Structure and conformational behavior of N-phenylpiperidine studied by gas-phase electron diffraction and quantum chemical calculations

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In honour of Professor Georgiy Girichev on the occasion of his 70th birthday

ABSTRACT

Molecular structure and conformational behavior of N-phenylpiperidine (**NPhP**) were investigated by synchronous gas-phase electron diffraction / mass spectrometry (GED/MS) and quantum chemistry. Due to influence of steric repulsion and hyperconjugation, **NPhP** may exist in two conformers, equatorial and axial chair forms. Both experiment and theoretical calculations suggest a C_1 symmetry of the conformers, with the plane perpendicular to the phenyl group turned by ca. 30–40° (equatorial) and 0–20° (axial) about the plane perpendicular to the piperidine ring symmetry plane. According to the QC calculations, **NPhP** may exist as two conformers, equatorial and axial, with a ratio of Eq:Ax=92:8 (B3LYP), 87:13 (B3LYP-GD3), 84:16 (M06-2X), 83:17 (MP2/6-311G**) and 76:24% (MP2/cc-pVTZ). Except for the latter, these values are in good agreement with the experimental GED data of 90(10):10(10)%.

A comparative analysis of similar compounds, phenylcyclohexane and 1-phenylheterocyclohexanes, was performed. Conformational properties depend on the $C_{Ph}-X$ bond distance and hyperconjugation between the phenyl ring and the lone pair on the heteroatom. The contribution of the axial form of 1-phenylcyclohexane derivatives increases in the series of the heteroatom X in the cyclohexane ring: $C \rightarrow N \rightarrow Si \rightarrow P$.

Keywords: Phenylpiperidine, Gas electron diffraction, Quantum chemical calculations, Hyperconjugation, Conformational analysis, Phenylheterocyclohexanes

INTRODUCTION

Piperidine and its derivatives are ubiquitous building blocks in the synthesis of organic compounds, including pharmaceuticals. The conformational properties of saturated heterocyclic six-membered rings, including the several derivatives of piperidine and its salts, were reviewed in [1]. To our knowledge, there are very few publications in the literature concerning the structure and conformations of N-phenylpiperidine (**NPhP**). From experimental measurements of electric dipole moments in benzene solution at 298 K [2] it was concluded that **NPhP** ‘should contain the piperidino-ring as a chair to which a phenyl group, being large, would be attached by an equatorial bond’, and the angle between aromatic carbon-nitrogen bond and the dipole moment was found to be 36°. However, no ratio of axial-to-equatorial conformers was suggested. Theoretical calculations support the predominance of the equatorial form of **NPhP**, by $\Delta E = 1.5$ kcal/mol at B3LYP/6-31G* [3].

From the ultraviolet spectra of several N-phenyl-substituted cyclic imines [4], it was found that the resonance energy due to interaction between nitrogen and the phenyl ring increas-

es in the series N-phenylpyrrolidine<N-phenylazetidine<N-phenylpiperidine<N-phenylaziridine. The authors [4] concluded that the rotation about the aromatic carbon-nitrogen bond is restricted not only by the variation of the phenyl ring-nitrogen resonance with the “angle of twist” but also by the steric interaction between α - and *ortho*-hydrogen atoms.

From the ^{13}C NMR spectroscopic measurements [5], the chemical shifts for cyclic imines and N,N-dialkylanilines in benzene were determined but no conclusions concerning axial or equatorial conformers of **NPhP** were given.

Recently we started a systematic study of the molecular structures and conformational properties of N-substituted piperidines, including N-cyclohexylpiperidine [6] and alkyl- and nonalkylpiperidines [7], as well as piperazines [8,9].

In this paper, we report the results of a study combining gas-phase electron diffraction / mass spectrometric (GED/MS) experiments and extended quantum chemical calculations for **NPhP**.

EXPERIMENTAL SECTION

GED-MS experiment

A sample of **NPhP** was purchased from the TCI Company, 97%. The diffraction patterns of **NPhP** were obtained in a synchronous gas-phase electron diffraction and mass-spectrometric experiment carried out using the *EMR-100/APDM-1* unit [10,11]. The sample of **NPhP** was evaporated from a molybdenum cell at 317 K. All operations with the sample were carried out under argon atmosphere. The conditions of the GED/MS experiment and data refinement details are given in Supporting Information, Table S1 and related chapters.

Mass spectra (EI, 50 eV) of the effusing molecular beam were recorded simultaneously with collecting the diffracted electrons. The mass spectrum is in good agreement with the NIST data [12], Fig. S1. As in the case of piperidine, the most likely dissociative ionization route is the ion formation by disclosure of hydrogen atom. The major ion peaks in the mass spectrum of **NPhP** are M^+ (65%), $(\text{M}-1)^+$ (100%), C_6H_5^+ (30%), $\text{C}_6\text{H}_5\text{-NCH}_2^+$ (30%) and $\text{C}_6\text{H}_5\text{-NC}_2\text{H}_5^+$ (15%). No fragment ions with m/e higher than 162 Da were detected. The relative intensities of the ions in the mass spectra showed no change during the course of the experiment. In addition, we performed mass spectra recordings at different ionizing electron energies. The contribution of the fragment ions decreases with lower electron energy. At the energy as low as *ca.* $U_i=12$ eV the electron impact produces the molecular ion, $m/z=161$ Da, exclusively (see Fig. S2) which is the evidence that the only species present in the gas phase is **NPhP**.

Computational details

Quantum chemical (QC) calculations of the **NPhP** conformers were performed with Gaussian 09 [13] and Firefly QC, package version 8.0.0 [14], which is partially based on the GAMESS (US) [15] source code (in case of MP2/cc-pVTZ for vibrational calculations). Geometry and vibrational calculations were performed with 6-311G** and cc-pVTZ basic sets by using DFT (with B3LYP, B3LYP-GD3, M06-2X functionals) and MP2 methods. Relative total electron energies and free Gibbs energies along with predicted conformer contributions are summarized in Table 1. Geometric parameters are compiled in Table 2.

The potential energy surface (PES) profiles were obtained by varying the C1–N–C6–C7 dihedral angle with a step of 10° using B3LYP and MP2 levels of theory with the 6-311G** basis set while optimizing all other geometrical parameters. Other PES profile scans, for the nitrogen inversion, were obtained by optimizing all geometric parameters at fixed C3···N–C6 angle values with a step of 10°. The transition structures were calculated using the Berny algorithm implemented into the Gaussian program package, keyword TS and using the quadratic synchronous transit approach, *Synchronous Transit-Guided Quasi-Newton* STQN [16,17] (see Fig. S3 in Supporting Information), with keyword QST2.

The Natural Bond Orbital (NBO) analysis [18] was performed at the B3LYP-GD3, M06-2X and MP2 levels with 6-311G** basis set using the Gaussian 09 built-in NBO version 3.1 package to calculate the orbital interactions.

RESULTS AND DISCUSSION

Energies and barriers

It is well known that the six-membered piperidine ring is *chair*-like in its lowest energy conformations (see, for instance, [1,19]). In **NPhP**, the phenyl ring, being attached to the nitrogen atom, may be located in axial or equatorial positions about the piperidine ring.

The phenyl group rotation. The PES profiles (see Fig. 1) were obtained by varying the dihedral angle C1–N–C6–C7, responsible for rotation of the two rings about the N–C6 bond of **NPhP**. For ease of visualization, these PES profiles are plotted as the energy vs. ϕ dihedral angle. The ϕ angle is defined as formed by two planes: (a) the plane through the N–C_{Ph} bond perpendicular to the benzene ring and (b) the plane through the N–C_{Ph} bond and the axis of symmetry of the electron lone pair (Lp) of the nitrogen atom, (see Fig. 2). The Lp was placed in the plane bisecting the C–N–C bond angle of the piperidine ring.

Fig. 1. Lowest pathway for axial and equatorial conformers by rotating the phenyl group around the N–C6 bond.

The minima of the PES profiles at $\phi=\pm 20^\circ$ and $\phi=\pm 30^\circ$ are mirror enantiomers of the axial and the equatorial conformers, respectively, see also Fig. 2. The structural parameters of both conformers corresponding to the predicted energy minima were completely optimized at the B3LYP, M06-2X and MP2 levels of theory with 6-311G** and cc-pVTZ basis sets.

All methods predict the equatorial position of the phenyl ring at the nitrogen atom to be more stable than the axial one (see Fig. 1 and Table 1): the relative total electron energy difference $\Delta E=E_{\text{ax}}-E_{\text{eq}}$ is *ca.* 1.7 and 0.9–1.1 kcal/mol and $\Delta G^\circ(298)=G^\circ_{\text{ax}}-G^\circ_{\text{eq}}$ is *ca.* 1.5 and 0.7–0.9 kcal/mol, from B3LYP and M06-2X along with MP2, respectively. The B3LYP-GD3 results, where an empirical dispersion correction has been added, are in very good agreement with M06-2X and MP2/6-311G** calculations. The conformer contributions derived from the Gibbs energies vary from 76:24 to 92:8, depending on the particular calculation. These results are in agreement with the experimental [2] and theoretical [3] data.

The B3LYP calculations predict that the ΔE and ΔG values are by 0.6 and 0.3 kcal/mol, respectively, higher than those with the other functionals. Such a situation was found for several saturated heterocyclic six-membered compounds in refs. [20,21,22]. Those authors concluded that the popular B3LYP functional performs quite badly for those systems, compared to CCSD(T)/CBS, while they found good agreement between the M06-2X and CCSD(T) results.

The transition structures of **NPhP** at the points of maxima were obtained using the Berny algorithm with TS keyword implemented into the Gaussian program package. The transition structures at $\phi=0^\circ$ or $\phi=\pm 90^\circ$ have Cs symmetry configuration.

The energy barriers between the optical isomers of the *equatorial* conformers are predicted rather differently by the two computational methods. In the DFT-B3LYP calculation, the lowest energy pathway is via $\phi=0^\circ$ with a barrier of 1.1 kcal/mol, Fig. 1, while another pathway, via $\phi=\pm 90^\circ$, has a two times higher barrier, 2.4 kcal/mol, showing the influence of hyperconjugation.

tion to be stronger than the steric repulsion between the α - and *ortho*-hydrogens. The MP2 method, on the contrary, predicts the pathway via orthogonal orientation of the rings to be most favorable, with barriers of 1.8 and 1.0 kcal/mol, respectively.

Table 1. Relative total electron energy, free Gibbs energy (kcal/mol) and molar fraction of conformers of **NPhP**

QC calculations				GED, 317 K
Method ^a	ΔE ^b	ΔG ^b	X_{eq} , %	X_{eq} , %
B3LYP	1.68–1.71	1.43–1.46	92	90(10) % $\Delta G^{\circ}=1.38(51)^c$
B3LYP-GD3	1.00–1.03	1.13–1.14	87	
M06-2X	0.90–0.98	0.93–1.03	83–85	
MP2/6-311G**	1.11	0.94	83:17	
MP2/cc-pVTZ	0.86	0.69	76:24	

^a The DFT methods with 6-311G** and cc-pVTZ basis sets, see also Table S2 for detail; ^b $\Delta E=E_{ax}-E_{eq}$, $\Delta G^{\circ}(298K)=G_{ax}^{\circ}-G_{eq}^{\circ}$; ^c Uncertainties were estimated on the base of that for the x value, $\pm 10\%$ (see Fig. 6)

Fig. 2: Conformers of the **NPhP** with atom numbering and illustration of the definition of the angle ϕ

In the case of the *axial* conformer, the barrier between the enantiomers is very low, 0.02 (MP2) to 0.24 (DFT-B3LYP) kcal/mol, for the transition via $\phi=0^{\circ}$, but is much higher, 4 to 5 kcal/mol, via $\phi=\pm 90^{\circ}$. This may be caused by a strong repulsion between the phenyl ring protons in *ortho*-position, i.e. H11 or H15, and the H3 and H7 protons of the piperidine ring at $\phi=\pm 90^{\circ}$. Moreover, at this phi value, the electron lone pair is perpendicular to the π -system of the phenyl ring, and the hyperconjugation, hence, disappears. Therefore these factors, the steric effect and the hyperconjugation disappearance, result in the high barrier.

The barrier between the enantiomers is much lower than the thermal energy and comparable with the vibrational energy of the “twist” vibration around the N–C_{Ph} bond (22 to 40 cm⁻¹, i.e. 0.06 to 0.11 kcal/mol).

Thus, rotation of the phenyl group around the N–C_{Ph} bond is competitively influenced by two factors: (i) the hyperconjugation between Lp of nitrogen atom and π -system of benzene ring and (ii) the steric repulsion between the α - and *ortho*-hydrogens.

Nitrogen inversion. The nitrogen inversion path between equatorial and axial positions of the benzene ring was calculated by optimizing all geometric parameters at fixed C3...N–C6 angle values from 100° to 180° for the axial, and from 140° to 180° for the equatorial conformers, with a step of 10°. For ease of visualization, these PES profiles are plotted as the energy vs. β angle. The β angle is 180°– $\angle$ (X...N–C6) for **Ax** and $\angle$ (X...N–C6)–180° for **Eq**, where X is a dummy atom between the two carbon atoms in α -positions, see Fig. 3. The transition state located using the keyword TS in the Gaussian input has a nearly planar form of the nitrogen atom bond configuration and lies by *ca.* 1.9 kcal/mol (B3LYP/6-311G**), 2.4 (M06-2X/6-311G**) and 3.5 kcal/mol (MP2/6-311G**) above the equatorial form. The lower barrier from DFT results may possibly be explained by a minor change of the electron density on the nitrogen atom during this process. The pathway calculated by using the STQN approach with QST2 keyword yielded the same results, see Fig. S3 in Supporting Information.

Fig. 3. The energy pathway for the nitrogen inversion of **NPhP** calculated by using B3LYP and MP2 methods with 6-311G** basis sets (see text above for the definition of the β angle).

The nitrogen inversion barrier in **NPhP** is lower than in piperidine, 4.93 kcal/mol (MP2/6-311++G**) [23], in N-alkyl substituted piperidines, 4.2 to 7.1 (Me), 3.8 to 6.8 (Et) kcal/mol, but comparable with N-alkenyl substituted piperidines, 1.9 to 3.3 (Vinylpiperidine), 2.7 to 4.2 (*i*Propenylpiperidine) and 1.6 to 3.1 (Ethynylpiperidine) kcal/mol [7].

GED analysis

The molecular structures of the **NPhP** conformers with atom numbering are shown in Fig. 2. The following independent geometric parameters were used to describe the geometry: (*equatorial*) bond distances N–C1, C1–C2, C6–C7, C1–H; bond angles N–C1–C2, C1–C2–C3, C1–N–C6, N–C6–C7, C6–C7–C8, N–C1–H1, C6–C7–H11; dihedral angles N–C1–C2–C3, C7–C6–N–C1, C8–C7–C6–N; (*axial*) dihedral angle C7–C6–N–C1. For both conformers, the benzene ring was fixed to be planar since the QC calculations showed very small deviations from planarity. All other geometrical parameters for the equatorial and axial conformers were described by the parameters analogous to those in the equatorial conformer and corrected by adding the differences taken from MP2/6-311G** calculations. The exocyclic C–N bond was described by the C6–C7 distance of the benzene ring with the difference mentioned above.

Vibrational amplitudes for all three conformers were refined in eight groups according to the specific regions in the radial distribution: 0 – 1.2, 1.2 – 1.8, 1.8 – 2.7, 2.7 – 3.1, 3.1 – 4.0, 4.0 – 4.5, 4.5 – 5.4, 5.4 – 10 Å. The differences between the amplitudes within each group were constrained to the calculated values. The vibrational corrections $\Delta r = r_{hl} - r_a$ and starting root-mean square amplitudes were calculated with the SHRINK program [24,25] using the so-called second approximation, in which a harmonic approach with nonlinear relation between Cartesian and internal coordinates were applied on the basis of the force field estimated in the QC calculations at the MP2/6-311G** level.

With these constraints, the independent geometric parameters and eight groups of vibrational amplitudes were refined simultaneously along with molar fractions of the conformers. Experimental and theoretical $sM(s)$ curves along with their differences $\Delta sM(s)$ are given in Fig. 4. The experimental radial distribution function $f(r)$ derived by Fourier transformation of the molecular intensities is shown in Fig. 5, together with difference curves between experimental and calculated (MP2/6-311G**) $f(r)$ functions for the both structures. Geometric parameters and vibrational amplitudes are summarized in Table 2 and Table S5 in Supporting Information, respectively.

The refinement of the molar fraction of equatorial and axial conformers simultaneously with the refinement of structural parameters converged on a vapour composition of Eq: Ax=90(7):10(7)%, where the uncertainties are $3\sigma_{LS}$.

Fig. 4. Molecular scattering intensities $sM(s)$: experimental (dots) and theoretical (line) for a refined mixture of 90:10% of **Eq:Ax** conformers; the differences "Experim.–Theor." are given at the bottom. The agreement factor is $R_f=3.16\%$.

Fig. 5. Experimental (black dots) and theoretical (black line) radial distribution curves $f(r)$ for refined mixture 90:10% of **Eq:Ax** conformers; colored lines correspond to refinement of all parameters under assumptions of the individual conformers. Differences $\Delta f(r)$ "Experim.–Theor." are given at the bottom.

Results of the refinement of all parameters at fixed conformer contributions are plotted in Fig. 6. The optimal conformer ratio was found to be Eq:Ax = 90(10):10(10)% with the uncertainty estimated using Hamilton's criterion [26] at 0.05 significance level ($R_{f, \min}=3.2\%$). Calculated (MP2/6-311G**) geometric and vibrational parameters without any refinement demonstrated a somewhat worse fit to the experimental $sM(s)$ function, $R_f = 6.4$ (**Eq**) and 9.3 % (**Ax**).

The free Gibbs energy was estimated on the basis of the conformer ratio determined from the least squares analyses of GED data, Eq:Ax=90(10):10(10)%, as $\Delta G(317\text{K})=1.38(51)$ kcal/mol. Within the uncertainty limit, the conformer ratio Eq:Ax=90(10):10(10)%, derived from the GED data, coincides with that predicted by QC calculations, see Table 1.

Fig. 6. Agreement factor, R_f , versus fixed contributions (molar fractions) of the conformers. The best fit was found for the composition Eq:Ax=90(10):10(10)% with the uncertainties estimated by the Hamilton criterion [26] at the 0.05 significance level.

We have also estimated the temperature-dependence of the conformer ratio. Based on the relative electronic energies and vibrational characteristics obtained from the QC calculations, we calculated the equilibrium constants of the process $\text{Eq} \leftrightarrow \text{Ax}$ at different temperatures from 100 to 1000 K with a 50 K step by programs TDF and KP-IZ (by Dr. V.V. Sliznev). With increasing temperature, the concentration of the **Eq** conformer decreases, approaching 60-70% at 1000 K, see Fig S4 in Supporting Information.

Geometry and NBO analysis

Selected experimental (GED) along with the calculated (QC) geometric parameters of the **Eq** and **Ax** conformers are compiled in Table 2, see also Tables S2 and S3 in the Supporting Information for more details. The natural charges on atoms and the second-order perturbation energies $E(2)$ (donor-acceptor) of both conformers of **NPhP** calculated at B3LYP and MP2 levels with 6-311G** basis sets are given in Table 3.

Table 2: Theoretical (with 6-311G** basis set) and experimental geometric parameters ^a of **NPhP**

Conformer	Eq				Ax			
Method	B3LYP-GD3	M062X	MP2	GED ^b	B3LYP-GD3	M062X	MP2	GED ^b
Bond distance								
N–C1	1.471	1.467	1.470	1.478(6)	1.463	1.459	1.464	1.472(6)
N–C5	1.461	1.457	1.459	1.468(6)	1.469	1.464	1.468	1.476(6)
N–C6	1.412	1.412	1.419	1.420(3)	1.404	1.403	1.409	1.410(3)
C1–C2	1.529	1.524	1.526	1.528(3)	1.538	1.533	1.534	1.536(3)
C2–C3	1.533	1.528	1.529	1.531(3)	1.537	1.532	1.534	1.536(3)
C6–C7	1.408	1.404	1.409	1.410(3)	1.409	1.404	1.413	1.414(3)
C6–C11	1.404	1.399	1.406	1.407(3)	1.411	1.407	1.413	1.415(3)
C7–C8	1.388	1.384	1.394	1.395(3)	1.393	1.391	1.398	1.400(3)
C1–H _{ax}	1.106	1.105	1.108	1.111(2)	1.097	1.096	1.098	1.101(2)
C1–H _{eq}	1.089	1.089	1.092	1.095(2)	1.090	1.090	1.093	1.095(2)
C7–H11	1.084	1.084	1.087	1.089(2)	1.081	1.081	1.083	1.086(2)
Bond angle								
N-C1-C2	111.2	110.9	110.5	110.8(6)	112.5	112.4	112.3	112.6(6)
C1-C2-C3	110.6	110.4	110.3	110.6(6)	109.9	109.7	109.8	110.1(6)
C1-N-C5	112.3	111.7	110.9	110.9(6)	110.7	110.4	109.1	108.9(6)
C1-N-C6	116.3	115.0	113.2	113.5(5)	119.9	118.7	117.3	117.6(5)
C6C7C8	121.1	121.0	120.9	121.1(2)	121.2	121.1	121.2	121.4(2)
Σ∠CNC	346.5	343.5	339.8	340.4(16)	350.0	347.3	343.3	343.7(16)
Torsion angle								
NC1C2C3	55.9	56.8	57.1	57.2(30)	56.0	56.3	56.9	57.0(30)
C1C2C3C4	−53.5	−54.0	−53.7	−53.8(30)	−52.0	−52.6	−52.0	−52.2(30)
C7C6NC1	−57.1	−59.5	−64.8	−60.1(4)	−0.8	2.2	13.6	33.0(16)
φ ^c	34	34	37	36(4)	20	20	12	7(58)
α ^d	18	15	12	11(3)	82	87	87	89(3)

^a Distances in Å, angles in degrees; r_e and $\angle_e$ values (calculations) and r_{hl} ($r_{hl}=r_a+\Delta r$) and $\angle_{hl}$ (GED) are given. The vibrational corrections Δr were calculated by the SHRINK program [24,25], see text above.

^b Values in parentheses for the GED data are full errors estimated as $\sigma(r_{hl}) = [\sigma_{scale}^2 + (2.5\sigma_{LS})^2]^{1/2}$, where $\sigma_{scale} = 0.002r$ and σ_{LS} is a standard deviation in least-squares refinement for internuclear distances and as $3\sigma_{LS}$ for angles. The place-value is such that the last digit of the uncertainty lines up with the last digit of the nominal value.

^c – see text and Fig. 2 for the angle ϕ definition; the uncertainty was adopted as that of C7–C6–N–C1.

^d – angle between N–C6 bond and C1–C2...C4–C5 plane.

Comparing the molecular parameters of the conformers, one can see that the endocyclic C1–N bond distance in **Eq** is longer than that in the **Ax** conformer by 0.002–0.004 Å. The bond distance N–C6, connecting the two rings of the molecule, is longer by 0.010 Å in **Eq** than in **Ax**, presumably because the α -ortho hydrogen repulsion in **Eq** is stronger than that in the **Ax** conformer. This difference may be also explained by the influence of hyperconjugation between Lp and the benzene ring, which is stronger in **Ax** than in **Eq** (see Table 3). The hyperconjugation probably makes the exocyclic C–N bond 0.05–0.06 Å shorter than the endocyclic one. For com-

parison, the exocyclic C–N bond lengths of N-cyclohexylpiperidine **NCHP** [6] is longer than that in **NPhP** by 0.06 Å, because of the absence of the phenyl-ring nitrogen resonance in **NCHP**.

Probably due to a steric interaction between α - and *ortho*-hydrogens, the endocyclic CNC angle is by 2–4° and by 8–10° smaller than the exocyclic one in the equatorial and axial conformers, respectively. The endocyclic CNC bond angle in **Eq** is larger than that in **Ax**, while an opposite tendency for the exocyclic CNC bond angles is observed.

The theoretical bond and dihedral angles are in good agreement with the GED values, Table 2. The endocyclic C–N bond distances obtained from the GED experiment with major uncertainties are *ca.* 0.01 Å longer than the calculated values. The experimental C–C bond distances are well reproduced by the calculated values. The dihedral angle ϕ was reliably refined for the **Eq** conformer, 36(4)° and agrees well with the theoretical predictions. In case of the **Ax** conformer, this angle is smaller, 7(58)°, correlating with the theoretical tendency; the huge uncertainty is caused by the low concentration of this species in the gas phase and by a shallow minimum region on the PES (see Fig. 1). The atoms C1, C2, C4 and C5 of the piperidine ring form a nearly regular rectangle with a deviation of less than 1°.

NBO analysis. The natural charges of the atoms do not depend significantly on the conformer, see Table 3. Among the three carbons directly linked to the nitrogen atom, only one, the C_{Ph} atom, is positively charged, while the two others are slightly negative.

The second-order perturbation energies $E(2) \text{ BD}(\text{N}, \text{C1}) \rightarrow \text{BD}^*(\text{C6}, \text{C11})$ and $\text{Lp}(\text{N}) \rightarrow \text{BD}^*(\text{C}_\alpha, \text{H}_{\text{ax}})$ in **Eq** are noticeably higher than those of the **Ax** conformer. This probably causes the longer N–C1 and C $_{\alpha}$ –H $_{\text{ax}}$ bonds in **Eq** than in **Ax**.

The orbital interaction energy between the Lp on the nitrogen atom and the benzene ring $\text{Lp}(\text{N}) \rightarrow \text{BD}^*(\text{C6}, \text{C}_{\text{ortho}})$ of **NPhP**, see Table 3 and Fig. 7, is in the axial form 9 (B3LYP) to 15 (MP2) kcal/mol higher, stabilizing the axial conformer. Because of this, the MP2 method predicts a higher contribution, up to 24%, of the **Ax** form as compared with the B3LYP value of up to 8%, see Table 1.

Table 3. Selected natural charges and the second-order perturbation energies E(2) (donor-acceptor) of both conformers of **NPhP**.

Conformer	Eq			Ax		
Method ^a	B3LYP-GD3	M062X	MP2	B3LYP-GD3	M062X	MP2
Natural charge						
N	−0.506	−0.530	−0.584	−0.483	−0.506	−0.561
C1	−0.162	−0.167	−0.090	−0.173	−0.178	−0.102
C5	−0.177	−0.183	−0.107	−0.163	−0.166	−0.093
C6	0.188	0.192	0.227	0.184	0.189	0.240
C7	−0.232	−0.237	−0.229	−0.268	−0.276	−0.277
Energy E(2), kcal/mol						
BD(N,C1)→BD*(C6,C11)	3.65	4.50	5.42	2.88	3.32	3.91
BD(C6,C11)→BD*(N,C1)	4.17	4.45	4.37	3.55	3.87	3.82
BD(N,C5)→BD*(C6,C7)	2.75	3.13	3.46	3.24	4.85	4.38
BD(C6,C7)→BD*(N,C5)	3.22	3.50	3.45	4.66	4.48	4.56
Lp(N)→BD*(C1,H _{ax})	7.35	8.70	10.25	3.18	3.42	3.31
Lp(N)→BD*(C5,H _{ax})	8.09	8.54	11.19	3.24	3.39	3.23
Lp(N)→BD*(C6,C _{ortho})	24.07	26.95	25.73	33.00	38.16	40.20

^a 6-311G** basis set was applied

Fig. 7. Orbital interaction of **NPhP** between Lp on nitrogen atom and benzene ring, Lp(N)→BD*(C6,C_{ortho}) in Table 3.

1-phenyl-heterocyclohexanes

The molecular structure and conformational properties of **NPhP** were compared with those of analogous, phenyl-substituted six-membered cyclic compounds: phenylcyclohexane **PhCH**, 1-phenylsilacyclohexane **PhSiC** and 1-phenylphosphorinane **PhPhr** (Table 4 and Table 5).

The relative total electron and free Gibbs energies of conformers of 1-phenylcyclohexane and 1-phenylheterocyclohexanes are given in Table 4. It is to be noted that for all these compounds, except for **NPhP**, the total number of conformers is three to five, differing in the axial or equatorial positioning of the phenyl ring and/or by rotation angle of the latter relative to the saturated ring. As follows clearly from Table 4, the predictions of the relative abundance of conformers depends strongly on the method/basis set combination applied.

For the ‘parent’ compound in this series, **PhCH**, the values of $\Delta E = E_{Ax} - E_{Eq}$ are 2.0–3.1 [27], 3.66 (force field method) [28], 4.36 (HF/6-31G*), 3.82 (B3LYP/6-311G*) and 2.88 (MP2/6-31G*) kcal/mol [29]. Thus, for the compounds with small atoms, carbon or nitrogen, in the cyclohexane ring to which the phenyl group is attached, both QC methods, DFT-B3LYP and MP2, predict the equatorial conformer to be much more stable than the axial one.

At the same time, for the bulkier heteroatoms in the cyclohexane ring, Si or P, the theoretical predictions are principally contradictory. The equatorial conformer is, in terms of ΔE , 1.07 [30] and 0.48 kcal/mol more stable than the axial when calculated with DFT-B3LYP, but opposite tendencies were observed in the MP2 calculations, –0.38 [30] and –0.90 kcal/mol, for silicon and phosphorus heteroatoms, respectively. The B3LYP-GD3/6-311G** calculations predict the ΔE values to be –0.09 and –1.13 kcal/mol for **PhSiC** and **PhPhr**, respectively, while, from the Gibbs energies, the equatorial (**PhSiC**) and the axial (**PhPhr**) conformers are preferable. Comparison with the experimental data allows to conclude that the M06-2X approach predicts the conformation properties of the pheny-heterocyclohexanes very well.

Table 4. Relative total electron energies, free Gibbs energies (kcal/mol) of phenylcyclohexane and 1-phenyl-heterocyclohexanes from QC calculations (B3LYP, M062X and MP2 level with 6-311G** basis set) and experimental data

X ^a	QC calculations							Experiment		
	B3LYP-GD3		M062X		MP2		Ref.	ΔG	Method	Ref.
	ΔE^b	ΔG	ΔE	ΔG	ΔE	ΔG				
C	3.82 3.70 ^e 2.92	– 4.39 ^e 3.36	2.22	3.49	2.88 ^c 2.60	2.8 ^d 3.12	29	2.7(3)	¹ H, ¹³ C NMR 973K	31
N	1.5 ^f 1.68 ^e 1.00	– 1.46 ^e 1.13	0.90	1.03	–	–	3	1.38(51)	GED (317K)	
Si	1.07 ^e –0.09	0.67 ^e 0.55	–0.36	0.19	–0.38	–0.07	30	0.29(25) 0.25	GED (293K) NMR (103K)	30 32
P	0.48 ^e –1.13	0.48 ^e –0.72	–0.98	–0.17	–0.86	–0.61		–0.19(10) 0.16(8)	³¹ P NMR (300K) ^g ³¹ P NMR (163K)	33

^a X is an atom of the cyclohexane ring bonded with the phenyl ring; ^b $\Delta E = E_{Ax} - E_{Eq}$, $\Delta G(298K) = G_{Ax} - G_{Eq}$, where Ax and Eq are most stable axial and equatorial forms, respectively (see text for details); ^c MP2/6-31G*; ^d estimated value; ^e B3LYP; ^f B3LYP/6-31G*; ^g extrapolated value

As follows from Table 4, the values of ΔE and ΔG decrease in the series C>N>Si>P. This is mostly due to the increasing size of the heteroatom and, consequently, the X–C_{Ph} bond elongation (Table 5) and the decrease of steric repulsion in the axial conformers. Moreover, of the compounds in which the X–C_{Ph} bond lengths are similar, those with a lone pair at the X atom

are characterized by a higher contribution of the axial conformer, compare C with N and Si with P in Table 4.

The ϕ angles and the X-C_{Ph} bond distances of the most stable equatorial and axial conformers of 1-phenyl-heterocyclohexanes are compared in Table 5.

It should be noted that in these compounds the orientation of the phenyl ring relative to the saturated ring is different. In the equatorial conformers of **PhCH** and **PhSiC**, the phenyl group is oriented strictly orthogonal relative to the saturated ring because of the symmetrizing α -*ortho*-hydrogen repulsion. In **NPhP**, the phenyl group is rotated at an angle of 31–37° degrees (see Table 5) because of the competition between two types of interactions – α -*ortho*-hydrogen repulsion and hyperconjugation between the Lp and the π -system of the benzene ring. In the case of **PhPhr**, where the C_{Ph}–P bond is longer than the C_{Ph}–N bond of **NPhP**, the influence of hyperconjugation is weaker than the α -*ortho*-hydrogen repulsion, which allows strictly orthogonal orientation of the phenyl ring relative to the saturated cycle.

Table 5. The ϕ angle ^a (deg.) and R=C_{Ph}–X (X=C, N, Si, P) bond distance (Å) of the most stable equatorial and axial forms of 1-phenyl-heterocyclohexanes from QC calculations (B3LYP, M062X and MP2 with 6-311G** basis set) and experimental data.

	QC calculations							Experiment			
	B3LYP		M062X ^c		MP2		Ref.				
X	ϕ	R	ϕ	R	ϕ	R			ϕ	R	Method
Equatorial											
C	90	1.519	90	1.513	90	1.509	29	90			31
N	31	1.412	34	1.412	37	1.419		36(4)	1.420(3)	GED (317K)	
Si	90	1.886	90	1.877	90	1.875	30	81(6)	1.872(4)	GED (293K)	30
P	90	1.856	90	1.848	90	1.840					
Axial											
C	31	1.532	25	1.527	24	1.525	29	0 ^d			31
N	21	1.401	20	1.403	12	1.409		7(58)	1.410(3)	GED(317K)	
Si	20	1.894	16	1.885	10	1.875	30	20(27)	1.882(4)	GED(293K)	30
P	0	1.856	0	1.848	0	1.840					

^a The angle of twist ϕ is defined by the plane through the C_{Ph}–X bond perpendicular to the benzene ring and the bisector of the cyclohexane rings; ^b MP2/6-31G* for phenylcyclohexane; ^c the results from M062X method for all compounds were calculated in this work; ^d estimated value.

The phenyl group in the axial position is rotated by 10 to 30°, which is a result of the competitive influence of three types of interactions – α -*ortho*-hydrogen and 1,3-diaxial repulsions and hyperconjugation. Despite close C_{Ph}–P and C_{Ph}–Si bond lengths, the phosphorous compound **PhPhr** is an exception from this series – the major role of hyperconjugation in this case results in the strictly symmetric orientation with $\phi=0^\circ$.

For comparison, the angle between the phenyl rings in biphenyl is $\theta=0^\circ$ in the solid state [34], $\theta=19\text{--}26^\circ$ in the liquid state [35] and $\sim 40^\circ$ in the gas phase [35,36].

CONCLUSIONS

According to the QC calculations, **NPhP** may exist as two conformers, equatorial and axial, with a ratio of Eq:Ax=92:8% (B3LYP), 84:16% (M06-2X), 83:17% (MP2/6-311G**) and 76:24 (MP2/cc-pVTZ). Except for the latter, these values are in good agreement with the experimental GED result of 90(10):10(10)%.

In our recent study [6] of N-cyclohexylpiperidine, **NCHP**, it was found that in the gas phase at room temperature the molecule exists as equatorial conformers only. This is caused by steric interactions between the cyclohexane and piperidine rings. The conformer EqN-EqC-orth with perpendicular cycles is more stable than the conformer EqN-EqC-twist with almost coplanar cycles.

In the case of **NPhP**, the orientation of both rings is affected by several interactions: hyperconjugation between the Lp and the π -system of the phenyl ring, α -ortho-hydrogen and 1,3-diaxial repulsions. The 1,3-diaxial repulsion has no influence on the orientation of the phenyl group in equatorial form. The most stable form is the equatorial conformer, in which the phenyl ring is rotated by the 'twist angle' ϕ of $30\text{--}37^\circ$ QC and $36(4)^\circ$ GED away from co-planarity of the rings. In the less abundant axial conformer, the PES profile vs. ϕ is rather shallow, see Fig. 2: the calculated value is $0\text{--}20^\circ$ depending on the method/basis set combination applied. For such a shape of the PES and a low concentration in the vapor, the uncertainty of the experimental value, $7(58)^\circ$, is expectedly large.

The contribution of the axial form of 1-phenyl-heterocyclohexanes increases in the series **PhCH<NPhP<PhSiC<PhPhr**, and depends on the C_{Ph} -heteroatom bond distance and the presence of hyperconjugation between the phenyl ring and the lone pair on the heteroatom.

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Graphical abstract