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ВЛИЯНИЕ СТЕРИЧЕСКОГО И ОРБИТАЛЬНОГО ВЗАИМОДЕЙСТВИЙ НА МОЛЕКУЛЯРНУЮ СТРУКТУРУ N-ПРОИЗВОДНЫХ ПИПЕРИДИНА

Конформационные свойства и молекулярная структура некоторых N-производных пиперидина, содержащих гетероатомы подгрупп Va и VIa, были изучены методами квантовой химии (R_nX -пиперидины, $R=H$ или CH_3 ; $n=1$: $X=O$ или S ; $n=2$: $X=N$ или P). Эти соединения могут существовать в виде трех или четырех конформеров, отличающихся аксиальным и/или экваториальным положением, а также гош- и транс- или цис- и транс- ориентацией заместителей относительно пиперидинного кольца. 1,3-диаксиальное отталкивание влияет на аксиальное/экваториальное доминирование, в то время как орбитальное взаимодействие влияет на гош-, цис- и транс- ориентации заместителей. Гош-экваториальные конформеры более стабильны, чем другие формы в случаях R_2X -пиперидинов, тогда как транс-экваториальная форма более стабильна в случае RO -пиперидинов, и цис-экваториальная – в случае RS -пиперидинов. Энергетический барьер процесса азотной инверсии увеличивается в ряду $P \rightarrow S \rightarrow N \rightarrow O$.

Ключевые слова: N-замещенный пиперидин, квантово-химические расчеты, конформационные свойства, орбитальное взаимодействие, стерическое отталкивание

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THE INFLUENCE OF STERIC AND ORBITAL INTERACTIONS ON MOLECULAR STRUCTURE IN N-SUBSTITUTED PIPERIDINES

The conformational behavior and molecular structures of several N-substituted piperidines containing heteroatoms of the Va and VIa subgroups were studied by quantum chemical (QC) calculations (R_nX -piperidines, $R=H$ or CH_3 ; $n=1$: $X=O$ or S ; $n=2$: $X=N$ or P). These compounds may exist as three or four conformers differing by axial and/or equatorial positions and gauche and trans or cis and trans orientation of the substituent relative to the piperidine ring. The axial/equatorial preference is strongly influenced by the 1,3-diaxial interaction, while mostly the orbital interaction governs the gauche, cis and trans orientation of the substituent. The gauche-equatorial conformers are more stable than other forms in case of R_2X -piperidines, but the trans-equatorial form is most stable in the RO-, and cis-equatorial – in the RS-piperidines. The energy barrier for nitrogen inversion increases in the series $P \rightarrow S \rightarrow N \rightarrow O$.

Key words: N-substituted piperidine, quantum chemical calculation, conformational properties, orbital interaction, steric repulsion

INTRODUCTION

The molecular structures and conformational behaviors of saturated six-membered rings containing a heteroatom is an attractive field in chemistry. Steric repulsions and orbital interactions influence the equilibrium between axial and equatorial structures and the orientation of substituents relative to the heterocycles. The conformational properties of saturated heterocyclic six-membered rings were reviewed in [1]. The difference in energy between axial and equatorial conformations in six-membered saturated ring systems is mainly caused by steric repulsion caused by 1,3-syn-diaxial interactions, which are absent when a substituent is located in equatorial position. In turn, the anomeric effect stabilizes an axial form [2-4].

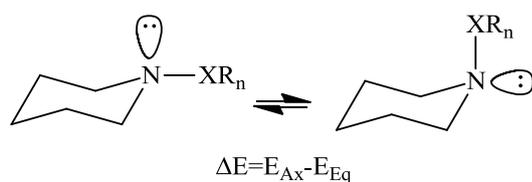
Piperidine and its derivatives are ubiquitous building blocks in the synthesis of organic compounds, including pharmaceuticals; nevertheless, the conformational properties of N-substituted piperidines and their structures are poorly studied. The nitrogen interconver-

sion of several N-substituents was theoretically explored in [5] at the B3LYP/6-311+G(d,p)/B3LYP/6-31G(d) level, even though the orientation of the proton in hydroxypiperidine was not specified.

This paper continues our systematic study of the molecular structures and conformational properties of N-substituted piperidines. In recent publications, a variety of the conformations and conformational preferences were described for alkyl-, alkenyl-, alkynyl- and aryl-piperidine derivatives [6-8]. The N-substituted piperidines were sorted by three groups, according to the preference of the substituent's position. We concluded that the hyperconjugation between the electron lone pair (Lp) on the nitrogen atom and the π -system of the substituents and steric repulsion influence the orientation of substituents relative to the piperidine ring [6].

In this paper, we represent results of detailed theoretical calculations performed for N-substituted piperidines in which the external substituent contains an electron lone pair. In this case, the orbital interac-

tion between the N atom of the piperidine ring and X atom of the substituent is expected to affect the conformational properties. The following N-substituted piperidines have been computed in this work: 1-amino- (H_2Npi), 1-(N,N-dimethyl)amino- (Me_2Npi), 1-phosphin- (H_2Ppi), 1-dimethylphosphin- (Me_2Ppi), 1-hydroxy- (HOpi), 1-methoxy- (MeOpi), 1-thio- (HSpi) and 1-methylthio-piperidines (MeSpi). The axial/equatorial equilibrium is shown in Scheme 1.



R=H, CH_3 ; n=1: X=O, S; n=2: X=N, P

Scheme 1
Схема 1

COMPUTATIONAL DETAILS

A recent benchmark study of DFT methods confirmed the general success of both M06-2X and B2PLYP-D in calculating the energies of main-group molecules [9]. Moreover, the B3LYP-D results of the monosubstituted cyclohexanes and silacyclohexane, where an empirical dispersion correction has been added, are in good agreement with the CCSD(T) results [4]. Thus, in this paper, geometry and vibrational calculations were performed with 6-311G** and cc-pVTZ basic sets by DFT, with the M06-2X and B3LYP-GD3 functionals, and with the MP2 method using the Gaussian 09 program package [10].

The potential energy surface (PES) profiles were obtained by varying the $\text{C}\alpha\text{-N-X-Y}$ (X = N, P, O or S, Y = H or C) dihedral angle with a step of 10° using DFT-M062X level and the 6-311G** basis set while optimizing all other geometrical parameters. For ease of visualization, these PES profiles are plotted as the energy vs. the φ dihedral angle (Fig. 1). The φ angle is defined as $\varphi = 180^\circ - \angle(\text{Lp-N-X-Y})$ for X = O and S, and as $\varphi = \text{Lp-N-X-Lp}$ for X = N, P. The Lps were placed in the plane bisecting the C-N-C bond angle of the piperidine ring and the R-X-R bond angles of substituents with X = N or P atom. Other PES profile scans, for the nitrogen inversion, were obtained by optimizing all geometric parameters at fixed $\text{C}_\gamma\text{-N-X}$ angle values with a step of 10° , and calculating at the M06-2X/6-311G** level.

The Natural Bond Orbital (NBO) analyses [11] were performed at the M06-2X/cc-pVTZ level using the Gaussian 09 built-in NBO version 3.1 package to calculate the orbital interactions.

RESULTS AND DISCUSSIONS

Energies

It is well known that the six-membered piperidine ring is *chair*-like in its lowest energy conformations [1, 12]. In these compounds, the substituents, being attached to the nitrogen atom, may be located in axial or equatorial positions with reference to the piperidine ring.

In the PES profiles of the compounds H_2Npi , Me_2Ppi , ROpi and RSpi , four minima were located – to two axial and two equatorial conformers. Two axial and one equatorial conformer were located for Me_2Npi , and one axial and two equatorial ones for H_2Ppi .

The structures with torsion angle $\varphi = 0^\circ$ are so-called *cis* conformers (*c-Eq* and *c-Ax*), torsion angles of $\varphi \approx 70\text{-}100^\circ$ are the *gauche* conformers (*g-Eq* and *g-Ax*), and $\varphi = 170\text{-}180^\circ$ are *trans* conformers (*tr-Eq* and *tr-Ax*). The molecular structures of *cis* and *trans* conformers of X=N or O, H_2Ppi and HSpi are of C_s symmetry equilibrium structure, and the *gauche* conformers of C_1 symmetry. For MeSpi , the *cis* conformers have C_s symmetry, and the *trans* conformer are C_1 for both axial and equatorial forms. In the case of Me_2Ppi , the *tr-Eq* conformer has C_s symmetry, while the *tr-Ax* form is C_1 . Relative total electron energies and free Gibbs energies along with predicted conformer contributions at 298 K are summarized in Tables 1 and 2.

The *gauche* forms of the compounds with X=N or P are more stable than the *trans* ones due to the steric repulsion between the two terminal groups (H or CH_3) of substituents and the hydrogen atoms in the α -positions of piperidine ring.

The strong repulsion leads to the disappearance of the *tr-Eq* conformer of compound Me_2Npi and the *tr-Ax* conformer of compound H_2Ppi . The $\Delta E = E_{\text{Ax}} - E_{\text{Eq}}$ values are 2.4-3.1, 4.2-5.4, 0.8-1.5 and 0.3-1.0 kcal/mol for H_2Npi , Me_2Npi , H_2Ppi and Me_2Ppi , respectively, where, Eq and Ax are the most stable equatorial and axial forms, see Table 1. Except for the Me_2Ppi , the ΔG values are close to the total electron energy differences. In the case of Me_2Ppi , the ΔG value is 0.8-1.0 and 1.3 kcal/mol from the DFT and MP2/6-311G** calculations, respectively.

As follows from the QC calculations for H_2Npi and Me_2Npi , these compounds are expected to exist in form of the *g-Eq* conformer in gas phase at the room temperature. In the case of R_2P -piperidine, the long P-N distance, see Table 3, decreases the 1,3-diaxial repulsion, which may lead to the existence of the *g-Ax* conformer with a contribution of 12-21% (DFT) and 5-10% (MP2).

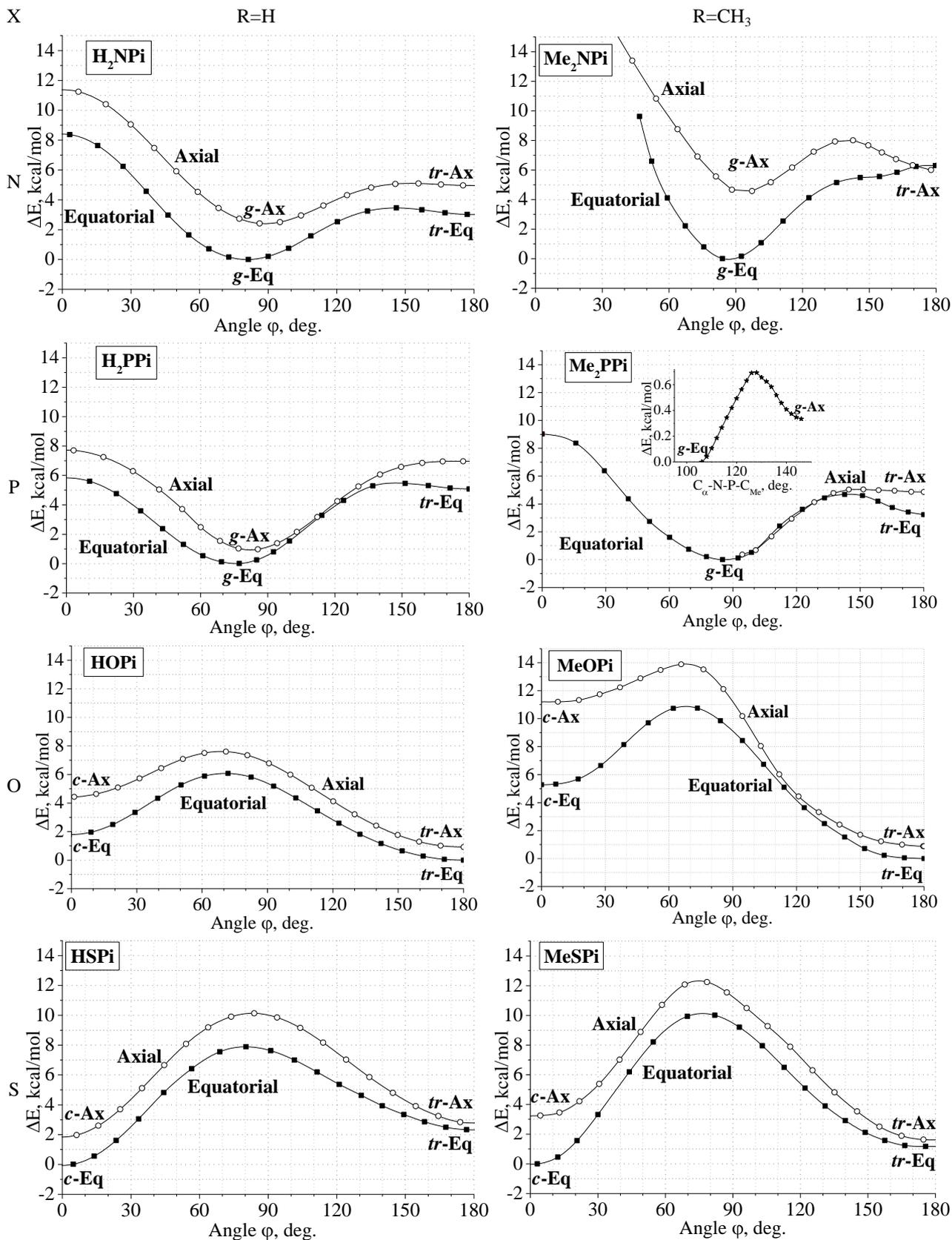


Fig. 1. Lowest pathway for axial and equatorial conformers by rotating the substituent around N–X bond calculated at M06-2X/6-311G** level; see Computational details for the ϕ angle definition

Рис. 1. Пути минимальной энергии для аксиальных и экваториальных конформеров при вращении заместителя вокруг связи N–X, рассчитанные методом M06-2X/6-311G**, см. раздел Детали расчетов для определения угла ϕ

Table 1

Relative total electron energy, free Gibbs energy (kcal/mol) of conformers of compounds with N and P atoms in the substituent ^a

Таблица 1. Относительная полная электронная энергия, свободная энергия Гиббса (ккал/моль) конформеров соединений, содержащих атомы N и P в заместителе ^a

| Conformer | ΔE | | | | $\Delta G(298K)$ | | | |
|--------------------------|-------------|--------------|-------------|--------------|------------------|--------------|-------------|--------------|
| | <i>g-Eq</i> | <i>tr-Eq</i> | <i>g-Ax</i> | <i>tr-Ax</i> | <i>g-Eq</i> | <i>tr-Eq</i> | <i>g-Ax</i> | <i>tr-Ax</i> |
| H₂NPi | | | | | | | | |
| B3LYP-GD3 | 0 | 3.3-3.4 | 2.6-2.7 | 5.6-5.9 | 0 | 2.8-3.0 | 2.7-2.9 | 5.2-5.4 |
| M06-2X | 0 | 3.0-3.1 | 2.4-2.7 | 5.0-5.5 | 0 | 2.9-3.0 | 2.6-2.8 | 4.8-5.0 |
| MP2 | 0 | 2.4-2.7 | 2.9-3.1 | 4.9-5.2 | 0 | 2.4 | 3.1 | 4.7 |
| Me₂NPi | | | | | | | | |
| B3LYP-GD3 | 0 | – | 4.2-4.4 | 7.3-7.4 | 0 | – | 4.3-4.5 | 7.8-7.8 |
| M06-2X | 0 | – | 4.5-4.8 | 6.0-6.1 | 0 | – | 4.5-4.8 | 6.6-6.7 |
| MP2 | 0 | – | 5.4 | 5.1 | 0 | – | 5.6 | 5.8 |
| H₂PPi | | | | | | | | |
| B3LYP-GD3 | 0 | 5.2-5.4 | 0.9-1.0 | – | 0 | 4.9-5.0 | 1.1-1.2 | – |
| M06-2X | 0 | 4.9-5.1 | 0.8-0.9 | – | 0 | 4.5-4.5 | 0.8-0.9 | – |
| MP2 | 0 | 4.8-5.1 | 1.2-1.5 | – | 0 | 4.6 | 1.7 | – |
| Me₂PPi | | | | | | | | |
| B3LYP-GD3 | 0 | 3.9-4.0 | 0.3-0.4 | 5.6-5.7 | 0 | 4.2-4.2 | 0.8-0.9 | 5.8-5.9 |
| M06-2X | 0 | 3.2-3.2 | 0.3-0.4 | 4.9-4.9 | 0 | 3.5-3.6 | 0.8-1.0 | 4.9-4.9 |
| MP2 | 0 | 2.8-2.9 | 0.8-1.0 | 4.8-5.1 | 0 | 3.0 | 1.3 | 5.1 |

Note: ^a The intervals are given for the computations with 6-311G** and cc-pVTZ basis sets

Примечание: ^a Интервалы значений приведены для расчета с базисными наборами 6-311G** и cc-pVTZ

Table 2

Relative total electron energy, free Gibbs energy (kcal/mol) of conformers of the compounds with O and S atoms in the substituent

Таблица 2. Относительная полная электронная энергия, свободная энергия Гиббса (ккал/моль) конформеров соединений, содержащих атомы O и S в заместителе

| Conformer | ΔE | | | | $\Delta G(298K)$ | | | |
|--------------|--------------|-------------|--------------|-------------|------------------|-------------|--------------|-------------|
| | <i>tr-Eq</i> | <i>c-Eq</i> | <i>tr-Ax</i> | <i>c-Ax</i> | <i>tr-Eq</i> | <i>c-Eq</i> | <i>tr-Ax</i> | <i>c-Ax</i> |
| HOpi | | | | | | | | |
| B3LYP-GD3 | 0 | 1.7-1.8 | 1.1-1.4 | 4.6-4.7 | 0 | 1.7-1.9 | 1.2-1.6 | 4.6 |
| M06-2X | 0 | 1.5-1.8 | 0.9-1.4 | 4.4-4.5 | 0 | 1.7-2.0 | 1.2-1.5 | 4.9-5.0 |
| MP2 | 0 | 1.9-2.1 | 1.4-1.6 | 5.3-5.4 | 0 | 2.0-2.2 | 1.5-1.8 | 5.4-5.5 |
| MeOpi | | | | | | | | |
| B3LYP-GD3 | 0 | 5.1-5.6 | 1.1-1.4 | 10.7-11.0 | 0 | 5.4-5.8 | 1.1-1.5 | 10.7-10.9 |
| M06-2X | 0 | 4.6-5.3 | 0.9-1.3 | 10.9-11.2 | 0 | 5.4-5.7 | 1.1-1.4 | 11.0-11.2 |
| MP2 | 0 | 5.6-6.3 | 1.2-1.5 | 12.8-13.3 | 0 | 6.5 | 1.4 | 12.6 |
| HSpi | | | | | | | | |
| B3LYP-GD3 | 2,6-2,7 | 0 | 3,3-3,4 | 1,7-1,9 | 2,5-2,6 | 0 | 3,4-3,5 | 2,0-2,1 |
| M06-2X | 2,4-2,6 | 0 | 2,9-3,2 | 1,8-1,9 | 2,5-2,7 | 0 | 2,8-3,1 | 2,0-2,2 |
| MP2 | 2,4-2,6 | 0 | 3,4-3,5 | 2,2-2,7 | 2,2 | 0 | 3,6 | 2,9 |
| MeSpi | | | | | | | | |
| B3LYP-GD3 | 1,0-1,2 | 0 | 1,8-1,9 | 2,4-2,5 | 0,6-0,7 | 0 | 1,6-1,7 | 2,5-2,7 |
| M06-2X | 1,2-1,3 | 0 | 1,7-1,8 | 3,1-3,2 | 0,9-1,0 | 0 | 2,0-2,1 | 3,0-3,2 |
| MP2 | 0,7-9 | 0 | 1,6-1,7 | 3,6-4,0 | 0,2 | 0 | 1,5 | 3,9 |

For the compounds with a P atom substituent, the MP2 method predicts the axial form to be less favorable when compared with the DFT method. On the other hand, an opposite tendency was found for 1-alkenyl- and 1-phenylpiperidines [6, 8]. In addition,

the sophistication of the basis set increases the $\Delta E = E_{Ax} - E_{Eq}$ values.

In the case of O or S heteroatoms in a substituent, the *gauche* form becomes a transition structure between the *cis* and *trans* conformers due to interac-

tion between the Lp on the nitrogen atom of the piperidine ring and the two Lps on the heteroatom of the substituents. Note that in the case of methoxycyclohexane and N-ethylpiperidine, in which such interactions are absent, the *gauche* form is most stable [2, 3, 6].

Because of steric repulsion, the *trans* forms of the compounds with an oxygen atom substituent are more stable than the *cis* forms. The $\Delta E = E_{Ax} - E_{Eq}$ values are from 0.9 to 1.6 kcal/mol for both **ROPi** compounds, and the contribution of the axial conformers is 3-11%. The calculations show that the substitution of the hydrogen atom in the hydroxyl group by a methyl group has no influence on the energy difference between the two *trans* forms, axial and equatorial, see Fig.1 and Table 2. However, this substitution considerably decreases the stability of the *cis* conformers. Therefore the energy of the *c-Ax* conformer of **MeOPi** is less stable, by 11.0-13.3 kcal/mol, than *tr-Eq*. For these compounds, **HOPI** and **MeOPi**, the MP2/6-311G** method also predicts a smaller contribution of the axial conformers, compared with the DFT/6-311G** results. Changing to more sophisticated basis sets also increases the ΔE and ΔG values between *tr-Eq* and *tr-Ax* forms.

For the **RSPi** compounds the tendencies are somewhat different comparing with **ROPi**s. In the case of **HSPI**, the *cis* forms are more stable than *trans*, and the *c-Ax* is less stable than *c-Eq* $\Delta E = 1.7-2.7$ and $\Delta G = 2.0-2.9$ kcal/mol. Note that in the case of **HSPI**, increasing the sophistication of the basis set decreases the ΔE value, but increases the ΔG value.

For **MeSPi**, the *c-Eq* conformer is more stable than *tr-Eq*, but the *c-Ax* form is less stable than *tr-Ax* due to strong steric repulsion; both equatorial conformers are more stable than axial ones. It is obvious from the calculations that the substitution of the hydrogen atom in the SH group by a methyl group considerably decreases the stability of the *c-Ax* conformer, due to an increased 1,3-diaxial repulsion. At the same time, the orbital interaction stabilizes *cis* forms in cases of these compounds, see section NBO analysis.

The concentration of axial conformers does not exceed 5% in the both **RSPi** compounds.

Nitrogen inversion

The energy barriers for the nitrogen inversion process from the Eq form to the Ax form via a planar nitrogen bond configuration of all compounds calculated at M06-2X/6-311G** level increase in the series P→S→N→O, see Table 3.

The donor property of the methyl group decreases the energy barrier. Comparing with **R₂NPi**, the longer R–P bond distance in **R₂PPi** decreases these values. A similar situation was found for **ROPi**

and **RSPi**. In spite of the close R–X bond distances in **R₂NPi** and **ROPi**, the interaction between the two Lps on the oxygen atom and the Lp on the nitrogen atom of the piperidine ring nevertheless leads to a higher barrier in **ROPi**. Thus, the donor properties and the long R–X bond distance decrease the energy barrier, but the Lp-Lp interaction increases this value.

Table 3

The energy barriers, kcal/mol, of nitrogen inversion of all compounds calculated at M06-2X/6-311G** level

Таблица 3. Энергетические барьеры, ккал/моль, процесса азотной инверсии всех соединений, рассчитанные методом M06-2X/6-311G**

| Compound | H₂NPi | Me₂NPi | H₂PPi | Me₂PPi |
|----------------------------|-------------------------|--------------------------|-------------------------|--------------------------|
| <i>g-Eq</i> → <i>g-Ax</i> | 9.8 | 7.4 | 2.0 | 0.6 |
| Compound | HOPI | MeOPi | HSPI | MeSPi |
| <i>c-Eq</i> → <i>tr-Ax</i> | 13.7 | 9.3 | 5.7 | 4.3 |
| <i>tr-Eq</i> → <i>c-Ax</i> | 16.6 | 15.2 | 3.7 | 2.9 |

Geometry and NBO analysis

Selected geometric parameters, natural charges and the second-order perturbation energies $E(2)$ (donor-acceptor) of the most stable **Eq** and **Ax** conformers of all compounds calculated at the M06-2X/cc-pVTZ level are given in Table 4.

As follows from the calculations, the substitution of a hydrogen atom by a methyl group slightly changes the N–X bond distances and natural charges on the nitrogen atom of the piperidine ring. At the same time, this substitution considerably decreases the electron density on the X atoms. Comparing the molecular parameters of the both conformers of all compounds, except for **Me₂NPi**, **H₂PPi** and **Me₂PPi**, one can see that the endocyclic C_α–N bond distances in *g-Ax* are somewhat longer than those in the *g-Eq* conformer, by 0.003-0.006 Å. In the case of **Me₂PPi**, the endocyclic C_α–N bond distances in *g-Ax* are shorter than those in *g-Eq*. The difference between the two C_α–N bond distances within the same conformer of compounds with nitrogen or phosphorus atoms does not exceed 0.004 Å.

In **H₂NPi** and **H₂PPi**, the φ angle in *g-Ax* is larger than that in *g-Eq* by 8°. However, in **Me₂NPi** and **Me₂PPi**, the φ angles in both *gauche* conformers, axial and equatorial, are almost identical. The N–N bond distance in the *g-Eq* form is longer than the one in *g-Ax*, due to steric repulsion between the substituents and CH₂ groups in α -positions of the piperidine ring. Because of the higher orbital interaction energy $E(2)$ Lp(N)→ $\sigma^*(N-C_{Me})$, the N–N bonds in the *g-Ax* form of **Me₂NPi** is shorter than in **H₂NPi**. For **H₂PPi** and **Me₂PPi**, the N–P bond in the equatorial conformer is up to 0.012 Å longer than in the axial form. The NBO analysis shows that the differences ΔE_{g-Ax-g}

$E_{\text{Eq}}(2)$ $\text{Lp}(\text{N}) \rightarrow \text{Ry}^*(\text{P})$ are 0.90 and 1.86 kcal/mol for **H₂PPi** and **Me₂PPi**, respectively. Thus, the orbital interaction between the Lp on the nitrogen atom of the piperidine ring and the Rydberg orbital of the P atom decreases the energy difference $\Delta E = E_{\text{Ax}} - E_{\text{Eq}}$, and, therefore, stabilizes the axial conformer.

For the compounds with an oxygen atom, the N–O bond distance in the *tr*-**Ax** conformer is 0.005–0.006 Å longer than in *tr*-**Eq**, while the O–H (or O–C_{Me}) bonds in both, axial and equatorial forms are identical. The orbital interaction energies $E(2)$ ($\text{Lp}(\text{N}) \rightarrow \sigma^*(\text{O–H/C}_{\text{Me}})$) in both *trans* forms are equal, so that in the **ROPi** compounds the steric repulsion plays an important role in the axial/equatorial orientation of the substituents.

For **HSPi**, the orbital interaction energies $E(2)$ ($\text{Lp}(\text{N}) \rightarrow \sigma^*(\text{S–H})$) in the *cis* forms are higher than in the *trans* forms, which stabilizes the *cis* orientation. A similar situation was found for the equatorial conformers of **MeSPi**. The 1,3-diaxial repulsion in axial forms of **MeSPi** destabilizes the *c*-**Ax** conformer, making it less stable than *tr*-**Ax**, despite higher energy $E(2)$ ($\text{Lp}(\text{N}) \rightarrow \sigma^*(\text{S–C}_{\text{Me}})$) in *c*-**Ax** than in *tr*-**Ax**. The N–S bond distance in the *c*-**Eq** conformer of **MeSPi** is 0.02 Å shorter than in *tr*-**Ax**. However, due to orbital interaction between Lp on the nitrogen atom of the piperidine ring and S–C_{Me} bond in *c*-**Eq**, the latter is 0.01 Å longer than in *tr*-**Ax**.

Table 4

Theoretical geometric parameters, natural charge and energy $E(2)$ (donor-acceptor) of the most stable **Eq** and **Ax** conformers of all compounds calculated at M06-2X/cc-pVTZ level

Таблица. 4. Теоретические геометрические параметры, натуральные заряды и энергия $E(2)$ (донор-акцептор) наиболее стабильных экваториальных и аксиальных конформеров всех соединений, рассчитанные методом M06-2X/cc-pVTZ

| Compound Conformer | H₂NPi | | Me₂NPi | | H₂PPi | | Me₂PPi | |
|--|-------------------------|-----------------------|--------------------------|-----------------------|-------------------------|----------------------|--------------------------|-----------------------|
| | <i>g</i> - Eq | <i>g</i> - Ax | <i>g</i> - Eq | <i>g</i> - Ax | <i>g</i> - Eq | <i>g</i> - Ax | <i>g</i> - Eq | <i>g</i> - Ax |
| Bond distance (Å) and dihedral angle φ (°) | | | | | | | | |
| N–C _{α1} | 1.456 | 1.461 | 1.454 | 1.454 | 1.463 | 1.461 | 1.460 | 1.456 |
| N–C _{α2} | 1.457 | 1.463 | 1.459 | 1.459 | 1.459 | 1.460 | 1.457 | 1.455 |
| N–X | 1.419 | 1.422 | 1.421 | 1.414 | 1.713 | 1.705 | 1.715 | 1.703 |
| X–H/C _{Me} | 1.023 | 1.018 | 1.455 | 1.456 | 1.432 | 1.429 | 1.855 | 1.854 |
| φ | 80 | 88 | 86 | 87 | 75 | 83 | 86 | 86 |
| Natural charge | | | | | | | | |
| N | –0.306 | –0.309 | –0.330 | –0.332 | –0.764 | –0.766 | –0.795 | –0.797 |
| X | –0.657 | –0.672 | –0.305 | –0.307 | 0.540 | 0.531 | 1.008 | 1.007 |
| H or C _{Me} | 0.346 | 0.347 | –0.408 | –0.401 | –0.081 | –0.081 | –0.943 | –0.943 |
| Energy $E(2)$ (donor-acceptor) (kcal/mol) | | | | | | | | |
| $\text{Lp}(\text{N}) \rightarrow \text{Ry}^*(\text{X})$ | – | – | – | – | 4.42 | 5.32 | 3.32 | 5.18 |
| $\text{Lp}(\text{N}) \rightarrow \sigma^*(\text{X–H/C}_{\text{Me}})$ | 7.56 | 7.54 | 10.10 | 10.45 | 8.09 | 8.53 | 8.00 | 8.38 |
| | 2.36 | 3.15 | 1.60 | 2.84 | 2.61 | 4.36 | 4.23 | 6.02 |
| $\text{Lp}(\text{X}) \rightarrow \sigma^*(\text{N–C}_{\alpha})$ | 8.41 | 8.89 | 10.02 | 11.03 | 6.36 | 7.47 | 7.87 | 8.94 |
| Compound Conformer | HOPI | | MeOPI | | HSPi | | MeSPi | |
| | <i>tr</i> - Eq | <i>tr</i> - Ax | <i>tr</i> - Eq | <i>tr</i> - Ax | <i>c</i> - Eq | <i>c</i> - Ax | <i>c</i> - Eq | <i>tr</i> - Ax |
| Bond distance (Å) and dihedral angle φ (°) | | | | | | | | |
| N–C _α | 1.459 | 1.464 | 1.458 | 1.464 | 1.462 | 1.465 | 1.461 | 1.466 |
| N–X | 1.426 | 1.432 | 1.422 | 1.427 | 1.696 | 1.693 | 1.695 | 1.713 |
| X–H/C _{Me} | 0.960 | 0.960 | 1.410 | 1.410 | 1.358 | 1.357 | 1.817 | 1.806 |
| φ | 180 | 180 | 180 | 180 | 0 | 0 | 0 | 180 |
| Natural charge | | | | | | | | |
| N | –0.179 | –0.174 | –0.191 | –0.186 | –0.607 | –0.611 | –0.626 | –0.626 |
| X | –0.608 | –0.626 | –0.430 | –0.447 | 0.184 | 0.178 | 0.396 | 0.344 |
| H or C _{Me} | 0.466 | 0.469 | –0.207 | –0.204 | 0.063 | 0.063 | –0.755 | –0.711 |
| Energy $E(2)$ (donor-acceptor) (kcal/mol) | | | | | | | | |
| $\text{Lp}(\text{N}) \rightarrow \text{Ry}^*(\text{X})$ | 0.71 | 0.60 | 0.96 | 0.79 | 4.85 | 5.85 | 4.85 | 5.12 |
| $\text{Lp}(\text{N}) \rightarrow \sigma^*(\text{X–H/C}_{\text{Me}})$ | 1.64 | 1.63 | – | – | 8.31 | 10.01 | 9.88 | 5.63 |
| | | | | | 5.37 ^a | 6.00 ^a | 4.92 ^b | 13.16 ^c |
| $\text{Lp}(\text{X}) \rightarrow \sigma^*(\text{N–C}_{\alpha})$ | 3.35 | 3.56 | 3.28 | 3.50 | 3.02 | 4.28 | 4.23 | 3.83 |

Note: ^a – the *trans* forms of **HSPi**; ^b – for *tr*-**Eq**; ^c – for *c*-**Ax**

Примечание: ^a – транс-формы **HSPi**; ^b – для *tr*-**Eq**; ^c – для *c*-**Ax**

CONCLUSION

In this study, the molecular structure and conformational properties of the several N-substituted piperidines containing heteroatoms X of the VIa and VIa subgroups of the type of $C_5H_{10}N-X-R_n$, where R = H or Me, and n = 1 or 2, were investigated by QC calculations.

These compounds may exist as three or four conformers differing by axial and/or equatorial positions and relative (*gauche* and *trans* or *cis* and *trans*) orientation of the piperidine ring and the substituent.

The 1,3-diaxial interaction strongly influences on axial/equatorial orientations. At the same time, the orbital interaction $L_p(N) \rightarrow \sigma^*(X-R)$ influences the relative *gauche*, *cis* and *trans* orientation of the substituent. For these compounds, the first of the two factors is stronger, making the equatorial forms more stable.

In all cases, except Me2PPi and MeSPi, the MP2 method predicts higher ΔE and ΔG values (axial–equatorial) compared to the DFT results. Increasing the sophistication of the basis set, from 6-311G** to cc-pVTZ, resulted in a lower contribution of the axial form.

According to the calculations, for the compounds containing N or P atoms, the *g-Eq* conformers are more stable than the other forms; the torsion angles are $\varphi = 80-86^\circ$ for H2NPi, Me2NPi and Me2PPi and $\varphi = 75^\circ$ for H2PPi. Except for the **R₂PPi**, the energy difference between the most stable *gauche*-axial and *gauche*-equatorial conformers exceeds 2,4 kcal/mol, and, therefore, the contribution of the *g-Eq* conformer is ca. 100%.

In the case of compounds containing atoms of the VIa subgroup, the compounds with heteroatoms O and S demonstrate the opposite tendency: the *tr-Eq* form is more stable than *c-Eq* in HOPi and MeOPi, but is less stable in HSPi and MeSPi. The NBO analysis shows that the orbital interaction between the L_p on the nitrogen atom in the piperidine ring and $\sigma^*(S-R)$ stabilizes the *cis* form. The contribution of axial conformer is 4-11, 1-4, 7-14 and 3-5%, for the HOPi, HSPi, MeOPi and MeSPi, respectively.

The energy barrier for the nitrogen inversion process from the equatorial to the axial conformer increases in the series $P \rightarrow S \rightarrow N \rightarrow O$.

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