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Experimental Quantification of Anion−π Interactions in Solution Using Neutral Host−Guest Model Systems

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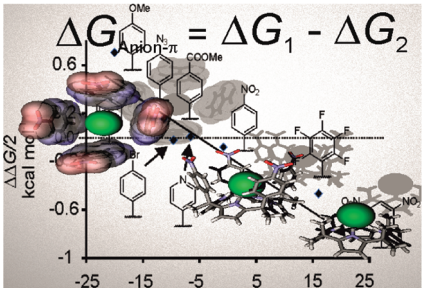

Chemical intuition suggests that anions and π-aromatic systems would repel each other. Typically, we think of cations as being attracted to electron-rich π-systems of aromatic rings, and the cation−π interaction, a well-established noncovalent interaction, plays an important role in nature. Therefore the anion−π interaction can be considered the opposite of the cation−π interaction. Computational studies of simple models of anion−π interactions have provided estimates of the factors that govern the binding geometry and the binding energy, leading to a general consensus about the nature of these interactions. In order to attract an anion, the charge distribution of the aromatic system has to be reversed, usually through the decoration of the aromatic systems with strongly electron-withdrawing groups. Researchers have little doubt about the existence of attractive anion−π interactions in the gas phase and in the solid state. The bonding energies assigned to anion−π interactions from quantum chemical calculations and gas phase experiments are significant and compare well with the values obtained for cation−π interactions. In solution, however, there are few examples of attractive anion−π interactions.

In this Account, I describe several examples of neutral molecular receptors that bind anions in solution either solely through anion−π interactions or as a combination of anion−π interactions and hydrogen bonding. In the latter cases, the strength of the anion−π interaction is indirectly detected as a modulation of the stronger hydrogen bonding interaction (enforced proximity). The dissection of the energy contribution of the anion−π interaction to the overall binding is complex, which requires the use of appropriate reference systems.

This Account gives an overview the experimental efforts to determine the binding energies that can be expected from anion−π interactions in solution with examples that center around the recognition of halides. The studies show that anion−π interactions also exist in solution, and the free energy of binding estimated for these attractive interactions is less than 1 kcal/mol for each substituted phenyl groups. The quantification of anion−π interactions in solution relies on the use of molecular recognition model systems; therefore researchers need to consider how the structure of the model system can alter the magnitude of the observed energy values. In addition, the recognition of anions in solution requires the use of salts (ion pairs) as precursors, which complicates the analysis of the titration data and the corresponding estimate of the binding strength. In solution, the weak binding energies suggest that anion−π interactions are not as significant for the selective or enhanced binding of anions but offer potential applications in catalysis and transport within functional synthetic and biological systems.

Introduction

In close analogy to the cation−π interaction,[1] the term anion−π interaction was coined in 2002 by Frontera, Deyà, and co-workers to describe the attractive and noncovalent contact geometry, derived from quantum chemistry calculations, in which an anion is placed above the center of an aromatic ring.[2] In the same year, three other reports also dealing with theoretical calculations supported the existence "in silico" of attractive interactions between arenes decorated with electron-withdrawing substituents,[3,4] as well as *s*-triazine,[5] and anions centered over their π-cloud. These findings ignited great interest in the scientific community for the study of the physical nature of anion−π interactions and their quantification by means of theoretical

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and experimental investigations. Several reviews of these investigations have already appeared in recent years.[6–15] I refer the reader to this recent literature for a more exhaustive coverage of some of the topics briefly mentioned here.

Computational studies on simple models of anion–π interactions have provided estimates of the factors that govern the binding geometry and the binding energy. These studies yield a general consensus on the noncovalent nature of the interaction for most anions. Evidence that this binding motif leads to stable halide–hexafluorobenzene complexes in the gas phase is indisputable.[16,17] The results of several searches performed in the CSD database for examples of anion–π interactions involving neutral C_6 and $C_{6-n}N_n$ aromatic rings provided puzzling conclusions.[2,4,18] The problem is how to define the type of contact geometry that constitutes evidence of anion–π contact. I will not dwell on these theoretical, gas-phase, and solid-state studies here; rather, this Account focuses on the experimental investigations providing real quantifiable evidence of anion–π interactions in solution.

The origin of this supramolecular interaction can be traced to many years prior to 2002;[10] in fact as early as 1986 Chowdhury and Kebarle discussed the bonding of hexafluorobenzene (C_6F_6) with chloride in the gas phase, despite the absence of hydrogen atoms in C_6F_6.[17] Anion–π interactions were neglected for many years as a suitable noncovalent interaction for anion binding in solution. This was mainly because chemical intuition suggests a repulsive force for the interaction of anions with π-systems of aromatic compounds. Today, however, great enthusiasm exists concerning the potential application of anion–π interactions for the design of novel hosts, carriers, catalysts, and materials. Recent reports of anion–π interactions in biological systems have engendered further interest.[12,19,20] All this is reflected in the rapidly increasing number of examples of anion–π interactions that are reported. Even so, the detailed and accurate thermodynamic characterization of anion–π interactions in solution has not been achieved. In the following section, I will guide the reader in a more or less chronological order through a series of selected experimental findings, which are relevant in order to shed some light on the magnitude of the interaction energies that can be expected from anions interacting with uncharged aromatic rings in solution. Because of the unique Lewis and Brönsted basicity properties of fluoride, the interaction of this anion with aromatic systems usually produces different results from those obtained with other halides or other anions. In most of the examples presented in the next section, the special behavior observed for the fluoride–π interaction will not be commented upon.

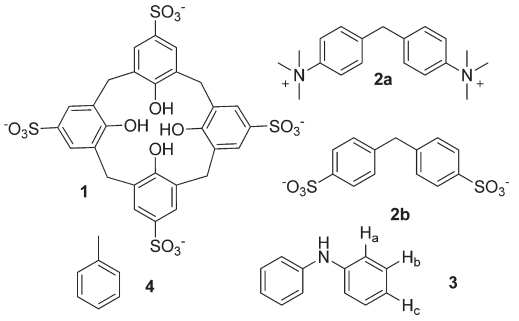


FIGURE 1. Structures of the hosts **1** and **3** and guests **2a**, **2b**, and **4**.

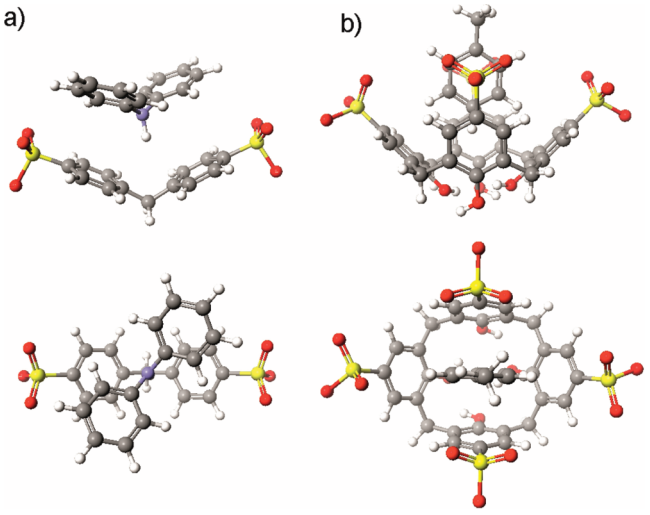


FIGURE 2. Side and top views of the CAChe[23] minimized structures of complexes (a) **2b**·**3** and (b) **1**·**4**.

Experimental Investigations of Anion–π Interactions in Solution

In 1993, using simple force-field calculations, Schneider et al.[21] selected several host–guest systems capable of adopting a complex conformation in which a negatively charged residue ($-SO_3^-$) is placed in perpendicular arrangement and close contact with a π-surface (Figures 1 and 2).

Values in the range of -0.5 kcal/mol were reported for the attraction between the aromatic system and the negatively charged residue.[22] The similar association constant values obtained for **2a** and **2b** upon binding **3** were used as evidence of the analogy between the interactions of positive or negative charges and polarizable aromatic groups. In striking contrast, the assignment of putative structures for the complexes **2a**·**3** and **2b**·**3** indicated a very different arrangement of the interacting partners in the corresponding complexes. Thus, the **2a**·**3** complex adopted a complex

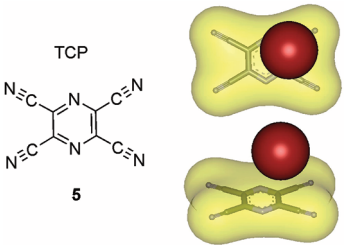


FIGURE 3. Molecular structure of TCP and illustrations of the anionic complex [TCP/Br]$^-$ formed in solution.

geometry with all the *para*-carbons and the CH_2 and NH atoms of both host and guest in one plane. In contrast, the binding geometry assigned for the **2b**·**3** complex showed a displacement of the aryl rings of the interacting partners (Figure 2).

The free energy for the **1**·**4** complex is of the same order of magnitude as the value measured for **2b**·**3**. In the former case, however, the ion-induced dipole attraction provided by the two sulfonato groups perpendicularly oriented to the phenyl ring of the guest could be assisted by attractive interactions between the two parallel oriented sulfonato groups and the positively charged protons of the toluene guest (anion–π interaction displaying hydrogen bond mode contact). These early measurements of anion–π interaction energies likely represent a combination of both π-stacking and anion–arene interactions.

In 2004, the behavior of halides in acetonitrile solution with a series of cyano-derivatives of arenes and the heterocyclic compound tetracyanopyrazine (TCP) **6** was reported (Figure 3).[24] The existence of a clear Mulliken correlation between the energy of the lower energy band that appeared in the spectra of the UV–vis titrations and the oxidation potential of the anion was used to establish the charge-transfer (CT) character of these complexes. A Job plot indicated that the anionic [TCP/Br]$^-$ complexes formed in solution had a 1:1 stoichiometry. The stability constant values reported for the complexes of TCP with Br^- as different tetraalkylammonium salts using UV–vis titrations were in the range of 7–9 M^{-1} ($\Delta G = -1.3$ kcal/mol). In acetonitrile solution and at the concentration used in this study, the halide salt and the ion-paired complex can be considered to be almost fully dissociated. In fact, the analysis of the solution titration data (Drago procedure) was performed considering complete dissociation of the halide ion pair and exclusive formation of a 1:1 anionic species.

More recently, Furuta et al. described[25,26] the outstanding properties of metalated (M = Ni(II), Pd(II), Cu(II)) N-confused porphyrins (NCP) **6**·M (Figure 4) as molecular receptors for

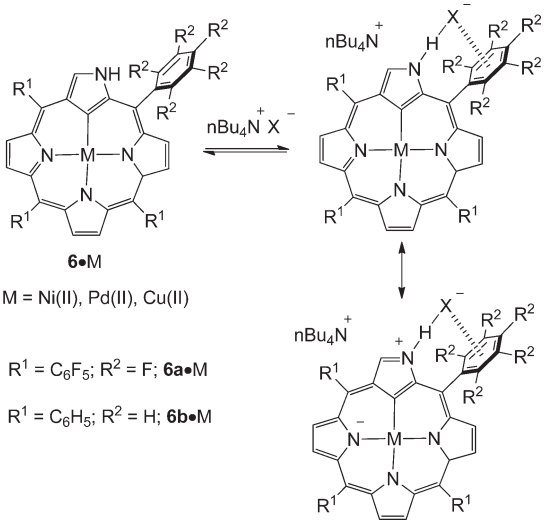


FIGURE 4. Molecular structures of the NCPs **6**·M and their complexes with TBAX.

halides in dichloromethane solution. The zwitterionic resonance form of the NCP provides a rationale for the complexation properties of these hosts as ditopic ion-pair receptors. The analysis of the UV–vis titration data was performed using a 1:1 binding model, which implicitly assumed that the reported association constants for the 1:1 complexes should be of the form:

$$\mathrm{NCP} + n\mathrm{Bu_4N^+X^-} \rightleftharpoons \mathrm{NCP}\cdot n\mathrm{Bu_4N^+X^-}$$

$$K_{\mathrm{a,exp}} = \frac{[\mathrm{NCP}\cdot n\mathrm{Bu_4N^+X^-}]}{[\mathrm{NCP}][n\mathrm{Bu_4N^+X^-}]}$$

Because the binding studies were performed in dichloromethane solutions, it is sensible to assume that the salt and the complex were both mainly ion-paired species. An experimentally equivalent expression would apply if the salt and the complex were both fully dissociated ionic species as was considered in the previous example in acetonitrile solution. Generally, the lack of consideration of the dissociation of the salt ion pair, as well as the formation of an ion-paired complex, which are significant processes in nonpolar solvents, renders the values of the experimentally determined association constants for the 1:1 complexes ($K_{\mathrm{a,exp}}$) concentration- and cation-dependent. In any case, the measured 1:1 binding constants of the tetrakis(pentafluorophenyl)-NCP **6a**·M metal complexes increased in the order $Cl^- > Br^- > I^-$. The binding affinities for each halide showed small differences among different metal complexes of the NCP receptors and was attributed to the modification of the NH acidity by the core cation (Table 1).

Surprisingly, the association constant values of *meso*-tetraphenyl-substituted NCP **6b**·M (M = Ni(II) and Pd(II);

TABLE 1. Association Constant Values ($K_{a,exp}$, 10^4 M^{-1}) of the Complexes Formed by Divalent Metal NCPs and TBAX

porphyrin	salt	M = Ni(II)	M = Pd(II)	M = Cu(II)
6a·M	TBACl	5.7 ± 0.4	4.6 ± 0.7	4.9 ± 0.4
	TBABr	0.8 ± 0.04	1.4 ± 0.1	0.7 ± 0.02
	TBAI	0.1 ± 0.002	0.03 ± 0.002	0.1 ± 0.002
6b·M	TBACl	<0.0001	<0.0001	
7·M	TBACl	4.4		
8·M	TBACl	4.2		
9·M	TBACl	2.6		

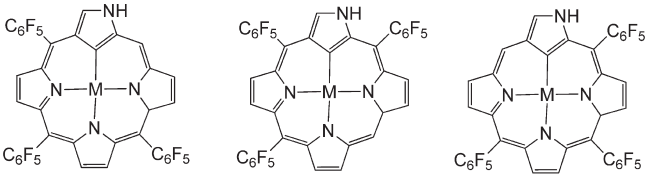


FIGURE 5. Ni(II) tri-C_6F_5-substituted N-confused porphyrins.

$R^1 = C_6H_5$) with Cl^- were extremely small compared with the pentafluorophenyl-substituted analogs **6a**·M ($R^1 = C_6F_5$). The higher binding affinities of the **6a**·M series compared with the **6b**·M analogs were ascribed not only to the enhancement of the acidity of the outer NH by the electron-withdrawing effect of the *meso*-pentafluorophenyl substituents but also to the existence of additional anion−π interactions. The chemical shift changes experienced by the ^{19}F NMR signals of the C_6F_5 substituent neighboring the peripheral NH in **6a**·Ni upon incremental addition of TBACl were used to evidence the existence of anion−π interaction. In a subsequent study, Furuta et al. reevaluated the importance of the anion−π interactions[27] synthesizing a series of three tri-C_6F_5-substituted NCP−Ni(II) porphyrins (Figure 5).

The experimentally determined association constants values of the Cl^- complexes with **7**·Ni, **8**·Ni, and **9**·Ni are very similar and slightly smaller than that of the tetra-C_6F_5-substituted **6a**·Ni (Table 1). Remarkably, despite lack of a C_6F_5 substituent at the *meso*-position closer to the outer NH, the anion binding affinity of **7**·Ni is nearly the same as tetrasubstituted **6a**·Ni and larger than that of trisubstituted **9**·Ni with a C_6F_5 substituent at the *meso*-position closer to the outer NH. Taken together, these results suggested that the anion−π interaction is not large, if indeed it is present at all; rather, it seems to be repulsive. This work demonstrated that changes in the chemical shifts of the ^{19}F NMR signals of the C_6F_5 group neighboring the peripheral NH can simply be indicative of the shielding effect of the negative charge of the anion associated at this binding site and do not require the existence of attractive anion−π interactions.

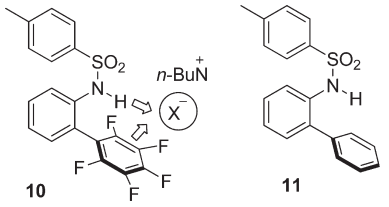


FIGURE 6. Molecular structures of the receptors **10** and **11**.

TABLE 2. Stability Constant Values and Free Enthalpies of Binding for the Sulfonamide Receptor **10** with XTBA

receptor	salt	$K_{a,exp}$ (M^{-1})	ΔG (kcal/mol)
10	ClTBA	30	−2.0
	BrTBA	20	1.8
	ITBA	34	−2.0

Johnson et al. also combined an aromatic substituent with a hydrogen bond donor in their first design of molecular receptors for the investigation of anion−π interactions in $CDCl_3$ solution.[28] They chose a pentafluorophenyl substituent as the aromatic group and a sulfonamide proton as the hydrogen bond donor for the two-point-recognition motif implemented in the structure of receptor **10** (Figure 6). The analog receptor **11** in which the C_6F_5 group was substituted by a phenyl was used as a reference.

The sulfonamide proton when positioned directly above the aromatic ring allowed for a ditopic interaction with the anion both through the hydrogen bond and the aromatic ring. The magnitude of the experimentally determined binding affinities of receptor **10** for the halides using the simple 1:1 binding model is quite low and similar for Cl^-, Br^-, or I^- (Table 2). Receptor **11** did not show signs of halide binding in the same range of concentrations used in the titrations of **10**.

The obtained results indicated an influence of the aromatic substituent on halide binding. The authors concluded that by comparing the association constant values measured for **10** and **11** with the halide series it was possible to arrive to an initial estimation of anion-arene interactions in solution. When the difference in the reported stability constants is used to estimate the anion−π interaction a minimum value of -2 kcal/mol emerges.

Johnson et al. also described tripodal receptors that utilize only aromatic rings, substituted with two nitro groups, in the binding of halides in C_6D_6 solution.[29] Receptor **12** was capable of halide binding exclusively through anion−π interactions (Figure 7). Conversely receptor **13** preferred to interact with halides through CH···X^- interactions. Receptor **14** did not show signs of halide binding.

Larger association constants were obtained when the halide preferred to interact solely through contacts to the

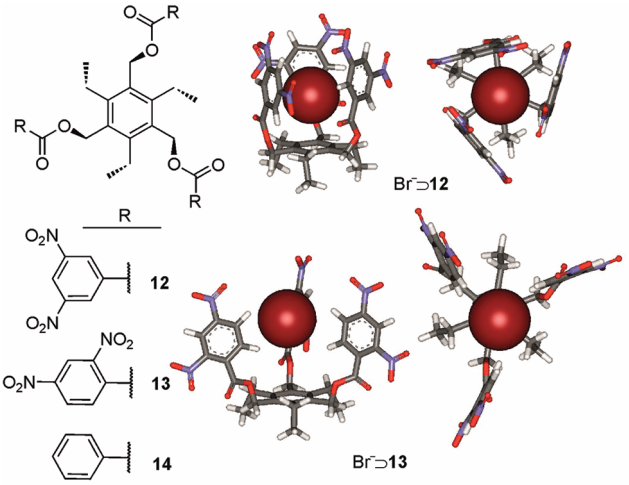


FIGURE 7. Anion tripodal receptors and CAChe-minimized[23] structures of the Br^- inclusion complexes with **12** and **13** (side and top views).

TABLE 3. Average Stability Constant Values and Free Energies of Binding for Receptors **12** and **13** with XTBA Using a Simple 1:1 Binding Model

receptor	salt	$K_{a,exp}$ (M^{-1})	ΔG (kcal/mol)
12	ClTBA	53	−2.4
	BrTBA	35	−2.1
	ITBA	26	−1.9
13	ClTBA	26	−1.9
	BrTBA	18	−1.7
	ITBA	11	−1.4

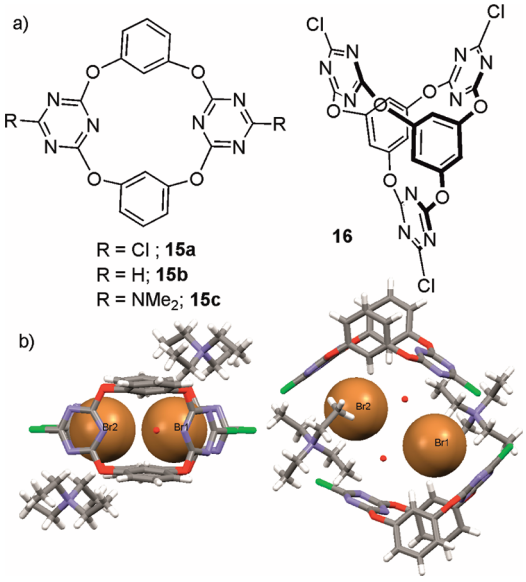
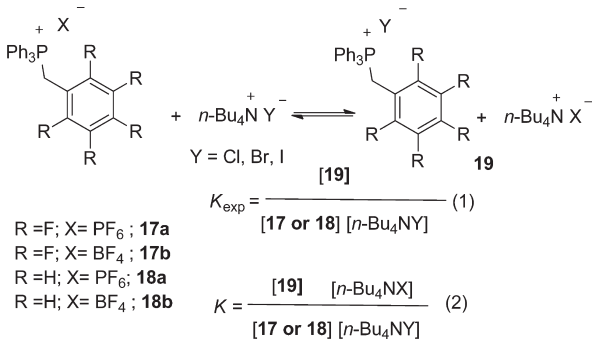


FIGURE 8. (a) Molecular structures of receptors **15** and **16** and (b) top and side views of the dimeric X-ray structure of the 1:1:1 complex of **15a** binding bromide and one water molecule.

π-system. This model system allows for the quantification of an energetic difference between the anion–aryl H-bonds and the anion–π arene interactions, of ~0.5 kcal/mol in favor of the later (Table 3).

SCHEME 1. Anion-Exchange Equilibrium with the Definition of the Thermodynamic Constants



Wang et al. used tetraoxacalix[2]arene[2]triazene receptors **15** for the recognition of halides in acetonitrile solutions (Figure 8).[30] The addition of chloride or bromide did not affect the UV–vis spectrum of host **15a** nor did it change its ^1H or ^{13}C NMR spectrum. However, the interaction of **15a** with Cl^- produced a weak emission band at 379 nm. From the fluorescence titration data, an association constant value of $K_a = 4.2 \times 10^3\ M^{-1}$ was calculated for the $Cl^- \cdot$ **15a** complex. In all cases, the fit of the titration data was done using a simple 1:1 binding model.

The effect of the triazine substituent in the tetraoxacalix[2]arene[2]triazene receptor series **15** was also evaluated. Macrocyclic receptors **15b** and **15c** showed no change in either absorption or emission spectrum when titrated with chloride or bromide. The dichloro-substituted receptor **15a** exhibited stronger binding affinity toward chloride. Surprisingly, when the same binding motif is incorporated into the conformationally more rigid molecular cage receptor **16** and the binding constant for chloride is assessed using ITC experiments in acetonitrile solution, a significant reduction in the macroscopic value of the binding interaction is obtained, $K_{Cl^-@16} = 146\ M^{-1}$.[31]

Albrecht, Rissanen, and co-workers have also been active in the investigation of anion–π interactions.[32,33] They performed NMR titration experiments with the hexafluorophosphate **17a** and tetrafluoroborate **17b** salts and analogues **18a** and **18b** having a phenyl instead of the pentafluorophenyl unit. *n*-Tetrabutylammonium halides (Cl^-, Br^-, I^-) were incrementally added to the PF_6^- and BF_4^- salts, and the equilibrium constant for the anion exchange was determined.[34] Because the titrations were performed in $CDCl_3$, the solution equilibrium is assumed to occur between ion-paired species. However, the reported equilibrium constants

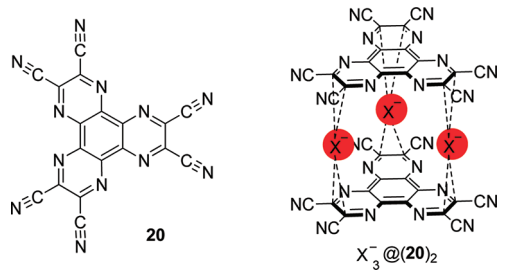


FIGURE 9. Molecular structure of **20** and the proposed binding geometry for the (TBAX)$_3$@**20**$_2$ CT complexes formed in solution.

TABLE 4. Spectroscopic and Thermodynamic Features of the CT Complexes (TBAX)$_3$@**20**$_2$ in THF Solvent

	Cl^-	Br^-	I^-
λ_{max} (nm)	408	419	630
$K_{a,exp}$ (M^{-1})	3780	2200	940
ΔG (kcal/mol)	−4.9	−4.7	−4.1

are in units of M^{-1} (Scheme 1, eq 1), implicitly assuming that they correspond to the equilibrium of formation of a 1:1 ion-paired complex **19** caused by the anion exchange.

Because all reported equilibrium constants K_{exp} are in the range of (1–2) × 10^3 M^{-1} (960–1610 M^{-1}), it is reasonable to suppose that the addition of 1 equiv of halide salt to 1 mM concentration solutions of **17** or **18** induces the formation of the ion-paired complex **19** with the exchanged anion and the corresponding exchanged tetrabutylammonium salt to an extent close to 50%. Consequently, the equilibrium constant for the overall exchange process K can be estimated as 0.5–1 (Scheme 1, eq 2). In other words and as already stated by the authors, there is no preference of the cation for a specific anion and no preference of the anion for either the fluorinated or non-fluorinated cations.

Dunbar et al. reported solution studies of the halide binding properties of 1,4,5,8,9,12-hexaazatriphenylene-hexacarbonitrile HAT(CN)$_6$, **20**, an extended aromatic compound with multiple sites available to establish anion–π interactions (Figure 9).[35,36] In the UV–vis studies, addition of colorless solutions of TBAX salts (X^- = Cl^-, Br^-, and I^-) to a yellow solution of **20** in THF provoked the appearance of new absorption bands in the visible region. The Mulliken correlation that exists between the energy of the band and the oxidation potential of the anion was used to assign a charge-transfer (CT) character to these bands and in turn an electron donor–acceptor nature to the corresponding complex.[24] The Job plots were not centered at the 0.5 molar fraction ratio but shifted toward a value of 0.6. This observation was used as evidence for the formation of complexes with a 3:2 stoichiometry (TBAX)$_3$@**20**$_2$ in solution, in

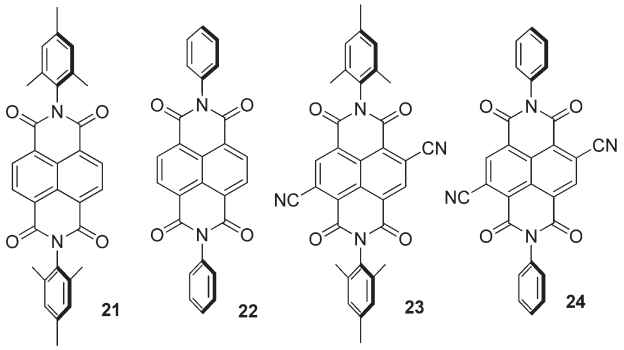


FIGURE 10. Structures of monomeric NDIs used as anion transporters through bilayer membranes.

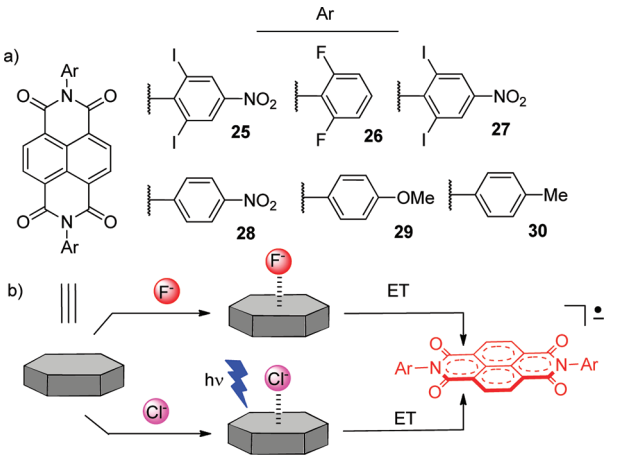


FIGURE 11. (a) Molecular structures of NDIs involved in ET processes with anions and (b) illustrations of the thermal- and photo-induced ET processes.

accordance with the 3:2 ratio of halides to **20** determined from the X-ray structures of the complexes. Surprisingly, a simple 1:1 binding model was used in the fitting procedure of the titration data, and thus the determined stability constants have units of M^{-1} (Table 4). The trend in the experimentally measured association constant values $K_{Cl^-} > K_{Br^-} > K_{I^-}$ is in complete agreement with the order of Lewis basicity and electron-donating ability of the halides. Remarkably, the stability constant values measured for the charge transfer complexes (TBAX)$_3$@**20**$_2$ are several orders of magnitude higher than those typically measured for related halide complexes with other aromatic systems in solvents of comparable polarity.[24]

Matile's group has put anion–π interactions to work in the selective transport of anions across lipid bilayer membranes (Figure 10).[37] They prepared a collection of monomeric **21**–**24** oligonaphthalenediimides.[38] The ability of the naphthalenediimide (NDI) unit to exert anion–π interaction was demonstrated by ESI tandem mass spectrometry.[39]

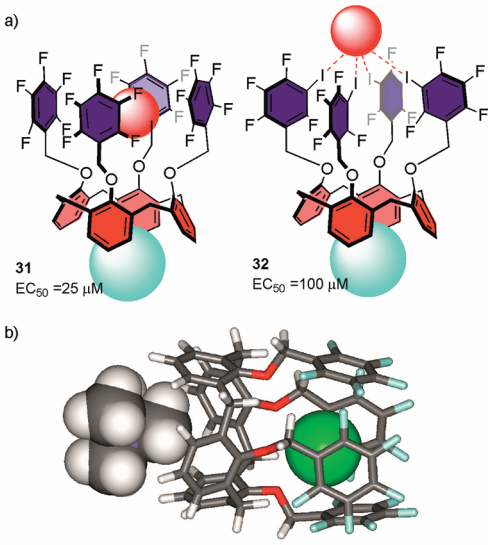


FIGURE 12. (a) Molecular structures of ditopic calix[4]arene receptors **31** and **32** and (b) CAChe[23] energy-minimized complex of TMACl@**31**.

This structural evidence was directly related to the anion transport activity of suprastructures of NDIs across the bilayer membrane.

The interaction of monomeric NDI **21** in a 9:1 mixture of acetonitrile/chloroform with TBAI was probed by absorption spectroscopy. A new band emerged with λ_{max} at ca. 475 nm and was assigned to a charge transfer between the iodide and **21**. The stability constant value for the complex I^-@**21** was experimentally determined as 0.2 M^{-1} assuming the exclusive formation of a complex with 1:1 stoichiometry.

Saha et al. demonstrated the existence of electron transfer (ET) processes from certain anions to suitable NDIs (Figure 11).[40,41] It was possible to channel the anion to NDI ET processes either thermally or photochemically by electronic regulation, that is by adjusting the reducibility (LUMO level) of the NDI aromatic system with respect to the Lewis basicity (HOMO level) of the anion. Both pathways generate anion-radical NDIs ($NDI^{\bullet-}$) probably through the intermediacy of a noncovalent anion−π complex. UV−vis titration of NDI **25** with Cl^- in *ortho*-dichlorobenzene (ODCB) displayed an absorption spectrum that was used as diagnostic for the formation of the $NDI^{\bullet-}$ species.

Interestingly, in acetonitrile, a more polar solvent than OCDB, all Cl^- to NDI thermal ET processes were essentially turned off. ^{1}H NMR experiments in the more polar acetonitrile solution confirmed that while F^- or AcO^- generates paramagnetic **25**$^{\bullet-}$, Cl^- does not do so. However, irradiation of the sample containing **25** and Cl^- quickly generates paramagnetic **25**$^{\bullet-}$. Conversely, less basic Br^- or I^- did not produced any **25**$^{\bullet-}$. However, a large excess of I^- produced a

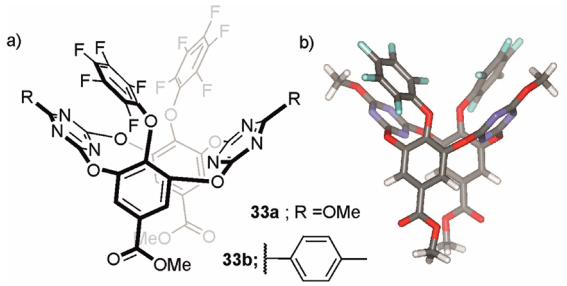


FIGURE 13. (a) Structures of receptors **33** and (b) CAChe-minimized structure of **33a**.

broad and weak CT brand with a concentrated solution (millimolar) of **25** in ODCB. The analysis of the anion-induced absorption changes using the Benesi−Hildebrand method showed good agreement for 1:1 interactions with F^- and AcO^- affording decreasing affinity values of 1225 and 70 M^{-1}, respectively, in OCDB solution.

Very recently, Matile's group described a series of calix[4]arene derivatives designed to dissect the individual contributions of halogen bonds, hydrogen bonds, and anion−π interactions in anion transport.[42] The obtained trend in activity demonstrated that the best anion transporter was receptor **31** in which anion−π interactions are used alone in anion binding (Figure 12). A dramatic drop of activity was observed for receptor **32**, which suggested that chloride/hydroxide binding by four proximal activated halogen bonds in **32** takes place but does not lead to transport. ^{19}F NMR titrations of **32** with TBACl in CD_3COCD_3 solutions afforded an association constant value of $K_{a,exp} = 55$ M^{-1} for the Cl^-@**32** complex assuming simple 1:1 binding. Under identical titration conditions, no detectable chloride binding was observed for receptor **31**. This work represents a nice example of the functional relevance of anion−π interactions, independent of the motif in which they are involved and the thermodynamically weak complexes that they produce.

Wang et al. used the heteroatom-bridged calix[2]arene-[2]triazine scaffold exploited in receptors **15** (Figure 8) to construct a better defined aromatic cavity or space for the inclusion of anions by introducing two extra pentafluorophenyl substituents on the lower rim of the aryl rings (Figure 13).[43]

No spectral changes were observed when both receptors **33** were titrated in acetonitrile solution with most anionic species including halides, thiocyanate, nitrate, and phosphate. Curiously, the titrations of receptors **33a** and **33b** with tetrabutylammonium azide gave rise to emerging new absorption bands centered at 322 and 365 nm. The resulting

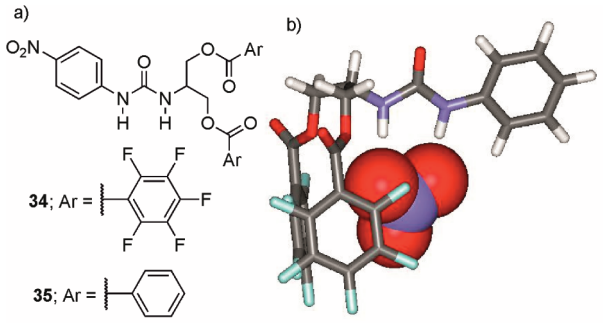


FIGURE 14. (a) Molecular structures of anion receptors **34** and **35** and (b) minimized structure of the NO_3^-@**34**′ (lacking the NO_2 group) calculated by DFT (B3LYP/6-31++G(d,p), gas phase).[44]

TABLE 5. Association Constants of Receptors **34** and **35** with Anions and Estimated Free Energy Contributions of the Anion–Arene Interactions

receptor	anion	K_a ($\times 10^2$ M^{-1})	$\Delta\Delta G$ kcal/mol
34	Cl^-	25	-0.1 ± 0.1
35	Cl^-	23	
34	Br^-	4.9	-0.1 ± 0.1
35	Br^-	4.6	
34	Br^-	0.6	0 ± 0.1
35	Br^-	0.55	
34	BzO^-	1400	-0.5 ± 0.1
35	BzO^-	660	
34	TsO^-	9.6	-0.3 ± 0.1
35	TsO^-	5.5	

Job plot indicated the formation of complexes with 1:1 stoichiometry for which association constant values on the order of 10^3 M^{-1} were calculated using simple 1:1 binding models. Similar association constant values were obtained from fluorescence titrations. It is worth noting that when the complexation of N_3^- anion with receptors **33a** and **33b** was probed using ^{1}H NMR titrations, no changes were detected in the chemical shifts of the hosts. The observation of spectroscopic changes only in the absorption and emission spectra of the oxacalix[2]arene[2]triazine receptors **33** but not in their NMR spectra when titrated with anions was in agreement with previous findings of the group using related hosts.[30,31] The interaction of **33b** with an excess of N_3^- during crystallization caused the destruction of the receptor.

Taylor et al. developed a series of receptors capable of anion binding by a combination of halogen-bonding and hydrogen-bonding interactions.[44] Urea-based receptors incorporating two pentafluoroaryl moieties, that is, **34**, were used as "control" receptors in the above-mentioned investigations of halogen-bonding interactions (Figure 14). To estimate the potential existence of anion–arene interactions in the complexes of **34** with anions, the analogous receptor with a benzoate ester **35** was prepared. The difference in binding

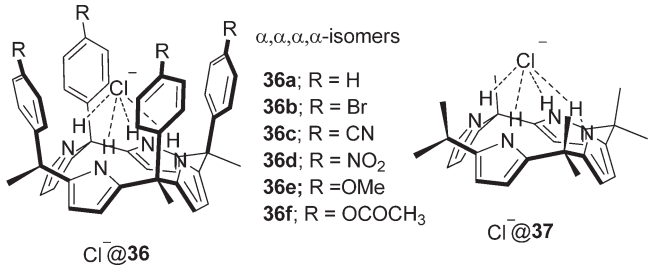


FIGURE 15. Structures of α,α,α,α-isomers of **36** and receptor **37** used as reference for the estimation of chloride–π interactions.

energies $\Delta\Delta G = \Delta G_{X^-@\mathbf{35}} - \Delta G_{X^-@\mathbf{34}}$ should provide an estimate of the strength of the anion–arene interactions in this model system. The titration binding data in acetonitrile solution revealed the existence of very weak interactions of the halides with the pentafluorophenyl units ($\Delta\Delta G < -0.1$ kcal/mol, Table 5). More significant values of $\Delta\Delta G$ ($\Delta\Delta G <$ -0.1 to -0.3 kcal/mol) were experimentally determined for the interaction with oxoanions. This result is noteworthy because the evaluation of the interaction of oxoanions with arenes is scarcely documented in solution.

My group is also involved in the study and quantification of anion–π interactions in solution.[45] In order to take advantage of the additivity property of the anion–π interaction, we designed a model system based on a series of "four wall" aryl-extended calix[4]pyrrole receptors. Calix[4]pyrroles are a known class of receptors for anions, and the binding of the halide organizes the receptor in the cone conformation.[46] We prepared a series of neutral α,α,α,α-tetraaryl calix[4]pyrroles **36** containing deep aromatic cavities with fixed walls (Figure 15). The formation of four hydrogen bonds between the halide and the NH groups of the calix[4]pyrrole scaffold constitutes a reliable interaction for including the anion in the receptor's aromatic cavity and positioning it above the planes of the π-systems of the four *meso*-aryl substituents. Different *para* substituents in the *meso*-aryl units were used to tune and alter the electronic density of the aromatic rings. The interaction of the halides with the aryl-extended calix[4]pyrrole receptors **36** was probed using ^{1}H NMR spectroscopy providing additional information on the geometry of the complex. We used TBACl as the precursor of the chloride guest and acetonitrile as solvent because in the range of concentration used this electrolyte and the resulting host–guest complex are predominantly dissociated. Thus, the binding process of calix[4]pyrrole receptors **36** with Cl^- is expected to produce simple 1:1 anionic complexes. The results obtained from ^{1}H NMR titrations constituted a clear indication that in

TABLE 6. Association Constant Values, $K_{a,exp}$, for the 1:1 Complexes of Receptor Series **36** and Reference Compound **37** with Chloride and Statistically Corrected Free Energies Estimated for Chloride−π Interactions

receptor	$K_{a,exp}$ ($\times 10^3$ M^{-1})	$\Delta\Delta G^a$ (kcal/mol)
36a; R = H	0.25	0.9
36b; R = Br	3.80	0.5
36c; R = CN	33.0	0.1
36d; R = NO_2	189	−0.1
36e; R = OMe	0.13	1.0
36f; R = $OCOCH_3$	1.10	0.7
37	108	

[a] $\Delta\Delta G/4 = (\Delta G_{Cl^-@\mathbf{36}x} - \Delta G_{Cl^-@\mathbf{37}})/4$.

solution the Cl^-@**36** complexes adopt a binding geometry featuring the calix[4]pyrrole core in the cone conformation and the chloride located deep within the aromatic cavity. The chloride experiences anion−π interactions with the four *meso*-aryl groups.

The quantitative assessment of the binding constants of chloride with the receptor's series was performed by integration of ^1H NMR spectra or by means of isothermal titration calorimetry (ITC) experiments or both. All complexes showed a 1:1 stoichiometry, and a simple 1:1 binding model was used in the analysis of the titration data. In general, the magnitude of the association constant increased with the electron-withdrawing character of the *para*-substituent in the *meso*-aryl groups. The difference in free energy of binding between two Cl^-@**36** complexes provided a direct measurement of the relative interaction energy of Cl^- with the different aromatic systems. Using this approach, we determined that the maximum contribution of the chloride−π interactions to the overall binding free energy in the receptor series, $\Delta\Delta G = \Delta G_{Cl^-@\mathbf{36}e} - \Delta G_{Cl^-@\mathbf{36}a}$, was −4.4 kcal/mol (1.1 kcal/mol per aromatic ring). This value represents the difference in free energies of binding between the best, **36e**, and the worst receptor, **36a**, for chloride in the series. However, because repulsive π−chloride interactions are surely operative in the Cl^-@**36a** complex, the value of 1 kcal/mol represents an overestimation of the stabilizing energy for the attraction between Cl^- and the π-system of a *para*-nitrophenyl group. The octamethyl calix[4]pyrrole receptor **37** represents a suitable reference to better quantify chloride−π interactions in solution. The statistically corrected chloride−π energy values, $\Delta\Delta G = (\Delta G_{Cl^-@\mathbf{36}x} - \Delta G_{Cl^-@\mathbf{37}})/4$, determined using **37** as reference correlated well with the corresponding Hamment constants for the *para* substituents (Table 6). In all cases, except for R = NO_2, the estimated energy for the chloride−π interaction is repulsive. The magnitude of the repulsion is

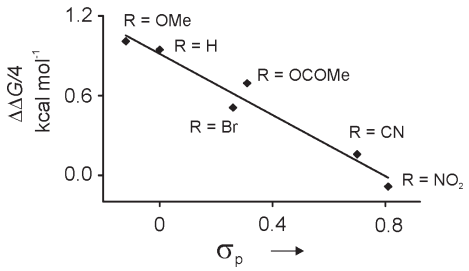


FIGURE 16. Experimental chloride−π interactions energies ($\Delta\Delta G/4$) derived from the "four wall" system correlated with the σ_p value for R.

sensitive to the nature of the *para*-substituent. The observed trend in the magnitudes of binding for chloride−π interactions is consistent with the existence of an interaction that is dominated by electrostatic effects involving the anion and the aromatic ring (Figure 16). This simple model system suggests that only the *para*-nitro substituent in the *meso*-aryl groups renders the chloride−π interaction slightly attractive (ca. −0.1 kcal/mol per aromatic ring).

Conclusions and Outlook

To date, experimental data in solution phase supporting and quantifying noncovalent or weakly covalent reversible interaction between anions and charge-neutral arenes are limited. Most of the studies dealing with anion−π interactions in solution are based on molecular recognition models (synthetic receptors) that combine hydrogen bonding with a single or multiple anion−π interactions. In these cases, the strength of the anion−π interaction is detected indirectly as a modulation of the stronger hydrogen-bonding interaction (enforced proximity). But, this modulation can result from the addition of free binding energy due to an attractive anion−π interaction or from a repulsive interaction that lowers the free binding energy. In both cases, the same substituent effects are expected. If the aim of a binding study in solution is to provide evidence of attractive anion−π interactions, great care must be taken to show that the substituent effects are not only modulating a repulsive interaction. This constitutes a challenging task in many cases, that is, selecting the appropriate reference, and should be done before claiming attractive anion−π interactions. Synthetic receptors capable of binding anions or ion pairs efficiently in solution *only* with multiple anion−π interactions are even scarcer. The magnitude of the interaction of anions with a single electron-deficient aromatic system is very weak. The picture that emerges from all these studies is that anion−π interactions do exist in solution and that the free energy of binding that can be assigned to these attractive interactions is less than 1 kcal/mol. In solution, effective

attractive anion−π interactions require electron-deficient rings, that is, aromatic rings or aromatic heterocycles with strong electron-withdrawing substituents. Because the quantification of anion−π interactions in solution relies on the use of molecular recognition model systems, an additional word of caution seems appropriate regarding the obtained results and assigned energy values. As noticed by Baldridge et al.,[47] the chemical structure of the model may strongly affect the magnitude of the measured effect. Moreover, the dissection of binding forces contributing to the overall binding energy of the model system is complicated and can be contaminated by solvation effects. In addition, the recognition of anions in solution requires the use of salts (ion pairs) as precursors, which complicates the analysis of the titration data and the assignment of the nature of the complex: ion paired or ion separated. In other words, the solvent and the counterion must be considered as important variables impacting the estimated energy values. The weak values experimentally measured for the anion−π interactions in solution suggest that their importance in the selective or enhanced anion binding must be less important than their application in synthetic and biological systems that are functional in catalysis and transport.

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BIOGRAPHICAL INFORMATION

Pablo Ballester was born in 1959 in Palma de Mallorca, Spain. He studied Chemistry at the University of the Balearic Islands (UIB) where he also completed the Ph.D. degree in 1986. He worked as a postdoctoral fellow with Prof. J. Rebek, Jr. (U. Pittsburgh and MIT) and Prof. J. M. Saá (UIB). In 1990, he joined the Chemistry Department of UIB where he rose to the rank of Associate Professor. In 2003, he was awarded an ICREA Research Professorship and moved to the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, Spain.

FOOTNOTES

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The authors declare no competing financial interest.

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