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# Cyanocyclohexane: Axial-to-equatorial "seesaw" parity in gas and condensed phases

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ABSTRACT

Conformational properties and molecular structure of cyanocyclohexane **1** were studied by gas-phase electron diffraction (GED) and dynamic NMR as well as by detailed quantum chemical (QC) computations. This compound violates the so called 'equatorial rule' according to which the substituents attached to one of the carbon atom of the ring prefers to occupy an equatorial position relative to the frame of cyclohexane. In case of **1**, both conformers contribute nearly equally in gas and liquid phases, with slight domination of the equatorial form as found from the experimental data, Eq:Ax of ca. 3:2. The QC calculations predict contradictive conformer preference depending on method/basis set combination applied. Enthalpy and entropy contributions to Eq↔Ax equilibrium are analyzed.

## 1. Introduction

Saturated six-membered cyclic compounds are widely used in pharmaceutics, chemistry, are part of a number of food products, polymers and dyes. For this reason, their structures extensively in various phases are widely studied, see, for example, [1,2].

Physicochemical behavior of these compounds is essentially dependent on a heteroatom(s) embedded into the cycle, such as piperidines [3,4], tetrahydropyrans [5,6], silacyclohexanes [7,8], etc. Another property-modifying factor is substitution of a hydrogen atom by another atom or group of atoms R (R = halogen [9], alkyl [10], alkenyl or aromatic radicals [11], methoxy [12], etc.). In this case, an alternative occurs for the substituent to occupy either equatorial or axial position relative to the cycle. The identification of the laws of equatorial-axial equilibrium in the derivatives of saturated six-membered heterocyclic compounds is a valuable information on the nature of steric and orbital interactions in organic molecules.

The conformational axial-equatorial equilibrium of cyanocyclohexane $NC{-}C_6H_{11}$ 1 was studied by microwave spectroscopy, Raman scattering in liquid, IR spectroscopy in the Xe matrix, NMR spectroscopy, and quantum chemical calculations [13–16]. It is to be noted that the published results indicate some dominance of either one or another conformer (equatorial or axial), depending on the method applied. In the case IR spectroscopy, in the Xe matrix at a temperature 218–173 K, $\Delta H = -0.18$ (3) kcal/mol, and the ratio $X_{Eq}$:$X_{Ax}$ = 42(8):58(8)% was evaluated for ambient temperature; the enthalpy of $\Delta H = -0.13$ (5) kcal/mol obtained from Raman data in the liquid at 296–333 K coincide with the IR results [13]. The opposite situation is observed in NMR spectroscopy of 1 in $CCl_4$, $X_{Eq}$:$X_{Ax}$ = 54.5 ± 1.7:45.5 ± 1.7% at 303 K [14], from which we estimated $\Delta G$ (303 K) = 0.11 (8) kcal/mol.

Quantum chemical calculations (QC) for gas phase also give contradictory data for the $\Delta E$ values: 0.52 (B3LYP), −0.73 to −0.34 (MP2), with 6-311 + G** or 6-311G** basis sets [13], and −0.15 (M06-2X/aug-cc-pVTZ) and $\Delta G$ (298 K) = −0.06 kcal/mol [15]. It is important to note that only $\Delta E$ values are given in Ref. [13], but not $\Delta G$ which determines the conformer ratio. A microwave (MW) study performed in Ref. [13] at ambient temperature provided with

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structural information on the conformers of gaseous 1 though no evident information on the axial-to-equatorial ratio is recommended.

In this work, we represent the results of combined gas-phase electron diffraction/mass-spectrometric (GED/MS) study along with QC calculations which provides with the first experimental data on conformational axial-equatorial equilibrium in the gas phase. This study is also of interest in connection with the fact that this particular substituent, a carbonitrile group, has a significant effect on the conformational equilibrium due to a strong conjugation. Comparison of the structural and conformational properties of 1 with our recent results on 1-cyano-1-silacyclohexane [15], N-cyanopiperidine and 1-cyanophosphorinane [17] may clarify tendencies in the series of the 1-heterocyclohexanes. We also present a dynamic NMR study, which allows us to measure the frozen conformational equilibrium and obtain thermodynamic parameters like the free energy of activation. In addition, a detailed exploration of the cycle inversion potential energy surface of 1 was carried out for the axial-to-equatorial transition, and more sophisticated, that in earlier works, calculations taking into account dispersion interactions, such as B3LYP-D3, were applied.

## 2. Experimental

### 2.1. GED-MS experiment

A sample of cyanocyclohexane was purchased from Sigma-Aldrich Chemical Company, 98%, and used without further purification. The diffraction patterns were recorded during a combined gas-phase electron diffraction and mass-spectrometric experiment carried out using the EMR-100/APDM-1 unit [18,19].

The sample of the cyanocyclohexane was evaporated from a molybdenum cell with a cylindrical effusion nozzle of 0.6 × 1.2 mm$^2$ size (diameter x length) at 297 (3) K. The conditions of the GED/MS experiment and data refinement details are given in Supporting Information.

Mass spectra (EI, 50 eV) of the effusing molecular beam were recorded simultaneously with the collection of the diffracted electrons. The mass spectrum is in good agreement with the NIST data [20].

### 2.2. NMR experiment

A 400 MHz NMR spectrometer (Bruker Avance 400) was used for all NMR experiments. Toluene-*d*8 was used as solvent for the low-temperature $^{13}$C NMR measurements. The temperature of the probe was calibrated by means of a type K (Chromel/Alumel) thermocouple inserted into a dummy tube. The readings are estimated to be accurate within ±2 K. The NMR spectra were loaded into the data-handling program IGOR (WaveMetrics) for analysis, manipulations, and graphic display. Line shape simulations of the NMR spectra were performed by using the WinDNMR program [21].

### 2.3. Computational details

Quantum chemical (QC) calculations of the cyanocyclohexane conformers were performed with the use of the Gaussian 09 program system [22].

In this paper, the geometry and vibrational calculations were performed using DFT (with B3LYP, B3LYP-D3, where an empirical dispersion correction has been added, and M062X functionals) and MP2 methods with the 6-311G$^{**}$ and cc-pVTZ basic sets.

Geometry optimizations of the axial and equatorial conformers were performed under $C_s$ symmetry. Calculated relative energies and free Gibbs energies along with the equilibrium population of these conformers in the gas phase at room temperature are summarized in Table 1.

Potential energy surface (PES) of the ring conversion was obtained by synchronous scanning two opposite dihedral angles of the ring at M062X/6-311G$^{**}$ level.

Lowest energy pathway for the *axial-to-equatorial* interconversion of the cyanocyclohexane was calculated with the use of the quadratic synchronous transit approach (Synchronous Transit-Guided Quasi-Newton – STQN) [23,24] method with keywords QST2 and PATH at M062X/aug-cc-pVTZ level.

Chemical shift calculations were performed using the gauge-independent atomic orbital (GIAO) method [25]using ORCA 4.0 [26]on the RI-MP2/def2-TZVP geometries at the PBE0 level of theory [27]and using the pcSseg-2 basis set [28]on carbon atoms and def2-TZVP on other atoms [26]. Tetramethylsilane was used as a computational reference for converting calculated shieldings into chemical shifts.

## 3. Results and discussion

### 3.1. Energies

The geometry and vibrational calculations for **1** were performed using DFT (with B3LYP, B3LYP-D3 and M062X functionals) and MP2 methods with the 6-311G$^{**}$ and cc-pVTZ basic sets. Theoretical relative total energy, free Gibbs energy, and the molar fraction of the conformers are summarized in Table 1. Experimental values of ΔG, ΔH and conformer contributions are compiled in Table 2.

All calculations performed show the axial and equatorial conformers to coexist in gas phases at room temperature, both possessing a $C_s$ equilibrium symmetry, Fig. 1. However, the conformational ratios are predicted in different way. The DFT methods in combination with both, B3LYP and B3LYP-D3, functionals resulted in the relative Gibbs energies from ca. 0.3–0.7 kcal/mol that corresponds to some domination of the Eq conformer, 59–77 mol.%. The two basis sets, 6-311G$^{**}$ and cc-pVTZ, applied with the M06-2X functional yielded slightly opposite estimates, 41 and 51 mol.%, respectively. At the same time, all the second order perturbation theory calculations coincide in an axial conformer preference, 60–70 mol.%. More sophisticated calculations, coupled cluster with complete basis set extrapolation, performed by Belyakov et al. [15], show a trend similar to that from the DFT method, and best agreement is with the one which takes into

**Table 1**
Relative total electron energies ΔE, free Gibbs energies ΔG for the Eq↔Ax interconversion) of cyanocyclohexanes from QC calculations.

| QC calculations | ΔE | ΔG | $X_{Eq}:X_{Ax}$ |
|---|---|---|---|
| B3LYP/6-311G$^{**}$ | 0.41 | 0.57 | 72:28 |
| B3LYP/6-311 + G$^{**}$ | 0.52[a] | | |
| B3LYP/cc-pVTZ | 0.57 | 0.72 | 77:23 |
| B3LYP-D3/6-311G$^{**}$ | 0.03 | 0.26 | 59:41 |
| B3LYP-D3/cc-pVTZ | 0.21 | 0.38 | 66:34 |
| M06-2X/6-311G$^{**}$ | −0.56 | −0.21 | 41:59 |
| M06-2X/cc-pVTZ | −0.33 | 0.02 | 51:49 |
| M06-2X/aug-cc-pVTZ[b] | −0.15 | −0.06 | 47:53[c] |
| MP2(FC)/6-311G$^{**}$ | −0.73[a]/-0.69 | −0.40 | 34:66 |
| MP2(FC)/cc-pVTZ | −0.43 | | |
| MP2(FC)/6-311 + G$^{**}$ | −0.49[a]/−0.45 | −0.28 | 38:62 |
| MP2(Full)/6-311 + G$^{**}$ | −0.34[a]/−0.49 | −0.32 | 37:63 |
| CCSD(T)/CBS + therm.corr | 0.03[b] | 0.16[b] | 57:43[c] |

[b] Calculated in this work from the $X_{Eq}:X_{Ax}$ ratio [15].
Data from: [a] [13], [b] [15].
[c] Calculated in this work from ΔG value [15].