

Theoretical *ab initio* study of the interplay between hydrogen bonding, cation– π and π – π interactions

Carolina Estarellas · Daniel Escudero ·
Antonio Frontera · David Quiñonero ·
Pere M. Deyà

Received: 14 November 2008 / Accepted: 17 January 2009 / Published online: 10 February 2009
© Springer-Verlag 2009

Abstract The interplay among three important non-covalent interactions involving aromatic rings is studied by means of *ab initio* calculations (RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ, and RI-MP2/CBS levels of theory). They demonstrate that synergetic effects are present in complexes where hydrogen bonding interactions, cation– π , and π – π interactions coexist. These synergetic effects have been studied using the genuine non-additivity energies and the molecular interaction potential with polarization partition scheme.

Keywords Noncovalent interactions · Synergetic effects · Stacking · Anion– π interaction · Cation– π interaction

1 Introduction

The development of fields such as supramolecular chemistry and molecular recognition relies on the understanding of non-covalent interactions and the interplay among them [1]. Interactions involving aromatic rings are crucial binding forces in both chemical and biological systems and they have been reviewed by Meyer et al. [2] For instance, cation– π interactions [3–8] are supposed to be an important factor to the ion selectivity in potassium channels [9, 10]; they are also important for the binding of acetylcholine to the active site of the enzyme acetylcholine esterase [11].

The cation– π interaction is dominated by electrostatic and ion-induced polarization terms [12]. The nature of the electrostatic term can be rationalized by means of the permanent quadrupole moment of the arene. The hydrogen bond interaction is mainly dominated by electrostatic effects (dipole–dipole interactions) [13]. Last, π – π interactions [14, 15] are weak non-covalent forces that play an essential role in the folding of proteins [16], in the structure of DNA as well as in its interactions with small molecules [17]. The physical nature of the π – π interaction has been extensively studied by Hobza's group [18, 19].

We have recently reported experimental [20] and theoretical [21, 22] evidence of interesting synergetic effects between ion– π and π – π interactions [23]. We have demonstrated that there is a remarkable interplay between ion– π and π – π interactions in complexes where both interactions coexist. We have also demonstrated interesting synergetic effects between ion– π and hydrogen bonding (HB) interactions [24, 25]. This interplay can lead to strong cooperative effects. In this letter, we study how the HB, the ion– π and the π – π interactions influence each other in complexes where the three interactions are present. We have observed this distribution of noncovalent interactions in biological systems by exploring the PDB database and in crystallographic structures retrieved from the CSD database. In Fig. 1 we represent two selected examples. The first one corresponds to the interaction of magnesium dication with a tyrosine residue of the P chain of the mammalian 20S proteasome [26] (left side of Fig. 1). This tyrosine is simultaneously establishing two noncovalent interactions. First, a hydrogen bonding interaction with a water molecule (W12) and, second a stacking interaction with a nearby tyrosine of the same chain (TYR82). The second X-ray structure corresponds to a polyoxo calix [4] arene (left side of Fig. 1) [27]. In this structure the oxygen

C. Estarellas · D. Escudero · A. Frontera (✉) ·
D. Quiñonero (✉) · P. M. Deyà
Department of Chemistry, Universitat de les Illes Balears, Crta.
de Valldemossa km 7.5, 07122 Palma de Mallorca, Spain
e-mail: toni.frontera@uib.es

atoms are coordinated to tungsten. The tungsten atoms and their ligands have been omitted for the sake of clarity. It can be observed that in the structure a potassium atom is interacting with an arene ring of the calix [4] arene, which at the same time interacts (inter-molecular π - π stacking) with an arene ring belonging to other calix [4] arene molecule. Additionally, a hydrogen bond between a hydrogen atom of the *tert*-butyl substituent and the oxygen atom of the arene is formed.

For the theoretical study reported herein, we have selected two aromatic rings (**1** and **2**), see Fig. 2, that contain substituent groups in the structure which can participate in HB interactions (σ interactions) acting as donors (**1**) or acceptors (**2**). Obviously, from a chemical point of view, the choice of the model interacting molecules, namely 1,4-diaminobenzene and terephthalaldehyde, react to form imines. Therefore, a mixture of 1,4-diaminobenzene and terephthalaldehyde in the adequate conditions, will produce a polyimine [28, 29]; however, the present study is of interest in a fundamental point of view. We have first computed the π - π binary complexes **3a** and **3b** present in Fig. 2. Interestingly, the π - π interaction is accompanied by HB interactions in complex **3a**, which are not present in complex **3b**. Second, we have computed the cation- π binary complexes **4**-**7**, in order to evaluate the cation- π interaction in **1** and **2**, free from other influences. Third, we have computed the cation- π - π ternary complexes **8**-**15** present in Fig. 3, in order to study the interplay between the cation- π and π - π interactions in the presence (**8**-**11**) and absence (**13**-**15**) of HB interactions. We have utilized the molecular interaction potential with polarization partition scheme [30] to investigate the physical nature of the interplay between both interactions.

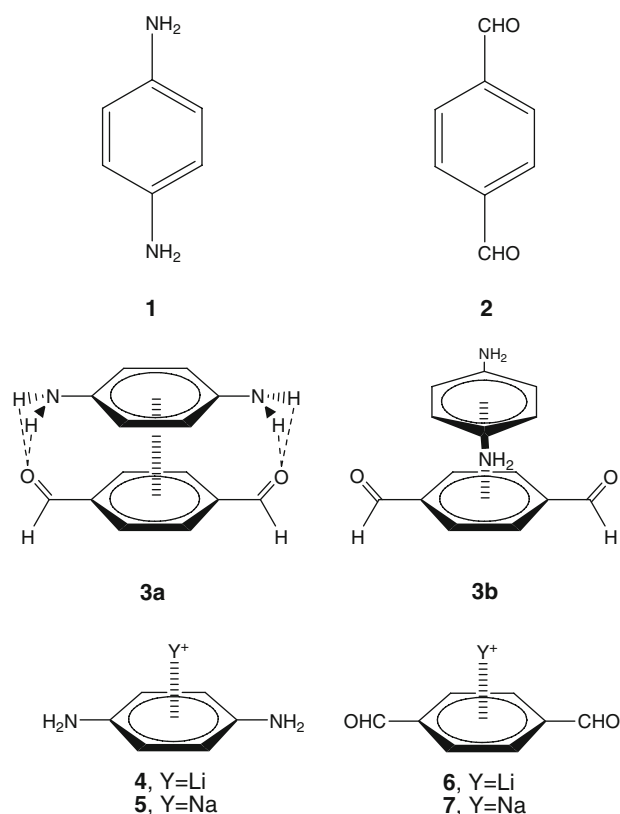
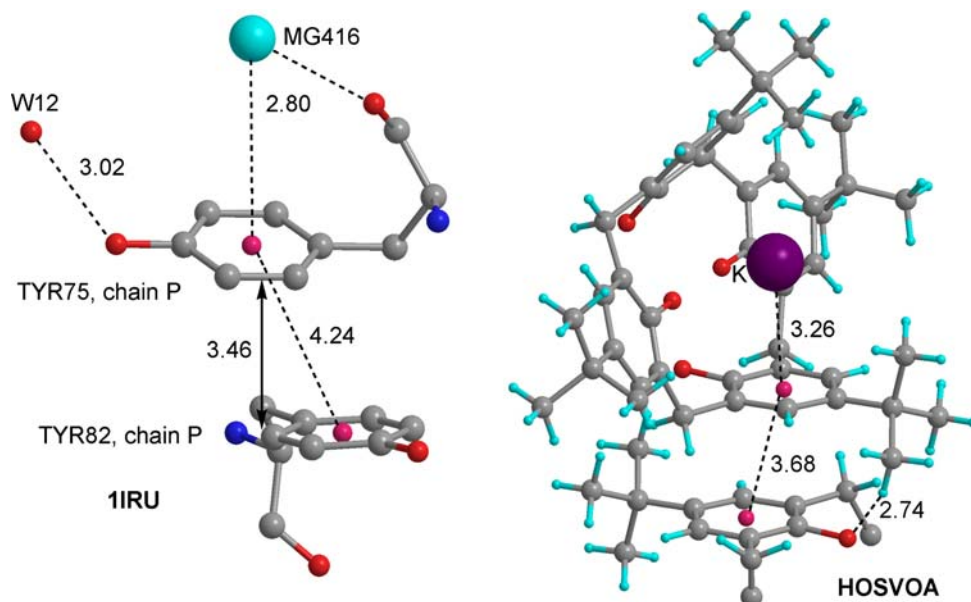


Fig. 2 Compounds **1**-**2** and binary complexes **3**-**7** studied in this work

2 Computational methods

The geometry of all the complexes included in this study was fully optimized at the RI-MP2/aug-cc-pVDZ level of theory within the program TURBOMOLE version 5.7

Fig. 1 Partial views of two X-rays structures exhibiting the combination of three noncovalent interactions. The PDB and CSD codes are shown. Distances in Å



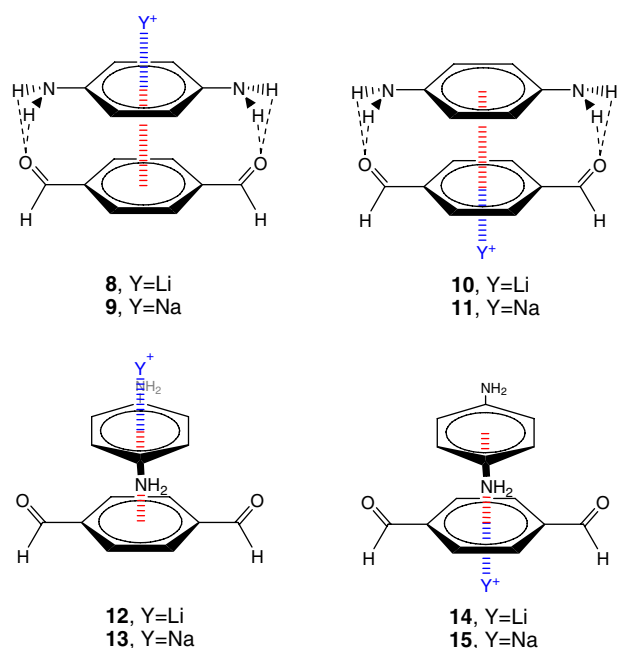


Fig. 3 Ternary complexes **8–15** studied in this work

[31]. The RI-MP2 method [32, 33] applied to the study of cation– π and anion– π interactions is considerably faster than the MP2 and the interaction energies and equilibrium distances are almost identical for both methods [34, 35]. These geometries were used to perform single point calculations using the augmented correlation-consistent polarized valence triple- ζ (aug-cc-pVTZ) basis set. The binding energies calculated at this level of theory were corrected for the basis set superposition error (BSSE) using the Boys–Bernardi counterpoise technique [36]. We have also extrapolated the complete basis set (CBS) limit using the two point method of Helgaker et al. [37]. The optimization of the molecular geometries has been performed imposing C_{2v} symmetry. Other possible conformations of complexes have not been considered because the ultimate aim of this study is to verify the mutual influence of the several non-covalent interactions studied herein.

In complexes where hydrogen bonding and cation– π interactions coexist, we have computed the genuine non-additivity energies ($E - E_A$) using Eq. 1. Thus the non-additivity energies are computed by subtracting the binding energy of the sum of all pair interaction energies (E_A) from the binding energy of the complex (E).

$$E - E_A = E_{abc} - (E_{ab} + E_{ac} + E_{bc}) \quad (1)$$

The contributions to the total interaction energy have been computed using the molecular interaction potential with polarization (MIPp) methodology [30], which is an

improved generalization of the molecular electrostatic potential (MEP) where three terms contribute to the interaction energy: (1) an electrostatic term identical to the MEP [38], (2) a classical dispersion–repulsion term, and (3) a polarization term derived from perturbation theory [39]. Calculation of the MIPp of **1** with Li^+ and Na^+ cations was performed using the HF/6-311++G**//RI-MP2/aug-cc-pVDZ wavefunction of the aromatic rings by means of the MOPETE-98 program [40]. The ionic van der Waals parameters for Li^+ and Na^+ were taken from the literature [41]. Some basic concepts of MIPp follow (see reference [30] for a more comprehensive treatment). The MEP can be understood as the interaction energy between the molecular charge distribution and a classical point charge. The formalism used to derive MEP ($Q_B = 1$) remains valid for any classical charge; therefore, it can be generalized using Eq. 2 where Q_B is the classical point charge at R_B . ϕ stands for the set of basis functions used for the quantum mechanical molecule A , $c_{\mu i}$ is the coefficient of atomic orbital μ in the molecular orbital i .

$$\text{MEP} = \sum_A \frac{Z_A Q_B}{|R_B - R_A|} - \sum_i \sum_{\mu} \sum_v c_{\mu i} c_{v i} \left\langle \phi_{\mu} \left| \frac{Q_B}{|R_B - r|} \right| \phi_v \right\rangle \quad (2)$$

The MEP formalism permits the rigorous computation of the electrostatic interaction between any classical particle and the molecule. Nevertheless, nuclear repulsion and dispersion effects are omitted. This can be resolved by the addition of a classical dispersion–repulsion term, which leads to the definition of MIP [30] (Eq. 3), where C and D are empirical van der Waals parameters.

$$\text{MIP} = \text{MEP} + \sum_{A'B'} \left(\frac{C_{A'B'}}{|R_{B'} - R_{A'}|^{12}} - \frac{D_{A'B'}}{|R_{B'} - R_{A'}|^6} \right) \quad (3)$$

The definition of MIPp is given by Eq. 4, where polarization effects are included at the second order perturbation level [39]; ϵ stands for the energy of virtual (j) and occupied (i) molecular orbitals. It is worth noting that Eq. 4 includes three important contributions: first, the rigorous calculation of electrostatic interactions between quantum mechanical and classical particles; second, the introduction of an empirical dispersion–repulsion term, and third, the perturbative treatment of the polarization term.

$$\text{MIPp} = \text{MIP} + \sum_j^{\text{vir}} \sum_i^{\text{occ}} \times \frac{1}{\epsilon_i - \epsilon_j} \left\{ \sum_{\mu} \sum_v c_{\mu i} c_{v i} \left\langle \phi_{\mu} \left| \frac{Q_B}{|R_B - r|} \right| \phi_v \right\rangle \right\}^2 \quad (4)$$

3 Results and discussion

3.1 Energetic and geometrical details

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_c) of complexes **3–7** at two levels of theory. The optimized geometries of the complexes are shown in Figs. 4 and 5. From the inspection of the results, several interesting points emerge. First, complexes **3a** and **3b** are isoenergetic. This result is unexpected since in **3a**, two sets of bifurcated hydrogen bonds are present between the $-\text{NH}_2$ and $-\text{CHO}$ groups, see Fig. 4. A likely explanation is that the π - π stacking interaction between the electron rich benzene-1,4-diamine (**1**), and the electron poor terephthalaldehyde (**2**) is stronger in **3b** than in **3a** compensating the additional hydrogen bonds present in **3a**. Second, the cation- π complexes of **1** with Li^+ and Na^+ (**4** and **6**, respectively) are considerably more favorable (about 15 kcal/mol in terms of E_{BSSE}) than the cation- π complexes of **2** (**5** and **7**), as expected by the substituent effect of the electron donor $-\text{NH}_2$ and electron withdrawing $-\text{CHO}$ groups. Comparison of these results with the additional calculations of benzene (BEN) interacting with Li^+ and Na^+ cations, which are also included in Table 1, corroborate the electron donor/acceptor effect of the substituent groups in **1** and **2** upon the cation- π interaction. It should be mentioned that in complexes **6** and **7**, the orientation of the $-\text{CHO}$ groups is not the most favorable since the oxygen atoms of the aldehyde moieties are pointing away from the cation. This orientation has been used in order to allow direct comparisons of the binding energies of **6** and **7** with the binding energies of ternary complexes **10–11**. This comparison is useful to know the influence of the hydrogen

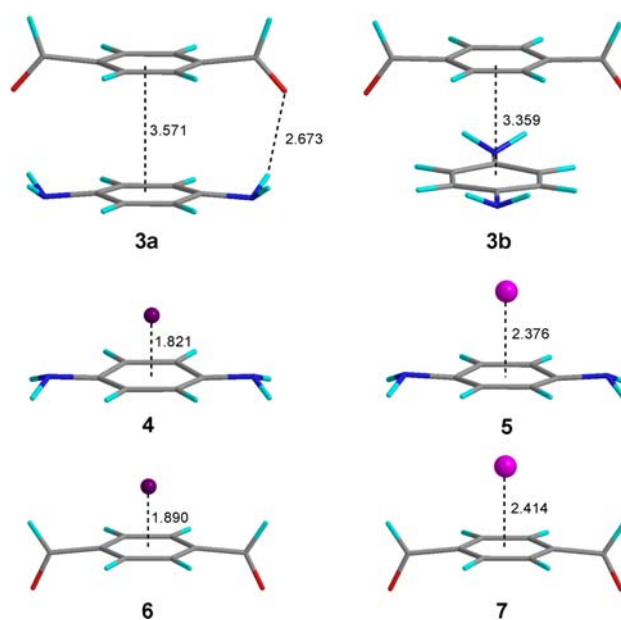


Fig. 4 RI-MP2/aug-cc-pVDZ optimized geometries of complexes **3–7**

bonding on the cation- π interaction free from other effects, which is studied further on.

The binding energies obtained using the extrapolation to the CBS limit using the two-point method (E_{CBS}) are very similar to the ones obtained at the RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ level of theory without the BSSE correction. This result indicates that the energetic values obtained by extrapolation using only two points are not especially trustworthy.

The geometric and energetic results computed for the ternary complexes **8–15** are summarized in Table 2. Some interesting points can be extracted from the geometrical results. The equilibrium distance of the HB interaction in complexes **8** and **9** is shorter than in **3a**, indicating that the presence of the cation- π interaction strengthens the hydrogen bonds when the ring is acting as a donor, in agreement with previous reports [25, 42]. The equilibrium distance of the π - π interaction is also shortened in complexes **8** and **9** with respect to **3a**, indicating a reinforcement of the π -stacking interaction. The variation of the cation- π distance in **8** with respect to **4** is almost negligible and a small shortening is observed in **9**. In complexes **10** and **11**, the cation is interacting with the electron deficient terephthalaldehyde. In both complexes, a shortening of the cation- π interaction is observed in comparison with the binary complexes **6** and **7**, indicating a reinforcement of this interaction. A significant variation is observed in the π - π interaction. For instance the equilibrium distance of **10** is 0.11 Å shorter than **3a**, indicating an important strengthening of the π - π interaction when Li^+ interacts with the terephthalaldehyde ring. Curiously, in

Table 1 Binding energies without and with the BSSE correction (E and E_{BSSE} , kcal/mol, respectively) and equilibrium distances ($R_{\pi-\pi}$, and $R_{\text{C}\pi}$, Å) at the RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ level of theory for complexes **3–7**

Complex	E	E_{BSSE}	E_{CBS}	$R_{\pi-\pi}$ or $R_{\text{C}\pi}$
3a (1 + 2)	-9.23	-6.78	-8.18	3.571 (2.673) ^a
3b (1 + 2)	-9.39	-6.94	-8.18	3.359
4 (1 + Li^+)	-50.94	-47.34	-51.56	1.821
5 (1 + Na^+)	-38.94	-31.20	-40.63	2.376
6 (2 + Li^+)	-28.37	-24.62	-27.86	1.890
7 (2 + Na^+)	-20.52	-10.69	-22.02	2.414
BEN + Li^+	-41.32	-37.22	-41.59	1.823
BEN + Na^+	-29.75	-22.58	-30.72	2.260

The binding energies at the RI-MP2/CBS level of theory are denoted as E_{CBS} (kcal/mol)

^a This value corresponds to the HB interaction, see Fig. 3

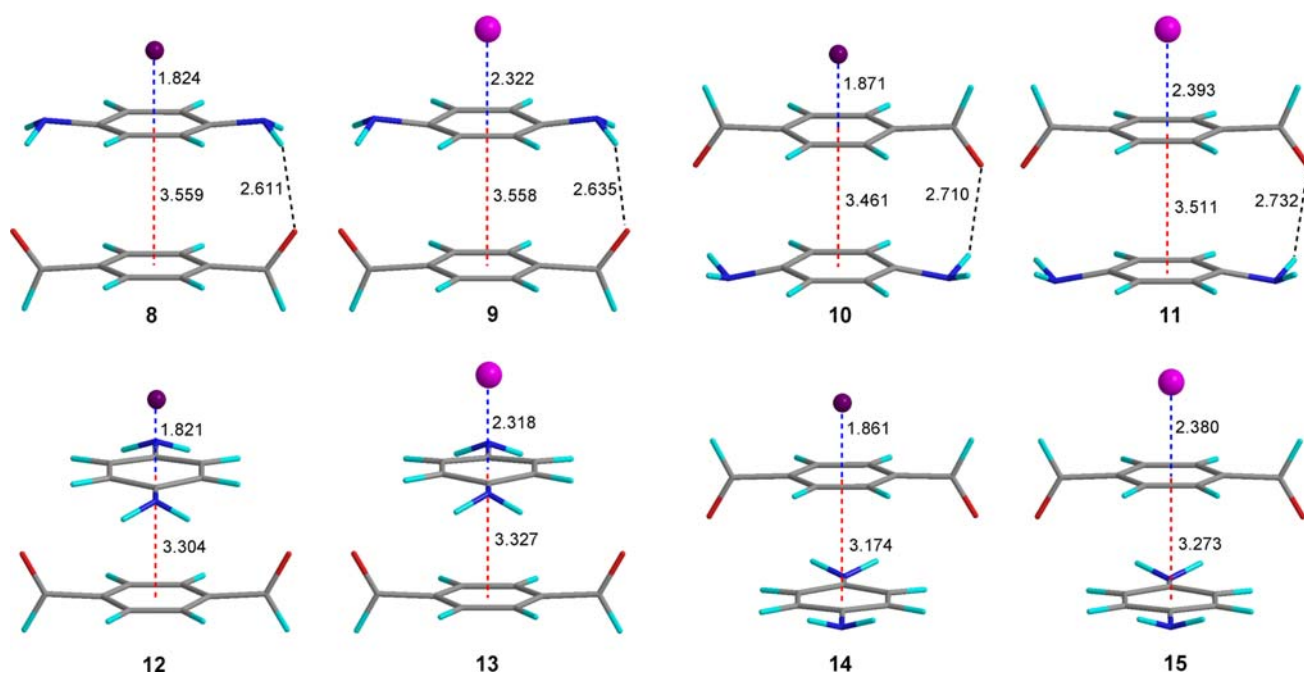


Fig. 5 RI-MP2/aug-cc-pVDZ optimized geometries of complexes **8–15**

both complexes a lengthening of equilibrium distance of the HB interaction is observed, indicating a negative cooperation between the cation- π and HB interactions, which reflects a weakening of the hydrogen bond. The geometric features of complexes **12–15** indicate that the presence of the cation- π interaction strengthens the π - π interaction. This effect is more important in complexes **14** and **15**, where the cation interacts with the electron-deficient ring. The same behavior is observed for the cation- π interaction. In complexes **13–15** the equilibrium distance shortens with respect to complexes **4–7**, indicating a reinforcement of the interaction. In complex **12** the equilibrium distance remains unaltered. Therefore, a synergetic effect between the cation- π and π -stacking interactions is expected in all situations, with some slight modulation of

the effect depending on the π -electronic nature of the aromatic ring.

We have also included in Table 2 the computed values of what we entitle synergetic energy (E_{syn}), which is the difference between the binding energy of the ternary complexes **8–15** and the binding energy of the related HB/ π - π (**3a** and **3b**) and cation- π (**4–7**) complexes. For instance, in complex **11** (**1...2...Na⁺**), we have computed the synergetic energy by subtracting the interaction energies of **2...Na⁺** (complex **7**) and **2...1** (complex **3a**) from the binding energy of **11** (i.e., $E_{syn} = E_{11} - E_{3a} - E_7$). This value gives valuable information regarding the interplay between both non-covalent interactions present in the complexes. It is worth mentioning that this term is negative in all complexes indicating that the mutual influence of the

Table 2 Binding, synergetic and non-additivity energies with BSSE correction (E_{BSSE} , E_{syn} , $E - E_A$ kcal/mol, respectively) and equilibrium distances (R_c , Å) at the RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ level of theory computed for complexes **8–15**

Complex	E	E_{BSSE}	E_{CBS}	E_{syn}	$E - E_A$	$R_{\pi-\pi}$	$R_{c-\pi}$	R_{HB}
8	-67.94	-61.24	-66.43	-7.12	-3.80	3.559	1.824	2.611
9	-59.79	-44.49	-61.53	-6.51	-7.70	3.558	2.322	2.635
10	-39.92	-32.95	-37.91	-1.55	-3.88	3.461	1.871	2.710
11	-34.37	-18.11	-36.11	-0.64	-6.36	3.511	2.393	2.732
12	-69.03	-61.72	-67.28	-7.45	-2.34	3.304	1.821	-
13	-62.28	-44.51	-64.68	-6.37	-7.47	3.327	2.318	-
14	-44.13	-36.86	-43.63	-5.30	-2.78	3.310	1.869	-
15	-38.40	-19.99	-40.51	-2.35	-7.94	3.273	2.380	-

The binding energies at the RI-MP2/CBS level of theory are denoted as E_{CBS} (kcal/mol)

^a The CBS approximation using the two point method gives a poor result in this complex

non-covalent interactions has a favorable effect. It should be mentioned that the synergetic energy is very modest in complexes **10** and **11**. In both complexes an enlargement of the equilibrium distance of the HB interactions is observed. This effect is compensated by the reinforcement of the other two non-covalent interactions (cation- π and π - π) giving rise to modest synergetic energies. We have also studied the mutual influence between the interactions computing the genuine non-additivity energies for complexes **8–15**, which are summarized in Table 2. The non-additivity energy ($E - E_A$) is the difference between the binding energy of the ternary complex and the binding energy of the sum of all pair interaction energies (denoted as E_A), see Eq. 1. For instance, in complex **9** (**3a**... Na^+) we have computed the non-additivity energy by subtracting the sum of three pair interaction energies: (i) **1**... Na^+ , (ii) **1**...**2** and (iii) **2**... Na^+ from the binding energy of **9**. It is worth mentioning that this term is negative in all complexes, in agreement with the E_{syn} energies, confirming the mutual influence and cooperativity of the interactions. It is also interesting to note that the non-additivity energies make in some cases very large contributions to the binding energies of the complexes. The amount of this contribution is especially important in complexes **11** (35%) and **15** (40%).

In order to further investigate the mutual influence of the interactions we have computed the energy of the ternary complexes (only for Li^+ cation) treated as binary complexes. For instance, the binding energy of complex **8** can be computed considering either the initial formation of the dimeric specie **3a** and the subsequent addition of the lithium cation or the initial formation of the 1,4-dianiline- Li^+ complex **4** and the subsequent addition of terephthalaldehyde **2** to form the ternary complex. For complexes **8**, **10**, **12** and **14**, the interaction energies computed using both methods are summarized in Table 3. The comparison of these values to the binding energies of the binary complexes gives knowledge of which non-covalent interaction is more reinforced. For all ternary complexes, the binding energies are more favorable than the corresponding one computed for the binary complexes (see Table 1). This indicates that the simultaneous presence of both cation- π and π - π interactions in the ternary complexes represents a reinforcement of both. The results also indicate that the π - π stacking interaction is more reinforced than the cation- π interaction.

3.2 MIPp analysis

We have used the MIPp partition scheme to analyze the physical nature of the cation- π interaction involved in the complexes and to understand the bonding mechanism and the synergetic energies. We have computed the MIPp of

compounds **1–3** interacting with Li^+ and Na^+ in order to analyze the cation- π interaction in the absence (**1–2**) and presence (**3a** and **3b**) of π - π and HB interactions (**3a**). The results are summarized in Table 4. A good agreement between the MIPp energies and the computed interaction energies of the complexes at the RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ with BSSE correction can be observed. These interaction energies have been computed considering the ternary systems as binary systems, where the dimers **3a** and **3b** have been previously formed. These results give reliability to the MIPp partition scheme. In fact, the representation of the two sets of values gives a

Table 3 Binding, energies without and with BSSE correction computed for the ternary complexes **8**, **10**, **12** and **14**, considering them as binary systems

Complex	Binary System	E	E_{BSSE}	E_{CBS}
8	3a + Li^+	-58.70	-54.53	-58.25
	4 + 2	-16.99	-13.84	-14.86
10	3a + Li^+	-30.69	-26.35	-29.72
	6 + 1	-11.55	-8.35	-10.04
12	3b + Li^+	-59.63	-55.44	-59.11
	4 + 2	-18.08	-14.34	-15.72
14	3b + Li^+	-34.73	-30.46	-35.44
	6 + 1	-15.75	-11.98	-15.76

The two possible combinations have been computed at the RI-MP2/aug-cc-pVTZ//RI-MP2/aug-cc-pVDZ level of theory. The binding energies at the RI-MP2/CBS level of theory are denoted as E_{CBS} (kcal/mol)

^a The CBS approximation using the two point method gives a poor result in this complex

Table 4 Electrostatic (E_e), polarization (E_p) and van der Waals (E_{vw}) contributions to the total (E_t) interaction energy (kcal/mol) computed using MIPp for **1–3** interacting with Li^+ at 2.0 Å and Na^+ at 2.5 Å from the ring centroid

Compound ^a	E_e	E_p	E_{vw}	E_t	E_{BSSE}
1 + Li^+	-22.74	-25.86	0.37	-48.22	-47.34
1 + Na^+	-20.29	-16.70	0.59	-36.40	-31.20
2 + Li^+	2.61	-30.67	2.27	-25.79	-24.62
2 + Na^+	3.85	-17.03	0.59	-12.39	-10.69
3a + Li^+ (via BDA)	-27.96	-31.06	1.91	-57.10	-54.53 ^b
3a + Na^+ (via BDA)	-24.74	-18.07	0.53	-42.28	-37.77 ^b
3a + Li^+ (via TPA)	4.28	-32.25	1.42	-26.55	-26.35 ^b
3a + Na^+ (via TPA)	6.19	-19.90	0.46	-13.24	-11.41 ^b
3b + Li^+ (via BDA)	-28.83	-31.63	2.23	-58.24	-55.44 ^b
3b + Na^+ (via BDA)	-25.38	-18.48	0.58	-43.28	-38.14 ^b
3b + Li^+ (via TPA)	1.62	-32.92	2.08	-29.22	-30.46 ^b
3b + Na^+ (via TPA)	3.51	-19.37	0.56	-15.31	-13.70 ^b

^a BDA, benzene-1,4-diamine (**1**); TPA, terephthalaldehyde (**2**)

^b Computed as two component systems

linear regression plot with a coefficient $R^2 = 0.986$ and the following regression equation: $E_{\text{MIP}} = 0.96 \times E_{\text{RI-MP2}} + 0.69$.

The comparison of the results obtained for the interaction of **3a**, **1** and **2** with cations gives some very interesting information. The computed electrostatic (E_e) and polarization (E_p) terms for the interaction of **3a** with Li^+ and Na^+ cations via the benzene-1,4-diamine (BDA) moiety are more negative than the ones computed for **1**. Therefore, both terms contribute to the cooperative effect. In contrast when **3a** interacts with Li^+ and Na^+ cations via the terephthaldehyde (TPA) moiety the electrostatic term becomes more positive compared to compound **2**. Thus, in these complexes the cooperative effect is due to the E_p term that compensates the E_e term. For compound **3b** interacting with cations, via either BDA or TPA, both E_e and E_p terms became more negative compared to **1** and **2**, indicating that the π - π interaction reinforces the cation- π interaction, in agreement with the previous results.

4 Concluding remarks

The results reported in this manuscript stress the importance of non-covalent interactions involving aromatic systems and the interplay among them, which can lead to cooperative effects. The cation- π influences positively the hydrogen bonding interaction when the arene acts as a hydrogen bond donor and the contrary is observed when it acts as acceptor. In **3b**, where hydrogen bonds between the arenes are not present, electrostatic and induction effects are responsible for the reinforcement of the cation- π interaction. In **3a**, where hydrogen bonds are present, the polarization term is always favorable and the electrostatic term is only favorable when the cation interacts with the BDA ring (hydrogen bond donor).

Acknowledgments We thank the DGICYT of Spain (project CTQ2008-00841/BQU) for financial support. We thank the Govern Balear project PCTIB-2005GC3-08 for financial support. We thank the Centre de Supercomputació de Catalunya (CESCA) for computational facilities.

References

- Hunter CA, Sanders JKM (1990) *J Am Chem Soc* 112:5525. doi: [10.1021/ja00170a016](https://doi.org/10.1021/ja00170a016)
- Meyer EA, Castellano RK, Diederich F (2003) *Angew Chem Int Ed* 42:1210. doi: [10.1002/anie.200390319](https://doi.org/10.1002/anie.200390319)
- Ma JC, Dougherty DA (1997) *Chem Rev* 97:1303. doi: [10.1021/cr9603744](https://doi.org/10.1021/cr9603744)
- Gallivan JP, Dougherty DA (1999) *Proc Natl Acad Sci USA* 96:9459. doi: [10.1073/pnas.96.17.9459](https://doi.org/10.1073/pnas.96.17.9459)
- Gokel GW, Wall SLD, Meadows ES (2000) *Eur J Org Chem* 2967. doi: [10.1002/1099-0690\(200009\)2000:17<2967::AID-JIOC2967>3.0.CO;2-O](https://doi.org/10.1002/1099-0690(200009)2000:17<2967::AID-JIOC2967>3.0.CO;2-O)
- Gokel GW, Barbour LJ, Wall SLD, Meadows ES (2001) *Coord Chem Rev* 222:127. doi: [10.1016/S0010-8545\(01\)00380-0](https://doi.org/10.1016/S0010-8545(01)00380-0)
- Gokel GW, Barbour LJ, Ferdani R, Hu J (2002) *Acc Chem Res* 35:878. doi: [10.1021/ar000093p](https://doi.org/10.1021/ar000093p)
- Hunter CA, Singh J, Thornton JM (1991) *J Mol Biol* 218:837. doi: [10.1016/0022-2836\(91\)90271-7](https://doi.org/10.1016/0022-2836(91)90271-7)
- Kumpf RA, Dougherty DA (1993) *Science* 261:1708. doi: [10.1126/science.8378771](https://doi.org/10.1126/science.8378771)
- Heginbotham L, Lu Z, Abramson T, Mackinnon R (1994) *Bio-phys J* 66:1061. doi: [10.1016/S0006-3495\(94\)80887-2](https://doi.org/10.1016/S0006-3495(94)80887-2)
- Dougherty DA (1996) *Science* 271:163. doi: [10.1126/science.271.5246.163](https://doi.org/10.1126/science.271.5246.163)
- Cubero E, Luque FJ, Orozco M (1998) *Proc Natl Acad Sci USA* 95:5976. doi: [10.1073/pnas.95.11.5976](https://doi.org/10.1073/pnas.95.11.5976)
- Jeffrey GA (1997) *An introduction to hydrogen bonding (Topics in physical chemistry)*. Oxford University Press, USA
- Hunter CA (1994) *Chem Soc Rev* 23:101. doi: [10.1039/cs9942300101](https://doi.org/10.1039/cs9942300101)
- Kawase T, Kurata H (2006) *Chem Rev* 106:5250. doi: [10.1021/cr0509657](https://doi.org/10.1021/cr0509657)
- Bhattacharyya R, Samanta U, Chakrabarti P (2002) *Protein Eng* 15:91. doi: [10.1093/protein/15.2.91](https://doi.org/10.1093/protein/15.2.91)
- Gurrath M, Müller G, Hölting H-D (1998) *Perspect Drug Discov Des* 12:135. doi: [10.1023/A:1017034122059](https://doi.org/10.1023/A:1017034122059)
- Müller-Dethlefs K, Hobza P (2000) *Chem Rev* 100:143. doi: [10.1021/cr9900331](https://doi.org/10.1021/cr9900331)
- Wang W, Pitonak M, Hobza P (2007) *ChemPhysChem* 8:2107. doi: [10.1002/cphc.200700415](https://doi.org/10.1002/cphc.200700415)
- García-Raso A, Albertí FM, Fiol JJ, Tasada A, Barceló-Oliver M, Molins E, Escudero D, Frontera A, Quiñero D, Deyà PM (2007) *Inorg Chem* 46:10724. doi: [10.1021/ic701555n](https://doi.org/10.1021/ic701555n)
- Frontera A, Quiñero D, Costa A, Ballester P, Deyà PM (2007) *N J Chem* 31:556. doi: [10.1039/b612848c](https://doi.org/10.1039/b612848c)
- Quiñero D, Frontera A, Garau C, Ballester P, Costa A, Deyà PM (2006) *ChemPhysChem* 7:2487. doi: [10.1002/cphc.200600343](https://doi.org/10.1002/cphc.200600343)
- Barrios LA, Aromí G, Frontera A, Quiñero D, Deyà PM, Gamez P, Roubeau O, Shotton EJ, Teat SJ (2008) *Inorg Chem* 47:5873. doi: [10.1021/ic800215r](https://doi.org/10.1021/ic800215r)
- Escudero D, Frontera A, Quiñero D, Deyà PM (2008) *Chem Phys Lett* 456:257. doi: [10.1016/j.cplett.2008.03.028](https://doi.org/10.1016/j.cplett.2008.03.028)
- Escudero D, Frontera A, Quiñero D, Deyà PM (2009) *J Comput Chem* 30:95. doi: [10.1002/jcc.21031](https://doi.org/10.1002/jcc.21031)
- Unno M, Mizushima T, Morimoto Y, Tomisugi Y, Tanaka K, Yasuoka N, Tsukihara T (2002) *Structure* 10:609. doi: [10.1016/S0969-2126\(02\)00748-7](https://doi.org/10.1016/S0969-2126(02)00748-7)
- Giannini L, Solari E, Floriani C, Re N, Chiesi-Villa A, Rizzoli C (1999) *Inorg Chem* 38:1438. doi: [10.1021/ic9811796](https://doi.org/10.1021/ic9811796)
- Turek W, Edyta-Stochmal-Pomorzanska, Pron A, Haber J (2000) *J Catal* 189:297. doi: [10.1006/jcat.1999.2678](https://doi.org/10.1006/jcat.1999.2678)
- Manassen J, Khalif S (1966) *J Am Chem Soc* 88:1943. doi: [10.1021/ja00961a017](https://doi.org/10.1021/ja00961a017)
- Luque FJ, Orozco M (1998) *J Comput Chem* 19:866. doi: [10.1002/\(SICI\)1096-987X\(199806\)19:8<866::AID-JCC6>3.0.CO;2-N](https://doi.org/10.1002/(SICI)1096-987X(199806)19:8<866::AID-JCC6>3.0.CO;2-N)
- Ahlrichs R, Bär M, Hacer M, Horn H, Kömel C (1989) *Chem Phys Lett* 162:165. doi: [10.1016/0009-2614\(89\)85118-8](https://doi.org/10.1016/0009-2614(89)85118-8)
- Feyereisen MW, Fitzgerald G, Komornicki A (1993) *Chem Phys Lett* 208:359. doi: [10.1016/0009-2614\(93\)87156-W](https://doi.org/10.1016/0009-2614(93)87156-W)
- Vahtras O, Almlöf J, Feyereisen MW (1993) *Chem Phys Lett* 213:514. doi: [10.1016/0009-2614\(93\)89151-7](https://doi.org/10.1016/0009-2614(93)89151-7)
- Frontera A, Quiñero D, Garau C, Ballester P, Costa A, Deyà PM (2005) *J Phys Chem A* 109:4632. doi: [10.1021/jp044616c](https://doi.org/10.1021/jp044616c)
- Quiñero D, Garau C, Frontera A, Ballester P, Costa A, Deyà PM (2006) *J Phys Chem A* 110:5144. doi: [10.1021/jp056976l](https://doi.org/10.1021/jp056976l)

36. Boys SB, Bernardi F (1970) *Mol Phys* 19:553. doi:[10.1080/00268977000101561](https://doi.org/10.1080/00268977000101561)
37. Helgaker T, Klopper W (1997) *J Chem Phys* 106:9639. doi:[10.1063/1.473863](https://doi.org/10.1063/1.473863)
38. Scrocco E, Tomasi J (1973) *Top Curr Chem* 42:95
39. Francl MM (1985) *J Phys Chem* 89:428. doi:[10.1021/j100249a012](https://doi.org/10.1021/j100249a012)
40. Luque FJ, Orozco M (1998) MOPETE computer program. Universitat de Barcelona, Barcelona
41. Clark M, Cramer RDIII, Opdenbosch N (1989) *J Comput Chem* 10:982. doi:[10.1002/jcc.540100804](https://doi.org/10.1002/jcc.540100804)
42. Vijay D, Zipse H, Sastry GN (2008) *J Phys Chem B* 112:8863. doi:[10.1021/jp804219e](https://doi.org/10.1021/jp804219e)