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EFFECT OF THE ELECTRONIC STRUCTURE OF THE HETEROATOM ON THE BASICITIES OF HETEROCYCLIC COMPOUNDS

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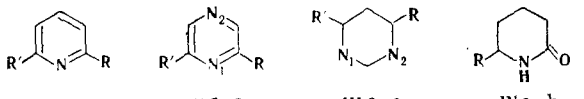
The proton-acceptor capacities of heterocyclic nitrogen compounds (pyridine, pyrazine, pyrimidine, and some of their derivatives) were subjected to a theoretical study by means of the molecular electrostatic-potential method. The wave functions of the examined compounds were obtained by the INDO method. It was found that the difference in the proton-acceptor capacities of the examined compounds is due to the difference in the electronic structures of the unshared pairs of the most basic atoms in these compounds.

The accurate description of the protonation of polybasic molecules requires a determination of the effectiveness of protonation of each center. This is often a complex task from an experimental point of view [1]. For a theoretical evaluation it is convenient to use the molecular electrostatic potentials (MESP), which are the energies of the electrostatic interactions of an individual positive charge with the unperturbed charge distribution of the molecule. The set of MESP values at all points of the space that surrounds the molecule determines the hypersurface of the electrostatic energy of the interaction of the molecule with the individual positive charge. Despite the fact that this surface is an initial approximation of the total potential surface of the interaction, an analysis of it makes it possible to obtain diverse information regarding the reactivity of the molecules [2, 3].

The aim of the present research was to make a theoretical study of the reactivities of a number of heterocyclic nitrogen compounds and to establish the relationship between the electronic structures of the heteroatoms and the basicities of the examined compounds by means of the indicated approach.

The MESP values were calculated in this research by means of the wave functions obtained by various methods based on the zero-differential-overlap (ZDO) approximation by means of the program described in [4].

In the present research we investigated pyridine, pyrimidine, pyrazine, and their derivatives (Ib-f, IIb, c, IIIb, c, and IVa, b) in the ground electronic state.



Ia-f IIa-c IIIa-c IVa, b

I—IV a R=R′=H; b R=NH_2, R′=H; c R=R′=NH_2; d R=OH, R′=H; e R=OH, R′=NH_2; f R=O^-, R′=H

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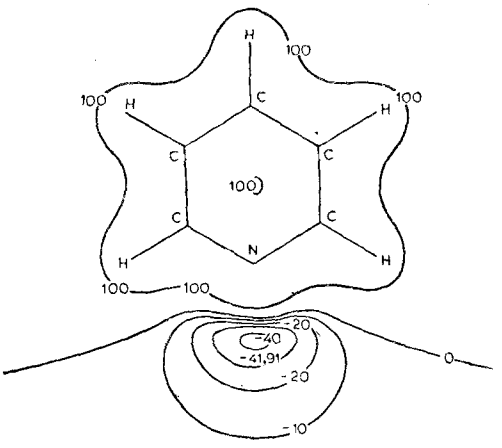

Fig. 1

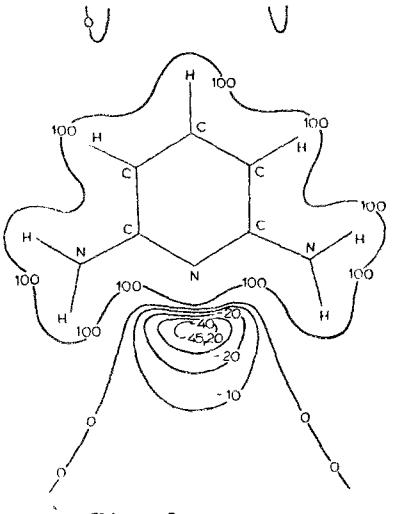

Fig. 2

Fig. 1. Map of the MESP for the pyridine molecule in the xy plane (z = 0).

Fig. 2. Map of the MESP for the 2,6-diaminopyridine molecule in the xy plane (z = 0).

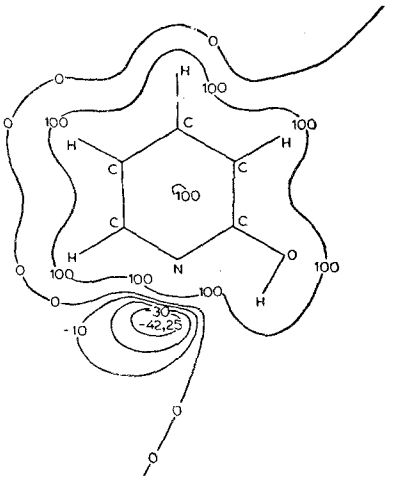

Fig. 3

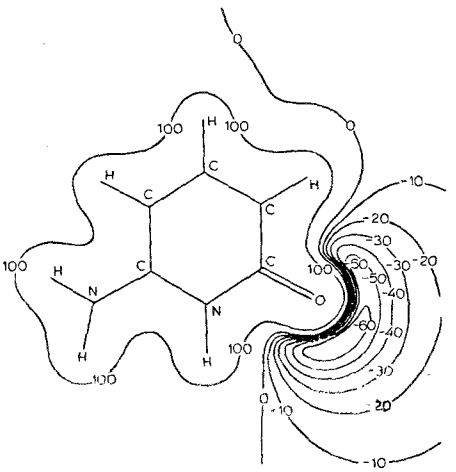

Fig. 4

Fig. 3. Map of the MESP for the 2-hydroxypyridine molecule in the xy plane (z = 0).

Fig. 4. Map of the MESP for the 6-amino-2-pyridone molecule in the xy plane (z = 0).

Maps of the MESP values for some of the investigated nitrogen heterocycles (Ia, c, d and IVb) are presented in Figs. 1-4. The energies of interaction (W) of the positive unit charge with the charge distribution of the molecule (in kilocalories per mole) are indicated on the maps. The regions with W < 0 correspond to attraction of the positively charged reagent, while the regions with W > 0 correspond to repulsion.

The W values depend directly on the approximations used in the calculation of the wave functions [2]. When the ZDO approximation is used for this purpose, the maps of the values obtained are in rather poor agreement with the maps obtained when nonempirical wave functions are used [6]. The agreement is improved if one rejects the ZDO approximation and passes to a deorthogonalized basis of the atomic orbitals [4]. A similar approach was used in the present study to refine the W values at the minima and the coordinates of the minima. These calculations gave larger W values at the minima, but the coordinates of the minima and the qualitative character of the maps remained unchanged. The figures presented above therefore correspond to the calculations obtained within the framework of the ZDO approximation.

TABLE 1. Electronic Characteristics of Ia-e, IIa-c, IIIa-c, and IVa, b

Compound	Q_0	q_n	MESP σ		MESP π, z = 1.2 Å	pK_a*
			z=0	z=1,2 Å		
Ia	−0,258	1,704	−41,91	−22,15	−5,60	5,2 [14]
Ib	−0,308	1,697	−43,82	−36,72	−17,10	6,71 [11]†
Ic	−0,354	1,690	−45,20	−28,30	−18,20	
Ic‡	−0,327	1,692	−44,82	−20,62	None	
Id	−0,260	1,698	−42,30	−23,56		
IVa	−0,451	1,831	−44,51		−22,90 (above C=O)	
Ie	−0,370	1,684	−44,01	−13,80	−28,68 (above OH)	
					−12,50 (above NH_2)	
IVb	−0,693	1,840	−68,40		−36,37 (above C=O)	
IIa	−0,230	1,705	−33,50	−16,90	−4,20	0,65 [14]
IIb	−0,280	1,699	−38,81	−19,62	−11,02	3,14 [13]
IIc	−0,230**	1,710	−38,01	−19,02		
	−0,328	1,691	−37,12	−18,20	−13,18	
	−0,231**	1,713	−42,40	−22,86		
IIIa	−0,264	1,706	−24,83	−13,88		1,30 [14]
IIIb	−0,300	1,700	−28,15	−16,18		
	−0,314	1,697	−37,42	−25,14	−2,01	5,58 [11]†
	−0,345	1,692	−42,86	−3,88		6,01 [13]

*Heteroring nitrogen. †The pK_a values for the amine nitrogen atom are 2.5 for Ib [11] and −02 [sic] [11] for IIIb. ‡Noncoplanar amino group. **Data for the N_2 atom.

TABLE 2. Calculated and Observed Dipole Moments (μ, in Debyes) for Ia-e, IIb, c, IIIa-c, and IVa, b

Compound	μ_{calc}	μ_{exp} [15]
Ia	2,5	2,2; 2,37
IIIa	2,77	2,4
Ib	2,43	2,0; 2,23
Ic	1,00	1,46
Ic*	5,38	
IIb	1,76	
IIc	1,39	
IIIb	4,12	
IIIc	4,86	
Id	1,75	1,99; 1,73
IVa	3,07	
If	10,45	
IVb	8,48	

*Noncoplanar amino group.

Vast regions of negative W values surrounding the heteroatoms were obtained for unsubstituted pyridine, pyrazine, and pyrimidine. In the case of Ia the W value at the minimum (see Table 1) is greater than for IIa, which is in agreement with both the experimental data of Taft and with Del Bene's calculation for nonempirical wave functions [7] of the proton affinities. The minima of the W values for unsubstituted nitrogen heterocycles (Ia, IIa, and IIIa) are located at ∿1.3 Å from the nitrogen atom (in the nonempirical calculation of Pullman [5] of the Ia molecule this N.....H^+ distance corresponds to the length of the hydrogen bond, viz., 1.06 Å), which is in agreement with the experimental data on the nitrogen atom as the most reactive site in the ring with respect to electrophilic reagents. The reason for the deep minimum of the potential for the nitrogen atoms is the anisotropy of the unshared pairs of electrons on these atoms. The minima of the MESP lie on the axis of the orbital of the unshared pair, and the structures of the possible complexes with a hydrogen bond are determined by the degree of localization of the charge on the unshared pair.

In analyzing the maps of W for Ia and IIa one can note yet another general feature for these compounds: There is a certain probability that they may be protonated from outside of the molecular plane (in the ring). Mulliken [9] has expressed a hypothesis regarding the existence of such interaction in pyridine.

However, a minimum W above the plane of the ring is absent in the case of pyrimidine, and this constitutes evidence for the small possibility that this compound interacts via a mechanism of the π type.

Since the results that we obtained for unsubstituted Ia, IIa, and IIIa are in qualitative agreement with the results obtained for these compounds (Ia and IIa) by means of the method of evaluation of the MESP for nonempirical wave functions, we may assume that our results with respect to substituted nitrogen heterocycles (Ib-f, IIb, c, and IIIb, c) accurately convey the proton-acceptor properties of these systems. We are as yet unable to compare our data with more accurate calculations, since calculations of the MESP of these molecules for either semiempirical or nonempirical wave functions are unknown at the present time.

Monoamino and diamino substitution lead to an increase (which is particularly significant for aminopyrimidines) in the proton-acceptor capacity of the nitrogen atom (compare Figs. 1 and 2). Our data are in good agreement with the experimental increase in the basicities of heterocyclic nitrogen compounds in the case of amino substitution. It follows from Table 1 that the MESP correlate with the total charge on the nitrogen atom but not with the charge on the orbital of the unshared pair of electrons and that substitution leads to

the development of new reaction centers with respect to the substituents (Table 1). However, the probability of this sort of interaction of the π type is very low for aminopyrimidines.

In the case of Ic the calculation was carried out with two variants: a) with the amino group lying in the plane of the molecule; b) with the hydrogen atoms of the amino group forming angle α = 39°21' with the plane of the molecule, as in the aniline molecule [10], since no experimental data on the structure of the amino group are available for the examined compounds. The dipole moments obtained show that in the case of noncoplanar amino groups the calculated dipole moment of Ic is too high and is not in agreement with the experimental data, in contrast to Ic with a planar amino group (Table 2). In addition, allowance for the possible noncoplanarity of the H atoms of the amino group, by having virtually no effect on the depth of the minimum of the MESP in the region of the ring nitrogen atoms in the plane of the molecule, leads to disappearance of the weaker minima that are located above the amino groups (Table 1). At the same time, our values of the minima of the W value above the planes of the amino groups correlate with the basicity constants for the amino groups obtained experimentally in [11]. Consequently, it may be assumed that deviation from coplanarity, if it does occur, is considerably smaller in amino-substituted nitrogen heterocycles than in aniline.

As in the case of amino substitution, the introduction of a hydroxy group in the molecule (Fig. 3) leads to an increase in the proton-acceptor capacity of the heterocyclic nitrogen atom, although to a lasser extent. Tautomaric transformations [12] that markedly change the electronic structure and the properties of the molecules are possible for hydroxy-substituted heterocyclic nitrogen compounds. Thus, after conversion of 2-hydroxypyridine to 2-pyridone, the unshared pair of p electrons is not found on the aromatic nitrogen atom but rather on the oxygen atom of the carbonyl group; because of the greater total charge on the heteroatom, the lactam (pyridone) form has more significant proton-acceptor capacity (Table 1).

The tautomeric conversion of 2-hydroxypyridine to the keto form decreases the s character of the unshared pair of electrons (∿14%), which becomes even smaller (∿8%) when an amino group is introduced in the pyridine molecule. As in the case of aliphatic carbonyl compounds [3, 8], the probability that the proton approaches from both sides of the C=O group in the plane of the molecule exists for the keto forms of IVa,b (Fig. 4), but the tautomeric keto forms of nitrogen heterocycles have deeper minima of the W values because of the effect of the vast π system of the ring. These data explain the structures of 1:2 complexes with a hydrogen bond that have been observed by IR and UV spectroscopy [8] and are also in agreement with the widely known concepts regarding the carbonyl oxygen atom as the atom that has two equivalent unshared pairs. The difference in the proton-acceptor capacities of Id, e and their keto forms IVa, b is due to the difference in the electronic structures of the unshared pairs of the O and N atoms (the almost pure pair in the p_y orbital of the oxygen atom and the pair on the heteroring nitrogen atom with sp^2 hybridization).

In conclusion, it should be noted that the approach used in this study made it possible to obtain information regarding the proton-acceptor capacity and the sites of protonation of some nitrogen heterocycles and to explain the change in the basicity under the influence of substitution and tautomeric transformations. The ring nitrogen atom was found to be the most probable site of protonation of the investigated compounds (except for the pyridones), although the possibility of interaction at the amino group in amino-substituted nitrogen heterocycles may increase under some conditions (for example, by selection of the solvent). It is expedient to use the method employed in this research for the identification of the site of protonation and to predict the basicities of various reaction centers of molecules.

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UTILIZATION OF A BENZYL PROTECTIVE GROUP IN THE SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES

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The corresponding N-benzyl-1,2,3,4-tetrahydroisoquinolines, the debenzylation of which is realized by hydrogenation in the presence of Pd black, were synthesized by the reaction of 1-(3-hydroxyphenyl)-2-benzylaminoethanol with aldehydes.

The modification of the Pictet—Spengler reaction proposed by Kametani and Fukumoto [1] has proved to be a convenient method for the synthesis of hydroxy-containing derivatives of tetrahydroisoquinoline that are of interest as potential biologically active and medicinal substances. However, in a number of cases, particularly when primary hydroxyphenylethylamines are used as the starting substances, the yields of the desired products are low because of the necessity for thorough purification to remove significant amounts of impurities. To avoid this, it was recently proposed [2] that the intermediates, viz., the Schiff bases of the hydroxyphenylethylamines with carbonyl compounds, be isolated prior to cyclization; however, this cannot always be accomplished, and this method does not always give positive results.

The utilization of a benzyl group to protect the amino group in the starting hydroxyphenylethylamine, which can be easily removed after the cyclization step, may serve as one of the possible ways to simplify this reaction. Thus the corresponding 1-aryl-2-benzyl-1,2,3,4-tetrahydroisoquinoline-4,6-diones (IIa-c) were synthesized by the reaction of 1-(3-hydroxyphenyl)-2-benzylaminoethanol (I) with vanillin, 3,4,5-trimethoxybenzaldehyde, and 4-dimethylaminobenzaldehyde.

The debenzylation of IIa-c was carried out by hydrogenation over palladium black without pressure at room temperature in aqueous alcohol in, where necessary, an acidic or alkaline medium.

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