Reviews

Conformational flexibility of six-membered dihydrocycles

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The conformational flexibility of six-membered 1,4- and 1,2-dihydrocycles caused by a flattened shape of the minimum on the potential energy surface is discussed. The effect of the conformational flexibility of the rings on the physicochemical characteristics of compounds is considered.

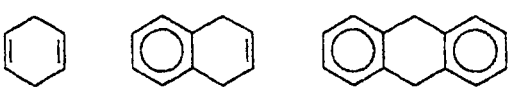
Key words: six-membered dihydrocycles, conformational flexibility.

The classical conformational analysis of cyclic systems involves identification of stable conformations and the energy barriers between them. However, it is known that atoms in a molecule oscillate and, therefore, the geometric parameters of the molecule vary within certain limits. Thus, in reality, a certain area on the potential energy surface rather than a single minimum point corresponds to each conformer. The size of this area is determined by the structure of the molecule. In the case of cyclic systems, the dynamic properties of the ring caused by the thermal motion of the atoms can substantially change the ring conformation and, hence, the physicochemical properties of compounds. A classic example of conformational dynamics is the pseudo-rotation in cyclopentane and cyclohexane[1] leading to fast transitions between conformers at room temperature and caused by the fact that the barriers to these transitions are low.

Recently, yet another type of flexible six-membered rings has been found. The potential energy surfaces for their molecules contain only one minimum, but this minimum is flattened. Consequently, conformers, whose energies are close to the minimum point but whose geometries are markedly different, become populated. This type of conformational dynamics of the ring was found to be typical of many six-membered dihydrocycles. Recent studies have shown that conformational flexibility is encountered much more often than pseudo-rotation. This stimulated our attempt to describe systematically the published data on this type of conformational dynamics for six-membered dihydrogenated rings, because compounds of this class have been studied most thoroughly in this respect.

Cyclohexa-1,4-diene and its derivatives

The conformational flexibility of the ring caused by a flattened minimum in the potential energy surface was found for the first time in a study of cyclohexa-1,4-diene (**1**) and its derivatives (**2**, **3**).



1 **2** **3**

Contradictory experimental data on the equilibrium conformation of **1** served as the starting point for this

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discovery. First, it has been found by gas electron diffraction[2] that **1** exists in a boat conformation. However, more recent studies carried out by microwave spectroscopy[3] resulted in the conclusion on the planar structure of the molecule. It has been suggested[3] that in molecule **1**, fast transitions between the planar equilibrium conformation and a boat-like conformation occur; they were not taken into account in the processing of the electron-diffraction experiment, and this led to the apparent contradiction.

Subsequent studies of the structure of compound **1** carried out by vibrational spectroscopy,[4,5] NMR,[6] and X-ray diffraction[7] as well as non-empirical quantum-chemical calculations[8,9] have confirmed the planar structure of the molecule. The hypothesis[3] about substantial conformational flexibility of the cyclohexa-1,4-diene ring has been verified theoretically by molecular mechanics[10,11] and by the MNDO [11] and *ab initio*[12,13] methods. It was found that the minimum in the potential energy surface in molecule **1** is markedly flattened. As a result, the transition from the equilibrium planar conformation to a boat-like conformation in which the angle between the planes of the double bonds is ±160° increases the molecular energy by less than 1 kcal mol^{-1}.

This property of the dihydrogenated ring is due to the fact that its conformation is determined by two factors acting in opposite directions.[3,11,14,15] One of these factors is the angular strain arising due to the deformation of the endocyclic bond angles at the saturated carbon atoms in the planar conformation, while the other factor is the 1,2-allylic strain caused by nonvalence interactions between the hydrogen atoms of the methylene groups and the double bonds; this stabilizes the planar geometry of the ring. The transition of the cyclohexa-1,4-diene ring into the boat conformation decreases the angular strain but, simultaneously, it enhances the 1,2-allylic interaction. Consequently, the overall change in the molecular energy proves to be insignificant.

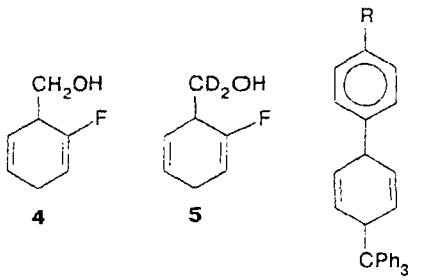
The electronic interactions between the π-systems of the double bonds in **1** also have a substantial effect on the conformation of the dihydrocycle.[16] It is known[17,18] that the double bonds in cyclohexa-1,4-diene are not isolated and can interact both through the direct overlap of the p_z-AO through space (through-space interaction) and due to overlap with the pseudo-π-orbitals of the methylene groups (through-bond interaction). The former type of interaction depends on the distance between the double bonds and, hence, it stabilizes the nonplanar conformation of the ring. The efficiency of the interaction through bonds is determined by the mutual orientation of the p_z-AO of the carbon atoms at the double bonds and the pseudo-π-orbitals of the methylene groups and thus it is the maximum in the planar ring. AM1 calculations have shown[16] that the energy of the through-space interaction in molecule **1** is negligibly small (less than 0.003 eV) and that it slightly changes when the ring is bent. Conversely, the energy of interaction through bonds is fairly large (1.46 eV) and sharply decreases on passing into the boat conformation. Thus, this interaction is an additional factor stabilizing the planar conformation of the cyclohexa-1,4-diene ring.

On going to benzannelated derivatives of **1**, 1,4-dihydronaphthalene **2** and 9,10-dihydroanthracene **3**, the conformational flexibility of the dihydrocycle substantially increases, which has been confirmed both in theoretical[11] and in experimental[19] (^{1}H NMR) studies.

This has been explained[10,11,14,15] by the increase in the angular strain due to the fact that $C(sp^3)$—C(Ar)—C(Ar) bond angles are more rigid than $C(sp^3)$—$C(sp^3)$—H angles. The fact that the barrier to rotation around the $C(sp^3)$—C(Ar) bond is lower than that around the $C(sp^3)$—$C(sp^2)$ bond has been considered as an additional factor responsible for the increase in the flexibility of the ring in the **1**—**2**—**3** series.[20] However, its role seems to be relatively small.

The introduction of a substituent to a saturated carbon atom in the dihydrogenated ring results in its transition into a boat conformation with the pseudoaxial orientation of the substituent,[14] owing to the appearance of asymmetry in the nonvalence interactions of the 1,2-allylic type along the $C(sp^2)$—$C(sp^3)$ bonds.

Based on the ^{1}H NMR data, it has been shown[21,22] that the rings in compounds **4** and **5** are less flexible. However, a certain flexibility of the ring is retained even in the presence of bulky substituents, for example, in molecules **6** and **7** containing triphenylmethyl groups, despite the substantial steric restrictions.[23,24]



4 **5**

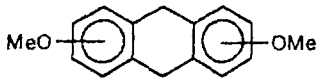
6: R = H
7: R = Br

6, 7

No data on the effects of substituents in 1,4-dihydronaphthalene can be found in the literature. The influence of substituents on the conformational flexibility has been studied most extensively for 9,10-dihydroanthracene derivatives, apparently, due to the fact that these compounds are obtained relatively easily and are fairly stable.

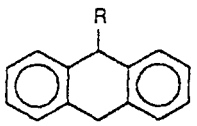
An ^{1}H NMR study of the dynamics of the ring in the methoxy derivative **8** has led to contradictory results.

First, it was shown that compounds of this type are conformationally rigid.[25] However, more recent studies[26] have led to the opposite conclusion, and the earlier results[25] have been explained by false interpretation of spin-spin coupling constants.



8

As in the case of compounds **4**—**7**, the dihydrogenated ring in alkyl derivatives **9** remains flexible.[27] This feature is also retained in the dimethyl-substituted derivative **10**, despite the fact that the 1,2-allylic strain stabilizing the planar conformation becomes substantially stronger.[28]



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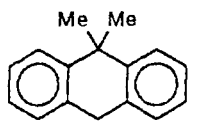
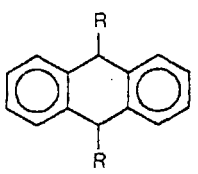


10

R = Me, Pr^i, Bu^t

Study of the conformational flexibility of the partially hydrogenated ring in 9,10-disubstituted derivatives **11** and **12** by ^{1}H and ^{13}C NMR spectroscopy and by molecular mechanics has shown[29,30] that *cis*- and *trans*-isomers are appreciably dissimilar in this respect. The unfavorable nonvalence interactions between the alkyl group and the hydrogen atoms in the *peri*-positions of the benzene rings cause a sharp increase in the rigidity of the *cis*-isomer with diaxial orientation of substituents and with flattened ring. An increase in the degree of folding of the partially hydrogenated ring in this case enhances the repulsion between the alkyl groups, which also increases somewhat the rigidity of the ring conformation. In the case of *trans*-isomers, one of the substituents is always located near the *peri*-hydrogen atoms of the benzene rings, which destabilizes the equilibrium conformation and is favorable for the dihydroanthracene fragment being flexible. An exception is 9,10-dinitro-derivative **13**. According to ^{1}H NMR data, the dihydrogenated ring is conformationally flexible in both isomers of **13**;[31] this is apparently due to the strong electrostatic interactions between the substituents and between the oxygen atoms of the nitro groups and the *peri*-hydrogen atoms, which stabilize both conformations.



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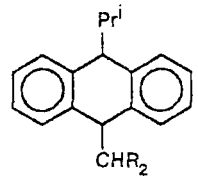
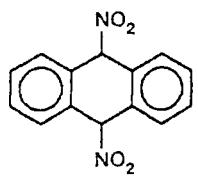


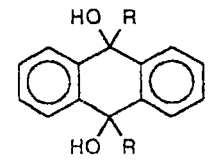
12

R = Me, Et, Pr^i, Bu^t

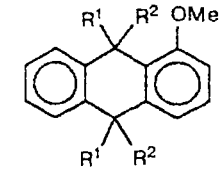


13

The decisive role of the interactions between the substituents at the saturated carbon atoms and the hydrogen atoms in *peri*-positions of the benzene rings has also been confirmed in a ^{1}H NMR study[32] of tetra-substituted derivatives **14**. In these compounds, the above-mentioned interactions occur in both isomers and account for the retention of the ring flexibility. However, for the same reason, the introduction of a methoxy group in the *peri*-position (compound **15**) leads to a substantial increase in the rigidity of the partially hydrogenated ring.



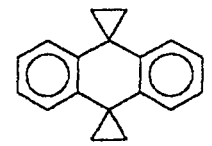
14



15

R = Me, Et, Pr, $(CH_2)_2Ph$; R^1 = H, OH; R^2 = Me, Et, Pr, $(CH_2)_2Ph$

A molecular mechanics calculation has shown[33] that the ring remains flexible even in dispiro derivative **16**.



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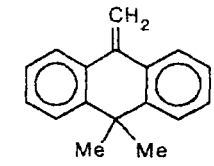
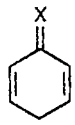


17

The replacement of one of the methylene groups in cyclohexa-1,4-diene by an exocyclic double bond enhances the flattening factors, because it decreases the angular strain and because a system of conjugated bonds is formed in the ring. However, according to *ab initio* quantum-chemical calculations in the 6-31G basis set, the dihydrogenated ring in 1-oxocyclohexa-1,4-diene is only slightly more rigid than that in the unsubstituted molecule. On passing from the planar equilibrium conformation to the boat-like conformation with a C=C—C(sp^3)—C= torsion angle of ±20°, the energy of the molecule increases by 1.82 kcal mol^{-1}. The conformational flexibility of the dihydrogenated rings in the ylidene derivatives of 9,10-dihydroanthracene has also been confirmed[34] in a ^{1}H NMR study of compound **17**.

According to *ab initio* calculations, the flexibility of the partially hydrogenated ring increases on going from oxo to imino and then to the methylene derivative of cyclohexa-1,4-diene[35] (compounds **18**). The introduction of substituents to the exocyclic double bond in compounds **19** results in the fixation of the equilibrium conformation of the ring and in the loss of flexibility,[36] due to the repulsion between the methyl groups and the hydrogen atoms in the *peri*-positions of the benzene rings. In all cases, the presence of a conjugated system of bonds in the ring disturbs the symmetry of the boat conformation. The saturated carbon atom deviates from the root-mean-square plane of the double bonds much more substantially than the second bridging carbon atom.



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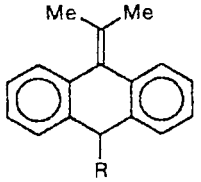

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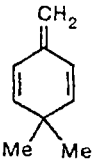


20

X = O, NH, CH_2

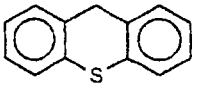
The high conformational flexibility of the dihydrogenated ring in ylidene derivatives of cyclohexa-1,4-diene makes it possible to explain the contradictions in the experimental data on the equilibrium geometry of compound **20**. Initially, it has been found by microwave spectroscopy[37] that the dihydrogenated ring exists in a boat conformation with an angle between the planes of the double bonds of 172°. However, a more recent and more thorough study led to the conclusion that it exists in a planar conformation,[38] which is also in agreement with theoretical results.[35,39]

1,4-Dihydrogenated heterocycles

According to molecular mechanics,[40] AM1,[41,42] and *ab initio* (HF/3-21G [43] and HF/6-31G [35]) calculations, the replacement of one of the methylene groups in cyclohexa-1,4-diene by a heteroatom (compounds **21**—**23**) increases the rigidity of the ring but to a lesser extent than the introduction of an exocyclic double bond. In fact, in the 1,4-dihydropyridine molecule, the transition from the planar equilibrium conformation into a boat conformation with a C=C—C(sp^3)—C= torsion angle of ±20° increases[35] the energy of the molecule by 0.84 kcal mol^{-1}. The results of calculations were confirmed by ^{1}H NMR studies[44] of compound **24**.

It has been found by AM1 calculations[42] that the change in the nature of the double bonds in 1,4-dihydro derivatives of pyridine (**22**), pyrimidine (**25**), pyridazine (**26**), and 1,3,5-triazine (**27**) has no noticeable effect on the flexibility of the partially hydrogenated ring. The replacement of the bridging heteroatom is more significant. Compound **22** and 4*H*-pyran (**23**) are characterized by close changes in energy following the bending of the ring by 20° (~0.9 kcal mol^{-1}).[35] However, in the case of 4*H*-thiopyran, this value is much smaller[35] (0.1 kcal mol^{-1}), which is apparently due to the additional angular strain resulting from the fact that in the planar conformation, the endocyclic C—S—C bond angle markedly deviates from its "natural" value (~100°).[45,46]

21—23



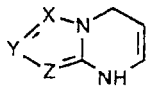
24

25

21: X = S, **22**: X = NH, **23**: X = O

26

27

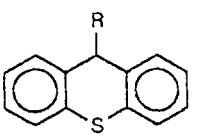


28

X, Y, Z = CH, N

Annelation of a benzene[14,47] or an azole[48,49] ring to one of the double bonds of the 1,4-dihydrogenated heterocycle enhances its flexibility. This is due to the same reasons as in the case of cyclohexa-1,4-diene derivatives. However, an MNDO study of this feature in 4,7-dihydroazolo[1,5-*a*]pyrimidines (**28**) has demonstrated that the energy change following the bending of the dihydropyrimidine ring depends on the nature of the five-membered ring.[49] The dihydrogenated ring in the imidazole derivative proved to be the most flexible, while that in the pyrazole derivative was found to be the most rigid. This sequence is inconsistent with the variation of the π-electron character of the azole rings; therefore, it has been explained by different energies of interaction of the π-system of the five-membered ring with the C=C double bond through the methylene group.

The introduction of substituents to a carbon atom, closest to the bridging heteroatom, at the double bond has no significant effect on the conformational flexibility of the dihydrocycle.[40,48] An increase in the bulk of the substituent attached to the other carbon atom at the double bond results in a decrease in the mobility of the partially hydrogenated ring, because it enhances 1,2-allylic interactions. Alkyl groups attached to the saturated carbon atom exert a similar effect.[40,48] The flexibility of the dihydrogenated ring in the latter case has been confirmed by studies[14,50] of the ^{1}H NMR spectra of compounds **29** and **30**.



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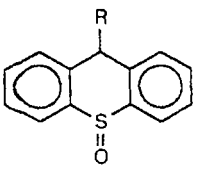


30

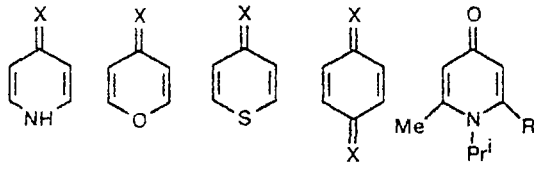
R = Me, Et, Pr^i

Table 1. Ranges of variation of endocyclic torsion angles (τ) in various compounds containing some types of dihydrogenated rings, according to X-ray diffraction data

Dihydrocycle	Number of structures with $R < 0.1$	Torsion angle	τ/deg
p-Quinone	155	C=C—C(=O)—C	−21.4—21.1
4-Pyridone	61	C=C—C(=O)—C	−9.4—7.9
4*H*-Pyranone	59	C=C—C(=O)—C	−26.2—28.4
2-Pyridone	165	=C—C(=O)—NH—C=	−11.4—8.1
2*H*-Pyranone	252	=C—C(=O)—O—C=	−11.2—13.8
Uracil	469	NH—C(=O)—NH—C(=O)	−12.5—11.0
Cytosine	264	=N—C(=O)—NH—C=	−14.0—11.3
Isocytosine	208	=C—NH—C(=O)—C=	−10.5—12.4

1,4-Dihydrogenated rings containing no saturated carbon atoms

The replacement of the second methylene group in ylidene derivatives or in heterocyclic analogs of cyclohexa-1,4-diene (**31—34**) by an exocyclic double bond removes the angular strain, and, hence, it eliminates the factor destabilizing the planar conformation of the partially hydrogenated ring. A dynamic NMR study of substituted pyridones **35** made it possible to assume[51] that the conformational flexibility of the ring is retained within certain limits. The possibility of relatively easy deformation of the endocyclic torsion angles in these compounds has also been confirmed by analysis of the distribution of the magnitudes of the endocyclic torsion angles in the crystals of various types of derivatives containing 1,4-dihydrogenated rings with no saturated carbon atoms, carried out using the Cambridge Crystal Structure Database[52] (Table 1). For comparison, the corresponding range for benzene derivatives is ±4°.



31 **32** **33** **34** **35**

R = Me, Et, Pr^i

Quantum-chemical AM1 [53,54] and *ab initio* (HF/6-31G)[35] calculations have shown that in compounds **31—34**, the conformational flexibility of the partially hydrogenated ring somewhat decreases. However, in general, this property is retained. For example, the transition of the partially hydrogenated ring in the molecule of 4-pyridone from the planar equilibrium conformation into the boat conformation with a C=C—C(=O)—C= torsion angle of ±20° increases[35] the energy by less than 2.4 kcal mol^{-1}. For comparison a similar deformation of the ring in pyridine requires[43] more than 8 kcal mol^{-1}.

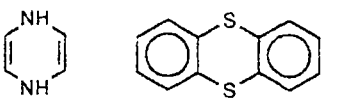
The fact that the flexibility of the dihydrogenated ring incorporating no saturated carbon atoms is retained implies that a new factor destabilizing the planar conformation has appeared. Since in these molecules, steric effects are relatively insignificant, this new factor has obviously an electronic nature.

Analysis of the electronic structures of 1,4-dihydrogenated rings has shown[35,54] that the π-MO, which are most strongly deformed on bending of the ring, have the same general form for all types of 1,4-dihydrogenated rings (Fig. 1). The replacement of the methylene group by a heteroatom or by an exocyclic double bond changes the polarities of these MO; however, their overall symmetry is retained.

The presence of a cyclic conjugated system in molecules **31—34** make it possible to consider them in terms of the aromaticity concept. According to the Hückel rule, all these compounds can be formally divided into two groups: compounds with aromatic 6π-electron conjugated systems (for example, quinone) and those containing nonaromatic 7π-electron conjugated systems (ylidene derivatives of 1,4-dihydrogenated heterocycles). In the former case, a decrease in the polarity of the exocyclic double bond should lead to an increase in the extent of aromaticity of the π-system and, as a consequence, to a decrease in the flexibility of the ring. In the latter case, the opposite effect should be observed. The results of AM1 [54] and HF/6-31G [35] calculations fully confirm this hypothesis. In the quinone—quinonimine—quinonemethide series, the conformational flexibility of the ring decreases, whereas in the oxo-imino-methylene series of 1,4-dihydropyridine derivatives, it increases. Thus, it can be assumed that it is the disturbance of aromaticity of a cyclic conjugated system that acts as the new factor destabilizing the planar conformation of the dihydrogenated ring.

The crucial role of the degree of aromaticity in the conformational dynamics of six-membered 1,4-dihydrogenated rings is also confirmed by the large coefficients of correlation (0.90—0.98) between the change in the molecular energy following bending of the ring by 30° and the Bird[55] and Pozharskii[56] aromaticity indices found from the results of non-empirical[35] and semi-empirical[54] quantum-chemical calculations.

The dihydrogenated ring in 1,4-dihydropyrazine (**36**) incorporating an antiaromatic cyclic conjugated system is even more flexible.[43] A similar π-system is also present in molecule **37**. However, in this case, quantum-chemical calculations[57,58] led to the conclusion that the partially hydrogenated ring is rigid. However, it should be borne in mind that the methods of calculation used in these studies were not perfect; therefore, this conclusion appears to be conjectural.



36 **37**

The conformational flexibility of the heterocycle in the carbonyl derivatives of 1,4-dihydroazines, unlike that for unsubstituted compounds, depends on the nature of the exocyclic double bond.[53,54] According to AM1 calculations, the dihydrogenated ring in 4-oxo-1,4-dihydro-1,3,5-triazine is the most flexible, while that in 4-pyridone is the most rigid. This may indicate that the conformational rigidity of the partially hydrogenated ring depends not only on such an integral factor as the degree of aromaticity of the cyclic π-system, but also on differential factors such as the efficiency of conjugative interactions of the bridging groups with endocyclic double bonds.

Cyclohexa-1,3-diene and its derivatives

According to microwave spectroscopy[59,60] and gas electron diffraction,[2,61,62] the molecule of cyclohexa-1,3-diene (**38**) exists in a conformation with C_2 symmetry; this conformation is intermediate between the sofa and half-chair conformations and can be characterized as a distorted sofa. The torsion angle between the endocyclic double bonds, according to several estimates, ranges from 12° to 18°.

38

The equilibrium conformation of the ring in **38** is determined, as in the case of cyclohexa-1,4-diene, by two opposing groups of factors.[2,14,15] One of them is the conjugation between the double bonds, which promotes flattening of the molecule, while the other group includes the angular strain arising due to the deformation of the endocyclic bond angles at the saturated carbon atoms, which is the maximum when the ring is planar, and the tendency to attain a staggered conformation along the $C(sp^3)—C(sp^3)$ bond. The geometrical parameters of the ring found experimentally indicate that the bending factors predominate.

Over a long period of time, this dihydrogenated ring has been considered as conformationally rigid (see, for example, a review[15]). However, a detailed study of the ring inversion in compound **38** has shown[63] that only the $=C—C(sp^3)—C(sp^3)—C=$ torsion angle can act as the reaction coordinate for the conformational transition. Conversely, the change in the angle between the double bonds does not lead to the transition into the mirror-symmetric conformer. The molecular mechanics calculation of the potential energy surface as a function of the two torsion angles mentioned above[63,64] has revealed a number of unusual features. It was found that the valley, in which the points of minima and the transition states of inversion are located, is *Z*-shaped. Thus, the change in the torsion angle between the double bonds toward flattening of the butadiene fragment results in the movement of the molecule to an

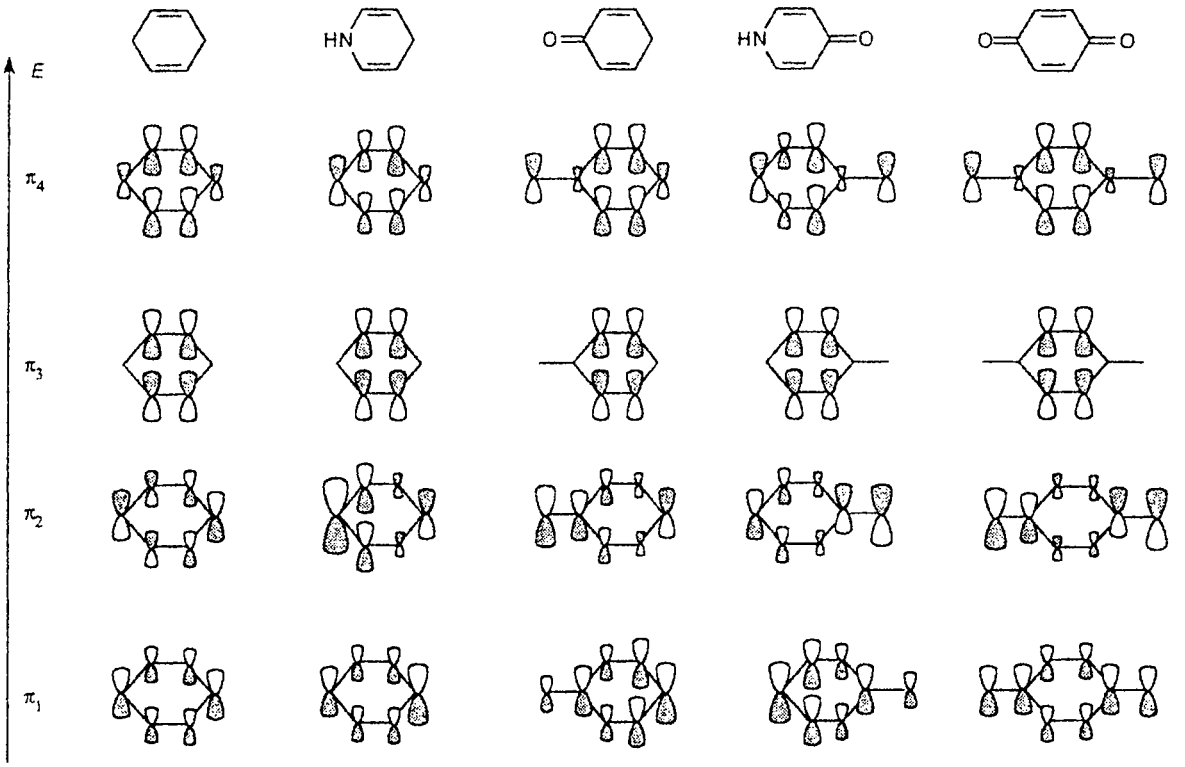
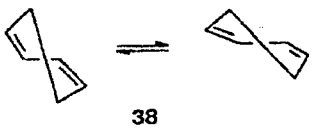


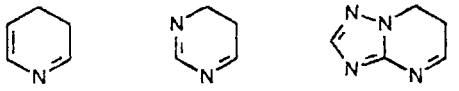
Fig. 1. General view of π-MO in various types of 1,4-dihydrogenated rings.

appendix of the valley, which does not lead to the transition state. As this takes place, the torsion angle between the single bonds remains virtually constant, and the C=C bonds become markedly twisted. The calculations show[63] that flattening of the π-system in cyclohexa-1,3-diene increases the energy of the molecule by less than 1.5 kcal mol^{-1}.



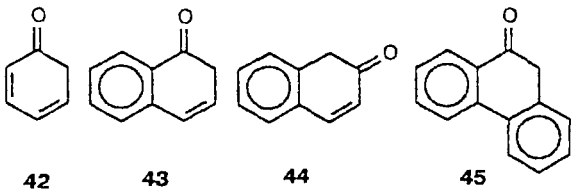
38

Thus, in this case, only the saturated fragment of the dihydrogenated ring proves to be conformationally rigid. The conjugated system can execute twisting vibrations with a fairly large amplitude. A similar effect has also been observed[65,66] in heterocyclic analogs of **38** (compounds **39**—**41**).



39 **40** **41**

When one of the methylene groups in molecule **38** is replaced by an exocycic C=O double bond, the conformation of the dihydrogenated ring is flattened,[67,68] because the angular strain decreases, the CH_2—CH_2 fragment disappears, and the conjugated system is extended. The partially hydrogenated ring remains nonrigid; however, the type of flexibility becomes similar to that found in cyclohexa-1,4-diene derivatives. According to calculations by molecular mechanics and by the MNDO [67] and AM1 [68] methods, the transition of the ring in molecule **42** from the equilibrium planar conformation into the distorted sofa conformation with a =C—C(=O)—C—C= torsion angle of ±20° increases the energy of the molecule by less than 1 kcal mol^{-1}.



42 **43** **44** **45**

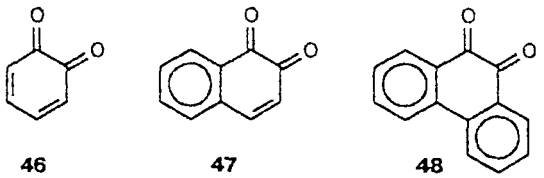
The introduction of alkyl substituents to the saturated carbon atom leads to the transition of the partially hydrogenated ring into the distorted sofa conformation and to a substantial decrease in the flexibility of the ring owing to enhancement of the 1,2-allylic interactions.

The molecular mechanics and MNDO calculations have shown[67] that the ring in molecule **42** is insensitive to the steric and electronic effects of substituents at the double bonds.

The increase in the angular strain in naphthalene derivatives **43** and **44** results in an increase in the conformational flexibility of the partially hydrogenated ring.[68] As in the case of benzannelated derivatives of cyclohexa-1,4-diene, this is due to the appearance of the rigid benzene ring in the structure. This effect is more pronounced in compound **44** than in **43**, because in the former case, the saturated carbon atom is directly linked to the aromatic ring.[68]

In 9,10-dihydrophenanthrene derivative **45**, the dihydrogenated ring exists in the distorted sofa conformation, which is due to the repulsion of the hydrogen atoms in the *peri*-positions of the benzene rings in the planar conformation of the molecule. These interactions are responsible for the substantial increase in the rigidity of the partially hydrogenated ring,[68] because further deviation of the molecule from the planar conformation would result in an appreciable disruption of the conjugation between the benzene rings, whereas its flattening would lead to a sharp increase in the unfavorable H...H interactions.

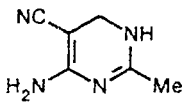
The replacement of the second methylene group by a carbonyl group, *i.e.*, transition to *o*-quinone **46**, removes the angular strain. However, the planar conformation of the ring proves to be destabilized by the repulsion of the lone electron pairs of the oxygen atoms in the vicinal carbonyl groups.[68] According to AM1 calculations, this effect is stronger than the angular strain. The transition of molecule **46** from the equilibrium planar conformation into the distorted sofa conformation with a =C—C(C=O)—C(=O)—C= torsion angle of ±20° requires[68] less than 0.5 kcal mol^{-1}. The dihydrogenated ring in naphthoquinone **47** is even more flexible. In the case of phenanthroquinone **48**, the partially hydrogenated ring is markedly more rigid, which is due to the reasons discussed above.



46 **47** **48**

1,2-Dihydrogenated heterocycles

One of the most interesting problems in the theoretical conformational analysis of 1,2-dihydrogenated heterocycles is determination of the equilibrium conformations for 1,2- and 1,6-dihydroazines and 2*H*-pyran. According to molecular mechanics and quantum-chemical calculations,[69—73] the rings in 1,2- and 1,6-dihydropyridines, pyrimidines, and 2*H*-pyran are planar. However, an X-ray diffraction analysis of derivatives of these heterocycles containing no substituents at the saturated carbon atom (for example,[74,75] **49** and **50**) has demonstrated the existence of distorted sofa conformations with various degrees of folding. This inconsistency has been explained only when the conformational flexibility of these heterocyclic derivatives has been considered.



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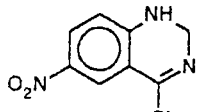

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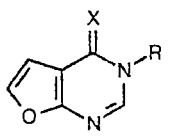
As shown by AM1 calculations,[71–73] the transition of the dihydrogenated ring from the equilibrium planar conformation into a distorted sofa type conformation with a =C—C(sp^3)—X—C= torsion angle (X = NH, O) of ±20° increases the energy of the molecule by less than 1 kcal mol^{-1}; the difference between the flexibilities of 1,2-dihydropyridine and 2*H*-pyran is slight. It should be noted that the changes in the energy of the molecules considered here are much smaller than those observed for the corresponding 1,4-dihydrogenated derivatives.

Thus, intermolecular interactions in the crystal can easily change the geometry of 1,2-dihydrogenated heterocycles, which results in the contradictions between theoretical and experimental data.

When the methylene group is replaced by an exocyclic double bond, the rigidity of the ring increases; however, generally, the ring remains flexible.[71–73] The transition of the 2-pyridone molecule from the equilibrium planar conformation into the distorted sofa conformation with a =C—C(=O)—NH—C= torsion angle of ±20° increases the energy by 1.4 kcal mol^{-1}. The reasons for these effects are similar to those discussed above for 1,4-dihydrogenated heterocycles. It should be noted that the calculated[72] coefficients of correlation between the aromaticity indices and the energies required to bend the ring by 30° are substantially larger than those for the 1,4-dihydrogenated analogs (r = 0.98—0.99).

Annelation of the 1,6-dihydropyrimidine ring to a furan ring (compounds **51**) somewhat increases the rigidity of the ring,[73] unlike the situation observed for 4,7-dihydroazolopyrimidines.[48] Apparently, in this case, the extension of the conjugated system has a stronger effect on the conformational behavior of the partially hydrogenated ring than the enhancement of the angular strain. The introduction of substituents to the nitrogen atom of the imino group has the opposite effect due to the repulsion between the alkyl radical and the vicinal exocyclic double bond.[73]



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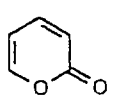


52

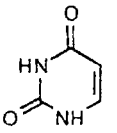
X = H_2, O, NH, CH_2; R = H, Me

Analysis of the thermal vibrations in molecule **52** made it possible[76] to assume that out-of-plane vibrations of the ring occur with a noticeable amplitude even in the crystalline phase.

Conformational flexibility of the ring in biologically active molecules

It is clear that such a fundamental feature as the conformational flexibility of the partially hydrogenated ring should have an appreciable effect on the physicochemical properties of compounds containing these rings. The allowance for the dynamic properties of the partially hydrogenated rings is especially significant when the molecule participates in intermolecular interactions of the "host—guest" type, for example, in biological systems.

Quantum-chemical calculations by the AM1 method have shown[77] that tetrahydro-2,4-dioxopyrimidine and oxodihydropyrimidine rings incorporated in the nucleic bases uracil (**53**), thymine (**54**), cytosine (**55**), isocytosine (**56**), and guanine (**57**) possess fairly high conformational flexibilities. The transition from the equilibrium planar conformation into the distorted sofa conformation with a corresponding torsion angle equal to ±20° increases the molecular energies by less than 1.5 kcal mol^{-1}. The tetrahydrogenated rings in uracil and thymine containing formally antiaromatic cyclic conjugated systems are especially flexible.



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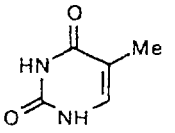

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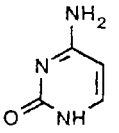

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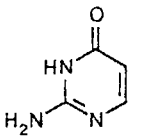

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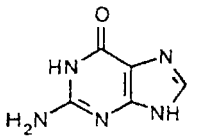

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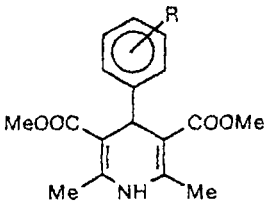
The relative ease of deformation of these rings is also supported by an analysis of the distribution of the magnitudes of the torsion angles in uracil, cytosine, and isocytosine based on X-ray diffraction data (see Table 1).

The results point to the occurrence of "breathing" vibrations in DNA and RNA molecules associated with the change in the conformations of the partially hydrogenated rings of pyrimidine and pyrine bases incorporated in these molecules. In addition, the generally accepted distance between the pairs of bases linked by stacking interactions (3.4 Å) is apparently the averaged value and can vary within certain limits.

Yet another example of the role of flexibility of biologically active molecules is provided by the agonists and antagonists of the cell calcium channels of the general formula **58**. Studies on structure—activity correlations carried out for several years[78–80] have led to the conclusion that there is a correlation between the physiological action and the degree of folding of the

1,4-dihydropyridine ring found from X-ray diffraction data for the crystals. However, calculations by a molecular mechanics method[81] have shown that the partially hydrogenated rings in all of these molecules possess fairly high conformational flexibilities. The range in which the variation of the C=C—C—C= torsion angle is accompanied by an increase of the molecular energy by no more than 1 kcal mol^{-1} with respect to its equilibrium conformation amounts to ~40°. Even if the imperfection of the calculation procedures and the influence of the solvent are taken into account, this value remains fairly large and completely covers the region in which the structure—property correlation was observed. Therefore, the different biological activities of these compounds cannot be due to the differences in the conformations of their dihydrogenated heterocycles and are caused apparently by other factors.



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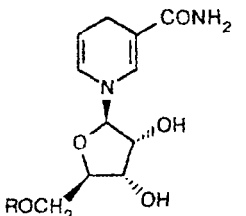


59

A significant role is played by the conformational flexibility of the 1,4-dihydropyridine ring in the NADH (**59**) molecule, which participates in important redox processes in a living organism.

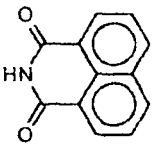
According to the data of NMR spectroscopy[82] and AM1 [41,83] and HF/3-21G *ab initio*[43] calculations, the dihydrogenated heterocycle in **59** possesses high conformational flexibility. The nonplanar conformation of the pyridine ring is[84] a necessary condition for the occurrence of stereospecific enzymatic reactions involving NADH. The high degree of flexibility of the 1,4-dihydropyridine ring ensures a population of the boat conformation needed for this purpose and thus facilitates the interaction with the active site of an enzyme.

Thus, while considering the interaction of molecules containing six-membered dihydrogenated rings with bioreceptors, one should take into account not only the particular geometry of the molecule but also the set of possible conformations of the reacting molecule with endocyclic torsion angles varying within a certain range. Therefore, any search for more or less strict relationships between the geometric parameters of a molecule and its biological activity without allowance for the dynamics of the cyclic system appears to have few prospects.

Rigid-chain heterocyclic polymers

Yet another example of the relationship between the dynamic properties of partially hydrogenated rings and physicochemical characteristics of compounds are rigid-chain heterocyclic polymers based on naphthylimide (for example, **60**). The main and the most significant characteristic of these polymers is the Kuhn segment, *i.e.*, the length of a straight section in the macromolecule. In the ideal case, when there are no fragments that disturb the rod-like shape of the monomeric unit, the Kuhn segment would be infinitely long. However, experimental measurements lead to finite although fairly large values.[85,86] This result could not be explained from the viewpoint of thermal vibrations of atoms, incomplete cyclization of the imide fragment, or other factors.

Calculations by the AM1 method have shown[87] that the imide rings in the molecules of naphthylimide (**61**) and naphthyldiimide (**62**) can be easily transformed into the sofa conformation. A change in the C(Ar)—C(=O)—NH—C(=O) torsion angle by ±20° increases the molecular energy by less than 1 kcal mol^{-1}. The energies required for the symmetric and antisymmetric changes in these torsion angles in two imide rings in molecule **62** are virtually identical. Therefore, the rod-like shape of these polymers can be disturbed as a result of flexibility of the imide rings. Monte Carlo modeling of the structure of polymers with allowance for the contribution of nonplanar conformations of the imide ring has fully confirmed this hypothesis.[88]



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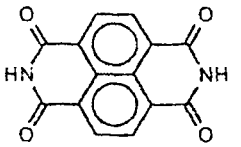

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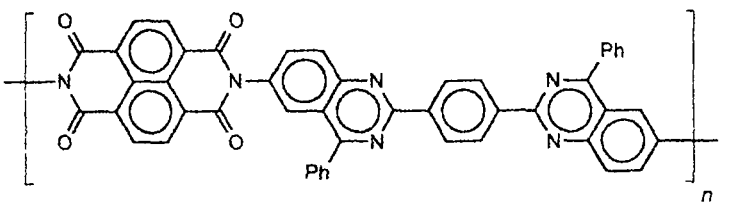
Thus, the studies surveyed in this review demonstrate that conformational flexibility is a general fundamental feature of six-membered dihydrogenated rings, which is intimately connected with their electronic structure. The conformational flexibility of the ring can exert a



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substantial effect on the physicochemical characteristics of compounds.

References

1. P. L. Eliel and S. M. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, 983 pp.
2. H. Oberhammer and S. H. Bauer, *J. Am. Chem. Soc.*, 1969, **91**, 10.
3. J. Laane and R. C. Lord, *J. Mol. Spectrosc.*, 1971, **39**, 340.
4. L. A. Carreira, R. O. Carter, and J. R. Durig, *J. Chem. Phys.*, 1973, **59**, 812.
5. H. Hagemann, H. Bill, D. Joly, P. Muller, and N. Pautex, *Spectrochim. Acta*, 1985, **A41**, 751.
6. M. C. Grossel and M. J. Perkins, *Nouv. J. Chem.*, 1979, **3**, 285.
7. G. A. Jeffrey, J. Buschmann, C. W. Lehmann, and P. Luger, *J. Am. Chem. Soc.*, 1988, **110**, 7218.
8. G. Ahlgren, B. Akermark, and J. E. Backvall, *Tetrahedron Lett.*, 1975, 3501.
9. S. Saeboe and J. E. Boggs, *J. Mol. Struct.*, 1981, **73**, 137.
10. N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, 1972, **94**, 5734.
11. K. B. Lipkowitz, P. W. Rabideau, D. J. Raber, L. E. Hardee, P. v. R. Schleyer, A. J. Koss, and R. A. Kahn, *J. Org. Chem.*, 1982, **47**, 1002.
12. A. Sygula and T. A. Holak, *Tetrahedron Lett.*, 1983, **24**, 2893.
13. T. Schaefer and R. Sebastian, *J. Mol. Struct., THEOCHEM*, 1987, **153**, 55.
14. *Conformational Analysis of Cyclohexenes, Cyclohexadienes and Related Hydroaromatic Compounds*, Ed. P. W. Rabideau, VCH, New York, 1989, 296 pp.
15. A. N. Vereshchagin, *Usp. Khim.*, 1983, **52**, 1879 [*Russ. Chem. Rev.*, 1983, **52** (Engl. Transl.)].
16. O. V. Shishkin, A. S. Polyakova, S. M. Desenko, O. V. Prezhdo, V. D. Orlov, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1676 [*Russ. Chem. Bull.*, 1994, **43**, 1587 (Engl. Transl.)].
17. R. Hoffman, *Acc. Chem. Res.*, 1971, **4**, 1.
18. R. Gleiter and W. Schaefer, *Acc. Chem. Res.*, 1990, **23**, 369.
19. W. B. Smith and B. A. Shoulders, *J. Phys. Chem.*, 1965, **69**, 2022.
20. U. Burkert and N. L. Allinger, *Molecular Mechanics*, Am. Chem. Soc., Washington, 1982, 364 pp.
21. J. W. Paschal and P. W. Rabideau, *J. Am. Chem. Soc.*, 1974, **96**, 272.
22. P. W. Rabideau, J. W. Paschal, and L. E. Patterson, *J. Am. Chem. Soc.*, 1975, **97**, 5760.
23. M. C. Grossel, A. K. Cheetham, D. A. O. Hope, and S. C. Weston, *J. Org. Chem.*, 1993, **58**, 6654.
24. A. K. Cheetham, M. C. Grossel, and J. M. Newsam, *J. Am. Chem. Soc.*, 1981, **103**, 5363.
25. F. G. Jimenez, M. C. Perezamador, and J. R. Alcayde, *Can. J. Chem.*, 1969, **47**, 4489.
26. P. W. Rabideau, *J. Org. Chem.*, 1971, **36**, 2723.
27. P. W. Rabideau, L. M. Day, C. A. Husted, J. L. Mooney, and D. M. Wetzel, *J. Org. Chem.*, 1986, **51**, 1681.
28. D. K. Dalling, K. W. Zilm, D. M. Grant, W. A. Heesen, W. J. Norton, and R. J. Pugmier, *J. Am. Chem. Soc.*, 1981, **103**, 4817.
29. P. W. Rabideau, J. L. Mooney, and K. B. Lipkowitz, *J. Am. Chem. Soc.*, 1986, **108**, 8130.
30. P. W. Rabideau, W. K. Smith, and B. D. Ray, *Magn. Res. Chem.*, 1989, **27**, 191.
31. G. L. Squadrito, F. R. Fronczek, S. F. Watkins, D. F. Church, and W. A. Pryor, *J. Org. Chem.*, 1990, **55**, 4322.
32. N. Ahmad, C. Cloke, I. K. Hatton, N. J. Lewis, and J. MacMillan, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1849.
33. S. Rosenfeld, C. W. Tingle, J. P. Jasinski, J. E. Whittum, and R. C. Wondenberg, *J. Am. Chem. Soc.*, 1994, **116**, 12049.
34. D. Y. Curtin, C. G. Carlson, and C. G. McCarthy, *Can. J. Chem.*, 1964, **42**, 565.
35. O. V. Shishkin, *J. Mol. Struct.*, 1997, **412**, 115.
36. H. Cho, R. G. Harvey, and P. W. Rabideau, *J. Am. Chem. Soc.*, 1975, **97**, 1140.
37. M. Traetteberg, P. Bakken, A. Almenningen, W. Luttke, and J. Janssen, *J. Mol. Struct.*, 1982, **81**, 87.
38. W. Hutter and H.-K. Bodenseh, *J. Mol. Struct.*, 1993, **291**, 151.
39. W. Hutter and H.-K. Bodenseh, *J. Mol. Struct.*, 1994, **319**, 713.
40. O. V. Shishkin, T. V. Timofeeva, S. M. Desenko, V. D. Orlov, S. V. Lindeman, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1217 [*Russ. Chem. Bull.*, 1993, **42**, 1160 (Engl. Transl.)].
41. O. Almarsson, R. Karaman, and T. C. Bruice, *J. Am. Chem. Soc.*, 1992, **114**, 8702.
42. O. V. Shishkin, A. S. Polyakova, S. M. Desenko, and Yu. T. Struchkov, *Mendeleev Commun.*, 1994, 182.
43. D. J. Raber and W. Rodriguez, *J. Am. Chem. Soc.*, 1985, **107**, 4146.
44. A. Ricci, D. Pietropaolo, G. Distefano, D. Macciantelli, and F. P. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 1977, 689.
45. S. Hosoya, *Acta Cryst.*, 1963, **17**, 310.
46. M. B. Hossain, C. A. Dwiggins, D. Helm, P. K. Sen Gupta, J. C. Turley, and G. E. Martin, *Acta Crystallogr.*, 1982, **B38**, 881.
47. K. A. Jorgensen, *Tetrahedron*, 1986, **42**, 3707.
48. O. V. Shishkin, S. M. Desenko, V. D. Orlov, S. V. Lindeman, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1394 [*Russ. Chem. Bull.*, 1994, **43**, 1320 (Engl. Transl.)].
49. O. V. Shishkin, S. M. Desenko, V. D. Orlov, S. V. Lindeman, Yu. T. Struchkov, A. S. Polyakova, and E. I. Mikhed'kina, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1418 [*Russ. Chem. Bull.*, 1994, **43**, 1343 (Engl. Transl.)].
50. K. Lipkowitz, A. Burkert, and J. Landwer, *Heterocycles*, 1986, **24**, 2757.
51. G. Bartolli, M. Bosco, L. Lunazzi, and D. Macciantelli, *Tetrahedron*, 1994, **50**, 2561.
52. Cambridge Crystal Structure Database, Release 1996.
53. O. V. Shishkin, *Monatsch. Chem.*, 1996, **127**, 883.
54. O. V. Shishkin and A. S. Polyakova, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1938 [*Russ. Chem. Bull.*, 1996, **45**, 1836 (Engl. Transl.)].
55. C. W. Bird, *Tetrahedron*, 1993, **49**, 8441.
56. A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 1985, 867 [*Chem. Heterocycl. Compd.*, 1985 (Engl. Transl.)].
57. A. Chandra, *Tetrahedron*, 1963, **19**, 471.
58. P. T. Lansbury, *Acc. Chem. Res.*, 1969, **2**, 210.
59. S. S. Butcher, *J. Chem. Phys.*, 1965, **42**, 1830.
60. G. Luss and M. D. Harmony, *J. Chem. Phys.*, 1965, **43**, 3768.
61. G. Dallinga and L. H. Tonneman, *J. Mol. Struct.*, 1967, **1**, 11.

62. M. Traetteberg, *Acta Chem. Scand.*, 1968, **22**, 2305.
63. O. V. Shishkin, V. B. Zarkhin, T. V. Timofeeva, S. M. Desenko, V. D. Orlov, S. V. Lindeman, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1142 [*Russ. Chem. Bull.*, 1993, **42**, 1100 (Engl. Transl.)].
64. O. V. Shishkin, V. B. Zarkhin, S. M. Desenko, V. D. Orlov, T. V. Timofeeva, S. V. Lindeman, and Yu. T. Struchkov, *Teor. Eksp. Khim.*, 1992, 334 [*Theor. Exp. Chem.*, 1992 (Engl. Transl.)].
65. O. V. Shishkin, A. S. Polyakova, S. M. Desenko, V. D. Orlov, S. V. Lindeman, and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1994, 1009 [*Russ. Chem. Bull.*, 1994, **43**, 944 (Engl. Transl.)].
66. O. V. Shishkin, Ph. D. (Chem.) Thesis, Khar'kov State University, Khar'kov, 1994, 198 pp. (in Russian).
67. O. V. Shishkin and Yu. T. Struchkov, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 849 [*Russ. Chem. Bull.*, 1995, **44**, 823 (Engl. Transl.)].
68. O. V. Shishkin, *J. Mol. Struct.*, 1997, **403**, 167.
69. N. Bodor and R. Pearlman, *J. Am. Chem. Soc.*, 1978, **100**, 4946.
70. S. Bohm and J. Kuthan, *Coll. Czech. Chem. Commun.*, 1981, **46**, 2068.
71. O. V. Shishkin, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1934 [*Russ. Chem. Bull.*, 1996, **45**, 1833 (Engl. Transl.)].
72. O. V. Shishkin, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2650 [*Russ. Chem. Bull.*, 1996, **45**, 2509 (Engl. Transl.)].
73. O. V. Shishkin and D. M. Antonov, *J. Mol. Struct.*, 1996, **385**, 55.
74. A. Edenhofer, H. Spiegelberg, and W. E. Oberhansli, *Helv. Chim. Acta*, 1975, **58**, 1230.
75. A. T. Jonson, D. A. Keszler, K. Sakuma, and J. D. White, *Acta Crystallogr.*, 1989, **C45**, 1114.
76. A. J. Blake, R. O. Gould, S. G. Harris, H. McNab, and S. Parsons, *Acta Crystallogr.*, 1994, **C50**, 1938.
77. O. V. Shishkin, *J. Chem. Soc., Chem. Commun.*, 1995, 1539.
78. R. Fossheim, K. Svarteng, A. Mostad, C. Romming, E. Shefter, and D. J. Triggle, *J. Med. Chem.*, 1982, **25**, 126.
79. D. A. Lange and D. J. Triggle, *Acta Crystallogr.*, 1984, **A40**, 83.
80. K. S. Atwsll, G. C. Rownyak, J. Schwartz, S. Moreland, A. Hedberg, J. Z. Gougoutas, M. F. Malley and D. M. Floyd, *J. Med. Chem.*, 1990, **33**, 1510.
81. O. V. Shishkin, *J. Mol. Struct.*, 1996, **385**, 209.
82. H. Deng, J. Zheng, D. Sloan, J. Burgner, and R. Callender, *Biochem.*, 1992, **31**, 5092.
83. O. Almarsson and T. C. Bruice, *J. Am. Chem. Soc.*, 1993, **115**, 2125.
84. M. E. Brewster, E. Pop, M.-J. Huang, and N. Bodor, *Heterocycles*, 1994, **37**, 1373.
85. I. I. Ponomarev, I. A. Ronova, S. V. Lindeman, A. L. Rusanov, S. V. Vinogradova, and Yu. T. Struchkov, *Vysokomolek. Soedin.*, 1992, **34**, 123 [*Polym. Sci. USSR*, 1992, **34** (Engl. Transl.)].
86. N. V. Pogodina, A. B. Mel'nikov, A. L. Rusanov, S. V. Vinogradov, and I. I. Ponomarev, *Vysokomolek. Soedin.*, 1991, **A33**, 755 [*Polym. Sci. USSR*, 1991, **A33** (Engl. Transl.)].
87. O. V. Shishkin and I. I. Ponomarev, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 64 [*Russ. Chem. Bull.*, 1997, **46**, 59 (Engl. Transl.)].
88. I. A. Ronova, I. I. Ponomarev, and O. V. Shishkin, *Vysokomolek. Soedin.*, 1997, in press [*Polym. Sci.*, in press (Engl. Transl.)].

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