Electronic structure and conformational flexibility of 1,2-dihydropyridine, 1,2- and 1,6-dihydropyrimidines, and their ylide derivatives

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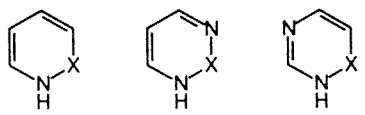
Molecular and electronic structures of 1,2-dihydropyridine, 1,2- and 1,6-dihydropyrimidine, and their oxo, imino, and methylene derivatives were studied by the semiempirical quantum-chemical AM1 method. In all compounds, the heterocycle exhibits a high conformational flexibility. The transition from a planar equilibrium conformation to a distorted sofa conformation with the =C—NH—C—C(N)= torsion angle of ±20° causes an increase in the energy by less than 1.7 kcal mol^{-1}. All molecules have similar π-electronic structures, which, apparently, determines the similarity in their conformational behavior. The bending strain and the nonaromatic character of the cyclic π-system are the factors that stabilize the nonplanar conformation of the ring in unsubstituted dihydroazines and ylide derivatives, respectively.

Key words: 1,2-dihydropyridine, 1,2-dihydropyrimidine, 1,6-dihydropyrimidine, ylide derivatives, AM1 method, electronic structure, conformational analysis.

Derivatives of 1,2- and 1,6-dihydroazines belong to one of the most important classes of natural organic compounds.[1] In particular, nucleic bases (cytosine and guanine) belong to this group of compounds. In addition, many derivatives of 1,2- and 1,6-dihydroazines exhibit a broad spectrum of biological activities.[2,3] Studies of characteristic features of the spatial structures and the conformational behavior of these molecules may provide important data for an understanding of the mechanism of their physiological action.

We carried out a theoretical study of the spatial and electronic structures and the conformational flexibility of 1,2-dihydropyridine, 1,2- and 1,6-dihydropyrimidine, and their oxo, imino, and methylene derivatives (**1**—**3**).



1a—d **2a—d** **3a—d**

X = CH_2 (**a**), C=O (**b**), C=NH (**c**), $C=CH_2$ (**d**)

Calculation procedure

The spatial structures of compounds **1**—**3** were calculated by the semiempirical quantum-chemical AM1 method[4] with full geometry optimization. The conformational flexibility of the heterocycle was studied by scanning the =C—NH—C—C(N)= torsion angle in the range of ±30° with a step of 5° by the reaction coordinate method.

The degree of aromaticity of the cyclic π system was characterized by Bird's aromaticity index[5] I_6:

$$I_6 = 100(1 - V/V_k), \quad V = \frac{100}{N} \cdot \frac{\sum (N_i - N_0)^2}{n},$$

where N_i is the order of the i-th bond, N is the average bond order in the ring, and n is the number of bonds. The value of V_k was determined analogously to V; in this case, the fully localized model of the ring was considered. The aromaticity index for the benzene molecule calculated by this method is equal to 100.

Results and Discussion

Equilibrium conformations of unsubstituted molecules **1a**—**3a** are determined by the counterbalance of two groups of opposite factors. The first group involves the conjugation between the double bonds and the lone electron pair of the nitrogen atom of the NH group and the 1,2-allylic strain occurring through nonbonded interactions between the methylene hydrogen atoms and the adjacent double bond. These interactions favor a planar conformation of the ring. The second group of factors involves the bending strain occurring owing to the deformation of the endocyclic bond angle at the saturated carbon atom; this strain is maximum in the case of a planar conformation of the ring.

Calculations have demonstrated that the equilibrium conformation of the dihydroazine ring in these com-

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 8, pp. 1934—1937, August, 1996.

1066-5285/96/4508-1833 $15.00

Table 1. Changes in the energy (ΔE/kcal mol^{-1}) upon bending of the ring in molecules **1**—**3** calculated by the AM1 method

Compound	Torsion angle*/deg			
	0	10	20	30
1a	0.0	0.0	0.4	1.1
1b	0.0	0.4	1.7	3.8
1c	0.0	0.3	0.9	2.2
1d	0.0	0.2	0.9	2.2
2a	0.0	0.1	0.7	1.6
2b	0.0	0.3	1.5	3.4
2c	0.0	0.3	1.0	2.3
2d	0.0	0.3	1.0	2.4
3a	0.0	0.1	0.5	1.5
3b	0.0	0.3	1.4	3.3
3c	0.0	0.3	1.1	2.7
3d	0.0	0.2	0.9	2.1

* Torsion angles =C—NH—C—C in compounds **1** and **3** and =C—NH—C—N= in **2**.

pounds is planar. This is indicative of the predominance of the factors causing flattening. The results obtained agree well with the results of calculations by alternative quantum-chemical methods including the *ab initio* method with the 4-31G basis set.[6,7]

As in the case of 1,4-dihydroazines,[8] the occurrence of opposite factors determining conformations of the rings in molecules **1a**—**3a** results in high conformational flexibility of the partially hydrogenated azine ring (Table 1). The transition from a planar equilibrium conformation to a distorted sofa conformation with the =C—NH—C—C(N)= torsion angle of ±20° causes an increase in the energy by less than 0.7 kcal mol^{-1}; unlike 1,4-dihydroazines, the flexibility of the ring in these compounds substantially depends on the mutual arrangement of the nitrogen atoms. The most flexible and the most rigid rings occur in 1,2-dihydropyridine **1a** and 1,2-dihydropyrimidine **2a**, respectively.

When the methylene group is replaced by the exocyclic double bond, the factor causing flattening (bending strain) disappears. Therefore, the equilibrium conformation of the ring should remain planar, which is confirmed by the results of calculations as well as by the experimental data.[9—17]

Because of the absence of the factor stabilizing a nonplanar conformation of the ring, the partially hydrogenated rings in ylide derivatives **1**—**3** would be expected to be conformationally rigid. However, the results of calculations demonstrated (see Table 1) that the rigidity of the heterocycle increases only slightly. A transition from a planar equilibrium conformation to a distorted sofa conformation with the =C—NH—C—C(N)= torsion angle of ±20° causes an increase in the energy of the molecule by less than 1.7 kcal mol^{-1}. For comparison, an analogous distortion of the geometry of pyridine leads to a change in the energy by ~8 kcal mol^{-1}.[18]

The fact that the rings in ylide derivatives **1b**—**d**, **2b**—**d**, and **3b**—**d** retain conformational flexibility indicates that a new factor appears, which stabilizes the nonplanar conformation of the ring. Because of the absence of steric hindrances in these molecules, this stabilization may be of an electronic character only. The cyclic conjugated system in ylide derivatives involves seven π-electrons and, therefore, this system is nonaromatic. Because a planar conformation is not the most favorable for these molecules, a distorted sofa conformation may be stabilized owing to the nonaromatic character of the π-system. In this case, a decrease in the polarity of the exocyclic double bond should lead to an increase in the nonaromaticity of the cyclic conjugated system and, therefore, to an increase in the flexibility of the heteroring. A comparison of the results of calculations for oxo and methylene derivatives of dihydroazines (see Table 1) confirms our suggestion.

To gain a more sophisticated insight into the similarity in the conformational behavior of 1,2- and 1,6-dihydroazines and their ylide derivatives, it seems reasonable to consider their π-electronic structures. Unsubsti-

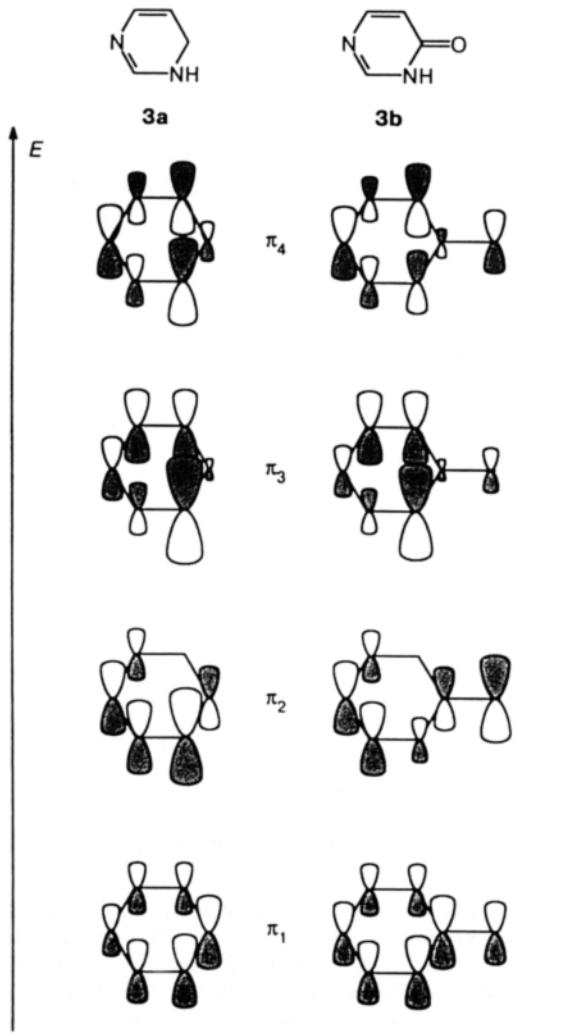


Fig. 1. Overall view of MOs π_1—π_4 in 1,6-dihydropyrimidine and 6-oxo-1,6-dihydropyrimidine.

Table 2. Energies of π-MOs (E_π/eV) and the aromaticity indices I_6 and $I_6(\pi)$ of molecules **1—3** calculated by the AM1 method

Compound	π_1	π_2	π_3	π_4	I_6	$I_6(\pi)$
1a	−15.7	−12.4	−11.7	−8.0	20.3	53.4
1b	−15.7	−12.8	−11.4	−9.0	36.1	74.5
1c	−14.9	−11.6	−11.2	−8.3	33.8	70.3
1d	−14.5	−10.9	−10.7	−7.6	32.2	68.2
2a	−15.9	−12.2	−11.9	−8.5	18.4	53.2
2b	−16.2	−13.2	−12.5	−9.6	35.0	74.8
2c	−15.4	−12.4	−11.8	−8.8	31.6	69.7
2d	−15.0	−12.1	−10.9	−8.0	29.8	67.7
3a	−15.6	−12.8	−11.2	−8.4	25.2	56.1
3b	−16.2	−13.7	−11.9	−9.7	36.3	75.2
3c	−15.5	−12.6	−11.6	−8.9	33.8	70.5
3d	−15.3	−11.9	−11.1	−8.1	32.3	68.8

tuted molecules **1a—3a** have four π-MOs (π_1—π_4) formed by p_z-AOs of the atoms of the double bonds, the nitrogen atom of the NH group, and the pseudo-π-orbital of the methylene group. In Fig. 1, the π-MOs of molecules **3a,b** are shown as an example. The replacement of the methylene group by the exocyclic double bond does not lead to a qualitative change in the symmetry of π-MOs (see Fig. 1). In molecules of ylide derivatives, a decrease in the polarity of the exocyclic double bond causes an increase in the energy of all these MOs (Table 2).

Therefore, molecules **1—3** have very similar π-electronic structures. A change in the conformation of the ring causes primarily the disruption of the overlap of p_z-AOs; this fact, apparently, determines the similarity in the conformational behavior of 1,2- and 1,6-dihydroazines and their ylide derivatives.

The presence of the cyclic conjugated system in the compounds under consideration (or the quasi-cyclic conjugated system in the case of nonsubstituted molecules **1a—3a**) makes it possible to consider these compounds in terms of aromaticity. We characterized the degree of aromaticity with the use of Bird's aromaticity index I_6[5], which was calculated based on the bond orders in the ring (see Table 2). On the whole, the values of I_6 qualitatively correlate with the changes in the energy of the molecules that occur upon bending of the ring by 30°. The use of the linear regression model gives the following equation:

$$E = 0.112I_6 - 1.029, \; r = 0.84.$$

Because a change in the overlap of p_z-AOs is the governing factor determining the conformational flexibility, the π-components of the total bond orders are of interest. The aromaticity indices $I_6(\pi)$ calculated with the use of the orders of the bonds between p_z-AOs of the atoms of the ring are given in Table 2. In this case, the use of the linear regression model gives the following equation:

$$E = 0.088I_6(\pi) - 3.493, \; r = 0.89.$$

The dihydroazine ring in imino derivatives **1c—3c** has a higher conformational flexibility than those in the corresponding methylene derivatives, which is inconsistent with the relationship between the flexibility of this ring and the polarity of the exocyclic double bond. Changes in the energy upon bending of the ring in these compounds are substantially underestimated; this apparently is associated with the fact that their description within the framework of the AM1 method is inaccurate. When molecules **1c—3c** are excluded from the linear regression model, the correlation coefficients substantially increase:

$$E = 0.121I_6 - 1.201, \; r = 0.88;$$

$$E = 0.093I_6(\pi) - 3.763, \; r = 0.92.$$

A larger value of the correlation coefficient indicates that the indices $I_6(\pi)$ are more suitable for describing the relationship between the degree of aromaticity and the conformational flexibility of the dihydroazine ring. It follows from the data obtained that the conformational flexibility is the common property of 1,2- and 1,6-dihydroazines.

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Received February 26, 1996