The effect of substituents on the conformational mobility of the heterocycle in 1,4-dihydropyrimidine and its derivatives

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The equilibrium geometry of 1,4-dihydropyrimidine, 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine, and their alkyl (Me, Et, Pr^i, Bu^t) and phenyl derivatives has been calculated by molecular mechanics method. The equilibrium conformation of unsubstituted molecules is planar, but it is easily transformed to the boat conformation with a small change in the conformational energy. The effect of substituents on the geometry and conformational mobility of the dihydropyrimidine ring has been studied.

Key words: 1,4-dihydropyrimidine, 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine, conformational analysis, molecular mechanics, conformational mobility, partially hydrogenated heterocycles.

Unlike structurally uniform (completely saturated or aromatic) nitrogen-containing heterocycles, for which the regularities of the molecular geometry and conformational characteristics have been properly studied,[1,2] partially hydrogenated derivatives of azines have not been systematically studied in this respect until recently. These compounds, incorporating both saturated and unsaturated parts, are rather convenient models for investigating the relationship between conjugation and conformation and for comparing the roles of steric and electronic factors in the conformational behavior of molecules. The conformational characteristics of these compounds are of great importance in connection with the problems of the tautomerism of dihydroazines,[3,4] specifically, for determining factors that stabilize one or another tautomer.

Study of the spatial structure of dihydroazines is also of interest from the practical viewpoint, since many of them possess a wide range of biological activity (cardiovascular, tocolytic, antioxidant, etc.[5,6]).

The present work is devoted to the conformational analysis of 1,4-dihydropyrimidine, 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine, and their alkyl and phenyl derivatives by the MMP2 molecular mechanics method[7] modified for calculation of nitrogen-containing heterocycles.[8]

The missing force field parameters were fitted using literature data on the experimentally determined molecular geometry and rotation barriers for a series of model compounds. As the initial approximation, we used parameters for hydrocarbon analogs from the standard force field of method. The values fitted as the parameters are listed in Table 1.

The conformation of the dihydropyrimidine ring was described by the puckering parameters,[9] where s is the degree of puckering of the ring, and θ and φ are polar angles characterizing the type of conformation.

The results of the calculations are given in Tables 2 and 3.

Results and Discussion

The conformation of the 1,4-dihydropyrimidine ring in the compounds under consideration is determined, on the one hand, by the 1,2-allylic strain and conjugation that try to make the molecule planar and, on the other hand, by the bending strain at the saturated carbon atom, which is maximum in the planar conformation.

The former two factors obviously prevail, since the equilibrium conformation of the dihydro cycle in unsubstituted molecules **1** and **6** is planar. However, the existence of the two oppositely directed factors, which determine the spatial structure of the dihydro cycle, causes high conformational mobility of the partially hydrogenated ring. Transition of the dihydropyrimidine ring to a boat conformation with a $\pm 30°$ variation in the dihedral angle between the planes of the double bonds results in an increase in the conformational energy of less than 1 kcal mol^{-1}. A study of the dependence of the conformational energy of the molecule on the C(2)—N(3)—C(4)—C(5) (α_2) and N(3)—C(2)—N(1)—C(6) (α_1) torsion angles (Fig. 1) showed that the ring-puckering

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Table 1. Additional parameters of force field potentials of molecular mechanics for dihydroazines

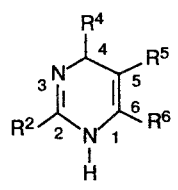
Bond	k_s/mdyn Å^{-1}	l_0/Å
1—37	3.0	1.44
1—9	3.4	1.45

Bond angle	k_B/mdyn deg^{-1}	θ_0/deg
1—37—20	0.5	127.5
1—37—2	0.55	114.0
1—2—37	0.55	115.1
37—1—1	0.5	108.0
2—9—1	0.35	120.0
9—2—37	0.5	126.0
9—1—1	0.6	110.0
9—1—2	0.45	109.0
9—1—5	0.5	109.0
9—37—20	0.45	122.0
37—9—1	0.65	117.0
9—2—9	0.6	120.0
37—1—2	1.0	110.0
9—2—1	1.4	116.5

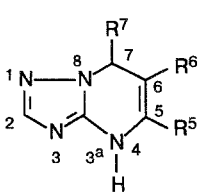
Torsion angle	Torsion constants / kcal mol^{-1}		
	V_1	V_2	V_3
37—2—1—1	0.0	0.0	−0.2
37—1—1—1	0.0	0.0	0.2
2—37—1—1	0.0	0.0	−0.2
37—2—37—1	0.0	15.0	0.0
20—37—1—5	0.0	0.0	0.0
2—9—1—1	0.0	0.0	−0.46
2—9—1—5	0.0	0.0	−0.1
2—2—9—1	0.0	15.0	0.0
1—9—1—5	0.0	0.0	0.2
37—9—1—1	0.0	0.0	−0.1
9—37—2—1	0.0	15.0	0.0
2—37—9—1	0.0	15.0	0.0
1—9—37—20	0.0	0.0	0.0

Torsion angle	Torsion constants / kcal mol^{-1}		
	V_1	V_2	V_3
2—9—37—20	0.0	0.0	0.0
37—9—2—9	0.0	15.0	0.0
9—2—9—23	0.0	15.0	0.0
9—1—2—5	0.0	0.0	0.2
37—1—2—2	0.0	0.03	0.5
2—37—1—2	0.7	0.0	1.5
5—1—37—20	0.0	0.0	0.0
2—9—2—1	0.0	15.0	0.0
1—2—9—23	0.0	15.0	0.0
9—1—2—1	0.0	0.0	0.4
9—1—1—5	0.0	0.0	0.2
2—1—9—37	0.0	0.0	0.35
2—37—1—5	0.0	0.0	−0.95
37—1—1—5	0.0	0.0	0.1
1—37—2—1	0.0	15.0	0.0
37—2—37—2	0.0	10.0	0.0
2—9—1—2	0.0	0.0	0.4
37—2—9—1	0.0	15.0	0.0
37—2—1—6	0.0	0.0	0.3
9—1—2—2	0.0	0.0	0.45
37—9—1—5	0.0	0.0	−0.4
2—37—9—2	0.0	15.0	0.0
2—9—37—20	0.0	0.0	0.0
9—2—2—1	−1.2	16.3	0.0
1—9—37—20	0.0	0.0	0.0
9—2—9—2	0.0	15.0	0.0
9—2—9—1	0.0	15.0	0.0
37—1—2—1	0.0	0.0	0.4
37—1—2—5	0.4	0.03	0.5
2—1—37—20	0.0	0.0	0.0
9—2—1—5	0.0	0.0	−0.25
2—2—37—1	0.0	15.0	0.0
9—2—1—1	0.0	0.0	−0.2
9—1—1—1	0.0	0.0	0.4
1—9—2—2	0.0	15.0	0.0

Note: The numbers of the types of atoms: 1 is C(sp^3), 2 is C(sp^2), 5 is H, 6 is O of the hydroxy group, 9 is the pyrrole N, 20 is the lone electron pair, 23 is H of the imino group, 37 is the pyridine N. This numbering of the types of atoms was taken from the MMP2 program.[7]



1: $R^2 = R^4 = R^5 = R^6 = H$
2: $R^4 = R^5 = R^6 = H$
R^2 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).
3: $R^2 = R^5 = R^6 = H$
R^4 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).
4: $R^2 = R^4 = R^6 = H$
R^5 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).
5: $R^2 = R^4 = R^5 = H$
R^6 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).



6: $R^5 = R^6 = R^7 = H$
7: $R^6 = R^7 = H$
R^5 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).
8: $R^5 = R^7 = H$
R^6 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).
9: $R^5 = R^6 = H$
R^7 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**).

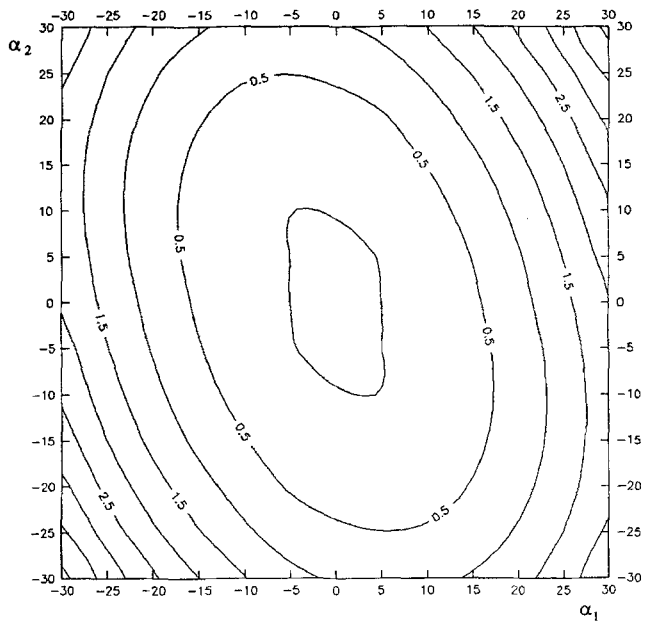


Fig. 1. The dependence of the conformational energy (kcal mol^{-1}) of 1,4-dihydropyrimidine on the N(3)—C(2)—N(1)—C(6) (α_1) and C(2)—N(3)—C(4)—C(5) (α_2) torsion angles. The iso-energetic lines are drawn with a spacing of 0.5 kcal mol^{-1}.

oscillations of the dihydropyrimidine ring are asymmetrical: the deflection of the N(1) atom from the plane of the nonhydrogen atoms of the double bonds is substantially smaller than that of the C(4) saturated carbon atom. In addition, at great oscillation amplitudes, a certain twisting of the boat conformation of the dihydro ring occurs, which, in our opinion, is due to the asymmetry of the nonvalent interactions involving the methylene group (the absence of allylic interaction along the N(3)—C(4) bond).

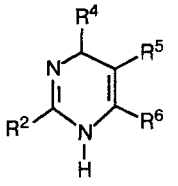
Annelation of the dihydropyrimidine ring with a triazole ring results in strengthening of the bending strain in the molecule and, as a consequence, in an increase in the conformational mobility of the partially hydrogenated ring.

The substituents at the double bonds (compounds **2**, **4**, **5**, **7**, and **8**) do not have much effect on the equilibrium planar conformation of the dihydroheterocycle. The phenyl derivatives **4e** and **8e** are an exception, since nonvalent interactions between the hydrogen atoms in the *ortho*-positions of the aromatic ring and the neighboring olefin and methylene hydrogen atoms in these compounds result in rotation of the phenyl ring ≈25° with respect to the plane of the double bond and transformation of the dihydropyrimidine ring to a boat conformation.

The substituents in compounds **4** and **8** substantially restrict the mobility of the dihydro ring due to strengthening of the allyl-type nonvalent interactions. In compounds **2** and **7**, introduction of substituents does not affect the conformational mobility of the partially hydrogenated ring.

Introduction of substituents to the saturated carbon atoms (compounds **3** and **9**) leads to the transition of the dihydropyrimidine ring to the conformation of an irregularly flattened boat. This is caused by the asymmetry of the nonvalent interactions involving the methylene group with respect to the mean plane of the ring. The degree of puckering of the dihydro ring is determined by the size of the radical introduced. The flexibility of the partially hydrogenated ring is also substantially restricted.

Table 2. The equilibrium conformational characteristics of the dihydro ring in the 1,4-dihydropyrimidines



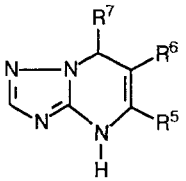
α_1: N(3)—C(2)—N(1)—C(6)

α_2: C(2)—N(3)—C(4)—C(5)

Compound	R^4	R^5	Torsion angle		Puckering parameters		
			α_1	α_2	*s*	θ	ψ
3a	Me	H	−1.3	2.6	0.04	23.0	2.8
3b	Et	H	−1.5	3.0	0.04	22.6	2.4
3c	Pr^i	H	−2.1	4.1	0.06	22.0	2.9
3d	Bu^t	H	−8.3	17.6	0.25	23.9	3.0
3e	Ph	H	−6.1	19.0	0.26	29.8	7.1
4e	H	Ph	−7.1	13.8	0.20	23.4	0.8

Note: The dihydropyrimidine ring in compounds **1**, **2a—e**, **4a—d**, and **5a—e** is planar.

Table 3. The equilibrium conformational characteristics of the 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine



α_1: N(8)—C(3a)—N(4)—C(5)

α_2: C(3a)—N(8)—C(7)—C(6)

Compound	R^5	R^6	R^7	Torsion angle		Puckering parameters		
				α_1	α_2	*s*	θ	ψ
8e	H	Ph	H	0.1	−0.2			
9a	H	H	Me	1.2	−2.7	0.04	24.0	5.5
9b	H	H	Et	3.8	−10.2	0.14	27.6	6.5
9c	H	H	Pr^i	8.9	−20.1	0.28	27.0	1.2
9d	H	H	Bu^t	6.1	−17.2	0.23	31.0	2.7
9e	H	H	Ph	2.3	−20.8	0.27	39.5	15.2

Note: The dihydropyrimidine ring in compounds **6**, **7a—e**, and **8a—d** is planar.

Thus, the 1,4-dihydropyrimidine ring possesses high conformational mobility, which can be appreciably restricted by substituents at the carbon atoms of the ring. Annelation of the dihydropyrimidine ring with a triazole ring along the N=C double bond results in an increase in the amplitudes of the ring-puckering oscillations of the six-membered ring.

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