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N-substituted akyl- and nonalkylpiperidines: Equatorial, axial or intermediate conformations?

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ABSTRACT

Detailed quantum chemical calculations for a series alkyl- and nonalkyl-derivatives were performed continuing a systematic study of N-substituted piperidines. Three groups have been proposed to sort out the compounds distinguishing from each other by preference of the substituent's position: (a) adopting exclusively equatorial position (alkylpiperidines); (b) with no exceptional priority of any of the conformers; (c) a peculiar group for which the terms 'equatorial and axial' are not applicable – the nitrogen bond configuration is planar or nearly planar (formyl, carbonyl, etc.). Geometry, pathways and barriers for nitrogen and ring inversions were calculated. Most of the MP2 calculations predict higher axial form contribution as compared with those by DFT-B3LYP.

1. Introduction

The piperidine ring is one of the most important six-membered saturated heterocycles, due to its occurrence in many alkaloids including pharmacological ones. N-substituted piperidines may be shaped in two ways differing by axial or equatorial orientation of the substituent. As a rule, for monosubstituted saturated six-membered ring, the equatorial conformation is more stable than the axial one. For example, in the 'parent' compound, piperidine, the equatorial conformation was found to be more stable than axial in non-interacting solvents [1] and in gas phase [2–4] by 0.2–0.9 kcal/mol.

This paper continues a systematic study of molecular structure and conformational behavior of piperidine derivatives – recently, a double-cycled compound, N-cyclohexylpiperidine (**NCHP**) was explored by detailed quantum chemical (QC) calculations, gas-phase electron diffraction (GED) and infrared (IR) spectroscopy [5]. Of eight possible conformers, only three were most stable, in which the cyclohexyl substituent has an equatorial orientation relative to the piperidine ring.

The simplest *N-alkyl-substituted* derivative is N-methylpiperidine (**NMeP**). From the electrical dipole moments (EDM) of **NMeP** measured in cyclohexane and benzene [6,7] at 298 K it was found that the equatorial conformer is most preferable, 73–75%. Predominance of the equatorial conformer was confirmed by IR spectrum [8] of **NMeP** in CCl_4 as a solvent, the free Gibbs energy difference for the equilibrium equatorial $\rightleftharpoons$ axial $\Delta G^o = 1.61$ kcal/mol and by ^{13}C NMR [9], 1.35–1.77 kcal/mol as measured in chloroform. Twice higher value was determined from kinetically controlled protonation (KCP) [10], 2.4–3.0 kcal/mol in solutions at 293 K and 3.3 ± 0.1 kcal/mol in gas phase at 288 K.

Conformational equilibrium of N-ethylpiperidine (**NEtP**) and N-isopropylpiperidine (**NiPrP**) was experimentally studied in the 1970s by EDM [11]. **NEtP**: as $\Delta G^o = 0.87$ and 0.95 kcal/mol at 298 K in benzene and cyclohexane, respectively, **NiPrP**: The ratio of equatorial:axial conformers 92:8% ($\Delta G^o = 1.44$ kcal/mol) in cyclohexane at 298 K. However, later the authors [11] reinterpreted in the work [7] the ratios to be Eq:Ax = 85:15% ($\Delta G^\circ = 1.03$ kcal/mol) for **NEtP** and Eq:Ax = 94:6% ($\Delta G^\circ = 1.58$ kcal/mol) for **NiPrP** in cyclohexane at 298 K. From IR spectra in CCl_4 it was found that the contribution of the equatorial conformer is 69%, 94% and 100% for piperidine, N-methylpiperidine and N-isopropylpiperidine, respectively [8]. It is to be noted the orientation of the terminal methyl group(s) was not specified.

The stereochemistry of the piperidine ring systems has been reviewed in [12]. The free energy barrier for the ring inversion of *piperidine* in methanol-d_4 is known to be 14.5 ± 0.5 kcal/mol from

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Table 1
Relative total electron energy, free Gibbs energy (kcal/mol) and molar fraction (%) of conformers of **NMeP**, **NEtP** and ***Ni*PrP**.

	QC calculations							Experiment[a], $\Delta G = G_{ax}-G_{eq}$
NMeP								
Method [b]	ΔE[c]			ΔG[c]			X_{eq}	EDM[d]: 0.42–0.65[e] [6,7], 0.39[f] [6]; IR [8]: 1.61[g,k]; ^{13}C NMR [9]:
B3LYP	3.72–3.88			3.73–3.89			100	1.35–1.77[h]; KCP [10]: 2.4 ± 0.1[h], 3.0 ± 0.1[i], 3.2 ± 0.1[j]
MP2	3.38–3.69			3.54–3.80			100	
	QC calculations (equatorial forms **I** and **II**)							Experiment[a]
NEtP								
Method [b]	ΔE[m]			ΔG[m]			$X_{\mathbf{I}}$:$X_{\mathbf{II}}$	$\Delta G = G_{ax}-G_{eq}$
B3LYP	1.04–1.12			1.19–1.25			89:11	EDM[d]: 0.95[e], 0.87[f] [11], 1.03[e] [7]
MP2	1.00–1.21			1.29–1.34			90:10	
NiPrP								
Method	ΔE[m]			ΔG[m]			$X_{\mathbf{I}}$:$X_{\mathbf{II}}$	X_{Eq}:X_{Ax}, %
B3LYP[b]	0.99–1.20			0.78–0.83			80:20	EDM[d]: 92:8[e] [11], 94:6[e] [7] IR [8]: 100:0[g,k]
MP2[n]	0.50–0.68			0.23–0.25			60:40	
	I	**II**	**II***	**I**	**II**	**II***	$X_{\mathbf{I}} : X_{\mathbf{II}} : X_{\mathbf{II'}}$	
MP2[o]	0	0.91	0.92	0	0.37	0.75	55:30:15	

[a] See Introduction section for the method abbreviations.
[b] With basis sets 6-311G**, 6-311+G**, cc-pVTZ and options (for MP2) 'frozen core' and 'full core', see Tables S1, S3 and S5 for details.
[c] $\Delta E = E_{ax} - E_{eq}$, $\Delta G(298\ K) = G_{ax} - G_{eq}$.
[d] Measurements performed for 4-(p-chlorophenyl)- and 4-(p-nitrophenyl)-1-methylpiperidine compounds, room temperature.
[e] In solutions: C_6H_{12}.
[f] In solutions: C_6H_6.
[g] In solutions: CCl_4.
[h] In solutions: $CHCl_3$.
[i] Dodecane.
[j] In gas phase.
[k] Temperture not specified.
[m] $\Delta E = E_{\mathbf{II}} - E_{\mathbf{I}}$, $\Delta G(298\ K) = G_{\mathbf{II}} - G_{\mathbf{I}}$, **I** and **II** – equatorial conformers *g*-Eq **I** and *tr*-Eq **II**, see Fig. 1.
[n] With cc-pVTZ basis set.
[o] With 6-311G** basis set.

^{1}H dynamic NMR data [13,14], so that ring inversion below 210 ± 1 K is slow on the NMR time scale. Free activation energy $\Delta G^{\#}$ = 6.1 ± 0.2 kcal/mol of *piperidine* was found in [15] from ^{13}C NMR spectra and the ratios of 80:20% at 131 K and 65:35% at 298 K were obtained for the equatorial-to-axial conformers. The energy difference between the *chair* and *boat* or *twist* piperidine ring conformations is high enough [16,17] to consider, for piperidine derivatives, only the *chair* structure.

Free activation energies were obtained for the *chair* to *chair* ring inversion process using temperature-dependent ^{1}H NMR spectroscopy in the range 277–303 K $\Delta G^{\#}$(298 K) = 12.0 ± 0.1 kcal/mol in a gas phase [18] which is by 2.4 kcal/mol [14] lower than that in methanol-d_4.

Theoretical calculations also witness for predominance of the equatorial form of **NMeP**, by ΔE = 1.4 MNDO/H [19], 3.60 HF/6-31G* [20], 2.01–3.91 (HF and MP2 methods with difference basis sets) [2], from −1.47 to +3.60 (AM1, HF and MP2 with 6-31G*) [21] and 3.9 kcal/mol MP2/cc-pVTZ [22]. The authors [22] gave an explanation of this phenomenon by 1,3-diaxial interaction which destabilizes the axial conformation, since the C—N bond length for **NMeP** of 1.460 Å is shorter than C—C bond length 1.520 Å for methylcyclohexane.

In contrast to the N-alkyl-piperidines, no information, to our knowledge, was published for such N-substituted compounds as alkenyl, alkynyl, aryl, formyl, and carbonyl. The only exceptions are early works of N-phenyl-piperidine [23,24] in which the authors declared a purely equatorial conformation. To our knowledge, the geometry of the mentioned compounds has not been hitherto experimentally studied in any aggregate state. Moreover, no literature data are available on QC calculations for any of the non-alkyl derivatives.

In this paper we performed a detailed theoretical study of a series of alkyl- and non alkyl-piperidines, aiming at data on (i) conformational behavior, (ii) ring and nitrogen inversion barriers and (iii) molecular structure.

2. Computational details

Quantum chemical (QC) calculations were performed with Gaussian 09 [25] program and Firefly QC package version 8.0.0 [26], which is partially based on the GAMESS (US) [27] source code (in case of MP2/cc-pVTZ). Geometries optimization and vibrational calculations were performed with 6-311G** and cc-pVTZ basic sets by using DFT-B3LYP and MP2 approximations. The results of QC calculations of the conformers are summarized in Tables 1 and 3. Calculations at MP2 level for all compounds were carried out in two ways: (i) using all electrons and all molecular orbitals in the calculations (Full) and (ii) using the frozen core (FC) approximation. The optimized structures with atom numbering are drawn in Figs. 1, 6 and 8.

The potential energy surface (PES) profile for the nitrogen inversion process of **NMeP**, **NEtP**, **NVP**, ***Ni*PrnP** and **NEtnP** was scanned by varying the C3···N—C6 angle with a step of 10° by DFT-B3LYP and MP2 methods, see Figs. 3, 4 and 6.

The PES profile for the *chair*-to-*chair* ring inversion process of **NMeP** was calculated at DFT-B3LYP/cc-pVTZ level by varying the dihedral angle N—C1—C2—C3 (see Fig. 3). The transition structures of **NMeP** were calculated with the use of the quadratic synchronous transit approach (*Synchronous Transit-Guided Quasi-Newton* – STQN) [28,29] implemented into the Gaussian program package. Rotation of the methyl groups about the N—C6 bond was studied at DFT-B3LYP/6-311G** level by varying the H—C6—N—C1 angle with a step of 10° (Fig. S1).

The PES of **NEtP** was obtained by varying two angles – valence C3···N—C6 and torsion C1—N—C6—C7 with a step 10° at DFT-B3LYP/6-311G** level and optimization of all other geometrical parameters, see map in Fig. S2. The PES profiles obtained by varying the dihedral angle Lp—N—C6—H (***Ni*PrP**) and φ = Lp—N—C6—C7 (**NEtP**, **NVP**, ***Ni*PrnP**) with a step 10° at DFT-B3LYP/6-311G** and MP2/6-311G** levels are plotted in Figs. 2 and 5, where Lp is a lone pair of nitrogen atom. The transition structures of all compounds