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MP2 Study of Cation−$(\pi)_n$−π Interactions (n = 1−4)

Antonio Frontera,*,[†] David Quiñonero,[†] Carolina Garau,[†] Antoni Costa,[†] Pablo Ballester,[‡] and Pere M. Deyà*,[†]

Department of Chemistry, Universitat de les Illes Balears, Crta. de Valldemossa km 7,5,
07122 Palma de Mallorca, Spain, and ICREA and Institute of Chemical Research of Catalonia (ICIQ),
Avinguda Països Catalans 16, 43009 Tarragona, Spain

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Ab initio calculations at the MP2(full)/6-31++G**, RI-MP2(full)/6-31++G**, and RI-MP2(full)/6-311++G-(2d,2p) levels of theory demonstrate important synergic effects between two noncovalent interactions that involve aromatic rings, that is, cation−π and π−π interactions. The presence of a cation interacting with the π cloud of an aromatic ring favors the face-to-face stacking interaction with additional aromatic rings. This effect is extended in the space up to five stacked aromatic rings.

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 aromatics is a strong noncovalent binding force, namely, 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 has been demonstrated in neurotransmitter receptors.[6] In addition, attractive interactions between π systems are very important forces that govern molecular recognition and influence structures of proteins, DNA, and solid materials.

In this communication, we study how the π−π interaction[7] influences the cation−π interaction. We have optimized the geometry of complexes present in Figure 1 and computed the complexation energies using high-level ab initio calculations in order to study the interplay between both interactions. Recently, a theoretical study regarding the interaction of cations with benzene monomer and dimer has been published.[8] We have found synergic effects between both interactions, and they are transmitted through the space by the addition of more stacked benzene rings.

The geometry of complexes **1**−**3** and (**BEN**)$_2$ was fully optimized at the Moeller−Plesset (MP2, full electron) level using the 6-31++G** basis set by means of the Gaussian 03 program.[9] The binding energies were calculated with correction for the basis set superposition error (BSSE) by using the Boys−Bernardi counterpoise technique.[10] The optimization of the complexes has been performed imposing C_{6v} symmetry, and the optimization of the benzene dimer has been performed imposing D_{6h} symmetry. Furthermore, we have optimized complexes **1**−**5** using the resolution of the identity MP2 (RI-MP2) level and the 6-31++G** and 6-311++G(2d,2p) basis sets. The RI-MP2 calculations were done using the program TURBOMOLE, version 5.7.[11] The RI-MP2 method applied to the study of cation−π and anion−π interactions is considerably faster than the MP2 method, and the interaction energies and equilibrium distances are almost identical for both methods.[12]

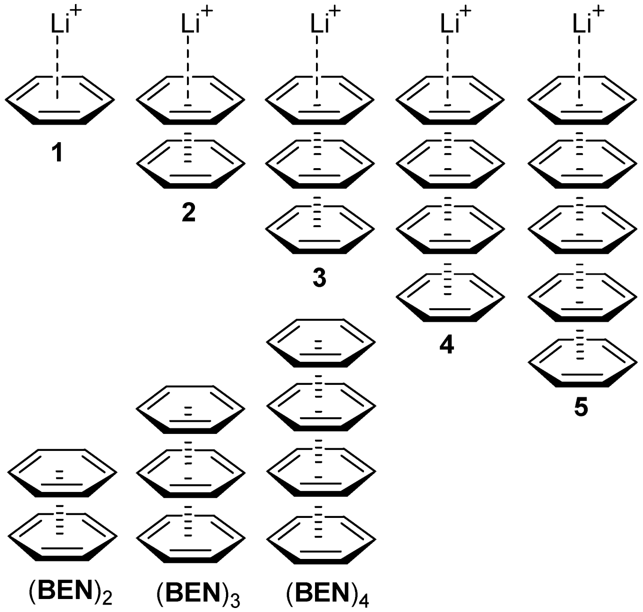

Figure 1. Cation−π complex **1**, cation−π−$(\pi)_n$−π complexes **2**−**5**, and the benzene dimer, trimer, and tetramer, (**BEN**)$_2$, (**BEN**)$_3$, and (**BEN**)$_4$, respectively.

The complexation energies and equilibrium distances obtained at both levels of theory are summarized in Table 1. We present

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* To whom correspondence should be addressed. E-mail: toni.frontera@uib.es (A.F.).

[†] Universitat de les Illes Balears.

[‡] ICREA and Institute of Chemical Research of Catalonia (ICIQ).

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TABLE 1: Complexation Energies with the BSSE Correction (E_{CP}, kcal/mol) and Equilibrium Distances (R, Å) for Complexes 1−5 as well as the Synergic Stabilization Energy (E_{syn}, kcal/mol) Resulting from the Addition of Successive Benzene Molecules for Complexes 2−5 (the Meaning of the Values in Parentheses Is Given in the Text)

	RI-MP2(full)/6-31++G**				RI-MP2(full)/6-311++G(2d,2p)			
complex	E_{CP}	E_{syn}	R_1	R_2	E_{CP}	E_{syn}	R_1	R_2
1	−33.7		1.914		−36.4		1.864	
2	−39.1	4.1	1.886	3.591	−43.6	4.7 (4.7)	1.828	3.462
3	−41.7	5.4	1.879	3.552	−47.6	6.2 (6.1)	1.824	3.455
4	−43.4	5.8	1.876	3.546	−50.6	6.7 (6.4)	1.822	3.446
5	−44.9	6.0	1.875	3.545	*a*	*a*	*a*	*a*
$(\mathbf{BEN})_2$	−1.3			3.800	−2.5			3.616
$(\mathbf{BEN})_3$					−5.1			3.602
$(\mathbf{BEN})_4$					−7.8			3.615/3.646[b]

[a] This complex has not been optimized due to an unsolvable convergence problem. [b] Outer/inner distances, respectively.

two equilibrium distances for complexes **2**−**5**, which are R_1 that stands for the distance between the lithium cation and the ring centroid and R_2 that stands for the distance between the ring centroid of the benzene that is interacting with the cation and the ring centroid of the subsequent benzene ring. First of all, it should be mentioned that for complexes **1**−**3** and the benzene dimer, $(\mathbf{BEN})_2$, we have computed the geometries and energies at the MP2(full)/6-31++G** level of theory and compared them with the ones computed at the RI-MP2(full)/6-31++G** level of theory, and we have obtained almost identical results (see Supporting Information Table S1). This preliminary finding gives reliability to the RI-MP2 approximation and, consequently, to the results obtained for complexes **4** and **5**, which have been optimized only at the RI-MP2 level due to its computational cost at the MP2(full)/6-31++G** level of theory. From inspection of the results present in Table 1, several interesting considerations arise. First, both theoretical levels give similar trends, despite the fact that the complexation energies using the larger basis set are more negative and the equilibrium distances are shorter. Second, at both levels, the complexation energy of the ternary system **2** is considerably more negative than **1**. Taking into account that the interaction energy of the benzene dimer, $(\mathbf{BEN})_2$, is modest at both levels of theory, this result indicates that either the cation−π interaction has an important influence on the π−π interaction or vice versa. Actually, complex **2** has considerably shorter equilibrium distances (R_1 and R_2) than **1** and $(\mathbf{BEN})_2$ at both levels of theory, indicating that the interplay between both interactions contributes to the global stabilization of the system. Third, we have included in Table 1 what we entitle the synergic stabilization energy (E_{syn}) for multicomponent complexes **2**−**5**. This term is computed by subtracting from the complexation energy (E_{CP}) of each complex the E_{CP} of **1** and n times the E_{CP} of $(\mathbf{BEN})_2$, where n is the number of π−π interactions in the complex. This term accounts for the synergic effect of cation−π and π−π interactions. It is worth noting that this effect is important in all complexes, even in **5**, though the influence of additional stacked rings progressively diminishes upon going from **2** to **5**. The optimization of complex **5** at the higher level of theory did not succeed due to convergence problems; however, the synergic energies computed for complexes **2**−**4** are similar at both levels of theory. Therefore, the value of E_{syn} obtained for complex **5** at the RI-MP2/6-31++G** level is expected to be consistent. The equilibrium distance of the lithium cation to the ring centroid (R_1) progressively shortens as the number of benzene rings increases. The same effect is observed in the equilibrium distance of the π−π interaction (R_2), indicating that the subsequent addition of benzene rings also strengthens the π−π interaction. The inter-ring distances of the successive benzene rings in complexes **3**−**5** range from 3.65 to 3.68 Å at the RI-MP2/6-31++G** level of theory, considerably shorter than that of $(\mathbf{BEN})_2$, 3.80 Å. The same effect is observed at the higher level of theory in complexes **3** and **4**. As suggested by one referee, we have also calculated the synergic energy using another methodology. Since there may be some synergism in the interaction of several benzene rings even in the absence of the cation, we have computed, at the higher level of theory, explicitly the energies of $(\mathbf{BEN})_3$ and $(\mathbf{BEN})_4$ and we have used these values in the calculation of the synergic stabilization. The results are present in Table 1 in parentheses. The E_{syn} values obtained using both methodologies are almost identical, confirming the synergic effect between the cation−π and the π−π interactions.

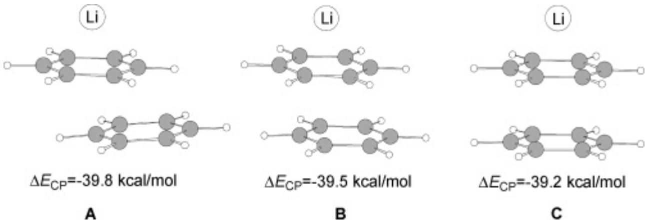

Figure 2. MP2(full)/6-31++G** optimized structures of benzene dimer−Li^+ complexes.

As aforementioned, the optimization of complexes **1**−**5** has been performed imposing C_{6v} symmetry. Other stacking arrangements of the π systems, such as combinations of T shape and parallel displaced geometries, have not been considered, since the aim of this work is to demonstrate and communicate the existence of synergic effects between the cation−π and aromatic π−π interactions. Nevertheless, in Figure 2, we show and compare the C_{6v} optimization of **2** (**C**) with two fully relaxed complexes (**A** and **B**) that we have found exploring the potential hypersurface, which is very flat and all stacked orientations have very similar energies. Several theoretical[13] and experimental[14] works indicate that the benzene dimer prefers parallel displaced and T-shaped orientations over the parallel sandwich orientation in 1−2 kcal/mol. The presence of the cation stabilizes the sandwich orientation, since the energy difference between **A** and **C** is 0.6 kcal/mol, and the displacement in **A** and **B** is only 1.1 and 0.55 Å, respectively, compared with the benzene parallel displaced orientation of the benzene dimer, which is 1.6 Å.[13] This effect is in part supported by results previously reported by our group,[15] where we have demonstrated that an aromatic ring can interact favorably with concentrations of negative charge, for instance, anions or a lone pair of electronegative atoms whenever it is simultaneously interacting with a cation by the opposite side of the ring.

It is quite clear that, without the results of crystallographic experiments, molecular modeling would be a highly speculative activity at best. To obtain experimental evidence of the synergic effect of both interactions, we have performed a search in the Cambridge Structural Database (CSD).[16] Crystal structures are so rich in geometrical information and often reveal effects that have not been noticed by the original authors. The utility of crystallography and the CSD in analyzing geometrical parameters and noncovalent interactions is clearly established.[17] In exploring the CSD, we have found 18 fragments in which noncovalent cation−π and π−π interactions coexist.[18] In Figure 3, we show two examples of crystal structures in which the simultaneous cation−π and π−π interactions are evident. The VIXKEY X-ray structure where the distance between both

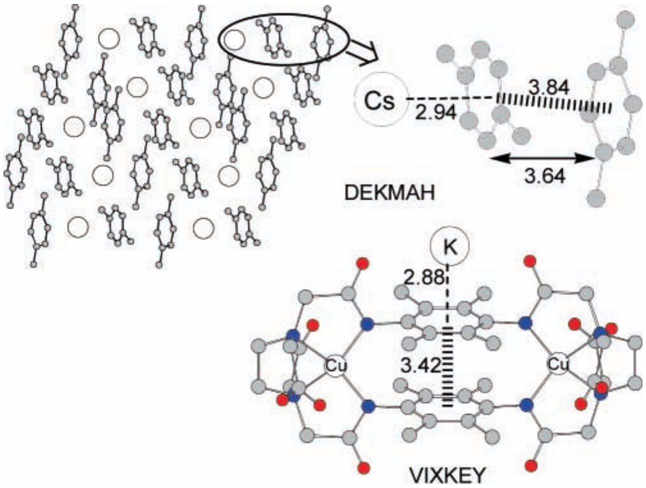

Figure 3. X-ray crystal structures DEKMAH and VIXKEY. The hydrogen atoms and anions have been omitted for clarity. Distances are in angstroms.

aromatic rings is very short compared to standard π stacking is remarkable, and it is similar to that predicted by the calculations present in Table 1. In addition, the K^+ ion is placed at a distance of 2.88 Å from the aromatic ring, shorter than the reported distance for $K^+-\pi$ complexes (2.904 Å).[12] The results of the CSD search reported here are in disagreement with the results reported by G. N. Sastry et al.,[8] where they state that the presence of $M-\pi-\pi$ motifs in the database is comparable to that of exclusively $M-\pi$ configurations. The disagreement is probably due to different search procedures, since they only use distance cutoffs to perform the selection of hits instead of nonbonded contacts based on the sum of van der Waals radii.

In summary, the results derived from high-level ab initio calculations reported in this study reveal that synergic effects exist between the cation$-\pi$ and the $\pi-\pi$ interactions. Due to the presence of a great number of cation$-\pi$ and $\pi-\pi$ interactions in biological systems, this effect can be important and might help one to understand some biological processes where the interplay between both interactions exist. It also should be taken into account in supramolecular chemistry and crystal engineering fields.

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Supporting Information Available: MP2 results of complexes **1**−**3**, complete ref 9, and Cartesian coordinates of all reported structures. The CSD reference codes of the structures having simultaneous cation$-\pi$ and $\pi-\pi$ interactions are also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) A hit was stored when six nonbonded contacts, as defined by the QUESTv5 CSD software, exist between an alkaline cation and the six carbon atoms of an aromatic ring, which, simultaneously, is forming stacking with another aromatic ring. This interaction was characterized defining six nonbonded contacts between the six carbon atoms of one ring with the six carbon atoms of the other ring.