Conformational flexibility of six-membered 1,2-dihydrocycles based on the results of AM1 calculations

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The conformational flexibility of 2*H*-pyran, 1,2-dihydropyridine, 2*H*-thiopyran, their oxo, imino, and methylene derivatives, and the 5-oxo, imino, and methylene derivatives of 1,3-cyclohexadiene was studied by the semiempirical quantum-chemical AM1 method. All compounds have planar equilibrium conformations and similar electronic structures. The transition to a distorted sofa conformation with the =C—X—C(=Y)—C= torsion angle (X = CH_2, NH, O, or S; Y = H_2, O, NH, or CH_2) of ±20° increases the energy of the molecule by less than 1.5 kcal mol^{-1}. The reasons for the high conformational flexibility of these dihydrocycles were analyzed. The nonaromatic character of the cyclic π-system is the factor that determines the conformational flexibility of the dihydrocycle in ylide derivatives.

Key words: 1,3-cyclohexadiene, 2*H*-pyran, 2*H*-thiopyran, 1,2-dihydropyridine, oxo, imino, and methylene derivatives, conformational analysis, conformational flexibility, AM1 method.

Six-membered dihydrocycles enter into the composition of important natural compounds. Many of these compounds exhibit high biological activity.[1] Studies of the conformational behavior of dihydrocycles[2—6] have demonstrated that they can readily change conformation without a substantial increase in the energy of the molecule. Using 1,4-dihydrocycles[5] as examples, it has been established that conformational flexibility is typical of a partially hydrogenated ring regardless of the nature of substituents and the conjugated system. Analogous results were obtained for some 1,2-dihydrocycles.[6] Thus, it has been demonstrated previously[7] that the 1,2-dihydropyrimidine ring in cytosine, isocytosine, and guanine exhibits high conformational flexibility.

The aim of this work is to study systematically the conformational flexibility of six-membered 1,2-dihydrocycles containing heteroatoms and exocyclic double bonds.

Calculation procedure

The equilibrium conformations of molecules **1—15** were calculated by the semiempirical quantum-chemical AM1 method[8] with full optimization of geometry. The conformational flexibility of the dihydrocycles was studied by scanning the =C—X—C(=Y)—C= torsion angle in the range of ±30° with a step of 10° and with full optimization of the other geometric parameters of the molecules.

Bird's aromaticity indices[9] (I_6) were calculated using the following formulas:

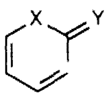
$$I_6 = 100(1 - V/V_k),$$

$$V = (N/100n)\Sigma(N_i - N_0)^2,$$

where N_i is the order of the *i*-th bond, N_0 is the average bond order in the ring, and *n* is the number of bonds in the ring. The value of V_k was determined analogously to V, but in this case, the fully localized model of the molecule was considered. The aromaticity index for the benzene molecule calculated by this method is equal to 100. Pozharsky's aromaticity indices[10] were calculated using the following formula:

$$\Delta\bar{N} = (1/n)\Sigma(N_i - N_j),\ i < j,$$

where N_i and N_j are the orders of different bonds in the ring. The value of $\Delta\bar{N}$ for the benzene molecule is equal to 0.



Compound	X	Y	Compound	X	Y
1	CH_2	O	**8**	NH	H_2
2	CH_2	NH	**9**	NH	O
3	CH_2	CH_2	**10**	NH	NH
4	O	H_2	**11**	NH	CH_2
5	O	O	**12**	S	H_2
6	O	NH	**13**	S	O
7	O	CH_2	**14**	S	NH
			15	S	CH_2

Results and Discussion

The equilibrium conformations of dihydrocycles in 2*H*-pyran, 2*H*-thiopyran, 1,2-dihydropyridine, and

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5-ylide derivatives of 1,3-cyclohexadiene are determined by two groups of opposite factors. The first group involves conjugation and 1,2-allylic strain, which stabilize the planar equilibrium conformation. The second group of factors involves the bending strain occurring owing to the deformation of the endocyclic bond angle at the saturated carbon atom in the planar conformation. The results of calculations of equilibrium conformers **1—4**, **8**, and **12** demonstrated that the dihydrocycle is nearly planar (the torsion angles are no more than 3°).

However, the opposite groups of factors determining the conformations of the dihydrocycle results in high conformational flexibility of the partially hydrogenated ring. A change in the =C—X—CH$_2$—C= torsion angle (X = C=O, C=NH, C=CH$_2$, O, NH, or S) by ±30° increases the energy of the molecule by less than 1 kcal mol^{-1} (Table 1). The most flexible and the most rigid rings occur in 2*H*-pyran **4** and 1,2-dihydropyridine **8**, respectively. Among the 5-ylide derivatives of 1,3-cyclohexadiene, oxo and methylene-substituted compounds have close energies of the bending of the ring. The substantially lower value of the energy for compound **5** is, apparently, underestimated. Similar overestimation of the conformational flexibility of the dihydrocycle in compounds with an exocyclic C=NH bond was obtained previously for derivatives of 1,4-dihydroazines.[5]

The replacement of the methylene group in 2*H*-pyran, 2*H*-thiopyran, and 1,2-dihydropyridine by an exocyclic double bond results in the disappearance of the bending strain that stabilizes a nonplanar conformation of the dihydrocycle However, as in the case of 1,4-dihydroazines,[5] the partially hydrogenated ring remains conformationally flexible. The transition from a planar equilibrium conformation to a distorted sofa conformation (Fig. 1) with a =C—X—C(=Y)—C= torsion angle of ±20° causes the energy to change less than 2 kcal mol^{-1}. For comparison, an analogous distortion of the pyridine ring causes an increase in the energy of more than 8 kcal mol^{-1}.[11]

Table 1. Changes in the energies (ΔE/kcal mol^{-1}) with bending of the ring and the aromaticity indices for compounds **1—15**

Compound	ΔE at torsion angle/deg				Aromaticity indices			
	0	10	20	30	I_6	$\Delta\bar{N}$	$I_6(\pi)$	$\Delta\bar{N}(\pi)$
1	0.12	0.03	0.35	0.99	11.8	1.19	51.3	0.99
2	0.0	0.01	0.18	0.50	13.0	1.17	49.1	1.01
3	0.0	0.08	0.33	0.86	14.9	1.15	50.1	1.01
4	0.0	0.04	0.22	0.62	16.5	1.15	50.2	1.03
5	0.0	0.31	1.27	2.93	25.8	1.04	68.0	0.73
6	0.0	0.16	0.66	1.56	24.0	1.05	63.0	0.81
7	0.0	0.18	0.73	1.74	23.0	1.05	60.8	0.84
8	0.0	0.03	0.37	1.08	20.3	1.12	53.4	0.99
9	0.0	0.44	1.66	3.75	36.1	0.92	74.5	0.63
10	0.0	0.28	0.92	2.16	33.8	0.94	70.3	0.73
11	0.0	0.21	0.90	2.19	32.2	0.95	68.2	0.75
12	0.0	0.02	0.27	0.74	18.5	1.12	49.1	1.06
13	0.0	0.33	1.34	3.08	29.2	0.99	70.0	0.69
14	0.0	0.19	0.78	1.88	26.7	1.03	64.4	0.80
15	0.0	0.20	0.84	2.02	26.3	1.01	62.1	0.83

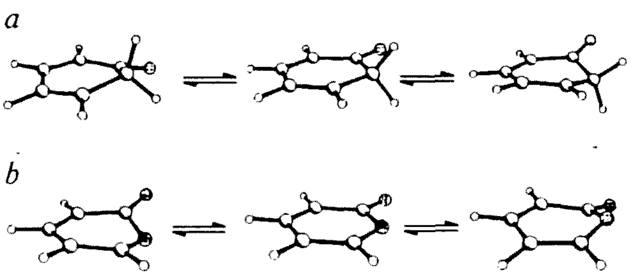

Fig. 1. Conformational changes in 5-oxo-1,3-cyclohexadiene (*a*) and 2-oxopyran (*b*).

Previously,[5,6] it was demonstrated that the nonaromatic character of the cyclic π-system could destabilize the planar conformation of a dihydrocycle. Actually, the conjugated systems in the rings of ylide derivatives **5—7**, **9—11**, and **13—15** involve seven π-electrons. A decrease in the polarity of the exocyclic double bond leads to an increase in the π-electron density in the ring and, therefore, to an increase in the nonaromaticity of the conjugated system, which, in turn, should lead to an increase in the conformational flexibility of the dihydrocycle. The results of calculations by the AM1 method confirmed this suggestion (Table 1). In imino derivatives, as in the case of 1,4-dihydrocycles, the change in the energy that occurs with bending of the ring is evidently underestimated.

The π-electronic structures of molecules **1—15** are in principle similar (Fig. 2). All molecules have four 4π-MOs formed by the p$_z$-AOs of the atoms of the double bonds, the AO of the lone electron pair of the heteroatom, and the fragment pseudo-π-orbital of the methylene group. Replacement of the methylene group by a heteroatom or by an exocyclic double bond results only in a change in the polarization of the above-mentioned MOs, but their symmetry remains basically the same.

The similarity of the π-electronic structures of molecules **1—15** makes it possible to use the concept of the degree of aromaticity to describe the conjugated systems in all the compounds under consideration. The Bird's (I_6) and Pozharsky's ($\Delta\bar{N}$) aromaticity indices calculated with the use of the endocyclic bond orders are given in Table 1. The use of the linear regression model to search for the relationship between the change in the energy as the ring bends (ΔE_{30}) and the aromaticity indices gave the following equations:

$$\Delta E_{30} = -0.874\ I_6 + 0.111, \qquad r = 0.86,$$

$$\Delta E_{30} = 11.878\ \Delta\bar{N} - 9.576, \qquad r = 0.86.$$

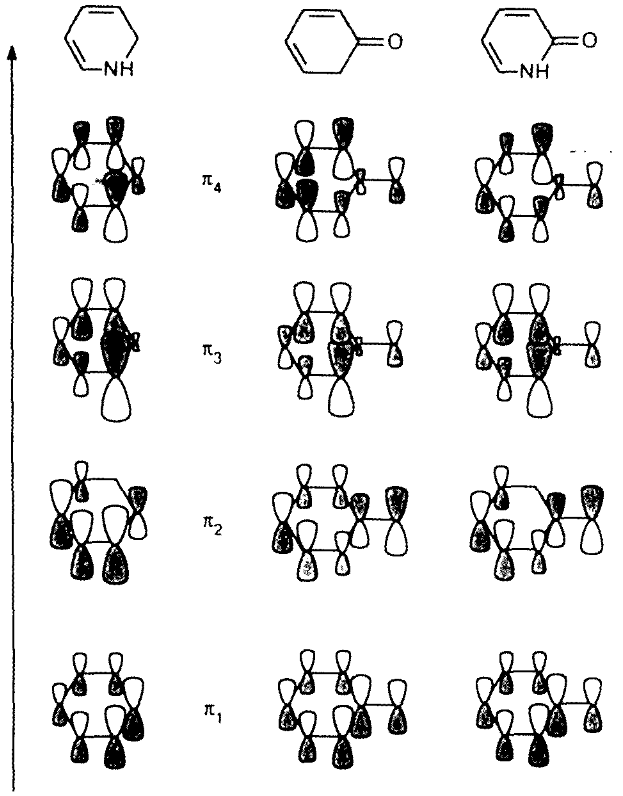

Fig. 2. General view of the π-MOs in 1,2-dihydropyridine, 5-oxo-1,3-cyclohexadiene, and 2-oxo-1,2-dihydropyridine.

The results confirmed the suggestion that the conformational flexibility of the dihydrocycle in the imino derivatives calculated by the AM1 method is overestimated. When these compounds are excluded from the regression analysis, the correlation coefficients increase:

$$\Delta E_{30} = -1.082\ I_6 + 0.125, \quad r = 0.89,$$

$$\Delta E_{30} = 13.021\ \Delta\bar{N} - 10.541, \quad r = 0.88.$$

Because a change in the conformation of the dihydrocycle primarily disrupts the overlap of the p_z-AOs of the atoms of the ring, it is reasonable to consider the π-components of the total bond orders. The aromaticity indices $I_6(\pi)$ and $\Delta\bar{N}(\pi)$ calculated with the use of the bond orders between the p_z-AOs of the atoms of the ring are given in Table 1. In this case, the use of the linear regression model gives the following equations:

$$\Delta E_{30} = -4.426\ I_6(\pi) + 0.102, \quad r = 0.94,$$

$$\Delta E_{30} = 7.356\ \Delta\bar{N}(\pi) - 6.529, \quad r = 0.95,$$

When the imino derivatives are excluded, the equations are as follows:

$$\Delta E_{30} = -4.845\ I_6(\pi) + 0.111, \quad r = 0.98,$$

$$\Delta E_{30} = 7.741\ \Delta\bar{N}(\pi) - 6.821, \quad r = 0.98.$$

The substantially higher correlation coefficients indicate that, as in the case of 1,4-dihydrocycles, the indices $I_6(\pi)$ and $\Delta\bar{N}(\pi)$, are more suitable for describing the relationship between the conformational flexibility of the six-membered dihydrocycle and the degree of aromaticity. The results of calculations allow also the conclusion that conformational flexibility is a common property of six-membered dihydrocycles regardless of the mutual arrangement of the double bonds and the presence of substituents, heteroatoms, and saturated carbon atoms.

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