Electronic structure and conformational flexibility of 1,4-dihydroazines and their 4-ylide derivatives

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The conformational flexibility of 1,4-dihydropyridine, 1,4-dihydropyrimidine, 1,4-dihydropyridazine, 1,4-dihydro-1,3,5-triazine, and their 4-oxo, imino, and methylene derivatives was studied by the semiempirical quantum-chemical AM1 method. It was demonstrated that the replacement of the methylene group in the dihydroazine ring by the exocyclic double bond results only in an increase in the rigidity of the heterocycle rather than leading to a loss of its conformational flexibility. It was suggested that nonplanar conformations of rings in ylide derivatives are stabilized by the nonaromatic cyclic π-system. Introduction of the exocyclic double bond does not cause a substantial change in the π-electronic structure of the heterocycle. The aromaticity indices I_6 and $I_6(\pi)$ were calculated. The correlation between these indices and a change in the energy upon bending of the heterocycle was established.

Key words: 1,4-dihydroazines, ylide derivatives, conformational analysis, conformational flexibility, semiempirical quantum-chemical AM1 method, electronic structure, aromaticity.

One of the most interesting characteristics of medium-sized and large cyclic systems is their conformational lability under ordinary conditions, which may have a pronounced effect on the physicochemical properties and reactivities of the molecules. The classical example of conformational flexibility is the pseudorotation in cyclopentane and cyclohexane.[1,2] This characteristic feature of saturated rings is determined by low barriers separating different conformers, which allows conformational transitions owing to thermal energy alone.

Recently, conformationally flexible rings of the second type were found. For these molecules, the minimum on the potential energy surface has a flattened shape. As a result, the conformers that are close in energy to the equilibrium structure but differ from this structure in geometric parameters are abundant. 1,4-Cyclohexadiene,[3] quinone,[4] 1,3-cyclohexadiene,[5] and its 5-oxo derivatives[6] can serve as examples.

Previously, the *ab initio*,[4] AM1,[7,8] and molecular mechanics[9] calculations demonstrated that the six-membered ring in 1,4-dihydropyridine is also conformationally flexible. Analogous results have been obtained for other 1,4-dihydroazines[8,10] as well. The conformational flexibility of the dihydrocycle in these compounds is determined by two groups of opposite factors, which determine the conformation of the ring.[8,9]

On the one hand is conjugation between double bonds and the lone electron pair of the nitrogen atom of the NH group and the 1,2-allylic strain owing to nonbonded interactions along C_{sp^2}—C_{sp^3} bonds. These factors are favorable for a planar conformation of the ring. On the other hand is the bending strain because of the deformation of the endocyclic bond angle at the saturated carbon atom; this strain is maximum in the planar conformation. A transition from a planar or nearly planar equilibrium conformation to a boat conformation leads to a decrease in the bending strain; however, at the same time the conjugation decreases and the allylic strain increases. Therefore, the total change in the energy of the molecule is insignificant over a rather wide range of endocyclic torsion angles.

Because the nonplanar conformation of the 1,4-dihydroazine ring is stabilized by bending at the saturated carbon atom, it may be suggested that the replacement of the methylene group by the exocyclic double bond will result in the loss of conformational flexibility of the ring. However, based on the studies of conformational characteristics of substituted 4-pyridones by the DNMR, it was suggested[11] that dihydropyridine rings in these compounds may be flexible. With the aim of testing this suggestion, we have studied the molecular and electronic structures and conformational flexibility of 1,4-dihydropyridine, 1,4-dihydropyrimidine, 1,4-dihydropyridazine, 1,4-dihydro-1,3,5-triazine, and their 4-oxo, imino, and methylene derivatives.

Calculation procedure

The equilibrium geometry of molecules **1**—**4** was calculated by the semiempirical quantum-chemical AM1 method.[12] The

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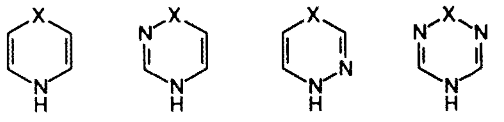
conformational flexibility of the ring was studied by scanning the C=C—C—C= torsion angle (molecules **1a—d**) or analogous torsion angles in molecules **2—4** in the range of ±30° with a step of 5°.



1a—d **2a—d** **3a—d** **4a—d**

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

The degree of aromaticity was characterized by Bird's aromaticity index[13,14] (I_6). Previously, it has been demonstrated[15] that among indices based on geometric criteria, this index is best suited for the description of cyclic π-systems. The value of I_6 was calculated using the following formula:

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

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

According to the results of AM1 calculations, equilibrium conformations of the rings in molecules **1—4** are planar or nearly planar (the endocyclic torsion angles are no more that 7°), which agrees well with the results of *ab initio* quantum-chemical calculations.[16,17] Previously, it was demonstrated[8] that the ring in 1,4-dihydroazines exhibits high conformational flexibility. The transition from an almost planar equilibrium conformation to a boat conformation with the C=C—C—C= torsion angle of ±20° causes an increase in the energy of the molecule by less than 1 kcal mol $^{-1}$. The presence of the conjugated system in molecules **1a—4a** results in a lesser deviation of the nitrogen atom of the NH group from the mean plane through the atoms forming double bonds as compared to that of the saturated carbon atom. A change in the nature of the endocyclic double bond (C=C or C=N) has virtually no effect on the flexibility of the heterocycle (Table 1).

The replacement of the methylene group by the exocyclic double bond results in a substantial increase in the rigidity of the partially hydrogenated ring. However, the heterocycle in these molecules remains substantially flexible. The transition to a boat conformation with the C=C—C—C= torsion angle of about ±20° causes an increase in the energy of the molecule by less than 2 kcal mol^{-1}. Therefore, the 1,4-dihydroazine ring in ylide derivatives retains conformational flexibility.

The absence of a saturated carbon atom in ylide derivatives of 1,4-dihydroazines is responsible for the absence of bending strain. Therefore, the factor stabilizing a nonplanar conformation of the dihydroring disappears. The fact that the partially hydrogenated heterocycle retains flexibility is indicative of the occurrence of another interaction that destabilizes the planar conformation.

Table 1. Changes in the energies (ΔE/kcal mol^{-1}) upon bending of molecules **1—4** calculated by the AM1 method

Compound	Torsion angle*/deg						
	0	5	10	15	20	25	30
1a	0.5	0.0	0.1	0.5	0.7	1.3	2.9
1b	0.0	0.1	0.4	0.9	1.7	2.6	3.9
1c	0.0	0.0	0.3	0.7	1.3	2.0	3.1
1d	0.0	0.1	0.3	0.8	1.4	2.3	3.5
2a	0.0	0.0	0.1	0.3	0.7	1.3	2.8
2b	0.0	0.1	0.4	0.8	1.5	2.4	3.5
2c	0.0	0.1	0.3	0.8	1.4	1.9	3.2
2d	0.0	0.1	0.3	0.7	1.3	2.0	3.3
3a	0.1	0.0	0.1	0.3	0.7	1.2	2.7
3b	0.0	0.1	0.5	1.0	1.9	3.0	4.4
3c	0.0	0.1	0.3	0.9	1.3	1.9	3.2
3d	0.0	0.1	0.2	0.8	1.3	1.8	3.1
4a	0.0	0.1	0.2	0.3	0.6	1.5	2.5
4b	0.0	0.1	0.4	0.8	1.5	2.4	3.5
4c	0.0	0.1	0.3	0.8	1.2	1.8	2.9
4d	0.0	0.1	0.3	0.8	1.3	1.8	3.2

* The C=C—C—C= angle in compounds **1** and **3**, C=C—C—N= in **2**, and C=N—C—N= in **4**.

The cyclic conjugated system in ylide derivatives of 1,4-dihydroazines involves seven π-electrons and, therefore, has a nonaromatic character. For these molecules, a planar conformation of the ring is not the most favorable. Therefore, it can be suggested that it is the nonaromatic character of the conjugated system that stabilizes a boat conformation of dihydroazine and determines its flexibility. In this case, a decrease in the polarity of the exocyclic double bond, which leads to an increase in the π-electron density on the endocyclic carbon atom and, therefore, to an increase in the degree of nonaromaticity of the cyclic conjugated system, should cause an increase in the flexibility of the heterocycle.

A comparison of the results of the calculations for 4-oxo and 4-methylene derivatives of 1,4-dihydroazines confirms this suggestion (see Table 1). A decrease in the polarity of the exocyclic double bond in the series C=O > C=NH > C=CH_2 results in an increase in the flexibility of the partially hydrogenated ring. The exceptions are molecules **1c** and **4c**, in which the heterocycles are more flexible as compared to those in methylene derivatives **1d** and **4d**.

The presence of the cyclic conjugated system in ylide derivatives of dihydroazines determines the difference in the conformational flexibility of their heterocycles (see Table 1). It is most clearly seen in the case of methylene derivatives **1d—4d**. The partially hydrogenated ring is most flexible in 4-methylene-1,4-dihydropyridazine **3d** and most rigid in molecule **1d**. Analogous results were

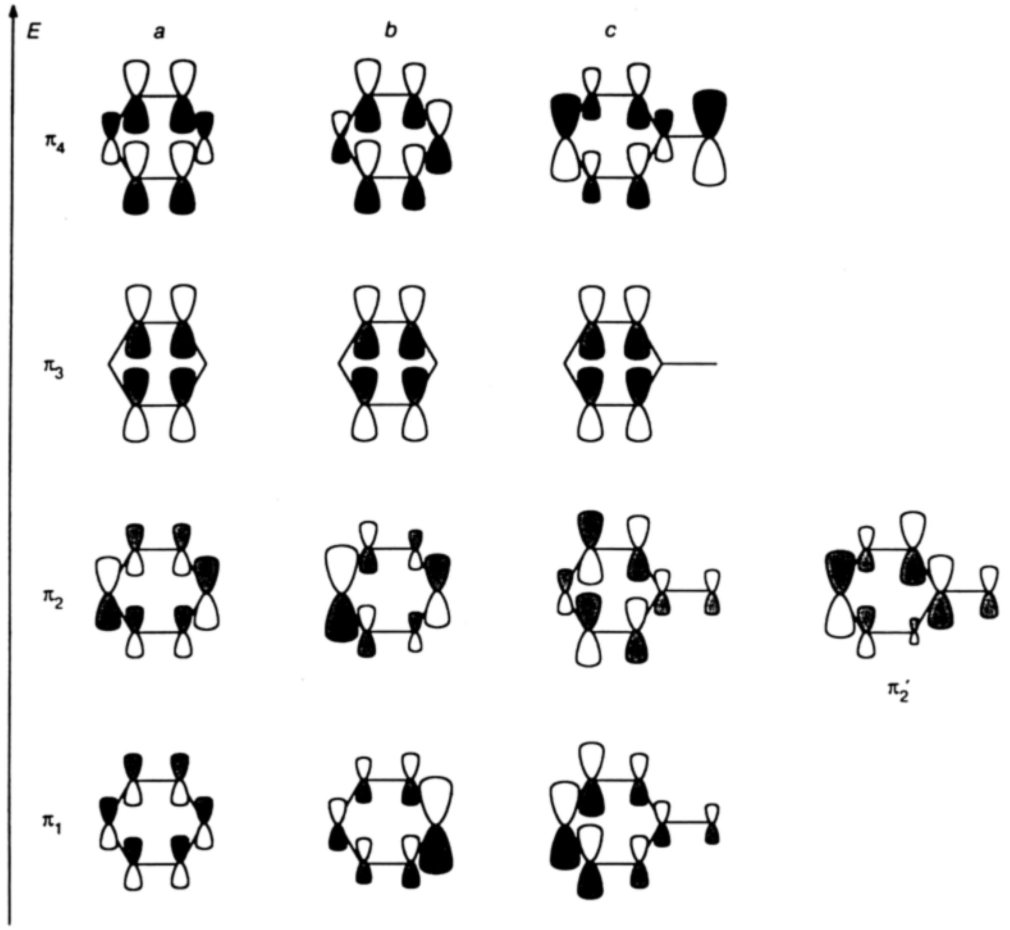


Fig. 1. General view of π-MOs in 1,4-cyclohexadiene (*a*), 1,4-dihydropyridine (*b*), and 4-oxo-1,4-dihydropyridine (*c*).

obtained also for oxo derivatives. Among the compounds with the exocyclic C=NH bond, molecules **2c** and **3c** have the most rigid heterocycles.

The similarity in characteristic features of the conformational behavior of 1,4-cyclohexadiene, 1,4-dihydroazines, and their ylide derivatives suggests that their π-electronic structures are similar. As in the case of 1,4-cyclohexadiene,[18—20] four π-MOs occur in molecules **1**—**4** (Fig. 1); these π-MOs are formed through the interaction between the bonding combination of the fragment π-orbitals of the double bonds with p_z-AO of the lone electron pair of the nitrogen atom of the NH group and either with the pseudo-π-orbital of the methylene group (in unsubstituted 1,4-dihydroazines) or with p_z-AO of the carbon atom of the exocyclic double bond.

In nitrogen heterocycles, π-MOs are substantially polarized as compared to π-MOs in 1,4-cyclohexadiene (see Fig. 1). However, the general form of MOs is retained. Therefore, the occurrence of the cyclic conjugated system in 1,4-dihydroheterocycle leaves the π-electronic structure of the molecule essentially unchanged, which apparently determines the similarity in the conformational behavior of these rings.

An increase in the number of nitrogen atoms in the ring causes a decrease in the energies of π-MOs (Table 2). An increase in the polarity of the exocyclic double bond exerts an analogous effect. Of note are some characteristic features of π_2-MO. In methylene derivatives **2d**—**4d**, this MO has a somewhat different type (the π_2' orbital in Fig. 1) as compared to those in 1,4-cyclohexadiene and other 1,4-dihydroazines, whereas in molecule **4d** this orbital has a slightly higher energy as compared to π_3-MO (see Table 2).

The presence of the cyclic conjugated system (or the quasi-cyclic conjugated system in unsubstituted 1,4-dihydroazines) makes it possible to characterize it in terms of aromaticity. The calculated Bird's aromaticity indices I_6 (see Table 2) qualitatively correlate with the change in the flexibility of molecules **1**—**4**. The use of the linear regression model gives the following equation:

$$E = 0.060 I_6 - 0.007;\ r = 0.83.$$

Because the overlap of p_z-AOs of the atoms is the governing factor determining the conformational flexibility of 1,4-dihydroheterocycles, it is possible to consider

Table 2. Energies of π-MOs (E_π/eV) and the aromaticity indices I_6 and $I_6(\pi)$ of molecules **1—4**

Compound	π_1	π_2	π_3	π_4	I_6	$I_6(\pi)$
1a	−15.2	−12.9	−10.2	−8.0	15.3	50.3
1b	−15.3	−13.6	−10.7	−8.9	29.0	68.9
1c	−14.8	−12.2	−10.5	−8.2	27.6	65.6
1d	−14.5	−11.3	−10.2	−7.5	27.8	64.5
2a	−15.5	−13.1	−11.1	−8.4	13.5	53.1
2b	−15.9	−13.9	−11.7	−9.6	23.4	68.2
2c	−15.4	−12.6	−11.4	−8.8	21.5	63.8
2d	−15.0	−11.9	−10.9	−7.9	26.2	63.4
3a	−15.7	−13.3	−11.3	−8.6	12.9	48.9
3b	−16.1	−14.1	−11.7	−9.4	27.1	68.1
3c	−15.7	−12.7	−11.4	−8.7	23.9	63.7
3d	−15.5	−11.7	−11.2	−8.1	23.0	61.6
4a	−16.0	−13.4	−12.1	−9.1	10.1	52.9
4b	−16.5	−14.2	−12.7	−10.4	18.4	67.3
4c	−15.9	−13.1	−11.6	−9.4	17.0	63.3
4d	−15.5	−12.0	−12.1	−8.4	18.7	62.3

the individual π components of the endocyclic bond orders (the orders of the bonds between p_z-AOs). The π-aromaticity indices $I_6(\pi)$ calculated with the use of these values are given in Table 2. In this case, the use of the linear regression model leads to a larger correlation coefficient:

$$E = 0.057 I_6(\pi) - 2.260;\ r = 0.87.$$

A comparison of the aromaticity indices I_6 and $I_6(\pi)$ with the energies of the bending of the ring suggests that the description of the conformational flexibility of 4-imino derivatives of 1,4-dihydroazines is somewhat inaccurate within the framework of the AM1 method. When these compounds are excluded from the regression analysis, the correlation coefficients for both I_6 and $I_6(\pi)$ increase:

$$E = 0.064 I_6 - 0.120;\ r = 0.88.$$

$$E = 0.059 I_6(\pi) - 2.367;\ r = 0.91.$$

The results indicate that the π-aromaticity indices $I_6(\pi)$ are best suited for the qualitative description of the conformational flexibility of 1,4-dihydroazines and their 4-ylide derivatives.

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