MP2 Study of the Dual *σ*/*π*−Anion-Binding Affinity of Fluorinated Phthallic Acid Anhydrides

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Several complexes of fluorine-substituted phthallic acid anhydrides with chloride anion have been optimized at the RI-MP2(full)/6-31++G** level of theory. The presence of fluorine atoms attached to the aromatic ring increases the acidity of the aromatic hydrogen atoms. The dual *σ*/*π*-binding affinity of title compounds have been studied by means of ab initio and molecular interaction potential with polarization (MIPp) calculations and Bader's theory of "atoms-in-molecules".

Introduction

Noncovalent interactions are crucial in many areas of modern chemistry, especially in the field of supramolecular chemistry and molecular recognition.[1] Interactions involving aromatic rings are important binding forces in both chemical and biological systems, and they have been reviewed by Meyer et al.[2]

At the same time, Mascal et al.,[3] Alkorta et al.,[4] and our group[5] have demonstrated theoretically that the *π*-interaction of anions with electron deficient aromatic rings is favorable. Our group has used the term "anion−*π*-interaction"[6] to describe the interaction between anions and hexafluorobenzene, where the anion is positioned over the ring along the C_6 axis.[5] The anion−*π*-interaction is dominated by electrostatic and anion-induced polarization terms.[4,5] The strength of the electrostatic component depends upon the value of Q_{zz} and the anion-induced polarization term correlates with the molecular polarizability ($\alpha_{||}$) of the aromatic compound.[7] Recently, anion−*π*-complexes have been observed experimentally, supporting the theoretical predictions and the promising proposal for the use of anion receptors based on anion−*π*-interactions in molecular recognition.[8−12] These interactions are also important in ADN bases like adenine.[13] Moreover, Berryman et al. have reported structural criteria for the design of anion receptors based on the interaction of halides with electron-deficient arenes.[14] Recent excellent reviews deal with anion-binding involving *π*-acidic heteroaromatic rings.[15]

The anion−*π*-binding properties of aromatic rings substituted with electron-withdrawing groups that include a carboxyl group [formula C(=O)X, X = N, O] are scarcely found in the literature. An exception that should be highlighted is the interesting and recent works of Matile's group, where *π*-acidic oligonaphtalendiimide rods have been proposed as transmembrane anion−*π*-slides.[16,17] In this paper, we report a computational study where we analyze the geometrical and energetic features of anion−*π*-complexes of chloride with phthallic anhydride **1** and several fluorinated derivatives **2**−**5**, with an increasing number of fluorine atoms in the structure. These compounds are commercially available and can be considered as potential binding blocks for the design and synthesis of receptors for anions, taking advantage of the reactivity of the acid anhydride group. These compounds are also interesting for studying their dual *σ*/*π*−anion-binding properties. A combined experimental and theoretical study has been recently reported that deals with the structural criteria for the design of anion receptors based on electron-deficient arenes.[14] The presence of electron-withdrawing groups (EWG) increases the acidity of the arene C−H donors and, consequently, it has a double effect. First, the anion can interact via hydrogen bonding with the arene, since the presence of EWG strengthens the C−H···X$^-$ interaction. Second, the anion can also interact with the *π*-cloud of the arene, since the presence of EWG increases the *π*-acidity of the ring. A recent related work of Weber's group reports interesting experimental results regarding the dual *σ*/*π*-binding affinity of fluorinated benzenes with several anions.[18]

Theoretical Methods

The geometry of all the complexes included in this study was fully optimized at the RI-MP2/6-31++G** level of theory within the program TURBOMOLE, version 5.7.[19] The RI-MP2 method[20,21] 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.[22,23] 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.[24] No symmetry constrains have been imposed in the optimizations, and all compounds and complexes belong to the C_1 symmetry point group.

The contributions to the total interaction energy have been computed using the molecular interaction potential with polarization (MIPp) methodology,[25] which is an improved generalization of the molecular electrostatic potential (MEP), where three terms contribute to the interaction energy: (i) an electrostatic term identical to the MEP,[26] (ii) a classical dispersion−repulsion term, and (iii) a polarization term derived from perturbation theory[27] Calculation of the MIPp of **1**−**5** with Cl$^-$ was performed using the HF/6-31++G**//RI-MP2(full)/6-31++G** wavefunction of the aromatic rings by means of the

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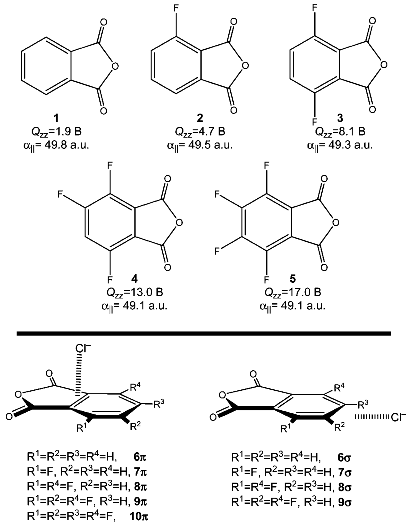


Figure 1. Top: Phthallic acid anhydride **1** and its fluorinated derivatives **2**−**5**. Bottom: anion−π/σ-complexes **6**−**10**.

TABLE 1: Interaction Energies at the RI-MP2(full)/6-31++G Level of Theory without and with the BSSE Corrections (E and E_{BSSE}, kcal/mol) and Equilibrium Distances from Cl^- to the Middle of the C−C(O) Bond (R_e, Å) for Anion−π-Complexes 6π−10π and from Cl^- to the Hydrogen Atom for σ-Complexes 6σ−9σ and the Computed Merz−Kollman Charge of Cl^- (q) for Both σ- and π-Complexes**

compd	E	E_{BSSE}	R_e	q (e)
6π	−16.90	−10.10	2.866	−0.83
6σ	−21.22	−17.84	2.610[a]	−0.95
7π	−19.73	−12.72	2.836	−0.82
7σ	−23.48	−19.88	2.559[a]	−0.94
8π	−22.87	−15.12	2.854	−0.81
8σ	−25.88	−22.06	2.537[a]	−0.93
9π	−25.57	−18.04	2.797	−0.80
9σ	−24.33	−19.84	2.110	−0.91
10π	−28.32	−20.83	2.839	−0.80

[a] R_e is the mean distance of two C−H···Cl^- distances.

MOPETE-98 program.[28] Calculations of MIPp using the MP2 wavefunction are not available.[25] The ionic van de Waals parameters for Cl^- were taken from the literature.[29]

The topological analysis of the electron charge density performed for the complexes of **1**−**5** with Cl^- was determined using Bader's theory of "atoms-in-molecules" (AIM).[30] The electronic density analysis was performed using the AIM2000 program[31] at the MP2//RI-MP2 level of theory. The quadrupole moment of compounds **1**−**5** was computed using the CADPAC program[32] at the MP2/6-31G* level, since previous studies[33] have demonstrated that quantitative results are obtained at this level of theory.

Results and Discussion

Energetic and Geometrical Details. Table 1 reports the energies and equilibrium distances corresponding to the interaction of **1**−**5** with chloride via either hydrogen bonding (**6**σ−**9**σ) or anion−π (**6**π−**10**π) binding modes, apart from **5**, where only the π-complex has been studied, since it does not have hydrogen atoms in the molecule. For all complexes, the interaction energies are large and negative, indicating that the interaction of chloride with phthallic acid anhydrides **1**−**5** is favorable. From the inspection of the energetic results, several interesting points arise. First, the interaction energy of the σ-complexes **6**σ−**8**σ increases as the number of fluorine atoms increases, indicating that the presence of electron-withdrawing substituents augments the acidity of arene C−H donors. In complex **9**σ, the interaction energy is less favorable than in **8**σ, because the Cl^- interacts only with one hydrogen atom instead of two. In spite of this, the interaction energies of complexes **8**σ and **9**σ are similar, indicating that the acidity of the C−H bond in **9**σ is higher than **8**σ. Second, the interaction energy of the anion−π-complexes **6**π−**10**π also increases as the number of fluorine substituents increases. These results can be related to the value of the quadrupole moment of compounds **1**−**5**, which varies from 1.9 B for **1** to 16.9 B for **5** (see Figure 1). As stated in the introduction, the strength of the anion−π interaction depends upon the value of the Q_{zz} and the molecular polarizability of the arene. The effect of adding fluorine substituents progressively augments the value of Q_{zz} and, conversely, the values of $\alpha_{||}$ are almost constant (see Figure 1). Third, the BSSE correction alters the energetic order of complexes **9**π and **9**σ. This is due to the fact that both complexes have very similar interaction energies without the BSSE correction and that the BSSE values computed for π-complexes are, in all cases, greater in magnitude than the values computed for σ-complexes. A likely explanation is that the geometry of the anion−π-complex (the anion interacting with several carbon atoms) allows a larger basis set superposition than the geometry of the σ-complex (the anion interacting with one hydrogen atom in **9**σ).

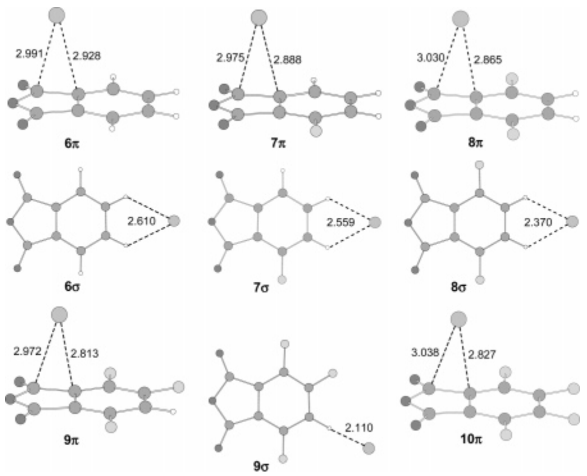


Figure 2. RI-MP2(full)/6-31++G**-optimized complexes **6**−**10**. Distances in Å.

TABLE 2: Contributions to the Total Interaction Energy (kcal mol^{-1}) Calculated with MIP_P for 1−5 Interacting with Cl^- at the Minima Located above the Molecular Plane (π) and at the Molecular Plane (σ)[a]

compd	E_e	E_p	E_{vw}	E_t	E_{MP2}
1π+**Cl**$^-$	−7.35	−10.26	0.75	−16.86	−16.90
1σ+**Cl**$^-$	−15.10	−4.57	0.42	−19.25	−21.22
2π+**Cl**$^-$	−10.35	−10.20	0.70	−19.85	−19.73
2σ+**Cl**$^-$	−18.16	−5.25	1.90	−21.51	−23.48
3π+**Cl**$^-$	−13.34	−10.12	0.72	−22.74	−22.87
3σ+**Cl**$^-$	−21.25	−5.77	3.68	−23.34	−25.88
4π+**Cl**$^-$	−16.97	−9.62	0.29	−26.30	−25.57
4σ+**Cl**$^-$	−17.91	−5.30	1.15	−22.06	−24.33
5π+**Cl**$^-$	−20.41	−9.52	0.18	−29.76	−28.32

[a] For comparison purposes the binding energies of complexes **6**−**10** at the RI-MP2(full)/6-31++G** level are included.

In Table 1, we also include the charge of Cl^- in the complexes in order to study charge-transfer effects. We have used the Merz−Kollman scheme for deriving atomic charges, because it has been reported that this method provides high quality

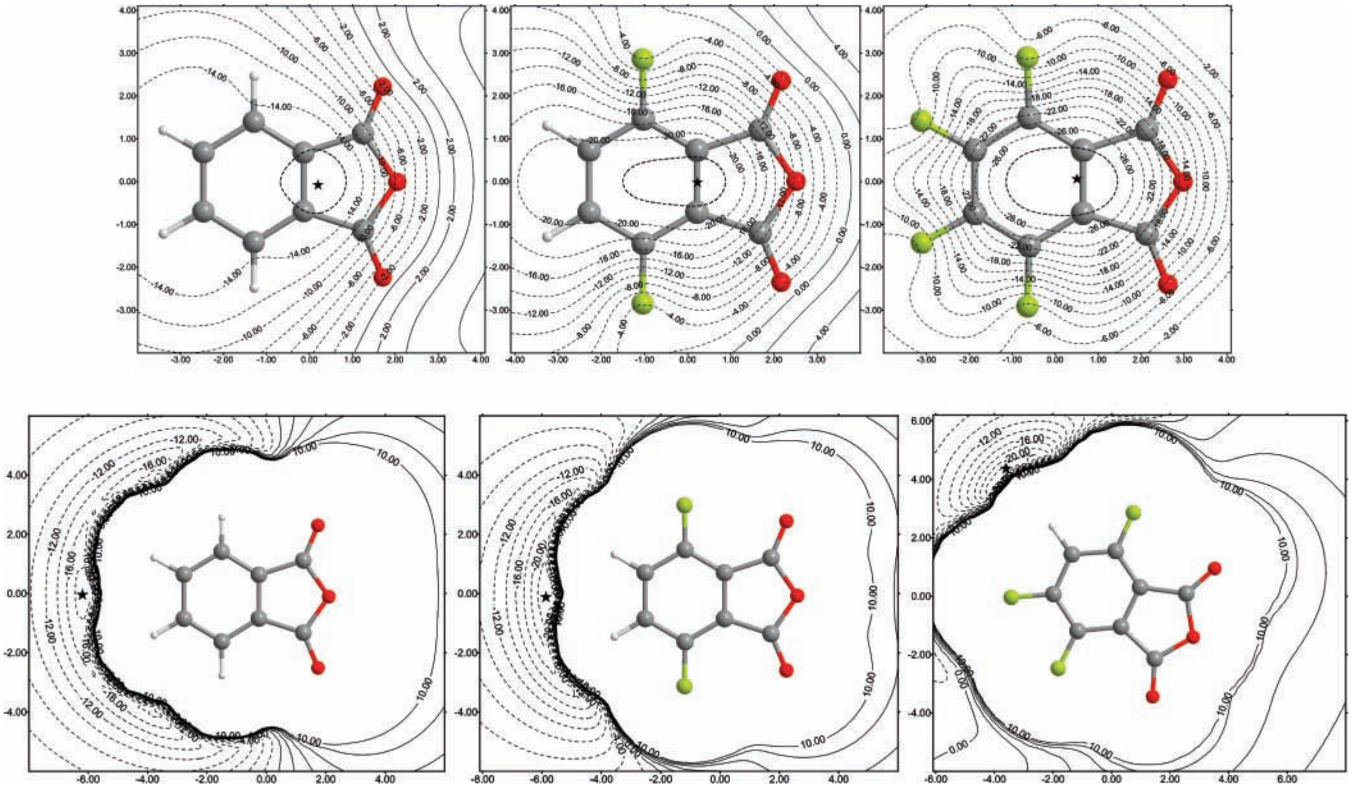
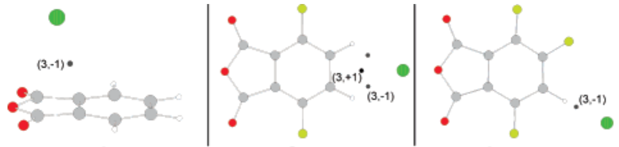


Figure 3. Top: 2D-MIPp(Cl$^-$) energy maps computed for **1**, **3**, and **5** computed at 3 Å above the molecular plane. Isocontour lines are plotted every 2 kcal/mol. Dashed lines correspond to negative values and solid lines to positive values of the potential energy. The minimum is represented by a star. Axes units are Å and energies in kcal/mol. Bottom: 2D-MIPp(Cl$^-$) energy maps computed for **1**, **3**, and **4** computed at the molecular plane. Isocontour lines are plotted every 2 kcal/mol. Dashed lines correspond to negative values and solid lines to positive values of the potential energy. The minimum is represented by a star.



6π **8σ** **9σ**

Figure 4. Schematic representation of the critical points that emerge upon complexation of the anion for complexes **6**π, **8**σ, and **9**σ.

charges.[34] It can be observed that the charge transfer in anion−π-complexes is about 0.2 e and it increases as the level of fluorination increases. Moreover, charge-transfer effects are less important (<0.1 e) in σ-complexes and the variation trend is parallel to that of the π-complexes.

The geometries of complexes **6**−**10** are represented in Figure 2. For the anion−π-complexes, it can be observed that the chloride anion is not located over the center of the aromatic ring. In all cases, it is located above the C−C(O) bond. In the unfluorinated phthallic acid anhydride complex **6**π, it is positioned almost equidistant from both carbon atoms of the bond. As the number of fluorine substituents increases, the chloride anion slightly moves to the aromatic carbon atom. For hydrogen-bonded complexes **6**σ−**8**σ the Cl$^-$ interacts simultaneously with two hydrogen atoms. Bifurcated hydrogen bonds to two neighboring CH groups are energetically favored over linear hydrogen bonds to a single CH group, in agreement with experimental results in unfluorinated[35] and fluorinated benzenes.[18] The mean distance measured from the chloride anion to two hydrogen atoms shortens as the number of fluorine substituents increases, indicating an augmentation of the acidity. For complex **9**σ, the equilibrium distance is the shortest because the chloride anion interacts with the single hydrogen atom.

TABLE 3: Electron Density (ρ) and Its Laplacian ($\nabla^2\rho$) in Atomics Units at the Critical Points (CP) Originated upon Complexation and the Number (n) of Each CP in the Complex

compd	n	CP	$10^2\rho$	$10^2\nabla^2\rho$
6π	1	(3, −1)	1.7935	5.6690
6σ	2	(3, −1)	1.2410	4.2127
	1	(3, +1)	0.7984	3.7885
7π	1	(3, −1)	1.9227	5.9773
7σ	2	(3, −1)	1.3323	4.5018
	1	(3, +1)	0.8517	4.1040
8π	1	(3, −1)	2.0265	6.1471
8σ	2	(3, −1)	1.4289	4.8043
	1	(3, +1)	0.9141	4.4568
9π	1	(3, −1)	2.2238	6.5894
9σ	1	(3, −1)	3.0803	7.3545
10π	1	(3, −1)	2.1832	6.5113

MIPp Analysis. With the purpose of analyzing the nature of the anion−π/σ-interaction in the phthallic acid anhydride and its fluorine-substituted derivatives and understanding the importance of electrostatic and polarization terms, we have performed the calculation of MIPp of **1**−**5** interacting with Cl$^-$ using the HF/6-31++G**//RI-MP2(full)/6-31++G** wavefunction. In the calculation, the Cl$^-$ ion was considered as a classical nonpolarizable particle. In Figure 3 we represent the bidimensional MIPp (2D-MIPp) maps obtained for **1**−**5**. For compounds **1**−**4**, we have computed two 2D-MIPp maps, one at the molecular plane and the other at 3.0 Å over the molecular plane and parallel to it, in order to study the anion-binding ability of **1**−**4**, first via hydrogen bonding using the hydrogen atoms of the ring and, second, via an anion−π-interaction, respectively. For compound **5**, we have only computed the 2D-MIPp maps at 3.0 Å over the molecular plane. For compounds **1**−**3**, the

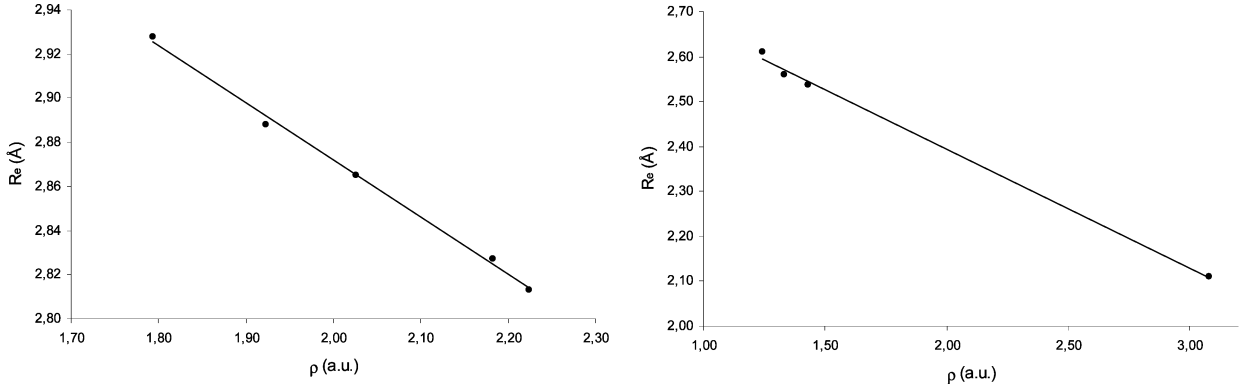


Figure 5. Regression plots between the charge density ρ ($\times 10^2$) at the bond critical point and the equilibrium distances R_e of the anion−π (left) complexes **6**π−**10**π and anion−σ (right) complexes **6**σ−**9**σ.

2D-MIPp energy maps computed at the molecular plane presents one global minimum as a result of the interaction of Cl^- with two hydrogen atoms. The energy of these minima varies from −19.25 kcal/mol of **1** to −23.34 kcal/mol of **3** (see Table 2). For compound **4**, the 2D-MIPp energy map computed at the molecular plane presents one global minimum as a result of the interaction of Cl^- with the single hydrogen atom. The 2D-MIPp energy maps computed over the molecular plane present a unique global minimum located approximately over the center of the C−C common bond of the two rings. The energy at the minimum varies from −16.86 kcal/mol for **1** to −29.76 kcal/mol for **5** (see Table 2). It is worth mentioning that the position of the MIPp minimum in the 2D-MIPp maps computed at the molecular plane agrees with the geometry of the optimized complexes **6**σ−**9**σ. In addition, the interaction energy computed at the MIPp minimum is similar to the complexation energy computed at the RI-MP2/6-31++G** level of theory, which gives reliability to the MIPp method. In contrast, the position of the MIPp minimum in the 2D-MIPp maps computed at 3.0 Å above the molecular plane does not coincide with the position of Cl^- in the optimized complexes. It should be mentioned that the potential energy surface is very flat. The interaction energies computed at the MIPp minimum and at the position that the Cl^- adopts in the complex are very similar, as can be deduced by the topology of the lowest isocountour line in the 2D-MIPp maps. A likely explanation of the disagreement between the location of the MIPp minima and the geometry of the optimized complexes is that the MIPp analysis has been performed using the HF wavefunction, since it is a requirement of the MOPETE program, and the complexes have been computed using the RI-MP2 method. To verify this hypothesis, we have computed the complexes at the HF/6-31++G** level of theory and the position of the anion coincides with the location of the MIPp minimum. It is interesting to note the variation of the lowest contour size in the 2D-MIPp maps (dashed bold line) with the level of fluorination. In **1** (Figure 3, top left), it is mainly located over the five-membered ring. Conversely, for compounds **3** (top, middle) and **5** (top, right), the lowest isopotential contour line includes both rings and for the most part the six-membered ring.

In order to understand the physical nature of the anion−π/σ-bonding in **1**−**5** interacting with Cl^-, we have explored the electrostatic (E_e), polarization (E_p), van der Waals (E_{vw}), and total (E_t) interaction energies at the MIPp minima. The results, summarized in Table 2, point out the importance of the electrostatic contribution to the total interaction energy in the σ-complexes. As the number of fluorine atoms increases, the E_e term becomes more negative, whereas the E_p term does not vary. In the π-complexes, the polarization term is very important, specially in compounds **1**π, **2**π, and **3**π. The energetic value of the electrostatic term increases as the number of fluorine atoms increases and it clearly dominates the interaction in **5**π. The MIPp energy at the minimum agrees well with the binding energy computed at the RI-MP2 level of theory without he BSSE correction, which is also included in Table 2 for comparison purposes.

AIM Analysis. Topological analysis of the charge density ρ(r) distribution and properties of critical points (CP) were determined for complexes **6**−**10** using Bader's theory of "atoms-in-molecules", which provides an unambiguous definition of chemical bonding,[36] using the MP2(full)/6-31++G** wavefunction. The AIM theory has been successfully used to characterize anion−π interactions.[5,7] For complexes **6**σ−**8**σ, the exploration of the CPs revealed the presence of two bond CPs that connect the anion with two hydrogen atoms. As a consequence of the geometry of the complexes, one ring CP is also generated. In Figure 4 we represent the distribution of CPs that are generated upon complexation of the anion in complex **8**σ, as a representative example of σ-complexes **6**σ−**8**σ (see Figure 4, middle). For complex **9**σ, the exploration of the CPs revealed the presence of one (3, −1) CP that connects the anion with one hydrogen atom (see Figure 4, right). For complexes **6**π−**10**π, the exploration of the CPs revealed the presence of only one bond CP that connects the anion with one carbon atom of the ring (see Figure 4, left). Quantitative values for ρ(r) and $\nabla^2\rho$(r) at the CPs give hints on the character and strength of the interaction. The Laplacian of the (3, −1) CPs is positive, indicating a depletion of the electron density, as is common in closed-shell interactions. For each series of complexes (π and σ) the interaction energies correlates with the values of ρ(r) at the cage/bond CPs (see Table 3). We have found an interesting and strong ($r^2 = 0.998$) relationship between the charge density at the bond CP and the equilibrium distances of the complexes for each series (see Figure 5). These relationships indicate that the value of the charge density at the bond CP can be used as a measure of bond order in both interactions. These linear correlations are probably due to the small range of distances present in these complexes. An exponential relationship is expected in a large range of distances.[37]

Conclusion

In summary, results derived from this study reveal that the perfluorinated phthallic acid anhydride **5** is a promising binding block for the design and synthesis of anion receptors. We have studied the dual σ/π-binding ability of the fluorinated derivatives of phthallic acid anhydride **1** and we have demonstrated that both interactions strengthen as the level of fluorination increases. The MIPp analysis indicates that the polarization effects are more important in anion−π than in hydrogen-bonding complexes and that the latter are more directional than the former. Finally, from the AIM analysis, we learn that the value of the charge density at the bond CP is a good measure of the bond order of both interactions.

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Supporting Information Available: Cartesian coordinates of RI-MP2/6-31++G**-optimized structures **1**−**5**, and anion−π/σ-complexes **6**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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