The effect of the azole ring on the conformational mobility of the dihydropyrimidine ring in 4,7-dihydroazolo[1,5-*a*]pyrimidines as judged from MNDO calculations

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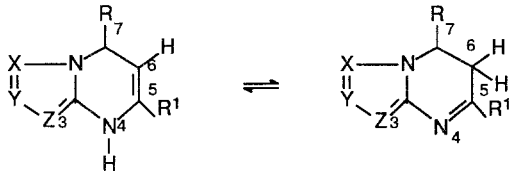
The equilibrium geometries of 4,7-dihydropyrazolo[1,5-*a*]pyrimidine, 4,7-dihydrotetrazolo[1,5-a]pyrimidine, 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine, and 1,4-dihydropyrimido[1,2-*a*]imidazole were calculated by the semiempirical quantum-chemical MNDO method. The dihydropyrimidine ring exhibits high conformational mobility in all of these compounds. The change in the energy occurring in the transition of the molecule to the boat conformation with an angle between the planar fragments of ±20° does not exceed 1 kcal mol^{-1}. The mobility of the dihydro ring increases as interactions between the π-systems of the azole ring and the C=C double bond separated by an imino group and a methylene bridge decrease.

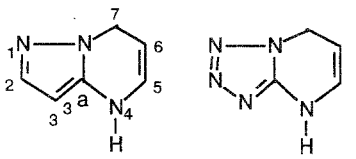
Key words: 4,7-dihydroazolopyrimidines, MNDO method, electronic structure, conformational mobility.

Derivatives of dihydroazolopyrimidines have attracted increasing interest in recent years due, first of all, to the fact that they possess a broad range of biological activity (cardiovascular, tocolythic, antioxidant, etc.).[1,2] Investigation of the spatial structure and conformational behavior of these compounds is important for understanding the mechanism of their physiological action. In addition, dihydro derivatives of azolopyrimidines exist in solution as mixtures of enamine (**A**) and imine (**B**) tautomers.[3] It was noted previously[4] that the position of the tautomeric equilibrium can depend on steric effects of the substituents.

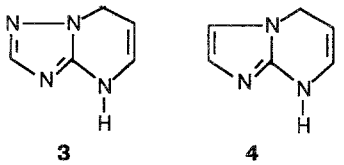


A **B**

In the present work we have analyzed the conformational characteristics of the enamine forms of four dihydroazolopyrimidines (**1**—**4**) with various azole rings.



1 **2**



3 **4**

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The procedure of the calculations

The equilibrium geometry and the electronic structure of compounds **1—4** were calculated by the MNDO[5] method with full optimization of the structural parameters. To determine the mobility of the dihydropyrimidine ring, the C(3a)—N(8)—C(7)—C(6) torsion angle was varied from 0 to 30° at 5° intervals, and the other bond lengths and angles of the molecule were optimized at each point. Interactions through space (TSI) and through bond (TBI)[6] were characterized by the sums of the energies of two-electron interactions between the p_z orbitals of the C(3a), N(8), and C(5), C(6) atoms for TSI and of the C(3a), N(8), C(5), C(6) and N(4), C(7) atoms for TBI.

Results and Discussion

The equilibrium conformation of the dihydropyrimidine ring is determined by two factors acting in opposite directions: 1) the allylic strain and conjugation that try to make the molecule planar and 2) the angular strain of saturated carbon atom, which is maximum in the planar conformation. According to the calculations, at the potential energy minimum, the dihydro cycle in compounds **1—4** is planar. However, the dihydropyrimidine ring can readily turn into a boat conformation. A ±20° change in the C(3a)—N(8)—C(7)—C(6) angle causes an increase in energy of less than 1 kcal mol^{-1} (Fig. 1). Thus, the dihydropyrimidine ring in compounds **1—4** possesses high conformational mobility.

The plots of energies *versus* the C(3a)—N(8)—C(7)—C(6) torsion angles (Fig. 1) for compounds **1—4** indicate that the mobility of the partially hydrogenated ring is substantially affected by the type of the five-membered heterocycle. Molecule **4** is the most mobile, and structure **1** is the most rigid. Since the steric influence of all of the azole rings considered is approximately equal, this distinction most likely results from electronic effects. Since the NH—C=C enamine fragment as a whole has an electron-donating character, its conjugation with the azole ring should increase in the series **1—4—3—2**, *i.e.*, as the acceptor properties of the azole ring increase. The factors flattening the molecule become more pronounced and, hence, the rigidity of the ring increases. However, the results obtained are not fully consistent with this inference.

The mobility of the dihydropyrimidine ring also can not be explained by the Coulomb repulsion between the similarly charged atoms of the azole ring and the C=C double bond, since the calculated charges (Fig. 2) imply the strongest repulsion in the case of compound **4**, which exhibits the highest mobility. However, the π-systems of the double bond and the azole ring can interact not only through the bridging N(4) atom, but also through the pseudo π-orbital of the methylene group (TBI) or directly through space (TSI).[6] Estimations (Table 1) showed that the TSI effects for compounds **1—4** are negligibly small.

Interaction through bonds depends essentially on the mutual orientation of the orbitals, *i.e.*, on the conformation of the dihydro ring. It is maximum when the molecule is planar, and thus it favors flattening of the

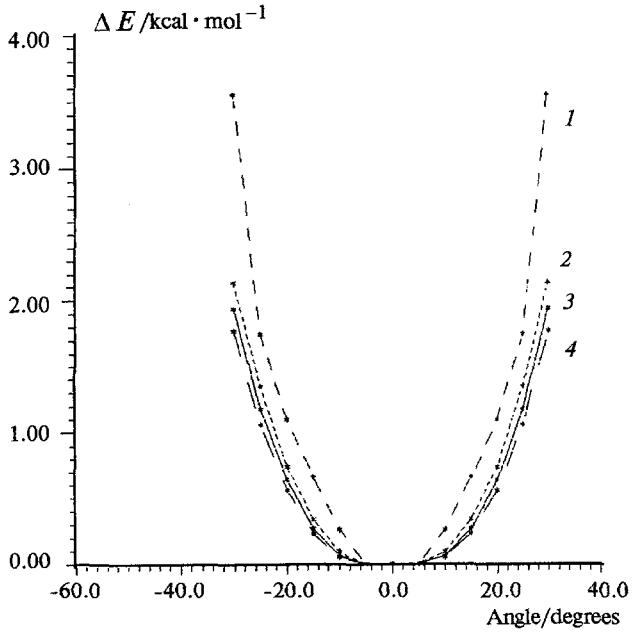

Fig. 1. The plot of energy *vs* the C(3a)—N(8)—C(7)—C(6) torsion angle for compounds **1—4** .

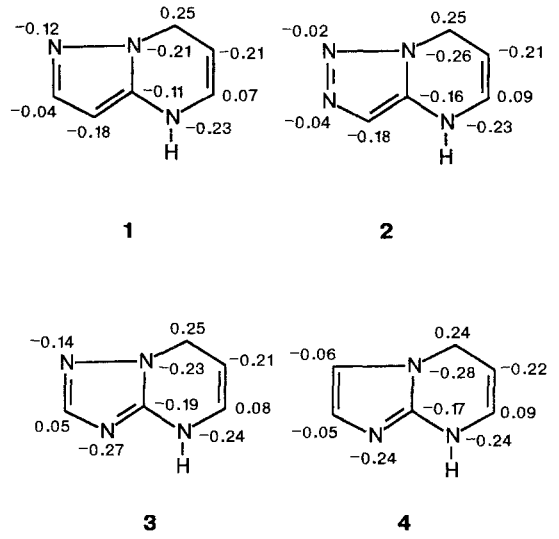

Fig. 2. Charge distribution in 4,7-dihydroazolopyrimidines.

Table 1. The TSI and TBI magnitudes (eV) for 4,7-dihydroazolopyrimidines

Characteristic	**1**	**2**	**3**	**4**
TSI	0.01	0.01	0.01	0.01
TBI	2.56	2.09	2.04	2.01

molecule. From Table 1 it can be seen that the energy of TBI decreases over the series **1—4**, in parallel with the change in the conformational mobility of the dihydropyrimidine ring in these compounds. This allows one to conclude that interactions through valent bonds are the crucial factor determining the conformational mobility of this ring in 4,7-dihydroazolopyrimidines.

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