Ab Initio Study of [*n.n*]Paracyclophane (*n* = 2, 3) Complexes with Cations: Unprecedented Through-Space Substituent Effects

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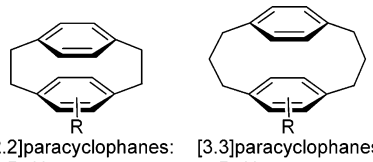
Several cation−π complexes between substituted [*n.n*]paracyclophanes (*n* = 2, 3) and cations have been studied using high level ab initio calculations. The chemical substitution at the aromatic ring that is not interacting with the cation has a strong influence upon the binding energy. This strong through-space substituent effect has been studied using the "atoms-in-molecules" theory, which has been found useful to explain the energetic results.

Introduction

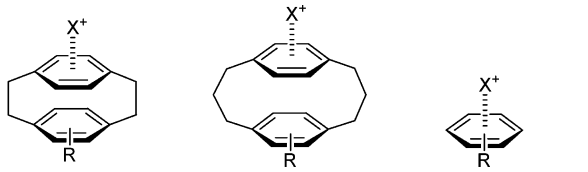
Noncovalent interactions play a key role in many areas of modern chemistry, especially in the field of supramolecular chemistry and molecular recognition.[1] In particular, interactions involving aromatic rings are key processes in both chemical and biological recognition and they have been recently reviewed by Meyer et al.[2] The interaction between alkali metal cations, as well as tetraalkylammonium groups, and the π face of aromatic compunds is a strong noncovalent binding force, namely, a cation−π interaction. A great deal of experimental and theoretical work has been published to evidence that these cation−π interactions play a prominent role in several areas of chemistry and biology.[3] For instance, cation−π interactions are an important factor to the ion selectivity in potassium channels;[4] they are also important for the binding of acetylcholine to the active site of the enzyme acetylcholine esterase,[5] and recently, their importance in neurotransmitter receptors has been demonstrated.[6] The cation−π interaction is in general dominated by electrostatic and cation-induced polarization forces.[7] The nature of the former force is rationalized by emphasizing the role of the permanent quadrupole moment of benzene[8] and the latter force is explained by the polarization of the π-electron system by the cations that have a significant contribution, whereas the reverse effect is expected to be sensibly lower.



[2.2]paracyclophanes:
1, R=H
2, R=2xNH$_2$ (*para*)
3, R=4xCN

[3.3]paracyclophanes:
4, R=H
5, R=2xNH$_2$ (*para*)
6, R=4xCN

We have recently reported[9] a combined crystallographic and theoretical ab initio study where we analyze the geometrical and energetic features of cation−π complexes involving one aromatic ring of [2.2]paracyclophane. Energetically, the complexes are considerably more favorable than those of the related single-deck benzene. In this communication, we report high level ab initio calculations of π-complexes between cations (Li^+ and Na^+) and substituted [*n.n*]paracyclophanes (*n* = 2, 3), see Figure 1. In these complexes, the strength of the cation−π interaction is deeply influenced by the substitution of the opposite ring due to through space effects.



7, X=Li, R=H
8, X=Li, R=2xNH$_2$
9, X=Li, R=4xCN
10, X=Na, R=H
11, X=Na, R=2xNH$_2$
12, X=Na, R=4xCN

13, X=Li, R=H
14, X=Li, R=2xNH$_2$
15, X=Li, R=4xCN
16, X=Na, R=H
17, X=Na, R=2xNH$_2$
18, X=Na, R=4xCN

19, X=Li, R=H
20, X=Li, R=2xNH$_2$
21, X=Li, R=4xCN
22, X=Na, R=H
23, X=Na, R=2xNH$_2$
24, X=Na, R=4xCN

Figure 1. Schematic representation of [*n.n*]paracyclophane (*n* = 2, 3) and benzene complexes with cations **7**−**24**. In **8**, **11**, **14**, **17**, **20** and **23**, the relative position of the amino substituents is *para*.

Computational Methods

Several theoretical works have stressed the importance of using electron correlation in the study of $\pi-\pi$ interactions in paracyclophanes.[10] The MP2 method is the least expensive post HF procedure that takes into account dispersion forces, which are neglected in currently popular DFT approaches. Nevertheless, the main obstacle to a more widespread use of the MP2 method is its high computational requirement, principally in medium to large systems. Because of the time-consuming nature of the MP2 calculations on the systems studied in this work, especially the structures where cyano groups are present, we have used a computationally faster treatment than the traditional MP2 method. This method is the resolution of the identity MP2 (RI-MP2),[11,12] which uses an auxiliary fitting basis to avoid treating the complete set of two-electron repulsion integrals. The RI-MP2(full) calculations without imposing any symmetry

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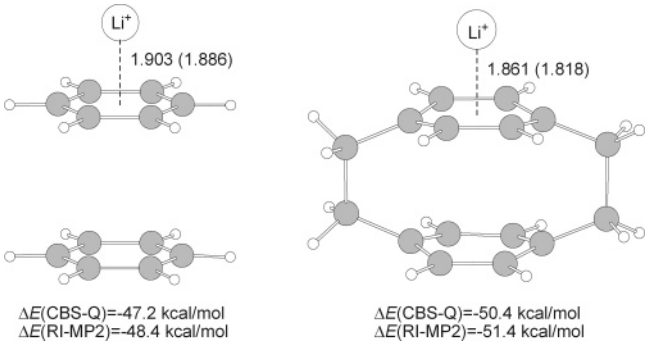

Figure 2. CBS-Q optimized structures of a dimer of benzene and **1** interacting with Li^+. Distances are in Å, the values in parentheses correspond to the RI-MP2(full)/6-31++G** optimized complexes.

constraint were done using the program TURBOMOLE version 5.7.[13] The RI-MP2 method applied to the study of cation− and anion−π interactions is considerably faster than the MP2 and the interaction energies and equilibrium distances are almost identical for both methods.[14] The BSSE correction for the binding energies has been applied using the counterpoise method.[15] To further validate that the RI-MP2/6-31++G** level of theory is adequate to study these systems, we have optimized two model compounds using the CBS-Q methodology and compared the geometries and energies with the RI-MP2/6-31++G** results. The CBS-Q method specifies the complete basis set (CBS) method of Peterson et al.[16] for computing very accurate energies. It combines extrapolation to the complete basis set second-order limit for the MP2 calculation with the use of relatively small basis sets for the higher-order correlation energy (MP4(SDQ) and QCISD(T) methods). In Figure 2 we show the results obtained using the CBS-Q and the RI-MP2/6-31++G** levels of theory for the dimer of benzene interacting with lithium cation imposing C_{6v} symmetry and the [2.2]paracyclophane complex with Li^+. It can be observed that both methods give comparable results, emphasizing the reliability of the RI-MP2/6-31++G** level of theory.

The contributions to the total interaction energy have been computed using the molecular interaction potential with polarization (MIPp)[17] partition scheme, which is an improved generalization of the MEP where three terms contribute to the interaction energy, (i) an electrostatic term identical to the MEP,[18] (ii) a classical dispersion-repulsion term, and (iii) a polarization term derived from perturbational theory.[19] Calculation of the MIPp of **1**−**6** interacting with Li^+ was performed using the HF/6-31++G**//RI-MP2(full)/6-31++G** wave function by means of the MOPETE-98 program.[20] The ionic van de Waals parameters for Li^+ were taken from the literature.[21]

Results and Discussion

In Table 1 we summarize the binding energies without and with the basis set superposition error (BSSE) correction (E and E_{BSSE}, respectively) and equilibrium distances (R_e) of complexes **7**−**24** at the RI-MP2/6-31++G** level of theory. From the energetic results some interesting points arise, first, the binding energy of **1** interacting with either lithium or sodium cations (complexes **7** and **10**) is dramatically reduced or considerably increased depending on the substitution of the ring that is not directly involved in the interaction. The binding energy of complex **9** is 20.3 kcal/mol more positive than that for **8** and the binding energy of complex **12** is 17.4 kcal/mol more positive than that for **11**, indicating that the activating $-NH_2$ substituents favor the interaction and the deactivating −CN groups reduce

TABLE 1: Binding Energies without and with the Basis Set Superposition Error Correction (E and E_{BSSE}, kcal/mol, Respectively) and Equilibrium Distances (R_e, Å) at the RI-MP2/6-31++G Level of Theory**

complex	E	E_{BSSE}	R_e	$10^2\rho^a$ (3,+3)	$10^5\Delta\rho^{a,b}$ (3,+3)
[2.2]Paracyclophane Complexes:					
7 (**1** + Li^+)	−51.4	−43.6	1.818	0.4757	2.29
8 (**2** + Li^+)	−57.8	−49.6	1.806	0.4694	2.16
9 (**3** + Li^+)	−37.9	−29.3	1.845	0.4554	−4.55
10 (**1** + Na^+)	−37.1	−29.3	2.318	0.4720	1.92
11 (**2** + Na^+)	−42.6	−34.5	2.288	0.4650	1.72
12 (**3** + Na^+)	−25.1	−17.1	2.394	0.2671	−19.3
[3.3]Paracyclophane Complexes:					
13 (**4** + Li^+)	−53.5	−45.1	1.819	0.5963	9.26
14 (**5** + Li^+)	−59.0	−50.3	1.802	0.4672	14.5
15 (**6** + Li^+)	−41.4	−32.5	1.830	0.3470	0.44
16 (**4** + Na^+)	−38.1	−29.7	2.308	0.5611	5.74
17 (**5** + Na^+)	−42.8	−34.2	2.297	0.4015	7.93
18 (**6** + Na^+)	−27.3	−19.1	2.337	0.3422	−0.04
Benzene Complexes:					
19 (**BEN** + Li^+)	−38.5	−33.7	1.914	-	
20 (**BNH** + Li^+)	−48.7	−43.6	1.879	-	
21 (**BCN** + Li^+)	−0.9	4.8	2.093	-	
22 (**BEN** + Na^+)	−26.1	−21.4	2.393	-	
23 (**BNH** + Na^+)	−35.5	−29.9	2.354	-	
24 (**BCN** + Na^+)	3.9	8.8	2.679	-	

[a] The computed value of electron density (ρ) in atomic units at the cage critical point located between the rings and its variation upon complexation ($\Delta\rho$) is given for complexes **7**−**18.** [b] **1**, $10^2\rho = 0.4528$; **2**, $10^2\rho = 0.4478$; **3**, $10^2\rho = 0.4600$; **4**, $10^2\rho = 0.5037$; **5**, $10^2\rho = 0.3222$; **6**, $10^2\rho = 0.3426$ au.

the strength of the cation−π interaction of the opposite ring. Second, despite the aryl−aryl distance being greater in [3.3]-paracyclophanes than in [2.2]paracyclophanes, the results obtained for the [3.3]paracyclophane complexes are comparable. The computed binding energy of complexes of **4**−**6** interacting with Li^+ and Na^+ is strongly affected by the substitution of the opposite "spectator" ring. For instance, the difference in binding energy between **14** and **15** is 17.8 kcal/mol; see Table 1. Third, for comparison purposes, we have also included in Table 1 the binding energies of the related single-deck benzene (**BEN**) and substituted benzene complexes, i.e., 1,4-diaminobenzene (**BNH**) and 1,2,4,5-tetracyanobenzene (**BCN**) with Li^+ and Na^+ cations. As expected, it can be observed that the binding energies become more negative and the equilibrium distances shorten as the aromatic ring increases its electron richness. The differences in both the binding energies and equilibrium distances are important, for instance, between **20** and **21** complexes the difference in the binding energy (E_{BSSE}) is 48.6 kcal/mol and in the equilibrium distance is 0.196 Å. Obviously the differences are greater in the single-deck than in the corresponding double-deck complexes, where the effects are transmitted through the space. Nevertheless, approximately 41% of the substituted effect is conserved when going from single-deck to double-deck compounds. Such a percentage is very high and represents an unprecedented trough-space substituent effect that can reduce in more than 20 kcal/mol the binding energy of the complexes depending on the substitution. In addition, the binding energies of double-deck paracyclophanes complexes are always more favorable than the corresponding single-deck **BEN** and benzene derivatives (**BNH** and **BCN**) complexes. This fact can be related with some results previously reported by our group,[22] where we demonstrated that an aromatic ring can interact favorably with concentrations of negative charge, for instance, anions or lone pair of electronegative atoms if it is simultaneously interacting with a cation by the opposite side of the ring. In the

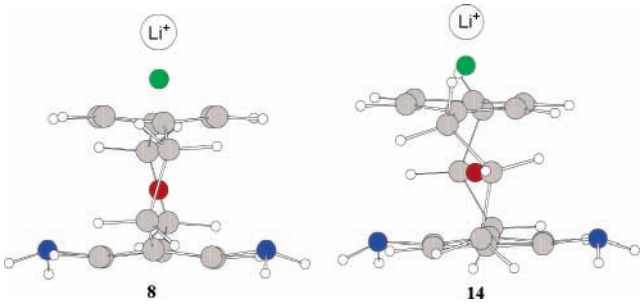

Figure 3. Location of the (3, +3) cage CPs in complexes **8** and **14**.

particular compounds studied here, the concentration of negative charge is the π-cloud of the lower aromatic ring.

In Table 1, we also summarized the change of the electron charge density ($\Delta\rho$) at the cage critical point (CP) that is located between the aromatic rings of the cyclophanes upon complexation of the cation. The location of this (3, +3) cage CP is represented in Figure 3 (red circle), where we also include the location of the other cage CP (green circle) that is obtained from the AIM[23] analysis of the complexes, which appears upon complexation of the cation. In Figure 3 we show the location of the cage CPs obtained for complexes **8** and **14** as representative examples of the other [2.2]paracyclophanes and [3.3]-paracyclophane complexes, respectively, studied in this work. The utility of the value of ρ at the green cage CP for studying cation$-\pi$ interactions has been described in the literature.[24] In fact, the value of ρ at this cage CP can be used as a measure of the bond order of the interaction. In this manuscript, we pay attention to the value of ρ at the red cage CP, which gives hints about the strength of the ring$-$ring interaction. More interestingly, the change of this value upon complexation $\Delta\rho$ gives information of how the ring$-$ring interaction is affected by the complexation.

It is worth mentioning that in [2.2]paracyclophane complexes **7**, **8**, **10** and **11** the variation of the $\Delta\rho$ value is positive, indicating that the interaction between both rings is enhanced upon complexation of the cation, being either less repulsive or even attractive.[25] In sharp contrast, the variation of the charge density at the cage CP in complexes **9** and **12** is negative, indicating that the ring$-$ring interaction is disfavored upon complexation of the cation. A likely explanation is that the otherwise perfect stacking interaction between an electron rich and an electron poor aromatic ring is modified by the presence of the cation, which is interacting with the electron-rich ring.

TABLE 2: Contribution to the Total Interaction Energy (kcal/mol) Calculated with MIPp and 1$-$6 Paracyclophanes Interacting with Li^+ at Several Distances (*d*, Å) from the Center of the Ring and Perpendicular to It along the Main Symmetry Axis[a]

d	E_e	E_p	E_{vw}	E_t	E_{RI-MP2}	R_e
			1			
1.0	10.01	−89.15	802.47	723.33		
1.5	−18.43	−55.38	79.47	5.66		
2.0[b]	−23.09	−33.09	3.91	−52.27	−51.44	1.818
2.5	−19.87	−19.42	−1.58	−40.87		
3.0	−15.67	−11.61	−1.15	−28.44		
			2			
1.0	−5.07	−83.54	540.18	451.57		
1.5	−27.67	−51.95	51.39	−28.23		
2.0[b]	−29.43	−31.16	1.61	−58.98	−57.8	1.806
2.5	−24.97	−18.44	−1.61	−45.02		
3.0	−20.05	−11.16	−1.07	−32.28		
			3			
1.0	20.61	−83.60	512.13	449.14		
1.5	−2.97	−51.79	48.25	−6.51		
2.0[b]	−7.25	−30.83	1.34	−36.74	−37.9	1.845
2.5	−5.81	−18.17	−1.62	−25.6		
3.0	−3.37	−11.01	−1.06	−15.44		
			4			
1.0	4.20	−85.05	703.51	622.67		
1.5	−20.88	−53.23	68.15	−5.97		
2.0[b]	−23.61	−32.09	2.88	−52.83	−53.5	1.819
2.5	−19.61	−18.97	−1.67	−40.24		
3.0	−15.16	−11.42	−1.16	−27.74		
			5			
1.0	−2.22	−88.29	802.50	711.99		
1.5	−27.74	−55.81	78.73	−4.82		
2.0[b]	−30.02	−33.93	3.73	−60.22	−59.0	1.802
2.5	−25.18	−20.14	−1.66	−46.98		
3.0	−19.91	−12.16	−1.21	−33.28		
			6			
1.0	15.92	−83.76	556.36	448.52		
1.5	−6.83	−52.57	53.34	−6.06		
2.0[b]	−9.97	−31.70	1.67	−40.00	−41.4	1.830
2.5	−7.61	−18.82	−1.71	−28.14		
3.0	−4.92	−11.47	−1.14	−17.51		

[a] For comparison purposes the binding energies and the equilibrium distances of the paracyclophane complexes **1**$-$**6** with lithium are included. [b] Distance where the MIPp is minimum.

A similar behavior is observed in the [3.3]paracyclophane complexes. For example, in complexes **13**, **14**, **16** and **17**, where the rings are electron-rich, the variation of ρ is positive and

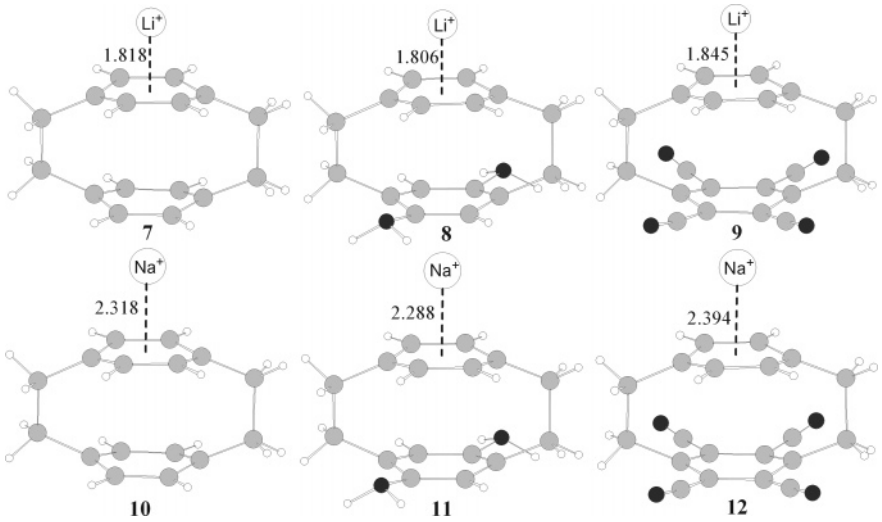

Figure 4. RI-MP2/6-31++G** optimized structures of [2.2]paracyclophane complexes **7**$-$**12**. Distances are measured in Å.

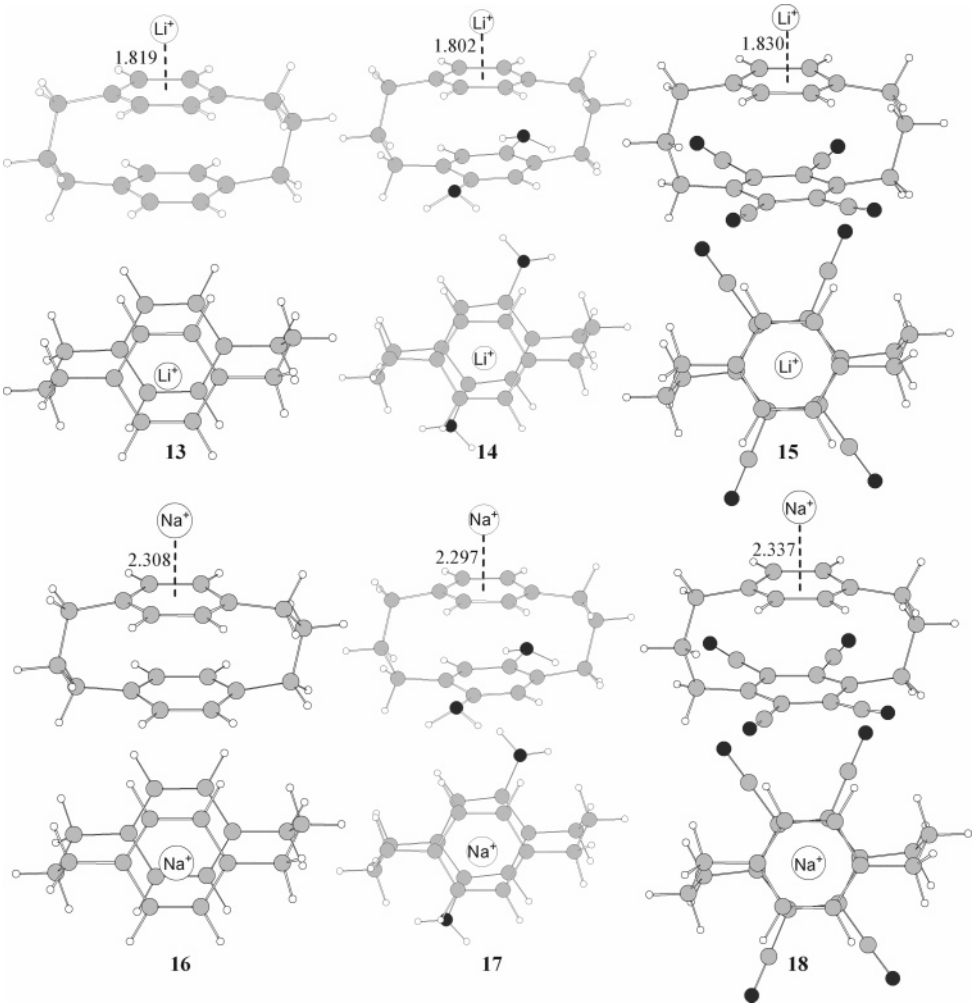

Figure 5. RI-MP2/6-31++G** optimized structures of [3.3]paracyclophane complexes **13**, **14**, **15**, **16**, **17** and **18** from two points of view. Distances are measured in Å.

large in comparison to the corresponding [2.2]paracyclophane complexes, indicating that the interaction between the rings is enhanced upon complexation of the cation. In contrast, the $\Delta\rho$ values obtained for complexes **15** and **18** are very small, indicating that the complexation of the cation does not induce a more favorable ring−ring interaction. The AIM analysis agrees with the energetic and geometric results; in particular, the value of ρ at the cage CP located between the aromatic rings of [*n.n*]-paracyclophanes not only gives information on the nature of the ring−ring interaction itself it but also gives information related to the strength of the cation−π interaction. A likely explanation is that the complexation of the cation reinforces the $\pi-\pi$ stacking interaction of the [*n.n*]paracyclophanes ($n = 2, 3$) apart from **3** and **6**, where the lower ring is substituted by electron-withdrawing groups.

Geometrically, some interesting issues arise from the inspection of the optimized geometries, which are shown in Figures 4 and 5. First, the equilibrium distances are influenced by the substitution of the ring and they are larger in the complexes where the electron-withdrawing cyano groups are present, and shorter in the complexes where electron-donating groups are attached to the ring, in agreement with the binding energies. Second, the geometries of the [3.3]paracyclophane complexes reveal strong aryl−aryl interactions that influence the conformation of the cyclophane, which is different depending on the substitution. For instance, complexes **13**, **14**, **16** and **17** where the lower ring is either unsubstituted or substituted with two amino groups adopt a geometry where both rings of the [3.3]-paracyclophane are not completely stacked; they are to some extent displaced, as can be observed in Figure 5. These results agree with some theoretical[26] and experimental works,[27] which indicate that the parallel displaced orientation of the benzene dimer is preferred with respect to the face-to-face geometry.

In Figure 5, we also represent the optimized geometries of complexes **15** and **18**, where the lower ring is substituted by four electron-withdrawing cyano groups. In these two complexes the orientation of the rings is face-to-face, similar to the benzene−hexafluorobenze complex that presents a face-to-face stacking orientation in its crystal structure.[28] As stated by the AIM analysis, the strong stacking interaction between the electron donor and electron acceptor rings weakens the capacity of the upper ring for interacting with cations.

To gain knowledge on the physical nature of the interaction, we have performed the calculation of MIPp of **1**−**6** compounds interacting with Li^+. In the calculation the Li^+ ion was considered as a classical nonpolarizable particle. We have explored the electrostatic (E_e), polarization (E_p), van der Waals (E_{vw}), and total (E_t) interacting energies when a lithium ion approaches to the aromatic ring perpendicular to it along the main symmetry axis. The results, summarized in Table 2, point out the importance of the polarization and electrostatic contributions to the total interaction energy. For all compounds the MIPp minimum is found at 2.0 Å. When the results at the MIPp minimum are compared, several considerations arise: first, there is an excellent agreement between the interaction energy predicted by the MIPp method (E_t) and the complexation

energies obtained at the RI-MP2/6-31++G** level of theory, confirming the reliability of the MIPp partition scheme. Second, one important factor that explains the difference in binding energy between the [*n.n*]paracyclophanes depending on the substitution is the electrostatic term (E_e), which is considerably higher in the diamino-substituted [*n.n*]paracyclophanes **2** and **5**. The ion-induced polarization term is very important in all cases, especially in the tetracyano-substituted [*n.n*]paracyclophanes **3** and **6** where the polarization term clearly dominates the interaction. Third, the polarization term is almost constant in the [*n.n*]paracyclophanes **1**−**6** interacting with Li^+ and the electrostatic term behaves the same as the total interaction energy, being responsible for the differences in the total energy. Fourth, the van der Waals dispersion−repulsion term is in all cases small and does not have influence on the observed behavior.

Conclusion

In summary, we have optimized several complexes of substituted [*n.n*]paracyclophanes ($n = 2, 3$) with cations. The substitution of the "spectator" (lower) ring has a strong influence in both the binding energy and the equilibrium distance of the complexes, indicating trough-space interactions. The atoms-in-molecules analysis demonstrates that the ring−ring interaction is strongly influenced by the complexation of the cation even in [3.3]paracyclophanes, in agreement with the differences in the binding energy of the complexes. The MIPp partition scheme demonstrates that both electrostatic and cation-induced polarization terms dominate the cation−π interaction. The polarization term is approximately constant in all complexes, and the differences found in the total interaction energy depending on the substitution of the lower ring are due to electrostatic effects.

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