentioned finding that the effect of substituents on the ^{13}C values is manifested predominantly via the position 1.

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