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Energetic vs Synergetic Stability: A Theoretical Study

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The aim of this manuscript is to define a new concept, namely synergetic stability, which can be useful in systems where the interplay of noncovalent interactions is important. Usually, the stability of a noncovalent complex is related to the complexation energy, which is directly proportional to the strength of the noncovalent interactions that are involved in the complex. In ternary complexes characterized by the presence of two different noncovalent interactions, three situations regarding the variation of the strength of the interactions (in comparison to the binary complexes) can be present. 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. This study deals with ternary complexes where ion−π and either hydrogen bonding, dihydrogen bonding, or halogen bonding interactions coexist.

Introduction

The understanding of noncovalent interactions and the interplay among them[1] are of pivotal importance to the development of fields such as supramolecular chemistry and molecular recognition. The interactions involving aromatic rings are crucial binding forces in both chemical and biological systems.[2] For instance, cation−π interactions[3−8] are supposed to be an important factor for ion selectivity in potassium channels,[9,10] and they are also important for the binding of acetylcholine to the active site of the enzyme acetylcholine esterase.[11] Another noncovalent interaction that involves aromatic rings is the anion−π interaction,[12] which has attracted considerable attention in last years. Anion−π complexes have been observed experimentally, sustaining the theoretical predictions and the promising proposal for the use of anion receptors based on anion−π interactions in molecular recognition.[13−17] These interactions are also important in DNA bases such as adenine.[18] Moreover, Berryman et al. have reported structural criteria for the design of anion receptors based on the interaction of halides with electron-deficient arenes.[19] Recent excellent reviews deal with anion-binding involving π-acidic heteroaromatic rings.[20] The ion−π interaction is dominated by electrostatic and ion-induced polarization terms.[21] The nature of the electrostatic term can be rationalized by means of the permanent quadrupole moment of the arene. Hydrogen, dihydrogen, and halogen bonding interactions are mainly dominated by electrostatic effects (dipole−dipole interactions).[22]

We have recently reported experimental[18,23] and theoretical[24,25] evidence of interesting synergetic effects between ion−π and π−π interactions. 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.[26,27] This interplay can lead to strong cooperative effects. In this manuscript, we report a theoretical study where we compare several ternary complexes where two different noncovalent interactions are responsible for their formation. This is performed in an effort to define a new concept, namely synergetic stability. Usually, the stability of a complex is measured using the complexation energy, which is directly proportional to the strength of the noncovalent interactions that are involved in the formation of the complex. In ternary complexes characterized by the presence of two different noncovalent interactions, three situations regarding the variation of the strength of the interactions (in comparison to the binary complexes) can exist. First, the coexistence of the interactions causes a strengthening of both interactions, second, it causes a weakening of both, and, third, it causes a strengthening of one interaction at expense of weakening of the other. This study deals with ternary complexes where several types of interactions coexist. For a given ternary complex (A+B+C), three orientations are possible, which are obtained from the combination of the three monomers, i.e., A···B···C, A···C···B, and B···A···C. Computing and comparing their interaction energies, we ascertained the most stable complex. However, in most cases, the most stable complex (for instance A···B···C) usually implies a weakening of the noncovalent interactions in comparison to the binary complexes (A···B and B···C). Other combinations can lead to favorable cooperativity effects between the noncovalent interactions. We can define the complex that is characterized by the most favorable cooperativity as the most synergistically stable complex.

For the theoretical study reported herein, we have selected three aromatic rings (**1**−**3**), see Figure 1, with different π-electronic nature which can participate in cation−π, anion−π, lone pair(lp)−π, and X-H/π interactions. We have computed a great deal of binary complexes **4**−**20**, which are present in Figure 1. They cover a variety of noncovalent interactions, including the aforementioned aromatic interactions and hydrogen, dihydrogen, and halogen bonds. We have also computed the ternary complexes **21**−**38** as shown in Figure 2, in order to study the interplay between the different types of interactions. We have used Bader's theory of "atoms in molecules", which provides an unambiguous definition of chemical bonding,[28] to

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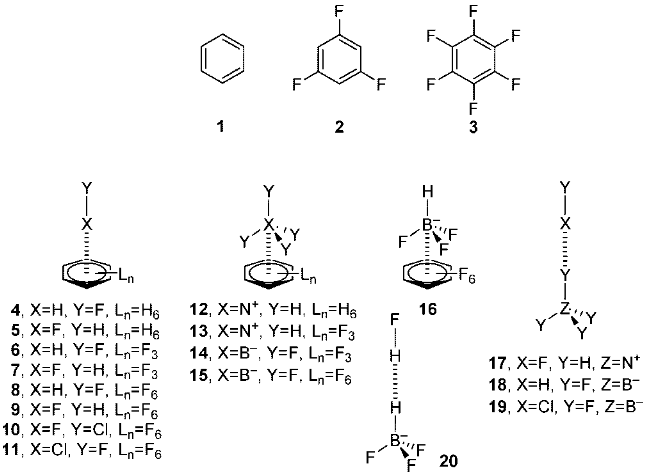


Figure 1. Compounds **1**−**3** and binary complexes **4**−**20** studied in this work.

analyze the interplay between the interactions in the complexes. The AIM theory has been successfully used to characterize a great variety of interactions including the ones studied herein.

Theoretical Methods. The geometry of all the complexes included in this study was fully optimized at the RI-MP2(full)/6−31++G** level of theory within the program TURBOMOLE version 5.7.[29] The RI-MP2 method[30,31] 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.[32,33] The binding energy was calculated at the same level with and without correction for the basis set superposition error (BSSE) using the Boys−Bernardi counterpoise technique.[34] The optimization of the molecular geometries has been performed imposing either C_{6v} or C_{3v} 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 noncovalent interactions studied herein. We have also performed calculations in the presence of solvent (water, $\varepsilon = 78.39$) using the Conductor-Like Screening Model (COSMO)[35] as implemented in TURBOMOLE.

We have evaluated the possible existence of cooperativity in the ternary complexes, by using the equation indicated in eq 1.

$$E_{\text{coop}} = E_{\text{BSSE}}(\text{ABC}) - E_{\text{BSSE}}(\text{AB}) - E_{\text{BSSE}}(\text{BC}) - E_{\text{BSSE}}(\text{AC}) \quad (1)$$

where E_{BSSE}(ABC), E_{BSSE}(AB), and E_{BSSE}(BC) terms correspond to the interaction energies (BSSE corrected) of the corresponding optimized binary and ternary structures which are gathered in Tables 1 and 2. E_{BSSE}(AC) is the attractive interaction of these two molecules as they stand in the ABC ternary system.

Results and Discussion

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_e) of binary complexes **4**−**20** at the RI-MP2(full)/6−31++G** level of theory. The optimized geometries of the complexes are shown in Figures 3 and 4. From the inspection of the results, several interesting points emerge. First, complexes **4**−**9** consist of the interaction of benzene (**1**), trifluorobenzene (**2**), and hexafluorobenzene (**3**) with HF via either the hydrogen atom (complexes **4**, **6**, and **8**) or the fluorine atom (complexes **5**, **7**, and **9**). For the former complexes, the interaction energy of the F−H/π interaction is progressively decreased on going from **4** to **8**, and for the latter, the interaction is progressively enhanced on going from **5** to **9**. This result can be easily explained taking into account the values of the quadrupole moments of the aromatic rings ($Q_{zz}(\mathbf{1}) = -8.45$B, $Q_{zz}(\mathbf{2}) = 0.19$B, $Q_{zz}(\mathbf{3}) = 9.50$B). The dual behavior of the trifluorobenzene ring is remarkable in that it is able to interact favorably with HF via any end. Second, in complexes **10** and **11**, the FCl molecule interacts with **3**. When the fluorine atom points toward the center of the ring (complex **10**), the interaction is favorable. The contrary is observed when the chlorine atom points toward the center of the ring (complex **11**), which is explained by means of the dipole moment of the $F^{\delta-}Cl^{\delta+}$ molecule. Third, the noncovalent interaction responsible of the formation of complexes **12**−**16** is either cation−π (complexes **12** and **13**) or anion−π (complexes **14**−**16**). For this set of complexes, the duality of **2** toward concentrations of negative or positive charge is again observed (complexes **13** and **14**). At this point, an interesting issue comes into sight. Previous reports have shown that the anion−π interaction is less favorable than the cation−π interaction because the van der Waals radii of anions are longer than cations and, consequently, the equilibrium distances are larger in anion−π than in cation−π complexes.[36] The energetic terms that contribute to the stabilization of ion−π interactions (electrostatic and polarization) are very dependent on the distance. Curiously, in complexes **13** and **14** an almost identical binding energy is obtained for the cation−π and anion−π interactions. The binding energy computed for the complex of hexafluorobenzene with BF_3H^- (**16**) is more negative than the one computed for BF_4^- (**15**) because the amount of charge born by the fluorine atoms is more negative in the BF_3H^- anion. Fourth, in complexes **17**−**20** aromatic rings are not present. In **17** and **18**, the noncovalent interaction involved is a hydrogen bond between HF and either a cation (**17**) or an anion (**18**). The interaction energy of **18** is more negative than the one for **17** because the formal charge of the fluorine atom in BF_4^- is higher, in absolute value, than the formal charge of the hydrogen atom in NH_4^+. Consequently, the equilibrium distance is also significantly shorter in **18** than in **17**. Finally, complex **19** is characterized by a halogen bond between ClF and BF_4^-, and complex **20** is characterized by a dihydrogen bond between HF and BF_3H^-. The computed binding energy for both complexes is comparable to **17** and **18**, indicating that these noncovalent interactions (halogen and dihydrogen bonds) are of similar strength to the hydrogen bonding interaction in the systems studied here.

A global view of the energetic results gathered in Table 1 indicates that the ion−π, hydrogen, dihydrogen, and halogen bonds are strong interactions. As expected, the F−H/π and lp−π interactions are modest, and depending upon the nature of the aromatic ring, they can lead to positive interaction energies (complexes **5**, **8**, and **11**).

The geometric and energetic results computed for the ternary complexes **21**−**38** are summarized in Table 2. Some previous considerations must be done before discussing the results. The numbering of the compounds has been ordered in such a way that the three first complexes (**21**−**23**) have the same interacting molecules (**1**, NH_4^+, and HF). The same is applicable to the next three complexes **24**−**26** (interacting molecules: **2**, NH_4^+, and HF) and so on. This allows a direct comparison between

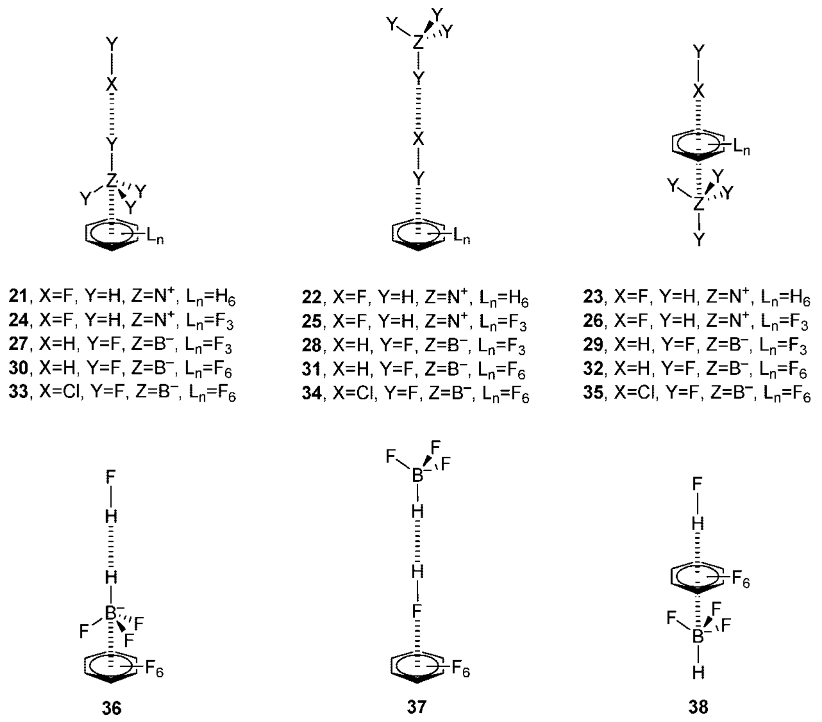


Figure 2. Ternary complexes **21**−**38** studied in this work.

TABLE 1: Binding Energies without and with the BSSE Correction (E and E_{BSSE}, kcal/mol, respectively) and Equilibrium Distances (R, Å) at the RI-MP2(full)/6-31++G Level of Theory for Complexes 4−20**[a]

complex	interaction	E	E_{BSSE}	R	$\rho \times 10^2$
4 ($FH:C_6H_6$)	F−H/π	−5.13	−2.99	2.258	0.6983
5 ($HF:C_6H_6$)	lp−π	−0.31	1.32	3.039	0.4094
6 ($FH:C_6H_3F_3$)	F−H/π	−1.96	−0.33	2.445	0.5119
7 ($HF:C_6H_3F_3$)	lp−π	−1.78	−0.26	2.973	0.4660
8 ($FH:C_6F_6$)	F−H/π	0.09	1.97	2.936	0.4951
9 ($HF:C_6F_6$)	lp−π	−3.61	−1.85	2.937	0.5454
10 ($ClF:C_6F_6$)	lp−π	−3.97	−1.15	2.831	0.6003
11 ($FCl:C_6F_6$)	lp−π	−2.35	0.47	3.341	0.4010
12 ($NH_4^+:C_6H_6$)	cation−π	−17.11	−14.66	2.950	0.9258
13 ($NH_4^+:C_6H_3F_3$)	cation−π	−8.45	−4.79	3.148	0.5620
14 ($BF_4^-:C_6H_3F_3$)	anion−π	−8.18	−4.74	3.591	0.7318
15 ($BF_4^-:C_6F_6$)	anion−π	−16.23	−11.67	3.392	1.0411
16 ($HBF_3^-:C_6F_6$)	anion−π	−17.64	−13.05	3.403	1.0938
17 ($HF:HNH_3^+$)	H-bond	−12.60	−11.97	1.808	2.4616
18 ($FH:FBF_3^-$)	H-bond	−16.93	−15.37	1.593	4.1371
19 ($FCl:FBF_3^-$)	hal. bond	−11.50	−9.58	2.414	2.6322
20 ($FH:HBF_3^-$)	DH bond	−13.79	−12.81	1.426	3.3637

[a] The value of the charge density (ρ, a.u.) at the bond critical point that emerges upon complexation is also summarized.

each triad of complexes in terms of binding and cooperative energy (see Figure 4).

From the results of Table 1 we have learned that some noncovalent interactions are considerably more favorable than others. Therefore, for each triad of ternary complexes, one of them will have two strong interactions, and the other two complexes will have one strong and one modest interaction. Thus, a priori, the former should be considerably more stable than the latter. The examination of the results summarized in Table 2 gives some interesting and unexpected results. The most favorable combination of **1**, NH_4^+, and HF (triad **I**) is complex **21** where the cation is establishing a strong cation−π interaction with **1** and a strong hydrogen bonding interaction with HF. However, this arrangement is only 5.06 kcal/mol (E_{rel}) more stable than complex **22**, where a very modest F−H/π interaction and a strong hydrogen bonding interaction are formed. The least favorable arrangement is complex **23**, where a very modest lp−π interaction and a strong cation−π interaction are present. A likely explanation for the small difference between the interaction energies of **21** and **22** is that the cooperativity between the noncovalent interactions is opposite. Complex **21** is characterized by two strong interactions; however, the mutual influence of both leads to a positive value (unfavorable) of E_{coop}. This means that the presence of the hydrogen bonding interaction in **21** weakens the simultaneous cation−π interaction and vice versa. This fact is confirmed by taking into account the geometrical features of the ternary complex with respect to binary complexes **12** and **17**. The cation−π distance enlarges by 0.06 Å and the hydrogen bonding distance enlarges by 0.041 Å. The contrary is found in ternary complex **22**, where both noncovalent interactions strengthen with respect to the binary complexes as confirmed by the computed $E_{coop} = -1.69$ kcal/mol. A clear indication of the strengthening of both interactions (F−H/π and hydrogen bonding) is the significant shortening of the equilibrium distances, 0.235 Å for the hydrogen bonding and 0.113 Å for the F−H/π interaction. In complex **23**, the cooperative energy is also negative, indicating an overall stabilization of the interactions in the ternary complex with respect to the binary complexes, in agreement with the values of ΔR. In the next triad of ternary complexes **24**−**26** (triad **II**), the benzene ring has been substituted by trifluorobenzene (**2**) and its behavior is similar to triad **I**. In the most stable ternary complex (**24**), the noncovalent interactions are cation−π and hydrogen bonding. However, the interaction energy of **24** is only 2.39 kcal/mol more favorable than the one computed for **25**, where a strong hydrogen bonding and a modest F−H/π interaction are formed in the complex. In **24** the E_{coop} is positive, indicating that the mutual influence of both interactions (cation−π and H-bonding) is adverse, which is confirmed by the enlargement of the equilibrium distances with respect to the corresponding binary complexes. In contrast, **25** has a negative value of E_{coop}, indicating that the mutual influence of both interactions (F−H/π and H-bonding) is beneficial, which is

TABLE 2: Binding, Cooperativity, and Relative Energies with BSSE Correction (E_{BSSE}, E_{coop}, and E_{rel}, respectively) and Equilibrium Distances (R_1 and R_2, Å) at the RI-MP2/6-31++G Level of Theory**[a]

triad	compound	interactions	E_{BSSE}	E_{coop}	E_{rel}	$E_{rel\text{-}w}$	R_1	R_2	ΔR_1	ΔR_2
I	**21** ($HF:NH_4^+$:**1**)	HB and Cπ	−25.26	0.83	0.00	0.98	1.849 (HB)	3.010 (Cπ)	0.041	0.060
	22 ($NH_4^+:FH$:**1**)	HB and FHπ	−20.21	−1.69	5.05	0.00	1.695 (HB)	2.023 (FHπ)	−0.113	−0.235
	23 (HF:**1**:NH_4^+)	lpπ and Cπ	−17.73	−1.45	7.53	2.18	3.037 (lpπ)	2.963 (Cπ)	−0.002	0.013
II	**24** ($HF:NH_4^+$:**2**)	HB and Cπ	−16.26	0.36	0.00	1.05	1.824 (HB)	3.149 (Cπ)	0.016	0.001
	25 ($NH_4^+:FH$:**2**)	HB and FHπ	−13.87	−1.07	2.39	0.00	1.749 (HB)	2.173 (FHπ)	−0.059	−0.272
	26 (HF:**2**:NH_4^+)	lpπ and Cπ	−9.43	−1.17	6.83	1.22	2.895 (lpπ)	3.079 (Cπ)	−0.078	−0.069
III	**27** ($FH:BF_4^-$:**2**)	HB and Aπ	−19.44	0.05	0.00	0.00	1.616 (HB)	3.608 (Aπ)	0.023	0.017
	28 ($BF_4^-:HF$:**2**)	HB and lpπ	−17.24	−1.24	2.20	0.82	1.557 (HB)	2.901 (lpπ)	−0.036	−0.072
	29 (FH:**2**:BF_4^-)	Aπ and FHπ	−9.26	−0.83	10.18	6.05	2.361 (FHπ)	3.519 (Aπ)	−0.084	−0.072
IV	**30** ($FH:BF_4^-$:**3**)	HB and Aπ	−27.93	1.39	0.00	0.00	1.625 (HB)	3.389 (Aπ)	0.032	−0.003
	31 ($BF_4^-:HF$:**3**)	HB and lpπ	−21.21	−2.03	6.72	2.72	1.516 (HB)	2.741 (lpπ)	−0.077	−0.196
	32 (FH:**3**:BF_4^-)	FHπ and Aπ	−13.99	−3.15	13.94	8.77	2.432 (FHπ)	3.349 (Aπ)	−0.504	−0.043
V	**33** ($FCl:BF_4^-$:**3**)	hal. and Aπ	−20.11	0.87	0.00	0.00	2.454 (hal.)	3.388 (Aπ)	0.040	−0.004
	34 ($BF_4^-:ClF$:**3**)	hal. and lpπ	−13.34	−1.62	6.77	1.77	2.350 (hal.)	2.750 (lpπ)	−0.064	−0.081
	35 (FCl:**3**:BF_4^-)	lpπ and Aπ	−13.59	−0.24	6.52	1.68	3.226 (lpπ)	3.361 (Aπ)	−0.115	−0.031
VI	**36** ($FH:HBF_3^-$:**3**)	DH and Aπ	−24.09	1.17	0.00	0.00	1.471 (DH)	3.399 (Aπ)	0.045	−0.004
	37 ($BF_3H^-:HF$:**3**)	DH and lpπ	−18.53	−1.92	5.56	2.69	1.332 (DH)	2.751 (lpπ)	−0.094	−0.186
	38 (FH:**3**:BHF_3^-)	FHπ and Aπ	−15.44	−0.06	7.65	6.43	2.386 (FHπ)	3.356 (Aπ)	−0.550	−0.047

[a] The variation of the equilibrium distances with respect to binary complexes is also summarized (ΔR, Å). Interactions legend: HB: hydrogen bond, Cπ: cation−π, Aπ: anion−π, lpπ: lone pair−π, hal.: halogen bond, DH: dihydrogen bond, and FHπ: F−H/π.

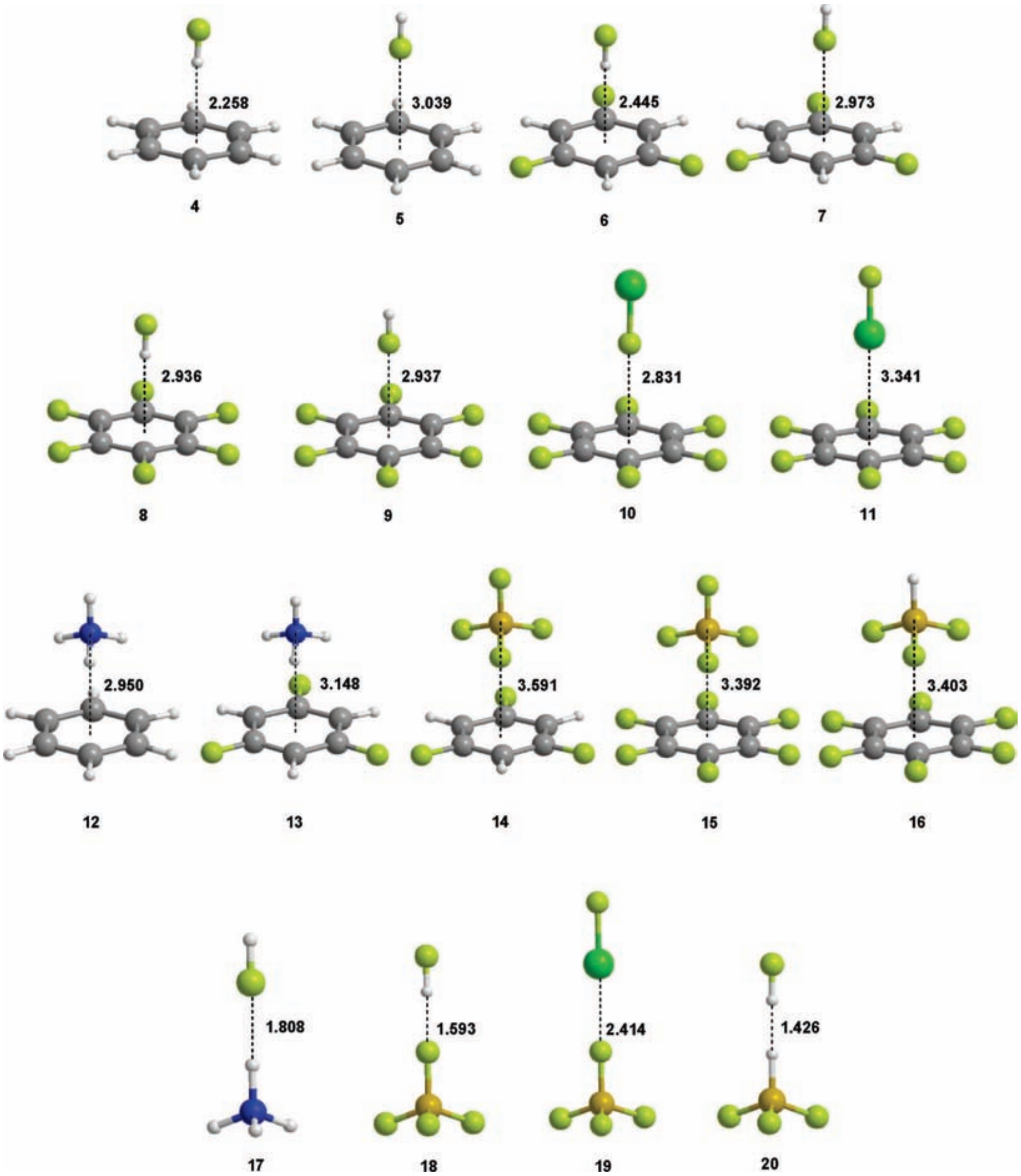


Figure 3. RI-MP2/6−31++G** optimized geometries of complexes **4**−**20**.

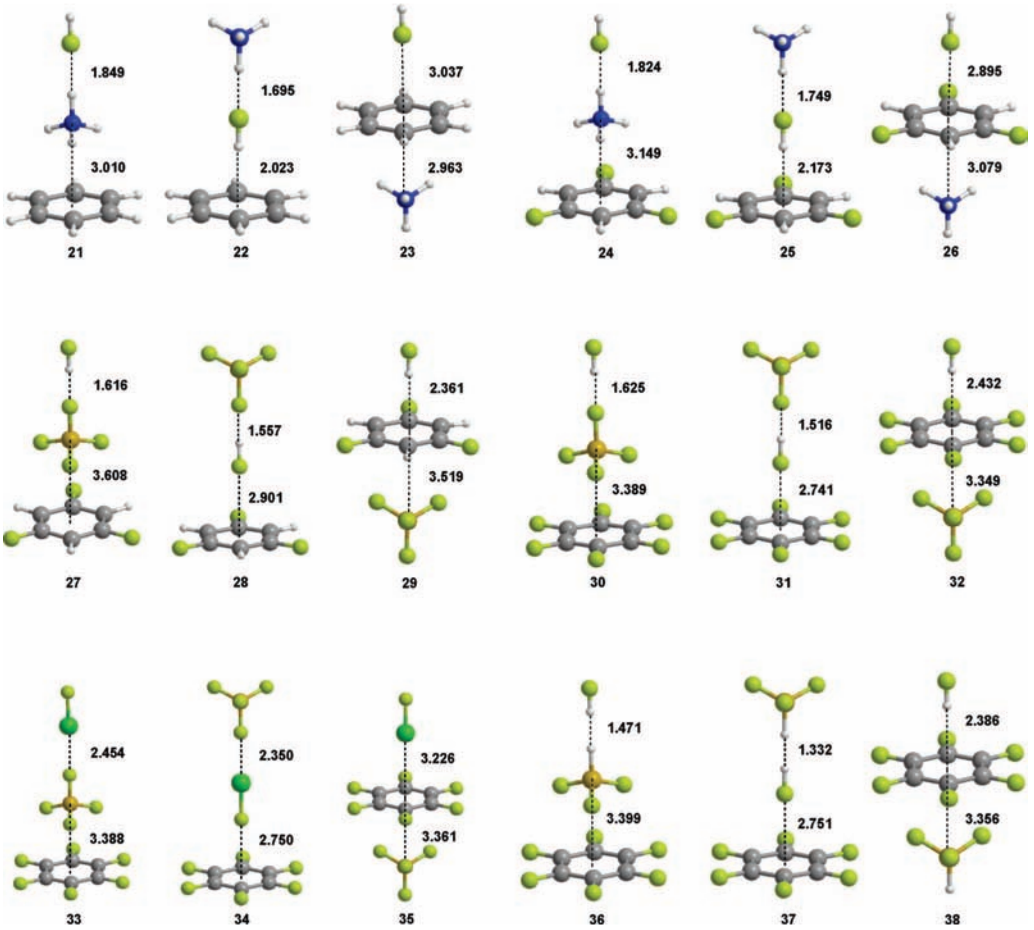


Figure 4. RI-MP2/6−31++G** optimized geometries of complexes **21**−**38**.

confirmed by the shortening of the equilibrium distances with respect to the corresponding binary complexes. A favorable cooperativity is also found in complex **26**, though the interacting energy is considerably lower in energy than **24**. In the next three complexes **27**−**29** (triad **III**), the cation has been changed by an anion, taking advantage of the dual anion/cation-π binding ability of **2**. Again, complex **27** (two strong interactions) is the most favorable but only 2.20 kcal/mol more favorable than **28** (one strong and one modest interaction). This fact is related with the unfavorable cooperativity effect between the noncovalent interactions observed in complex **27** and the favorable cooperativity observed in complex **28**, as deduced by the values of E_{coop} and ΔR. In the next triad of ternary complexes **30**−**32** (triad **IV**), the trifluorobenzene (**2**) has been changed by hexafluorobenzene (**3**). The behavior is parallel to the previous triads of complexes. Complex **30** (two strong interactions) is the most favorable but only 6.7 kcal/mol more favorable than **31** (one strong and one modest interaction). This issue can be explained by means of the divergent values of cooperativity energies observed in complexes **30** and **31**, which are 1.39 and −2.03 kcal/mol, respectively. For this triad of complexes, the most negative value of E_{coop} is observed in complex **32**, where the aromatic ring interacts with the anion by one face and with HF by the other face of the ring. In the next three complexes **33**−**35** (triad **V**), the hydrogen bonding interaction has been changed by a halogen bonding interaction. To achieve this, we have used ClF instead of HF. For this triad of complexes, the difference between the ternary complex **33** that presents two strong interactions and complexes **34** and **35** (only one strong interaction) is small, 6.7 and 6.52 kcal/mol, respectively. The value of E_{coop} is positive in **33** and negative in **34** and **35**, in agreement with the values of ΔR. In this triad the geometric features of the complex characterized by two strong noncovalent interactions (**33**) indicate that the hydrogen bonding weakens ($\Delta R = +0.040$) while the anion−π interactions slightly strengthens ($\Delta R = -0.004$ Å), the global effect gives rise to a unfavorable cooperativity. This behavior is also observed in complexes **30** of triad **IV** and **36** of triad **VI**. Finally, in the last triad of complexes studied here (triad **VI**) a dihydrogen (DH) bond is established between the HF and the anion. Therefore the BF_4^- anion has been changed by BF_3H^- in order to make possible the formation of the DH bond. It can be observed that complex **36**, which is characterized by two strong interactions, is the most stable; however, it has a positive value of cooperativity energy. From the values of ΔR we deduce that the DH bond weakens in the ternary complex with respect to binary complex **20**. A very small shortening of the anion−π distance is observed in **36** with respect to the binary complex **16**. On the contrary, complex **37** has a negative value of cooperativity energy, indicating that both noncovalent interactions present in this complex strengthen. This fact explains the small difference in interaction energy between complexes **36** and **37** (5.5 kcal/mol), taking into account that in complex **37** a very modest lp−π interaction is present. Complex **38** also has a negative cooperativity energy and it is 3 kcal/mol less favorable than **37**, in agreement with a small reinforcement of the interactions as can be deduced by the variation of the equilibrium distances ΔR_1 and ΔR_2.

We have also studied the cooperativity effects in the presence of a continuum model of solvent. In order to investigate the maximum effect of the solvent on the relative energies of each triad of complexes, we have used water. The results are

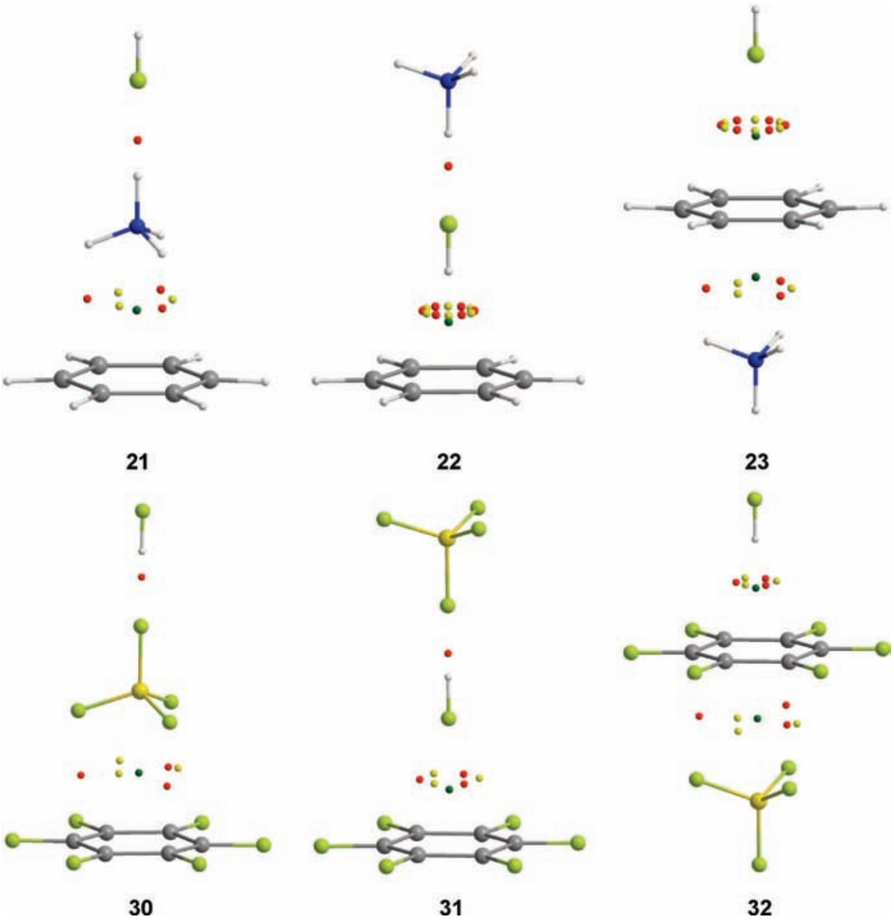


Figure 5. Distribution of critical points (CP) in complexes **21**−**23** and **30**−**32**. Bond CPs are depicted in red, ring CPs in yellow, and cage CPs in green.

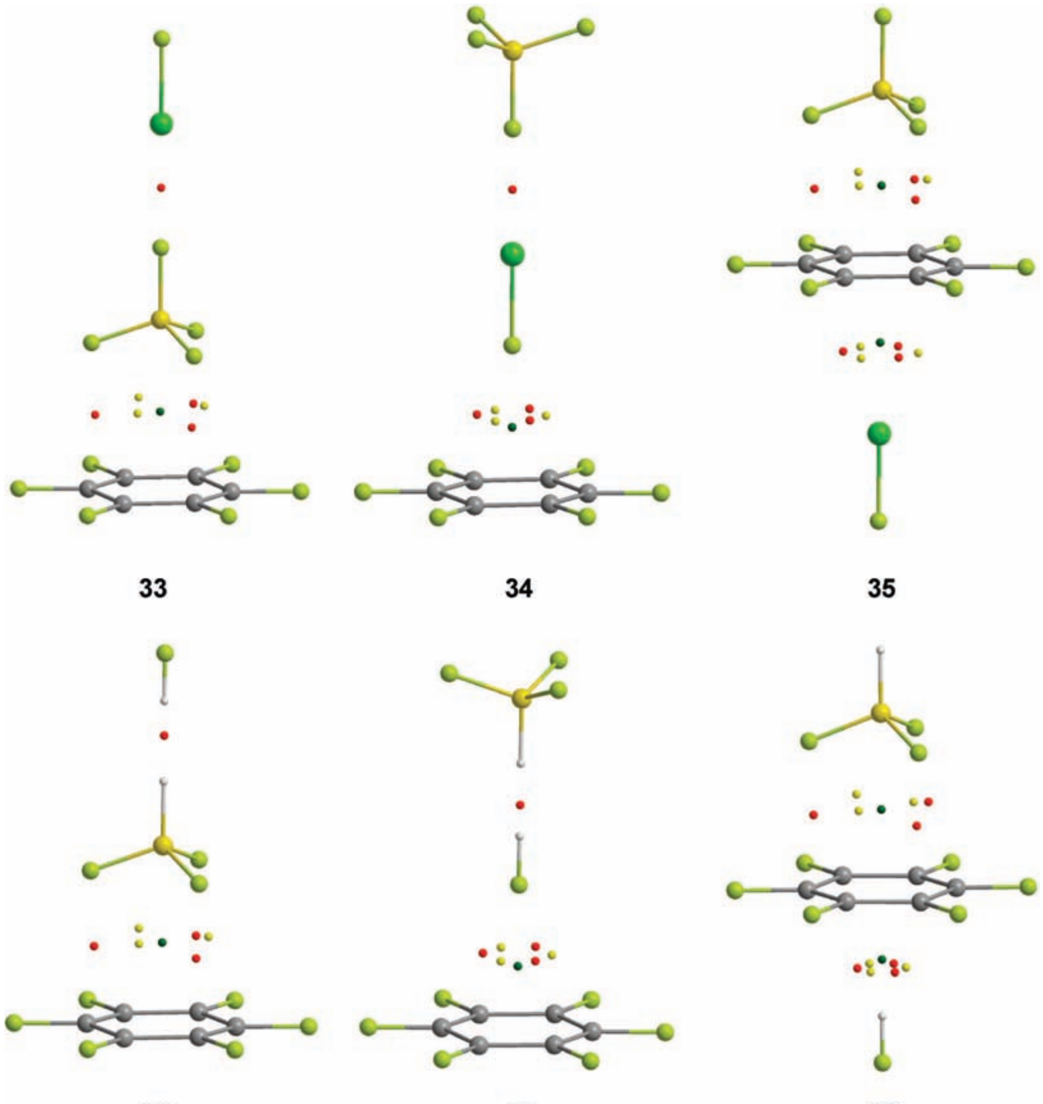
TABLE 3: Electron Charge Density (ρ, a.u.) Values and Their Variation ($\Delta\rho_1$ and $\Delta\rho_2$, a.u.) at the MP2/6-31++G//RI-MP2/6-31++G** Level of Theory Measured at the Bond CP**[a]

triad	compound	interactions	$10^2 \times \rho_1$	$10^2 \times \rho_2$	$10^2 \times \Delta\rho_1$	$10^2 \times \Delta\rho_2$
I	**21** (HF:NH_4^+:**1**)	HB and Cπ	2.2439 (HB)	0.8278 (Cπ)	−0.218	−0.098
	22 (NH_4^+:FH:**1**)	HB and FHπ	3.3219 (HB)	1.0550 (FHπ)	0.860	0.357
	23 (HF:**1**:NH_4^+)	lpπ and Cπ	0.3889 (lpπ)	0.9106 (Cπ)	−0.021	−0.015
II	**24** (HF:NH_4^+:**2**)	HB and Cπ	2.3822 (HB)	0.5488 (Cπ)	−0.079	−0.013
	25 (NH_4^+:FH:**2**)	HB and FHπ	2.8784 (HB)	0.8371 (FHπ)	0.417	0.325
	26 (HF:**2**:NH_4^+)	lpπ and Cπ	0.5139 (lpπ)	0.7587 (Cπ)	0.048	0.197
III	**27** (FH:BF_4^-:**2**)	HB and Aπ	3.9002 (HB)	0.6670(Aπ)	−0.237	−0.065
	28 (BF_4^-:HF:**2**)	HB and lpπ	4.5706 (HB)	0.5409 (lpπ)	0.434	0.075
	29 (FH:**2**:BF_4^-)	Aπ and FHπ	0.6194 (FHπ)	0.7813(Aπ)	0.108	0.050
IV	**30** (FH:BF_4^-:**3**)	HB and Aπ	3.7607 (HB)	0.9725(Aπ)	−0.376	−0.069
	31 (BF_4^-:HF:**3**)	HB and lpπ	5.1390 (HB)	0.7457 (lpπ)	1.002	0.200
	32 (FH:**3**:BF_4^-)	FHπ and Aπ	0.5601 (FHπ)	1.1346(Aπ)	0.065	0.094
V	**33** (FCl:BF_4^-:**3**)	hal. and Aπ	2.3721 (hal.)	0.9966(Aπ)	−0.260	−0.045
	34 (BF_4^-:ClF:**3**)	hal. and lpπ	3.0620 (hal.)	0.7269 (lpπ)	0.430	0.134
	35 (FCl:**3**:BF_4^-)	lpπ and Aπ	0.5281 (lpπ)	1.1076(Aπ)	0.127	0.067
VI	**36** (FH:HBF_3^-:**3**)	DH and Aπ	2.9536(DH)	1.0201(Aπ)	−0.410	−0.074
	37 (BF_3H^-:HF:**3**)	DH and lpπ	4.3045(DH)	0.7316 (lpπ)	0.941	0.196
	38 (FH:**3**:BHF_3^-)	FHπ and Aπ	0.6039 (FHπ)	1.1423(Aπ)	0.109	0.049

[a] Interactions legend: HB: hydrogen bond, Cπ: cation−π, Aπ: anion−π, lpπ: lone pair−π, hal.: halogen bond, DH: dihydrogen bond, and FHπ: F−H/π.

summarized in Table 2, denoted as $E_{\text{rel-w}}$. In general, it can be observed that the differences in binding energies become smaller in water than in vacuo. In addition, for triads **I** and **II**, where cation−π interactions are involved, the synergistically stable complexes turn out to be also the most stable complexes, indicating that the presence of solvent has a very important effect on the relative energy of the complexes, even changing the relative stability of some complexes. For the rest of triads (**III**−**VI**), the general trends observed for the results in vacuo are maintained in water. It is interesting to note than in triad **III**, the difference between complexes **27** and **28** is less than 1 kcal/mol in water.

We have further analyzed the interplay between the interactions using Bader's theory of "atoms in molecules" by comparing the values of the charge density computed at the bond critical points for the ternary complexes to the values of the binary complexes. Because these values have been related to the strength of the interactions and can be used as a measure of the bond order, its variation on going from the binary to ternary



33 **34** **35**

36 **37** **38**

Figure 6. Distribution of critical points (CP) in complexes **33**−**38**. Bond CPs are depicted in red, ring CPs in yellow, and cage CPs in green.

complexes is a good measure of the strengthening or weakening of the interactions.

In Figures 5 and 6 we show the critical points that emerge upon formation of the ternary complexes. A selection of complexes is shown in the figures that covers all type of interactions. The σ interactions (H-bond, DH-bond, and halogen bond) are characterized by the presence of one critical point. The π interactions (ion−π, FH/π, and lp−π interactions) are characterized by the presence of a variable number of bond and ring critical points (see Figures 5 and 6 for details). In addition, the interactions are further described by the presence of one cage critical point that connects the interacting molecule with the center of the aromatic ring. The complexes not shown in Figures 5 and 6 are provided in the Supporting Information (Figure S1).

In Table 3 we summarize the values of electron charge density (ρ, a.u.) computed at the bond critical points for the ternary complexes **21**−**38**. In addition, we also summarize the variation of these values ($\Delta\rho$, a.u.) with respect to values obtained for the binary complexes (see Table 1). A positive value of $\Delta\rho$ means a reinforcement of the interactions because it implies that the value of ρ is greater in ternary than in the binary complexes. The contrary is applicable to negative values of $\Delta\rho$. The values of ρ gathered in Table 3 confirm the general features deduced from the energetic and geometrical results. The complexes where two strong interactions coexist are characterized by negative values of $\Delta\rho$, indicating a weakening of both interactions. In contrast, the synergistically stable complexes are characterized by positive values of $\Delta\rho$, indicating a strengthening of both interactions. Finally, the ternary complexes where the aromatic compound is in the middle interacting with ions/molecules via both faces of the ring are also characterized by positive values of $\Delta\rho$, apart from **23**, indicating a strengthening of both interactions, in agreement with the energetic results of Table 2. A likely explanation for the anomalous behavior of complex **23** is that the related binary complex **5** has a positive value of interaction energy, after applying the BSSE correction. Therefore, the geometric features and AIM analysis of this unstable complex can inadequately influence on the ΔR and $\Delta\rho$ values computed for **23**.

Conclusion

The results reported in this manuscript stress the importance of the interplay between noncovalent interactions in ternary systems. The energetically most favorable combination of the three components (most stable complex) is at the same time the least synergistically favorable complex. This situation provokes that other less intuitive combination of the components (most synergistically stable complex) is also a very favorable situation. In the presence of a continuum model of solvent, some of these synergistically advantageous complexes are also the most energetically favorable, changing the relative order obtained in vacuo. Therefore, unexpected results can be obtained in the presence of solvent, where complexes that are a priori less stable in terms of the interactions involved, become more favorable due to cooperativity effects, which are enhanced in water because the relative energies of the different complexes are reduced.

The synergetic stability can be also understood as a term that balances cooperativity and anticooperativity effects. It is especially useful in multicomponent systems that exhibit intricate combinations of weak intermolecular interactions of various sorts. These effects may be important in different fields, such as supramolecular chemistry and host−guest interactions.

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Supporting Information Available: Figure S1 and the Cartesian coordinates of RI-MP2/6−31++G** optimized structures **1**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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