Conformational analysis of 3,4-dihydropyridine and its alkyl derivatives

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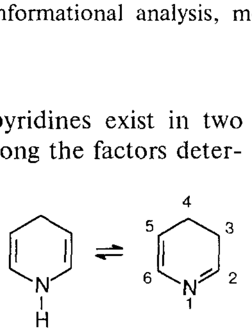
The geometry of dihydropyridine and its alkyl derivatives was studied by the molecular mechanics method. The dihydrocycle was found to be mobile; however, substituents exert little effect on its distorted sofa conformation. The alkyl groups attached to the saturated carbon atoms occupy pseudo-equatorial position in monosubstituted and pseudo-axial positions in disubstituted 3,4-dihydropyridines. Unusually high barriers to inversion of the dihydrocycle were observed in *cis*-3,4-dialkyl-3,4-dihydropyridines caused by the eclipse of the substituents in the transition state.

Key words: conformational analysis, molecular mechanics, 4,5-dihydropyridine, alkyl derivatives.

It is known that 3,4-dihydropyridines exist in two tautomeric forms,[1—3] and that among the factors determining the position of the tautomeric equilibrium steric effects of the substituents play the main role.[4] In this connection, it seemed proper to analyze the spatial structure and conformational flexibility of 3,4-dihydropyridine and its alkyl derivatives.



Experimental data about the spatial structure of 3,4-dihydropyridine derivatives[5—7] are very scarce. However, a comparison of the available data about the geometry of these compounds with those for the considerably better studied 1,3-cyclohexadiene derivatives[8] shows the great similarity in their structures. This makes it reasonable to assume that the factors determining the conformations of both dihydrocycles are similar. On the one hand, there is conjugation between the π-systems of double bonds, which reaches its maximum in the planar conformation of the molecule. On the other hand, there is deformation of valent angles of saturated carbon atoms, which is minimized in a non-planar conformation.[9,10] The actually observed conformation of the partially hydrogenated aromatic cycle, which is intermediate between the sofa and half-boat (identified according to the folding parameters of Zefirov—Palyulin—Dashevskaya[11] (Table 1) as a distorted sofa), attests to the predominance of the flattening factors.

In this work, the 3-dimentional structure and inversion barriers of 3,4-dihydropyridine and its alkyl derivatives have been calculated by the method of molecular mechanics using the MMP2[12] program modified for the calculation of nitrogen-containing heterocycles.[13] The parameters for the torsional angle N=C—C—C (V_1 = 0.0, V_2 = 0.0, V_3 = −0.2), absent in the standard force field, were selected by reproducing the experimental geometry of the model compounds.[5—7] The folding parameters characterizing the form of the cycle were calculated by adopting the results of Zefirov *et al.*[14] The data obtained in our study are presented in Tables 1 and 2.

Table 1. Conformational parameters, steric energy, and inversion barriers for 3,4-dihydropyridines with substituents at unsaturated atoms

R	φ_1 /deg	φ_2 /deg	E_{ster} /kcal mol^{-1}	Folding parameters S	θ	ψ	Inversion barrier /kcal mol^{-1}
H	13.9	39.8	6.40	0.51	37.5	29.9	1.68
2-Me	16.2	40.6	5.68	0.52	34.6	29.5	1.74
2-Et	16.1	41.1	7.56	0.53	35.0	28.2	1.78
2-*i*-Pr	15.3	40.8	7.88	0.52	36.1	28.9	1.78
2-*t*-Bu	16.1	41.3	9.03	0.53	35.1	28.9	1.89
3-Me	13.8	38.7	5.53	0.49	36.9	27.8	1.71
3-Et	14.5	40.1	7.35	0.51	36.4	28.8	1.80
3-*i*-Pr	14.7	40.9	8.90	0.52	36.6	29.8	2.12
3-*t*-Bu	14.4	42.4	11.47	0.53	37.4	27.4	1.94
6-Me	15.3	42.3	6.50	0.53	35.4	29.0	2.06
6-Et	15.2	43.0	7.69	0.53	35.7	29.3	2.29
6-*i*-Pr	15.1	43.5	9.01	0.55	37.1	26.2	2.33
6-*t*-Bu	15.7	44.5	10.79	0.56	36.5	26.4	2.65

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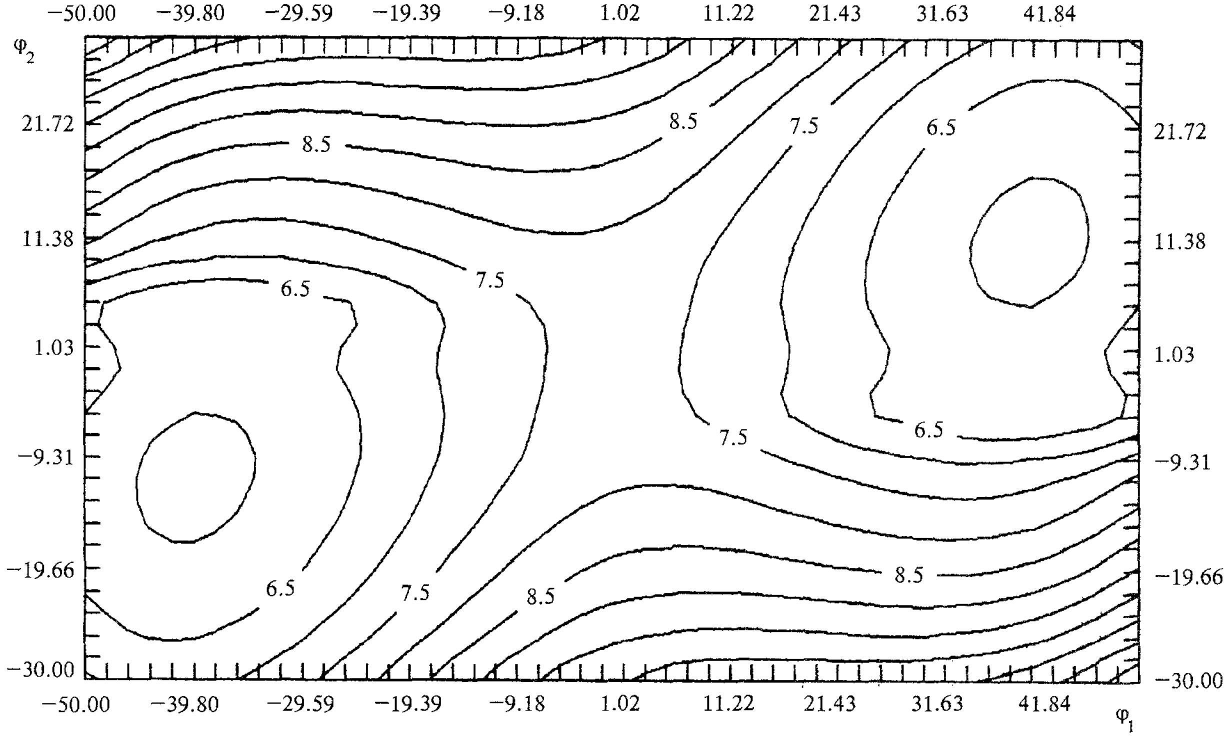
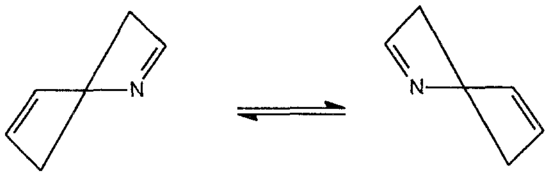


Fig. 1. Correlation between the steric energy (kcal mol^{-1}) and the torsional angles φ_1 and φ_2 in 3,4-dihydropyridine.

The molecules of 3,4-dihydropyridine and 1,3-cyclohexadiene exist as two mirror-symmetric conformers:



The transitions between them are possible by changing the torsional angles C(2)—N(1)—C(6)—C(5) (φ_1) or C(5)—C(4)—C(3) —C(2) (φ_2). The study of the inversion routes of the dihydropyridine cycle shows that only torsional angle φ_2 may be considered as the reaction coordinate. Changing the angle φ_1 results not in the inversion of the cycle but only in an increase in the steric energy, while the angle φ_2 remains almost unchanged. It is seen from the conformational pattern plotted in the space of torsion angles φ_1 and φ_2 (Fig. 1) that the valley in which the points of the minima and the transition state lie has a Z-like form. Thus, scanning over angle φ_1 results in a shift of the molecule from the minimum point to the side branch of the valley, which does not result in the transition state.

The replacement of the carbon atom in the conjugated 1,3-cyclohexadiene system with nitrogen brings about a decrease in the non-valent interactions in the unsaturated part of the molecule. As a result, the inversion barrier of the dihydrocycle in 3,4-dihydropyridine becomes considerably lower than that in 1,3-cyclohexadiene (1.68 and 3.15 kcal mol^{-1}, respectively).

In contrast to 1,4-dihydropyridine,[14] the attachment of alkyl substituents to the dihydroheterocycle has practically no affect on its conformation; only the degree of folding, *S*, is slightly changed. A comparison of the conformation of the dihydrocycle in the 2-alkyl derivatives of 3,4-dihydropyridine shows that sequentially increase the volume of the substituent has almost no affect on the folding parameters (see Table 1). The degree of folding is somewhat more sensitive to the increase in the volume of the alkyl group for 3- and 6-alkyl-substituted derivatives of 3,4-dihydropyridine due, possibly, to nonvalent interactions of the substituent with the hydrogen atoms of the adjacent methylene group, which are absent in the 6-alkyl derivatives.

The orientations with the syn-periplanar arrangement of the C—H- or C—C-bonds of the substituent with respect to the double bond are possible for ethyl and isopropyl substituents. The data of the calculations show that the eclipse with the C—H-bond is approximately by 0.3—0.4 kcal mol^{-1} more favorable.

Substituents at saturated carbon atoms affect the degree of folding of the dihydrocycle more strongly (see Table 2). The position of the alkyl group is very important. The axial conformers are more flattened than the equatorial ones due to the stronger non-valent interactions of the substituent with the other atoms of the cycle for the axial arrangement of the alkyl group. A similar tendency occurs in the case of disubstituted derivatives.

Table 2. Conformational parameters, steric energy, and inversion barriers for 3,4-dihydropyridines with substituents at saturated carbon atoms

R	Conformer	φ_1 /deg	φ_2 /deg	E_{ster} /kcal mol^{-1}	Folding parameters			Inversion barrier /kcal mol^{-1}
					S	θ	ψ	
4-Me	a	−14.4	−41.4	6.88	0.53	37.4	27.3	1.77
	e	14.3	40.8	6.49	0.52	37.3	27.8	
4-Et	a	−12.9	35.9	8.95	0.46	37.0	29.5	1.81
	e	14.1	40.8	8.71	0.53	37.2	27.1	
4-*i*-Pr	a	−13.3	37.3	10.59	0.49	37.2	29.8	2.12
	e	14.2	40.8	10.14	0.51	37.5	28.2	
4-*t*-Bu	a	−14.6	−39.4	12.36	0.51	36.7	27.9	2.95
	e	13.9	39.4	11.91	0.51	37.3	27.6	
5-Me	a	−13.9	40.1	6.77	0.51	37.7	28.7	2.01
	e	14.1	40.5	6.41	0.52	37.6	28.5	
5-Et	a	−12.3	−34.8	8.76	0.46	37.0	29.5	2.41
	e	14.0	39.8	8.64	0.51	37.4	29.8	
5-*i*-Pr	a	−12.8	−36.3	10.43	0.48	37.2	29.8	2.50
	e	13.6	38.5	9.82	0.51	38.0	27.4	
5-*t*-Bu	a	−13.6	−39.2	12.29	0.49	37.5	29.3	2.22
	e	13.6	38.5	11.92	0.49	37.5	29.3	
4,5-di-Me_2	aa	−14.6	−42.0	7.74	0.54	37.7	29.1	1.83
	ee	13.4	37.7	7.78	0.52	37.2	29.9	
	ae	15.0	43.1	8.42	0.55	37.8	30.0	3.13
4,5-di-Et_2	aa	−12.0	−32.9	11.73	0.42	36.8	29.0	1.59
	ee	15.1	43.4	11.98	0.55	37.7	29.4	
	ae	13.9	40.4	14.84	0.54	37.3	29.9	3.35
4,5-di-*i*-Pr_2	aa	−13.0	−35.2	14.27	0.36	37.6	29.5	2.28
	ee	14.2	39.7	14.76	0.51	37.5	27.4	
	ae	16.0	44.3	15.61	0.57	37.0	27.0	6.8

The orientation of the substituent with the antiperiplanar arrangement of the terminal methylene group with respect to the hydrogen atom of the corresponding methylene group in the cycle is the most favorable for the ethyl and isopropyl groups in 3- or 4-substituted derivatives.

By contrast, the axial conformers become energetically more favorable than the equatorial conformers for 3,4-disubstituted derivatives. For example, the conformer with the diaxial arrangement of the substituents is more stable for the *trans*-isomers with a lower energy than for *cis*-isomers, and increasing the volume of the alkyl groups results in a greater difference in the energies of the diaxial and diequatorial conformers. This change in the relative stability of axial and equatorial conformers as compared with the 3- and 4-monosubstituted derivatives is related to the appearance of unfavorable nonvalent interactions, which are particularly strong for the equatorial arrangement of the vicinal alkyl groups.

The calculation of the inversion barriers of the dihydropyridine cycle shows that increasing the volume of the alkyl group for all of the compounds studied primarily increases the energy of the ground state and affects the energy of the transition state less. This brings about only an insignificant increase in the inversion barrier as the steric capacity of the molecule increases. In some cases, for example, on passing from 5-isopropyl to 5-*tert*-butylsubstituted derivatives, the inversion barrier even decreases. It is noteworthy that the values of the barriers for the *cis*- and *trans*-3,4-dialkyl derivatives are markedly different (by 2—3 times). This is related to the eclipse of the two alkyl groups of the *cis*-derivatives in the transition state, which results in a sharp increase in the energy of the transition state.

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