DETERMINATION OF REACTIVITY CONSTANTS OF 5-SUBSTITUTED 2-INDOLYL GROUPS BY MEANS OF <sup>13</sup>C NMR

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Values have been reported for the  $\sigma_{I}$  constant, characterizing the inductive effect, for the 3-indolyl group [1] and the N-indolyl group [2]. There have been no quantitative evaluations of electronic effects of other indolyl groups, including substituted groups.

In the work reported here, we determined the  $\sigma_I$  and  $\sigma_R^{\circ}$  constants of 5-substituted 2-indolyl groups, on the basis of <sup>13</sup>C NMR data on 5-substituted 2-phenylindoles

X X = H, Me, Cl, OMe, NH<sub>2</sub>, CN, NO<sub>2</sub> H

obtained by heterogeneous catalytic cyclization of the corresponding 4-substituted phenylhydrazones of acetophenone in the vapor phase on AMFK catalyst [3]. By nitration of 2-phenylindole, in accordance with [4], we synthesized 5-nitro-2-phenylindole, the reduction of which gives 5-amino-2-phenylindole [4].

For the compounds that we obtained, we measured the <sup>13</sup>C chemical shifts (Table 1). The assignment of the indole-ring carbon signals in the 5-substituted 2-phenylindoles was performed by the use of the corresponding increments found from the data of [5, 6] for the 5-substituted indoles.

For the calculation of the  $\sigma$  constants of the 5-substituted 2-indolyl groups, we used correlation equations that we had found for monosubstituted benzenes [7], relating the  $\sigma$ constants of the substituents to the relative <sup>13</sup>C chemical shifts of the m- and p-carbon atoms ( $\Delta\delta C_m$  and  $\Delta\delta C_p$ ). Here, the substituted indole groups were regarded as substituents on the benzene ring. The magnitudes of the chemical shifts of the m- and p-carbon atoms of the phenyl group in the 5-substituted 2-phenylindoles relative to benzene ( $\delta$  <sup>13</sup>C 129.08 ppm) are listed in Table 2, along with the values calculated from these data for the  $\sigma_I$  and  $\sigma_R^c$ constants of the 5-substituted 2-indolyl groups. The 5-substituted 2-indolyl groups and the unsubstituted 2-indolyl group that we studied are electron-acceptor substituents in terms of their inductive effect; in terms of their mesomeric effect, they are weak electron-donor substituents, comparable to m- and p-substituted phenyl groups.

Previously, in the example of substituted phenyl [8] and pyrimidyl [9-11] groups, we had shown that the electronic effects of such complex substituents can be expressed in terms of the effects of the corresponding unsubstituted group and the substituent. In the present work, by means of a two-parameter correlation, we also found Eqs. (1) and (2), which can be used to evaluate the  $\sigma$  constants of any 5-substituted 2-indolyl group if the  $\sigma$  constants of the unsubstituted 2-indolyl group and the substituent X are known

$$\sigma_{I} (\text{Ind } X) = \sigma_{I} (\text{Ind}) + 0.10 \ \sigma_{I} (X) + 0.09 \sigma_{R}^{0} (X)$$

$$r = 0.993, S = 0.006$$
(1)

$$\sigma_R^0 (\text{Ind } X) = \sigma_R^0 (\text{Ind}) + 0.05 \ \sigma_I (X) + 0.03 \ \sigma_R^0 (X)$$

$$r = 0.992, \ S = 0.003$$
(2)

An analysis of the coefficients in Eqs. (1) and (2) shows that the electronic effects of the substituents in position 5 of the indole ring have little influence on the mesomeric

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 $^{13}\mathrm{C}$  Chemical Shifts of 5-Substituted 2-Phenylindoles (in acetone,  $\delta,$  ppm) TABLE 1.

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	Other C	1	21,52	I	55,72	1	1	120,98
	°,	133,51	133,61	132,91	133,45	133,56	132,21	132,37
	$c_p$	128,06	127,90	128,54	127,98	127,90	129,19	129,03
	$c_m$	129,62	129,57	129,68	129,55	129,50	129,84	129,78
	°°	125,79	125,68	125,95	125,68	125,74	126,28	126,22
	రి	138,31	136,69	136,63	133,45	135,18	142,46	139,96
	చ	130,11	130,38	131,13	130,54	130,43	129,19	130,36
	ď,	111,93	111,61	113,22	112,58	112,04	112,09	113,06
	ů	120,34	120,67	120,13	102,60	110,31	117,75	125,14
	Ů	122,50	129,08	125,52	155,19	145,42	142,46	103,41
	ŭ	120,99	124,17	122,45	112,95	116,35	117,75	126,22
	ů	99,85	99,41	99,41	66'16	99,68	101,73	100,28
	ů	138,68	138,74	140,41	139,22	139,17	141,22	141,44
	×	H	Me	CI	MeO	$\mathrm{NH}_2$	$NO_2$	, CN

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TABLE 2. Relative <sup>13</sup>C Chemical Shifts ( $\delta$ , ppm) of 5-Substituted 2-Phenylindoles, and Values Found from These Data for the  $\sigma$  Constants\* of 5-Substituted 2-Indolyl Groups

Substitu- ent on indole ting	ΔδC <sub>m</sub>	ΔðC <sub>p</sub>	σι	$\sigma_R^{m 0}$	Substitu - ent on indole ring	∆ծC <sub>m</sub>	∆ðС <sub>р</sub>	σι	$\sigma_R^{0}$
H Me Cl MeO	$\begin{array}{c} 0,54 \\ 0,49 \\ 0,60 \\ 0,47 \end{array}$	-1,02 -1,18 -0,54 -1,10	0,19 0,17 0,22 0,17	$\begin{array}{r} -0,07\\ -0,08\\ -0,06\\ -0,07\end{array}$	NH2 NO2 CN	0.42 0,76 0,70	-1,18 0,11 -0,05	0,15 0,27 0,25	$-0,08 \\ -0,04 \\ -0,04$

\*The calculations of the  $\sigma$  constants was performed by the use of the equations:

$$\begin{split} & \sigma_I = 0.034 + \mathfrak{d}.315 \, \operatorname{ldsc}_m + \mathfrak{d}.012 \, \operatorname{ldsc}_p \\ & \sigma_R^0 = \mathfrak{d}.003 - \mathfrak{d}.060 \, \operatorname{ldsc}_m + \mathfrak{d}.045 \, \operatorname{ldsc}_p \end{split}$$

effect of the 2-indolyl group, whereas its inductive effect is subject to the influence of the substituents to a greater degree.

## EXPERIMENTAL

The <sup>13</sup>C NMR spectra were measured at  $\sim 28^{\circ}$  in the pulse regime under conditions of complete spin decoupling from the protons, in a Bruker HX-90 spectrometer (22.63 MHz), relative to TMS, with a solution concentration of 0.35 M and the addition of approximately 5% (CD<sub>3</sub>)<sub>2</sub>CO. The pulse width was 15 µsec ( $\sim 60^{\circ}$ ), time between pulses 10 sec, sweep width 5000 Hz, number of scans 300-1000, accuracy of chemical shift measurement ±0.03 ppm.

The IR spectra were recorded in a UR-20 spectrometer, on a slurry in white mineral oil.

<u>5-Substituted 2-Phenylindoles (X = H, Me, Cl, MeO, CN)</u>. A 15-20% benzene solution of the appropriate 4-substituted phenylhydrazone of acetophenone was passed at 200-280°C at a rate of 0.5 ml/min over 10 cm<sup>3</sup> of AMFK catalyst that had been preactivated in a stream of dry air. At the end of the reaction, the liquid product was concentrated by evaporation. The substituted indole that was recovered was crystallized from a mixture of benzene and petroleum ether.

2-Phenylindole, yield 90%, mp 187-188°C (compare [4]); 5-methyl-2-phenylindole, yield 70%, mp 212-213° (compare [12]); 5-chloro-2-phenylindole, yield 65%, mp 195-196° (compare [12]); 5-methoxy-2-phenylindole, yield 70%, mp 171-172° (compare [13]); 5-cyano-2-phenylindole, yield 45%, mp 196°. Found: C 82.4; H 4.95; N 12.8%. C<sub>15</sub>H<sub>10</sub>N<sub>2</sub>. Calculated: C 82.6; H 4.58; N 12.8%. IR spectrum (ν, cm<sup>-1</sup>): 3320 (NH), 2229 (CN), 1455 (benzene ring).

## CONCLUSIONS

A series of 5-substituted 2-phenylindoles has been synthesized; the <sup>13</sup>C chemical shifts have been measured for these compounds in acetone, and these data have been used to determine the  $\sigma_{\rm I}$  and  $\sigma_{\rm R}^{\circ}$  constants of the 5-substituted 2-indolyl groups. Relationships have been found for the estimation of the  $\sigma$  constants of any 5-substituted 2-indolyl group.

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EVALUATION OF SOLVENT EFFECTS ON PARAMETERS OF CONFORMATIONAL EQUILIBRIUM ON THE BASIS OF <sup>1</sup>H NMR DATA IN THE EXAMPLE OF 1,3,2-DIOXAPHOSPHORINANES

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The difference in energies between the conformations of stereochemically nonrigid molecules is on the same order of magnitude as the energy of solvation of polar molecules in a polar medium; therefore, it should be expected that a change in the medium has a substantial effect on the conformational equilibrium [1]. Information on the effect of the solvent on the conformational equilibrium is needed for theoretical calculations of the energy properties of conformers and also for comparative analysis of experimental data obtained in different solvents. These statements apply equally to all thermodynamic parameters characterizing the conformational equilibrium: the enthalpy ( $\Delta$ H), the entropy ( $\Delta$ S), and the free energy ( $\Delta$ G). We have applied <sup>1</sup>H NMR in evaluating the influence of the solvent on these parameters of the conformational equilibrium in the example of 1,3,2-dioxaphosphorinanes

 $\begin{array}{ccc} CH_3 & X & X = 0, Y = OPh & (I); X = 0, Y = CH_3 & (II); \\ CH_3 & V & Y = 0, Y = H & (III); X = Se, Y = OPh & (IV) \end{array}$ 

On the basis of data obtained by various physical methods, it is well known that compounds of the type of (I)-(IV) exist in solution in an equilibrium of two chair forms, one with an axial P=O bond (Ch<sub>a</sub>) and the other with an equatorial P=O bond (Ch<sub>e</sub>) [2-6], the relative amounts of which are determined by the type of substituent on the phosphorus atom; the conformer with the e-orientation of the multiple bond has a larger dipole moment (5-6 D) than the *a*-conformer (3-4 D). It is also known that the vicinal phosphorus-proton SSCC (<sup>3</sup>JPOCH) in the systems (I)-(IV) varies considerably, depending on the geometry of the H-C-O-P fragment in the canonical chair conformation, with  ${}^{3}J_{POCH_{e}} = 20-25$  Hz and  ${}^{3}J_{POCH_{a}} =$ 0-4 Hz; the magnitude of this constant is practically independent of the orientation of the

substituents on the phosphorus atom [7].

These properties of the phosphorus—proton constants make it possible, through a procedure proposed in [8], to use the observed SSCC <sup>3</sup>JPOCH as an indicator of the conformational position of the compounds (I)-(IV), depending on the conditions of the experiment. Thus, changes in the temperature and in the type of solvent are reflected significantly in the spectral characteristics of the methylene fragment with  $C^{4,6}$  (AB is a part of the spin system ABX; X is the phosphorus atom):  $XC(\delta A, \delta B)$ , their difference ( $\Delta v_{AB}$ ), the phosphorus—proton SSCC (<sup>3</sup>J<sub>1</sub> is larger, and <sup>3</sup>J<sub>2</sub> is smaller than <sup>3</sup>J<sub>POCH</sub>; values of these constants, found at the boundary points of the temperature range of measurements, are listed in Table 1). It can be seen from these data that the sum <sup>3</sup>J<sub>1</sub> + <sup>3</sup>J<sub>2</sub> is invariant (within the limits of experimental error) for each of the compounds (I), (II), and (IV); it changes slightly with changes in temperature in the case of (III); and it changes very slightly with changes in the solvent for any of the compounds. From this it follows, in our opinion, that the change in the

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