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Unexpected Binding Affinity of [2.2]Paracyclophane to Cations[#]

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Abstract

Motivation. The interaction of a cation with an aromatic ring, namely cation–π interaction is a strong noncovalent force of great importance in many systems, including cation receptors and biomolecules. Cyclophanes and especially calixarenes are widely used cation receptors based on this interaction. [2.2]Paracyclophanes are not used for building cation receptors; however its binding capability toward cations is superior to benzene.

Method. HF and B3LYP calculations have been used to carry out the geometry optimizations of [2.2]paracyclophane (**1**) complexes with lithium and sodium cation. Benzene complexes are also studied for comparison purposes. Comparative AIM and NICS analyses of the complexes have been performed.

Results. Several cation–π complexes have been optimized and compared. Complexes of **1** are considerably more stable (~10 kcal/mol) than benzene complexes. This unexpected difference is explained by the reduction of the repulsive interaction of the π–systems in **1** due to the close proximity of the two benzene rings upon complexation. The AIM analysis is in agreement with this explanation.

Conclusions. From the results presented here, derived from the higher binding affinity of **1** in comparison to benzene toward cations, the following conclusion arises: [2.2]paracyclophane is an excellent binding unit for the construction of cation receptors.

Keywords. Cyclophanes; cation–π interactions; AIM; atoms in molecules; HF; Hartree–Fock; DFT; density functional theory; BSSE; basis set superposition error; host–guest.

Abbreviations and notations

AIM, Atoms–in–Molecules	CP, Critical Point
B3LYP, Becke's three parameter hybrid exchange functional and the Lee–Yang–Parr correlation functional	DFT, Density functional theory HF, Hartree–Fock
BSSE, Basis set superposition error	NICS, Nucleus–Independent Chemical Shift

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1 INTRODUCTION

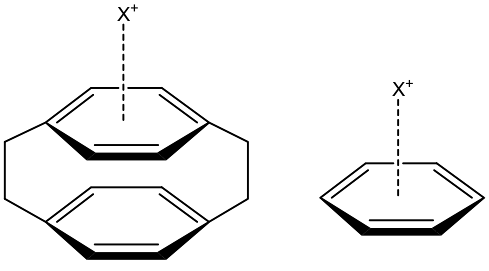
Interactions involving aromatic rings are important binding forces in both chemical and biological systems and they have been recently reviewed by Meyer *et al.* [1]. For instance arene–arene interactions play an essential role in the structure of DNA and proteins, as well as in their interaction with small molecules [2,3]. The interactions of cation and π–electrons, namely cation–π interactions [4], are strong noncovalent forces of great importance in many systems, including cation receptors and biomolecules [5].

The study of the chemistry of assemblies of molecules, which are held together and organized by means of weak noncovalent intermolecular forces is the matter that concerns to supramolecular chemistry [6,7]. Understanding the chemical origins (binding sites) as well as the physical nature (energetic) of those binding forces is now one of the main thrusts of host–guest chemistry. Molecular modeling techniques based on high–level *ab initio* calculations are incipient and incisive tools that provide insight into the behavior of the molecular systems involved in molecular recognition. Cations have been traditionally recognized by two families of receptors depending on the intermolecular forces involved: crown ethers [8] (hydrogen bond forces) and calixarenes [9] (cation–π interaction). The nature of latter interaction has been widely studied and it has been demonstrated that two contributions dominate the interaction, *i.e.* electrostatic and polarization [10]. [2.2]Paracyclophane (**1**) is the smallest stable member of the cyclophane series. The close proximity of the rings leads to a strong interaction of the π–systems. The cavity of **1** is too small for inclusion compounds and it is used as a building block to study intramolecular electron transfer phenomena. Its use as a building block for the construction of cation receptors has not been yet explored.

In this communication, we report a theoretical *ab initio* investigation on complexes of **1** and cations. We have compared their energetic and geometrical features with cation–π complexes of benzene. The interaction energies of **1** complexes are considerably more negative than benzene complexes. A likely explanation of this result is that the aryl–aryl repulsion due the proximity of the aromatic rings in **1** is diminished upon complexation of the cation. This presumption is in part supported by results previously reported by our group [11], where we have demonstrated that an aromatic ring can interact favorably with concentrations of negative charge, for instance anions or lone pair of electronegative atoms whenever it is simultaneously interacting with a cation by the opposite side of the ring. Results from the AIM analysis [12] present here also support this explanation. In addition, to further analyze the interaction of **1** with cations, we report the change in the aromaticity of the rings upon complexation by means of the NICS [13] criterion.

2 MATERIALS AND METHODS

The geometry of the complexes included in this study was fully optimized at the B3LYP/6–31++G** level of theory using the Gaussian 98 [14] program, since previous studies [15,16] have shown that reliable results are obtained at this level. The results at the HF level are also included for comparison purposes. No symmetry constrains have been imposed in the optimizations. The binding energies were calculated at the same level with and without correction for the basis set superposition error (BSSE) using the Boys–Bernardi counterpoise technique [17]. The topological analysis of the electron density performed for complexes **2**–**5** (Figure 1) was determined using Bader's theory of AIM [12]. The analysis was carried out using the AIMPAC program [18] at the HF/6–31++G** level of theory. We have used the NICS(0) criterion [14] at the GIAO–HF/6–31++G** [19] level of theory to evaluate the aromaticity.



2, X=Li
3, X=Na

4, X=Li
5, X=Na

Figure 1. Cation–π complexes **2**–**5**.

3 RESULTS AND DISCUSSION

Table 1 reports the energies and equilibrium distances of **2**–**5** complexes. Some interesting features can be appreciated from the inspection of the results. First, the interaction energies are about 10 kcal/mol more negative for **1** complexes than for benzene complexes. This unexpected difference is significant and a likely explanation is that the repulsion between the aromatic rings of **1** is drastically reduced upon complexation with the cation. This explanation is supported by the fact that the two aromatic rings move together upon complexation (0.012 Å in **2** and 0.011 Å in **3**), indicating a reduction in the π–π repulsions in the presence of the cation. Second, the equilibrium distances are shorter in **1** complexes (1.816 Å in **2** and 2.373 Å in **3**) in comparison with benzene complexes **4** (1.835 Å) and **5** (2.395 Å), at the B3LYP level of theory. Third, the effect of introducing electron correlation in the calculations is mainly observed in the equilibrium distances, which are shorter at the B3LYP than at the HF level, whilst the interacting energies are very similar at both levels (see Table 1).

Table 1. Interaction energies with the BSSE correction (E_{BSSE}, kcal/mol), equilibrium distances (R_e, Å) computed for complexes **2**–**5** at HF/6–31++G** and B3LYP/6–31++G** levels of theory. The density (ρ, a.u.) at the cage critical point generated upon complexation of the cation (CP^2) and the change of the density ($\Delta\rho$, a.u.) computed at the cage critical point located in the middle of the two parallel aromatic rings (CP^1) of [2.2]paracyclophane upon complexation. The change of the NICS(0) (ΔNICS(0), ppm) values computed in the middle of the aromatic rings for complexes **2**–**5**, values in parenthesis correspond to the lower ring of the [2.2]paracyclophane.

Compound	E_{BSSE} (HF)	E_{BSSE} (B3LYP)	R_e (HF)	R_e (B3LYP)	$10^2\rho$ (3,+3)	$10^4\Delta\rho$ (3,+3)	ΔNICS(0)
2	–46.99	–46.94	1.905	1.816	1.233	0.711	–0.069 (0.036)
3	–31.45	–31.72	2.464	2.373	0.833	0.257	1.067 (0.054)
4	–36.32	–37.21	1.907	1.835	1.163	–	–0.452
5	–23.19	–24.09	2.472	2.395	0.767	–	1.000

To corroborate the assumption that the superior binding ability of **1** in comparison to benzene for the complexation of cations is due to the reduction of the repulsive π–π interaction of the aromatic rings, we have performed an AIM analysis. It is well–known that the density at the cage critical point (CP) can be used as a measure of the bond order in π–interactions [20,21]. The AIM analysis of **1** revealed a unique cage CP (denoted as CP^1) located equidistant from both aromatic rings along the C_2 axis. Upon complexation of the cation, a second cage CP appears (denoted as CP^2), linking the cation with one aromatic ring of **1** and located along the C_2 axis (see Figure 2). The variation of the electron charge density at the cage CP^1 ($\Delta\rho$(3,+3)) upon complexation of the cation is present in Table 1 for complexes **2** and **3**. In both complexes the variation is significant, indicating that the complexation of the cation has a strong influence on the interaction of the rings. Moreover, the variation is positive indicating that the interaction between the aromatic rings is more favorable (or less unfavorable) than in **1**. In fact, for complex **2** $\Delta\rho$(3,+3) is considerably higher than in **3** in agreement with the difference in the complexation energy. The computed values of the electron charge density at the CP^2 are also present in Table 1 for all complexes. They are greater for **1** complexes than for benzene complexes in agreement with the interaction energies. Similarly, the values of the density in lithium complexes **2** and **4** are greater than the corresponding values obtained for sodium complexes **3** and **5**, in agreement with the complexation energies. Finally, we have studied the variation of the aromaticity of the rings upon complexation of the cation. For lithium complexes **2** and **4**, the variation of the aromaticity of the ring is small and negative indicating that the aromaticity of the ring is slightly affected by the complexation. On the contrary, for sodium complexes **3** and **5**, the variation is not negligible and it is positive, indicating that the aromaticity of the ring decreases upon complexation. In a previous study reported by our group on the aromaticity of benzene complexes with Li^+, Na^+ and K^+ [16], all three complexes behaved the same, i.e. they showed a positive variation of NICS upon complexation, however the Li^+ complex gave the smallest variation (0.16 ppm). In that study the NICS in the complexes was calculated 1 Å below the aromatic ring opposite to the cation. In the present manuscript, it has been calculated at the center of the ring, because it is not possible to compute NICS(1) in **1** obviously due to the presence of the other π–system. It is known that NICS(0) is influenced by π effects but also by the local (paratropic) effects arising mainly from the σ bonds and this is why NICS(1) gives more reliable results [22]. A likely explanation for the different behavior of the Li^+ and Na^+ complexes present in Table 1 is that the σ–effects are probably higher in Li^+ than in Na^+ complexes, since Li^+ becomes closer to the aromatic ring. This issue requires further investigation.

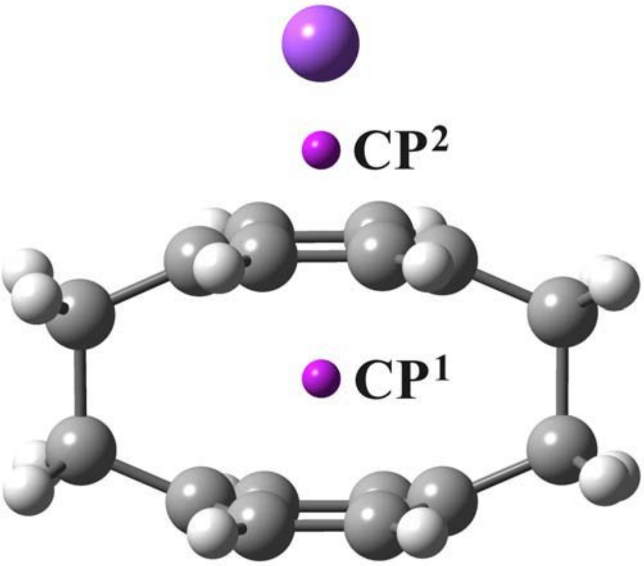


Figure 2. Optimized structure of complex **3** and the representation of the cage CPs is shown.

Finally, further experimental evidence can be obtained from the interesting work of Dyson et al. [23] where they demonstrate that **1** is markedly more reactive towards $[Cr(CO)_6]$ than related single–deck arene, *p*–xylene. The increased thermodynamic stability of the paracyclophane complex arises from the reduction of the π–π repulsions in the transition metal–**1** complex, a consequence of the electron–withdrawing nature of the $Cr(CO)_3$ fragment.

4 CONCLUSIONS

In summary, we have found that the π–interaction of [2.2]paracyclophane **1** with cations is markedly more effective than benzene. The complexation energies are about 10 kcal/mol more favorable in **1** than in benzene. A justification is that the repulsion between the π–clouds of both aromatic rings in **1** is reduced upon complexation. The AIM analysis supports this hypothesis. Finally, from the result present here we conclude that **1** can be used as an effective binding block for the construction of cation receptors.

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