EFFECT OF SUBSTITUENTS ON CHEMICAL SHIFT OF PROTONS OF THE AMINO GROUP IN PMR SPECTRA OF SUBSTITUTED AMINOPYRIDINES

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The effect of substituents on the chemical shift of the protons of the amino group in six series of m- and p-substituted 2-, 3-, and 4-aminopyridines (in DMSO) was studied by correlation analysis using the inductive and resonance constants. The peculiarities of the pyridine ring in the transmission of the electronic effects of substituents are discussed.

In the study of the specific characteristics of the intramolecular interactions in aza-aromatic systems the most adequate model structures are amino derivatives of azines [1]. It has been shown that the sufficiently high sensitivity of the chemical shift of the protons of the aromatic amino group to structural changes is virtually completely determined by the intramolecular electronic effects [2, 3]. The effects of the magnetic anisotropy of the substituents play an imperceptible role in series of m- and p-substituted amino compounds, whereas the effect of an aza fragment on the magnetic shielding of the protons of the amino group in each structural series can be considered to be constant as the substituents are varied. The comparative accessibility of heterocyclic amino derivatives and the possibility of a study of complete series of amino derivatives with the necessary set of substituents are important for correlation analysis.

We have previously studied intramolecular effects in aza-aromatic systems in the case of substituted aminopyrimidines [4, 5] and amino-sym-triazines [6]. The peculiarities revealed required verification in the pyridine series. In the present research we examined the results of correlation analysis of the relative chemical shifts of the protons of amino groups ($\Delta\delta_{NH_2}$) for six series of 2-, 3-, and 4-aminopyridines (Table 1) with substituents in the meta or para positions with respect to the amino group. Syntheses of the overwhelming majority of substituted aminopyridines have been published in numerous papers. However, some aminopyridines were found to be previously unknown compounds. We synthesized 2-amino-6-nitropyridine and 4-amino-2-nitropyridine via the Curtius reaction from the corresponding nitropyridine-carboxylic acids. Let us note that a certain amount of caution should be exercised in obtaining the chlorides of these acids, considering the ease of replacement of the nitro group by a chlorine atom. 2-Amino-6-dimethylaminopyridine was obtained by heating the aminochloropyridine with dimethylamine in the presence of a copper salt under pressure. The production of methyl 5-aminopicolinate by reduction of the corresponding nitro derivative was previously reported [7], but the amino compound was used in subsequent transformations without purification, and the physical constants for it were not presented in [7]. We modified the reaction conditions and purified the amino derivative.

Dimethyl sulfoxide (DMSO) was used as the solvent in recording the PMR spectra of the substituted aminopyridines. Since the dissolving of aromatic amino compounds in DMSO is accompanied by the formation of specific solvates with hydrogen bonds between the protons of the amino groups and the solvent molecules [2, 3], the amino group in such structures can be regarded as a chemical reaction center; the heterocyclic skeleton continues to retain its incapacity for specific solvation by molecules of aprotic dipolar solvents. This "chemical" reaction of the amino groups with DMSO depends on the lability of the hydrogen atoms of the amino groups, and the chemical shifts of the protons of the amino groups in each structural series of amino compounds therefore may model their kinetic NH acidity. The chemical character of such series becomes apparent when one compares data from the PMR spectra of aminopyridines and the kinetic characteristics of the alkaline hydrolysis of the methyl esters of substituted pyridinecarboxylic acids [8, 9]. One's attention is directed to the linear

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TABLE 1. Chemical Shifts* (Hz) of the Protons of the Amino Group of Substituted Aminopyridines I-VI** in DMSO at 60 MHz

Point No.	Substituent	δI	ΔδI	δII	ΔδII	δIII	ΔδIII	δIV	ΔδIV	δV	ΔδV	δVI	ΔδVI
1	$N(CH_3)_2$	317,5	29	310	36,5	320,5	26	295	17	329	25	259	53
2	OCH_3	343,5	3	323	23,5	345,5	1	315	−3	349,5	4,5	280,5	31,5
3	CH_3	339	7,5	333	13,5	342,5	4	306,5	5,5	346,5	7,5	297,5	14,5
4	H	346,5	0	346,5	0	346,5	0	312	0	354	0	312	0
5	Cl	368	−21,5	364	−17,5	377	−30,5	334,5	−22,5	377,5	−23,5	325	−13
6	Br	367	−20,5	364	−17,5	377,5	−31	332	−20	376	−22	326	−14
7	$COOCH_3$	372	−25,5	405	−58,5	374	−27,5	335,5	−23,5	375,5	−21,5	364,5	−52,5
8	NO_2	399,5	−53	447,5	−101	405	−58,5	356,5	−44,5	407,5	−53,5	405	−93

*Positive Δδ values correspond to a shift to strong field.

**4-Substituted (I), 5-Substituted (II), and 6-substituted (III) 2-aminopyridines; 5-substituted 3-aminopyridines (IV); 2-substituted 4-aminopyridines (V); 2-substituted 5-aminopyridines (VI).

TABLE 2. Parameters of the Correlation Equation $\Delta\delta_{NH_2}=\rho_I\sigma_I+\rho_R\sigma_R^-+c$

Series	Constants	Parameters of the equation					Transmission factors	
		ρ_I	ρ_R	c	r	s	γ_I	γ_R
		m-Substituted						
m-$XC_6H_4NH_2$*	σ_I, σ_R	−1,138	−0,430	0,008	0,990	0,053	1,00	1,00
I	σ_I, σ_R	−1,182	−0,664	0,007	0,995	0,050	1,04	1,54
III	σ_I, σ_R	−1,359	−0,629	−0,011	0,993	0,062	1,19	1,46
IV	σ_I, σ_R	−1,038	−0,432	−0,002	0,997	0,029	0,91	1,00
V	σ_I, σ_R	−1,210	−0,587	0,027	0,989	0,073	1,06	1,37
		p-Substituted						
p-$XC_6H_4NH_2$*	σ_I, σ_R^-	−1,210	−1,343	0,007	0,995	0,077	1,00	1,00
II	σ_I, σ_R^-	−1,287	−1,384	−0,002	0,999	0,022	1,06	1,03
VI	σ_I, σ_R^-	−1,165	−1,472	0,057	0,994	0,099	0,96	1,10

*Taken from [13].

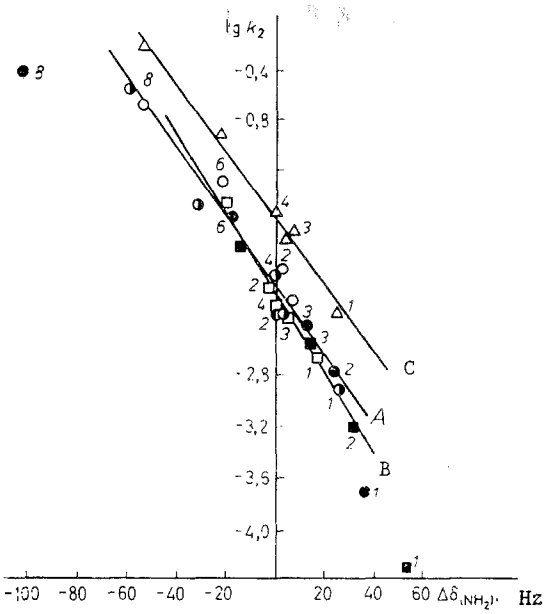

Fig. 1. Correlation of the rate constants k_2 [liters/(mole·sec)] for the alkaline hydrolysis of the methyl esters of pyridinecarboxylic acids (85% methanol, 25°C) [8, 9] with the chemical shifts of the NH_2 protons of the corresponding aminopyridines in DMSO: I) ○; III) ◑; IV) □; V) △; II) ●; VI) ■. The numbering of the points is presented in Table 1. A is the regression line of 2-aminopyridines, B is the regression line of 3(5)-aminopyridines, and C is the regression line of 4-aminopyridines.

character of the dependences presented in Fig. 1, which have virtually the same slope for all of the meta series (I, III-V). The points for the para series (II, VI) also lie satisfactorily on these lines, with the exception of the most extreme points, which correspond to the p-nitro and p-dimethylamino derivatives. At the same time, a graphical comparison of the $\Delta\delta_{NH_2}$ values of both pyridine para series (Fig. 2) graphically shows the different character of the intramolecular interactions of the electron-donor and electron-acceptor substituents with the amino group. A similar pattern is also observed for p-substituted aminopyrimidines [5]. In the case of electron-acceptor substituents the dependences for the pyridine and pyrimidine series coincide, and the slope of the line is close to unity. A difference shows up in the region of positive values of the relative chemical shifts, reflecting the stronger effect on the amino group of + M substituents from the α position of the azine ring than from the β position. One can form a more rigorous judgment regarding this on the basis of correlation analysis of the relative chemical shifts.

The development of a partial negative charge on the nitrogen atom of the solvated amino group promotes its polar conjugation with the para substituents, which required the use of the inductive and nucleophilic resonance constants of substituents in two-parameter correlations [10]. For most + M substituents (CH_3, Cl, Br, OCH_3) the nucleophilic resonance constants σ_R^- are numerically equal to the σ_R constants, whereas exalted values are characteristic for − M substitutents (σ_R^- for NO_2, $COOCH_3$) and for the very strong + M substituent $N(CH_3)_2$ (σ_R^0) [11]. In the case of alkaline hydrolysis of esters of pyridinecarboxylic acids the developing negative charge is localized on the oxygen atoms, and direct polar conjugation with the para substituents therefore cannot be realized, in contrast to the amino derivatives which is expressed in deviations of the points for the p-nitro and p-dimethylamino derivatives from the line (Fig. 1). In the correlations for the m-substituted pyridines we used the σ_I and σ_R constants as the variable parameters (the parameters of the equations are presented in Table 2). Correlation analysis makes it possible to reveal common features and some peculiarities in the transmission of the electronic effect of the substituents through the pyridine ring as compared with the benzene ring.

The inductive effects of substituents in pyridine and benzene rings are very similar; they are higher only in series of 2,6-disubstituted pyridines ($\gamma_I^{26} = 1.19$). Adhering to the point of view regarding the electrostatic nature of the inductive effect, this increase can be explained by the shorter distance between the 2 and 6 positions in the pyridine ring than in the benzene ring [12].

The transmission of the mesomeric effect of substituents in aza-aromatic systems has specific features. It is known that the perturbing effect of the heterocyclic nitrogen atom on the aromatic system is propagated primarily to the even-numbered positions (α and γ) and virtually does not involve the β positions; in 3,5-disubstituted pyridines the mutual effect of both substituents therefore differs little from their effect in m-disubstituted benzenes [1]. This is evidenced, in particular, by transmission factor γ_R^{35}. The effect of meta substituents from even-numbered positions of the pyridine ring becomes greater than the effect of substitutents in the benzene ring ($\gamma_R^{42} > \gamma_R^{26} > \gamma_R^{24} > 1$). As noted above, the effectiveness of the mesomeric effect of para substituents depends on the direction of transmission through the pyridine ring ($\gamma_R^{25} > \gamma_R^{52}$) similar to what has been described [5] for p-disubstituted pyrimidines.

EXPERIMENTAL*

The PMR spectra of solutions (4%) in dry DMSO were recorded with a Varian A 56/60 A spectrometer (60 MHz) at 37-38°C with the ^{13}C–H satellite of DMSO (221 Hz from TMS) as the internal standard. The chemical shifts were determined with an accuracy of ± 0.7 Hz. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer.

The results of elementary analysis of the compounds for C, H, and N were in agreement with the calculated values.

5-Amino-2-methoxycarbonylpyridine ($C_7H_8N_2O_2$). A mixture of 0.36 g (2 mmole) of 5-nitro-2-methoxycarbonylpyridine [7], 6 ml of methanol, and 1 ml of acetic acid was hydrogenated with hydrogen in the presence of 0.05 g of 10% palladium on carbon. The catalyst was separated, the filtrate was evaporated in vacuo, the residue was neutralized with $NaHCO_3$ solution, and the neutral mixture was extracted with $CHCl_3$. The extract was chromatographed on silica gel. The impurities were eluted with methanol, the eluate was evaporated in vacuo, and the residue was triturated with a few drops of benzene and acetone. The yield was 0.14 g (50%). For analysis, the product was sublimed at 130-140°C (0.1-0.5 mm) and crystallized from benzene with the addition of acetone to give a product with mp 152-154°C. IR spectrum: 1330, 1585 (NO_2); 1710 ($COOCH_3$); 1655, 3215, 3350, 3425 cm^{-1} (NH_2). PMR spectrum: 3.76 (3H, s, OCH_3), 6.08 (2H, broad, NH_2), 6.94 (1H, dd, $J_{4,6} = 2.5$, $J_{4,5} = 9.0$ Hz, 4-H), 7.78 (1H, d, J = 9.0 Hz, 2-H), 8.03 ppm (1H, d, J = 2.5 Hz, 6-H).

2-Amino-6-dimethylaminopyridine ($C_7H_{11}N_3$). A mixture of 2.25 g (17.5 mmole) of 2-amino-6-chloropyridine [14], 15 ml of a 30% solution of $HN(CH_3)_2$, 5 ml of ethanol, and 0.5 g of $CuSO_4 \cdot 5H_2O$ was heated in an autoclave at 180-190°C for 38 h, after which it was evaporated, and the residue was treated with 10% KOH solution. The alkaline mixture was extracted with ether, the extract was dried, the ether was removed by distillation, and the residue was fractionated in vacuo. The fraction with bp 135-143°C (16 mm), which crystallized on standing, was collected. The product was squeezed strongly between sheets of filter paper and sublimed at 100-110°C (16 mm). The yield was 0.55 g (24%); the product had mp 57.5-58.5°C (from hexane). PMR spectrum: 2.92 (6H, s, CH_3), 5.34 (2H, broad, NH_2), 5.73 (1H, d, J = 8.0 Hz, 5-H), 5.75 (1H, d, J = 8.0 Hz, 3-H), 7.15 ppm (1H, t, $J_{3,4} = J_{4,5} = 8.0$ Hz, 4-H).

2-Amino-6-nitropyridine ($C_5H_5N_3O_2$). A 0.42-g (2.5 mmole) sample of 6-nitropicolinic acid [15] was refluxed with 5 ml of $SOCl_2$. After the solid material had dissolved, the excess $SOCl_2$ was removed by vacuum distillation, and the residue was dissolved in 20 ml of dry acetone. A solution of 0.65 g (10 mmole) of NaN_3 in 2 ml of water was added with stirring to the acetone solution, another 5 ml of water was added, and the mixture was extracted with benzene (five 15-ml portions). The extract was dried and heated for 6 h at 60°C, after which 5 ml of concentrated HCl was added, and the mixture was heated for 1 h. The benzene solution was then extracted with concentrated HCl (two 3-ml portions), the hydrochloric acid extract was evaporated in vacuo, and the residue was treated with 2 ml of NH_4OH. The resulting mixture was extracted with ether, the extract was dried and evaporated, and the residue was crystallized from benzene with the addition of petroleum ether and sublimed at 130-140°C

*With the participation of S. N. Katankov.

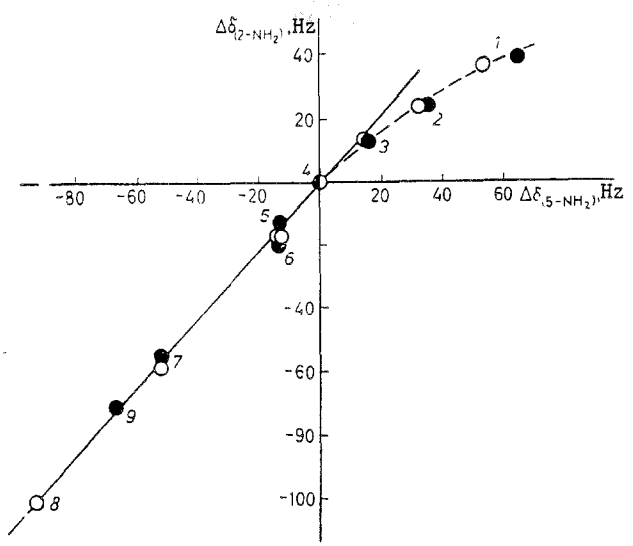

Fig. 2. Correlation of the chemical shifts of the NH_2 protons of p-substituted aminopyridines (○) and aminopyrimidines (●). The numbering of the points is presented in Table 1; point 9 corresponds to the CN group.

(5 mm) to give 0.09 g (26%) of product with mp 165-167°C (from acetone). IR spectrum: 1350, 1540 (NO_2); 1655, 3220, 3320, 3470 cm^{-1} (NH_2). PMR spectrum: 6.75 (2H, broad, NH_2), 6.83 (1H, d, J = 8.0 Hz, 3-H), 7.31 (1H, d, J = 8.0 Hz, 5-H), 7.70 ppm (1H; t, $J_{3,4} = J_{4,5}$ = 8.0 Hz, 4-H).

4-Amino-2-nitropyrydine ($C_5H_5N_3O_2$). A 0.5-g (3 mmole) sample of 2-nitroisonicotinic acid [15] was refluxed in 16 ml of $SOCl_2$ for 1 h, after which 5 ml of dry benzene was added, and the $SOCl_2$ was removed by distillation. Dry acetone (25 ml) was added to the residue, a solution of 1 g (15 mmole) of NaN_3 in 2.7 ml of water was added with cooling (with ice water), and the mixture was stirred for 1 h. It was then extracted with benzene (five 15-ml portions), and the extract was dried and refluxed for 10 h. Concentrated HCl (15 ml) was added, and the mixture was heated for 6 h at 80°C. The pH of the mixture was brought up to 8-9, and the mixture was extracted with ether. The extract was dried and evaporated in vacuo, and the residue was chromatographed on a thin layer of silica gel with ether as the mobile phase. The lower zone was collected and eluted with ethanol, and the eluate was evaporated to give 0.10 g (23%) of product. For analysis a sample was sublimed at 190-200°C (5 mm) and crystallized from ethyl acetate to give a sample with mp 199-201°C. IR spectrum: 1365, 1540 (NO_2); 1650, 3200, 3330, 3450 cm^{-1} (NH_2). PMR spectrum: 6.79 (2H, broad, NH_2), 6.81 (1H, dd, $J_{3,5}$ = 2.0, $J_{5,6}$ = 5.5 Hz, 5-H), 7.34 (1H, d, J = 2.0 Hz, 3-H), 8.01 ppm (1H, d, J = 5.5 Hz, 6-H).

The remaining substituted aminopyridines were obtained by known methods, and their constants were in agreement with those previously presented (see [16]); the individuality of the compounds was verified by chromatography.

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