Conformational analysis of 5,6-dihydropyrimidine and its derivatives

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The equilibrium geometry and inversion barriers of 5,6-dihydropyrimidine, 6,7-dihydroazolopyrimidines with node nitrogen atoms and their alkyl (Me, Et, Pr^i, Bu^t) and phenyl derivatives were calculated using a molecular mechanics approach. Annelation with azole cycles and the introduction of substituents have a slight effect on the equilibrium conformation of the dihydrocycle (distorted sofa). Alkyl substutuents at saturated carbons have an essentially equatorial orientation in 5,6-dihydropyridimine derivatives and are axial in the annelated analogs. On the other hand, the equatorial conformers are more stable in phenyl derivatives of dihydroazolopyrimidines. Factors determining the relative stability of conformers were analyzed.

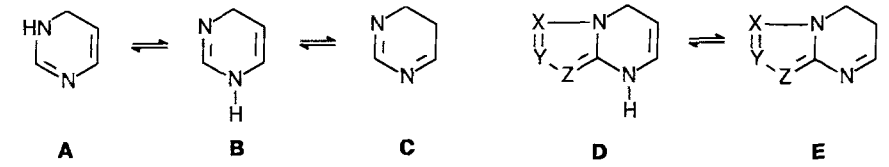
Key words: conformational analysis, molecular mechanics, dihydropyrimidines.

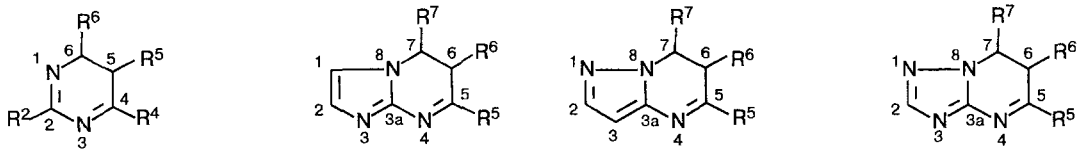
Studies of tautomeric equilibria in dihydropyrimidines[1–3] and dihydroazolopyrimidines[4,5] have shown that the steric effect of substituents, especially at saturated carbon atoms, can be one of the factors determining the tautomeric equilibrium. An increase in the volume of the radical results in stabilization of enamine forms **A**, **B**, and **D**. Therefore, it seemed necessary to study the steric structure and features of conformational behavior of dihydropyrimidine derivatives in the imine tautomeric forms **C** and **E** (Scheme 1).

Calculation Methods

Calculations of equilibrium geometry and conformational features of all compounds under investigation

Scheme 1





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**)
3: $R^2 = R^5 = R^6 = H$; R^4 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**)
4: $R^2 = R^4 = R^6 = H$; R^5 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**)
5: $R^2 = R^4 = R^5 = H$; R^6 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**)
6, 10, 14: $R^5 = R^6 = R^7 = H$
7, 11, 15: $R^6 = R^7 = H$; R^5 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**)
8, 12, 16: $R^5 = R^7 = H$; R^6 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**)
9, 13, 17: $R^5 = R^6 = H$; R^7 = Me(**a**), Et(**b**), Pr^i(**c**), Bu^t(**d**), Ph(**e**)

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Table 1. Additional force field parameters for dihydroazines

Bond angle	k_B / mD · Å^{-1}	θ_0 / deg
1—37—20	0.50	127.5
37—1—1	0.50	108.0
1—2—37	0.55	115.1
9—1—1	0.60	110.0

Torsion angle	V_1	V_2	V_3
	kcal mol^{-1}		
37—2—1—1	0	0	−0.20
37—1—1—5	0	0	0.10
2—37—1—1	0	0	−0.20
2—9—1—1	0	0	−0.46
9—1—1—6	0	0	0.50
37—9—1—1	0	0	−0.10
9—1—1—1	0	0	0.40
1—9—2—2	0	15.0	0
37—1—1—1	0	0	0.20
37—1—1—2	0	0	0.20
1—1—37—20	0	0	0
9—1—1—2	0	0	0.30
37—2—1—6	0	0	0.30
9—2—1—1	0	0	−0.20
9—1—1—5	0	0	0.20
2—1—9—37	0	0	0.35

Note. Labels of atomic types: 1, C(sp^3); 2, C(sp^2); 5, H; 6, O in the hydroxygroup; 9, N in pyrrole; 20, lone electron pair; 23, H in the imino group; 37, N in pyridine. Labeling is taken from the MMP2 program.[6]

Table 2. Conformational features of the dihydrocycle, relative energies of conformers (ΔE), and inversion barriers (ΔE_i) of 5,6-dihydropyrimidines **1—5**. φ_1= N(1)—C(2)—N(3)—C(4), φ_2= N(1)—C(6)—C(5)—C(4)

Compound	R^2	R^4	R^5	R^6	Cf	φ_1 / deg	φ_2 / deg	ΔE / kcal mol^{-1}	Folding parameters S	θ	ψ	ΔE_i / kcal mol^{-1}
1	H	H	H	H		16.0	43.1		0.53	35.2	27.0	1.92
2a	Me	H	H	H		17.2	44.3		0.55	34.2	28.6	1.76
2b	Et	H	H	H		17.0	44.3		0.55	34.6	28.9	1.13
2c	Pr^i	H	H	H		18.2	44.7		0.55	33.2	28.6	1.87
2d	Bu^t	H	H	H		19.1	45.4		0.56	32.4	29.0	1.94
3a	H	Me	H	H		16.5	41.7		0.52	33.7	29.5	1.47
3b	H	Et	H	H		16.5	42.4		0.52	34.1	28.8	1.68
3c	H	Pr^i	H	H		16.6	42.8		0.53	34.1	28.6	1.71
3d	H	Bu^t	H	H		16.9	43.6		0.54	34.1	28.3	1.89
4a	H	H	Me	H	a	16.1	45.2	0.01	0.56	36.0	26.9	2.21
					e	−16.2	−44.6	0.0	0.55	35.7	26.6	
4b	H	H	Et	H	a	16.5	46.7	0.0	0.58	36.3	26.3	2.75
					e	−15.7	−43.0	0.19	0.54	35.4	27.3	
4c	H	H	Pr^i	H	a	14.9	40.7	0.0	0.51	35.7	28.1	2.32
					e	−16.1	−43.6	0.17	0.54	35.4	27.3	
4d	H	H	Bu^t	H	a	15.7	44.0	0.0	0.55	36.3	27.6	1.75
					e	−15.8	−42.7	0.05	0.53	36.5	26.8	
5a	H	H	H	Me	a	16.0	44.6	0.43	0.55	36.0	29.9	2.16
					e	−16.1	−44.6	0.0	0.55	35.8	29.7	
5b	H	H	H	Et	a	16.4	45.8	0.38	0.57	36.1	29.4	2.29
					e	−16.2	−44.8	0.0	0.55	35.9	29.6	
5c	H	H	H	Pr^i	a	14.2	38.6	0.48	0.48	35.5	28.2	1.78
					e	−15.8	−43.1	0.0	0.54	35.8	29.9	
5d	H	H	H	Bu^t	a	15.2	41.9	0.93	0.52	35.9	28.4	2.33
					e	−15.8	−43.3	0.0	0.54	35.7	29.7	

Note. Cf is conformation, φ_1, φ_2 are torsion angles.

were carried out using the MMP2 molecular mechanics method[6] modified for nitrogen-containing heterocycles.[7] The conformation of the dihydropyrimidine cycle was characterized using the folding parameters described by Zefirov—Palyulin—Dashevskaya,[8] where s is the degree of folding of the cycle, and θ and φ are polar angles determining the folding pattern. Inversion barriers were calculated using the method described in Ref. 9 by scanning over the N—C(sp^3)—C(sp^3)—C(sp^2) torsion angle. The missing potential parameters (Table 1) were selected by reproducing the experimental data on molecular geometry and rotation barriers in a series of model molecules. The analogous values for hydrocarbons were used as an initial approximation.

Table 3. Conformational features of dihydrocycle, relative energies of conformers (ΔE), and inversion barriers (ΔE_i) of 6,7-dihydroazolopyrimidines **6—17**. φ_1 = N(8)—C(3a)—N(4)—C(5), φ_2 = N(8)—C(7)—C(6)—C(5)

Compound	R^5	R^6	R^7	Cf	φ_1 deg	φ_2 deg	ΔE kcal mol^{-1}	Folding parameters S	θ	ψ	ΔE_i kcal mol^{-1}
6	H	H	H		13.0	37.3		0.48	37.2	28.9	1.33
7a	Me	H	H		14.4	38.9		0.50	36.2	28.1	1.60
7b	Et	H	H		14.5	40.6		0.51	36.4	27.2	1.88
7c	Pr^i	H	H		14.9	41.4		0.52	36.2	26.6	1.92
7d	Bu^t	H	H		14.8	41.7		0.52	36.3	26.5	2.11
7e	Ph	H	H		17.1	43.3		0.54	33.8	29.3	
8a	H	Me	H	a	14.1	40.6	0.0	0.52	37.9	28.9	2.13
				e	−13.5	−39.3	0.12	0.50	38.0	29.4	
8b	H	Et	H	a	14.9	42.6	0.0	0.55	37.7	27.6	2.68
				e	−13.3	−38.2	0.23	0.49	37.8	29.5	
8c	H	Pr^i	H	a	13.3	37.3	0.0	0.48	37.4	29.8	2.41
				e	−13.1	−37.5	0.33	0.48	37.7	28.3	
8d	H	Bu^t	H	a	14.0	40.1	0.0	0.52	37.8	29.1	2.72
				e	−12.9	−37.6	0.5	0.48	38.1	29.3	
8e	H	Ph	H	a	12.6	38.3	0.75	0.50	38.7	23.2	2.10
				e	−12.5	−39.2	0.0	0.50	39.4	27.6	
9a	H	H	Me	a	14.0	37.2	0.08	0.48	36.0	28.2	1.41
				e	−14.0	−37.6	0.0	0.48	36.2	28.4	
9b	H	H	Et	a	15.5	39.8	0.0	0.51	35.3	29.1	2.00
				e	−13.6	−36.5	0.68	0.47	36.2	29.2	
9c	H	H	Pr^i	a	14.7	34.5	0.0	0.44	33.2	28.0	1.94
				e	−12.8	−33.0	0.91	0.43	35.5	26.3	
9d	H	H	Bu^t	a	15.7	37.6	0.0	0.48	33.7	28.7	2.14
				e	−11.0	−28.3	2.27	0.34	37.2	25.5	
9e	H	H	Ph	a	10.0	39.8		0.51	42.8	21.4	2.80
				e	−8.9	−28.5		0.37	39.9	29.8	
10	H	H	H		−12.0	36.2		0.47	38.4	28.6	1.27
11a	Me	H	H		14.3	38.8		0.49	35.8	25.3	1.59
11b	Et	H	H		14.2	39.2		0.50	36.5	25.3	1.92
11c	Pr^i	H	H		14.6	39.6		0.50	35.7	24.9	1.96
11d	Bu^t	H	H		14.4	40.2		0.51	36.1	25.0	2.15
11e	Ph	H	H		14.2	41.7		0.52	37.0	23.1	2.46
12a	H	Me	H	a	13.4	39.4	0.0	0.51	38.3	27.2	2.09
				e	−12.8	−38.2	0.10	0.49	38.5	27.4	
12b	H	Et	H	a	14.0	41.1	0.0	0.53	38.2	26.1	2.60
				e	−12.5	−36.9	0.19	0.48	38.4	28.1	
12c	H	Pr^i	H	a	12.8	36.2	0.0	0.47	37.6	28.2	2.36
				e	−12.9	−36.5	0.34	0.47	37.6	29.6	
12d	H	Bu^t	H	a	13.5	39.1	0.0	0.50	38.1	27.4	2.66
				e	−12.5	−36.6	0.46	0.47	38.3	28.8	
12e	H	Ph	H	a	11.4	33.7	0.32	0.44	38.4	26.3	1.55
				e	−12.8	−38.2	0.0	0.50	38.5	22.4	
13a	H	H	Me	a	11.8	35.3	0.21	0.45	38.5	27.4	1.23
				e	−11.5	−35.2	0.0	0.45	39.0	26.7	
13b	H	H	Et	a	14.3	38.1	0.0	0.49	36.1	26.5	1.13
				e	−11.1	−34.3	0.29	0.44	39.2	27.6	
13c	H	H	Pr^i	a	13.6	32.9	0.0	0.43	33.9	25.1	0.92
				e	−11.2	−31.9	0.77	0.41	37.5	25.5	
13d	H	H	Bu^t	a	15.5	36.3	0.0	0.47	33.1	24.7	1.14
				e	−14.5	−31.9	0.06	0.44	29.3	6.5	

Table 3 (*continued*)

Compound	R^5	R^6	R^7	Cf	φ_1 deg	φ_2 deg	ΔE kcal mol^{-1}	Folding parameters S	θ	ψ	ΔE_i kcal mol^{-1}
13e	H	H	Ph	a	5.9	33.1	0.77	0.44	46.6	17.8	2.39
				e	−3.8	−40.6	0.0	0.55	49.9	9.8	
14	H	H	H		13.6	35.9		0.46	35.9	25.8	1.24
15a	Me	H	H		16.1	38.4		0.49	32.7	22.1	1.56
15b	Et	H	H		16.1	39.2		0.50	33.1	21.1	1.53
15c	Pr^i	H	H		14.5	39.6		0.50	35.8	22.5	1.76
15d	Bu^t	H	H		14.7	40.3		0.51	35.9	22.6	1.96
15e	Ph	H	H		14.8	41.7		0.53	36.2	23.2	2.30
16a	H	Me	H	a	14.0	38.9	0.0	0.50	37.3	26.0	1.94
				e	−13.4	−37.7	0.12	0.49	37.6	26.8	
16b	H	Et	H	a	14.3	40.4	0.0	0.52	37.7	26.4	2.56
				e	−13.1	−36.5	0.17	0.47	37.4	26.8	
16c	H	Pr^i	H	a	13.2	35.6	0.0	0.46	36.8	27.3	2.19
				e	−13.5	−35.8	0.28	0.46	36.4	28.1	
16d	H	Bu^t	H	a	13.8	38.5	0.0	0.50	37.5	26.7	2.62
				e	−13.3	−38.5	0.43	0.47	37.1	27.1	
16e	H	Ph	H	a	11.4	32.3	0.24	0.42	37.5	24.2	2.22
				e	−13.5	−37.7	0.0	0.49	36.9	20.0	
17a	H	H	Me	a	12.1	34.5	0.25	0.45	37.8	26.7	1.10
				e	−11.9	−34.5	0.0	0.45	38.0	25.9	
17b	H	H	Et	a	14.5	37.0	0.0	0.48	35.2	25.4	1.25
				e	−11.6	−33.3	0.34	0.43	38.3	26.1	
17c	H	H	Pr^i	a	13.8	32.0	0.0	0.42	32.8	23.7	2.16
				e	−11.4	−32.2	0.89	0.41	36.9	25.1	
17d	H	H	Bu^t	a	15.2	35.1	0.0	0.46	32.8	23.9	1.34
				e	−14.4	−32.4	0.48	0.43	31.1	12.9	
17e	H	H	Ph	a	6.6	31.8	1.63	0.42	45.3	18.9	2.39
				e	−5.5	−41.5	0.0	0.56	47.7	9.1	

Note. Cf is conformation, φ_1 and φ_2 are torsion angles.

Results and Discussion

The presence of C=N conjugated double bonds in the dihydropyrimidine cycle enables us to assume that the equilibrium conformations of this dihydroheterocycle and 1,3-cyclohexadiene[10] are determined by the same factors. This conclusion agrees with X-ray structural studies of azolopyrimidines containing the 5,6-dihydropyrimidine moiety.[11,12] These factors include, on the one hand, conjugation between the π-systems of the double bonds, which is the greatest in the planar conformation, and, on the other hand, the strain caused by the deformation of the endocyclic valence angles at the saturated carbon atoms, and the tendency toward a twisted conformation along the $C(sp^3)—C(sp^3)$ bond made possible by the planar molecular structure. The equilibrium conformation of the dihydrocycle in 5,6-dihydropyrimidine **1** is a distorted sofa (see Table 2) indicating the predominance of twisting factors.

Annelation of the dihydropyrimidine ring with azole cycles along the C=N double bond (compounds **6**, **10**, **14**) does not significantly affect the equilibrium conformation of the former (Table 3); however, there is an increase in the conjugation chain together with an increase in the angular strain in the molecule. The introduction of substituents to carbon atoms in the dihydrocycle does not affect the equilibrium conformation, either (Tables 2 and 3), but the degree of folding of the dihydropyrimidine ring changes within a small range from 0.42 to 0.55.

Substituents at the saturated carbon atoms (compounds **4**, **5**, **8**, **9**, **13**, **16**, **17**) produce a stronger effect on the degree of folding of the dihydrocycle than substituents at unsaturated carbon atoms (compounds **2**, **3**, **7**, **11**, **15**, Tables 2 and 3). In all compounds under investigation, the most stable conformer also has the greater degree of folding.

The orientation of the substituents at the saturated carbon atoms is determined by three factors: nonvalent interactions of a substituent with the equatorial hydrogen atom of the adjacent methylene group; nonvalent interactions with the olefin hydrogen atom; and interations with the rest of the atoms of the dihydrocycle. The two former factors are greatest for the equatorial

orientation of a substituent, while the third one is greatest for the axial orientation. In 6-alkyl derivatives of 5,6-dihydropyrimidine (compound **5**), the nonvalent interactions of a substituent with vicinal hydrogen atoms result in the greater stability of the axial conformer. The absence of adjacent olefin hydrogen atoms in the case of 5-alkyl derivatives (compound **4**) results in the stabilization of the equatorial conformer. Thus, the saturated atoms in monoalkyl derivatives of 5,6-dihydropyrimidine become nonequivalent with respect to the relative stability of the axial and equatorial conformers.

In 6,7-dihydropyrimidines, the axial conformers are always more stable. The destabilization of the equatorial conformer in 7-alkyl derivatives **9**, **13**, and **17**, probably caused by unfavorable nonvalent interactions between the alkyl group and the azole cycle. The exception is provided by 7-methyl derivatives **9a**, **13a**, and **17a**, where the conformers with the equatorial orientation of the alkyl group have lower conformational energy.

When phenyl substituents are introduced (compounds **8e**, **9e**, **13e**, **14e**, **16e**, and **17e**), the equatorial conformers become more stable. Apparently, specific conformational features of the phenyl group, in particular, the possibility to reduce the unfavorable nonvalent interactions by the rotation of substituent around the $C(sp^3)$—Ph bond, have an effect in this case.

An increase in the volume of the substituents at the carbon atoms of the dihydropyrimidine cycle does not result in the regular enhancement of the inversion barriers. The reason seems to be the greater destabilization of the ground state with respect to the intermediate state when the size of the radical introduced increases. This effect is the most pronounced in 4-alkyl-5,6-dihydropyrimidines **4**, where an increase in the volume of the substituents reduces the inversion barrier.

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