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FEATURE ARTICLE

Cooperativity in multiple unusual weak bonds

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Abstract This review covers two aspects concerning cooperativity in multiple weak bonds: a summary of literature results and a theoretical study of a complete series of model complexes. All the 15 combination of five weak bonds were explored: hydrogen bonds, hydric bonds, dihydrogen bonds, halogen bonds and ion–π interactions. Since in several cases there were no examples reported, a systematic exploration has been carried out on simple models at the MP2/aug-cc-pVTZ level. The results thus obtained have been analyzed using the atoms in molecules methodology.

Keywords Hydrogen bonds · Hydric bonds · Dihydrogen bonds · Halogen bonds · Ion–π interactions

1 Introduction

Ten years ago, we published five papers with the titles: "An attractive interaction between the π-cloud of C_6F_6 and electron-donor atoms" [1], "Inverse hydrogen-bonded complexes" [2], "Unusual hydrogen bonds: H$\cdots\pi$ interactions" [3], and "Charge-transfer complexes between dihalogen compounds and electron donors" [4], that we summarized in a review "Non-conventional hydrogen bonds" [5]. Today, several of these topics have expanded considerably and even books have been published in the meantime [6–10].

We have also published several works studying the existence of cooperativity effects in systems where two or more non-covalent interactions coexist. In particular, we have analyzed synergetic effects between ion–π and π–π interactions in a variety of situations, finding an interesting interplay between cation–π and π–π interactions that are through-space transmitted. That is, we found synergetic effects for these interactions in complexes of lithium with the dimer, trimer, tetramer and even the pentamer of benzene [11, 12]. In addition, synergetic effects in cation–π–π and anion–π–π ternary systems where the aromatic rings used were benzene, 1,3,5-trifluorobenzene and hexafluorobenzene were studied. Depending on the nature of the aromatic ring and the ion, favorable or unfavorable cooperativity effects are found [13, 14]. Fortunately, experimental findings observed in crystal structures support the presence of cooperativity in anion–π–π complexes [15, 16].

We have also studied the interplay between cation–π and hydrogen bonding interactions in pyrrole and indole systems, which can participate simultaneously in both interactions [17]. Favorable cooperativity effects in these systems were found, where the aromatic rings participate in hydrogen bonding interactions as donors [18]. A similar study was also carried out for the study of the interplay between anion–π and hydrogen bonding interactions. In this case, the aromatic systems chosen to analyze the cooperativity effects were able to participate in hydrogen bonding interactions either as donors or acceptors. As a result, the cooperativity was favorable in hydrogen bond acceptors and unfavorable in donors [19]. Regarding the interplay of hydrogen bonding interactions with other non-covalent interactions involving aromatic rings, we have carried out a computational study where edge-to-face

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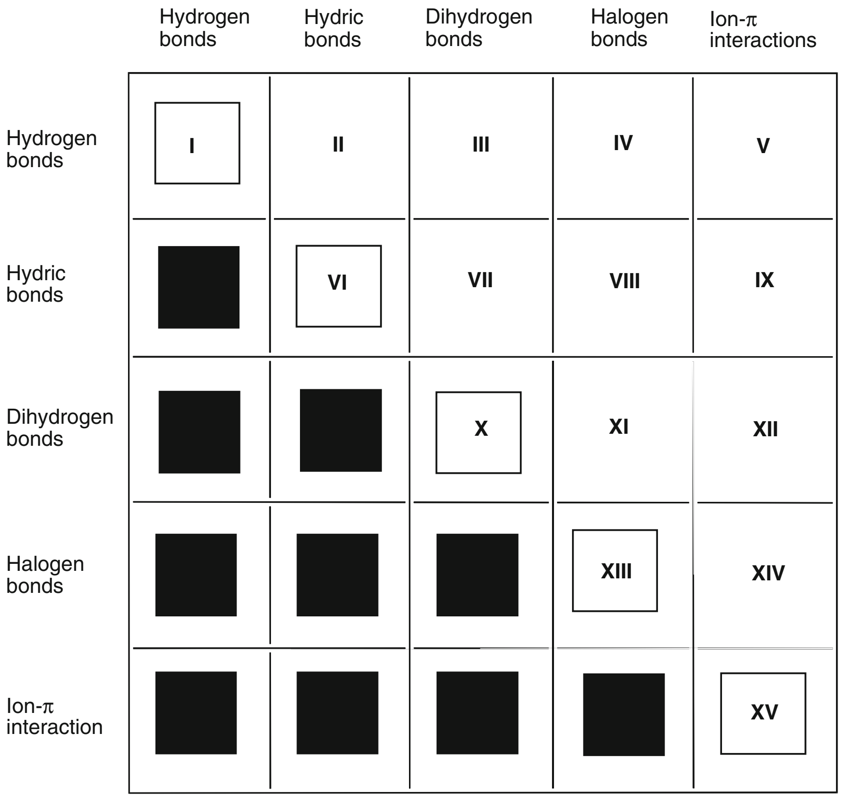
Fig. 1 The different combinations of the five situations



	Hydrogen bonds	Hydric bonds	Dihydrogen bonds	Halogen bonds	Ion-π interactions
Hydrogen bonds	I	II	III	IV	V
Hydric bonds	■	VI	VII	VIII	IX
Dihydrogen bonds	■	■	X	XI	XII
Halogen bonds	■	■	■	XIII	XIV
Ion-π interaction	■	■	■	■	XV

interactions are involved [20]. We found that the T-shape interaction is reinforced if the aromatic ring establishes hydrogen bonding interactions as acceptor. Experimental evidences could be obtained from the Cambridge Crystallographic Database. Additionally, we have studied synergetic effects between two weak interactions, that is π–π stacking and X-H/π (X = C, N, O) interactions. We found interesting synergetic effects between both interactions. In addition, we reported several examples retrieved from the PDB where both interactions are simultaneously present in the interactions of enzymes with either co-enzymes or substrates [21].

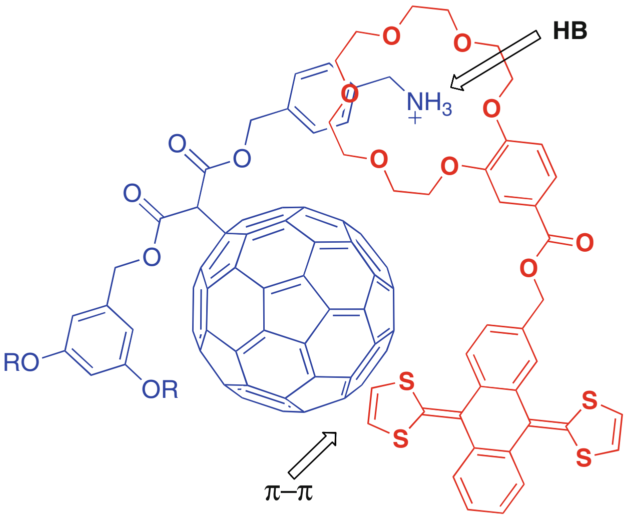
Finally, we have defined a new concept, namely synergetic stability, which can be useful in systems where the interplay of non-covalent interactions is significant. Usually, the stability of a non-covalent complex is related to the complexation energy, which is proportional to the strength of the interactions involved. In ternary complexes with two different non-covalent interactions three situations regarding the variation of the strength of the interactions (in comparison to the binary complexes) can be expected. The coexistence of the interactions causes, first a strengthening of both interactions, second, a weakening of both, and, third, a strengthening of one interaction at expenses of the weakening of the other. The synergetic stability complexes have been calculated in ternary systems where ion–π and either hydrogen bonding, dihydrogen bonding, or halogen bonding interactions coexist [22].

In this field, the emerging area is concerned with those situations where several of these bonds are simultaneously present in the same complex (Fig. 1). Note that some authors prefer the term “synergy” to positive cooperativity.

There are some recent publications dealing with only one of these non-covalent bonds, thus without cooperativity effects: halogen bonds [23], dihydrogen bonds [24–26], and ion–π interactions [27–31].

One aspect in common to all the situations of Fig. 1 is it concerns cooperativity, either positive (synergy) or negative (antagonism). We will use throughout this paper the following three abbreviations: HB (hydrogen or protic bond), hB (inverse or hydric bond), XB (halogen bond).

As with several other phenomena, the cooperativity depends on the distance between both weak bonds of Fig. 1. If they are far apart, the effect will be the sum of each one without any enhancement. For instance, complex **1** was described as presenting cooperativity between π–π and H-bonding interactions [32]. However, without proofs, this assumption is basically speculative and most probably the binding constant is simply due to the sum of both interaction energies.



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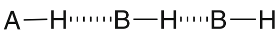
For quaternary and higher order systems, many-body interaction analyses are usually computed to accurately describe cooperativity effects. For instance, in a quaternary complex, the two- and three-body contributions to the total interaction energy are computed [33, 34]. The two body term can be calculated as the binding energy of each molecular pair in the quaternary complex minus the energy sum of the monomers with all of them frozen in the geometry of the complex. The three body term is calculated as the sum of the binding energy of each molecular triad in the quaternary complex minus the energy sum of the dyads. A more comprehensive treatment can be found in the literature [35]. The total relaxation energy is defined as the energy sum of the isolated interacting monomers that constitute the complex, all of them frozen in the geometry of the complex, minus the energy sum of the optimized monomers. Thus, the total interaction energy of the quaternary complexes is obtained as the sum of the relaxation, two-body and three-body energies. This methodology has been successfully used to study cooperativity effects in several combinations of non-covalent interactions, including ion–π [36] and hydrogen bonding interactions [37–39].

We have divided this feature article into two main parts: First, a “Bibliographic survey of related articles” (Sect. 2), and second, a “Comprehensive theoretical study of cooperativity in unusual weak bonds” (Sect. 3). In the second part, several cases will remain empty (VI–IX and XI) because, as far as our knowledge extends, there are no literature examples.

2 Bibliographic survey of related articles

2.1 I Multiple hydrogen bonds

The presence of several HBs in supramolecules such as **2** is a classical and very common situation [40]. This could include bifurcated (three-centered) HBs **3**: see the literature for a more comprehensive treatment [41, 42].



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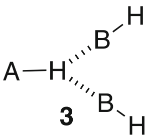

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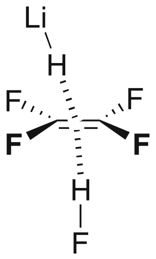
Cooperativity in multiple H-bonded complexes has been experimentally studied by Hunter et al. [43]. They built up four systems (Fig. 2, the last one containing two porphyrin rings). The free energy of complexation of supramolecular complexes containing phenol–carbamate H-bonds is an additive function of the number of H-bonds, with a constant increment of 6 kJ mol^{-1} per interaction in carbon tetrachloride.

Theoretical study on the cooperativity of hydrogen bonds in $(HNC)_2\cdots HF$ complexes has been published [44]. Ab initio calculations at the MP2(FC)/aug-cc-pVDZ level have been used to study the systems HNC···HNC···HNC, HF···HNC···HNC, HNC···HNC···HF and HF···HNC···HNC···HF. The binding distances, dipole moments, frequency shifts and interaction energies in these systems have been analyzed to study the cooperativity of hydrogen bond in the systems. The results indicate that the cooperativity of hydrogen bond is larger when a HF molecule acts as a proton donor in the system.

The cooperativity between O–H···π and N–H···O hydrogen bonds in imidazole has been studied theoretically as a model for interactions in crystal structures of DNA and RNA [45].

2.2 II Hydrogen (protic, HB) and hydric bonds

We have analyzed the structure of complexes having simultaneously an HB and a hydric bond (hB) such as **4** with tetrafluoroethylene in the middle [46].



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These complexes are stable and present cooperative effects. The simultaneous presence of hydrides and protons makes them possible models for studying transfer

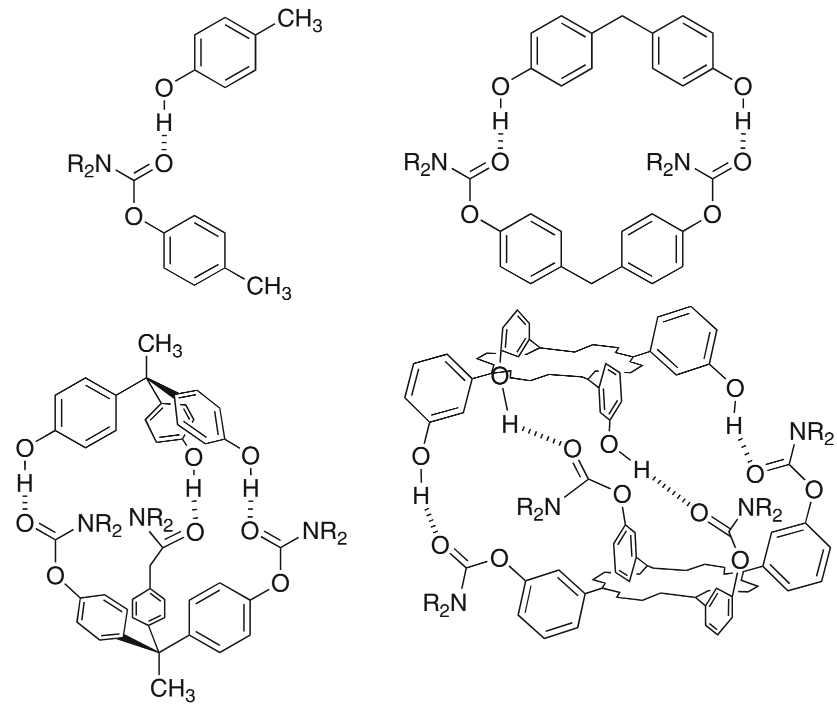


Fig. 2 Hunter's structures to study cooperativity in HBs

processes of both kinds that are of fundamental importance in biological systems.

2.3 **III** HB and DHB

It has been reported a mixed experimental (X-ray crystallography) and theoretical study about an unconventional cooperative effect in a C–H···S–H···H–B (mercaptane-metallacarborane) hydrogen/dihydrogen bond interaction [47].

The combined evidence from experimental and theoretical studies demonstrates the first example of a new DHB (SH···H–B) and its combination with a C–H···S hydrogen bond in a cooperative effect of the type C*c*–H···S–H···$(H–B)_2$ in a crystalline compound. The energy for this hydrogen/bifurcated DHB interaction is estimated at 6 kJ mol^{-1}. This unconventional cooperative effect, which seems to be responsible for self-assembly of the mercaptane complex, allowed the authors to predict the crystal packing of a related mercaptane–cobaltacarborane compound. In both complexes, the observed 2D supramolecular networks would be difficult to rationalize without considering the cooperative effect through the boron-attached SH group. The findings, besides documenting structurally the first S–H···$(H–B)_2$ dihydrogen bond and the unconventional cooperative ability of a boron-attached SH group, prove that substituted carboranes have the potential to serve as building blocks for assembling complex structures.

Li et al. [48] have published a paper entitled "Cooperativity between the dihydrogen bond and the N···HC hydrogen bond in LiH···$(HCN)_n$ complexes" ($n = 2$–3). They carried out ab initio calculations at the MP2/6-311++(2*d*, 2*p*) level of theory for investigating the equilibrium structures, energetics, dipole moments, atom charges, charge transfers, and stabilization energies in LiH–$(HCN)_n$ ($n = 2$ and 3) clusters. The cooperativity between the dihydrogen bond and the N···HC hydrogen bond in these clusters was analyzed. In LiH···HCN···HCN cluster, the interaction energy of the dihydrogen bond increases by 26%, whereas that of N···HC hydrogen bond increases by 49%. These results show significant cooperativity between both types of hydrogen bonds, as shown in the changes in the hydrogen bond lengths, CH bond lengths, and dipole moments. A similar result is also found for the LiH···HCN···HCN···HCN cluster.

2.4 **IV** HB and XB

Ugalde and co-workers [49] have studied theoretically an F–Cl···(H–C≡C–H) dimer, a necessary first step for analyzing trimers. Lankau et al. [50] have studied theoretically the cooperativity between hydrogen and halogen bonds in X···HCN···Y (X: C_2H_2, H_2O, NH_3, HCl, HCN, HF; Y:

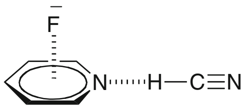
HF, BrF, Br_2) at the MP2/6-311++G(d,p) and DFT/6-311++G(d,p) levels of theory using the B3LYP and mPW1PW91 hybrid functionals. The results from the quantum chemical calculations are typically clustered in groups according to the Y-ligand. By choosing the X···HCN···HF group as reference, it is possible to describe the interaction between the hydrogen and the halogen bond with a two-parameter model. The value of the first parameter of the model describes the contribution of the X ligand to the inter bond cooperativity in the reference cluster. The second parameter of our model quantifies the changes in inter bond cooperativity upon varying the Y-ligand. This simple model can be used to predict the cooperativity in X···HCN···Y trimers with reasonable accuracy and thereby to organize the results systematically. It was further shown that the conclusions drawn from this ordering scheme are independent from the computational method and thereby generally applicable.

The simultaneous presence of hydrogen and halogen bonds has been used in crystal engineering [51]. Politzer, Murray and Concha published a very interesting work where cooperative effects in halogen bonds (case **13**) and competition between hydrogen and halogen bonds are discussed [52]. Cabot and Hunter [53] published an experimental paper about non-covalent interactions between perfluorohexyl iodide and hydrogen bond acceptors. AM1 calculations suggest that perfluorohexyl iodide should have molecular recognition properties comparable to a moderate hydrogen bond donor, like aniline, and should therefore form complexes with strong hydrogen-bond acceptors like pyridine. Hunter's experiments reported here demonstrate that interactions with iodo-perfluorocarbons have many similarities with hydrogen-bonding interactions and, to a first approximation, can be treated using a simple electrostatic model, where the positive electrostatic potential on the surface of the iodine interacts with the negative electrostatic potential on the surface of a hydrogen-bond acceptor. No evidence was found for anomalous induction or dispersion effects associated with the high polarizability of iodine.

An analysis of crystal structures of biomolecules led Voth et al. [54] to the notion that halogen bonds are orthogonal molecular interactions to hydrogen bonds, i.e. that are geometrically perpendicular. Theoretical calculations were carried out to sustain the experimental findings.

2.5 **V** HB and ion–π interactions

The simultaneous presence of a hydrogen bond and an ion–π interaction is possible with anions (**5**) and cations (**6**). We have analyzed complex **6** and related ones [18]. Some structures are reported in Fig. 3.



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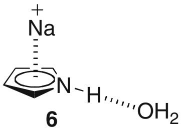

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The results reported stress the importance of non-covalent interactions involving aromatic systems and the interplay among them that can lead to synergetic effects. Due to the presence of a great number of aromatic rings containing heteroatoms in biological systems, this effect can be important and might help to understand some biological processes where the interplay between both interactions may exist. It also should be taken into account in supramolecular chemistry and crystal engineering fields.

In an extension of the work devoted to the interaction of hydride and hydrogen bonds with π-systems, **4**, the hydride molecule has been substituted by an anion [55]. The energetic results indicate that C_2F_4 is a weaker anion receptor than C_6F_6, but in combination with the anions, it became a stronger hydrogen bond acceptor than C_2H_4. Cooperativity effects are observed in $YH\cdots C_2F_4\cdots X^-$ clusters. In $C_2F_4\cdots X^-$ complexes the dominant attractive terms are the electrostatic and polarization ones, while in $YH\cdots C_2F_4{\cdot}X^-$ complexes the charge transfer increases significantly, becoming the most important term for most of the FH and ClH complexes studied here.

Wu and McMahon [56] have published a paper entitled "Investigation of cation–π interactions in biological systems" where structures **7** and **8** with simultaneous HBs and cation–π interactions are reported. Actually, these systems should be classified in class **1** because there are two HBs but since one of them is from an ammonium cation we have put them here.

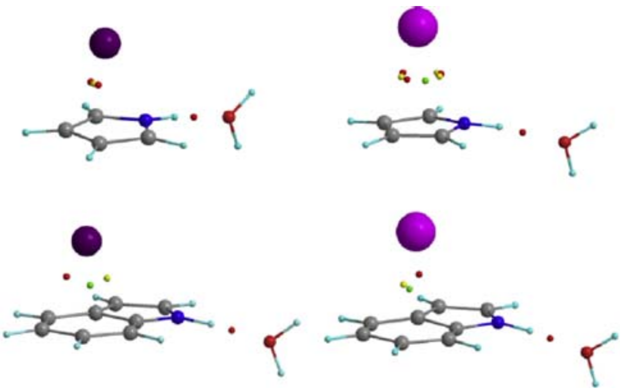
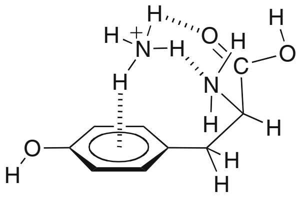


Fig. 3 Distribution of bond (*red*), ring (*yellow*) and cage (*light green*) critical points obtained for cation–π–σ ternary complexes



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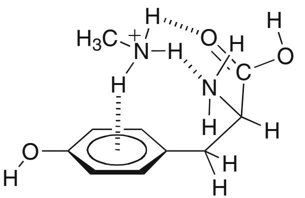

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Related to class **V**, it has been reported that besides multiple HBs, nicotine binding to brain receptors requires a strong cation–π interaction [57].

2.6 **VI** Multiple hydric bonds

No examples.

2.7 **VII** Hydric and DHB

No examples.

2.8 **VIII** Hydric and XB

No examples.

2.9 **IX** hB and ion–π interactions

No examples.

2.10 **X** Multiple DHB

We carried out a theoretical study on the clusters formed by the association of ethynylhydroberyllium (H–Be–C$\equiv$C–H)$_n$ monomers (n = 2–6) [58]. The analysis of the results shows that the most stable conformation corresponds to that where the interaction occurs between the proton hydrogen of one molecule and the π-cloud of another. Cooperative effects are observed in those configurations where DHBs are the main force holding together the clusters (Fig. 4). Thus, a shortening of the DHB distance and an increment in the interaction energy and dipole moment per monomer are observed.

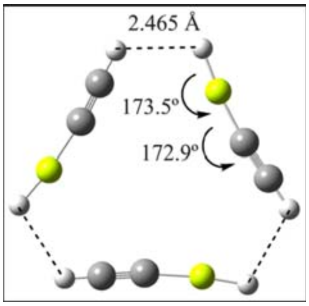


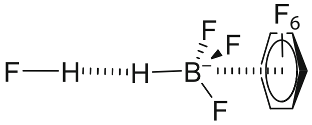
Fig. 4 Geometry of the optimized $(HBeCCH)_3$ cluster

2.11 **XI** DHB and XB

No examples.

2.12 **XII** DHB and ion–π interactions

We have recently studied cooperativity effects in a variety of systems where aromatic rings where involved. Among them a ternary system **9** where hexafluorobenzene simultaneously interacts with BF_3H^- anion and HF via anion–π interaction and dihydrogen bond, respectively, was studied [22]. For this system, unfavorable cooperativity between the non-covalent interactions was found.



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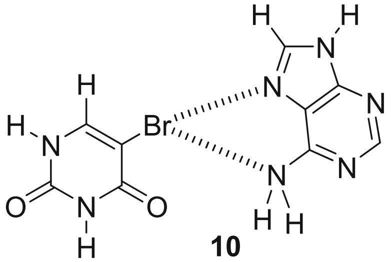
2.13 **XIII** Multiple XB

Although we will usually limit this review to ternary structures, bifurcated bonds allow for the existence of two interactions in dimers (Fig. 5):

This will include the bifurcated XB, such as **10**, present in the structure of adenine-5-bromouracil (AT^+) complexes [59].



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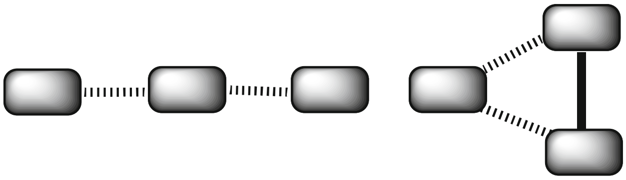
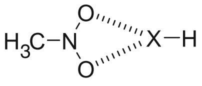
Theoretical calculations on a model compound **11** have been reported [60]. A crystallographic attempt to built up



Three molecules, two interactions Two molecules, two interactions

Fig. 5 Linear and cyclic models of two interactions systems presenting NO_2/X interactions had moderate success [61]. These interactions can be classified according to the approaching of the X atom to NO_2 group into three different motifs; (**a**) symmetric bifurcated motif, (**b**) asymmetric bifurcated motif and (**c**) the motif in which halogen (X) forms mono-coordinate interactions with one nitro O atom. In the first two categories, the X atom approaches both nitro O atoms in a bifurcated manner (X/O trans to C–N); the tendency to form such bifurcated motifs increases in the order C1 < Br < I whereas in the last category X/O is in a *cis* relationship to the nitro C substituent around the N–O bond. Several examples of class **c** were found. Several X-ray structures presenting multiple XB have been reported [51, 62, 63].



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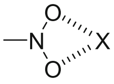
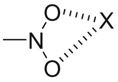


(a)



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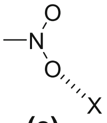


(c)

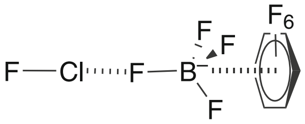
Grabowski and Bilewicz [64] published a paper entitled "Cooperativity halogen bonding effect—ab initio calculations on $H_2CO\cdots(ClF)_n$ complexes" (n up to 6). According to these authors, for the systems analyzed, the strength of Cl···O interaction increases if the number of ClF molecules increases. For this interaction, oxygen acts as the Lewis base while Cl atom as the Lewis acid, which may be explained as an effect of the anisotropy of the electron charge distribution for chlorine atom. The calculations performed for model systems indicate that the additional ClF molecules within the complex enhance the strength of halogen bond. This halogen bonding cooperative effect is very similar to the cooperativity exhibited by H-bonded systems; it seems that both effects are often responsible for the arrangement of molecules in crystals.

The clusters, up to four monomers, of the interhalogen derivatives (FCl, FBr, and ClBr) have been studied by means of ab initio (up to MP2/aug-cc-pVTZ level of theory) and DFT computational methods [65]. Two dispositions, linear and cyclic, of the clusters have been considered. In the trimers, the linear configuration is the most stable one for FCl and FBr molecules, while for the ClBr trimers and all the tetramers the cyclic configuration is more stable. Cooperative effects in the geometry, energy, and electron density have been observed in the linear and cyclic dispositions of these clusters. The Natural Energy Decomposition Analysis shows that the main source of the interaction corresponds to the polarization term.

An ab initio study was published concerning halogen/π interaction and cooperativity effects between dihalogen molecules and unsaturated hydrocarbons [66]. It reports calculations at the MP2 level using cc-pVDZ and aug-cc-pVDZ basis sets on the complexes formed between unsaturated hydrocarbon(R) and dihalogen molecules (XY), $R\cdots(XY)_n$ ($n = 1$–2). Geometrical structures, interaction energies and topological parameters derived from the theory of atoms in molecules (AIM) developed by Bader have been studied systematically to characterize the halogen···π interactions. The present theoretical investigation indicates that such interactions in all trimolecular complexes $R\cdots(XY)_2$ are significantly stronger than those in the corresponding bimolecular series R···(XY), demonstrating the existence of cooperativity effect.

2.14 **XIV** XB and ion–π interactions

Analogously to the study cited in point XII [22], we also analyzed a ternary system **12** where hexafluorobenzene interacts simultaneously with BF_4^- anion and ClF via a anion–π interaction and a halogen bond, respectively. For this system, the simultaneous presence of both interactions leads to unfavorable cooperativity energy.



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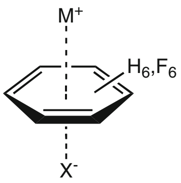
2.15 **XV** Multiple ion–π interactions

Since 2005, a series of publications have dealt with systems where several ion–π interactions are present. These works can be divided into two main types. First, studies where two ions of opposite sign interact with the same aromatic ring **13** ($M^+\cdots\pi\cdots X^-$) and second, systems where only one ion is interacting with several aromatic rings **14** ($\pi\cdots X^-\cdots\pi$). For the fist type of complexes **13**, several aromatic rings have been studied, including benzene and hexafluorobenze [67–69]. For these systems, very favorable binding energies were found and several crystallographic structures were retrieved from the CSD giving an experimental support to the theoretical studies. For the second type of systems **14**, a theoretical work studied the additivity of the anion–π interaction in triazine and trifluorotriazine rings [11]. The interaction is approximately additive on going from a single anion–π complex to a ternary anion–π_2 complex and even to a quaternary system anion–π_3 complex **15**. A similar work regarding the additivity of the cation–π interaction has been published by Liu et al. [70].



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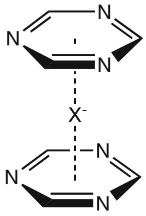

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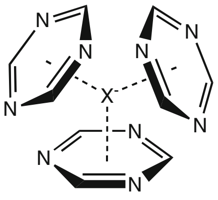

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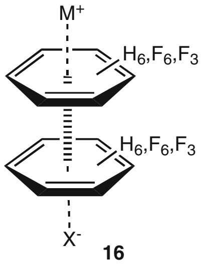

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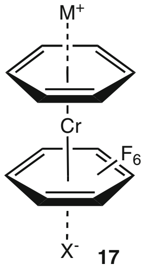

17

In addition to the previously described works, further studies regarding another type of systems than contain multiple ion–π interactions ($M^+\cdots\pi\cdots\pi\cdots X^-$) **16** have been published [14, 18]. In these complexes, a third type of interaction is involved, namely a stacking π–π interaction. Several systems have been studied, varying the aromatic ring and using either two equal or two different rings between the ions. Interesting cooperativity effects have been found between the three non-covalent interactions, depending principally on the nature of the aromatic ring. In complexes formed by one electron rich and one electron poor ring, the cooperativity effects are very important when the anion interacts with the electron rich ring and the cation with the electron poor ring.

Lastly, we have also reported a similar system where a transition metal is forming a sandwich complex that interacts with anions and cations **17** ($M^+\cdots\pi\cdots Cr\cdots\pi\cdots X^-$). Favorable cooperativity effects are also found when the anion and the cation interact simultaneously through opposite faces of the transition metal complex ($\pi\cdots Cr\cdots\pi$) [71].

Grabowski et al. [72] have shown the possibility to use a proton to complexate two simple π-systems. Vaden and Lisy [73] have studied the competition between cation–π interactions and intermolecular hydrogen bonds in alkali metal ion-phenol clusters. Finally, Zaccheddu et al. [74] have explored the anion–π and π–π cooperative interactions for the complexes formed by nitrate and triazine.

2.16 **XVI** Other simultaneous interactions

There are many other cooperative (synergetic) effects in supramolecular structures. The most important is the effect on a weak bond produced by the coordination of a lone pair to a metal. Coordination modifies the electronic nature of heteroaromatic rings and consequently their interactions with other molecules. Figure 6 depicts some examples: **18** [45], **19** [75], **20** [76], **21** [77], **22** [78, 79] and **23** [80]. See references [81] and [82] for a more comprehensive treatment.

3 Comprehensive study of cooperativity in unusual weak bonds

We carried out theoretical calculations over a family of complexes representative of the fifteen situations (Fig. 7). To the best of our knowledge **VI**, **VII**, **VIII** and **IX** cases have not been published in the literature. For computational economy, we selected complexes sharing some

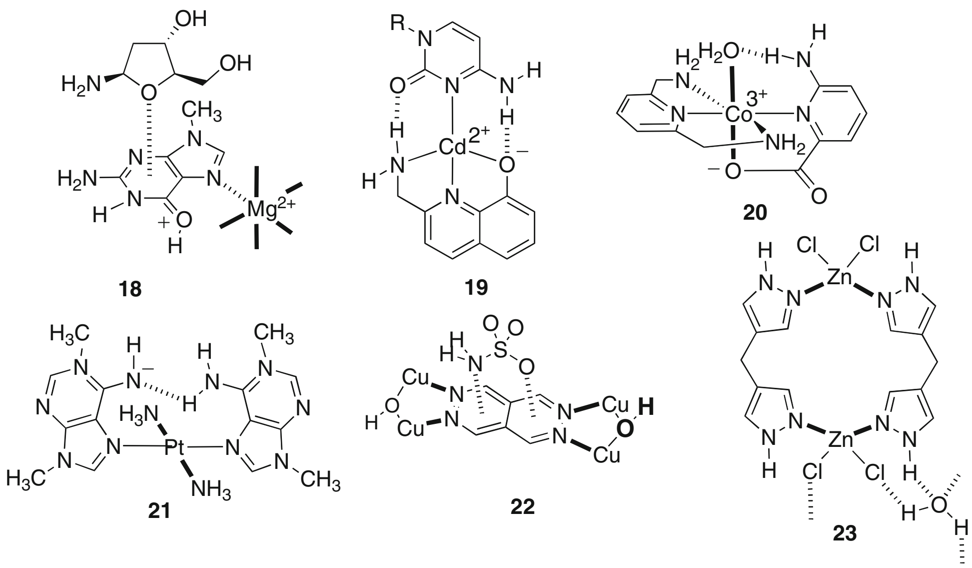

Fig. 6 Some examples of simultaneous interactions

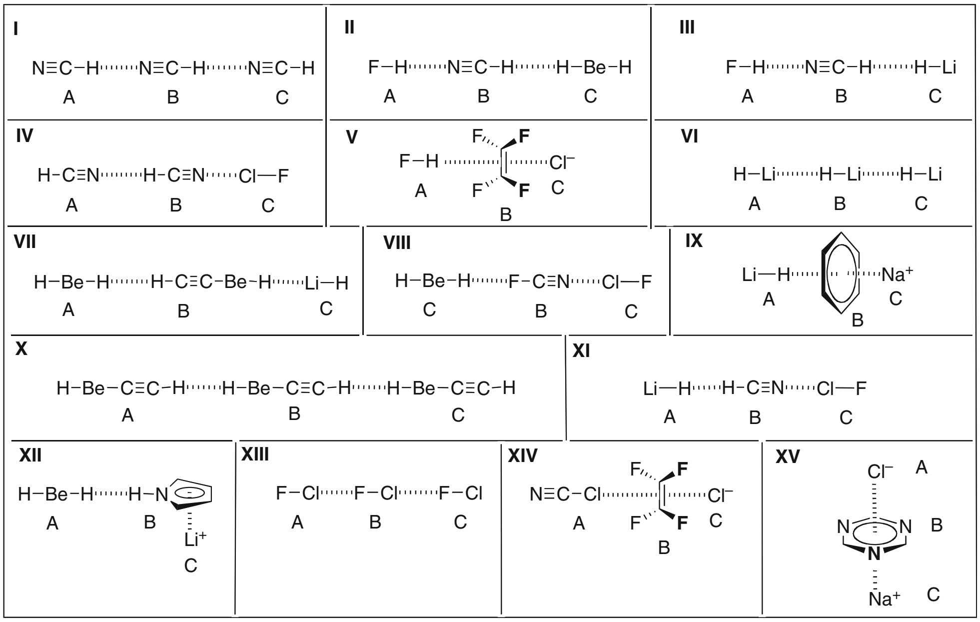

Fig. 7 Schematic representation of the fifteen studied complexes **I**–**XV**

common molecules. The results can be extrapolated to some other complexes, which can be easily figure out. Some of the complexes selected have been described for us recently [55, 58, 65].

In order to analyze the characteristics of the cooperativity in unusual weak bonds, a series of systems, one for each one of the possibilities shown in Fig. 7, have been calculated at the same computational level. The possible effect of the cooperativity has been analyzed using energetic, geometric, and electronic properties of the trimers, together with the corresponding dimers and monomers.

The systems chosen for this study are gathered in Fig. 7. The systems have been selected based on the small size of the molecules and, if possible, using the same dimer for several trimers. The optimized geometries are reported in Fig. 9.

The calculated interaction energies of the trimers and the three constituent dimers (Eq. 1) are gathered in Table 1. An energetic cooperativity parameter has been calculated using Eq. 1.

$$\text{Coop-Energy} = E_\mathrm{i}(\mathrm{ABC}) - E_\mathrm{i}(\mathrm{AB}) - E_\mathrm{i}(\mathrm{BC}) - E_\mathrm{i}(\mathrm{AC}) \quad (1)$$

where E_i(ABC) is the interaction energy of the trimer, E_i(AB) and E_i(BC) are the interaction energy of the isolated dimer within their corresponding minima configuration and E_i(AC) is the interaction energy of the molecules A and C in the geometry they have in the trimer.

Table 1 Interaction energies (kJ mol^{-1}) of the systems shown in Fig. 5 and the constituent dimers

System	ABC	AB	BC	AC	Coop-energy
I	−49.18	−22.26	−22.26	−1.79	−2.87
II	−34.75	−30.69	−2.95	0.04	−1.16
III	−82.65	−33.27	−37.80	−3.03	−8.55
IV	−50.93	−22.26	−24.32	−0.35	−4.01
V	−66.13	–[a]	−35.17	−18.75	−12.21
VI	−239.92	−106.03	−106.03	−14.28	−13.59
VII	−39.92	−6.69	−31.77	−0.35	−1.11
VIII	−26.03	−2.95	−22.27	0.14	−0.94
IX	−145.66	–[a]	−94.44	−49.19	−2.03
X	−13.91	−6.88	−6.88	−0.07	−0.07
XI	−71.33	−37.80	−24.32	−1.09	−8.13
XII	−195.72	−11.35	−167.12	−11.29	−5.95
XIII	−17.82	−8.43	−8.43	−0.22	−0.74
XIV	−63.01	−35.17	−5.54	−17.89	−4.40
XV	−353.11	−35.71	−19.37	−275.07	−22.97

The cooperativity parameter has been calculated using Eq. 1

[a] No stable complexes are formed in those cases

In all cases studied, a favorable cooperativity is observed. Note that the AC dimer is not a true complex but two molecules or ions separated by a spacer, molecule B. For the AC dimer, the interaction is very large for an anion/cation case (**XV**, Cl^-/Na^+, 275.1 kJ mol^{-1}), large for an ion/neutral case (**V**, Cl^- 35.2 kJ mol^{-1}, **IX**, Na^+ 49.2 kJ mol^{-1}, **XII**, Li^+ 11.3 kJ mol^{-1}; **XIV**, Cl^- 17.9 kJ mol^{-1}) and weak for the neutral/neutral cases ($\leq$3 kJ mol^{-1}) with the exception of **VI**, 14.3 kJ mol^{-1} where the monomers present very large dipole moments.

The geometrical characteristics of the trimers and constituent dimers are gathered in Table 2. In all cases, the distances observed within the dimers in the trimers are shorter than those of the corresponding dimers as

Table 2 Intermolecular distances (Å)

System	Trimer		Isolated dimer	
	A–B	B–C	A–B	B–C
I	2.146	2.135	2.188	2.188
II	1.843	2.738	1.849	2.788
III	1.771	1.681	1.835	1.773
IV	2.133	2.488	2.188	2.542
V	2.104[a]	2.997	–[b]	
VI	1.744	1.731	1.761	1.761
VII	2.111	1.887	2.164	1.895
VIII	2.748	2.568	2.788	2.578
IX	2.722[a]	2.416	–[b]	2.483
X	2.144	2.149	2.154	2.154
XI	1.693	2.431	1.773	2.542
XII	1.691	1.915[a]	1.922	1.933[a]
XIII	2.726	2.711	2.746	2.746
XIV	3.033	3.054	3.209	3.140
XV	2.791[a]	2.402[a]	3.152[a]	2.745[a]

[a] Distance between the interacting atom and the geometrical center of the π-system

[b] No stable complexes are formed in those cases

indication of positive cooperativity. The larger effects are those associated to the presence of ionic species. Thus for instance, the intermolecular distances in the constituent dimers of **XV** are shortened by 0.35 Å in the trimer.

Linear correlations can be found between the intermolecular distances in the dimers and trimers (Fig. 8). Three cases, which correspond to those cases with the largest variations (>0.23 Å) seems to follow a different behavior. In any case, the fitted linear relationships show a slope smaller than 1.0 as indication that the distances in the trimers are shorter than those of the dimers.

Among the electronic properties considered, we have study the effect of the complex formation on the dipole moment value of those systems where no ionic species are involved (Table 3). As in the case of the energy, a cooperativity parameter has been defined for the dipole moment enhancement due to the complex formation, Eq. 2:

$$\text{Coop-dipole} = \Delta\text{Dipole(ABC)} - \Delta\text{Dipole(AB)} - \Delta\text{Dipole(BC)} \qquad (2)$$

where the corresponding ΔDipole is calculated as the difference between the dipole moment in the cluster and the sum of the isolated monomers in their geometry of minimum energy configuration. In all the cases studied, a dipole moment enhancement is observed in the formation of the dimers as well as a positive Coop-dipole, which indicates that the dipole moment enhancement in the trimers is larger than that observed as the sum of the two dimers.

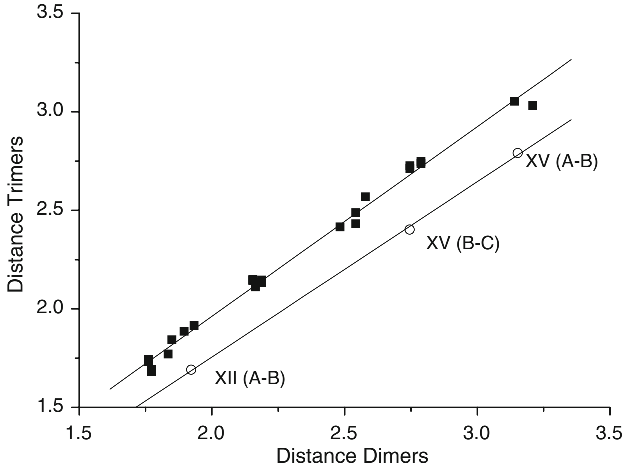

Fig. 8 Intermolecular distances (Å) in the dimers versus those corresponding ones in the trimers (Trimers = 0.029 + 0.965 × Dimers; $R^2 = 0.994$). The cases with the largest variations are shown in *empty circles* (Trimers = −0.025 + 0.890 × Dimers; $R^2 = 0.999$)

Table 3 Dipole moment enhancement (Debye) upon complex formation and cooperativity parameter as defined by Eq. 2 in the systems where no ionic molecules are involved

System	ΔABC	ΔAB	ΔBC	Coop-dipole
I	1.86	0.81	0.81	0.25
II	1.24	1.02	0.15	0.07
III	2.64	1.01	1.20	0.43
IV	2.43	0.81	1.24	0.39
V			Anion	
VI	3.51	1.63	1.63	0.25
VII	2.01	0.38	1.52	0.12
VIII	1.37	0.15	1.14	0.08
IX			Cation	
X	0.95	0.45	0.45	0.05
XI	3.24	1.20	1.24	0.80
XII		0.60	Cation	
XIII*	1.01	0.39	0.39	0.23
XIV		0.13	Anion	
XV		Anion	Cation	

* The direction of elongation of the change has been considered

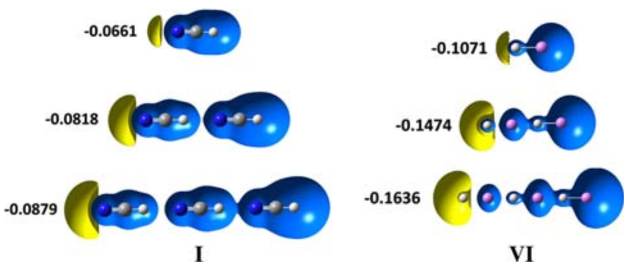

Fig. 9 Molecular electrostatic potential at ±0.05 (**I**) and ±0.1 au (**VI**) surfaces of the monomer, dimer and trimers of **I** and **VI**. The value of the MEP minima (au) is indicated

Table 4 Charge transfer (*e*) in the dimers and trimers obtained using the NBO method

	Dimers				Trimers		
	AB		BC				
	A	B	B	C	A	B	C
I	−0.015	0.015	−0.015	0.015	−0.018	−0.001	0.019
II	−0.023	0.023	0.001	−0.001	−0.024	0.024	−0.001
III	−0.025	0.025	−0.038	0.038	−0.036	−0.017	0.053
IV	−0.015	0.015	0.030	−0.030	0.019	0.022	−0.041
V			−0.014	−0.986	−0.048	0.015	−0.968
VI	0.101	−0.101	0.101	−0.101	−0.112	0.006	0.106
VII	0.003	−0.003	0.029	−0.029	0.003	0.026	−0.030
VIII	−0.001	0.001	0.024	−0.024	−0.001	0.026	−0.025
IX			0.039	0.961	0.004	0.045	0.951
X	−0.002	0.002	−0.002	0.002	−0.002	0.000	0.002
XI	0.038	−0.038	0.030	−0.030	0.051	0.003	−0.055
XII	0.006	−0.006	0.118	0.882	0.022	0.100	0.877
XIII	0.008	−0.008	0.008	−0.008	−0.008	−0.001	0.009
XIV	−0.008	0.008	−0.014	−0.986	−0.026	−0.002	−0.973
XV	−0.984	−0.016	0.021	0.979	−0.929	−0.011	0.940

Concerning cooperativity and the effect on the molecular electrostatic potential (MEP) we have represented in Fig. 9 the effect in the cases of **I** and **VI**. The negative regions at one end and the positive ones at the opposite became bigger with larger absolute values as the size of the clusters increases. Thus, new approaching molecules will interact strongly with their nucleophilic or electrophilic ends.

The analysis of the charge transfer in the dimers and trimers (Table 4) shows, in general, that the charges in the extreme molecules, A and C, is larger in the trimers than those obtained in the corresponding dimers. These results are in line with those obtained for the evolution of the MEP previously mentioned.

The calculated properties of the intermolecular bond critical points (bcp's) of the dimers and trimers have been gathered in Table 5. Larger values are obtained in the trimers than in the corresponding dimers as expected for the shorter distances observed in the former cases. These results are in agreement with other reports that have shown exponential relationship between the distance and the electron density and Laplacian in weak interactions [83].

4 Computational details

The geometry of the systems has been fully optimized at the MP2/6-311++G(d,p) computational level [84, 85] within the Gaussian-03 program [86]. Frequency calculations at the same computational level have been carried out to confirm that the structures obtained correspond to energetic minima. A further geometry optimization has been carried out, in all cases, at the MP2/aug-cc-pVTZ level [87, 88]. All analyses have been carried out with the data provided at the last computational level (Fig. 10).

Table 5 Electron density and Laplacian (au) at the intermolecular bcp

	Dimers				Trimers			
	AB		BC		AB		BC	
	Rho	Lap	Rho	Lap	Rho	Lap	Rho	Lap
I	0.0159	0.0574	0.0159	0.0574	0.0177	0.0617	0.0180	0.0627
II	0.0313	0.0807	0.0037	0.0156	0.0318	0.0811	0.0041	0.0174
III	0.0332	0.0811	0.0204	0.0393	0.0394	0.0840	0.0249	0.0421
IV	0.0159	0.0574	0.0275	0.1097	0.0180	0.0629	0.0315	0.1192
V			0.0138	0.0414	0.0260	0.0409	0.0197	0.0525
VI	0.0224	0.1027	0.0224	0.1027	0.0242	0.1085	0.0246	0.1123
VII	0.0074	0.0217	0.0127	0.0686	0.0083	0.0240	0.0130	0.0701
VIII	0.0037	0.0156	0.0247	0.1022	0.0040	0.0170	0.0253	0.1039
IX			0.0091	0.0524	0.0064	0.0186	0.0103	0.0586
X	0.0075	0.0220	0.0075	0.0220	0.0078	0.0224	0.0076	0.0223
XI	0.0204	0.0393	0.0275	0.1097	0.0243	0.0418	0.0363	0.1295
XII	0.0121	0.0329	0.0204	0.1269	0.0210	0.0446	0.0207	0.1294
XIII	0.0126	0.0639	0.0126	0.0639	0.0133	0.0671	0.0137	0.0693
XIV	0.0088	0.0326	0.0138	0.0414	0.0142	0.0443	0.0175	0.0484
XV	0.0080	0.0261	0.0048	0.0282	0.0151	0.0461	0.0104	0.0607

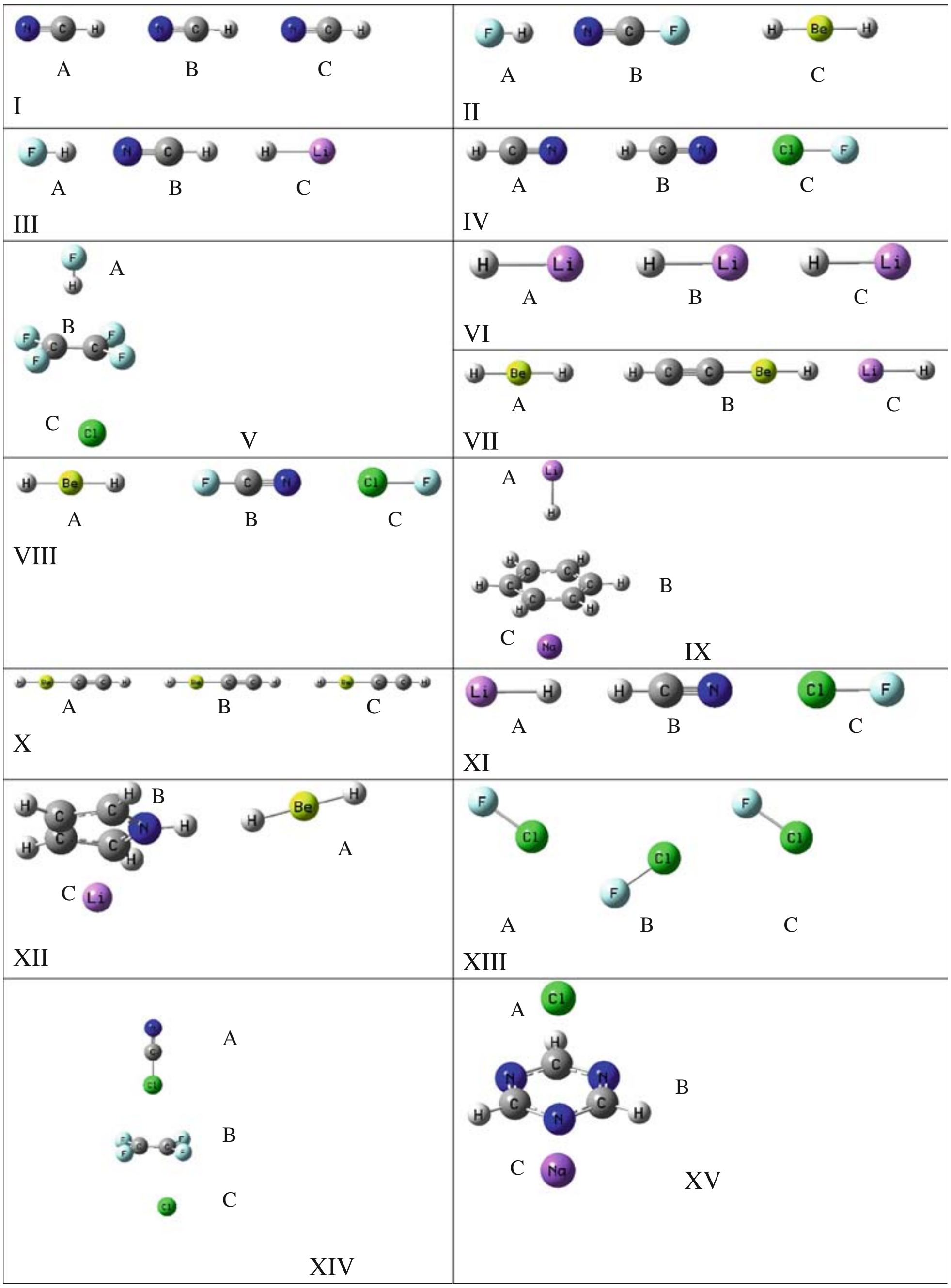

Fig. 10 Geometry of the 15 systems optimized at the MP2/aug-cc-pVTZ computational level

The interaction energies have been calculated as the difference between that of the clusters minus sum of the isolated monomers. The basis sets used in this work are of sufficient quality, thus basis set superposition errors (BSSEs) should be rather small [89]. Moreover, it has been shown that uncorrected MP2/aug-cc-pVTZ binding energies lie between corrected and uncorrected MP2/aug-cc-pVQZ energies [90]. BSSE corrections may not always improve binding energies of weakly bonded complexes, since in the counterpoise method [91] a monomer may utilize the valence and core functions of its partner, which are not available to the monomer in the complex. Thus, several studies [92, 93] have shown that the full counterpoise method overestimated the BSSE corrections providing BSSE-corrected interaction energies with larger error than the uncorrected ones at the computational method considered here.

The electron density of the systems, calculated at the MP2/aug-cc-pVTZ level, has been analyzed within the AIM methodology [94] with the AIMPAC [95] and AIM2000 programs [96].

5 Conclusions

In this article, the cooperativity in multiple unusual weak bonds has been reviewed. All the possible combinations of hydrogen bond, hydric bond, dihydrogen bond, halogen bond and ion–π interactions have been considered. For several combinations, no literature precedent has been described. In order to understand the mechanism in the cooperativity processes, one example has been studied for each of the 15 possible situations, including those not previously described in the literature. Similar tendencies are observed in the evolution of the intermolecular distances, energetic and electronic (electrostatic potential, dipole moment, charge transfer, electron density at the intermolecular bond critical point) when going from the dimers to the trimers.

References

1. Alkorta I, Rozas I, Elguero J (1997) J Org Chem 62:4687–4691
2. Rozas I, Alkorta I, Elguero J (1997) J Phys Chem A 101:4236–4244
3. Rozas I, Alkorta I, Elguero J (1997) J Phys Chem A 101:9457–9463
4. Alkorta I, Rozas I, Elguero J (1998) J Phys Chem A 102:9278–9285
5. Alkorta I, Rozas I, Elguero J (1998) Chem Soc Rev 27:163–170
6. Schuster P, Mikenda W (ed) (1999) Hydrogen bond research. Springer, Berlin
7. Desiraju GR, Steiner T (2001) The weak hydrogen bond. In: Structural chemistry and biology. Oxford University Press, Oxford
8. Grabowski S (ed) (2006) Hydrogen bonding: new insights. Springer, Berlin
9. Marechal Y (2006) The hydrogen bond and the water molecule: the physics and chemistry of water, aqueous, and bio-media. Elsevier, Amsterdam
10. Metrangolo P, Resnati G (eds) (2008) Halogen bonding: fundamentals and applications. Springer, Berlin
11. Garau C, Quiñonero D, Frontera A, Ballester P, Costa A, Deyà PM (2005) J Phys Chem 109:9341–9345
12. Frontera A, Quiñonero D, Garau C, Costa A, Ballester P, Deyà PM (2006) J Phys Chem A 110:9307–9309
13. Quiñonero D, Frontera A, Garau C, Ballester P, Costa A, Deyà PM (2006) Chem Phys Chem 7:2487–2491
14. Frontera A, Quiñonero D, Costa A, Ballester P, Deyà PM (2007) New J Chem 31:556–560
15. García-Raso A, Albertí FM, Fiol JJ, Tasada A, Barceló-Oliver M, Molins E, Escudero D, Frontera A, Quiñonero D, Deyà PM (2007) Inorg Chem 46:10724–10735
16. Barrios LA, Aromi G, Frontera A, Quiñonero D, Deyà PM, Gamez P, Roubeau O, Shotton EJ, Teat SJ (2008) Inorg Chem 47:5873–5881
17. Estarellas C, Frontera A, Quiñonero D, Deyà PM (2009) Chem Phys Lett 479:316–320
18. Escudero D, Frontera A, Quiñonero D, Deyà PM (2008) Chem Phys Lett 456:257–261
19. Escudero D, Frontera A, Quiñonero D, Deyà PM (2009) J Comput Chem 30:75–82
20. Escudero D, Frontera A, Quiñonero D, Deyà PM (2008) J Phys Chem A 112:6017–6022
21. Quiñonero D, Frontera A, Escudero D, Ballester P, Costa A, Deyà PM (2008) Theor Chem Acc 120:385–393
22. Estarellas C, Frontera A, Quiñonero D, Alkorta I, Deyà PM, Elguero J (2009) J Phys Chem A 113:3266–3273
23. Brammer L, Mínguez Espallargas G, Libri S (2008) Cryst Eng Comm 10:1712–1727
24. Krapp A, Frenking G, Uggerud E (2008) Chem Eur J 14:4028–4038
25. Alkorta I, Elguero J, Grabowski SJ (2008) J Phys Chem A 112:2721–2727
26. Bakhmutov VI (ed) (2008) Dihydrogen bonds: principles, experiments, and applications. Wiley, Hoboken
27. Berryman OB, Johnson DW (2009) Chem Commun 3143–3153
28. Yuan XL, Zhang H, Xie FJ (2009) J Mol Struct Theochem 900:103–109
29. Wang Y, Xu Z, Gao Y, Zhang L, Li H (2009) J Phys Chem A 113:7097–7102
30. Lucas X, Quiñonero D, Frontera A, Deyà PM (2009) J Phys Chem A 113:10367–10375
31. Abrahams BF, FitzGerald NJ, Hudson TA, Robson R, Waters T (2009) Angew Chem Int Ed 48:3129–3132
32. Santos J, Grimm B, Illescas BM, Guldi DM, Martín N (2008) Chem Comm 5993–5995
33. White JC, Davidson ER (1990) J Chem Phys 93:8029–8035
34. Valiron P, Mayer I (1977) Chem Phys Lett 275:46–55
35. Rivelino R, Chaudhuri O, Canuto S (2003) J Chem Phys 118:10593–10601
36. Lucas X, Estarellas C, Escudero D, Frontera A, Quiñonero D, Deyà PM (2009) Chemphyschem 10:2256–2264
37. Li QZ, Lin Q, Li W, Cheng JB, Gong BA, Sun J (2008) Chemphyschem 9:2265–2269
38. Moszynski R, Jeziorski B, Rybak S, Szalewicz K, Williams HL (1994) J Chem Phys 100:5080–5092
39. Tzeli D, Mavridis A, Xantheas SS (2002) J Phys Chem A 106:11327–11337
40. Scheiner S (1997) In: Hydrogen bonding. A theoretical perspective. Oxford University Press, Oxford
41. Rozas I, Alkorta I, Elguero J (1998) J Phys Chem A 102:9925–9932
42. Parra RD, Ohlssen J (2008) J Phys Chem A 112:3492–3498
43. Hunter CA, Ihekwaba N, Misuraca MC, Segarra-Maset MD, Turega SM (2009) Chem Commun 3964–3966
44. Li Q, Liu Z, Cheng J, Li W, Gong B, Sun J (2009) J Mol Struct Theochem 896:112–115
45. Egli M, Sarkhel S (2007) Acc Chem Res 40:197–205
46. Alkorta I, Blanco F, Elguero J (2008) J Phys Chem A 112:6753–6759
47. Giner Planas J, Viñas C, Teixidor F, Comas-Vives A, Ujarque G, Lledós A, Light ME, Hursthouse MB (2005) J Am Chem Soc 127:15976–15982
48. Li QZ, Hu T, An XL, Gong BA, Cheng JB (2008) Chemphyschem 9:1942–1946
49. García A, Cruz EM, Sarasola C, Ugalde JM (1997) J Phys Chem A 101:3021–3024
50. Lankau T, Wu YC, Zou JW, Yu CH (2008) J Theor Comp Chem 7:13–35
51. Saha BK, Nangia A, Jaskólski M (2005) Cryst Eng Comm 7:355–358
52. Politzer P, Murray JS, Concha MC (2007) J Mol Model 13:643–650
53. Cabot R, Hunter CA (2009) Chem Commun 2005–2007
54. Voth AR, Khuu P, Oishi K, Ho PS (2009) Nat Chem 1:74–79
55. Alkorta I, Blanco F, Elguero J, Estarellas C, Frontera A, Quiñonero D, Deya PM (2009) J Chem Theor Comput 5:1186–1194

56. Wu R, McMahon TB (2008) J Am Chem Soc 130:12554–12556
57. Xiu X, Puskar NL, Shanata JAP, Lester HA, Dougherty DA (2009) Nature 458:534–537
58. Alkorta I, Elguero J, Solimannejad M (2008) J Chem Phys 129:064115-1-8
59. Wang Y, Li L, Lu Y, Zou J (2007) Chin J Chem Phys 20:531–536
60. Ito Y, Kondo H, Shiota Y, Yoshizawa K (2008) J Chem Theor Comput 4:366–374
61. Ramana CV, Chatterjee S, Durugkar KA, Gonnada RG (2009) Cryst Eng Comm 11:143–150
62. Syssa-Magalé JL, Boubekeur K, Schöllhorn B (2005) J Mol Struct 737:103–107
63. Lucassen ACB, Karton A, Leitus G, Shimon LJW, Martin JML, van der Boom ME (2007) Cryst Growth Des 7:386–392
64. Grabowski SJ, Bilewicz E (2006) Chem Phys Lett 427:51–55
65. Alkorta I, Blanco F, Elguero J (2009) Struct Chem 20:63–71
66. Xu L, Zou JW, Lu YX, Yu QS, Zgang N (2009) J Mol Struct Theochem 897:12–16
67. Garau C, Quiñonero D, Frontera A, Ballester P, Costa A, Deyà PM (2003) New J Chem 27:211–214
68. Alkorta I, Elguero J (2003) J Phys Chem A 107:9428–9433
69. Quinonero D, Frontera A, Deya PM, Alkorta I, Elguero J (2008) Chem Phys Lett 460:406
70. Liu T, Zhu W, Gu J, Shen J, Luo X, Chen G, Puah CM, Silman I, Chen K, Sussman JL, Jiang H (2004) J Phys Chem A 108:9400
71. Alkorta I, Quiñonero D, Garau C, Frontera A, Elguero J, Deyà PM (2007) J Phys Chem A 111:3137–3142
72. Grabowski SJ, Sokalski WA, Leszczynski J (2004) J Phys Chem A 108:1806–1812
73. Vaden TD, Lisy JM (2005) J Chem Phys 123:074302-1-8
74. Zaccheddu M, Filippi C, Buda F (2008) J Phys Chem A 112:1627–1632
75. Mancin F, Chin J (2002) J Am Chem Soc 124:10946–10947
76. Chin J, Chung S, Kim DH (2002) J Am Chem Soc 124:10948–10949
77. Roitzsch M, Lippert B (2004) J Am Chem Soc 126:2421–2424
78. Gural'skiy IA, Solntsev PV, Krautscheid H, Domasevitch KV (2006) Chem Commun 4808–4810
79. Schottel BL, Chifotides HT, Dunbar KR (2008) Chem Soc Rev 37:68–83
80. Mondal R, Basu T, Sadhukhan D, Chattopadhyay T, Bhunia MK (2009) Cryst Growth Des 9:1095–1105
81. Sponer J, Leszczynski J, Hobza P (2001) J Mol Struct Theochem 573:43–53
82. Mordasini T, Curioni A, Andreoni W (2003) J Biol Chem 278:4381–4384
83. Picazo O, Alkorta I, Elguero J (2003) J Org Chem 68:7485
84. Zhao Y, Schultz NE, Truhlar DG (2006) J Chem Theory Comput 2:364–382
85. Frisch MJ, Pople JA, Binkley JS (1984) J Chem Phys 80:3265–3269
86. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JJA, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA (eds) (2003) Gaussian-03. Gaussian, Wallingford
87. Møller C, Plesset MS (1934) Phys Rev 46:618–622
88. Dunning TH (1989) J Chem Phys 90:1007–1023
89. Dunning TH (2000) J Phys Chem A 104:9062–9080
90. Bene JED, Shavitt I (1997) In: Scheiner S (ed) Molecular interactions: from Van der Waals to strongly bound complexes. Wiley, Sussex, pp 157
91. Boys SF, Bernardi F (1970) Mol Phys 19:553–566
92. Frey JA, Leutwyler S (2005) J Phys Chem A 9:6990
93. Frey JA, Leutwyler S (2006) J Phys Chem A10:12512–12518
94. Bader RFW (1990) Atoms in molecules: a quantum theory. Clarendon Press, Oxford
95. Biegler-König FW, Bader RFW, Tang THJ (1982) J Comput Chem 3:317–328
96. Biegler-König FW, Schonbohm J (2002) AIM2000 Program Package, Ver.2.0. University of Applied Sciences, Bielefield, Germany