CORRELATION OF THE PROTON CHEMICAL SHIFTS WITH THE HAMMETT–TAFT σ CONSTANTS IN 2-SUBSTITUTED PYRIDINES AND PYRAZINES

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UDC 547.821.861

Good correlation between the relative chemical shifts of the ortho and para protons and σ_i and σ_c^0 is observed in 2-substituted pyridines and pyrazines. An increase in the contribution of the inductive effect is observed for the relative chemical shifts of 4-H in 2-substituted pyridines as compared with monosubstituted benzenes. A considerable increase in the fraction of the conjugation effect is observed for the relative chemical shifts of 6-H in pyridines and pyrazines as compared with the meta position in benzenes. It is possible that this effect is associated with the fact that transfer of the effect is accomplished here through the nitrogen atom, while the interaction between the substituent and the nitrogen has resonance character.

A considerable number of studies have been devoted to the problem of the correlation between the chemical shifts (CS) and the σ constants in aromatic systems. The correlations between the CS of F^{19} nuclei and σ_i and σ_c^0 in a number of substituted fluorobenzenes are well-known [1]. Correlations have been made between the CS of H^1 and C^{13} nuclei and σ_i and σ_c^0 for monosubstituted benzenes [2, 3]. Correlations between the CS of the protons and σ^* and σ_c have been obtained for a number of monosubstituted benzenes, furans, and thiophenes [4]. The linear dependence between the CS of the protons and the substituent reactivity parameters, which is observed in many cases, is associated with the fact that both are determined to a considerable degree by the electron density on adjacent carbon atoms. However, both the reactivity and the CS also generally depend on a number of other factors that differ for each of these characteristics. For example, contributions to shielding that are transmitted through space (anisotropic, electrical, and steric effects of bonds and groups) are of substantial significance for proton CS. However, the theoretical calculation of these contributions cannot presently ensure the correct solution to the problem of the magnitude of the chemical shift caused exclusively by local shielding effects. In some cases, the correlation dependence of the CS on the substituent reactivity parameters and the electronic structure make it possible to judge the relationship between local shielding and the indicated specific contributions.

The conditions under which it is possible to examine the correlation relationships in heterocyclic systems are discussed in [5], and satisfactory correlations between the CS and the π-electron densities in monosubstituted derivatives of benzene, pyridine, and pyrazine were obtained for the o- and p-protons; it was also demonstrated that the CS in the m position is determined to a considerable degree by the field effect of the π charges of the aromatic ring.

The correlation between the CS in these same aromatic systems and the σ_i and σ_c^0 substituent constants [2] is examined in the present paper. This sort of correlation approach makes it possible to compare the effect of a substituent on the CS with the effect on the reactivity in these rings. We used the rela-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 345-350, March, 1972. Original article submitted June 3, 1971.

TABLE 1. Relative Chemical Shifts (RCS) of the Protons of I-III (δ) in Parts per Million

R	I			II								III					
	CCl_4			CCl_4				$(CH_3)_2SO$				$(CH_3)_2SO$			D_2O		
	3-H	4-H	5-H	3-H	4-H	5-H	6-H	3-H	4-H	5-H	6-H	3-H	5-H	6-H	3-H	5-H	6-H
CH_3	0,21	0,12	0,22	0,02	−0,06	0,03	0,13	0,11	0,01	0,16	0,08	0,07	0,23	0,16	0,15	0,24	0,19
NH_2	0,75	0,25	0,65	0,64	0,10	0,52	0,56	0,68	0,31	0,78	0,48	0,69	0,92	0,73	0,74	0,91	0,76
$NHCOCH_3$												−0,72	0,34	0,34	−0,42	0,30	0,28
F	0,28	−0,07	0,21	0,11	−0,41	−0,16	0,31	−0,10	−0,40	−0,12	−0,13	−0,10	−0,07	0,21			
Cl	−0,03	0,02	0,09	−0,25	−0,22	−0,16	0,19	−0,32	−0,29	−0,29	−0,10	−0,08	0,03	0,17	0,03	0,04	0,17
Br	−0,18	0,08	0,04	−0,41	−0,10	−0,18	0,19	−0,41	−0,17	−0,19	−0,02						
I	−0,39	0,21	0,00	−0,66	0,09	−0,21	0,22										
OCH_3	0,48	0,09	0,44	0,37	−0,07	0,26	0,44	0,53	0,03	0,40	0,32	0,32	0,41	0,41	0,38	0,47	0,47
$CONH_2$								−1,05	−0,47	−0,43	−0,43	−0,63	−0,27	−0,12	−0,51	−0,18	−0,11
COOH	−0,78		−0,28					−0,97	−0,43	−0,48	−0,42	−0,55	−0,19	−0,15	−0,65	−0,22	−0,18
$COOCH_3$	−0,71	−0,11	−0,21					−0,86	−0,39	−0,35	−0,35	−0,59	−0,31	−0,23	−0,59	−0,21	−0,11
CN	−0,36	−0,18	−0,28	−0,71	−0,52	−0,56	−0,19	−0,88	−0,38	−0,55	−0,39	−0,35	−0,28	−0,20	−0,44	−0,25	−0,20
NO_2	−0,95	−0,26	−0,38	−1,17	−0,70	−0,69	−0,09	−1,09	−0,67	−0,74	−0,26						
$COCH_3$	−0,62	−0,13	−0,21					−0,82	−0,37	−0,39	−0,28						
CHO	−0,56	−0,22	−0,29					−0,93	−0,42	−0,50	−0,44						

TABLE 2. Parameters of the Correlation Equations That Relate the RCS of the Protons in I-III to σ_i and σ_c^0 [a]

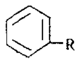
Proton	Ring	Solvent	A	B	C	R	d	n	$\alpha=\frac{B}{A}$
3-H	I[b]	CCl_4	−0,86	−1,96	−0,06	0,99	0,07	11	2,29
	II	CCl_4	−1,01	−1,77	−0,14	0,96	0,13	10	1,79
	II	$(CH_3)_2SO$	−1,22	−2,29	−0,20	0,98	0,13	14	1,87
	III	$(CH_3)_2SO$	−0,71	−1,51	−0,09	0,95		10	1,82
	III[c]	$(CH_3)_2SO$	−0,56	−1,61	−0,09	0,96		9	
	III	D_2O	−0,66	−1,75	−0,08	0,98	0,11	9	2,74
4-H	I[d]	CCl_4	−0,28	−0,41	0,03	0,95	0,04	14	1,48
	II	CCl_4	−0,73	−0,48	−0,06	0,92	0,12	9	0,65
	II	$(CH_3)_2SO$	−0,79	−0,71	−0,05	0,92	0,10	14	0,88
6-H	I	CCl_4	−0,28	−0,41	0,03	0,95	0,04	14	1,48
	II	CCl_4	−0,05	−1,00	0,04	0,97	0,06	10	20,00
	II	$(CH_3)_2SO$	−0,50	−1,02	−0,04	0,95	0,09	14	2,04
	III	$(CH_3)_2SO$	−0,32	−1,21	0,06	0,97	0,08	11	3,78
	III	D_2O	−0,34	−1,19	0,10	0,99	0,06	10	3,50
5-H	I	CCl_4	−0,45	−1,14	0,08	0,99	0,04	15	2,53
	II	CCl_4	−0,78	−1,08	−0,02	0,98	0,08	10	1,38
	II	$(CH_3)_2SO$	−1,02	−1,43	0,05	0,98	0,09	14	1,40
	III	$(CH_3)_2SO$	−0,84	−1,30	0,14	0,91	0,16	10	1,54
	III[e]	$(CH_3)_2SO$	−0,63	−1,50	0,09	0,96		8	2,40
	III	D_2O	−0,38	−1,34	0,08	0,99	0,10	10	3,60

[a] The correlation coefficients for I were obtained from our calculations. [b] N,N-Dimethylaniline and tert-butylbenzene were excluded from the correlations. [c] 2-Fluoropyrazine was excluded from the correlations. [d] Iodobenzene was excluded from the correlations. [e] 2-Fluoro- and 2-cyanopyrazines were excluded from the correlation.

tive CS (RCS)* (Table 1) of 2-substituted pyrazines (III) in D_2O and dimethyl sulfoxide (DMSO) [6] and of 2-substituted pyridines (II) in CCl_4 [7] and DMSO [8] for correlations with σ_i and σ_c^0; the RCS of monosubstituted benzenes (I) in CCl_4 [9] are also included in Table 1.

Correlation equations of the form

$$\delta = A\sigma_i + B\sigma_c^0 + C.$$



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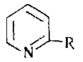

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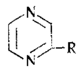

III

were calculated by the method of least squares. The A, B, and C coefficients, the multiple correlation coefficients (R), the mean-square deviations (d), and the number of correlatable substituents (n) are presented in Table 2.

The highest correlation coefficients were obtained for the 5-H protons in the p position relative to the substituent. For the p-proton in III, the ratio of the contributions of the inductive effect and the conjugation effect is close to the ratio in I. This may explain the previously noted [10] mutual correspondence of the shifts of the p-protons in III and I. The certain decrease in the correlation coefficient for 5-H in III in DMSO is due to the discrepancy in the data for the F and CN groups. In II, the contributions of the inductive effect and the conjugation effect to the CS of the p-proton are close.

The good correlation between the RCS of the 3-H protons in III and II and the RCS of the o-protons of I (Fig. 1) and the completely satisfactory correlation of the RCS of 3-H with the π-electron densities [5] presuppose the presence of a correlation with the σ constants. In fact, a completely satisfactory correlation can also be observed for the RCS of the o-proton in the rings under consideration (Fig. 2), despite the steric proximity of 3-H to the substituent. The roles of both effects (inductive and conjugation) in the transfer of the substituent effect are great, but the conjugation effect makes the chief contribution (up to 70%). The multiple correlation coefficients (0.95-0.98) are evidence for good correlation. Exclusion of the bulky $N(CH_3)_2$ and tert-C_4H_9 substituents from the correlations leads to an increase in the correlation coefficients

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*The relative CS (RCS) is the difference between the CS of a given proton in the substituted and unsubstituted compounds. The plus value corresponds to a shift in the signal of the proton of the substituted compound to stronger field as compared with the unsubstituted compound.

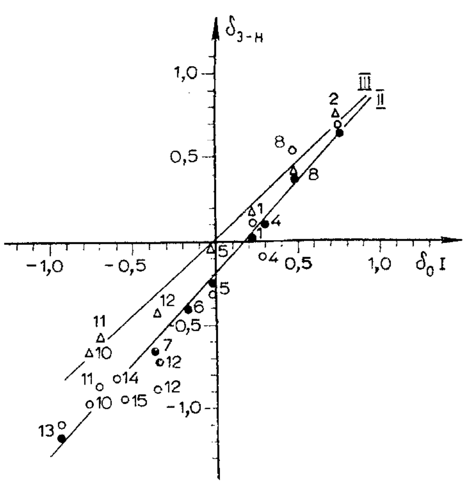

Fig. 1

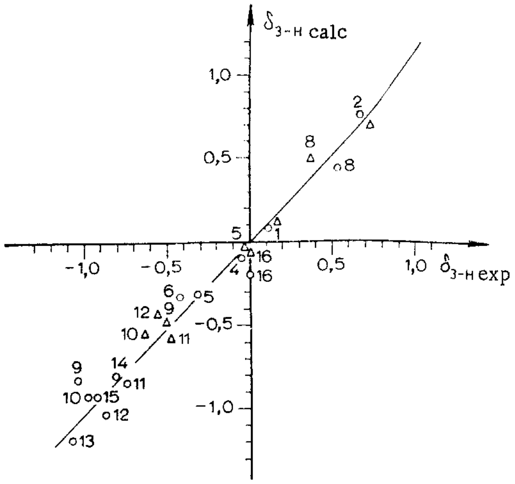

Fig. 2

Fig. 1. Dependence between the RCS of 3-H in II [in CCl_4 (●) and in $(CH_3)_2SO$ (O)] and III [in D_2O (Δ) and the RCS of the o-protons in I: R = CH_3 (1), NH_2 (2), F (4), Cl (5), Br (6), I (7), OCH_3 (8), $CONH_2$ (9), COOH (10), $COOCH_3$ (11), CN (12), NO_2 (13), $COCH_3$ (14), CHO (15), H (16).

Fig. 2. Dependence between the RCS_{calc} and the RCS_{exp} of the 3-H proton in II [in $(CH_3)_2SO$ (O)] and III [in D_2O (Δ)]. The symbols for the points are the same as in Fig. 1.

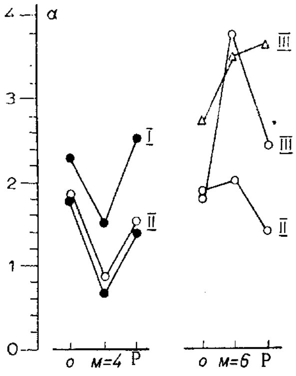

Fig. 3. Ratio of the inductive and substituent conjugation effects during transmission of the effect to various positions of rings I, II, and III [in CCl_4 (●), in $(CH_3)_2SO$ (O), and in D_2O (Δ)].

to 0.99. The electrical field effects and the steric and anisotropy factors are, on the whole, overlapped by local shielding for the usual substituents.

The correlation of the CS of the protons in the m position relative to the substituent is less successful. It is known that the RCS of C^{13} in the m position in I are small and almost identical for all of the measured substituents [2, 11]; of course, they do not correlate with the Hammett–Taft σ constants, the m-H^1 CS, or the F^{19} CS in fluoro-substituted benzenes. Moreover, in I it was found that the m-H^1 RCS, which correlate poorly with σ_i and σ_{meta}, correlate satisfactorily with σ_{para} [12, 13] and also with σ_i† and σ_C^0 [2, 3].

The RCS of the m-protons of the examined heterocyclic compounds change appreciably on passing from one ring to another (Table 1). In examining the data that we obtained, one should also note that the RCS of the 4-H and 6-H protons of II are different, and the RCS of 6-H does not coincide with the m-proton RCS in I.

Satisfactory correlation between the RCS of 4-H and the m-protons of I was observed in II [7]. The correlation equations for the RCS of 4-H in II demonstrate that the inductive effect makes the major contribution (60-70%) to the substituent effect on 4-H. An increase in the solvent polarity leads to a small increase in the contribution of the conjugation effect. The 4 position is characterized by rather low correlation coefficients (0.92), which attests to a weak correlation dependence.

The CS of 6-H in II does not correlate either with the m-shifts in I or with the RCS of 4-H in II themselves. Smith and Roark [7] have demonstrated the existence of a correlation between the RCS of 6-H and σ_{meta} for a limited set of substituents (NH_2, CH_3, F, Cl, Br, I, NO_2, and CN). An increase in the set of substituents to include the data in [8] for substituents of the COOX and COX type leads to considerable deterioration in this correlation, while the correlation of these RCS with σ_{para} gives somewhat better results. The correlation equations for the RCS of 6-H in II are characterized by a high contribution of the substituent conjugation effect: in a nonpolar solvent (CCl_4), the transfer of the effect as a whole is determined

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†As in Russian original — Publisher.

by the conjugation effect, while the contribution of the inductive effect (up to 50%) increases in a more polar solvent (DMSO). In the equation that we obtained,

$$\delta_{N^{14}} = 7\sigma_I - 84\sigma_c^0 + 6,\ R = 0.88,\ n = 9,$$

which relates the RCS of N^{14} in II [14] with the σ constants, the contribution of the conjugation effect also predominates. These results make it possible to assume that the effect of a substituent in the 2 position on the CS of 6-H is transmitted to a considerable degree through the nitrogen atom, which experiences a resonance effect on the part of the substituent. However, the problem of whether this effect is transmitted along the bonds or through space (due to a change in the magnetic anisotropy and electrical field of the nitrogen atom) is subject to further clarification.

The 6-H proton in III proves to be similar to the p-proton in I with respect to the contributions of the inductive and conjugation effects. As already noted above for derivatives of II, the contribution of the conjugation effect in III apparently increases owing to transmission of the substituent effect on 6-H through the nitrogen atom.

A comparison of the ratio of the contributions of the inductive and conjugation effects ($\alpha = B/A$) in the correlation equations for six-membered aromatic rings (Fig. 3) leads to the following conclusions. The role of the conjugation effect for I increases in the order $m < o < p$. The m-4 position for II is characterized by the greatest contribution of the inductive effect. However, the conjugation effect dominates for the m-6 position; the role of the conjugation effect in II increases in the order $m\text{-}4 < p < o < m\text{-}6$. For III, this order appears to be as follows: $o < m\text{-}6 < p$ in D_2O, and $o < p < m\text{-}6$ in DMSO. Thus, in II, the general character of the change in the contribution of the inductive and conjugation effects during transmission to the o-, m-4, and p positions is similar to that observed in I. The transmission of the effect to the m-6 position in II and III differs from that in I by a substantial predominance of the contribution of the conjugation effect.

The authors thank K. F. Turchin for providing us with the program for calculation by the method of least squares and V. F. Bystrov for his consultation and assistance in the interpretation of the results.

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