

Entropy versus aromaticity in the conformational dynamics of aromatic rings

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Received: 22 September 2012 / Accepted: 29 October 2012 / Published online: 22 November 2012
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Abstract Comparison of the results of Car-Parrinello molecular dynamics simulations of isolated benzene, pyrimidine and 1,2,4-triazine molecules reveals that the unusually low population of planar geometry of the benzene ring is caused by entropy effects despite its high aromaticity. The decrease in symmetry of the molecule results in smaller changes in entropy and Gibbs free energy due to out-of-plane deformations of the ring, leading to an increase in the population of planar geometry of the ring. This leads to differences in the topology of potential energy and Gibbs free energy surfaces.

Keywords Benzene · Aromaticity · Conformational flexibility · Car-Parrinello molecular dynamics · Entropy

Introduction

Aromaticity represents one of the most important cornerstones of modern organic chemistry. The presence of aromatic conjugated systems, especially in benzene molecules, is usually associated with bond equalization and planarity of the ring in agreement with numerous experimental and theoretical studies [1–3]. Based on such data, aromatic rings have therefore long been considered to be flat and strongly conformationally rigid.

However, recent Car-Parrinello molecular dynamics (CPMD) simulation of isolated benzene [4] performed at 298 K led to very unexpected results. It was found that the population of benzene rings with planar geometry is less than 7 % and the molecule exists as a set of two families of flattened boat and half-boat conformations with average values of endocyclic torsion angle of about 7°.

In general these results agree very well with the observed electronic spectra of benzene. It is well known that all electronic transitions in benzene should be forbidden due to its high symmetry. Therefore, out-of-plane deformations of the benzene ring represent one of the most important means of decreasing symmetry, thus allowing electronic transitions [5–7].

However, CPMD simulation results for nucleic acid bases [8] using the same CPMD protocol are also known. It has been found that the population of aromatic pyrimidine rings in adenine with planar geometry was about 30 %, which is significantly greater than the corresponding planar population in benzene (7 %). Even in the case of thymine—a molecule formally containing a tetrahydroaromatic pyrimidine ring population—the planar conformation was more

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than 10 %. These results appear to contradict the formal order of aromaticity, and to an even greater degree in the case of benzene.

It has been demonstrated previously that the energy of out-of-plane ring deformation is related closely to the degree of aromaticity and may be used to some extent as an aromaticity index [9–11]. According to this data, a decrease in the degree of aromaticity of a cyclic conjugated system results in increased conformational flexibility of the ring. In agreement with this assumption it was found that benzene possesses the lowest flexibility and the highest out-of-plane ring deformation energy. Therefore, one might expect that the benzene ring should also have the highest population of planar ring geometry. However, the results of CPMD simulation [4, 8] do not agree with this conclusion.

In this paper, we demonstrate that the most probable reason for these unusual conformational dynamics of the benzene molecule is the contribution from the change of entropy, which, together with the change of enthalpy, governs the equilibrium population of different conformations at non-zero K temperatures.

Computational details

A CPMD [12] study of pyrimidine and 1,2,4-triazine was performed at 298 K using the same protocol as was used for benzene [4]. The molecular dynamics (MD) simulation was carried out using the efficient Car-Parrinello propagation scheme [13] as implemented in the CPMD program package version 3.12.2 [14].

Following an initial equilibration period (ca. 25,000 steps of 2 ps), where each degree of freedom had a separate Nose-Hoover-chain (NHC) thermostat, data were collected over trajectories spanning 550,000 steps (around 40 ps). During the initial equilibration period, each atom was thermalized (difference from the desired temperature was not more than 5 %) before beginning the proper run with only one NHC thermostat. A kinetic energy cutoff of 100 Ry was used for the electron plane-wave basis and Γ -point sampling of the Brillouin zone. Troullier and Martin pseudopotentials [15] and the Perdew–Burke–Ernzerhof (PBE) exchange and correlation functional [16] were applied. The simulations were performed in the canonical ensemble at 298 K. To control the temperature of the system, the NHC thermostat [17, 18] was turned on (to control kinetic energy of the nuclei as well as the fictitious energy of the orbitals) and set at a frequency of $3,000\text{ cm}^{-1}$. A MD time step of $\delta t=3\text{ a.u.}$ (around 0.07 fs) was used for the integration of the Car-Parrinello equations of motion using a fictitious mass parameter for orbitals of 400 a.u. together with the proper atomic masses. The supercell was a cubic box of 16.0 Å in length, and cluster boundary conditions [19] were applied to properly treat the isolated system.

The equilibrium geometry of the molecules under consideration was optimized using Møller-Plesset second order perturbation theory [20] with standard cc-pvtz [21] basis set within C1 symmetry. The vibrational frequencies were calculated within harmonic approximation at the same level of theory.

The conformational flexibility of the molecules was investigated on the basis of the relaxed potential energy surface scans using the C–C–C–C, N–C–N–C and N–N–C–N torsion angles as reaction coordinates for benzene, pyrimidine and 1,2,4-triazine, respectively. Scans of the relevant torsion angles were performed in the range 0–30° in increments of 5° and optimization of the remaining geometrical parameters at every point by the MP2/cc-pvtz method. Ring out-of-plane deformation energy (E_{def}) was calculated as the difference in energy between the non-planar geometry of the ring with the value of the endocyclic torsion angle fixed at 30° and equilibrium geometry of molecule.

The aromaticity of the cyclic conjugated systems in the molecules under consideration was characterized by Bird's [22], Nuclear Independent Chemical Shift (NICS) [23] and HOMED [24] aromaticity indices. Bond orders for calculations of Bird's index were obtained using the Gordy equation [25]. Nucleus-independent chemical shifts were calculated as the zz-component of the magnetic shielding tensor in the point located 1 Å above the center (NICS1_{zz}) of the ring [26] using the gauge-including atomic orbital (GIAO) method [27]. All calculations were performed using the MP2/cc-pvtz method in the Gaussian03 program [28].

Ring conformations were described in terms of the puckering parameters developed by Zefirov et al. [29]. The three parameters S, θ and Ψ characterize the six-membered ring conformation: the S parameter describes the degree of puckering of the ring. Its value is less than 0.1 if the values of all the endocyclic torsion angles do not exceed $\pm 5^\circ$. Therefore, conformations with $S \leq 0.1$ may be considered as planar or almost planar. Two polar angles, θ and Ψ , describe the type of ring conformation. In the case of some ideal conformations these angles adopt following values: chair $\theta=0^\circ$, $\Psi=0^\circ$; boat $\theta=90^\circ$, $\Psi=0^\circ$; twist-boat $\theta=90^\circ$, $\Psi=30^\circ$; sofa $\theta=45^\circ$, $\Psi=0^\circ$; half-chair $\theta=45^\circ$, $\Psi=30^\circ$. However, it should be noted that these values of puckering parameters may be observed only in the case of ideal conformations. In real molecules one should consider some regions of values of polar angles around ideal values that should be assigned to a specific conformation. Hence, ranges of polar angle variations were taken as $\pm 15^\circ$ for the θ angle and $\pm 10^\circ$ for the Ψ angle. Conformations of rings with θ and Ψ values lying outside these regions were considered as intermediate. However, more detailed analysis of such conformations indicates that they can be described as asymmetric analogues of half-chair, chair and boat conformations. Therefore, all these conformations may be summarized as, for example, boat-like or chair-like conformations.

Results and discussion

Out-of-plane ring deformation energy has previously been demonstrated to correlate well with frequencies of the lowest ring out-of-plane normal vibrations [9]. Thus, values of such frequencies may be used to describe the conformational flexibility of aromatic rings. Results of calculations confirm this conclusion. The calculated frequency of the lowest normal out-of-plane ring vibration agrees very well with experimental data and correlates well with ring deformation energy (Table 1). The same value derived from CPMD simulation also demonstrates reasonable agreement with experimental data. This indicates the ability of the CPMD method to reproduce the conformational dynamics of aromatic rings correctly.

Before discussing the results obtained at room temperature, let us consider the known results of aromaticity estimates obtained at zero K (Table 1). A decrease in the degree of aromaticity of cyclic conjugated systems is observed with an increase in the number of nitrogen atoms within the ring. This leads to increased conformational flexibility of the molecule due to the decrease in ring out-of-plane deformation energy. Therefore, one may expect also a decrease in the population with planar ring geometry during CPMD simulations.

Analysis of variations of endocyclic torsion angles during CPMD simulation indicates that the average values of each angle in all molecules under consideration are close to zero, in agreement with planar equilibrium geometry. The range of variation of torsion angles correlates well with the decrease in the degree of aromaticity ($\pm 22.2^\circ$ for benzene [4], $\pm 23.3^\circ$ for pyrimidine and $\pm 27.1^\circ$ for 1,2,4-triazine). However, changes in the average value of torsion angle differ considerably from this trend. This magnitude for benzene (6.6°) is higher than that of pyrimidine (5.4°) and 1,2,4-triazine (6.0°), indicating a trend towards a more flattened but more flexible aromatic ring in heterocycles.

A more detailed analysis of the conformational characteristics of the ring requires more integral parameters than just torsion angles, i.e., the puckering parameters developed by Zefirov et al. [29], which have been applied successfully to the investigation of conformational dynamics of rings in nucleic acid bases [8, 33]. Analysis of populations of different values of puckering degree S during CPMD simulations revealed an unexpected stabilization of planar geometry of the ring in heterocycles as compared to benzene, despite the lower aromaticity of the former (Table 2). The most planar ring found was in pyrimidine. Some decrease in the population of planar geometry was observed for 1,2,4-triazine, in agreement with the lower aromaticity of this cyclic conjugated system. However, in both cases, the population with ring planar geometry is higher (by more than four times) than that of benzene. A similar trend is found for the average value of puckering degree, which was lowest for pyrimidine (0.13) and highest for benzene [4] (0.16). Additional considerations indicate the domination of boat-like conformations (boat and twist-boat), with populations of between 37.5 % for pyrimidine and 64.1 % for benzene (Table 2). This type of ring out-of-plane deformation of aromatic rings agrees very well with the character of the lowest vibrational normal modes that correspond to the transition to boat conformations.

Thus, the results of CPMD simulations clearly demonstrate the contradiction between classical concepts of organic chemistry, namely aromaticity and the dynamic behavior of the aromatic ring in a benzene molecule. Taking into account that the intramolecular interactions within all molecules under consideration are very similar, it is possible to hypothesize that the strong dynamic destabilization of benzene is not caused by differences in electronic structure.

In our opinion, the main peculiarity that could lead to such unusual behavior is the difference in the symmetry of their equilibrium geometry between benzene and the heterocycles considered. Benzene (D_{6h}) is significantly more symmetrical than pyrimidine (C_{2v}) and especially 1,2,4-triazine

Table 1 Calculated and experimental frequencies (cm^{-1}) of the lowest normal ring-out-of-plane vibration, ring out-of-plane deformation energy (E_{def} , kcal mol^{-1}), nuclear independent chemical shift $\text{NICS}_{1\text{zz}}$

Molecule	Frequency			Aromaticity indices			
	Experimental	MP2/cc-pvtz	CPMD	E_{def}	$\text{NICS}_{1\text{zz}}$	Bird	HOMED
Benzene	398 ^a	406	381	7.23	-30.5	100.0	100
Pyrimidine	349 ^b	356	303	6.49	-29.8	97.4	99.8
1,2,4-Triazine	323 ^c	325	255	5.27	-28.7	88.2	99.4

^a Data from [30]

^b Data from [31]

^c Data from [32]

and Bird's aromaticity indices for benzene, pyrimidine and 1,3,4-triazine. *CPMD* Car-Parrinello molecular dynamics, *HOMED* harmonic oscillator model of electron delocalization

Table 2 Population (%) of conformations of aromatic ring during CPMD simulations

Conformation	Benzene ^a	Pyrimidine	1,2,4-Triazine
Planar	6.6	30.1	26.7
Sofa	5.4	8.6	5.2
Boat	24.7	12.5	18.7
Twist-boat	49.4	25.0	35.7
Chair	1.6	3.7	1.5
Half-chair	12.3	20.1	12.2

^a Data from [4]

(C_s). Therefore, any decrease in symmetry should significantly influence the entropy of the molecule (a typical example is the influence of entropy on phase transitions in crystals [34]). Since the most significant change in symmetry should be observed for highly symmetrical structures, benzene will be accompanied by the strongest changes in entropy. The main consequence of this effect is the considerable decrease in Gibbs free energy for non-planar conformations of benzene as compared to planar conformations despite the increase in potential energy (enthalpy) of the molecule. This results in a significant difference in the topology of the potential energy surface (PES) and Gibbs free energy surface (GFES) of benzene. The PES has only one minimum, corresponding to the planar and highly symmetrical geometry of the ring. However, in the case of GFES this point corresponds to local maximum surrounded by set of local minima corresponding to different flattened twist-boat conformations of benzene. The decrease in symmetry of the pyrimidine molecule causes a considerably smaller increase in entropy due to the transition of the ring to a non-symmetrical non-planar conformation. The resulting contribution to Gibbs free energy becomes smaller than the increase in enthalpy due to ring deformation. A similar situation is observed also for 1,2,4-triazine, where a more flattened topology of the PES around one global minimum dominates over entropy effects, leading to a more flattened character of GFES as well. Therefore, the ring population with planar geometry in this molecule is smaller compared to pyrimidine. Thus, one may conclude that the conformational dynamics of aromatic rings is determined by two opposite effects, namely (1) the aromaticity of the cyclic conjugated system, which influences the character of the PES around the minimum; and (2) the change in entropy due to the decreased symmetry of the molecule with out-of-plane deformations of the aromatic ring leading to a change in character of the GFES.

It should also be noted that differences in the topology of the PES and GFES cannot be revealed by modern static

quantum-chemical methods, since publically available programs optimize geometry on the basis of potential rather than Gibbs free energy. This causes differences in data on conformational dynamics derived from static quantum chemistry operated by zero K geometry and molecular dynamics simulations performed at significantly non-zero K temperature.

Conclusions

The results of CPMD simulations show that the population of planar geometry of isolated pyrimidine and 1,2,4-triazine is significantly higher compared to that of benzene despite their considerably lower aromaticity. This fact also does not agree well with changes in ring out-of-plane deformation energy and frequencies of the lowest ring out-of-plane normal vibrations that characterize the ability of the aromatic ring to adopt a non-planar conformation. The very low populations of planar geometry of benzene at room temperature may be explained by the significant contribution of entropy to the total change in Gibbs free energy at the transition of ring to non-planar geometry due to the sharp decrease in the symmetry of the molecule. The lower symmetry of pyrimidine and 1,2,4-triazine results in a smaller contribution of entropy. Therefore, changes in potential energy (enthalpy) dominate over entropy.

Thus, benzene represents a first quite clear example of a molecular system where the topology of the PES differs considerably from the topology of the GFES. The planar geometry of benzene corresponds to the minimum PES and local maximum of GFES surrounded by sets of local minima where the benzene ring adopts flattened boat and twist-boat conformations.

It should be noted that differences in topology of PES and GFES for symmetrical molecules cannot be revealed by modern static quantum-chemical methods. In all cases, optimization of molecular geometry is performed as minimization of potential energy without consideration of entropy effects. However, in reality, any molecular structure exists as a point on a GFES but not on a PES. In the case of low molecular symmetry, the topology of both surfaces are close enough. However, for highly symmetrical molecules, the differences can be quite considerable and the results of conventional quantum-chemical calculations can be far from reality, not because of limitations of treatment of electron correlation or similar effects but just because of the absence of consideration of an entropy contribution.

Acknowledgments The authors gratefully acknowledge the Wrocław Supercomputer Center (WCSS), the Galera-ACTION Cluster and the Academic Computer Center in Gdansk (CI TASK) for providing computer time.

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