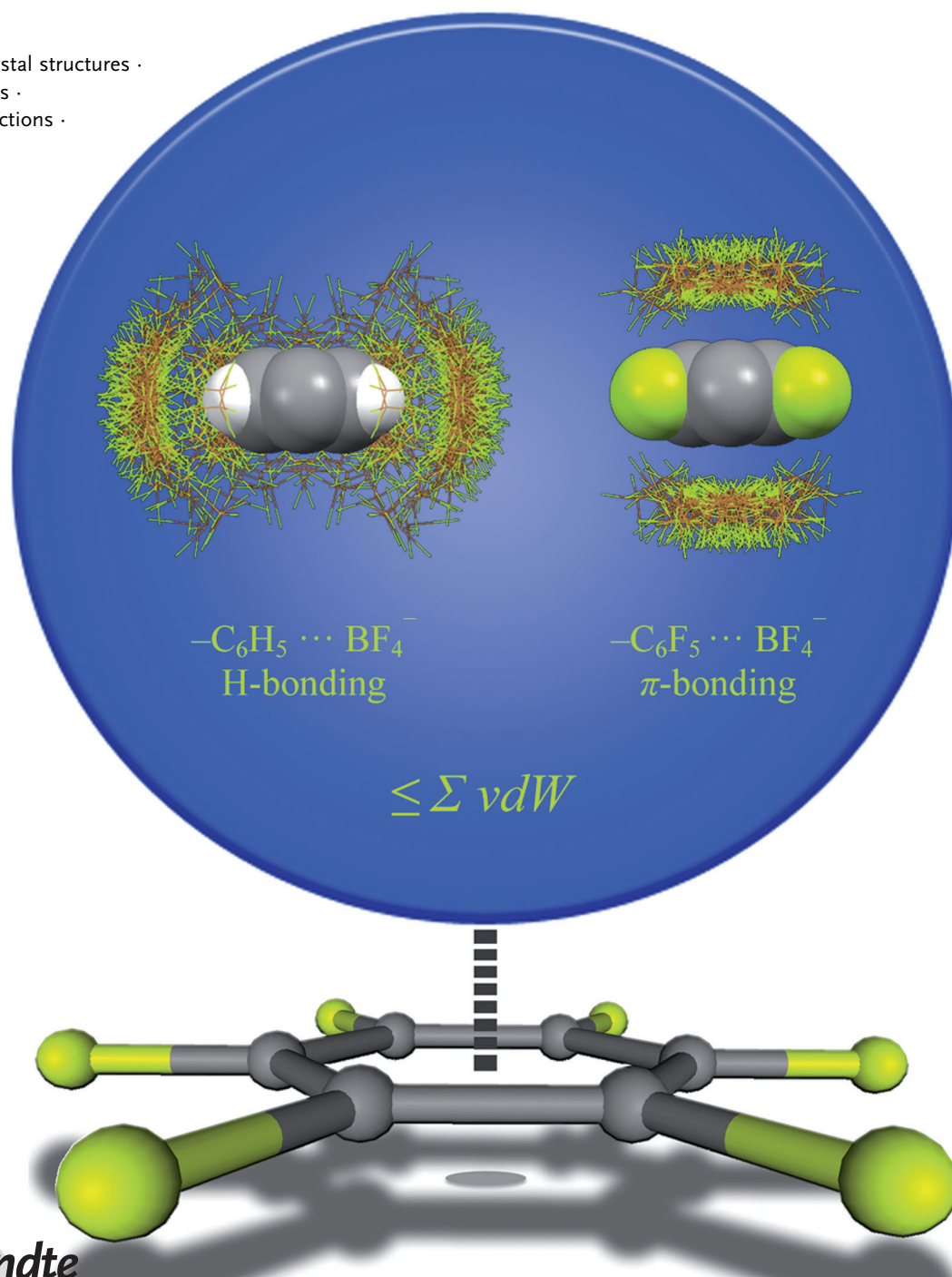


Putting Anion- π Interactions Into Perspective

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Supramolecular chemistry is a field of scientific exploration that probes the relationship between molecular structure and function. It is the chemistry of the noncovalent bond, which forms the basis of highly specific recognition, transport, and regulation events that actuate biological processes. The classic design principles of supramolecular chemistry include strong, directional interactions like hydrogen bonding, halogen bonding, and cation- π complexation, as well as less directional forces like ion pairing, π - π , solvophobic, and van der Waals potentials. In recent years, the anion- π interaction (an attractive force between an electron-deficient aromatic π system and an anion) has been recognized as a hitherto unexplored noncovalent bond, the nature of which has been interpreted through both experimental and theoretical investigations. The design of selective anion receptors and channels based on this interaction represent important advances in the field of supramolecular chemistry. The objectives of this Review are 1) to discuss current thinking on the nature of this interaction, 2) to survey key experimental work in which anion- π bonding is demonstrated, and 3) to provide insights into the directional nature of anion- π contact in X-ray crystal structures.

“*Itinerarium mentis ad veritatem*”

1. Introduction

Noncovalent interactions have a constitutive role in the science of intermolecular relationships. Processes of chemical and biological assembly orchestrated by noncovalent bonding are directed and, in many cases, elegant expressions of collective behavior on the molecular scale.^[1] In nature, these interactions are the foundation of the life process itself, the ultimate articulation of function, both mechanical and cognitive. In synthetic chemistry, interactions between rationally designed molecular subunits drive the assembly of nanoscopic aggregates with targeted structures. Research in this area is inspired by everything from the basic mechanisms of biological function to systems biology.^[2–20] A clear understanding and accurate description of the full compass of interactions between molecules is essential to the development of this field, particularly the science of biomimetics and the development of new synthetic applications in catalysis, materials science, and medicine.

Noncovalent interactions involving aromatic rings in particular play an essential role in chemistry and biology.^[12] This role becomes prominent in drug-receptor interactions, crystal engineering and protein folding.^[21] It has been estimated that around 60% of aromatic amino acid side chains (histidine, phenylalanine, tyrosine, tryptophan) participate in π - π stacking interactions in proteins.^[22] The role of stacking interactions in DNA and RNA is also of undisputed importance, wherein nucleobase intra- and interstrand stacking help to stabilize the structure of DNA duplexes.^[22,23] Moreover, biological processes involved in the control and regulation of gene expression are dependent on protein-

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DNA aromatic interactions, as is the action of intercalating drugs.^[24]

Another related function occurs within the active sites of various DNA repair enzymes that excise alkylated purines through a recognition mechanism based on π - π interactions with aromatic amino acid residues.^[25] These interactions also play a key role in the repair process where aromatic amino acids are inserted into the DNA strand to maintain stability when the damaged base is flipped out of the duplex and into the active site of the repair enzyme.^[25]

Cation- π bonding is an important and widely recognized noncovalent interaction that involves aromatic rings.^[26,27]

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Numerous studies have reported the occurrence of cation- π interactions in protein structures^[26–33] and in protein-ligand^[12,34] and protein-DNA^[35–37] complexes. These analyses have revealed the preferential localization of ammonium groups in the vicinity of aromatic rings.^[28,32] This interaction is calculated to be even more stabilizing than an analogous salt bridge,^[38] and is not as strongly attenuated in water.^[38] The side-chains of the aromatic amino acid residues provide a surface of negative electrostatic potential that can bind to a wide range of cations through a predominantly electrostatic interaction.^[26,39,40] The cation- π interaction has of course also found important applications in the field of supramolecular chemistry. Supramolecular aggregates like dendrimers,^[41,42] molecular tweezers, rotaxanes,^[43] catenanes,^[44–46] and foldamers^[47] have been associated by cation- π interactions.^[48–51]

In recent years, the inverse of the cation- π bonding, that is, contact between an anion and the region above the plane of an electron-poor aromatic ring, has also been recognized as a noncovalent bonding interaction. The nature of this interaction, designated an “anion- π bond,”^[52] has been described by numerous theoretical studies, which demonstrate that it is energetically favorable,^[52–58] in addition to several experimental investigations.^[59–67] Anion- π interactions continue to gain attention as their role in chemical and biological processes is being increasingly recognized.^[68] Moreover, their application to the design of highly selective anion receptors and channels^[69–75] is establishing their value in the field of supramolecular chemistry. The closely related lone pair- π interaction has also been observed in biological systems. For instance, Egli et al. have reported an interesting case of O- π interactions involving an RNA pseudoknot.^[76]

This work is not a bibliographic survey of the literature related to anion- π bonding. Several excellent reviews have been written for that purpose.^[68a,b,77–79] Instead, it is our mission here to showcase the bonding relationship between anions and π systems, describing work at the experimental and theoretical forefront of this noncovalent interaction. The narrative is developed under three headings. First, key aspects of the physical nature of the interaction are presented for assimilation by a wide readership. The directionality of the interaction also is discussed here and compared with that of the cation- π bond. Next, we present selected examples from the literature where molecular recognition driven by anion- π bonding is clearly in evidence. This part is subdivided into three sections, that is, complexes in solution, the solid state, and the gas phase. Finally, the results of a statistical analysis of anion- π contacts derived from the data in the Cambridge Structural Database (CSD)^[80] are presented in an easy to interpret, three-dimensional format.

2. Physical Nature of the Anion- π Interaction

The general concept of anion-aromatic bonding is depicted graphically in Figure 1. Thus, while cation- π complexes are described by a single type of minimum energy structure, interactions between anions and aromatic rings can be manifested in any one of three modes of contact. First, when hydrogen atoms are present on the ring, hydrogen

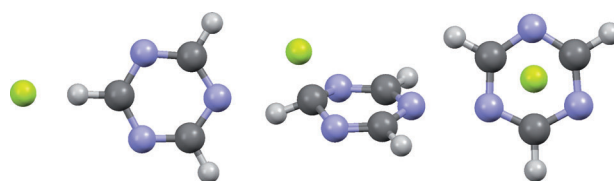


Figure 1. Depiction of three modes of contact between an electron poor aromatic ring and an anion (1,3,5-triazine and F^- in this case); left, H-bonding; center, σ -type interaction; right, anion- π bonding.

bonding can occur. Alternatively, a lone pair of the anion may interact with a π^* orbital in such a way as to give a nascent Meisenheimer-type complex, often called a σ complex. Finally, the anion may position itself at or near the ring centroid to describe a structure analogous to the cation- π complex.

The physical nature of the anion- π interaction has been extensively analyzed.^[53–58] From these studies, it has been concluded that electrostatic forces and ion-induced polarization are the main energetic contributors to the anion- π complex.^[81,82] The electrostatic term is explained by means of the permanent quadrupole moment of the arene, which is the first non-zero multipole moment in symmetric arenes. The quadrupole moment of benzene is negative, but can be turned positive by attaching electron withdrawing substituents to the ring (Figure 2). Accordingly, the a priori electrostatically

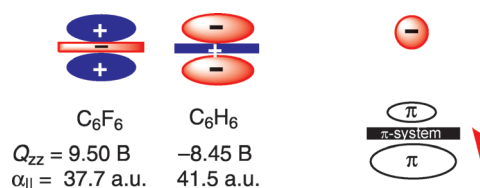


Figure 2. Schematic representation of the quadrupole moments of hexafluorobenzene and benzene (left) and the anion-induced dipole (right). The values of the quadrupole moments (Q_{zz}) in Buckingham (B) and molecular polarizabilities parallel to the main symmetry axis ($\alpha_{||}$) in atomic units (a.u.) are given.

repulsive interaction between an anion and an aromatic ring can become attractive. The polarization of the π -electron system by the anion is significant, whereas the reverse effect (distortion of the electronic distribution of the anion) is generally negligible. Therefore, a polarization contribution to the total interaction energy is derived from the interaction of the anion with the induced dipole in the π -system. On the other hand, dispersion forces, which are generally important in weak interactions involving aromatic rings, play only a minor role in anion- π bonding.^[55–58]

The understanding of the physical nature of the interaction as described above has been used in a predictive way. For example, a dual bonding mode exhibited by aromatic rings with negligible quadrupole moments has been identified.^[83,84] Since both anion- π and cation- π interactions are dominated by electrostatic and polarization effects, molecules such as 1,3,5-trifluorobenzene ($Q_{zz} = 0.57 \text{ B}$) and *s*-triazine ($Q_{zz} = 0.90 \text{ B}$) must be able to interact with *both* anions and

cations since the polarization term is always favorable. This is because the sign of the induced dipole is always opposite the sign of the ion. Thus, the modeled, gas-phase interaction energies for ion- π complexes of *s*-triazine with the chloride anion and lithium cation are -5.2 and -6.2 kcal mol $^{-1}$, respectively.^[83] Another such example involves the interaction of anions with electron-rich aromatic rings such as benzene, which is expected to be strongly repulsive. However, this supposition turns out to be false due to the opposing effects of electrostatic (unfavorable) and ion-induced polarization (favorable) forces, which largely cancel each other out. Hence, the ion- π interaction energies of both benzene with chloride or hexafluorobenzene with sodium are negligible.^[85] An interesting example of this compensating effect is observed in complexes of anions with cyanuric acid when the oxygen atoms are replaced by sulfur to give thiocyanuric acids (Figure 3).^[86] The binding energy of the complexes of

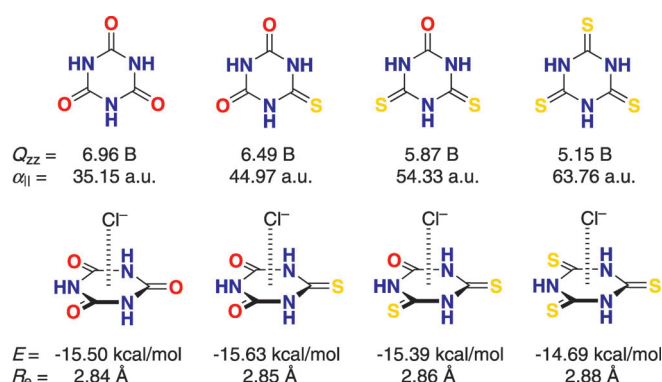


Figure 3. Top: Variation of the quadrupole moment (Q_{zz}) and molecular polarizability ($\alpha_{||}$) in cyanuric acid derivatives with increasing substitution of sulfur for oxygen. Bottom: Interaction energies (E) and equilibrium distances (R_e) of the chloride-(thio)cyanuric acid anion- π complexes.^[86]

chloride with the four possible (thio)cyanuric acids is essentially constant (ca. 15 kcal mol $^{-1}$). This can be explained by the fact that while the quadrupole moment progressively decreases on going from cyanuric acid to trithiocyanuric acid, the molecular polarizability increases.

From the considerations described above, it is apparent that to engineer a strong anion- π interaction, the aromatic ring should have a large and positive quadrupole moment as well as a large molecular polarizability. Second, depending on the magnitudes of these two physical properties, the interaction can be dominated by either electrostatic or polarization forces. In the latter case, for example, the molecular polarizability of 1,4,5,8,9,12-hexaazatriphenylene is almost three times the value of benzene, while the quadrupole moment is about the same as that of benzene. As a result, its interaction energy with bromide is -5.2 kcal mol $^{-1}$, while that of bromide with benzene is $+1.9$ kcal mol $^{-1}$.^[87]

The properties of the anion are also an important consideration for applications of anion- π bonding in supramolecular chemistry. Both the electrostatic and polarization contributions to the total interaction energy depend upon the

ion-arene distance. Small anions are more polarizing and present short equilibrium distances and, consequently, give rise to more negative interaction energies (Table 1). In

Table 1: Interaction energies (E , kcal mol $^{-1}$) with basis set superposition error correction and zero-point corrections and equilibrium distances (R_e , Å) measured from the anion to the center of the ring at the MP2/6-31++G** level of theory for several anion- π complexes.^[82–86]

Anion	E	R_e
Hexafluorobenzene		
H [−]	−12.1	2.69
F [−]	−18.2	2.57
Cl [−]	−12.6	3.15
Br [−]	−11.6	3.20
NO ₃ [−]	−12.2	2.92
CO ₃ ^{2−}	−34.7	2.72
Trifluorobenzene		
H [−]	−4.4	3.02
F [−]	−7.8	2.75
Cl [−]	−4.8	3.32
Br [−]	−4.5	3.36
NO ₃ [−]	−5.6	3.47
CO ₃ ^{2−}	−17.3	2.81
<i>s</i> -Triazine		
H [−]	−4.8	2.98
F [−]	−9.7	2.59
Cl [−]	−5.2	3.22
Br [−]	−5.0	3.34
NO ₃ [−]	−5.3	3.00
CO ₃ ^{2−}	−16.9	2.75
Trifluoro- <i>s</i> -triazine		
H [−]	−16.9	2.50
F [−]	−24.2	2.39
Cl [−]	−15.0	3.01
Br [−]	−14.0	3.14
<i>s</i> -Tetrazine		
F [−]	−19.3	2.24
Cl [−]	−10.9	2.86
Br [−]	−7.8	3.24
Cyanuric acid		
H [−]	−18.5	2.35
F [−]	−28.1	2.19
Cl [−]	−16.8	2.80
Br [−]	−15.5	3.00

addition, planar and linear anions such as NO₃[−] or N₃[−] can interact with the aromatic ring through π - π stacking. This theoretically predicted binding mode has been confirmed experimentally between nitrate ion and pyrimidinium rings.^[88]

Side-by-side comparison of analogous cation- π and anion- π complexes generally show the anion- π distance to be longer and the interaction to be energetically weaker.^[84] However, a different picture emerges when charged aromatic rings participate in anion- π bonding. Positive charges are easy to introduce onto azine rings by simply adjusting the pH of the medium, and this can be used to increment the anion binding ability of the ring (denoted as anion- π^+ interactions). There is no simple analog of this effect in cation- π bonding. The geometric and energetic features of anion- π^+ complexes between several aromatic cations (tropylium, quinolinizinium, protonated 2-aminopyrimidine, protonated adenine)

and various anions have been reported along with crystallographic structures that support the theoretical findings (Figure 4).^[65,88–91] As expected, in these complexes the interaction energies are large ($>80\text{ kcal mol}^{-1}$) and electrostatic effects dominate the anion– π^+ interaction.

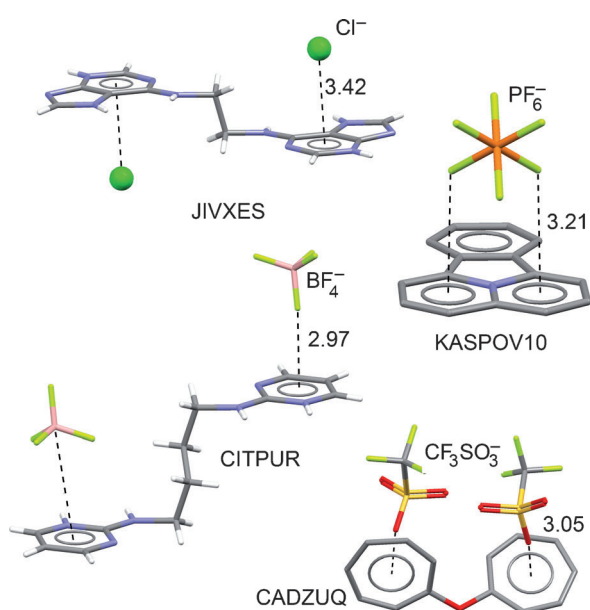


Figure 4. X-ray structures retrieved from the CSD in which anion– π^+ interactions are exhibited, with distances in Å.^[65,88–91] The CSD reference codes are indicated.

Another key aspect of the use of electron-deficient rings as design principles for the complexation of anions is the additivity of the anion– π interaction. Using *s*-triazine and trifluoro-*s*-triazine as examples, the additivity of the bonding interaction with halides has been examined.^[92] The energetic and geometric features of some of these complexes are summarized in Table 2. It can be seen that the interaction energies of the ternary complexes ($X^--\pi_2$) are essentially twice the interaction energies of the corresponding binary complexes ($X^--\pi$). For the quaternary complexes ($X^--\pi_3$),

Table 2: Interaction Energies (E , kcal mol^{-1}) with the basis set superposition error correction and equilibrium distances (R_e , Å) at the RI-MP2/6–31++G** level of theory for several complexes.^[92]

Anion– π_n complex	E	R_e
$\text{Cl}^-\cdots\text{C}_3\text{N}_3\text{H}_3$	–5.2	3.220
$\text{Br}^-\cdots\text{C}_3\text{N}_3\text{H}_3$	–5.0	3.338
$\text{Cl}^-\cdots(\text{C}_3\text{N}_3\text{H}_3)_2$	–10.4	3.213
$\text{Br}^-\cdots(\text{C}_3\text{N}_3\text{H}_3)_2$	–10.2	3.370
$\text{Cl}^-\cdots(\text{C}_3\text{N}_3\text{H}_3)_3$	–22.2	3.015
$\text{Br}^-\cdots(\text{C}_3\text{N}_3\text{H}_3)_3$	–21.7	3.372
$\text{Cl}^-\cdots\text{C}_3\text{N}_3\text{F}_3$	–15.1	3.008
$\text{Br}^-\cdots\text{C}_3\text{N}_3\text{F}_3$	–14.2	3.176
$\text{Cl}^-\cdots(\text{C}_3\text{N}_3\text{F}_3)_2$	–28.6	3.006
$\text{Br}^-\cdots(\text{C}_3\text{N}_3\text{F}_3)_2$	–26.8	3.170
$\text{Cl}^-\cdots(\text{C}_3\text{N}_3\text{F}_3)_3$	–41.0	3.019
$\text{Br}^-\cdots(\text{C}_3\text{N}_3\text{F}_3)_3$	–38.6	3.172

secondary interactions enter the picture. For triazine, $\text{CH}\cdots\text{N}$ hydrogen bonds are established between the rings, further stabilizing the $X^-\cdots(\text{C}_3\text{N}_3\text{H}_3)_3$ complexes. On the other hand, the interaction energies of the trifluoro-*s*-triazine quaternary complexes are less than additive because of unfavorable $\text{CF}\cdots\text{FC}$ contacts.

The influence of ion–arene contact on the aromaticity of benzene rings has also been studied. It has been reported that when the ring participates in anion– π interactions, its degree of aromaticity increases.^[84,93] The corresponding effect in cation– π complexes is the opposite. This observation is the result of a change in the C–C bond energy of the aromatic ring. Regarding charge transfer effects on anion– π interactions, the theoretically predicted values strongly depend on the method used to derive the atomic charges. In general, NPA and AIM charges predict negligible charge transfer effects, and Merz–Kollman and CHelpG charges predict values ranging from 0.1–0.25 e. A molecular orbital description of the anion– π interaction has also been developed^[84,94] and compared with the cation– π interaction, and again a totally different picture emerges, in that the atomic orbitals of the cation do not participate in the molecular orbitals of the cation– π complex, whereas the atomic orbitals of the anion have an active participation in the molecular orbitals of the anion– π complex.

An alternative take on the nature of anion– π interactions involving benzene rings was recently offered by Wheeler and Houk,^[95] who examined substituent effects in $\text{Cl}^-\cdots\text{C}_6\text{H}_{6-n}\text{X}_n$ complexes using density functional theory (DFT) and robust ab initio methods paired with large basis sets. The predicted interaction energies for a large number of model $\text{Cl}^-\cdots\text{C}_6\text{H}_{6-n}\text{X}_n$ complexes span a ca. 40 kcal mol^{-1} range and show an excellent correlation ($r=0.99$) with computed electrostatic potentials. In contrast to the aforementioned physical explanation of the anion– π interaction, which relies on substituent-induced changes in the aryl π system, Wheeler and Houk propose a model where substituent effects in these systems can be attributed mainly to direct interactions between the anion and local C–X dipoles. Specifically, interaction energies for $\text{Cl}^-\cdots\text{C}_6\text{H}_{6-n}\text{X}_n$ complexes could be matched using a model system in which the substituents are isolated from the aromatic ring and π -resonance effects are impossible. Additionally, they show that the curves for Cl^- interacting with prototypical anion-binding arenes can be qualitatively reproduced by adding a classical charge–dipole interaction to the $\text{Cl}^-\cdots\text{C}_6\text{H}_6$ interaction potential. From this point of view, when designing anion-binding motifs, phenyl rings should be viewed as a scaffold upon which appropriate substituents can be placed, not the attractive principle itself. Whether this interpretation of the anion– π interaction is accepted or not, the issue is largely semantic from a practical perspective, since in either case it is clear that the interaction, however constituted, is cohesive. It must also be emphasized that the interaction model offered by Wheeler and Houk applies only to substituted benzenes, and does not explain the nature of anion binding by heterocyclic aromatics. Other aspects of anion– π bonding that require a more profound analysis than offered by this theory are charge transfer effects, aromaticity and orbital interactions.

3. Interplay Between the Anion- π Interaction and other Weak Interactions

Manifestations of multiple, weak interactions turn up in all areas of chemistry.^[1–20] They determine material properties, orchestrate chemical reactions, drive molecular recognition, and are active in the regulation of biochemical processes.^[9–13] In these nanoscopic events, success relies on specificity and efficiency, which is accomplished by balancing intricate combinations of the intermolecular forces of attraction and repulsion. The organization of multicomponent supramolecular assemblies is often governed by multiple noncovalent interactions. In biological systems and particularly in the solid state, a host of interactions may operate simultaneously, giving rise to cooperativity effects. A recent review examined pairwise combinations of several weak interactions, including anion- π bonding, and described the synergy that operates between them.^[96]

3.1. Interplay Between Anion- π and Cation- π Interactions

As mentioned earlier, large and positive quadrupole moment ensures that an aromatic ring can participate in strong anion- π bonding. The presence of charge on the aromatic ring (anion- π^+) can further increase the strength of the interaction. Conversely, it is also possible to establish a strong anion- π interaction between anions and arenes bearing no polarizing substituents. This can be achieved in the situation where the aromatic system interacts with both a cation and an anion on opposing sides of the ring.^[85,97–99] Here, the aromatic ring mediates the transfer of information between the charged systems. For these ternary complexes the interaction energies are large and negative (Table 3), and the equilibrium distances are shorter than the corresponding distances of either binary ion- π complex, indicating a

reinforcement of both interactions. In addition, this behavior does not depend upon the nature of the arene, since negative E and small R_e values were obtained for three aromatic rings spanning the range of quadrupole moments (C_6H_6 , $Q_{zz} = -8.45$ B; $C_6F_3H_3$, $Q_{zz} = 0.19$ B; C_6F_6 , $Q_{zz} = 9.50$ B).

Experimental work that supports the above theoretical findings has been published by Atwood and co-workers.^[100–102] Using X-ray crystallography and 1H NMR titration experiments, they have shown that the host-guest behavior of calixarenes and cyclotrimeratrylenes can be inverted by complexation of the arene rings with transition metals (Ru, Ir, Rh), thus allowing anionic guest species (instead of cationic) to be included within the molecular cavity. One such example is shown in Figure 5 (top). Likewise, Fairchild and Holman^[103,104] have reported that the metalation of the exterior arene faces of the molecular capsule cryptophane-E with $[Cp^*Ru]^+$ moieties (Figure 5, bottom) results in a π -acidic cavity capable of encapsulating anions. The anion complexes have been crystallographically characterized and the encapsulation has been established by 1H and ^{19}F NMR spectroscopy.

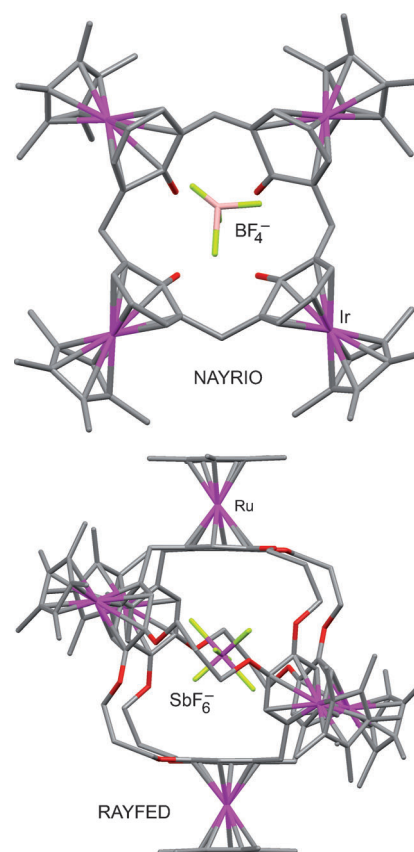


Figure 5. X-ray crystal structures of transition-metal complexed macrocycles NAYRIO^[102] and RAYFED^[104] exhibiting anion- π -cation bonding.

Table 3: Interaction energies of binary and ternary complexes (E , kcal mol⁻¹), and the total interaction energy minus the isolated $Na^+ \cdots X^-$ electrostatic bonding term with basis set superposition error correction (E_{int} , kcal mol⁻¹) and equilibrium distances (R_e , Å) for several cation- π -anion complexes at the MP2/6-31++G** level of theory.^[85]

Anion- π -cation	E	E_{int}	R_e (cation- π)	R_e (anion- π)
$Na^+ \cdots C_6H_6$	-21.0	—	2.429	—
$Na^+ \cdots C_6F_3H_3$	-8.21	—	2.552	—
$Na^+ \cdots C_6F_6$	+3.5	—	2.652	—
$C_6H_6 \cdots F^-$	+2.8	—	—	3.162
$C_6H_6 \cdots Cl^-$	+2.4	—	—	3.731
$C_6H_6 \cdots Br^-$	+1.9	—	—	3.840
$Na^+ \cdots C_6H_6 \cdots F^-$	-93.10	-22.39	2.280	2.482
$Na^+ \cdots C_6H_6 \cdots Cl^-$	-85.11	-21.93	2.304	3.049
$Na^+ \cdots C_6H_6 \cdots Br^-$	-84.26	-22.12	2.313	3.157
$Na^+ \cdots C_6F_3H_3 \cdots F^-$	-90.94	-19.48	2.353	2.368
$Na^+ \cdots C_6F_3H_3 \cdots Cl^-$	-80.35	-17.14	2.389	2.925
$Na^+ \cdots C_6F_3H_3 \cdots Br^-$	-78.89	-16.00	2.399	3.006
$Na^+ \cdots C_6F_6 \cdots F^-$	-88.42	-17.09	2.437	2.286
$Na^+ \cdots C_6F_6 \cdots Cl^-$	-75.63	-12.05	2.488	2.835
$Na^+ \cdots C_6F_6 \cdots Br^-$	-74.04	-11.23	2.495	2.913

Further experimental evidence for the interplay between anion- π and cation- π interactions in solution has been published by Dougherty and co-workers.^[105] Using 1H NMR spectroscopy, it was demonstrated that cyclophane receptors which present carboxylate groups in the annular periphery

have higher cation binding affinities than those without the anionic groups. This effect was attributed to the induced dipole generated in the aromatic ring by the presence of the carboxylate functions.

3.2. Interplay Between Anion- π and Hydrogen Bonding Interactions

The effect of combining anion- π and H-bonding interactions has also been studied theoretically.^[106–108] It has been demonstrated that a reinforcement of both interactions is observed when the aromatic ring is also engaged as a hydrogen bond acceptor, for example in pyrazine or pyridazino[4,5-*d*]pyridazine. In contrast, a weakening of both interactions is observed in complexes where the aromatic ring is a hydrogen bond donor, for instance pyromellitic diimide. The partitioning of the interaction energy shows that this synergy is basically due to electrostatic effects.^[106] These reciprocal effects were first reported for relatively small aromatic systems, where water molecules were used to generate the hydrogen bonding interactions with the arene at the normal H-bonding distances. In a second report, the aromatic systems studied were larger and the distance from the anion to the water molecules was as long as 11 Å.^[108] Even in these cases, significant interplay between both interactions was observed.

3.3. Influence of Metal Coordination on the Anion- π Interaction

The influence of metal coordination to heteroaromatic rings on the energetics of anion- π interactions has been analyzed in two recent papers.^[109,110] In the first, the coordination of both pyridine and pyrazine with Ag^I has been shown to dramatically enhance their disposition toward anion- π binding.^[109] Using high-level ab initio calculations, anion- π complexes of pyridine and pyrazine with Cl[−] were shown to be considerably more energetically favorable when Ag^I was coordinated to the nitrogen atom. In fact, the interaction of pyridine itself with chloride is actually unfavorable (+2 kcal mol^{−1}) indicating that the ring is not π -deficient enough to form a stable anion- π complex with Cl[−] (Figure 6). However, the interaction becomes favorable (−14.8 kcal mol^{−1}) when the nitrogen atom of pyridine is coordinated to silver. Analogous behavior is also observed in pyrazine complexes.

The second work^[110] combines theory and experiment to demonstrate that *s*-tetrazine is a powerful anion- π acceptor when it is coordinated to four Ag^I atoms. The calculated interaction energy of *s*-tetrazine with nitrate ion is −9.6 kcal mol^{−1} (Figure 6), and when tetracoordinated to Ag^I the interaction energy becomes −62.4 kcal mol^{−1}. A significant (0.3 Å) shortening of the equilibrium distance is also predicted. Experimentally, very close contact is observed between the anion and the *s*-tetrazine ring in the X-ray crystal structures (Figure 7) indicating strong anion- π interactions, in agreement with the theoretical predictions. In fact, the anion- π distance for the perchlorate anion in YOYTAI (Figure 7, left) is the shortest reported to date.

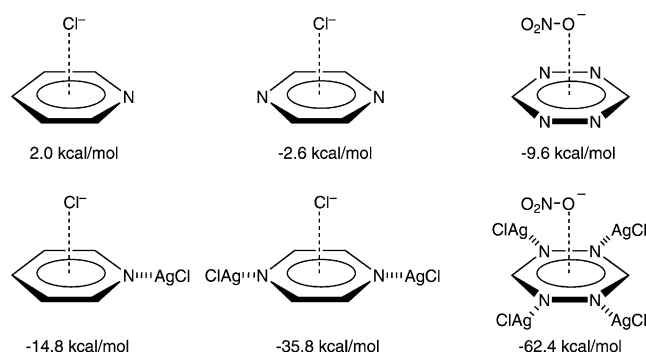


Figure 6. Pyridine, pyrazine and *s*-tetrazine anion- π complexes. The computed interaction energies are also given.^[109,110]

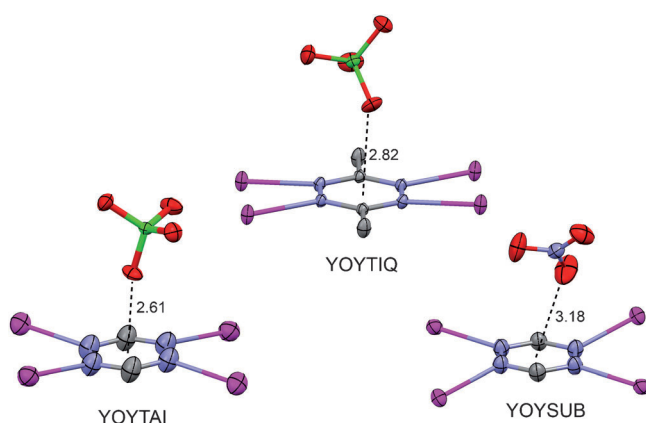


Figure 7. Fragments of the X-ray crystal structures containing μ^4 -coordination of 1,2,4,5-tetrazine and the relevant anion- π interactions, with distances in Å.^[110] The CSD reference codes are indicated.

4. Directionality of the Anion- π Interaction

It is important to define rational criteria which can be used to classify a given anion-aromatic contact as an anion- π bond. In the same sense that the hydrogen bond should not be restricted to linear XH...Y contacts at X–Y distances $< \Sigma \text{vdW radii}$, it is clearly incorrect to limit the anion- π interaction to situations where the anion is exactly over the center of the ring at anion-centroid distances $< \Sigma \text{vdW radii}$. In fact, since aromatic rings are often electronically asymmetric, the most favorable location is usually not directly above the center of the ring. Furthermore, anion- π complexes are generally observed in the solid state, and isotropy is almost never experienced in the local environment of a crystal, where counterions, possibly solvent molecules and, of course, other rings are packed into a lattice. Thus, the equilibrium position of the anion with respect to the aromatic ring will vary with the particular circumstances. Since the π -system encompasses the entire ring, the broadest, but arguably most appropriate, criterion would be to invoke anion- π bonding when the anion is located anywhere within the ring boundary at distances $\leq \Sigma \text{vdW radii} + d$, where “*d*” is an increment distance that has to be defined. In a high-level study of the energetics of anion- π bonding, Estarellas and co-workers recommended a value of 0.8 Å for *d*.^[111] In time, other values may be put

forward. Looking again to the hydrogen bond as an example, it is described by a wide range of interaction distances and angles, and for this reason may be classified as either strong, moderate or weak. However, neither the name, nor the nature of the interaction changes. The occurrence of the hydrogen bonding is generally rationalized using the concept of lone pairs of electrons as the acceptor, and thus hydrogen bonds involving carbonyl groups commonly have $\text{C}=\text{O}\cdots\text{H}$ angles near 120° . However, this is not a strict condition, and a wide scatter found in $\text{C}=\text{O}\cdots\text{H}$ angle histograms in different H-bonded systems.^[112]

The directionality of the anion- π interaction has been recently investigated and compared with that of the cation- π interaction. In one report,^[113] it was shown that anion- π interactions involving close interactions of anions with the center of neutral aryl rings are uncommon in the CSD. Given the restrictive geometric search criteria used in that work, and the fact that the majority of X-ray crystal structures in which anions and aromatic rings appear together involve charged aromatics (usually N-heterocycles), this was a foregone conclusion. As noted above, the equilibrium position of an anion is often displaced away from center of the ring in anion- π complexes, while cations show a stronger preference to align to the ring axis. This behavior can be explained by analyzing how the interaction energy is affected by incrementally moving an anion from the center to the periphery of the ring in an anion- π complex and comparing it to the same movement in a cation- π complex. Thus, the directionality observed for the chloride-hexafluorobenzene complex has been compared to that of the sodium-benzene complex.^[111] The results are useful to explain the experimental (crystallographic) differences between these ion- π interactions. Figure 8 shows the interaction energies calculated for the chloride-hexafluorobenzene system as the ion is translated

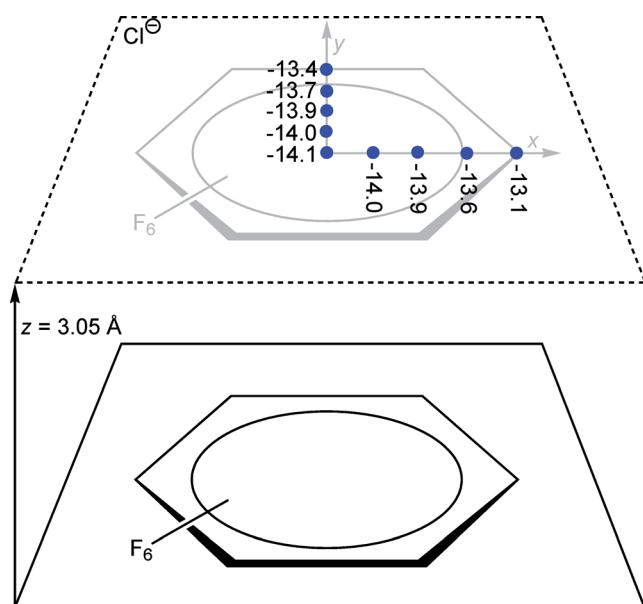


Figure 8. Points mapped in the plane parallel to the C_6F_6 ring and corresponding energies for interaction with the Cl^- ion. Energies with basis set superposition correction in kcal mol^{-1} .^[111]

along the x and y axes. Starting at the potential energy minimum point at the centroid ($z = 3.05 \text{ \AA}$), it can be seen that the interaction energy shows only a very modest change (less than 1 kcal mol^{-1}) when Cl^- is moved in either direction. Thus, the anion can be located at any point over the hexafluorobenzene ring without losing much in the way of interaction energy with respect to the minimum. The analogous results for the sodium-benzene complex are shown in Figure 9. In this case, the plane in which the cation moves is located at Na^+ -benzene centroid equilibrium point ($z = 2.42 \text{ \AA}$). Displacement in both directions shows that the energy loss is substantially greater here (ca. 20 %) than for the anion- π interaction (ca. 5 %) represented in Figure 8. This result offers an explanation for the experimental findings^[113] that show more scatter in the location of the ion in anion- π versus cation- π complexes when analyzing crystal structures in the CSD.

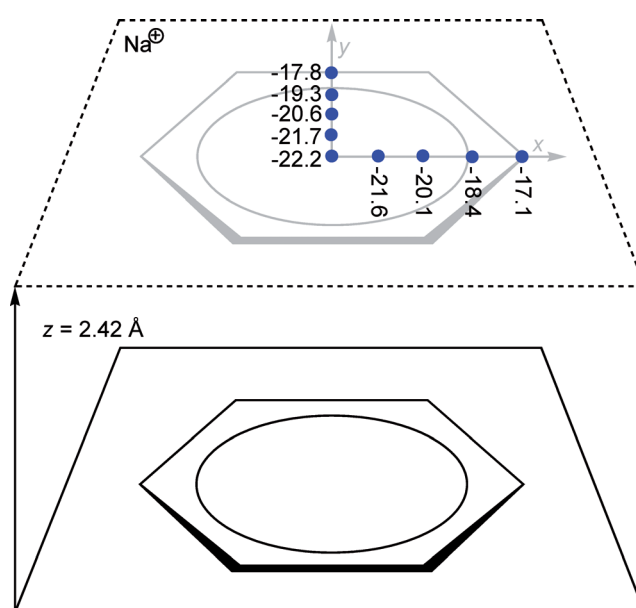


Figure 9. Points mapped in the plane parallel to the C_6H_6 ring and corresponding energies for interaction with the Na^+ ion. Energies with basis set superposition correction in kcal mol^{-1} .^[111]

Figure 10 shows the interaction energies and anion-centroid distances of the $\text{Cl}^- \cdots \text{hexafluorobenzene}$ complex computed at several points along the main symmetry (z) axis. The results show that the effect of moving the anion away from the centroid has a strong influence on the interaction energy. It was mentioned earlier that electrostatic and polarization effects dominate the anion- π interaction. Both contributions are dependent on distance, thus the interaction energy markedly decreases as the anion moves away from the origin. However, it should be noted that the relative decrease in energy for the anion- π interaction at the first increment ($0.35 \text{ \AA}$) is half that for cation- π . Thereafter, the bonding energy diminishes at about the same relative rate, although even at a $0.70 \text{ \AA}$ offset, the anion- π bond energy is still 80% of that at the origin. This indicates that the anion- π interaction has a more shallow minimum along all three

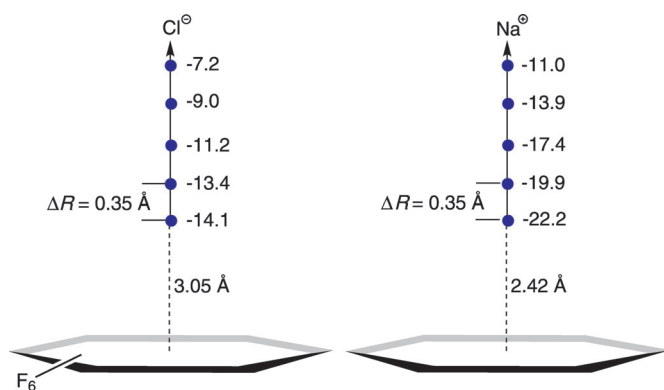


Figure 10. Schematic representation of the points along the C_6 axis in C_6F_6 (left) and C_6H_6 (right) where the interaction energies with Cl^- and Na^+ , respectively (blue points), have been computed. Energies with basis set superposition correction in $kcal\ mol^{-1}$.^[111]

axes of displacement from the aryl centroid than does cation- π .

5. Selected Experimental Examples of the Anion- π Interaction

While molecular modeling can provide valuable insights into the nature and energetics of previously unrecognized modes of bonding, the model remains a purely theoretical one in the absence of experimental validation and predictive ability. Crystal structures are the traditional proving ground for structural evidence of unconventional bonding relationships, and careful analysis often reveals features that had not been noticed by the authors who originally published the data. Since the earliest papers which described the anion- π interaction,^[52–54] the CSD^[80] has been used to provide experimental evidence of its occurrence in the solid state. To date, a great deal of experimental work has provided strong evidence of this emerging noncovalent design principle. In the following sections, we present selected experimental examples where anion- π interactions are strongly evident. These examples are organized with respect to the experimental medium (solution, solid state, and gas phase) in which they occur.

5.1. Evidence of Anion- π Interactions in Solution

Maeda et al. have recently published two papers devoted to the study of anion receptors based on tetra-perfluorophenyl-substituted N-confused porphyrin (**FNCP**) in solution (Figure 11).^[114,115] The association constant (K_a) values of divalent metal complexes of **FNCP** (M^{II} -**FNCP**) for anions in CH_2Cl_2 follow the order $F^- > Cl^- > Br^- > I^-$ (Table 4). The small differences between the metal complexes has been attributed to the total charge included in the core cation which affects the acidity of peripheral NH. The association constants of the analogous divalent metal complexes of tetraphenyl-substituted N-confused porphyrin (M^{II} -**HNCP**) with Cl^- are very small ($< 10M$), indicating that the influence

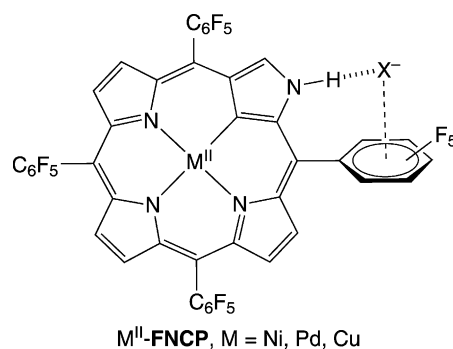


Figure 11. Representation of the interaction between a tetra-perfluorophenyl-substituted N-confused porphyrin divalent metal complex (M^{II} -**FNCP**) and a halide.^[114,115]

Table 4: Association constants (K_a , M^{-1}) of tetra-perfluorophenyl-substituted N-confused porphyrin M^{II} complexes with halides after Maeda et al.^[114]

Anion	Ni^{II}	Pd^{II}	Cu^{II}
F^-	$> 3 \times 10^5$	$> 3 \times 10^5$	$> 3 \times 10^5$
Cl^-	5.7×10^4	4.6×10^4	4.9×10^4
Br^-	8.4×10^3	1.4×10^4	6.9×10^3
I^-	1.2×10^3	3.0×10^2	1.2×10^3

of the pentafluorophenyl ring is important. The higher K_a values of M^{II} -**FNCP** than M^{II} -**HNCP** were attributed not only to the enhancement of acidity of the NH group due to electron-withdrawing effects but also to the accompanying anion- π interaction. The interaction of neighboring C_6F_5 group with anions was also implied by ^{19}F NMR experiments.

In related work, Berryman and co-workers prepared a receptor molecule incorporating a similar two-point recognition motif involving a hydrogen bond donor and a perfluorophenyl ring (Figure 12).^[116] As a control, an analogue lacking the fluoro substituents was also studied. Any enhanced affinity for anions that the former receptor exhibits over the latter should be chiefly the result of a favorable anion- π interaction. This was the first neutral receptor molecule designed to make use of the anion- π interaction to bind anions in solution. 1H NMR spectroscopic titration experiments were performed for both receptors with tetra-*n*-butylammonium chloride, bromide and iodide salts in $CDCl_3$. The reported K_a values are included in Figure 12, and show the significant differences between the two receptors and a given halide. The receptor incorporating the electron-defi-

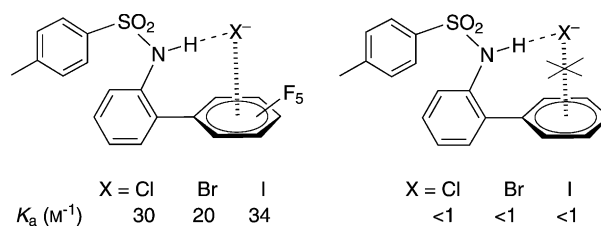


Figure 12. Anion receptors synthesized by Berryman et al.^[116] and their association constants with halides in $CDCl_3$.

cient ring binds all the halides with a measurable, albeit modest association constant. However, in the case of the receptor where no electron-deficient ring is present, there is no measurable association with any of the halides. It was also shown that the lower pK_a value of sulfonamide N-H in the fluorinated system could not explain the affinity difference. These data provide good support for anion- π bonding in solution, highlighting the possibility of utilizing the interaction in receptor design.

Berryman and co-workers have also published an experimental and theoretical study on a series of neutral tripodal hosts that solely employ electron-deficient arenes to bind halides in solution (Figure 13).^[117] The authors prepared 2,4,6-trisubstituted 1,3,5-triethylbenzene derivatives differing only

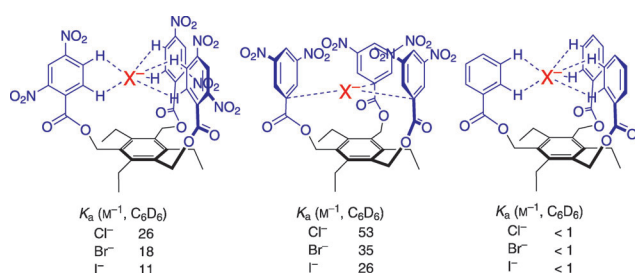


Figure 13. Anion-receptor synthesized by Berryman et al.^[117] and their association constants with halides in C_6D_6 .

in the position of their nitro substituents, which provided access for anions to interact with the electron-deficient cavities either by the π -system or by $CH\cdots X^-$ hydrogen bonding (Figure 13, left and middle receptors). The structures incorporate “steric gearing” to preorganize the electron-deficient cavity, and represent the first receptors designed to quantitatively measure weak bonding between anions and arenes. 1H NMR spectroscopy was used to determine the anion binding constants (K_a) and to establish the nature of the interaction. The key feature in the design strategy is that the middle receptor in Figure 13 cannot form hydrogen bonds to anions due to the bulky nitro groups being positioned *ortho* to the aryl hydrogens, thereby allowing the study of the interaction between the anion and the π -system. The receptor on the right was used as a control. The association constants determined for the hosts based on electron-deficient arenes was $11\text{--}53\text{ M}^{-1}$, while the control molecule exhibited no measurable binding. These results supported the hypothesis that electron-deficient aromatic rings are required to bind anions in this neutral system. Significantly larger 1H chemical shift changes were observed for the left receptor over those of the middle receptor, consistent with the fact that the former can participate in aryl $CH\cdots X^-$ H-bonds while the latter cannot. The highly electron-deficient middle receptor was determined to adopt a binding motif involving weak σ -type anion- π contact. The receptors exhibited the strongest interactions with Cl^- followed by Br^- and I^- , and the largest association constants were observed when the halide was forced to interact solely through contacts to the π -system (Figure 13, middle receptor).

Yet another study devoted to measuring the binding energy of anion- π interactions within neutral receptors has been published by Ballester and collaborators.^[118] In this work, a series of *meso*-tetraaryl calix[4]pyrrole receptors were used to quantify chloride- π interactions in solution (Figure 14). By means of 1H NMR spectroscopy and X-ray crystallography it was demonstrated that chloride-arene interactions are established deep within the electronically tunable cavity of this system. The derived quantitative Hammett free-energy relationship was used to show that the observed chloride- π interactions were dominated by electrostatic effects.

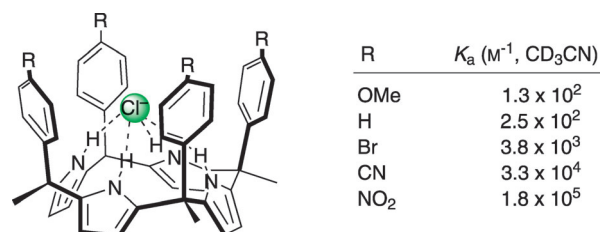


Figure 14. *meso*-Tetraaryl calix[4]pyrrole receptors synthesized by Ballester et al.^[118] and their association constants with chloride in CD_3CN .

Heteroatom-bridged heteroaromatic calixarenes are an emerging class of macrocycles that have been utilized recently as versatile host molecules in supramolecular chemistry.^[119,120] A representative example is tetraoxacalix[2]arene[2]triazine (Figure 15), which preferentially adopts a 1,3-alternate conformation, forming a cleft between the two π -electron-deficient triazine rings. Recently, Wang et al.^[121] reported halide recognition by tetraoxacalix[2]arene[2]triazines in which significant substituent effects were observed. Thus, macrocycles with *N,N*-dimethylamino substituents showed no change in either the absorption or emission spectra when titrated with fluoride, chloride, or bromide. The unsubstituted calixarene interacted weakly with fluoride but not with chloride or bromide. However, the chlorine-substituted host formed 1:1 complexes with both fluoride and chloride, with binding constants of $4036 \pm 36\text{ M}^{-1}$ and $4246 \pm 83\text{ M}^{-1}$, respec-

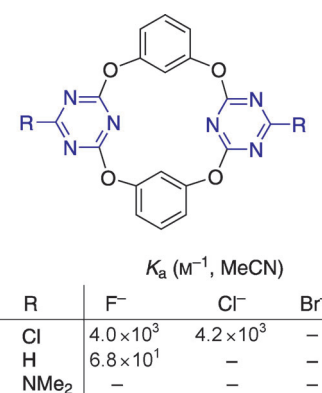


Figure 15. Macroyclic anion receptors synthesized by Wang et al. and their association constants with Bu_4N^+ halides in MeCN.^[121]

tively. This effect was attributed by the authors to the electron-withdrawing nature of the chloro substituent.

The work of Matile's group on the application of anion- π interactions to selective anion transport across lipid bilayer membranes merits special mention here.^[69–75] In biology, the selectivity of ion transport is of vital importance, and in the case of cations is generally achieved by ion coordination to preorganized arrays of oxygen lone pairs, with cation- π interactions also playing a potential role.^[122] In biological anion channels, hydrogen bonding, ion pairing, and anion-dipole interactions contribute to selectivity. Up to now, no anion- π bonding has been observed in natural anion channels. However, the challenge of bringing anion- π interactions to bear on transmembrane anion transport has been taken on by Matile. To achieve this, anion recognition must be combined with anion translocation. The combination involves a delicate balance of effects, because tight binding tends to hinder ion movement. In biological ion channels, the placement of multiple binding sites in series combines selectivity with favorable kinetics.^[123,124] The cooperative transport of ions by this means is referred to as multi-ion hopping.^[69–73] To achieve significant transmembrane transport using anion- π interactions, it is therefore necessary to present multiple π -deficient binding sites along the channel. Anions could then be transported quickly and selectively along these anion- π “slides.” Inspired by an earlier, closely related approach to transmembrane potassium ion transport through cation- π interactions,^[125] Matile and co-workers prepared π -acidic, shape-persistent, rigid-rod oligonaphthalenediimides (O-NDIs) for chloride-selective multi-ion hopping across lipid bilayers (Figure 16). Results from end-group engineering have suggested that self-organization into transmembrane O-NDI bundles is essential for activity. The reported halide topology implies strong anion binding along the anion- π slides with weaker contributions from size exclusion. Anomalous mole fraction effects supported the multi-ion hopping mechanism along the O-NDI rods.

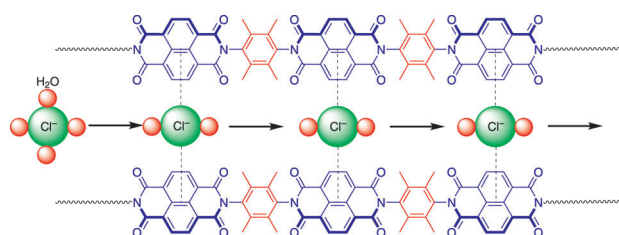


Figure 16. Schematic representation of the anion- π “slide” based on O-NDIs used by Matile and co-workers.^[70]

Matile et al.^[126] have also introduced simple sulfur redox chemistry into the naphthalenediimide framework^[127–131] in order to 1) generate enhanced π acidity, 2) demonstrate the functional relevance of the system by anion transport experiments,^[69–75,131] and 3) to create switchable, chiral, π -acidic surfaces that may be used for applications in asymmetric anion- π actuated catalysis. Thioether core-substituted naphthalenediimides (cNDIs)^[132,133] were oxidized to give chiral sulfoxides and then further to sulfone derivatives (Figure 17).

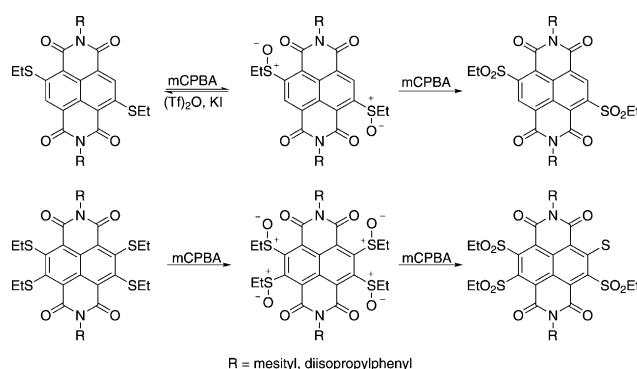


Figure 17. Structures of thioether, sulfoxide, and sulfone core-substituted naphthalenediimides, the anion affinity of which is dependent on the oxidation state of sulfur.^[126] mCPBA = *meta*-chloroperbenzoic acid.

Optoelectronic properties, anion transport activity and computational studies reveal that the tetrasulfone is the most π -acidic cNDI known, with a LUMO energy level 0.43 eV below that of NDI itself.

Chifotides et al.^[134] have carried out insightful studies involving an extended π -electron-deficient molecule with multiple sites available for interactions with anions, namely 1,4,5,8,9,12-hexaazatriphenylenehexacarbonitrile (HAT(CN)₆). The high π -acidity, high molecular polarizability, and positive quadrupole moment of HAT(CN)₆ render it an attractive, neutral heterocyclic system for exploring anion- π and lone pair- π bonding. Interactions between HAT(CN)₆ and the halide salts [*n*Bu₄N][X] (X = Cl[−], Br[−], I[−]) were unequivocally confirmed in solution by UV/Vis, ¹³C-, and halogen NMR spectroscopy. Experimentally, by means of Job plots, the authors found evidence of a 2:3 stoichiometric ratio of [HAT(CN)₆]:[X[−]] suggesting multicentered binding in an unprecedented η^2, η^2 -fashion (Figure 18). The measured association constants in THF at 25 °C are 3780, 2200 and 940 M^{−1} for Cl[−], Br[−], and I[−] respectively. These large *K_a* values are attributed to the high stability of the CT complexes of HAT(CN)₆ and its exceptional acceptor strength, which render it a sensitive, selective molecular scaffold for the effective recognition of anions and a promising colorimetric anion sensor.

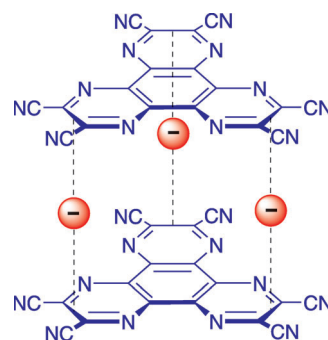


Figure 18. Schematic representation of multisite anion contacts observed in [HAT(CN)₆]₂[X[−]]₃ complexes reported by Chifotides, et al.^[134]

5.2. Evidence of Anion- π Interactions in the Solid State

The anion-aromatic interaction model above described by Chifotides and co-workers^[134] has also been corroborated in the solid state by an X-ray crystal structure of the HAT(CN)₆ bromide complex, in which the faces of HAT(CN)₆ are shown to be closely associated with three anions on one side and a single anion and three benzene rings on the opposite side (Figure 19). The propagation of this columnar structure is clearly orchestrated by anion- π contacts.

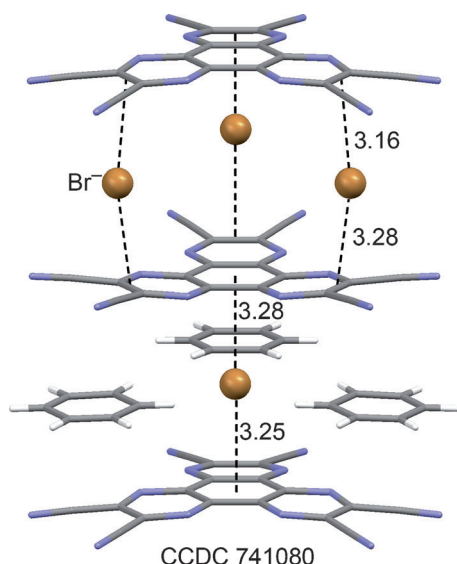


Figure 19. Fragment of the X-ray structure [HAT(CN)₆]₂[Br⁻]₃.^[134]

The first experimental work devoted to the study of anion- π interactions to appear after the publication of the original theoretical work^[52–54] was that of Demeshko et al.^[59] The synthesis and X-ray characterization of a host molecule based on the electron-deficient *s*-triazine ring was reported, where two triazine rings occur in a face-to-face arrangement (Figure 20). The most interesting feature of the crystal structure is the positions of the charge-compensating chloride and CuCl₄²⁻ ions. The chloride anion resides above one of the triazine ring centroids at a distance of 3.17 Å and an 87° Cl⁻-centroid axis-ring plane angle. Both values are in close agreement with those obtained from ab initio calculations for the parent 1,3,5-triazine-chloride complex.^[53] In a likewise manner, the opposite triazine face of the host is capped by the CuCl₄²⁻ ion at a distance of 3.11 Å between one chlorine of the complex ion and the ring centroid.

Another pioneering experimental work was published by de Hoog and co-workers,^[62] who described the synthesis and X-ray characterization of a tetranuclear copper complex of the octadentate ligand *N,N',N'',N'''*-tetrakis[2,4-bis(di-2-pyridyl-amino)-1,3,5-triazinyl]-1,4,8,11-tetraazacyclotetradecane, where four *s*-triazinyl groups stack two by two in a parallel fashion and the copper ions are coordinated by two dipyridylamino groups on the *s*-triazine rings. The coordination spheres of the metal centers are completed by a chloride

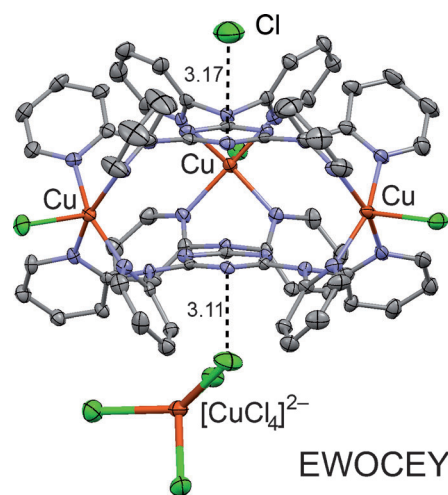


Figure 20. Fragment of the X-ray structure EWOCEY showing the *s*-triazine-based host interacting with Cl⁻ and CuCl₄²⁻ ions through anion- π interactions.^[59]

ligand at the apical position. The key feature of this assembly is the encapsulation of two uncoordinated chloride anions, which are the guests of two host cavities formed by four pyridine rings of the ligand (Figure 21). The anion- π interactions observed here are enabled by the coordination of the pyridine rings to copper, which enhances their π -acidic character.

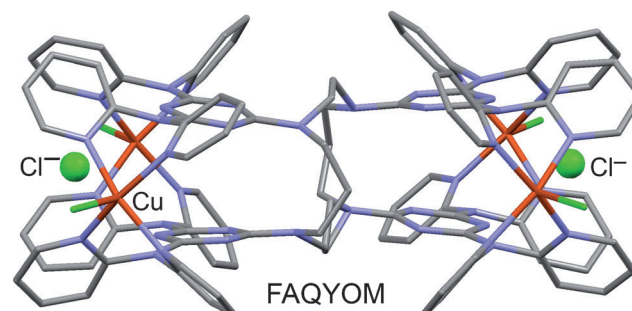


Figure 21. Fragment of the X-ray structure FAQYOM showing the encapsulation of two chloride ions.^[62]

An elegant piece of work by Dunbar and collaborators^[135] describes the comprehensive investigation of an anion-templated self-assembly reaction between first row transition metal ions M^{II} (M = Ni, Zn, Mn, Fe, Cu) and the bis-bipyridine ligand 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz; Figure 22). The formation of polygonal complexes was observed in the presence of certain anions (BF₄⁻, ClO₄⁻, SbF₆⁻), which were found to selectively determine the aggregation state both in the solid state and solution. The formation of molecular squares is dominant in the presence of the BF₄⁻ and ClO₄⁻ ions, while the SbF₆⁻ ion templates a pentagonal oligomer. The competing influence of the anions in stabilizing the different cyclic entities was also studied by mass spectrometry and X-ray crystallography. For example, the [Ni₅]¹⁰⁺ pentagon was found to be less thermodynamically

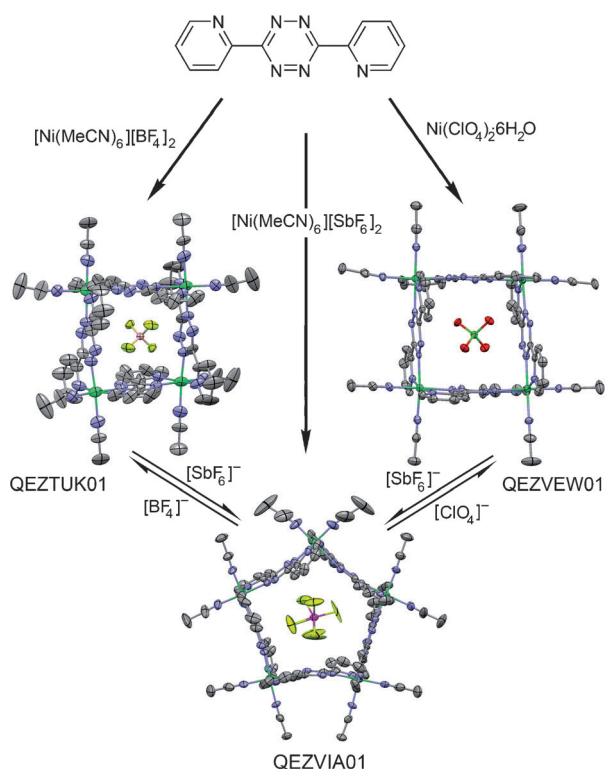


Figure 22. Representation of the cationic units $[\{\text{Ni}_5(\text{bptz})_5(\text{CH}_3\text{CN})_{10}\}\text{SbF}_6]^{9+}$ (QEZVIA01), $[\{\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8\}\text{ClO}_4]^{7+}$ (QEZVEW01), and $[\{\text{Ni}_4(\text{bptz})_4(\text{CH}_3\text{CN})_8\}\text{BF}_4]^{7+}$ (QEZTUK01) and their scheme of interconversion.^[135]

stable than the $[\text{Ni}_4]^{8+}$ square. Ion signals corresponding to the square complex begin to appear in the electrospray ionization mass spectrum after addition of $n\text{Bu}_4\text{N}^+\text{BF}_4^-$ or $n\text{Bu}_4\text{N}^+\text{ClO}_4^-$ to a solution of $[\{\text{Ni}_5(\text{bptz})_5(\text{CH}_3\text{CN})_{10}\}\text{SbF}_6]^{9+}$, and complete conversion of the Ni^{II} pentagon to the square is accomplished by adding an excess of either tetrahedral anion (Figure 22). It was concluded from this study that the nuclearity of the cyclic products is dictated by the identity of the anion present in solution during the self-assembly process, and this could be attributed to a template effect that stabilizes one particular cyclic structure over another due to favorable anion– π interactions between the anion inside the cavity and the bptz ligands.

Dunbar and co-workers have also investigated the role of anion– π interactions in the assembly of Ag^{I} complexes of the bptz ligand.^[136] This work was the first example of a comprehensive investigation of anion– π interactions as controlling elements in self-assembly reactions. The combination of bptz with AgX salts ($\text{X} = \text{PF}_6^-$, AsF_6^- , SbF_6^-) gave complexes of three different structural types, depending on the experimental conditions and the anion used. Reaction of Ag^{I} and bptz in a 1:1 ratio in the presence of PF_6^- ions afforded either a polymer or the discrete molecular compound, whereas in the presence of AsF_6^- ions, the reaction produces only a discrete molecular compound (dinuclear product). Reaction of Ag^{I} and bptz in a 1:1 ratio in the presence of SbF_6^- ions, however, yields the propeller-type compounds, as indicated by X-ray structure determinations (Figure 23). When the ratio of $\text{Ag}:\text{bptz}$ is 2:3, the propeller

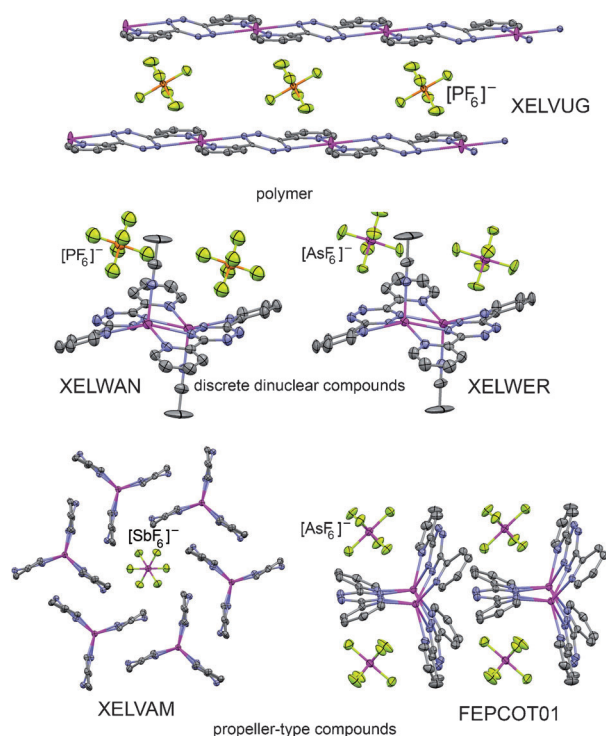


Figure 23. Thermal ellipsoid plots of fragments of crystal structures of several bptz complexes exhibiting different structural types.^[136] The CSD reference codes are indicated.

motif is observed in the presence of the AsF_6^- ions, but not in the presence of PF_6^- ions, where only the polymer or the dimer is obtained in low yield. Apart from the anion size, which plays a role in the packing of the resulting structures, anion– π interactions are a major factor in determining the preferred structural motif. This conclusion was corroborated by the fact that reactions of a similar ligand (bppn, where the central triazine ring has been substituted by a pyridazine) with AgX salts ($\text{X} = \text{PF}_6^-$, AsF_6^- , SbF_6^- , BF_4^-) in a 1:1 ratio lead only to the grid-type structures, regardless of the anion present.^[136]

An additional example of the self-assembly of Ag^{I} coordination networks directed by anion– π interactions has been reported by Zhou et al.^[137] In their study of Ag^{I} metal complexes with 2,4,6-tri(2-pyridyl)-1,3,5-triazine (tpt), they found that polyatomic anions (ClO_4^- , BF_4^- , and PF_6^-) directed the self-assembly of Ag –tpt coordination polymers through anion– π interactions (Figure 24). Reactions of AgX with tpt yielded highly symmetric, isostructural coordination networks where anion– π interactions could be observed between the anions and tpt ligands in the X-ray crystal structures. Notably, all anions in the structures were located on the C_3 -axis above the central triazine rings of the ligands.

A series of coordination polymers formed from Ag^{I} ions and bis(4-pyrimidylmethyl)sulfide have been observed to encapsulate BF_4^- , ClO_4^- , and PF_6^- anions through a uniform mode of anion– π binding.^[138] Bis(4-pyrimidylmethyl)sulfide is a flexible multimodal ligand, able to provide both strong N-donor sites and π -acidic ring centers. The combination of this ligand with AgX ($\text{X}^- = \text{BF}_4^-$, ClO_4^- , and PF_6^-) in a 1:1 molar

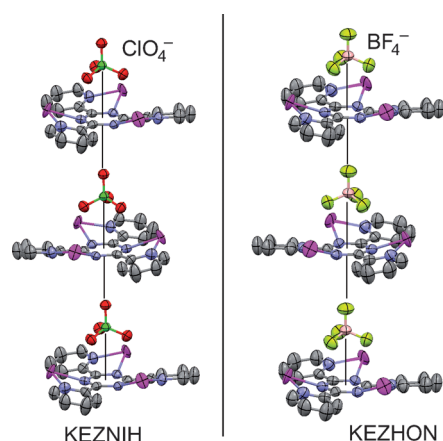


Figure 24. Anion- π assembled isostructural coordination networks of 2,4,6-tri(2-pyridyl)-1,3,5-triazine with ClO_4^- and BF_4^- .^[137] The CSD reference codes are indicated.

ratio gave complexes with two-dimensional (2D) sheet structures characterized by a (4,4) topology. Anions embedded in the cavities formed by this open network were held in place by four complementary π -anion- π sandwich interactions with two pyrimidine rings (Figure 25). Despite involving anions of different sizes, the three structures were isomor-

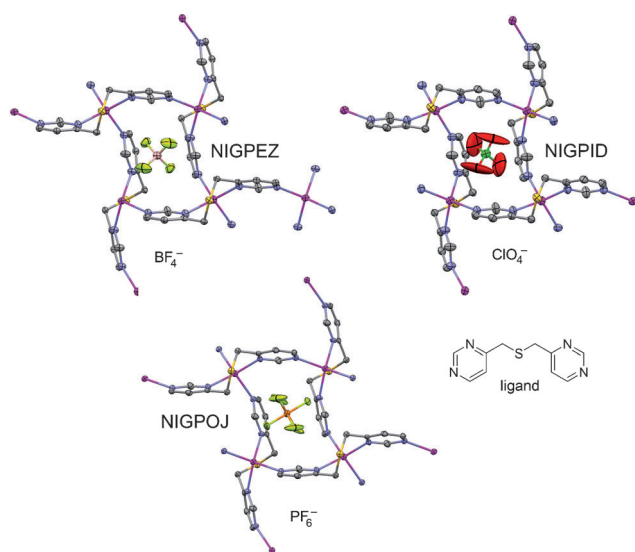


Figure 25. Thermal ellipsoid plots of fragments of the isomorphous structures based on bis(4-pyrimidylmethyl)sulfide.^[138] The CSD reference codes are indicated.

phous.^[138] This important investigation provides further experimental evidence for the usefulness of N-heterocycles in the design of anion receptors by interaction both with transition metals and their counterions through multiple anion- π interactions, demonstrating the potential for the use of anion- π bonding in a structurally directing role.

Mascal and co-workers recently described an application of π -anion- π sandwich bonding in the design^[139] and synthesis^[64] of a highly selective fluoride host. The molecular framework on which the receptor is based is the cylindro-

phane macrobicyclic, in which two planar, six-membered rings are bridged in a threefold symmetric manner by linking chains (Figure 26). In this case, the rings are π -acidic triazinetriones, and the linkers are trialkylamines. Protonation of the amine

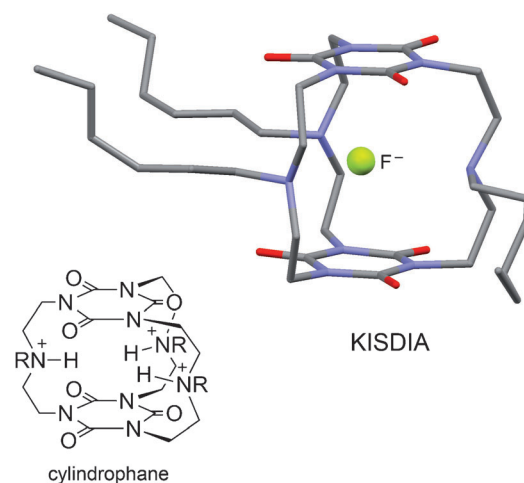


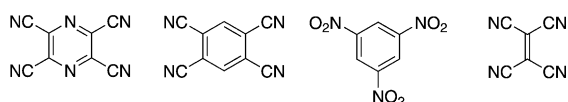
Figure 26. Structure of the fluoride-binding cylindrophane macrocycle and the experimental X-ray structure of the F^- complex (KISDIA).^[64, 139]

groups “arms” the receptor for inclusion through a combination of anion- π interactions and ion-pair-reinforced hydrogen bonding. A theoretical treatment of the receptor described how the two key design principles work together to establish selectivity. First, fluoride ion was shown to benefit from intrinsically stronger π -X- π interactions and $^+\text{NH}\cdots\text{X}^-$ hydrogen bonding than the next closest ion in size, that is, chloride. Next, the tight steric fit of fluoride in the cavity suggested that the inclusion of any other anion was not energetically feasible. Complexation studies were carried out by electrospray mass spectrometry, in which 1:1 binding of the receptor with fluoride was established, while no affinity for chloride was observed. An X-ray crystal structure of the fluoride complex shows F^- occupying the center of the cavity, in very close agreement with the theory. Although a number of halide complexing agents have been described,^[140] this receptor introduces a new genre of anion binding, wherein anion- π interactions operate alongside conventional ion pairing, hydrogen bonding, and the classic “preorganization” effect.

Kochi^[61] and collaborators have experimentally characterized anion- π interactions in an unambiguous way using a series of neutral, highly electron-deficient olefinic and aromatic π acceptors. X-ray crystal structures of well-defined 1:1 complexes between these molecules and halide anions, and the observation of diagnostic charge-transfer absorption bands both point to strong interactions. The authors proposed that charge-transfer effects are the origin of the anion- π interaction, and suggested that the distinctive color changes that attend strong anion- π bonding may be of use in the design of anion-sensing receptors. In follow-up work, the interaction between a series of planar π -acids (cyano- and nitrosubstituted pyrazine and benzene, as well as tetracyanoethylene) with various types of polyatomic anions (thiocya-

nate, nitrate, nitrite, sulfate, sulfite, tetrahalometallates) was investigated.^[61b] Four prototypical π -acids and four classes of anions were used to probe the concept of distinctive hapticities (η) and thus allow for the possibility of multisite interactions with the π -acids (Figure 27). From the viewpoint of supramolecular assembly, this two-component system

π -Acidic acceptors (A):



Anionic donors (D):

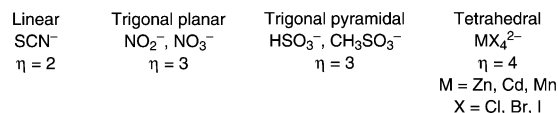


Figure 27. Examples of π -acceptors (A) and anionic donors (D) used by Kochi et al.^[61b] with indication of geometries and hapticities (η) of the anions.

consisting of an anion salt (D⁻) and a π -acid (A) is straightforward in that combination will either lead to separate crystals of the D⁻ salt and A, or cocrystals of [D⁻·A], which can be readily distinguished either by the superimposed electronic absorption spectra of the local bands of the D⁻ salt plus those of A or the hybrid CT band of [D⁻·A]. Since the CT absorption band commonly occurs in the visible spectral region, the formation of cocrystals will be visually apparent by a color change. An important part of this study was the X-ray crystallographic analysis to elucidate the nature of the anion– π interaction in the cocrystals. The self-assembly of the anions with the π -acids yielded a series of novel one-dimensional structures consisting of parallel stacks of alternating π -acids and anions. The organizational and spectroscopic features of these wire-like assemblies was shown to derive from anion– π recognition through charge-transfer.

As described in the previous section, Wang and co-workers^[121] reported halide recognition by tetraoxacalix[2]-arene[2]triazine host molecules in solution based on anion– π interactions. An X-ray crystallographic study of this system revealed the concurrent formation of noncovalent halide– π and lone-pair– π electron interactions between water, halide ion, and the dichlorosubstituted host (Figure 28). An interesting structural feature is that in both the Cl⁻ and Br⁻

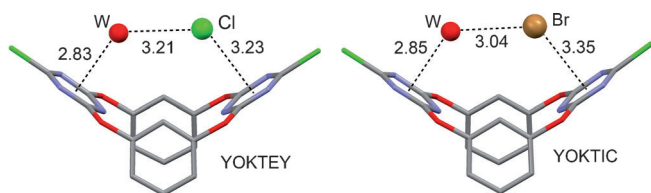


Figure 28. X-ray crystal structures of the complexes between tetraoxacalix[2]arene[2]triazine hosts and chloride (left) and bromide (right), with distances in Å.^[121] The CSD reference codes are indicated.

complexes, the calixarene macrocycle adopts a 1,3-alternate conformation with the two benzene rings being nearly face-to-face while the two π -deficient triazine rings form a V-shaped cleft. Both halides exhibit classic anion– π interactions with the triazine rings. Furthermore, both complexes cocrystallize with water molecules which form ternary complexes between the halide and host (Figure 28). In both cases, the hydrogen-bonded water molecule participates in a lone-pair– π interaction with a triazine ring, as evidenced by the location of the water above the triazine centroid at very short distances of 2.838–2.849 Å. Such close contact excludes the possibility of an OH... π interaction.

5.3. Evidence of Anion– π Interactions in the Gas Phase

Anion– π complexation in the gas phase has been investigated principally by mass spectrometry (MS) experiments. MS offers the advantage that non-solvated complexes are observed, which can be more easily compared to quantum chemical calculations than the corresponding complexes in solution or the solid state.

An early study that combined MS with theoretical modeling of the interaction of C₆F₆ with F⁻, Cl⁻, Br⁻, and I⁻ concluded that while a covalent σ complex was formed with F⁻, the other halides were clustered by C₆F₆ molecules with the ion at the intersection of the C₆ axes.^[141] This 1987 paper embodied the principal elements of the reports which have generally been recognized as the first to identify the anion– π interaction as a noncovalent bond,^[52–54] but was largely overlooked, with only three non-self citations prior to 2002 (the year in which the aforementioned reports appeared).

[HAT(CN)₆]_n:[X⁻] complexes have also been studied in the gas phase, which complements evidence for anion– π bonding in this system from the solution and the solid state.^[134] Results obtained from ESI-MS measurements provided strong evidence that anion– π interactions between halides and HAT(CN)₆ persist in the gas phase by observation of {[HAT(CN)₆]_n:[X⁻]}⁻ complex ions for X = Cl, Br, and I.

Another study^[74] employed electrospray ionization Fourier-transform ion cyclotron resonance tandem mass spectrometry (ESI-FTICR-MS-MS),^[142] which could be used to determine anion affinity sequences quantitatively. Equimolar solutions of naphthalenediimides (NDIs) **A–E** (Figure 29) and salts of different anions were subjected to electrospray

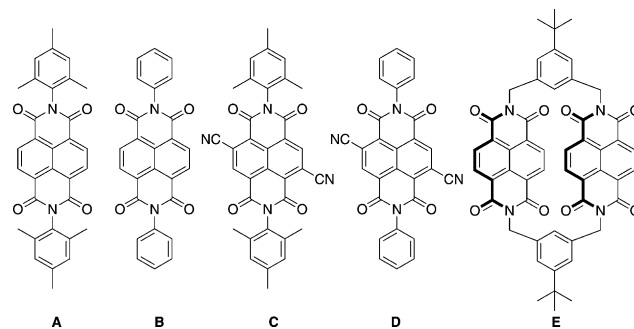


Figure 29. Representation of the structures of NDIs **A–E** used by Matile and co-workers^[74] to probe gas-phase anion affinity.

from acetonitrile under mild ionization conditions. NDI-anion complexes of **A–E** were confirmed for Cl^- , Br^- and NO_3^- . For macrocycle **E**, the further binding of I^- , H_2PO_4^- , OTf^- , and ClO_4^- was also reported. Competition experiments revealed a selectivity sequence for chloride of $\text{D} > \text{C} > \text{B} > \text{A}$, demonstrating an increasing anion affinity with increasing π -acidity and decrowding of the anion- π binding site.

6. Visualization of the Anion- π Interaction

6.1. Criteria Used to Search the CSD

In the past decade, a number of data-mining exercises using the CSD have been carried out in order to provide experimental evidence of anion- π interactions in the solid state. Depending on the search criteria applied in these investigations, the result has varied from the identification of numerous examples of anion- π bonding relationships^[52,77,82,85–88] to few, if any.^[113]

As discussed earlier, the choice of criteria that characterize a genuine anion- π bond is central to this undertaking. One approach has been to allow certain deviations from the DFT-calculated geometry for specific anion-molecule pairs, and to explore whether these are observed in the CSD.^[113] However, as discussed in Section 4, the geometric parameters for gas phase anion- π contact obtained by DFT calculations cannot be strictly applied as criteria for a statistical analysis of solid-state structures. Expanding on the issue of geometric criteria, it has been made clear, both in theoretical and experimental studies, that anion- π bonding is *not* the dominant mode of interaction between anions and electron poor aromatic rings; in fact, it is energetically the weakest of the three (versus H-bonding and σ -complexation). Thus, simple statistical studies that directly compare anion- π bonding to stronger interactions may come to misleading conclusions. Also, the representation/interpretation of the data retrieved from the CSD constitutes a further drawback. For all CSD surveys thus far reported, two-dimensional (2-D) scatter plots have been used to visualize data that are actually three-dimensional (3-D) in nature. Consequently, such plots can be difficult to interpret and are also potentially misleading.

With the aim to avoid the above pitfalls, we have re-evaluated selected CSD data of relevance to anion- π and lone-pair- π contact and have employed IsoStar^[143] to visualize the results. IsoStar is distributed as part of the CSD suite of programs,^[143] and can be used to produce contour plots that describe the 3-D distribution of a contact group around a specific central group. In carrying out this study, we have applied search criteria which are, according to the published literature, accepted by the majority of investigators working in the field (see Supporting Information for full details). The first criterion defines the interaction between an anion and an aromatic ring, when at least one atom of the anion and one atom of the aromatic ring are within the sum of their van der Waals radii. The exact position of the anion over the ring will then determine whether the interaction can be best described as a hydrogen bond (at the ring periphery, if hydrogen atoms are present on the ring), a σ complex (along a Dunitz-Bürgi-

like trajectory), or a π complex (in the vicinity of the ring centroid). The second criterion applied here states that any heterocyclic ring has to be neutral, that is, cannot be protonated. While we ourselves are strongly of the opinion that, even if the ring is charged, the interaction should still be characterized as an anion- π bond, we impose this criterion here in order to retrieve examples of what might be considered anion- π bonding in its “purest” form, uncomplicated by other potential structure-defining elements. Thus, if the pair meets these criteria, the interaction is considered an anion- π interaction for the purposes of this statistical exercise. Using this query dialog, unambiguous evidence of the directional character of the anion- π interaction, as well as the lone pair- π interaction, is obtained.

6.2. Anion- π Interactions in Three Dimensions

A combination of three different aromatic rings, that is, phenyl (C_6H_5), charge-neutral pyridine (NC_5H_5), and pentafluorophenyl (C_6F_5) with two common and weakly coordinating anions^[144] (BF_4^- and ClO_4^-) was subjected to the present CSD query (see Supporting Information for full details). The IsoStar plots shown in Figure 30 and 31 were generated from

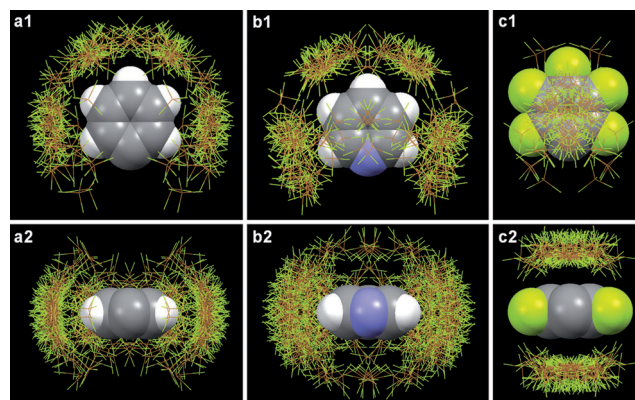


Figure 30. Top (1) and side (2) views of the distribution of the hits characterizing the contacts between BF_4^- anions and aromatic six-membered rings: a) $-\text{C}_6\text{H}_5$, b) NC_5H_5 , and c) $-\text{C}_6\text{F}_5$, as visualized with IsoStar. All hits are within the sum of the van der Waals radii of the interacting F atom of BF_4^- and an atom of the six-membered ring. C gray, H white, N blue, F yellow, B orange.

this data. As is apparent in Figure 30a, for the phenyl- BF_4^- pair, almost all of the anions are located at the periphery of the ring. A similar feature is observed for the neutral pyridine- BF_4^- pair (Figure 30b). In contrast, for the pentafluorophenyl- BF_4^- pair (Figure 30c), all anions are located above the ring, although not necessarily directly above the centroid (refer back to Section 4 for an interpretation of this scatter).

A comparable trend is found for pairs involving ClO_4^- anions. As is seen in Figure 31a, nearly all ClO_4^- anions are positioned at the periphery of the ring for the phenyl- ClO_4^-

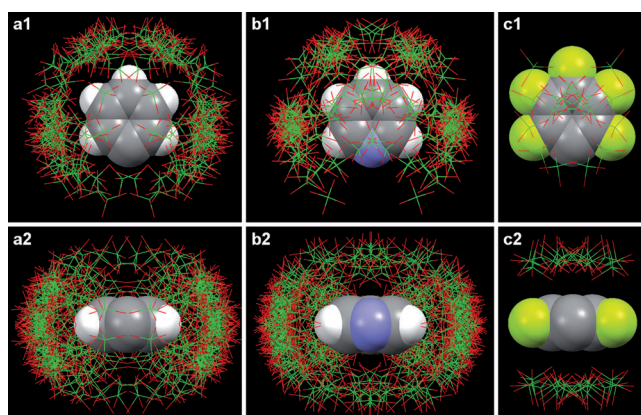


Figure 31. Top (1) and side (2) views of the distribution of the hits characterizing the contacts between ClO_4^- anions and aromatic six-membered rings a) $-\text{C}_6\text{H}_5$, b) NC_5H_5 , and c) $-\text{C}_6\text{F}_5$, as visualized with IsoStar. All hits are within the sum of the van der Waals radii of the interacting O atom of ClO_4^- and an atom of the six-membered ring. C gray, H white, N blue, F yellow, Cl green, O red.

pair. Likewise, for the pyridine- ClO_4^- pair (Figure 31 b), most of the anions are also located at the ring periphery, although some are found above the ring. This difference between the pyridine- BF_4^- and pyridine- ClO_4^- pairs may be explained by a higher number of hits for the pyridine- ClO_4^- contact. Once again, for the pentafluorophenyl ring, all anions are located above the ring (Figure 31 c). Hence, as the aromatic ring becomes more electron-deficient, anions cluster above it. A similar tendency was observed in a more general study of molecule-ion pairs involving BF_4^- or ClO_4^- anions and six-membered heteroaromatic rings (C_{6-n}N_n , $n = 0-3$). The anion clustering above the ring was found to increase along the series $[\text{C}_6] < [\text{C}_5\text{N}] < [(o,m,p)\text{-C}_4\text{N}_2] < [s\text{-C}_3\text{N}_3]$ (see Supporting Information for details).

6.3. Anion + Lone Pair- π Interactions in Three Dimensions

Stimulated by these findings, a comprehensive CSD search for interactions between a C_6F_5 entity and any common electron-rich heteroatom (N, O, F, S, Cl, Br, I) was undertaken, analogous to a similar study carried out in an earlier report.^[113] Since no charge is specified, this search will retrieve both anion- π and lone pair- π contacts. As is evidenced by the 3-D representation depicted in Figure 32 a, a large number of electron-rich atoms are located within a 7 Å envelope of space around the ring centroid. However, the only hits in which both fragments lie within the sum of their van der Waals radii are located above the ring (Figure 32 b). When the criterion is loosened to the sum of the van der Waals radii + 0.25 Å, most of the hits are still found above the ring (see Figure S5 in the Supporting Information). This result is further confirmed by the contour plots displayed in Figure 32 c. These data suggest that the electron-deficient pentafluorophenyl π -system has a strong affinity not only for BF_4^- and ClO_4^- anions, but for electron-rich atoms in general.

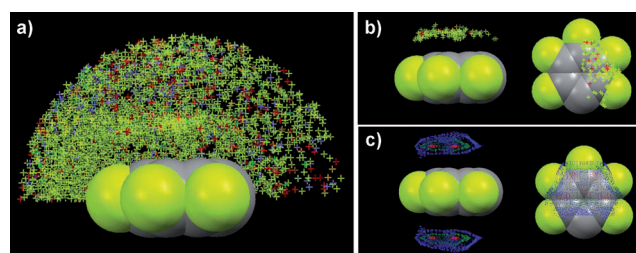


Figure 32. Distribution of the hits characterizing the contacts between a C_6F_5 group and a heteroatom (N, O, S, F, Cl, Br, or I) in the CSD using IsoStar: a) side view of the asymmetric unit; b) side and top view of all hits that are within the sum of the van der Waals radii of the interacting atom and an atom of the $-\text{C}_6\text{F}_5$ ring; c) side and top view of the IsoStar contour-plot, using the internal scaling option [75 (red), 50 (green), 25 (blue)]. In internal scaling, the position of the maximum contact-atom density is arbitrarily assigned a contour level of 100. Every other density value is then scaled relative to this). N blue, O red, S orange, F yellow, Cl green, Br brown, I pale green.

7. Concluding Remarks

The purpose of this Review has been to showcase the bonding relationship between anions and π systems by describing work at the experimental and theoretical forefront of this interaction and demonstrating its exceptional potential to impact the field of supramolecular science. In a 1997 review, Ma and Dougherty wrote: “It is now clear that cation- π interactions are prominent in a wide range of systems and should be considered as an important and general noncovalent binding force.”^[26] Even so today, in that same spirit, the scientific community is being awakened to the potential of the anion- π interaction and the corresponding opportunities it presents for the design of novel sensors, hosts, catalysts, and materials. We look ahead with great anticipation to what the future holds for the science of this newly recognized non-covalent bond.

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