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Conformational Flexibility of 1,4-Dihydroazines

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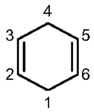
According to semiempirical quantum chemical AM1 calculations, dihydroazine molecules possess high conformational flexibility.

Various dihydroazine derivatives have recently attracted great attention, mainly due to their wide range of biological activity (cardiotonic, tocolithic, antioxidant, *etc.*[1–3]). Thus, the spatial structure and conformational behaviour of these molecules is very important for an understanding of the mechanism of their biological action.

Earlier, by theoretical[4] and experimental[5] methods, it was established that the 1,4-cyclohexadiene **1** molecule (the carbocyclic analogue of dihydroazines) exhibits a high conformational flexibility which is manifested in a change in the angle between the plane of the double bonds. The behaviour of **1** is defined by the opposing factors determining the dihydrocycle conformation: on the one hand the bending strain at the saturated carbon atoms which is at a maximum in the planar conformation, and, on the other hand, the 1,2-allylic strain which tends to flatten the molecule.[4]

Instead of two allylic interactions 1,4-dihydroazines have another flattening factor, *viz.* the conjugation between the lone electron pair of the bridging nitrogen atom and the π-systems of adjoining double bonds. However, the opposing effects which determine the equilibrium conformation of the dihydrocycle, are retained. Earlier,[6] based on the molecular mechanics calculations, we demonstrated the great conformational flexibility of 1,4-dihydropyridine **2**. However, it was not clear whether flexibility is a common property of all 1,4-dihydroazines. In the present communication we have studied the flexibility of dihydrocycles of 1,4-dihydropyridine **2**, 1,4-dihydropyrimidine **3**, 1,4-dihydropyridazine **4**, 1,4-dihydropyrazine **5** and 1,4-dihydro-1,3,5-triazine **6** by AM1 semiempirical quantum chemical methods.[7] The results of the calculations are shown in Table 1.

The equilibrium conformation of the dihydrocycles in all molecules studied is an irregular boat, approaching a sofa in the molecule **6** (Table 1). The bridging nitrogen atom has a pyramidal configuration and is displaced from the plane of the non-hydrogen atoms of the double bonds more than the saturated carbon atom. This result agrees well with non-empirical calculations on the spatial structure of 1,4-dihydropyridine.[8,9]



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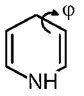

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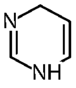

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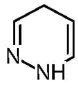

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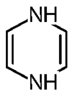

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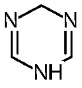

6

It is interesting to note that the asymmetry of the non-bonded interactions with participation of the methylene group (there is only one 1,2-allylic interaction) in molecules **3** and **4** does not lead to twisting of the equilibrium conformation. Such behaviour of these molecules is observed

Table 1 Geometry of molecules **2**–**6** calculated by the AM1 method.

Parameters	Compounds				
	2	**3**	**4**	**5**	**6**
Bond length/A					
1–2	1.402	1.414	1.344	1.418	1.415
2–3	1.349	1.295	1.304	1.378	1.297
3–4	1.486	1.446	1.501	1.418	1.461
4–5	1.486	1.494	1.488	1.418	1.462
5–6	1.349	1.351	1.350	1.358	1.298
1–6	1.402	1.403	1.419	1.418	1.415
Bond angles/°					
1–2–3	122.8	126.7	119.8	122.7	125.7
2–3–4	122.2	119.1	125.9	122.9	117.6
3–4–5	122.2	115.6	110.6	113.8	118.9
4–5–6	122.1	120.6	120.6	122.8	117.6
5–6–1	122.9	121.4	121.6	122.7	125.2
2–1–6	116.7	115.9	119.7	113.9	115.1
Torsion angles/°					
3–2–1–6	−10.2	−9.5	−14.0	8.8	7.4
2–1–6–5	10.4	9.1	13.9	−8.8	−6.6
2–3–4–5	5.0	3.9	5.8	−8.5	0.0
3–4–5–6	−4.8	−3.8	−5.7	8.5	0.5

only if the amplitudes of the out-of-plane vibrations are sufficiently high (about 20°), but the angle between the double bonds does not exceed 3–4°.

The flexibility of the dihydrocycles was studied by scanning the torsion angle φ with full optimization of the remaining geometrical parameters of the molecules, for every point. For all molecules studied, two energy minima were established with rather low (< 0.3 kcal mol^{-1}) barriers in molecules **2**–**4** and **6**.

The greater barrier in 1,4-dihydropyrazine **5** is due to the antiaromatic nature of its π-system which results in dramatic destabilization of the planar conformation. At the same time, increasing the angle between the double bond planes by 15° leads to an increase in energy of less than 0.8 kcal mol^{-1} for all molecules studied.

It is interesting to note that decreasing of allylic strain in the series 1,4-dihydropyridine, 1,4-dihydropyrimidine, 1,4-dihydropyridazine, 1,4-dihydropyrazine and 1,4-dihydro-1,3,5-triazine does not lead to an unflattening of the equilibrium conformation of the dihydrocycle and an increase in its flexibility. This is probably because of a simultaneous decrease of bending strain at the saturated carbon atom caused by a change in the easily deformed adjacent bond angles C=N–C (sp^3).

Thus, high conformational flexibility is the common feature of 1,4-dihydroazines. The amplitude of the out-of-plane vibrations does not depend on the number and mutual disposition of the nitrogen atoms in the ring (except for antiaromatic 1,4-dihydropyrazine). The data obtained show that molecules of biologically active derivatives of 1,4-dihydroazines are prone to a facile change of dihydrocycle conformation, thus creating more favourable conditions for interactions with a relevant biological receptor.

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