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Short Communication

Conformational Flexibility of 1,4-Dihydroazine Carbonyl Derivatives

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Summary. The molecular geometry of 4-oxo derivatives of 1,4-dihydropyridine, 1,4-dihydropyrimidine, 1,4-dihydropyridazine, and 1,4-dihydro-1,3,5-triazine has been calculated by the semi-empirical quantum-chemical AM1 method. It could be shown that the dihydrocycle in these compounds is not conformationally rigid. Changing the angle between the endocyclic double bond planes $\pm 15°$ causes less than 1 kcal/mol increase of energy.

Keywords. 1,4-Dihydroazines; Carbonyl derivatives; Conformational flexibility.

Konformative Flexibilität von 1,4-Dihydroazin-carbonyl-Derivaten (Kurze Mitt.)

Zusammenfassung. Die molekulare Geometrie von 4-Oxo-Derivaten von 1,4-Dihydropyridin, 1,4-Dihydropyrimidin, 1,4-Dihydropyridazin und 1,4-Dihydro-1,3,5-triazin wurde mittels der semiempirischen quantenchemischen AM1-Methode berechnet. Es konnte gezeigt werden, daß der zweifach hydrierte Ring in diesen Verbindungen nicht starr ist. Eine Änderung des Winkels zwischen den Ebenen der endocyclischen Doppelbindungen um $\pm 15°$ bewirkt eine Energieerhöhung von weniger als 1 kcal/mol.

Introduction

Interest in the structural and conformational characteristics of 1,4-dihydroazines and their derivatives is due to the wide range of biological activity of these compounds [1–3]. Investigation of the molecular structure and conformational behavior of these molecules is important for understanding the mechanism of their biological action. On the other hand, 1,4-dihydro derivatives of azines attract attention from the theoretical viewpoint as well. These compounds containing saturated and unsaturated fragments are very convenient models for the study of such phenomena as the influence of substituents on the imine-enamine tautomeric equilibrium state [4], interactions between double bonds through a methylene group [5, 6], mechanism of oxidation [7], *etc.*

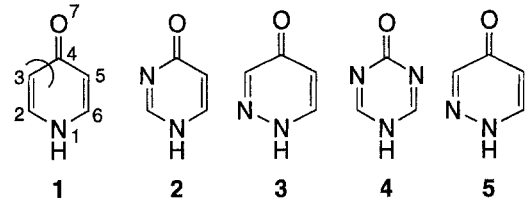
Recently we reported the high conformational flexibility of the dihydrocycle in all 1,4-dihydroazines [8]. This flexibility is determined by the presence of two groups of opposing factors influencing on the conformation of heterocycle.

1) conjugation between the π-systems of the two double bonds and the lone pair of the imino group nitrogen atom and 1,2-allylic strain along Csp^2–Csp^3 bonds and
2) bending strain caused by the deformation of the endocyclic bond angle at the saturated carbon atom in the planar conformation.

The factors summarized under 1) are minimal in the planar conformation of dihydrocycle; the bending strain one stabilizes the non-planar boat conformation. In the 4-oxo derivatives of the 1,4-dihydroazines, the saturated carbon atom is absent. Therefore, the factor stabilizing the non-planar conformation disappears, and the dihydrocycle has to be conformationally rigid.

Results and Discussion

We have studied the conformational flexibility of the dihydrocycle in 4-oxo-1,4-dihydropyridine (**1**), 4-oxo-1,4-dihydropyrimidine (**2**), 4-oxo-1,4-dihydropyridazine (**3**) and 4-oxo-1,4-dihydro-1,3,5-triazine (**4**). All calculations have been carried out by the semi-empirical quantum-chemical method AM1 [9].



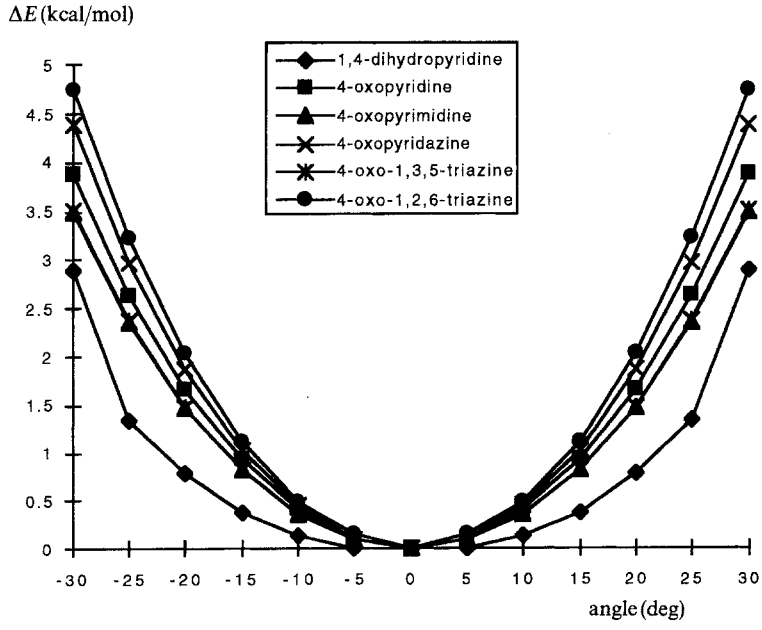


Fig. 1. Dependence of energy changes from the f torsion angle for 1,4-dihydropyridine and **1**–**5**

Table 1. Molecular geometry of **1**–**5** calculated by AM1 method (Å, deg.)

	1	**2**	**3**	**4**	**5**
1–2	1.383	1.397	1.325	1.401	1.334
2–3	1.361	1.305	1.315	1.306	1.319
3–4	1.464	1.429	1.486	1.447	1.483
4–5	1.464	1.479	1.461	1.446	1.483
5–6	1.362	1.361	1.366	1.306	1.319
1–6	1.383	1.388	1.391	1.400	1.334
4–7	1.243	1.241	1.238	1.238	1.233
1–2–3	122.0	126.0	118.9	124.6	117.9
2–3–4	121.2	118.5	124.7	117.4	123.0
3–4–5	114.4	117.1	112.9	119.8	111.3
4–5–6	121.2	120.1	119.6	117.4	123.0
5–6–1	121.9	120.6	120.8	124.6	117.9
6–1–2	119.3	117.7	123.1	116.2	126.9
3–4–7	122.8	120.6	122.4	120.1	124.3

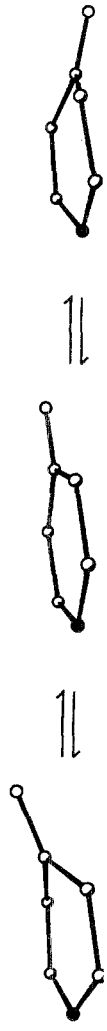


Fig. 2. Conformational change of 4-oxo-1,4-dihydropyridine

Conformational flexibility has been studied by a scan of the f angle in the range of $\pm 30°$ with geometry optimization at each point. The results of the calculations are shown in Fig. 1 and Table 1.

The equilibrium conformation of the dihydrocycle in all molecules is planar. As anticipated, molecules **1**–**4** possess more conformational rigidity than the 1,4-dihydroazines (Fig. 1). However, the dihydrocycle in these compounds is not as rigid as in aromatic rings. The transition from the planar conformation to the unsymmetrical boat form (Fig. 2) with the f angle in the bounds of $\pm 15°$ causes an energy increase of less than 1 kcal/mol. This result is unexpected because the bending strain stabilizing the boat conformation is absent in molecules **1**–**4**. Thus, deformation of the endocyclic bond angle is not the sole factor favouring the non-planar structure of the dihydrocycles.

Among the 4-oxo derivatives of the 1,4-dihydroazines, molecule **2** possesses the most conformational flexibility. The most rigid dihydrocycle is that of 4-oxo-1,4-dihydropyridazine (**3**). Evidently, such differences in the conformational flexibility of the heterocycle in molecules **1**–**4** can be explained only by features of the π-electronic interactions between different fragments of the molecules. In the 4-oxo-1,4-dihydropyridazine **3**, the electron-donating imino group is connected to the nitrogen atom of the C=N double bond. Such an arrangement increases the electron-withdrawing property of the azomethine group which is confirmed by shorter N–N bonds as compared with C–N (Table 1). Thus, this leads to a stronger π–π interaction between these fragments than in other molecules. Investigation of the conformational flexibility of 4-oxo-1,4-dihydro-1,2,6-triazine (**5**) confirms this assumption. In this molecule, the imino group is connected to the two nitrogen atoms of the C=N double bonds, and the molecule possesses the most conformational rigidity.

Analysis of the data obtained leads to the conclusion that the conformational flexibility of the 4-oxo derivatives of 1,4-dihydroazines is determined by their electronic structure and, perhaps, is a general property of all partly hydrogenated six-membered rings.

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