NITROGEN-CONTAINING BISHETEROCYCLIC SYSTEMS

I. Dipole Moments and Structure of 1-Pyridylpyrazoles

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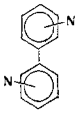
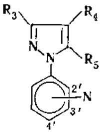
The dipole moments of some 1-pyridylpyrazoles and their 5-amino derivatives have been determined. On the basis of the experimental findings and of vector calculations of the magnitudes of the dipole moments, it has been established that the structure of the 1-pyridylpyrazoles and 1-(3'- or 4'-pyridyl)-5-aminopyrazoles is nonplanar, and the angle between the planes of the pyrazole and pyridine rings has been calculated. For 1-(2'-pyridyl)-5-aminopyrazoles, intramolecular hydrogen bonding leads to the occurrence of the planar trans configuration.

Conjugated bicyclic systems structurally analogous to biphenyl possess the nonplanar structure in solution. This is due to the bending of one of the exocyclic single C—C or C—N bonds, which possess a certain amount of double-bond character [1–3]. The nitrogenous bisheterocycles of type A [4, 5], and N-phenyl derivatives of azoles [6, 7] are prominent among similar systems.



A



B

The recently-synthesized pyridylpyrazoles (B) belong to this class of compounds [8, 9], and the investigation of the structure of these compounds with the aid of the dipole-moment method forms the subject of this paper.

The object of this work was to determine the conformation of the 1-pyridylpyrazoles in solution, a knowledge of which is necessary for the consideration of the spatial (ortho effect) [2] and electronic (conjugational) effects in molecules of type **B**. In addition, the structure of 1-(2-pyridyl)-5-aminopyrazoles, in which the intramolecular hydrogen bonds (IHB) can give rise to the stabilization of the planar trans configuration, is of great interest (cis and trans isomers, as is usually assumed [4, 5], are determined by the positions relative to each other of the nitrogen atoms in the pyrazole and pyridine rings). In order to resolve these problems, the experimental (μ_{exp}) and calculated (μ_{calc}) dipole moments were determined by the vector method for the 1-(pyridyl)pyrazoles (I–III, table) and their 5-amino derivatives (IV–XII).

The vector calculation of the dipole moments of **I–XII** was carried out by two methods. Method 1 [10, 11] was based on the calculation of the direction of the resultant moment of a fragment of the pyrazole ring from μ_{exp} for pyrazole and its 3-methyl derivative (1.57 and 1.43 D [12], respectively). In addition, the moment of the $C_{(3)}$—CH_3 group was taken as 0.4 D. The acceptability of this method for the calculation of the dipole moments of compounds of type B was fully confirmed by the completely satisfactory agreement of μ_{exp} with μ_{calc} (see table) for 1-(4'-pyridyl)-3,5-dimethylpyrazole (III), 1-phenyl-3-methyl-5-chloropyrazole (XIII), and 1-(4'-pyridyl)-3-ethyl-4-methyl-5-aminopyrazole (XII), in which rotation of the substituent in the 1-position of the pyrazole ring should not affect the vector value of the moment.

The essentials of method 2 are to be found in [13, 14]. In both methods, the following values for the group moments were assumed: C—NH_2, 1.53 D ($\theta = 48°$), [15], C_{Ar}—Cl, 1.58 D [16], and the moment of the pyridine ring, 2.20 D [12], in the direction from the center of the ring to the heteroatom [13]. Calculation of the angle φ between the plane of the heterocyclic nuclei in the molecules B was carried out by method 1.

The vector values of the moments for cis and trans planar configurations of compounds I and II, calculated by methods 1 and 2, differed substantially from the experimental values (see table), which allows the nonplanar structure

Dipole Moments of 1-Pyridylpyrazoles

Compound	R_3	R_4	R_5	N in pyridine ring	α_{av}	α_{av}	P_∞	R^{AD}	μ_{exp}^{25}, D	μ_{calc}, D (method 1)		φ_{calc}	μ_{calc}, D (method 2)	
										$\varphi=0°$	$\varphi=180°$		$\varphi=0°$	$\varphi=180°$
I	CH_3	H	CH_3	2′	2.5467	0.5473	129.537	52.768	1.87	0.69	3.66	58°	2.04	4.60
II	CH_3	H	CH_3	3′	5.4169	0.4873	226.980	52.768	2.87	1.52	3.92	84°	0.39	4.15
III	CH_3	H	CH_3	4′	5.2116	0.3819	222.931	52.768	2.84	3.14		≠0° *	2.59	
IV	CH_3	H	NH_2	2′	2.2164	0.6185	116.948	51.534	1.72	1.48	4.43	0° (trans)	2.65	5.37
V	$C_6H_5CH_2$	C_6H_5	NH_2	2′	1.9058	1.2540	141.552	96.260	1.32	1.76	4.73	(trans)	3.01	5.71
VI	C_2H_5	CH_3	NH_2	2′	2.1834	0.5636	126.874	60.830	1.71	1.41	4.61	(trans)	2.49	5.46
VII	n-C_3H_7	C_2H_5	NH_2	2′	2.3754	0.6903	139.444	68.734	1.76	1.41	4.61	(trans)	2.49	5.46
VIII	p-$NH_2C_6H_4$	H	NH_2	2′	4.3229	1.1523	199.429	74.428	2.40	2.29	4.46	(trans)	2.90	5.22
IX	n-C_3H_7	C_2H_5	NH_2	3′	8.8275	0.3161	364.900	70.126	3.75	2.10	4.87	66°	1.66	5.12
X	$C_6H_5CH_2$	C_6H_5	NH_2	3′	7.7498	1.2575	336.610	95.614	3.36	1.64	4.69	56°	1.67	5.12
XI	p-$CH_3C_6H_4$	H	NH_2	3′	9.6929	0.9177	386.291	75.662	3.85	1.79	4.55	80°	1.47	4.98
XII	C_2H_5	CH_3	NH_2	4′	9.9585	0.8944	377.702	60.830	3.90	3.92		≠0° *	3.57	
XIII	CH_3	H	Cl	1-C_6H_5	0.6801	0.4316	76.911	48.636	1.07	1.08		≠0° *	0.68	

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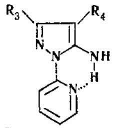
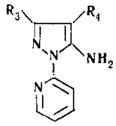
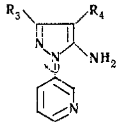
*Nonplanar molecules

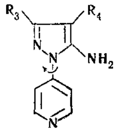
to be assigned to them.

Also the data presented in the table show the nonplanarity of those 5-amino derivatives of 1-pyridylpyrazoles in which the pyrazole ring is linked to the β-carbon atom of the pyridine ring (**IX–XI**):


C(*trans*, φ-0°)
V-VIII


D(*cis*, φ-180°)
V-VIII


IX-XI


XII

The amino structure for 1-pyridyl-5-aminopyrazoles follows from their IR spectra, which show strong absorption bands in the 1620–1630 cm^{-1} region, as is also the case with the 1-phenyl-5-aminopyrazoles [17]. The angle φ between the planes of the pyrazole and pyridine rings, derived from the experimental data, amounts for 1-(2'-pyridyl)pyrazole (I) to 58°, and for the analogous 3-pyridyl derivative II it is 84°. As also in the case of the 1-(3'-pyridyl)-5-aminopyrazoles (IX–XI), the values for the angle φ substantially exceed the analogous values calculated by the use of Braude's equation [18] for 1-phenylpyrazoles [7]. The reason for this may be that the calculation of the angle φ in [7] was based on the assumption of the planar structure for 1-phenylpyrazoles unsubstituted in the 5-position of the pyrazole ring. The results obtained here, therefore, demonstrate the noncoplanarity of the structure of the 1-phenylpyrazoles, which has previously been shown to be characteristic also of the bipyridyls [4], and even of unsubstituted biphenyl [19]. By the same argument the molecules of III, XII, and XIII must also be nonplanar, but the calculation of the angle φ for these compounds lies outside the scope of the vector method. Another conclusion may be drawn concerning the structure of the 1-(2'-pyridyl)-5-aminopyrazoles. The closeness of the values for the dipole moments determined experimentally and by calculation using methods 1 and 2 (although it should be pointed out that the values obtained by method 2 are somewhat high) for the trans structures IV–VIII (see table) indicate that these compounds exist in solution predominantly in the planar from ($\varphi = 0$). The stabilization of the trans form may be explained for compounds IV–VIII by the formation of IHB of the N—H... N type between a hydrogen of the amino group in the 5-position of the pyrazole ring, and the nitrogen atom of the pyridine ring. This is supported by the nonplanar structure of 1-(3'-pyridyl)-5-aminopyrazoles IX–XI, in which IHB formation is impossible as a result of the distance of the nitrogen atom from the sphere of influence of the hydrogen atoms of the amino group.

It is pertinent to point out that the difference in the spatial structures of 1-(2'-pyridyl)-5-aminopyrazoles IV–VIII on the one hand, and the 5-amino derivatives IX–XII on the other, are confirmed by their UV spectra [8, 9]. In the UV spectra of the 1-pyridyl-3-benzyl-4-phenyl-5-aminopyrazoles, the longest wavelength absorption is observed for the planar 2'-pyridyl derivative (λ_{max} 280 nm). At the same time, in the case of 1-(3'- and 4'-pyridyl)-5-aminopyrazoles, the absorption maxima are shifted toward shorter wavelengths, and appear at 253 and 267 nm, respectively. If it is assumed that the hypsochromic effect in systems of type A and N-phenylpyrazoles is related to an increase in the angle φ [2, 7], then the facts presented indicate a substantial amount of conjugation in compounds IV–VIII in comparison with compounds IX–XII. A comparison of the values of the moments obtained by methods 1 and 2 is worthy of note in this respect. In the cases of molecules with a nonplanar configuration, and consequently with a reduced degree of conjugation between the pyrazole and pyridine rings, both methods give similar results, the variation ($\Delta\mu$) amounting to 0.3–0.5 D (IX–XII, table). On the other hand, for the coplanar molecules IV–VIII, $\Delta\mu$ reaches a value of about 1 D. This constitutes, therefore, a more accurate use of the method of calculation 2 [13, 14] for the evaluation of the electrophilic influence of substituents, but does not lead to any conclusions concerning the structure of compounds which show a significant mesomeric effect.

In conclusion, we would point out that 1-pyridylpyrazoles similar to A [20] are of considerable interest as polydentate ligands in complex-formation. In the case of the formation of complexes involving the nitrogen atoms in the 2-position of the pyrazole and pyridine rings, for compounds I and IV–VIII it would be expected that the energetically-disfavored cis conformation of the ligands would occur.

EXPERIMENTAL

The synthesis of the starting materials I–XII was carried out by previously-described methods [8, 9]. The method used for the preparation of 1-phenyl-3-methyl-5-chloropyrazole (XIII) is described in [21].

The dipole moments (see table) were determined according to [22] on an IDM-2 apparatus [23], in benzene at 25 ± 0.1°, at concentrations between $5 \cdot 10^{-3}$ and $2 \cdot 10^{-4}$ molar.

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