Anion Binding Involving π-Acidic Heteroaromatic Rings

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ABSTRACT

Anions are essential species in biological systems and, particularly, in enzyme–substrate recognition. Therefore, the design and preparation of anion receptors is a topical field of supramolecular chemistry. Most host–guest systems successfully developed are based on noncovalent (ionic and hydrogen-bonded) interactions between anions and ammonium-type functionalities or Lewis acid groups. However, since the past 5 years, an alternative route toward the synthesis of efficient anion hosts has emerged, namely, the use of "anion–π" interactions involving nitrogen-containing electron-deficient aromatic rings, as the result of several favorable theoretical investigations. In this Account, the state of the (new) art in this growing area of anion-binding research is presented and several selected examples from our work and that of other groups will be discussed.

1. Introduction

Anions are omnipresent in biological systems, where they often play a crucial role.[1] For instance, more than two-thirds of enzyme substrates and cofactors are anionic.[2] Recently, it has been shown that the chloride channels do not only contribute in stabilizing the membrane potential but are also involved in a number of essential physiological and cellular tasks, such as the regulation of pH, volume homeostasis, organic solute transport, cell migration, cell proliferation, and cell differentiation.[3] Thus, the malfunction of these channels causes diseases, such as cystic fibrosis.[4] Therefore, a better understanding of the biochemical mechanisms of anion recognition is of prime importance to conceive efficient synthetic anion receptors for potential medicinal applications. In addition, anions such as phosphate and nitrate are largely incriminated as pollutants of drinking water.[5] Hence, anion-binding systems may be used as well for environmental purposes.

In 1968, Simmons and Park described the first example of a host system for a guest chloride anion.[6–8] A total of 10 years later, Lehn et al. reported a similar bicyclic azacryptand, i.e., [bis-tren](ClO$_4$)$_6$, capable of binding a linear azide anion through its six protonated amine functions (Figure 1).[9] Since these pioneering discoveries, the field of anion recognition has received increasing attention from the scientific community.[10] On the basis of the initial findings of Lehn et al., most anion receptors reported in the literature historically take advantage of the negative character of anions and thus contain positively charged and/or hydrogen-bond donor groups.[11,12] This approach has been extensively exploited, so that a number of topical reviews have been published in the past 2 years.[13–16]

Since 2004, a potential alternative strategy for the preparation of anion hosts involving supramolecular interactions has emerged[17,18] from earlier fundamental computational studies carried out by Alkorta et al.[19] Indeed, for the first time, theoretical calculations have shown that an electron-donor molecule, such as HF (through its F atom), can experience favorable binding

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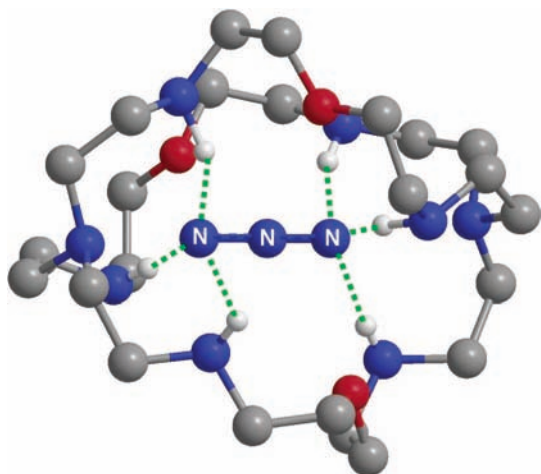
FIGURE 1. Schematic representation of the [bis-tren(N_3)]$^{5+}$ inclusion compound reported by Lehn et al. Only the hydogen atoms involved in hydrogen-bonding interactions with the azide anion are shown for clarity.[9]

interactions with the π cloud of an electron-deficient aromatic ring, namely, hexafluorobenzene.[19] In contrast to cation–π interactions,[20] anion–π interactions are expected to be repulsive. However, theoretical investigations have clearly established the potential binding interactions between a negatively charged species and an electron-poor π system.[21] These theoretical results have greatly encouraged the exploration of anion molecular recognition by aromatic systems.[22] This Account provides an overview of theoretical studies and experimental examples of anion–π interactions, a rapidly rising new area of supramolecular chemistry. Finally, the relevance of such anion–π contacts in biological processes is examined.

2. Theoretical Investigations on Anion–π Interactions

In 1997, Alkorta and co-workers reported the first density functional theory (DFT) calculations, revealing favorable binding interactions between an electron-rich molecule, i.e., HF, and an electron-deficient aromatic ring, namely, hexafluorobenzene.[19] These studies led to a calculated distance r between the interacting atom to the center of the aromatic ring (centroid) of 3.127 Å and a binding energy E_{I+BSSE} of -5 kJ mol^{-1} (Figure 2).

The potential existence of interactions between π-electron aromatic species and anions was suggested by nuclear magnetic resonance (NMR) studies reported by Schneider and co-workers 15 years ago.[23] It thus appeared that diphenylamine (**1**) could form 1:1 host/guest complexes with both the dication **2** and the dianion **3** (Figure 3).[23] Indeed, *complexation-induced shifts* (CIS) for the guest molecule **1** are observed in the NMR spectra of complexes **1** ⋯ **2** and **1** ⋯ **3**, which allow us to establish $\Delta G_{host–guest}$ (binding energy) values of 25 and 22 kJ mol^{-1}, respectively. These values clearly indicate that the association of **1** with the dianion **3** is almost as stable as the one with the dication **2**.[24]

A total of 1 decade later, the interest in anion–π interactions suddenly rose and several concurrent detailed model-
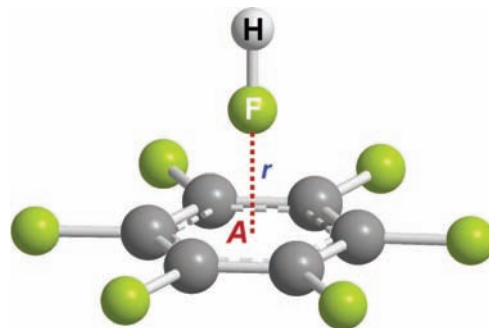
FIGURE 2. Optimized geometry of a complex [C_6F_6 ⋯ HF] using a hybrid HF/DFT method with the 6-311++G** basis set. $r = 3.127$ Å, and the interaction energy $E_{I+BSSE} = -5$ kJ mol^{-1}.[19]

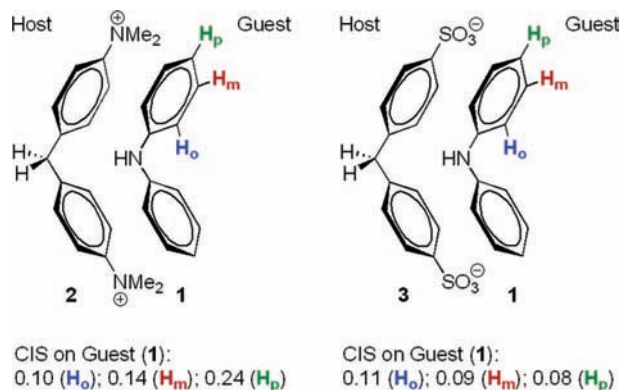CIS on Guest (**1**):
0.10 (**H_o**); 0.14 (**H_m**); 0.24 (**H_p**)

CIS on Guest (**1**):
0.11 (**H_o**); 0.09 (**H_m**); 0.08 (**H_p**)

FIGURE 3. CIS values for the supramolecular complexes **1** ⋯ **2** and **1** ⋯ **3**.[23]

Table 1. Calculated^a Binding Energies ΔE_{BSSE} (kJ mol^{-1}) and Centroid–Anion Distances r (Å) for Cl–π Complexes

aromatic host	ΔE_{BSSE}[b]	r	reference
1,3,5-triazine	-20	3.2	21
2,4,6-trifluoro-1,3,5-triazine	-62	3.0	21
hexafluorobenzene	-53	3.159	25
pentafluoropyridine	-59	3.092	25
tetrafluorofuran	-38	3.106	25
tetrafluorothiophene	-34	3.252	25
octafluoronaphthalene	-72	3.056^c	25
1,3,5-trinitrobenzene	-82^d	3.27	26

^{a} Calculated at the MP2 level. ^{b} BSSE stands for basis set superposition error. ^{c} The anion is located over the carbon atoms linking the two rings. ^{d} Optimized at the Hartree–Fock level.

ing studies on such supramolecular pairings appeared in the literature. Thus, in 2002, three outstanding computational investigations were reported almost simultaneously by Mascal et al.,[21] Alkorta et al.,[25] and Deya et al.[26] These calculations ascertained favorable noncovalent binding interactions between several anions and the aryl centroid of π-acidic aromatic rings. For instance, values of binding energies and host ⋯ guest distances for [chloride ⋯ (electron-deficient ring)] complexes are listed in Table 1, showing that this type of attractive interaction is comparable to a moderate–strong hydrogen bond (i.e., 16–60 kJ mol^{-1}).

After these initial encouraging results, more comprehensive theoretical investigations have been performed, and the aromatic rings as well as the anions considered for these calculations are depicted in Figure 4. In all cases,
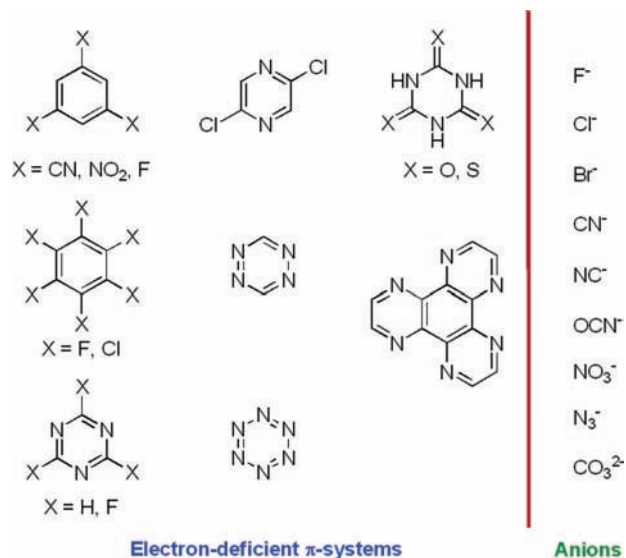
FIGURE 4. Non-exhaustive list of electron-deficient rings and anions taken into account for the computational estimation of their potential binding interactions.[21,25–37]

favorable binding interactions have been theoretically predicted.[21,25–37]

Lately, Clements and Lewis[38] have reported important results of a quantum mechanical study that supports earlier statements of Deya and Frontera.[33] Indeed, it has been theoretically demonstrated that haloaromatics, with negative molecular quadrupole moments (symbolized as Θ_{zz}), can experience attractive interactions with anions, albeit very weak (compared to electron-poor π rings).[38] This computational study thus suggests that not only electron-poor aromatic rings but also electron-rich aromatics can lead to binding contacts with anions. These findings are of great value regarding biochemical processes because aromatic groups are generally found in the active site of enzymes (see section 4).

3. Experimental Evidences of Anion–π Interactions

In 2004, the first crystallographic evidences of anion recognition by aromatic receptors had been described.[17,18] These ground-breaking experimental proofs of anion–π interactions have certainly promoted interest in this new field of supramolecular chemistry, and new examples of such supramolecular complexes are now regularly reported in the literature.

3.1. Solid-State Evidences. Meyer et al. reported crystallographic proofs of anion$\cdots\pi$ contacts involving the electron-deficient s-triazine ring.[17] The reaction of 3 equiv of copper(II) chloride with 1 equiv of the ligand dpyatriz[39] in methanol/dichloromethane gives dark green crystals of [Cu₃(dpyatriz)₂Cl₃][CuCl₄]Cl (Figure 5a). This compound exhibits remarkable structural features that are the attractive contacts between tetrachloridocuprate and chloride anions with triazine moieties (parts b and c of Figure 5, respectively). The value of the experimental Cl$\cdots$centroid distance, i.e., 3.170 Å (Figure 5c), is close to the theoretically predicted one (3.2 Å; Table 1).[21]
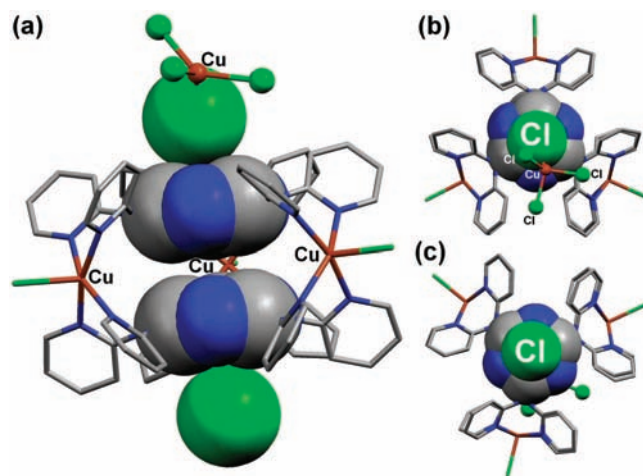

FIGURE 5. (a) [Cu₃(dpyatriz)₂Cl₃][CuCl₄]Cl complex.[17] (b) Top view showing the Cl₃Cu–Cl$\cdots$triazine interaction (Cl$\cdots$centroid distance of 3.112 Å). (c) Top view showing the Cl$\cdots$triazine interaction (Cl$\cdots$centroid distance of 3.170 Å).
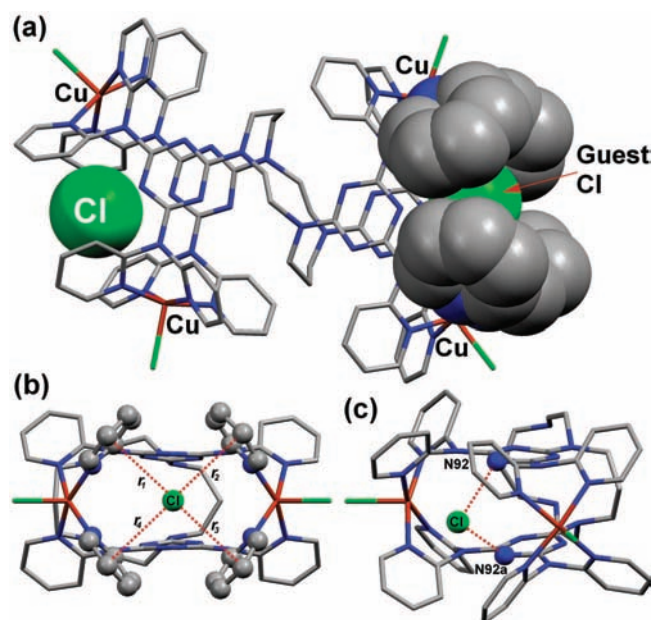

FIGURE 6. (a) Representation of the cation [Cu₄(azadendtriz)Cl₄]⁴⁺ revealing the host basket.[40] (b) Distances between the pyridine centroids and the chloride ion: r_1 = 3.525 Å, r_2 = 3.555 Å, r_3 = 3.555 Å, and r_4 = 3.525 Å. (c) Triazine nitrogen atom N92 and the chloride guest are separated by a distance of 3.012 Å.

Almost simultaneously, some of us described an outstanding supramolecular system formed by four pyridine units able to host an electron-rich guest molecule (Figure 6).[18] The reaction of copper(II) chloride with the ligand azadendtriz[40] in dichloromethane/water produces the tetracopper complex [Cu₄(azadendtriz)Cl₄]Cl₄(H₂O)₁₃ (Figure 6a). The coordination of the 16 pyridines from the dendritic ligand azadendtriz to four copper ions generates two cavities occupied by two chloride anions. Each chloride sitting in a "molecular basket" is in close contact with four pyridine rings (Figure 6b), with centroid$\cdots$Cl distances ranging from 3.5 to 3.7 Å.[18] These contact distances are somewhat longer than the values determined by theoretical calculations for electron-poor aromatics
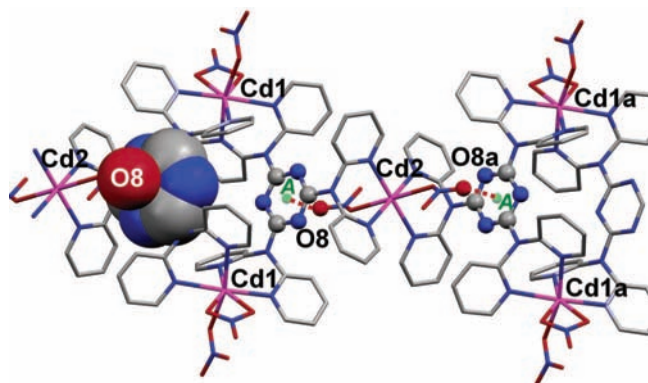
FIGURE 7. Representation of the 1D coordination polymer, generated from $[Cd_3(dpyatriz)_2(NO_3)_6]$ building blocks.[55] Distance between the triazine centroid *A* and the oxygen atom O8 of a coordinated nitrate $r = 3.26$ Å.

(Table 1). Anion–pyridine interactions have not been investigated thus far, but larger anion ··· centroid separations are logically expected, because the pyridine ring is less electron-deficient than aromatic derivatives, such as 1,3,5-triazine or hexafluorobenzene. However, it has to be noted that the electron-poor character of the pyridine moieties is enhanced by their coordination to the metal centers.

This outstanding result has encouraged new triazine-based ligands to be designed,[41] and their potential anion ··· triazine interactions have been investigated.[42] For instance, the reaction of cadmium(II) nitrate with dpyatriz[39] in acetonitrile at 105 °C in a pressure tube yields a one-dimensional coordination polymer, depicted in Figure 7. This polymeric chain is built from trinuclear $[Cd_3(dpyatriz)_2(NO_3)_6]$ units, which are linked via the Cd2 atom (Figure 7). This Cd2 atom is indeed coordinated to a second dipyridylamine moiety belonging to an adjacent trinuclear building block. Interestingly, these connections are further stabilized by nitrate–triazine interactions. The oxygen atoms O8 and O8a of the two nitrate anions axially coordinated to Cd2 are interacting with neighboring triazine rings (centroid ··· O8 distance of 3.26 Å; Figure 7). However, in the present example, one can sensibly assume that the nitrate–triazine interactions are facilitated by the fact that the anions are coordinated to the metal centers, thus forcing the anion–π contacts. The occurrence of such attractive interactions involving *free* nitrates is necessary to confirm this observation. Therefore, further investigations with nitrate metal salts and triazine-based ligands have been carried out.

The reaction of 3 equiv of zinc(II) nitrate with 1 equiv of the ligand dipicatriz[39] leads to the trinuclear complex $[Zn_3(dipicatriz)(NO_3)_6]$ (Figure 8a).[43] As expected, this compound exhibits anion–π interactions. Actually, two nitrate ions, coordinated to two different zinc atoms, interact with the same triazine ring (on each face of the aromatic ring; Figure 8b). As for the cadmium coordination polymer described above, the interactions involve coordinated nitrates; nevertheless, this result represents a very rare case[44] of anion–π–anion interactions.
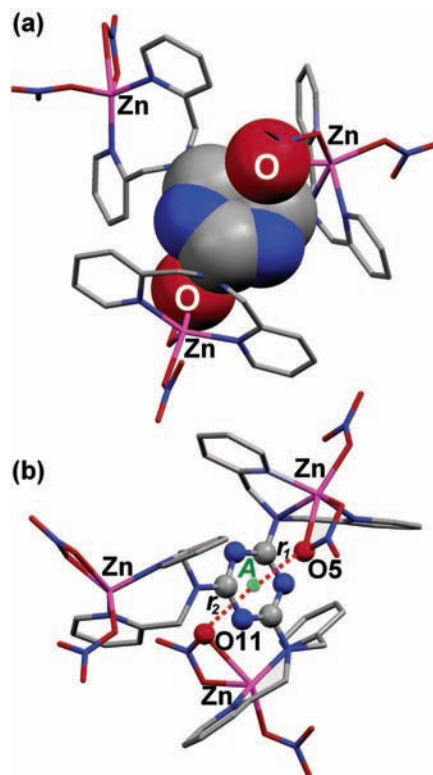

FIGURE 8. (a) Trizinc complex $[Zn_3(dipicatriz)(NO_3)_6]$.[43] Distances between the triazine centroid *A* and the oxygen atoms O5 and O11 of two coordinated nitrates: $r_1 = 3.097$ Å and $r_2 = 3.515$ Å, respectively.

The reaction of copper(II) nitrate with dipicatriz[39] using the same experimental conditions yields a comparable tricopper complex, namely, $[Cu_3(dipicatriz)(NO_3)_2(H_2O)_6](NO_3)_4$ (Figure 9a). Once again, the ability of the triazine ring to bind an electron-rich molecule is confirmed in this coordination compound. Similarly to the previous zinc complex, two nitrate anions are located on each face of a triazine ring (see Figures 8a and 9a). Furthermore, these two ions are now uncoordinated, which corroborate the statements made above. The oxygen atom O9 of one nitrate is in close contact (within theoretically predicted values; Table 1) with the triazine (centroid ··· O9 distance $r_1 = 3.201$ Å; Figure 9b). The second nitrate interacts via its oxygen atom O11 at a somewhat longer distance of the ring centroid (centroid ··· O11 distance $r_2 = 3.502$ Å; Figure 9b). This weaker interaction of the second anion is most likely due to the fact that the triazine moiety is already involved in a nitrate–centroid contact.

Because all computational studies performed thus far have been devoted to the potential binding interactions between one electron-rich molecule with one electron-poor aromatic ring, the present nitrate–triazine–nitrate system has been theoretically investigated. The interaction energies for 1:1 and 2:1 nitrate/triazine complexes (Figure 10) have been estimated with both the HF and MP2 methods, using the 6-311++G and 6-311++G(3df,p) basis sets.[43] At the MP2 level, an optimum distance of $r = 3.0$ Å (corresponding to a binding energy ΔE_{BSSE} of -22.38 kJ mol^{-1}) has been calculated for the 1:1 complex. A $r = r'$
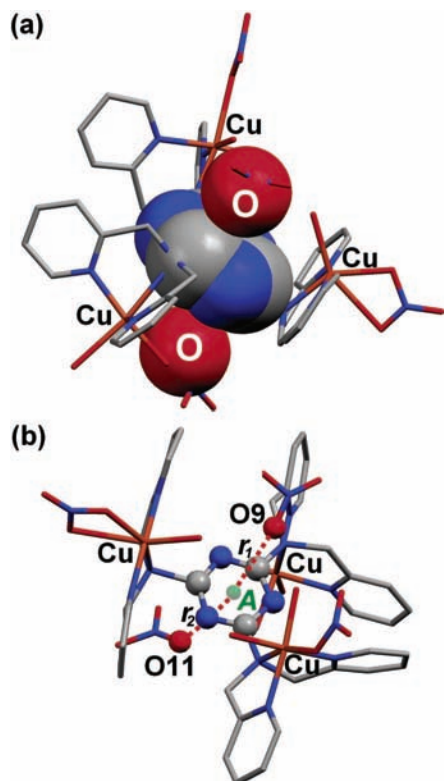
FIGURE 9. (a) Representation of the cation [Cu₃(dipicatriz)-(NO₃)₂(H₂O)₆]⁴⁺ showing the nitrate···triazine···nitrate interactions.[43] (b) Distances between the triazine centroid *A* and the oxygen atoms O9 and O11 of two free nitrates, $r_1 = 3.201$ Å and $r_2 = 3.502$ Å, respectively.
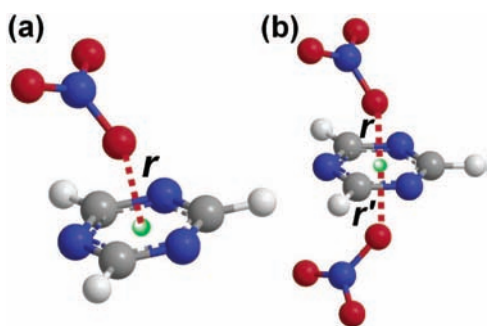

FIGURE 10. Geometries used for the calculations of the intermolecular interactions in the (a) 1:1 and (b) 2:1 nitrate/triazine complexes.[43]

FIGURE 11. Representation of the cation [Cu₄(dpatta)(NO₃)₄]⁴⁺ showing the nitrate···triazine interactions.[45] The separation between the nitrate oxygen atom O8 and the centroid *A* of the triazine ring is $r = 3.230$ Å.

FIGURE 12. (a) Computational optimization based on the nitrate–triazine model complex proposed by Kim et al.[35] (b) Optimization based on the crystal structure of [Cu₄(dpatta)(NO₃)₄](NO₃)₄.[45]

= 3.2 Å value has been obtained for the 2:1 host/guest system (corresponding to a binding energy ΔE_{BSSE} of -23.98 kJ mol⁻¹). The longer distance observed, when two anions are interacting with the triazine, can be rationally explained as follows: the binding of the first nitrate gives the electron density to the electron-poor ring; as a result, this ring becomes less electron-deficient and the interaction is weaker for the second anion (see r_1 and r_2 values in Figure 9).

Further investigations on nitrate–(electron-deficient arene) attractive interactions have been carried out using other triazine-based ligands. For instance, the reaction of copper(II) nitrate with the ligand dpatta[45] in acetonitrile under hydrothermal conditions yields the tetranuclear complex [Cu₄(dpatta)(NO₃)₄](NO₃)₄, whose cationic part
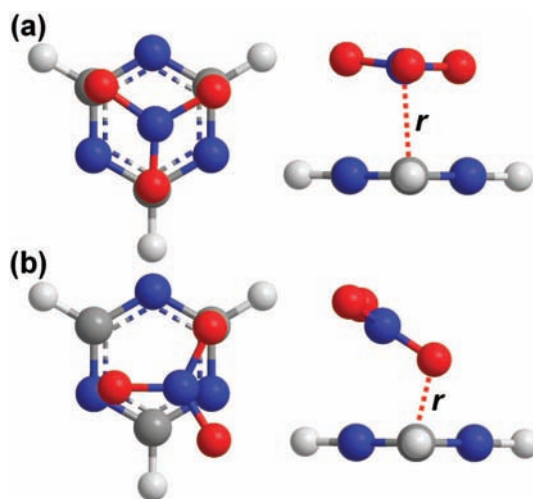
is represented in Figure 11. As evidenced in this figure, nitrate–triazine close contacts are also observed for this complex.[45] Indeed, two nitrates are facing two electron-poor aromatics via one of their oxygen atoms, with a O8···centroid *A* distance of 3.230 Å (Figure 11).

Similar to the previous example (see Figures 9 and 10), the spatial arrangement of the nitrate anions on the top of the triazine hosts is distinct to the one proposed by Kim et al. (parts a and b of Figure 12);[35] therefore, comparative DFT calculations have been carried out on both models (parts a and b of Figure 12).[45] The DFT–Becke–Lee–Yang–Parr (BLYP) geometry optimization for the model depicted in Figure 12a is comparable to the one reported by Kim et al. using MP2.[35] Thus, the distance *r* between the nitrogen atom and the centroid is estimated to 3.4 Å, while the MP2 value is 3.00 Å.[35] For the model based on the crystal structure of [Cu₄(dpatta)(NO₃)₄]-(NO₃)₄, the theoretical *r* value amounts to 3.67 Å. Surprisingly, this model (Figure 12b) is found to be energetically more stable ($\Delta E = -14$ kJ mol⁻¹) than the *a priori* more logical model (Figure 12a; $\Delta E = -11$ kJ mol⁻¹), where the electronegative oxygen atoms of the nitrate anion are
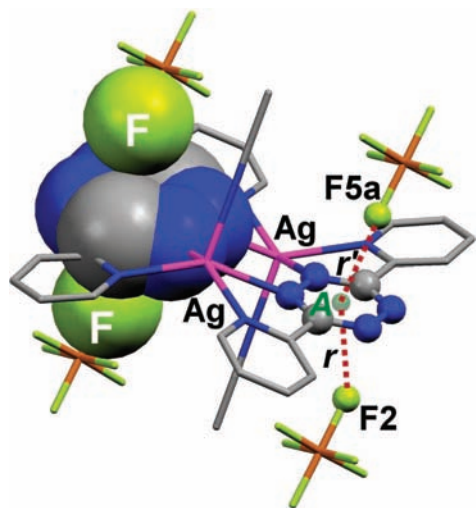
FIGURE 13. Representation of the complex $[Ag_2(bptz)_2(CH_3CN)_2][PF_6]_2$ showing the hexafluorophosphate–tetrazine–hexafluorophosphate interactions.[44] Distances between the tetrazine centroid *A* and the fluoride atoms F2 and F5a of hexafluorophosphate anions, $r = 2.806$ Å and $r' = 2.835$ Å, respectively.

located on the top of the electropositive carbon atoms of the triazine ring.

During the past year, a number of beautiful examples of anion–(N-containing arene) interactions have been described in the literature. Thus, Dunbar et al. recently reported a series of such attractive contacts between various polynuclear anions and the tetrazine-based ligand bptz or the pyridazine-based ligand bppn.[44] For instance, the reaction of silver(I) hexafluorophosphate with 1 equiv of bptz in acetonitrile leads to the formation of complex $[Ag_2(bptz)_2(CH_3CN)_2](PF_6)_2$, whose solid-state structure is represented in Figure 13. Strong binding interactions between the PF_6 ions and the tetrazine rings are observed (distance F2···centroid *A* of 2.806 Å; Figure 13). In addition, the two electron-deficient arenes are further interacting with two hexafluorophosphates from two neighboring dinuclear silver complexes (distance F5a···centroid *A* of 2.835 Å), giving rise to (anion–π–anion)-type motifs (Figure 13). All structural evidences of anion–π contacts have been corroborated by DFT calculations, which show that the strength of the fluoride–arene bonds is due to the high electropositive character of the tetrazine rings.[44]

Comparable strong anion–π bonding interactions have been illustrated with a new heteroaromatic derivative, namely, pyridazino[4,5-*d*]pyridazine (L).[46] Accordingly, a series of remarkable anion–pyridazine supramolecular associations have been observed by Domasevitch et al.[46] For example, the reaction of copper(II) perchlorate with pyridazino[4,5-*d*]pyridazine in water produces the complex $[Cu(H_2O)_2(L)_2](ClO_4)_2 \cdot nH_2O$, which represents the building unit of a square grid framework (Figure 14). Each square cavity composing the 2D network encloses two perchlorate ions, which are interacting, via two oxygen atoms, with two pyridazines, with O···centroid separations of 3.051 and 3.497 Å, respectively (Figure 14).

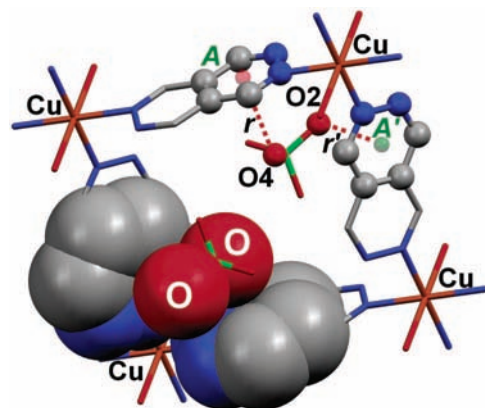**FIGURE 14.** Two-dimensional coordination network (square grid) formed by the complex $[Cu(H_2O)_2(L)_2](ClO_4)_2 \cdot nH_2O$ (L = pyridazino[4,5-*d*]pyridazine), showing the incorporation of two perchlorate anions inside a square cage.[46] Distance between the oxygen atom O4 of the perchlorate anion and the pyridazine centroid *A*, $r = 3.051$ Å; distance between the oxygen atom O2 of the perchlorate anion and the pyridazine centroid *A'*, $r' = 3.497$ Å.
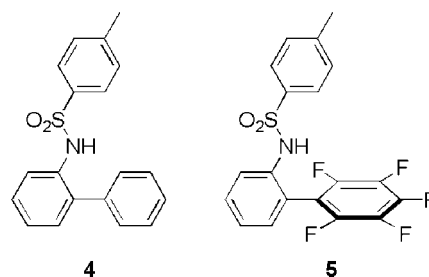

FIGURE 15. Receptors designed by Johnson et al. to investigate their comparative ability to generate anion–π interactions.[47]

3.2. Experimental Evidences in Solution. In the examples illustrated in section 3.1, all anion–(electron-poor aromatic ring) contacts are established on solid-state structures. Recently, Johnson et al.[47] reported experimental proofs of attractive interactions between a halide and a pentafluorophenyl group in solution. Two receptors, i.e., **4** and **5** (Figure 15), have been designed to investigate the influence of an electron-deficient arene on the binding abilities of halides in solution. The solid-state structure of receptor **5** already reveals its aptitude to favorably interact with electron-rich entities. Indeed, short anion–C_6F_5 contacts are observed between two molecules of **5** ($r = 2.956$ Å; Figure 16).

The comparative capacities of **4** and **5** to bind halides in solution have been studied by ^1H NMR in $CDCl_3$.[47] Thus, n-Bu_4NX salts (X = Cl, Br, and I) have been added to $CDCl_3$ solutions of **4** or **5**, and the binding constants K_a of the different halides have been determined from the respective chemical shifts. The results are reported in Table 2.

As evidenced in Table 2, the receptor **5**, holding the electron-deficient ring, is able to associate with a halide in solution, while no significant interactions could be detected with receptor **4**. This investigation clearly demonstrates the possibility to design and prepare host–guest systems for anion recognition, on the basis of electron-poor aromatic receptors.
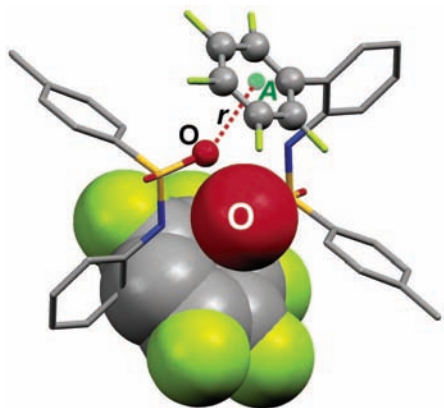
FIGURE 16. Representation of the crystal structure of receptor **5**. The crystal packing of **5** reveals attractive interactions between one oxygen atom of the sulfonamide group of **5** and the pentafluorophenyl group of an adjacent molecule. The distance r (O···centroid A) amounts to 2.956 Å.[47]

Table 2. Binding Constants K_a (M^{-1}) for Receptors 4 and 5 with Various Halides[47]

	4	5
Cl$^-$	<1^a	30 ± 3
Br$^-$	<1^a	20 ± 2
I$^-$	<1^a	34 ± 6

^{a} The binding constants for **4** were to small to be determined by ^{1}H NMR titration experiments.

4. Incidence of Anion–π Interactions in Biological Systems

Crucial biological systems very often involve aromatic rings (DNA, porphyrins, some amino acids, and so on). It would therefore be surprising if anion–arene interactions were not occurring in biochemical structural arrangements or processes. In fact, it appears that this type of interaction has thus far largely been overlooked. This negligence is most likely due to the fact that the attractive interaction between an electron-rich molecule and a π cloud is intuitively incongruous. However, as mentioned in sections 2 and 3, a number of theoretical studies and recent experimental results tend to confirm that such interactions should be considered.

Many electron-poor aromatic moieties can be found in biomolecules. For instance, the DNA bases are electron-deficient arenes, which play an important role in stabilizing the DNA double helix, through π–π stacking interactions. A thorough CSD search (CSD version 5.27, August 2006) for halide–nucleobase interactions results in five hits (CSD codes: CADCUC, ICIDII, GUANCU10, IBIDIG, and IVOROA). The three most representative examples of anion–base associations are depicted in Figure 17. A close contact (r = 3.271 Å; Figure 17a) between the six-membered ring centroid of a coordinated adenine and the fluoride atom of a lattice tetrafluoridoborate anion is observed in a cobalt complex (CSD code ICIDII). Similarly, a palladium complex (CSD code IBIDIG) exhibits anion–π interactions between a guanine derivative and the fluoride atom of a tetrafluoridoborate (r = 3.241 Å; Figure 17b). Finally, a case of thymine–tetrafluoridoborate pairing has

also been found in the CSD. Indeed, the crystal structure of the copper compound (CSD code IVOROA) depicted in Figure 17c shows tetrafluoridoborate–thymine binding interactions (r = 3.282 Å). These crystallographic cases of halide–nucleobase supramolecular associations clearly illustrate the possibility to generate anion–π binding contacts with natural arenes.

As pointed out in the Introduction section, chloride channels are vital for living beings. Its dysfunction will give rise to serious diseases.[4] Therefore, chloride channels have been intensively investigated, and the crystal structure of the chloride channel from *Salmonella enterica* serovar *typhimurium* (StClC) has been recently reported by MacKinnon et al.[48] The chloride-binding site of StClC is schematized in Figure 18. Interestingly, three of the six amino acids found in the binding site of this chloride channel are aromatic. This concentration of aryl groups is even more remarkable if one realizes that only 4 of the 20 natural amino acids contain aromatic rings. The presence of these arenes close to the binding site may thus not be innocent. As stated by MacKinnon et al., "*It is noteworthy that in the Cl$^-$ channel the ion does not make direct contact with a full positive charge from lysine or arginine residues. . . We suggest that a full positive charge would create a deep energy well and cause a Cl$^-$ ion to bind too tightly.*"[48] Therefore, the phenyl rings (and especially Phe348; Figure 18) may play a role in the chloride recognition and/or the sliding of the ions through the channel.

In that context, Matile et al. lately published a remarkable synthetic ion channel based on anion–π recognition.[49] The design and preparation of oligo-(*p*-phenylene)-*N,N*-naphthalenediimide rods (O-NDI; see Figure 19) have been achieved to create transmembrane anion–π slides. DFT calculations on the *N,N*-naphthalenediimide unit reveals a strong electron-deficient character in the center of the molecule (global quadrupole moment ΘE_{zz} of +19.4 B; B = Buckinghams). The activity of these O-NDI rods has been evaluated with large unilamellar vesicles.[49] Transport activities have been observed, with the following unusual sequence selectivity: F$^-$ > Cl$^-$ > Br$^-$ > I$^-$, which is the opposite of the common Hofmeister series and thus suggests the existence of very strong anion–π interactions (because the energetic cost for the dehydration of the anion is fully compensated by its binding to the anion slide).[49]

5. Interactions Between Neutral Electron-Rich Molecules and Electron-Poor Aromatics

In the previous sections, the importance of anion–arene interactions, as well as the rapidly rising scientific attention for this type of binding contact, has been highlighted. It has to be mentioned that another type of largely overlooked supramolecular interaction, i.e., the attractive interactions between an electron-rich, neutral molecule (such as water) and an aromatic group, is increasingly considered and described in papers, especially for biological systems.[50]
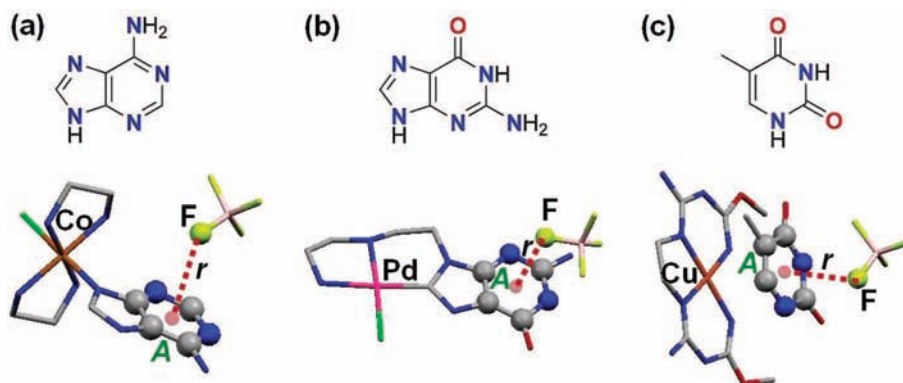
FIGURE 17. Attractive contacts with DNA bases. (a) Tetrafluoroborate–adenine interaction; distance of F···centroid *A*, *r* = 3.271 Å [Cambridge Structural Database (CSD) code ICIDII]. (b) Tetrafluoroborate–guanine interaction; *r* = 3.241 Å (CSD code IBIDIG). (c) Tetrafluoroborate–thymine interaction; *r* = 3.282 Å (CSD code IVOROA).
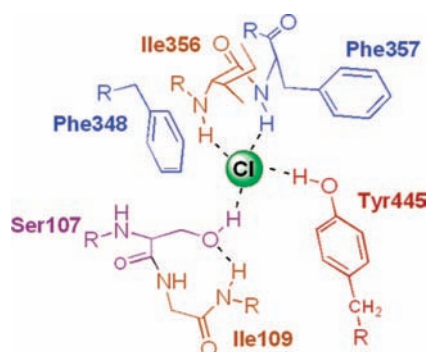

FIGURE 18. Schematic representation of the receptor site of a ClC chloride channel, revealing the presence of six amino acids at the binding site.[48]

In 2003, Egli et al. reported an interesting case of H_2O–π interactions within an RNA pseudoknot.[51] Indeed, the crystal structure of a ribosomal frame-shifting RNA pseudoknot has revealed strong lone pair–nucleobase contacts (Figure 20). The distance from the cytosine C8 centroid to the water W71 oxygen atom is only 2.93 Å (Figure 20a), which is clearly indicative of lone pair–π interactions. Actually, the interaction of the water W71 protons with the π face of the cytosine C8 residue is unlikely because this would imply a H···centroid distance of about 2 Å, which is sterically not possible. Similarly, lone pair–π interactions are observed between the water molecule W73 and the adenine nucleobase A20 (Figure 20b; *r′* = 3.01 Å). These water–nucleobase stabilizing interactions are considered to be of functional importance for the frame-shifting activity of the pseudoknot.[51]

Recently, some of us described the first crystallographic example of the lone pair–π association between a non-hydrogen donor, electron-rich molecule, namely, aceto-nitrile, and the electron-poor s-triazine ring.[52] The reaction of zinc(II) chloride with the ligand oxodendtriz[52] in methanol/acetonitrile yields the tetranuclear zinc complex [Zn_4(oxodendtriz)Cl_8](CH_3CN)$_2$, whose solid-state structure representation is depicted in Figure 21. As evidenced in this crystal structure, acetonitrile–triazine close contacts are present in this compound. The nitrogen atom of the acetonitrile molecule is pointing toward the center of the electron-deficient aromatic ring (N···centroid separation
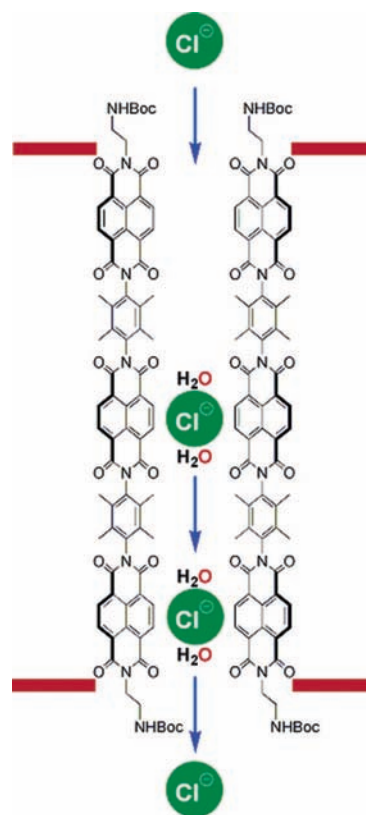

FIGURE 19. Electron-deficient rods (O-NDI) as chloride–π slides in lipid bilayer membranes.[49]

of 3.087 Å; Figure 21). DFT calculations, on the basis of the solid-state structure, indicate a binding energy ΔE_{BSSE} of −16.52 kJ mol^{-1} (which is comparable to a moderate hydrogen-bonding interaction) and an optimized N···centroid distance of 3.116 Å [at the MP2 level using the 6-311++G(3df,p) basis set].[52]

6. Concluding Remarks

Cation–π interactions are well-established interactions that have been extensively exemplified and thoroughly investigated.[53] On the contrary, the counter-intuitive anion–π interactions (or more generally electron-rich/electron-poor molecule pairing)[54] have been mainly overlooked by the scientific community. However, a simple survey of the CSD
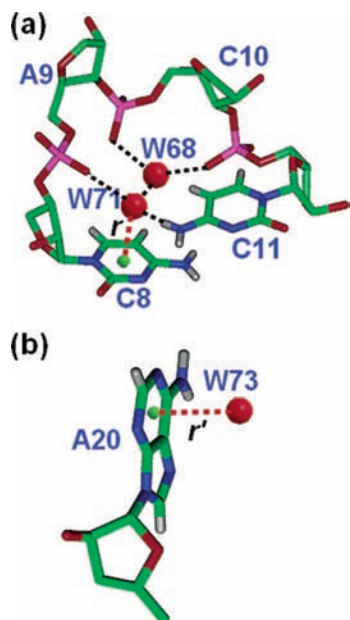
FIGURE 20. $O_{water}-\pi$ interactions observed in a RNA molecule.[51] (a) Distance of $O_{W71} \cdots$ centroid$_{C8}$, $r = 2.93$ Å. (b) Distance of $O_{W73} \cdots$ centroid$_{A20}$, $r' = 3.01$ Å.

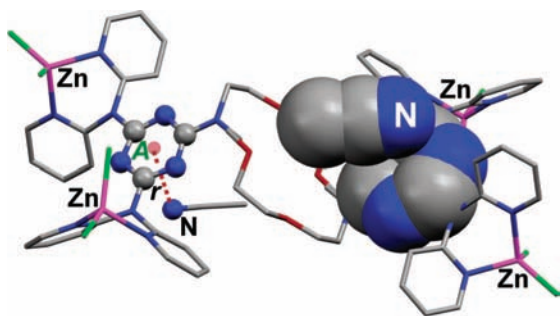**FIGURE 21.** Representation of the zinc complex $[Zn_4(oxo-dendtriz)Cl_8](CH_3CN)_2$ showing the interaction of acetonitrile molecules with each triazine unit of the ligand.[52] $N_{acetonitrile} \cdots$ centroid *A* separation, $r = 3.087$ Å.

shows that anion–π interactions are more frequent than one would actually expect. Two datasets were indeed created to examine potential anion–π short contacts in the crystal structures thus far deposited at the CSD. Thus, the search for interactions between anions and five-membered aromatic rings (taking into account the distances between the anion and each atom of the ring, as well as its centroid) resulted in 40 hits (with anion $\cdots$ π-ring separations below 3.8 Å), corresponding to 47 crystallographic evidences of anion–π close contacts (because some hits exhibit more than one anion–π interaction). For a comparison, a similar search has been performed for cation–(five-membered ring) interactions, which only generated 19 hits (corresponding to 24 interactions). Analogous comparative quests for anion– and cation–(six-membered aromatic ring) interactions produced 483 (554 examples of anion–π interactions) and 494 (494 examples of cation–π interactions) hits, respectively. This CSD study clearly demonstrates that this type of noncovalent contact should be considered by the supramolecular chemist, as are the well-accepted cation–π interactions.

This Account has briefly summarized and discussed chemical research recently carried out in the nascent and stimulating field of supramolecular chemistry, namely, anion recognition by π systems.

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