Physical Chemistry

Conformational analysis of 2-oxo-1,2,3,4-tetrahydropyridine and its alkyl- and phenyl-substituted derivatives

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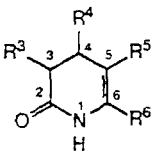
The molecular geometries and inversion barriers of the rings in 2-oxo-1,2,3,4-tetrahydropyridine and its alkyl-substituted (Me, Et, Pr^i, or Bu^t) and phenyl-substituted derivatives were calculated by the molecular mechanics method. The introduction of substituents has no substantial effect on the equilibrium conformation of the heterocycle (a distorted sofa). For 4-alkyl- and 3-alkyl-substituted derivatives (except for 4-Me and 4-Et derivatives), an axial orientation of the alkyl group is more favorable. The phenyl substituents have equatorial and axial orientations at positions 4 and 3, respectively.

Key words: 2-oxo-1,2,3,4-tetrahydropyridine, alkyl- and phenyl-substituted derivatives, conformational analysis; molecular mechanics.

Previously, we have studied the spatial structures and steric effects of the substituents in the 3,4-dihydropyridine[1] and 5,6-dihydropyrimidine[2] molecules, which contain two endocyclic double bonds. It has been demonstrated that the introduction of alkyl substituents affects only slightly the conformation of the dihydrocycle. Only the degree of puckering of the ring varies within some limits depending on the volume of the radical. Analysis of the published data on the geometry of the tetrahydro analogs of these dihydrocycles,[3–5] which have similar cyclic conjugated systems (for example, 2-oxo-1,2,3,4-tetrahydropyridine, which contains an alternative planar fragment, namely, the amide group with the exocyclic C=O bond, instead of the endocyclic C=N bond), demonstrated that the partially hydrogenated ring in these molecules adopts a conformation similar to that observed in the dihydrocycles. It can be suggested that replacing one endocyclic double bond in the molecules of these compounds with a single bond can increase the sensitivity of the partially hydrogenated ring with respect to steric effects of substituents due to the decrease in the barrier to rotation about this bond. Therefore, it is of interest to study the steric effects of the substituents in these compounds. In this work, we carried out a conformational analysis of 2-oxo-1,2,3,4-tetrahydropyridine and its alkyl- and phenyl-substituted derivatives **1**—**5**.



1—**5**

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

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Procedure of Calculations

The spatial structures and conformational characteristics of compounds **1**—**5** were calculated by the molecular mechanics MMP method[6] modified for nitrogen-containing heterocycles.[7] The parameters of the potentials, which were unavailable in the standard force field, were chosen by reproducing the experimental data from the data on the molecular geometries of a number of model compounds.[8,9] The additional parameters are given in Table 1.

The conformation of the tetrahydropyridine ring was characterized by the following puckering parameters:[10] S is the degree of puckering, and θ and ψ are polar angles that describe the conformational type.

The inversion barriers were calculated using the dihedral driver method[11] by scanning the C(2)—C(3)—C(4)—C(5) torsion angle. The results of calculations are given in Table 2.

Results and Discussion

The equilibrium conformation of the ring in molecule **1** is determined by two groups of opposing factors. The first group involves conjugation, which is maximum when the geometry of the ring is planar. The second group of factors involves the bending strain that occurs owing to the deformation of the endocyclic bond angles at the saturated carbon atoms in the planar conformation, and the tendency to a staggered conformation along the $C(sp^3)$—$C(sp^3)$ bond. The tendency to an eclipsed conformation of the carbonyl group and the vicinal H atoms is one more factor. Because such orientation of each proton of the $C(3)H_2$ group results in an unfavorable orientation of the second H atom, this interaction stabilizes the planar conformation of the ring in which both H atoms are equidistant from the C=O bond.

According to the results of calculations, the equilibrium conformation of unsubstituted 2-oxo-1,2,3,4-tetrahydropyridine **1** is a distorted sofa, which agrees well with the experimental data[3—5] and is indicative of a predominance of the factors that cause a distortion from planarity. The N(1), C(6), C(5), and C(4) atoms are in a single plane. The C(3) and C(2) atoms deviate from this plane by 0.68 and 0.20 Å, respectively. The analogous conformation is also typical of derivatives of 3,4-dihydropyridine.[12,13]

As in the case of the dihydro analog, the introduction of substituents at the C atoms of the partially hydrogenated ring leaves the conformation of the ring essentially unchanged. An increase in the size of the alkyl group in compounds **2** and **3** causes only a slight increase in the twist of the equilibrium conformation of the tetrahydropyridine ring owing to strengthening of the nonbonded interactions between the substituent and the adjacent H atoms.

The orientations of the substituents at the saturated C atoms are determined, on the one hand, by the

Table 1. Additional parameters (k, θ, V_1, V_2, and V_3)[a] of the molecular mechanics force field

Bond angle	θ /deg	Torsion angle	V_2	V_3
			kcal mol^{-1}	
C—C(=O)—N	114.0	C—C—C(=O)—N	0	0.4
O=C—N	120.0	C—C(=O)—N—C=	10	0
=C—N—C(=O)	121.0	C—C(=O)—N—LP	10	0
C(=O)—N—H	120.0	C=C—N—C(=O)	10	0
C=O—LP[b]	120.0	H—C(=C)—N—C(=O)	10	0
LP—O—LP	120.0	H—C—C(=O)—N	0	0.2
C—N—C(=O)	120.0	N—C=O—LP	0	0
		O=C—N—C(=C)	10	0
		O=C—N—H	10	0
		H—C—N—C(=O)	0	0.3
		H—C(=C)—N—C	10	0

[a] In all cases, k = 0.5 mdyn Å rad^{-1}. V are the torsion constants; in all cases, V_1 = 0.
[b] LP is a lone electron pair.

Table 2. Conformational characteristics (S, θ, and ψ) of the tetrahydropyridine ring, the relative stabilities of the conformers (ΔE, (a/e)), and the inversion barriers (ΔE_{inv}) of the ring in compounds **1**—**5**

Compound	R	Conformation*	Puckering parameters			$\Delta E(a/e)$	ΔE_{inv}
			S	θ	ψ	kcal mol^{-1}	
				deg			
1	—	—	0.6	42.6	17.6	—	3.00
2a	6-Me	—	0.6	41.7	17.6	—	2.11
2b	6-Et	—	0.6	41.8	18.6	—	3.10
2c	6-Pr^i	—	0.6	42.0	19.3	—	2.75
2d	6-Bu^t	—	0.6	40.1	20.3	—	3.48
2e	6-Ph	—	0.6	40.8	19.1	—	3.41
3a	5-Me	—	0.6	43.1	16.2	—	2.96
3b	5-Et	—	0.6	43.0	15.8	—	3.02
3c	5-Pr^i	—	0.6	42.2	18.0	—	3.36
3d	5-Bu^t	—	0.6	41.2	19.0	—	3.69
3e	5-Ph	—	0.6	41.0	22.4	—	3.32
4a	4-Me	*a*	0.6	42.1	20.2	0.2	
4a	4-Me	*e*	0.6	42.1	19.9	0	3.74
4b	4-Et	*a*	0.5	42.6	17.3	0.1	
4b	4-Et	*e*	0.6	42.3	19.5	0	3.32
4c	4-Pr^i	*a*	0.6	42.0	18.9	0	3.55
4c	4-Pr^i	*e*	0.6	42.2	19.7	0.17	
4d	4-Bu^t	*a*	0.6	41.3	20.4	0	4.02
4d	4-Bu^t	*e*	0.6	42.3	19.3	0.16	
4e	4-Ph	*a*	0.6	44.3	14.0	0	4.74
4e	4-Ph	*e*	0.6	42.3	21.4	1.81	
5a	3-Me	*a*	0.6	43.5	16.2	1.66	
5a	3-Me	*e*	0.6	43.7	14.9	0	4.33
5b	3-Et	*a*	0.6	44.1	14.8	0.99	
5b	3-Et	*e*	0.6	44.6	12.4	0	4.91
5c	3-Pr^i	*a*	0.7	44.2	14.9	0.85	
5c	3-Pr^i	*e*	0.6	45.3	19.8	0	5.04
5d	3-Bu^t	*a*	0.6	45.2	13.7	0.86	
5d	3-Bu^t	*e*	0.6	44.5	12.5	0	4.48
5e	3-Ph	*a*	0.6	41.2	21.8	2.06	
5e	3-Ph	*e*	0.6	42.3	18.8	0	4.25

* Notation: *a* is axial conformation, and *e* is equatorial conformation.

nonbonded interactions between the substituent and the remaining atoms of the partially hydrogenated ring and, on the other hand, by the repulsion between the alkyl (phenyl) group and the vicinal H atoms. The first effect is maximum when the substituent is in an axial orientation, whereas the second effect is maximum when the substituent is in an equatorial orientation.

In 4-alkyl-substituted derivatives **4** containing small alkyl groups (R = Me or Et), the conformer with the equatorial orientation of the substituent is more stable. However, an increase in the volume of the substituent leads to destabilization of this conformer owing to an increase in the nonbonded interactions between the alkyl group and the vicinal H atoms. As a result, the conformer with the axial orientation of the substituent is more stable in the case of compounds **4c—e**. In the molecules of 3-alkyl-substituted derivatives **5**, the substituent is located in proximity to the O atom of the carbonyl group, which stabilizes the axial conformer even when R = Me or Et.

Changes in inversion barriers as the substituent volume increases are caused by two factors, namely, strengthening of nonbonded interactions in a transition state that is close to planar, and increases in the strain of the ground state. The inversion barrier of the tetrahydropyridine ring decreases as destabilization of the ground state increases (for example, in going from **1** to **2a**) or increases as destabilization of the transition state increases (for example, in the series **3b** → **3c** → **3d**) depending on which effect is stronger.

Therefore, replacing one endocyclic double bond in the 3,4-dihydropyridine molecule with a single bond in 2-oxo-1,2,3,4-tetrahydropyridine does not cause an increase in the sensitivity of the conformation of the ring to steric effects of substituents.

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