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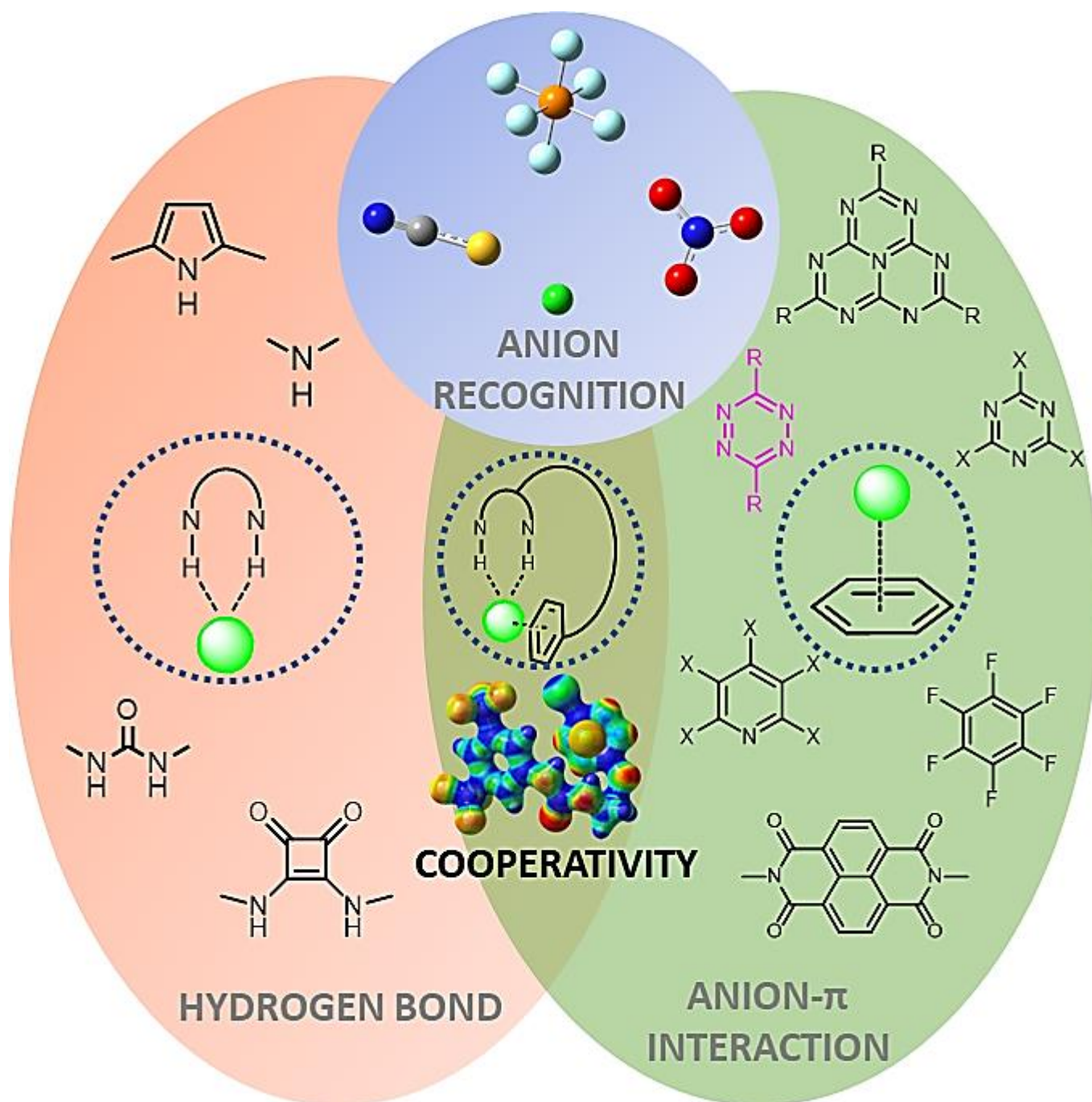
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# Anion- $\pi$ Interaction for Molecular Recognition of Anions : Focus on Cooperativity with Hydrogen Bonding

Romain Plais,<sup>\*[a]</sup> Gilles Clavier,<sup>[b]</sup> Jean-Yves Salpin,<sup>[c,d]</sup> Anne Gaucher,<sup>[a]</sup> and Damien Prim<sup>[a]</sup>



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**Abstract:** Anion recognition represents an intense area of research in supramolecular chemistry. The last two decades have been marked by spectacular advances in the design of new anion receptors. Moreover, the development of approaches combining experimental and theoretical studies has proved to be particularly relevant, allowing a better understanding and rationalization of the phenomena involved in anion complexation processes. In this context, the combination of weak interactions within the same receptor and their synergistic effects, called cooperativity, has attracted increasing interest within the scientific community. This review focuses on the combination of anion- $\pi$  and hydrogen bonds and the emerging concept of cooperativity. The most relevant anion- $\pi$  donor families are presented. The concept of cooperativity is illustrated using the most recent examples present in current literature.

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Romain Plais graduated from ENSICAen (National School of Engineering of Caen) and the University of Caen-Normandie in 2018. He then joined the laboratory of Pr. Damien Prim at University Paris-Saclay (Versailles, France) where he defended his PhD on the combination of hydrogen bonding and anion- $\pi$  interaction for the molecular recognition of anions and catalysis. In order to pursue an industrial career, he moved to Belgium to work as a Project Engineer at Baxter International Inc. He is currently Process Development Chemist at Polypeptide Group in Belgium.



Gilles Clavier graduated from the University of Bordeaux 1 in 1994 and received his M.Sc. from Ecole Polytechnique in 1996. He joined the team of Professor Bouas-Laurent in Bordeaux in 1995 and received his Ph.D. in 1999 for research on the synthesis and gel-forming abilities of dialkoxyarenes and structural study of their gels. He then joined the group of Professor Vince Rotello at the University of Massachusetts at Amherst as a post-doctoral fellow, where he worked on the syntheses and study of supramolecular plug and play polymers for two years. In 2001, he was recruited as Chargé de Recherche at the French CNRS and joined the ENS Paris-Saclay and was promoted to Directeur de Recherche in 2016. His research interests include the design, synthesis, and study of new fluorescent and multichromophoric organic molecules with special properties and their nanoformulation.



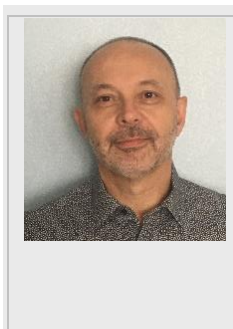
Jean-Yves Salpin got his PhD in chemistry from the University of Orsay in 1997. Then, from 1997 and 1999, he held postdoctoral positions at the University of Bielefeld (Germany) and at the Catholic University of Leuven (Belgium). Back in France, he works since 1999 as a full research scientist at the Centre National pour la Recherche Scientifique (CNRS). His research interests lie in the field of gas-phase ion chemistry by combining mass spectrometry and quantum chemistry. Promoted CNRS senior research scientist in 2012, his major field of research concerns the reactivity of metal ions (alkaline-earth, transition metal, heavy metals) towards organic molecules or biomolecules, and more recently the study of interactions of both anionic and cationic receptors.



Anne Gaucher studied chemistry at the University of Paris-Sud where she obtained her Ph.D in 1992 working on Amino Cyclopropane Carboxylic acids (ACCs) with Dr. J. Salaün. After a postdoctoral period at the University of Texas in Austin with Professor Stephen F. Martin, working on the total synthesis of breynolide, she obtained a one year teaching position at the University of Paris-Sud and then a permanent one at the University of Versailles St Quentin. Her research interests mainly focuses on the design, synthesis, properties of polycyclic molecules and the study of weak interactions.



Damien Prim studied chemistry at the Paul Verlaine University of Metz, where he received his Ph.D. in organic chemistry in 1994 under the guidance of Prof. Gilbert Kirsch. After a postdoctoral period with Prof. Léon Ghosez at UC Louvain-la-Neuve, Belgium, he was appointed as an assistant professor at Paul Verlaine University of Metz. In 1999, he moved to Pierre et Marie Curie University in Paris as a CNRS research associate. He then moved to the University of Versailles St Quentin as an assistant professor in 2001. In 2005, he was appointed as a full professor of chemistry at the University of Versailles St Quentin. His research focuses on homogeneous and heterogeneous catalysis, the syntheses and properties of polycyclic molecular architectures including weak interactions.



## 1. Introduction

Study of anion- $\pi$  interaction was pioneered by Hiraoka *et al.* in 1986 through examination of hexafluorobenzene-halogens interactions in the gas phase. They established the non-covalent nature of the interaction with Cl<sup>-</sup>, Br<sup>-</sup> and I<sup>-</sup>.<sup>[1]</sup> Nowadays, the existence of this non-covalent interaction is quite accepted in the literature.<sup>[2-4]</sup>

Anion- $\pi$  interaction, defined as being a non-covalent interaction between an electron deficient aromatic ring and an anion, have attracted increasing interest over the past two decades because of their involvement in supramolecular processes such as molecular recognition or biological machineries. Historically, first synthetic anion receptors were notably based on hydrogen bonding (see among others, pioneering works of Nobel Prizes Jean-Marie Lehn, Donald Cram and Charles J. Pederson, but also Chang H. Park and Howard E. Simmons).<sup>[5-10]</sup> These first examples rely on the NHs of amides, ureas, isophthalamides, or OHs of phenol derivatives as hydrogen bond donors.<sup>[11]</sup> At first, anion- $\pi$  interactions and hydrogen bonding were used and studied separately. Combinations of these non-covalent interactions in synthetic anion receptors only emerged recently. Following our research projects covering different topics such as 3D curved and/or helical molecular architectures to complex cations,<sup>[12-20]</sup> the fluorescent tetrazine chemistry<sup>[21-37]</sup> and gas-phase interaction between biomolecules and metals by mass-spectrometry techniques,<sup>[38-40]</sup> we recently focused on the formation of anionic complexes combining anion- $\pi$  interaction and hydrogen bonding.<sup>[41-43]</sup> The combination of such interactions leads to interesting synergic effects called cooperativity, whose rationalization remains a challenge.

Starting from this observation, this review aims to discuss the use of anion- $\pi$  interaction in cooperativity with hydrogen bonding for anion recognition. First, we propose a classification into different families of main up-to-date anion- $\pi$  donors observed in literature. Each family is described, and examples are presented. Selected literature is suggested to go further on the different families. Then, main examples of cooperativity between anion- $\pi$  interaction and hydrogen bonding classified by the type of anion- $\pi$  donor involved are introduced. Finally, some perspectives on future challenges are given.

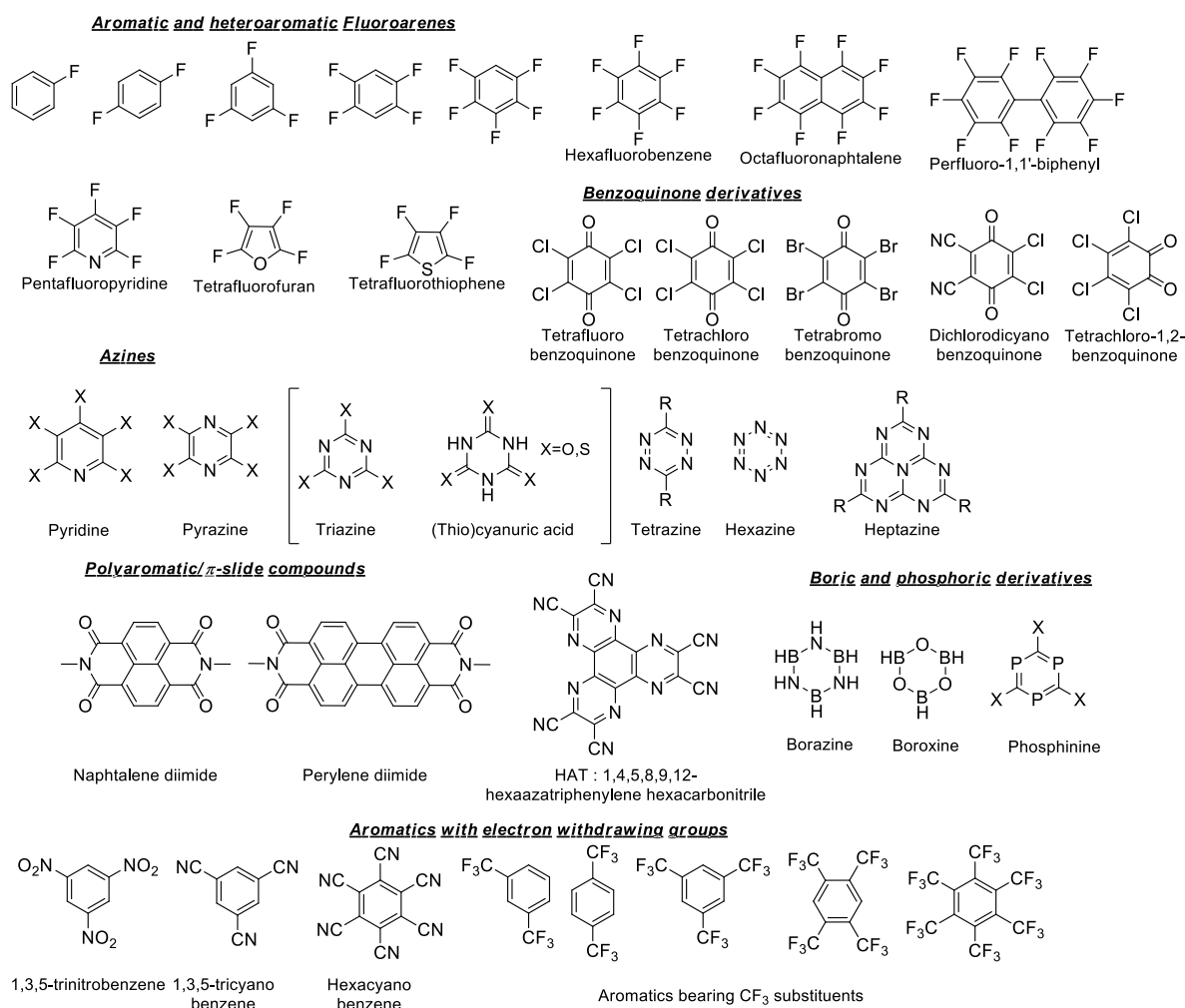
## 2. Anion- $\pi$ donors : from theoretical studies to molecular recognition

An anion- $\pi$  interaction is an interaction established between an anion and an electrodeficient aromatic group.<sup>[44]</sup> However, not all aromatic groups are prone to establish an anion- $\pi$  interaction. As a relevant example, the benzene molecule, only establishes repulsive interactions with anions despite its high molecular polarizability ( $\alpha_{||}$ = 41.5 a.u.). Thus a typical profile of an anion- $\pi$  interaction donor would imply strong electron withdrawing substituents to modify the distribution of charges above the aromatic ring (quantified by the quadrupole moment  $Q_{zz}$ ) or the ability of the electronic system to be distorted by the proximity of an anion (quantified by the molecular polarizability  $\alpha_{||}$ ).<sup>[2-4]</sup>

### 2.1 Diversity of anion- $\pi$ donors

A large diversity of anion- $\pi$  donors is reported in current literature. **Figure 1** summarizes the main anion- $\pi$  bond donors molecular architectures. Hereafter, we propose to classify them in different families: aromatic and heteroaromatic fluoroarenes, benzoquinone derivatives, azines, nitrobenzenes, polyaromatic compounds also called  $\pi$ -slides, boric and phosphoric derivatives and aromatics with electron withdrawing groups. Each family will be introduced separately in this chapter, and key examples will be given.

Few examples of benzoquinone derivatives as well as aromatic derivatives are used in anion receptors bearing hydrogen bond donors. However, as these structures are promising patterns for future anion receptors designs, we highlight these structures in **Figure 1** and encourage the reader to see the following references for more information.<sup>[45-51]</sup>



**Figure 1** Panel of reported anion- $\pi$  bond donors used alone or in combination with hydrogen bond donors.

## 2.2 Fluoroarenes

Anion- $\pi$  interactions involving fluoroarenes have been extensively reviewed by Giese, Albrecht and Rissanen.<sup>[52]</sup> We will therefore focus on main aspects of this family and encourage the reader to come through the aforementioned review for further details.

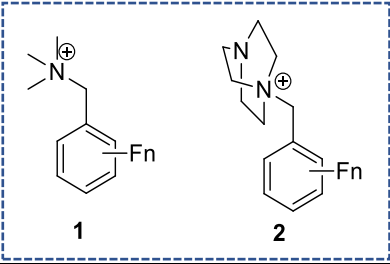

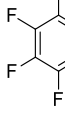
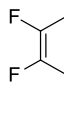
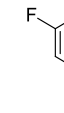
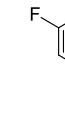
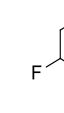
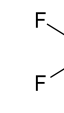
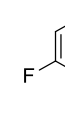
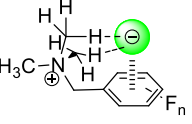
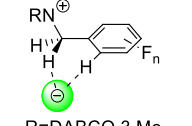
In 2002, Deyà *et al.* corroborated the pioneering results of Hiraoka *et al.* with a combined theoretical and crystallographic study, thus paving the way to the study of this non-covalent interaction. They ascertained the formation of favorable anion- $\pi$  interactions between hexafluorobenzene and various anions ( $\text{H}^-$ ,  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{CN}^-$ ,  $\text{NO}_3^-$  and  $\text{CO}_3^{2-}$ ).<sup>[4,53]</sup> It should be emphasized that in the particular case of hexafluorobenzene, no C-H bond are available, hence preventing the formation of a competing C-H $\cdots$ anion interaction and therefore confirming the anion- $\pi$  nature of the trapping site.<sup>[52]</sup>

Within the fluoroarene family, 1,3,5-trifluorobenzene has been studied theoretically by Deyà, Frontera *et al.* (**Figure 1**).<sup>[54]</sup> Their study demonstrated that the very weak quadrupole moment ( $Q_{zz}=0.57$  B) of the molecule is counterbalanced by a high molecular polarizability ( $\alpha_{||}=38.79$  u.a.). Thus, these two effects allow the formation of a complex with the fluoride anion with an estimated interaction energy of  $-7.77$  kcal.mol<sup>-1</sup> in vacuum (MP2/6-31++G\*\* including BSSE correction).

The same year, Alkorta *et al.* published a theoretical study of the interaction between various fluorinated (hetero)arenes and anions.<sup>[55,56]</sup> The calculated interaction energy values with chloride anion for perfluoropyridine ( $-14.08$  kcal/mol) and perfluoronaphthalene ( $-17.31$  kcal/mol) are quite similar to the one found for hexafluorobenzene ( $-12.76$  kcal/mol). On the other hand, the interaction energy is lower in the case of five-membered rings ( $-9.04$  kcal/mol for tetrahydrofuran, for instance). The anion-aromatic plane centroid distance remains in the 3.0-3.3 Å range in all cases.

Weber *et al.* described a combined theoretical and experimental (infrared photodissociation spectroscopy) study of the influence of the level of fluorination on anion- $\pi$  bond formation versus hydrogen bonding. [57] In the gas phase, the anion- $\pi$  interaction is observed only in the case of the perfluorinated derivative while at lower levels of fluorination, C-H...anion are always preferred in these complexes. Albrecht, Rissanen *et al.* [58,59] also studied the balance between the two phenomena by quantum chemistry with the model compounds **1** and **2**. The anion- $\pi$  interaction is attractive in cases where ortho positions are fluorinated. If at least one ortho position is hydrogenated, the establishment of a C-H...anion bonding with the ortho hydrogen of the electron deficient aromatic ring is favored (**Table 1**). This result was confirmed in solid state.

**Table 1** Influence of the level of fluorination on the coordination mode with bromide anion (insert : structure of **1** and **2**). [58]

	 <b>1</b> <b>2</b>								
Complex geometry									
	✓	✓	✓	✓	✗	✗	✗		
	✗	✗	✗	✗	✓	✓	✓		

R=DABCO,3 Me

The same group further confirmed this result by another theoretical study where it was examined the location of the anion above the plane of various benzene derivatives as a function of the level of fluorination. [60] What is particularly interesting is that at least three fluorine atoms are necessary to establish an anion- $\pi$  interaction. Consequently, the anion-aromatic distance increases when the level of fluorination decreases.

Finally, perfluoro-1,1'-biphenyl was recently identified by Albrecht *et al.* as a promising candidate for anion- $\pi$  bond donor (**Figure 1**). [61] However, to the best of our knowledge, no other anion receptor using this fragment is found in the literature.

### 2.3 Azines

The replacement of carbon atoms in benzene by nitrogen atoms impact (i) the electron deficiency, (ii) both the sign and value of the quadrupole moment and (iii) enhance the molecular polarizability, of the aromatic ring. [2] The source of the positive quadrupole moment that allows anion- $\pi$  interactions with azines, has been studied theoretically by Wheeler and Bloom. [62,63] Therefore, the ability of azines to establish anion- $\pi$  interactions arises from the  $\sigma$ -electron electron density distribution, while  $\pi$ -electrons only play a minor role in the polarization of the electron density. Anion- $\pi$  interactions are formed with azines because of a stronger nuclear attraction than the repulsive interaction between the anion and the aromatic group. [64]

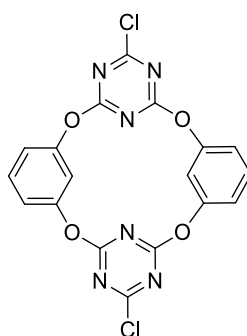
Pyridine interaction with chloride anion is unfavorable (+2 kcal/mol). Its weak electron deficiency prevents the establishment of a stable anion- $\pi$  interaction. However, it was shown that coordination with silver(I) reinforce the electron deficiency and allows a favorable pyridine – chloride interaction (-14.8 kcal/mol). [65,66]

2,5-dichloropyridazine possesses a weak positive quadrupole moment ( $Q_{zz} = 1.47$  B) and a high molecular polarizability ( $\alpha_{||}=44.32$  u.a.), enabling theoretically the formation of anion- $\pi$  interactions (**Figure 1**). [64] To the best of our knowledge, only a few studies in solution are available. [67],[45]



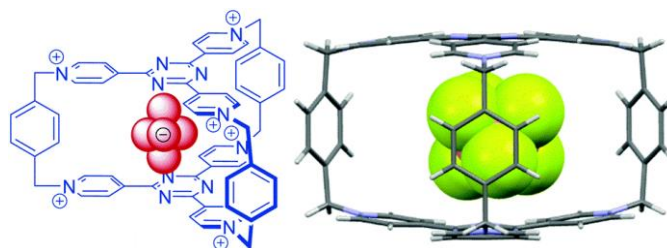
Triazines have been largely studied in the field of molecular recognition. Mascali *et al.* initially reported in 2001 an *ab initio* study on the interaction between 1,3,5-triazine ( $Q_{zz}=0.90$  B and  $\alpha_{||}=30.34$  u.a.<sup>[54]</sup>) or 1,3,5-trifluorotriazine (**Figure 1**) and a series of anions ( $F^-$ ,  $Cl^-$ ,  $N_3^-$ ). A theoretical calculation showed strong favorable interaction energies, paving the way to the use of this motif as an anion- $\pi$  bond donor.<sup>[68]</sup> Trichlorotriazine is a molecular moiety that has been extensively used to produce triazine derivatives thanks to the presence of the three chlorinated positions, that can undergo nucleophilic substitutions to prepare, for example, macrocyclic structures. Several families have been synthesized and studied in the field of anion complexation (for more details see the reviews by Gamez<sup>[56]</sup> and Dunbar *et al.*<sup>[4]</sup>).

Wang *et al.* synthesized and studied a particular class of receptors: oxacalix[2]arene[2]triazines (**Figure 2**). First, the complexation of various anions by these macrocyclic compounds was assessed both theoretically and experimentally in solid state, solution and gas phases. In all cases, complexes with a 1:1 stoichiometry were observed as well as association constants in the  $10^2$ - $10^4$   $M^{-1}$  range in acetonitrile.<sup>[69]</sup> A similar trend was found in the gas phase.<sup>[69]</sup> More recently, the same team extended its approach to the synthesis of macrocycles with multiple cavities named “supermacrocycles”, that allows the introduction of a balance between rigidity and flexibility.<sup>[70-72]</sup> This balance is particularly relevant regarding the complexation properties of molecular receptors as preorganization can deeply influence either positively or negatively, the interaction with anions of different geometries.<sup>[73]</sup> The initial proof of concept was demonstrated in the solid state with the capture of carboxylate anions in the cavity. Subsequently, a mass spectrometry study demonstrated that a wide variety of anions ( $ClO_4^-$ ,  $H_2PO_4^-$ ,  $HSO_4^-$ ,  $SO_4^{2-}$ ,  $PF_6^-$ ) are complexed in the gas phase. However, a weak interaction in solution prevents the observation of the complexation.



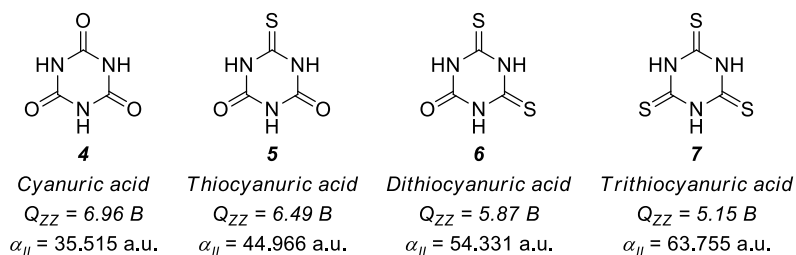
**Figure 2** Example of oxacalix[2]arene[2]triazine.

Stoddart *et al.* prepared a macrocyclic cyclophane **3** based on two triazines substituted with pyridinium cations, that form an electron deficient cavity allowing the capture of anions or polycyclic aromatics (**Figure 3**).<sup>[74]</sup>



**Figure 3** Triazine-based macrocyclic cyclophane (Reproduced from Ref.<sup>[59]</sup> with permission from The Royal Society of Chemistry).

Cyanuric acid derivatives are triazine tautomers, and the series of compounds **4-7** shown in **Figure 4** have been systematically studied in a theoretical approach by Frontera, Deyà *et al.*<sup>[59,75]</sup> Surprisingly, the calculated interaction energies are not affected by switching from oxygen to sulfur atoms due to opposite effects (decrease of quadrupole moment and increase of molecular polarizability), that compensate each other when oxygen is substituted by sulfur atoms.



**Figure 4** Cyanuric acid derivatives : calculated quadrupole moments and molecular polarizabilities.

In the azine series, tetrazine constitutes a rather peculiar case which will be discussed in the following section.

Heptazines are part of a poly-nitrogen heterocyclic family that have gained an increasing interest in recent years.<sup>[76-78]</sup> Kim *et al.* investigated their potential as anion- $\pi$  bond donors by a theoretical approach.<sup>[79]</sup> In heptazine, a strong positive partial charge is calculated ( $q=0.65$  a.u.). Halogen complexes studied have high interaction energies (F<sup>-</sup> 86.1 kcal/mol and Cl<sup>-</sup> 50.2 kcal/mol).

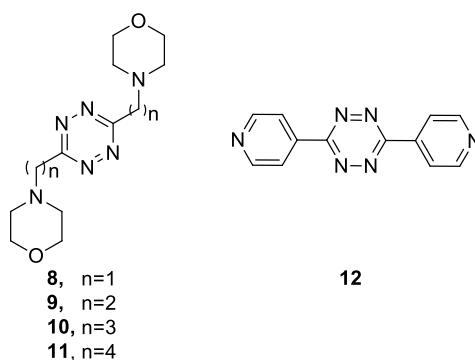
Finally, it must be noted that hypothetical derivatives have also been investigated by theoretical methods. For example, hexazine, an aromatic ring made of six nitrogen atoms ( $N_6$ ), was studied by Frontera, Deyà *et al.* (**Figure 1**).<sup>[80]</sup> Its positive quadrupole moment ( $Q_{ZZ}=+7.57$  B) and high molecular polarizability ( $\alpha_{||}=+25.94$  a.u.) should favor anion- $\pi$  bonds. The calculated interaction energy of its complex with chloride is important ( $E_{int}=-14.0$  kcal.mol<sup>-1</sup> at the MP2/6-31++G\*\* level of calculation with BSSE and ZPE corrections). However, synthesis of this highly unstable structure remains a goal to achieve, even if a recent attempt on an anionic analogue was recently proposed.<sup>[81]</sup>

## 2.4 Case of tetrazine

Tetrazine is a six-membered heterocyclic ring with the chemical formula  $C_2H_2N_4$ . It can exist as three isomeric forms: 1,2,3,4-, 1,2,3,5- and 1,2,4,5-tetrazine.<sup>[82]</sup> The subsequent section will focus on 1,2,4,5-tetrazines, also called s-tetrazines, which attracted intense interest.

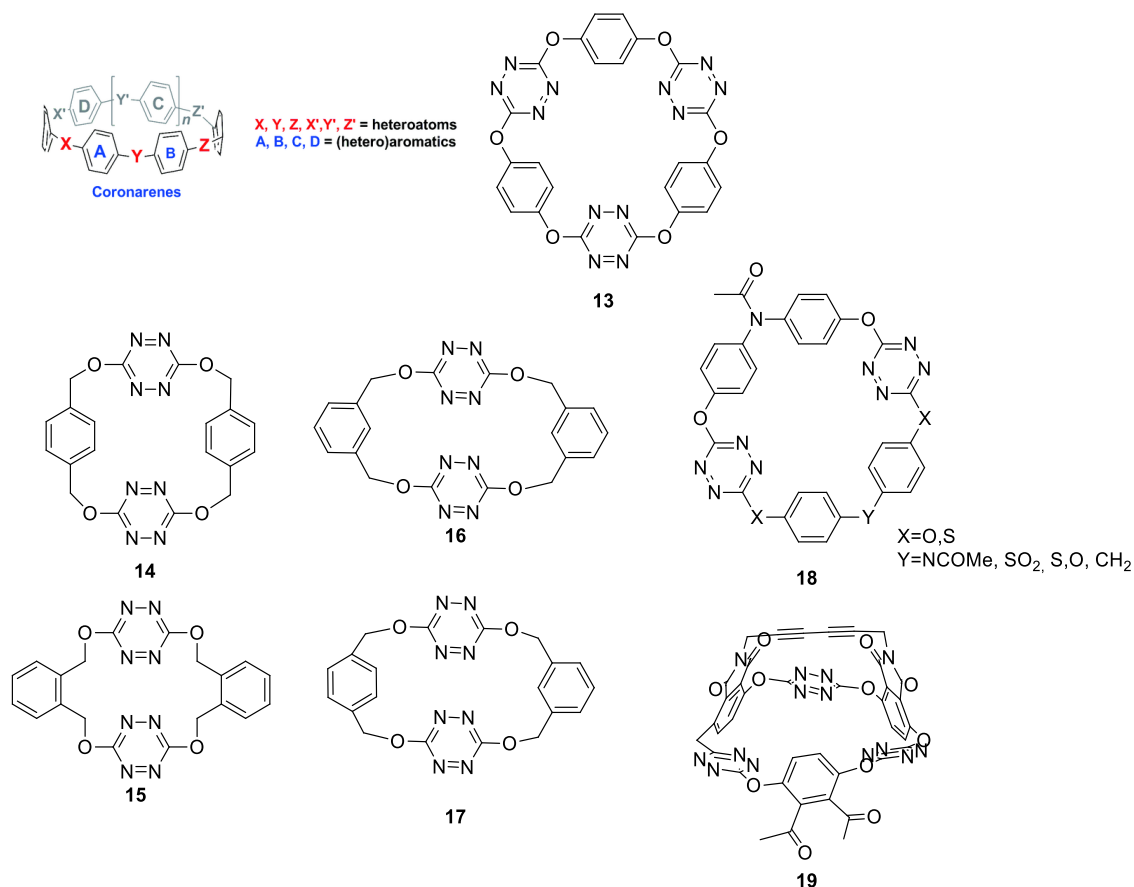
The pioneering theoretical works of Frontera, Deyà *et al.*, two decades ago, highlighted the potential of tetrazine to act as an anion- $\pi$  bond donor, due to an electron deficient character of tetrazine ( $Q_{ZZ}= +2.5$  B) as well as a large molecular polarizability ( $\alpha_{||}=58.7$  au), the latter being the main contributor to the anion- $\pi$  interaction.<sup>[83]</sup> They calculated various energy contributions upon interactions of F<sup>-</sup>, Cl<sup>-</sup> and Br<sup>-</sup> with the tetrazine ring.<sup>[83]</sup> Complexes are energetically favorable in the following order: -18.75 kcal/mol for F<sup>-</sup>, -10.91 kcal/mol for Cl<sup>-</sup> and -10.30 kcal/mol for Br<sup>-</sup> (MP2/6-311+G\*\* level of calculation with BSSE correction).

Bianchi, Melguizo *et al.* also extensively studied the anion binding properties of a series of ligands **8-11** made of a central tetrazine linked to two morpholines through spacers of various lengths (**Figure 5**).<sup>[2,84-90]</sup> 1:1 complexes have been observed both in the solid state and in solution with ligands **8** and **9** and a series of anions, namely F<sup>-</sup>, Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, NO<sub>3</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, SO<sub>4</sub><sup>2-</sup>, I<sub>3</sub><sup>-</sup>, SCN<sup>-</sup> and HO<sup>-</sup>.<sup>[84-86,88]</sup> The influence of both the length<sup>[90]</sup> and the rigidity<sup>[87]</sup> of the spacer on the anion binding behavior were also evaluated with **10**, **11** and **12**. The lengthening of that spacer leads to a weaker association and multiple complexes of different stoichiometries. In contrast, the rigidification of the receptor like in **12** causes various complexes with undefined stoichiometries.



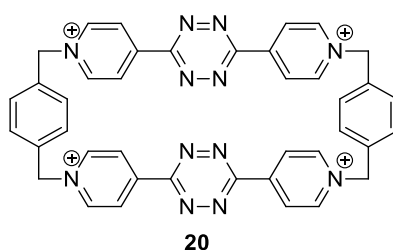
**Figure 5** Tetrazine based ligands studied by Bianchi and Melguizo.<sup>[2,84-90]</sup>

On the other hand, Wang *et al.* extensively studied cyclophane analogues incorporating tetrazine moieties: the corona[*n*]arene[*n*]tetrazines, whose generic and simplest structure **13** is reported in **Figure 6**.<sup>[72,91,95]</sup> The cyclic shape of these receptors induces a special selectivity for linear anions  $\text{N}_3^-$  and  $\text{SCN}^-$ . Interaction strengths with thiocyanate anion depends on the macrocycle structure : **14** ( $202 \pm 1 \text{ L}\cdot\text{mol}^{-1}$ ) > **16** ( $136 \pm 2 \text{ L}\cdot\text{mol}^{-1}$ ) > **17** ( $134 \pm 4 \text{ L}\cdot\text{mol}^{-1}$ ) > **15** ( $102 \pm 1 \text{ L}\cdot\text{mol}^{-1}$ ).<sup>[92]</sup> Rigid structures like **18** were also considered, enabling the anion complexation in gas phase but not in solution<sup>[93]</sup>. The bicyclic compound **19**, recently prepared by the same team, displays a remarkable selectivity towards the  $\text{SCN}^-$  anion.<sup>[94]</sup>



**Figure 6** General structure of coronarenes (Reprinted with permission from Springer Nature: Springer, Science China Chemistry<sup>[91]</sup>, Copyright 2018) and examples of coronarene isomers reported by the team of Wang.<sup>[92–94]</sup>

Finally, Stoddart *et al.* recently described the design and synthesis the “Tetrazinebox” **20**, a structurally transformative tetrazine-containing tetracationic cyclophane, which seems to be of great interest for the design of future molecular machines. (**Figure 7**).<sup>[96]</sup>



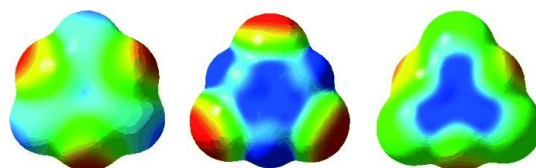
**Figure 7** Stoddart's TetrazineBox.<sup>[96]</sup>

## 2.5 Case of borazines, boroxines and phosphinines

Borazine itself has a negative quadrupole moment ( $Q_{zz} = -3.18 \text{ B}$ ) and a large molecular polarizability (**Figure 1**,  $\alpha_{||} = +41.1 \text{ a.u.}$ ). The quadrupole moment of B-trifluoroborazine, however is positive ( $Q_{zz} = +3.10 \text{ B}$ ), thanks to the electron withdrawing fluorine atoms and retains a large molecular polarizability ( $\alpha_{||} = +38.0 \text{ a.u.}$ ). Theoretical calculations show that this family

and notably the trifluoroborazine, can establish anion- $\pi$  complexes with very favorable interaction energies (from -15.5 kcal/mol with  $F^-$  to -5.7 kcal/mol with  $Br^-$  at the B3LYP/6-311+G\*\* level of calculation with BSSE correction).

The boroxine heterocycle was evaluated theoretically by Masci. [97] A substantial area of positive charge localized at the center of the cycle has been calculated similarly to triazine and cyanuric acid (**Figure 8**).



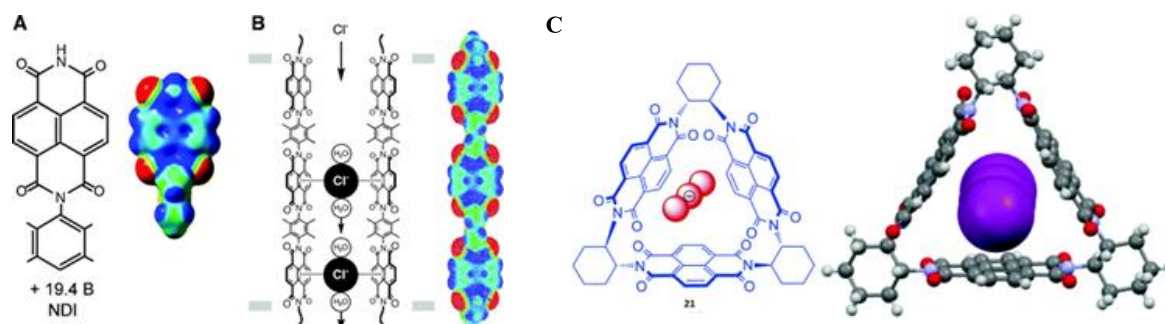
**Figure 8** Electrostatic potential surfaces of s-triazine (left), cyanuric acid (center) and boroxine (right) (Copyright (2006) Wiley. Used with permission from [97]).

Triphosphinine, the phosphorus analogue of cyanuric acid, has been synthesized for the first time and studied in solution by Grützmaier *et al.* in 2017 (**Figure 1**). [98] This electron deficient heterocycle has an aromaticity comparable to the one of benzene, and a strong potential as anion- $\pi$  bond donor.

## 2.6 Polyaromatic compounds/ $\pi$ -slides

The *N,N*-naphthalenediimide (NDI) unit has a strong electron deficient character localized in its center part and a positive quadrupole moment (**Figure 1**,  $Q_{zz} = +19.4$  B). [4] Matile *et al.* quantified by mass spectrometry the strength of anion- $\pi$  interactions formed by various derivatives of this family. [99] Saha *et al.* elegantly demonstrated the formation of NDI radical anions following electron transfer upon complexation of fluoride in acetonitrile, enabling application as colorimetric sensing of this anion. [59,100]

Larger supramolecular structures have been prepared for biomimetic applications. Matile *et al.* synthesized large oligo-(*p*-phenylene)-*N,N*-naphthalenediimides (O-NDI) that form channels in lipid bilayer membranes and are effective for anion transmembrane transport (**Figure 9**). [56,66] The unusual observed selectivity ( $[F^-] > [Cl^-] > [Br^-] > [I^-]$ ) is attributed to strong anion- $\pi$  interactions that compensate the desolvation energy. [4]



**Figure 9** Examples of NDI-based anion receptors : (A) NDI unit, (B) O-NDI in a lipid bilayer membrane and (C) triangular NDI based prism complexed with  $I_3^-$  (Adapted with permission from [101]. Copyright (2006), American Chemical Society, [59] – Published by The Royal Society of Chemistry).

Stoddart *et al.* synthesized chiral triangular NDI based prisms **21** (**Figure 9C**). Interaction with  $I_3^-$  anion leads to self-assembled helices of the supramolecular complex. [102,103]

Benzene triimide or mellitic triimide were introduced as an electron deficient aromatic structures by Hamilton in 2001 (**Figure 1**). [104] Their positive quadrupole moment ( $Q_{zz} = +14.5$  B) value has been exploited to prepare a cage that can selectively bind azide anion (*vide infra*). [105]

1,4,5,8,9,12-hexaazatriphenylene (HAT) has been studied by *ab initio* calculation by the group of Frontera (**Figure 1**). Despite its negative quadrupole moment ( $Q_{zz} = -8.53$  B), calculations show that HAT can form stable complexes with anions thanks to its high molecular polarizability ( $\alpha_1 = 54.03$  a.u.). [47,106] A HAT derivative substituted with nitrile groups, namely

2,3,6,7,10,11-hexacyano-1,4,5,8,9,12-hexaazatriphenylene (HAT-(CN)<sub>6</sub>) has been further studied theoretically by Frontera, Deya *et al.*, enabling a favorable anion- $\pi$  interaction with the CF<sub>3</sub>SO<sub>3</sub><sup>-</sup> anion.<sup>[47]</sup> In solution, 2:3 charge transfer complexes are observed with Cl<sup>-</sup>, Br<sup>-</sup> and I<sup>-</sup> anions, giving rise to new absorption bands in the visible region.<sup>[3,107-109]</sup>

After this overview of some current examples of anion- $\pi$  donors, the following section will be devoted to their combination with hydrogen bond donors. To help the reader identifying key partners for anion- $\pi$  interaction, the same distribution as per anion- $\pi$  donor families will be kept.

### 3. Towards the combination between anion- $\pi$ interaction and hydrogen bonding : notion of cooperativity

#### 3.1 Cooperativity concept

Some recent publications have highlighted the emerging area of cooperativity effects between non-covalent interactions in supramolecular chemistry.<sup>[110-113]</sup>

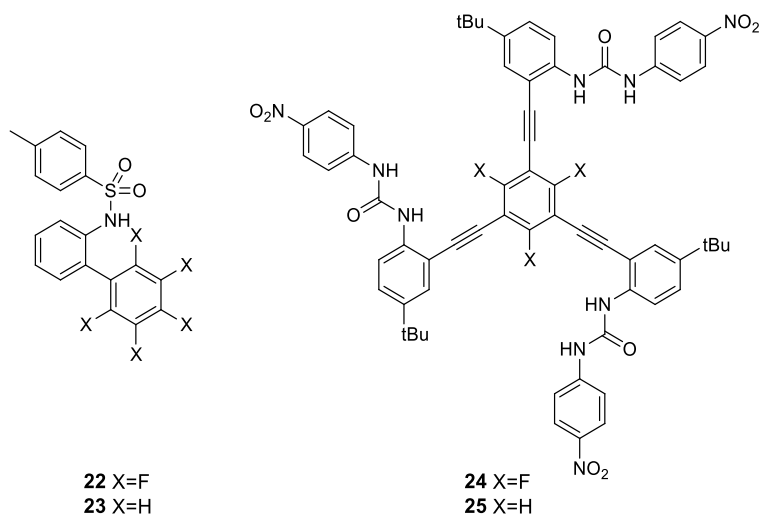
Cooperativity effects depend on both the nature and the number of interactions involved in the complexation process.<sup>[111]</sup> "Cooperativity", "positive cooperativity" or "synergy" corresponds to the case where the mutual non-covalent interactions strengthen each other. This implies that the total interaction within the complex is higher than the simple addition of the separate contributions. Conversely, "non-cooperativity" arises when the total interaction within the complex is equivalent to the simple addition of the interactions involved one by one. Lastly, when the individual interactions compete each other, the resulting interaction within the complex is weaker than the sum of the different interactions taken one by one. This case is called "anti-cooperativity" or "negative cooperativity".<sup>[111]</sup>

A guideline to identify cooperativity effects involved in each system will be provided in the next sections. Indeed, in solution, discrimination between non-cooperativity and positive cooperativity is of major concern and is often difficult to highlight. The lack of evaluation of the influence of the anion- $\pi$  interaction on the complexation process, or the lack of information concerning experimental conditions (control of temperature during the experiment for instance), does not enable an easy determination of the cooperativity effect involved in many cases.

#### 3.2 Cooperativity between anion- $\pi$ Interaction and Hydrogen Bonding : First Examples with Fluoroarenes

The combination of anion- $\pi$  interaction and hydrogen bonding represents a recent issue reported by Furuta *et al.*<sup>[114]</sup> Halide anions complexation by *N*-confused porphyrins bearing pentafluorophenyl groups was evaluated using <sup>1</sup>H and <sup>19</sup>F NMR titrations. The involvement of the two interactions in the complexation process was henceforth shown.

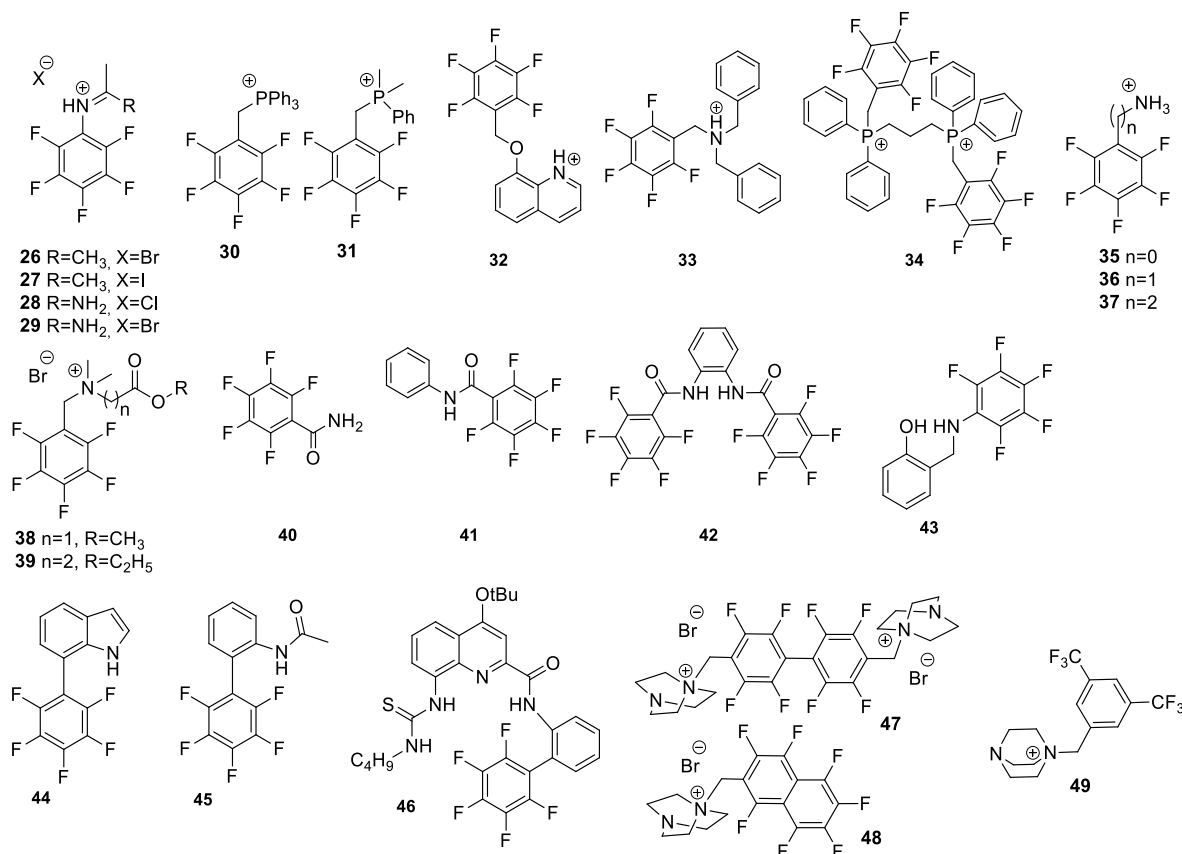
In 2006, Johnson *et al.* published their first study on the subject, highlighting the implication of the anion- $\pi$  interaction in the complexation process (**Figure 10**).<sup>[115]</sup> Anion receptor **22** is composed of a sulfonamide linked by an aromatic group to the pentafluorophenyl ring. This receptor shows a 1:1 moderate affinity for halide anions (30±3 M<sup>-1</sup> for Cl<sup>-</sup>, 20±2 M<sup>-1</sup> for Br<sup>-</sup> and 34±6 M<sup>-1</sup> for I<sup>-</sup> in CDCl<sub>3</sub>), whereas halide affinity for **23** is too weak to be measured. Anion interaction was confirmed by theoretical calculations, showing a global minimum conformation (HF/6-31+G\* level) where the two non-covalent interactions are involved in the complexation process.



**Figure 10** Anion receptors published by Johnson *et al.* [115,116]

Then, the anion receptor **24** shows a fluorinated aromatic ring with three pendant arms bearing electrodeficient ureas. [116] This molecule showed a selective recognition behavior towards nitrate anions in competitive solvent media such as [D<sub>6</sub>]-acetone or 10%-[D<sub>6</sub>]-DMSO/CDCl<sub>3</sub>, but also in solid state. Indeed, the selectivity for nitrate against chloride anion was shown in **24** (24100±1050 M<sup>-1</sup> for NO<sub>3</sub><sup>-</sup> vs. 12200±934 M<sup>-1</sup> for Cl<sup>-</sup>), whereas a reversed selectivity was observed in **25** (11800±1570 M<sup>-1</sup> for NO<sub>3</sub><sup>-</sup> vs. 63700±814 M<sup>-1</sup> for Cl<sup>-</sup>).

Rissanen, Albrecht *et al.* have focused their attention on using the pentafluorophenyl group as an anion-π interaction donor in combination with various hydrogen bond donors (**Figure 11**). [52] Starting from 2008, two families of anion receptors **26-29** and **30-31** were introduced in order to study interactions both in the solid state and in solution. [117,118] A combination of hydrogen bonding and anion-π interaction was underlined. Moreover, the notion of hapticity was extended to the anion-π interaction. A huge diversity was therefore obtained: η<sup>1</sup> for **26** and **27**, η<sup>6</sup> for **28** and **29**, η<sup>2</sup> for **30** and η<sup>1</sup> or η<sup>3</sup> for **31**. Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, PF<sub>6</sub><sup>-</sup> and BF<sub>4</sub><sup>-</sup> anion complexation was described with **30** and **31**. In these structures, the anion-π interaction, considered as weak, could not be observed in solution. [118]



**Figure 11** Some anion receptors studied by the group of Rissanen and Albrecht. <sup>45,51,119–121,54,112–118]</sup>

Studies on anion receptor **2** could then be extended to different anions. <sup>[58,119]</sup> In this compound, the DABCO unit anchored the anion by a C-H...anion interaction above the center of the fluorinated aromatic ring. In the solid state, a  $\eta^6$ -hapticity was observed for Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup> and BF<sub>4</sub><sup>-</sup> anions, representative of the position of the anion above the center of the pentafluorophenyl unit. With larger PF<sub>6</sub><sup>-</sup> and NO<sub>3</sub><sup>-</sup> anions, weaker interactions characterized by a  $\eta^2$ -hapticity are observed.

In 2010, the same team reported that molecules **32**, **33** and **34**, were capable to bind Br<sup>-</sup> and Br<sub>3</sub><sup>-</sup>, I<sub>3</sub><sup>-</sup> and I<sub>4</sub><sup>2-</sup>, 2 I<sup>-</sup> and 2 Br<sup>-</sup> and I<sup>-</sup> + I<sub>4</sub><sup>2-</sup>, respectively. Interestingly, Br<sub>3</sub><sup>-</sup>, I<sub>3</sub><sup>-</sup> and I<sub>4</sub><sup>2-</sup> exotic anions were obtained by oxidation following the precipitation of complexes.

Study of the anion position when a spacer of variable length is placed between the hydrogen bond donor and the pentafluorophenyl unit, was provided with molecules **35-37**. <sup>[120]</sup> This study revealed the establishment of the solely hydrogen bonding interaction, energetically more favorable than the anion- $\pi$  interaction. Therefore, the anion- $\pi$  interaction appears only when the spacer is long and flexible enough to promote a folding of the structure around the anion, thus maximizing non-covalent interactions. <sup>[120]</sup> A  $\eta^6$ -hapticity is observed with **38** and **39**, consecutive to a strong anion- $\pi$  interaction. <sup>[121]</sup>

Complexation properties of molecules **40-42** towards several anions in solution and in solid state were next investigated. <sup>[122]</sup> 1:1 complexes were obtained with anions of different geometries (Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>). Diverse conformations were hypothesized to explain the complexation behavior of **42**. The most stable conformation obtained confirmed the joint presence of two hydrogen bonds and two anion- $\pi$  interactions to stabilize the complex formed.

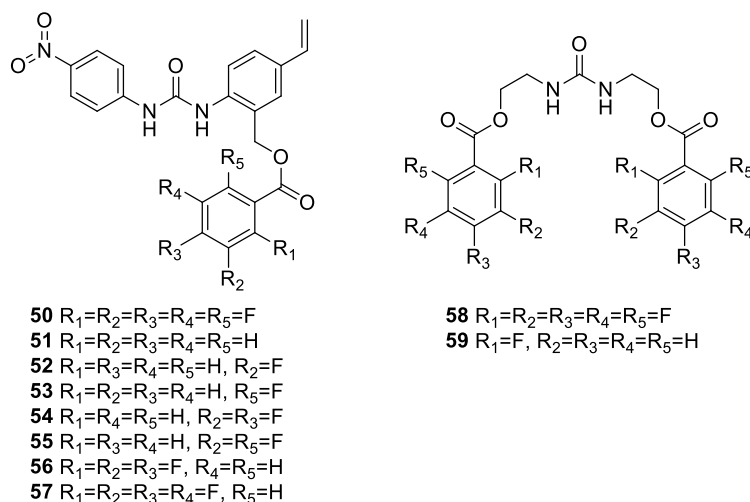
Then, complexation properties of **43** were studied in solution. <sup>[123]</sup> Involvement of anion- $\pi$  interaction was effective in solid state but proved not to be optimal in solution. Following Mata *et al.* work (see below), <sup>[124]</sup> anion receptors **44** and **45** based on a pentafluorophenyl as the anion- $\pi$  receptor, were further examined by Rissanen and Albrecht groups (**Erreur ! Source du renvoi introuvable.**) <sup>[125]</sup> The presence of an anion- $\pi$  interaction was characterized by NMR titrations with chloride anion ( $K_{a,Cl^-} = 46 \text{ M}^{-1}$  for **44** and  $K_{a,Cl^-} = 52 \text{ M}^{-1}$  for **45** in acetonitrile), compared to derivatives substituted by phenyl groups.

Anion receptor **46** was then studied. <sup>[126]</sup> An anion- $\pi$  interaction was postulated in solution but was not settled in solid state.

Thus, Rissanen and Albrecht groups proposed to combine DABCO units with new fluorinated units: perfluoro-1,1'-biphenyle in **47** and perfluoronaphthalene in **48**.<sup>[61]</sup> Solution studies were performed, confirming a complexation process and the establishment of the anion- $\pi$  interaction. A  $\eta^4$ -hapticity was observed in solid state.

Anecdotally, a hydrogen bond and a  $\eta^4$  anion- $\pi$  interaction were evidenced in the solid state between **49** and the bromide anion (**Figure 10**).<sup>[127]</sup> The presence of this interaction could not be confirmed in solution.

The team of Liu recently considered the study of anion receptors. Two series of receptors **50-57** and **58-59**, combining hydrogen bonding and anion- $\pi$  interaction were published (**Figure 12**).<sup>[128-131]</sup>, thereby allowing the influence of the degree of fluorination on the formation of the anion- $\pi$  interaction, to be thoroughly investigated.



**Figure 12** Anion receptors combining hydrogen bonding and anion- $\pi$  interaction studied theoretically by the team of Liu.<sup>[128-131]</sup>

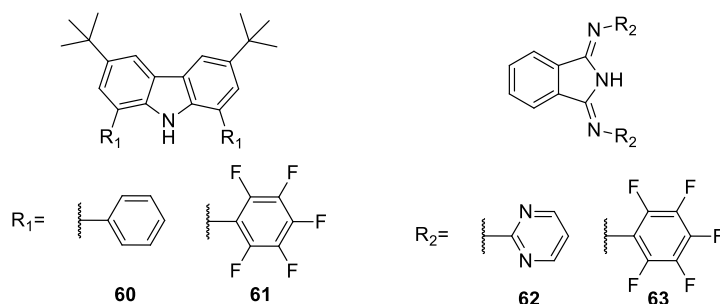
Study of complexes formed between **50** and halide anions enabled to establish the cooperativity between the two interactions involved. A selective binding of fluoride anion was predicted by theoretical calculations in case of competition during the complexation process with different anions.<sup>[128]</sup> By studying the degree of fluorination in molecules **51-57**, Liu *et al.* observed the formation of anion- $\pi$  interactions in molecules **53**, **55** and **57**. The other molecules **51**, **52**, **54** and **56** only showed the presence of hydrogen bonds. Therefore, three geometrical criteria were defined to establish the formation of an anion- $\pi$  interaction.<sup>[129]</sup> It should also be noted that the minimal degree of fluorination required to establish the formation of an anion- $\pi$  interaction differs from the criterium introduced by Weber (**Table 1**).

The second family of anion receptors studied combines a urea motif and two perfluorinated groups, enabling the formation of a tweezer. Theoretical calculations show the trapping of a large diversity of anions ( $F^-$ ,  $Cl^-$ ,  $Br^-$ ,  $I^-$ ,  $CO_3^{2-}$ ,  $NO_3^-$ ,  $SO_4^{2-}$ ) with the molecule **58**.<sup>[130]</sup> Relative stability of the different complexes formed was determined by calculating **58**-anion interaction energies ( $CO_3^{2-} > SO_4^{2-} > F^- > Cl^- > NO_3^- > Br^- \approx I^-$ ). Recently, the team of Liu studied the receptor **59** in interaction with different anions.<sup>[131]</sup> Despite a small degree of fluorination, complexes combining two hydrogen bonds and two anion- $\pi$  interactions were investigated by theoretical calculations with a panel of anions, and relative stabilities of **59**-anion were predicted ( $SO_4^{2-} > F^- > CN^- > Cl^- > I^- > Br^-$ ). However, in the case of iodide, the global minimum did not exhibit any anion- $\pi$  interaction. In the case of  $SO_4^{2-}$  anion, two global minima were obtained with 1:1 and 1:2 host:guest stoichiometries. It is worth noting that relative stabilities of the different anion complexes differ between **58** and **59**.<sup>[130,131]</sup> However, a direct comparison between **58** and **59** could not be done as the basis set used for theoretical calculations was different. Complexes formed between anion receptors **58** and **59** and anions are not symmetrical, thus confirming cooperativity effects between the two interactions. In both cases, the formation of charge-transfer complexes with fluoride anion was highlighted.

Mata, Meyer *et al.* reported the synthesis and study of two preorganized anion receptors **61** and **63** (**Figure 13**).<sup>[124]</sup> Molecule **61** offers a more rigid scaffold than **63**. The conformational freedom of the latter implies the presence of multiple conformations visible in solution, preventing the determination of the type of complex formed and the association constant in solution. Nevertheless, a shift of NMR signals is observed in  $^{19}F$  and  $^1H$  NMR spectra for **61** and **63**, whereas no significant shift was observed with **60** and **62**, thus confirming the occurrence of anion- $\pi$  interactions. Weak association constants were determined with **61** ( $K_a=12.0 M^{-1}$  for  $Cl^-$  and  $6.6 M^{-1}$  for  $Br^-$  in  $CD_3CN$ ). With **63**, a 1:1 host :guest complex was formed with  $Cl^-$ , whereas a 2:1 model is observed with  $Br^-$  in the solid state. Theoretical calculations at the B3LYP-D3/def2-TZVPP level enabled the determination of an interaction energy for **61**- $Cl^-$  complex ( $E_{int,1:1}=-42.6 kcal.mol^{-1}$ ).



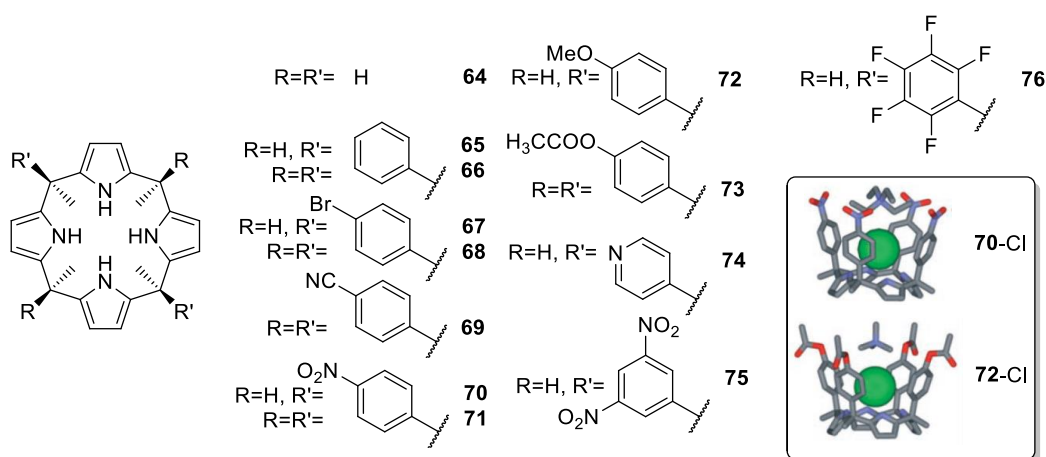
Finally, a non-additivity effect of association constants was observed between **63** and Cl<sup>-</sup> ( $E_{\text{int},1:1}=-43.8 \text{ kcal.mol}^{-1}$  and  $E_{\text{int},2:1}=-80.4 \text{ kcal.mol}^{-1}$ ).



**Figure 13** Anion receptors synthesized by Mata and Meyer. <sup>[124]</sup>

### 3.3 Cooperativity between anion- $\pi$ interactions and hydrogen bonding : the case of calix[4]pyrroles

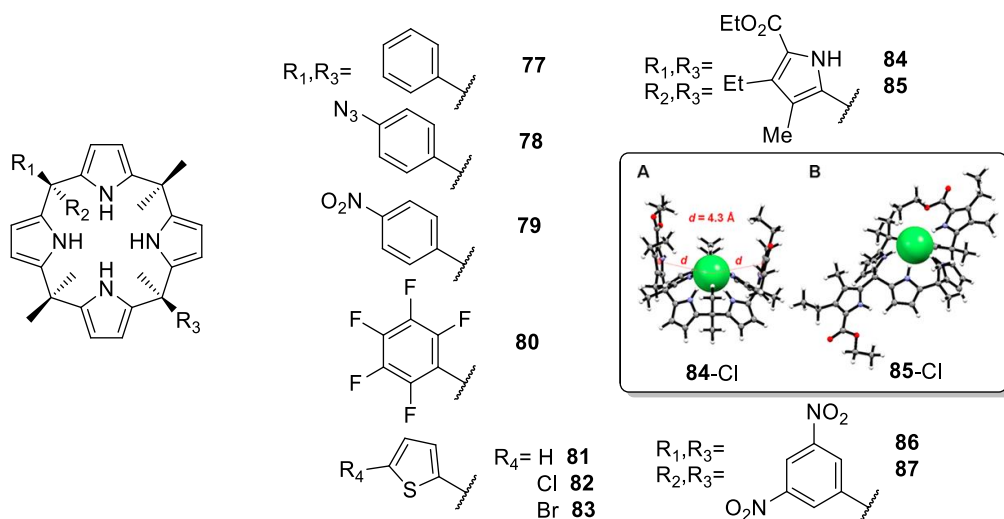
Grafting multiple anion- $\pi$  donors on calixpyrrole scaffolds to improve anion recognition was extensively studied by the Ballester group (**Figure 14**).<sup>[49,112,132,133]</sup>



**Figure 14** Scope of calix[4]pyrroles bearing anion- $\pi$  donors studied by Ballester <sup>[49,112,132,133]</sup> (insert : Some X-ray structures obtained, Copyright (2008) Wiley. Used with permission from <sup>[132]</sup>).

Based on the anion recognition properties of calix[4]pyrrole **64** ( $K_a=1.08 \cdot 10^5 \text{ M}^{-1}$  for Cl<sup>-</sup> in acetonitrile), the Ballester group reported on a decrease of association constants when R-substituents introduced are electron donors like **72** ( $K_a=1.06 \cdot 10^4 \text{ M}^{-1}$  for Cl<sup>-</sup>) or **65** ( $K_a=2.65 \cdot 10^4 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN). A reverse trend was observed with electron withdrawing R-substituents, such as in **67** ( $K_a=6.78 \cdot 10^5 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN), **70** ( $K_a=2.77 \cdot 10^5 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN), **74** ( $K_a=1.24 \cdot 10^5 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN), **75** ( $K_a=1.79 \cdot 10^6 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN) and **76** ( $K_a=5.53 \cdot 10^5 \text{ M}^{-1}$  for Cl<sup>-</sup>, CH<sub>3</sub>CN). Similar trends are observed with tetrasubstituted calix[4]pyrroles **66**, **68**, **69**, **71** and **73**. These results were confirmed by determination of X-ray structures of some of the complexes formed, highlighting the joint presence of cooperative hydrogen bonds and anion- $\pi$  interactions (insert, **Figure 14**).

Cooperativity effects were then studied in the case of “two-walled” calix[4]pyrroles. <sup>[49,134–137]</sup> This design allows the formation of two isomers *cis* (R<sub>1</sub>,R<sub>3</sub>) and *trans* (R<sub>2</sub>,R<sub>3</sub>). A large diversity of substituents was therefore studied (**Figure 15**).



**Figure 15** Scope of « Two-walled » calix[4]pyrroles studied <sup>[134–137]</sup> (insert : conformations obtained for the chloride complexes of A) **84** and B) **85** (level : B3LYP/6-31G\*, Reprinted with permission from <sup>[137]</sup>. Copyright (2014), American Chemical Society).

Ballester *et al.* examined the presence of two aromatic substituents in **77–80** and **86**.<sup>[135]</sup> Two-walled calix[4]pyrroles were found to minimize steric hindrance between substituents compared to “four-walled” analogues.<sup>[136]</sup> An enhanced anion recognition is observed for receptors based on electron deficient arenes or aromatics substituted by withdrawing groups ( $K_{a,Cl-,77} = 30 \text{ M}^{-1}$ ,  $K_{a,Cl-,78} = 40 \text{ M}^{-1}$ ,  $K_{a,Cl-,79} = 140 \text{ M}^{-1}$ ,  $K_{a,Cl-,80} = 710 \text{ M}^{-1}$ ,  $K_{a,Cl-,86} = 1550 \text{ M}^{-1}$  in acetonitrile at 298 K). Such anion receptors have been effective as transmembrane nitrate anions transporters.<sup>[135]</sup>

Calix[4]pyrroles bearing thiophene groups **81–83** were reported by Sripadi *et al.*<sup>[136]</sup> Surprisingly, thiophene fragments were found to establish anion- $\pi$  interactions with small anions, as evidenced by a combination of experimental techniques. A selective binding of fluoride anion was observed in solution. However, the larger size of chloride anion prevents adequate conformation allowing interaction with thiophene rings. In these cases, 1:1 complexes with halide anions were determined by mass spectrometry.

The impact of *cis* and *trans* isomers of “two-walled” calix[4]pyrrole on anion recognition was studied by comparing **86** and **87**.<sup>[49,134,135]</sup> A weaker anion recognition was found with **87** ( $K_{a,Cl-,87} = 85 \text{ M}^{-1}$  in acetonitrile at 298 K) due to the formation of only one anion- $\pi$  interaction. Moreover, the conformational study of **84** and **85** confirmed the crucial role of conformations on anion binding.<sup>[137]</sup> In **84**, Anzenbacher *et al.* showed the favorable formation of two non-intuitive anion- $\pi$  interactions with pyrrole rings by theoretical calculations (insert, **Figure 15**), enabling an increase of association constants compared to **85** ( $K_{a,Cl-,84} = 220000 \text{ M}^{-1}$  vs.  $K_{a,Cl-,85} = 1900 \text{ M}^{-1}$  in acetonitrile at 298 K). Though, a better selectivity is observed with **84** and acetate anion, due to the formation of a complementary hydrogen bond.

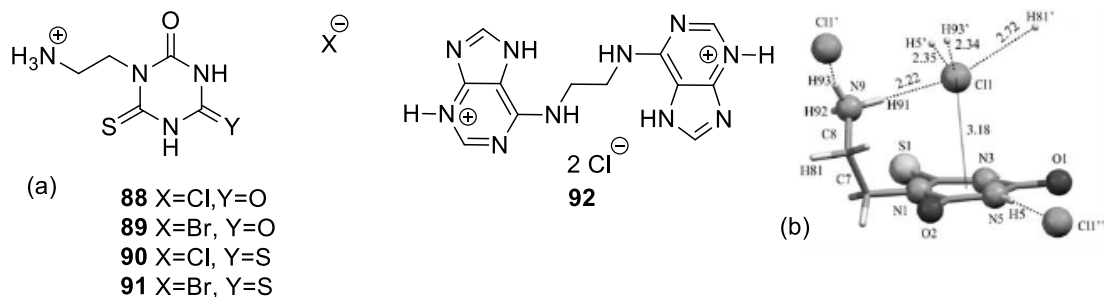
Compound **86** was then studied for the recognition of anions of multiple geometries (spherical, linear, trigonal and tetrahedral) in solid state and in solution.<sup>[134]</sup> For all the geometries studied, the joint formation of hydrogen bonds and anion- $\pi$  interactions was established.

The synthesis of calix[4]pyrroles bearing cyclohexyl groups was reported recently by the team of Aydogan.<sup>[138]</sup> Measurements of association constants by using isothermal titration calorimetry (ITC) showed that these cyclohexyl groups, compared to compound **64**, enable the formation of anion- $\pi$  interactions by increasing the association constant. Moreover, Sessler, Lee *et al.* described a calix[4]pyrrole topped by a crown containing two additional pyrrole rings and a fluorophore.<sup>[139]</sup> A selective colorimetric response was observed with several anions and notably fluoride. A better affinity was noticed for this compound with respect to the anion receptor **64**. An anion- $\pi$  interaction was postulated due to the downfield shift of  $\beta$ -pyrrolic protons observed by NMR spectroscopy.

Finally, it has to be mentioned that the Ballester group reported a macromolecular ion pair receptor composed of two stands calix[4]pyrroles linked together by two aromatic linkers able to generate anion- $\pi$  interactions and selectively bind ion pairs.<sup>[133]</sup> Depending on the salt considered, 2:1 host:guest complexes were observed.

### 3.4 Rationalization of cooperativity effects observed between hydrogen bonds and anion- $\pi$ interactions

Rationalization of cooperativity effects observed when combining anion- $\pi$  interactions and hydrogen bonding by mean of theoretical studies, has been recently reported by Deyà group. [75,140–143] In these studies, complexes of four anion receptors combining an ammonium group and a cyanuric acid **88**, **89**, **90** and **91** were investigated (**Figure 16a**). X-ray structures of subsequent complexes were also determined (**Figure 16b**). [75] The X-ray structure of the **88**-Cl complex showed the anion lying above the anion- $\pi$  donor site and interacting with one ammonium proton. The computed structure (level : MP2(full)/6-31++G\*\*) was in good agreement with experiments.



**Figure 16** (a) Some anion receptors reported by the team of Deyà (b) X-Ray structure of **88**-Cl complex (Copyright (2005) Wiley. Used with permission from [75]).

Thus, two theoretical studies subsequently examined a variety of potential anion- $\pi$  donors interacting with (i) an anion, and (ii) one or several water molecules. [140,141] These studies helped defining the concept of “synergistic energy”  $E_{syn}$ , defined as :

$$E_{syn} = E_{BSSE}(\pi A + HB) - E_{BSSE}(\pi A) - E_{BSSE}(HB)$$

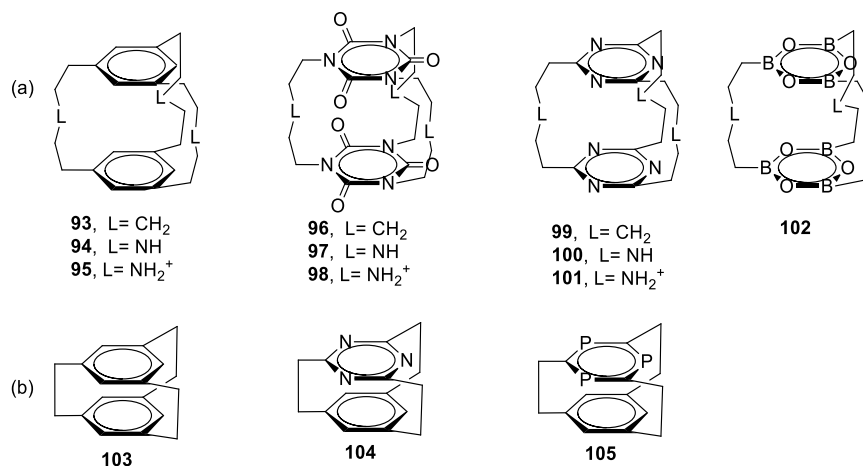
Where :  $E_{BSSE}(\pi A + HB)$ ,  $E_{BSSE}(\pi A)$  and  $E_{BSSE}(HB)$  are BSSE-corrected energies of anion- $\pi$ +H bond, anion- $\pi$  and H bond complexes. Then, if  $E_{syn} < 0$ , BSSE-corrected energy of anion- $\pi$ +H bond complex is lower than the sum of the contribution of each independent interaction. In this case, the complex involving the two interactions is more stable than the sum of independent interactions, determining a positive cooperativity effect. On the other hand, when  $E_{syn} > 0$ , an anti-cooperativity effect is shown. When  $E_{syn} = 0$ , a case of non-cooperativity is observed.

Recently, complexes combining s-triazine, HF or HCl molecules and anions were studied by Roohi and Safari in order to determine the influence of the different non-covalent interactions on anion binding. Huge positive cooperativity effects were highlighted for complexes with fluoride, chloride and cyanate anions. [144]

In 2007, bis-adenines derived molecules such as **92** (**Figure 16a**) were studied for anion recognition by Deyà and Frontera groups. [145,146] These molecules contain an electron acceptor aromatic ring able to interact with anions by anion- $\pi$  and hydrogen bond interactions. 2:2 complexes combining the two interactions were observed by X-ray structures. Theoretical calculations confirmed the stability of such complex. The quantification of both interactions shows similar contributions to the overall anion-complex interaction.

### 3.5 Cooperativity between hydrogen bonds and anion- $\pi$ interactions : case of cylindrophanes and cyclophanes

Different cylindrophane-type molecules bearing diverse electron deficient groups (triazine **101**, cyanuric acid **98** and boroxine **102**, **Figure 17a**) were studied theoretically by Mascal *et al.* [97] Favorable fluoride and chloride complexes were predicted, showing increasing selectivity in the order of **101**<**98**<**102**. In contrast, electronic repulsions that take place in **95**, prevent the anion binding.



**Figure 17** Examples of (a) cylindrophanes and (b) cyclophanes studied for the molecular recognition of anions.

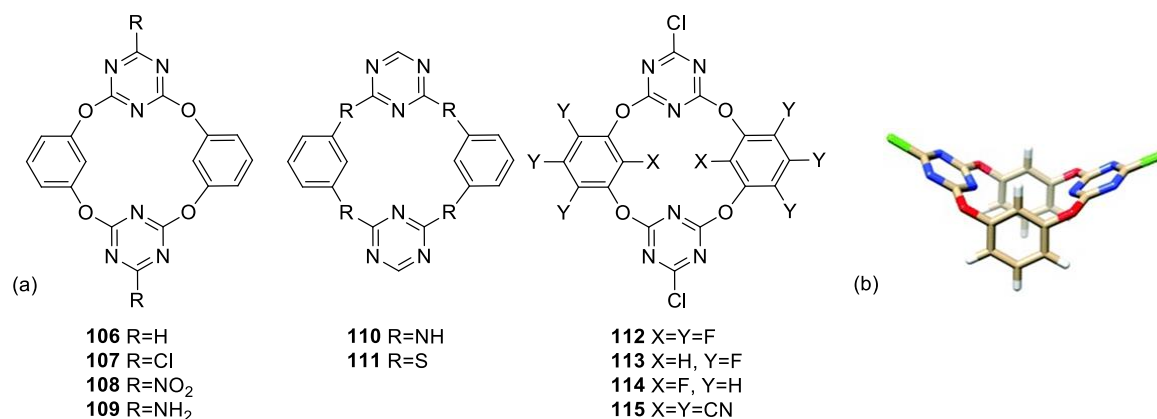
Later, the same group described a similar molecular cage bearing two cyanuric acids and two ammonium groups. [147] Selective fluoride binding was shown by mass spectrometry and confirmed by an X-ray structure.

Caramori and Mascali groups theoretically studied molecules **93-100**, thus varying the electron deficient aromatic ring and the linker in compounds **95**, **98** and **101**, in order to achieve a selective fluoride complexation (**Figure 17a**). [147,148] [149] Molecules bearing benzenic rings **93-95** do not promote any anion complexation. On the other hand, either cyanuric acids (**96-98**) or triazine compounds (**99-101**) display favorable interactions with anions. Consequently, the nature of aromatic groups seems to be a critical parameter to promote anion complexation. The subsequent selectivity was observed: cyanuric acid > triazine > benzene. The nature of the L linker used favors the stabilization of the complex by hydrogen bonds. Moving from L = CH<sub>2</sub>>NH>NH<sub>2</sub><sup>+</sup>, H...F- distances decrease, in agreement with the strengthening of hydrogen bonds. A partial covalent character is even observed with L = NH<sub>2</sub><sup>+</sup>. To sum up, an optimal fluoride complexation was obtained with compound **98**.

Following the same standards, the group of Caramori investigated cyclophane derivatives **103-105** (**Figure 17b**). [148,150] Theoretical calculations showed anion complexes with anions lying outside the cavity. Molecules **104** and **105** display an electron deficient character compared to **103**. However, hydrogen bonded complexes are obtained with **103**, while complexes with **104** display weak  $\sigma$ -complexes. In addition, strong  $\sigma$ -complexes with anions were obtained with **105**.

### 3.6 Cooperativity between hydrogen bonds and anion- $\pi$ interactions: case of azine derivatives

In this context, several calixarene-like anion receptors were modelled and theoretically studied by Caramori (**Figure 18a**). [151,152]



**Figure 18** (a) Calixarene anion receptors studied by Caramori group [151,152] (b) 1,3-alternated conformation of **107**. (Republished with permission of the PCCP Owner Societies, from Ref. [151]; permission conveyed through Copyright Clearance Center, Inc.).

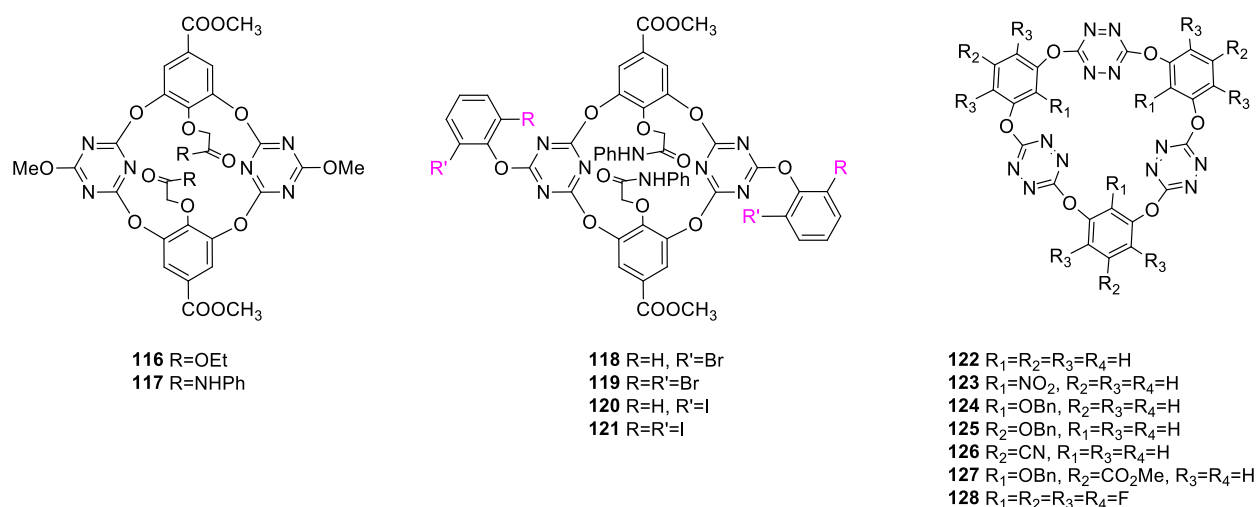
Taking the Cl-oxacalix[2]arene[2]triazine as a reference compound, the influence of the heteroatom connecting the different aromatic groups, on the interaction with a large anion diversity ( $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{BF}_4^-$ ,  $\text{H}_2\text{PO}_4^-$ ,  $\text{HSO}_4^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{CH}_3\text{COO}^-$ ,  $\text{NO}_3^-$ ,  $\text{NCS}^-$ ,  $\text{PF}_6^-$ ), was studied in compounds **106**, **107**, **110** and **111**.<sup>[151]</sup> Conformational studies highlight a 1,3-alternated conformation, showing an interesting pre-organized electron deficient region which is beneficial to the anion binding process (**Figure 18b**). NCI-plot analysis confirms the joint presence of hydrogen bonds and anion- $\pi$  interactions. Especially, in compound **111**, sulfur atom was deeply involved in the anion binding.

Then, two other structural modifications were theoretically studied: (i) the nature of the electron withdrawing groups installed at the triazine rings (**108** and **109**), (ii) the substitution pattern at the phenyl ring (for F or CN) in **112-115**.<sup>[152]</sup> Interaction energies of the different complexes studied were estimated ( $E_{\text{int,107-Cl}}=-37.0$  kcal/mol,  $E_{\text{int,113-Cl}}=-47.7$  kcal/mol and  $E_{\text{int,108-Cl}}=-42.6$  kcal/mol using BP86-D3/TZ2P level of calculation). Substitution of aromatic rings by electron withdrawing atoms or groups, causes an extra stabilization of the complexes formed. A possible application of this type of structures is the formation of solid-state self-assemblies.<sup>[72]</sup>

In 2007, Wu *and al.* published a theoretical study predicting the optimal binding of the fluoride anion by a oxabicyclicocalixarene in the gas phase ( $E_{\text{int}}=-80.5$  kcal/mol at the B3LYP/6-311++G\*\* level of calculation, including BSSE correction).<sup>[153]</sup> This macromolecule displays a fluoride anion size-optimal cavity, comprising both hydrogen bonds and anion- $\pi$  interactions. As far as we know, despite the great interest of this type of structure, no chemical synthesis of this compound was reported yet.

Using Hirschfeld surface analysis, Bianchi *et al.* examined different X-ray structures of anion receptors reported in the literature.<sup>[154]</sup> In this study, the complex between 2,4,6-tris(2-pyridyl)-1,3,5-triazine and  $\text{Br}_3^-$  shows a mix of hydrogen bonds and intermolecular anion- $\pi$  interactions.

Wang reported on the cooperativity between anion- $\pi$  interactions and hydrogen bonds in oxacalix[2]arene[2]triazine and coronarenes. (**Figure 19**).<sup>[155-157]</sup>

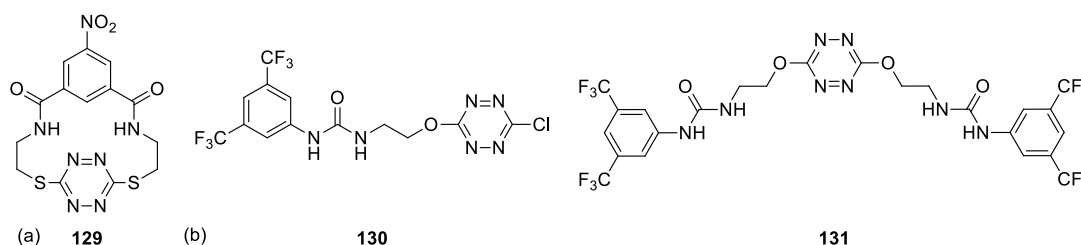


**Figure 19** Macrocycles developed by the Wang group.<sup>[155-157]</sup>

The anion receptor **116** proved to be selective for the  $\text{H}_2\text{PO}_4^-$  anion ( $K_a=8.14.10^2$  M<sup>-1</sup> in acetonitrile) as compared to  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{NO}_3^-$ ,  $\text{HSO}_4^-$ ,  $\text{SCN}^-$ ,  $\text{BF}_4^-$  and  $\text{PF}_6^-$  anions. Introducing two hydrogen bond donors like in **117**, leads to the same selectivity and an increase of the association constant ( $K_a=7.98.10^3$  M<sup>-1</sup> in acetonitrile), compared to **116**.<sup>[155]</sup> Based on this molecular design, the same group grafted chloride atoms on aromatic groups bearing hydrogen bond donors, leading to molecules **118-121**. In this case, no selectivity was observed and high association constants for halide anions, allow foreseeing transmembrane transport applications.<sup>[156,158]</sup> A new family of coronarene macrocycles **122-128** was synthesized by Wang *et al.*, trying to overcome the lack of selectivity observed in **13** (**Figure 6**).<sup>[157]</sup> This new family combines hydrogen bonds and anion- $\pi$  interactions. Formation of anion complexes with **122** was observed by mass spectrometry with  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{SCN}^-$ ,  $\text{NO}_3^-$ ,  $\text{BF}_4^-$  and  $\text{ClO}_4^-$  anions. In contrast, no interaction was observed with carbonate and carboxylate anions. In solution, 1:1 host:guest complexes were observed with huge NMR- and UV-deduced association constants ( $K_a=2.25.10^3$  M<sup>-1</sup> for  $\text{NO}_3^-$ ,  $1.01.10^3$  M<sup>-1</sup> for  $\text{Br}^-$  in acetone), whereas  $\text{ReO}_4^-$ ,  $\text{PF}_6^-$  and  $\text{CF}_3\text{SO}_3^-$  anions were not trapped in solution. Cooperativity effects were assessed, and introduction of electron withdrawing groups close

to the hydrogen bond donor (see **126**), leads to an increase of the association constant observed with the  $\text{NO}_3^-$  anion ( $K_a=2.22 \cdot 10^5 \text{ M}^{-1}$  in acetone).

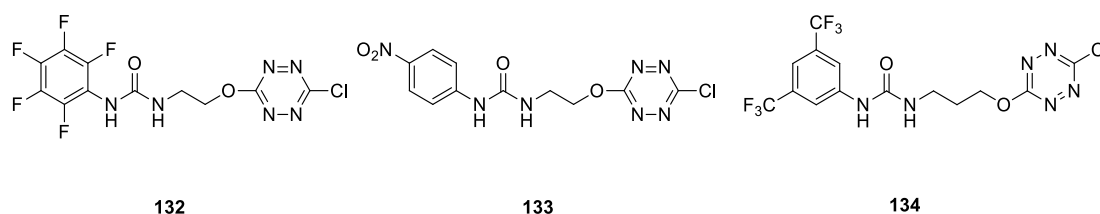
Simpler structures were also designed. Indeed, Li *et al.* reported the cyclic anion receptor **129** based on a tetrazine and amide groups to selectively bind fluoride anions (**Figure 20a**).<sup>[159]</sup> This colorimetric probe changes color in the presence of a fluoride anion, moving on from pink to green. The formation of a tetrazine radical anion, related to the charge transfer induced between the fluoride anion and the tetrazine ring, is observed. This was confirmed by electron spin resonance (ESR) spectrum measurement of the complex formed.



**Figure 20** First anion receptors combining anion- $\pi$  interaction and hydrogen bonding proposed by (a) Li's group and (b) Prim's group.<sup>[159]</sup>

Our research group started the exploration of binding properties of two flexible anion receptors combining a fluorescent anion- $\pi$  receptor and one or two hydrogen bond donor urea fragments **130** and **131** respectively (**Figure 20b**).<sup>[41,42]</sup> These designs combine urea and tetrazine moieties. Geometries of the complexes formed between **130** and **131** with different anions ( $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ,  $\text{SCN}^-$ ,  $\text{PF}_6^-$ ) were predicted by quantum calculations. In the case of **130**, theoretical interaction energies can even be predicted with a relatively good agreement between theory and experiments. Existence of these complexes in the gas phase was assessed by mass spectrometry. Moderate association constants could be determined for **130** in the ground state by NMR spectroscopy ( $K_{a,\text{Cl}^-}=4.89 \cdot 10^3 \text{ M}^{-1}$  et  $K_{a,\text{Br}^-}=3.8 \cdot 10^2 \text{ M}^{-1}$  in acetonitrile).<sup>[41]</sup> A synergistic effect of the two interactions was observed in this case. Studies with **131** revealed a large drop of association constants in the ground state, suggesting the presence of an anti-cooperativity effect between the three interactions. In the excited state, a reverse selectivity and different anion-depending quenching mechanisms were observed. A combination of static and dynamic quenching mechanisms was highlighted, the extent of each was dependent on the anion polarizability. While smaller anions ( $\text{Cl}^-$ ,  $\text{Br}^-$ ) displayed a prominent dynamic quenching, larger ones ( $\text{I}^-$ ,  $\text{SCN}^-$ ) showed an increased contribution of the static quenching. This latter fact was responsible for the more pronounced anion- $\pi$  interaction with polarizable anions.<sup>[42]</sup>

Recently, our research group proposed a new set of anion receptors **132-134** derived from receptor **130** (**Figure 21**).<sup>[43]</sup> A systematic study of chloride anion recognition both in ground and excited states, as well as gas and solution phases enabled the classification of complex by interaction energies as follows : **133-Cl** > **130-Cl** > **134-Cl** > **132-Cl**.

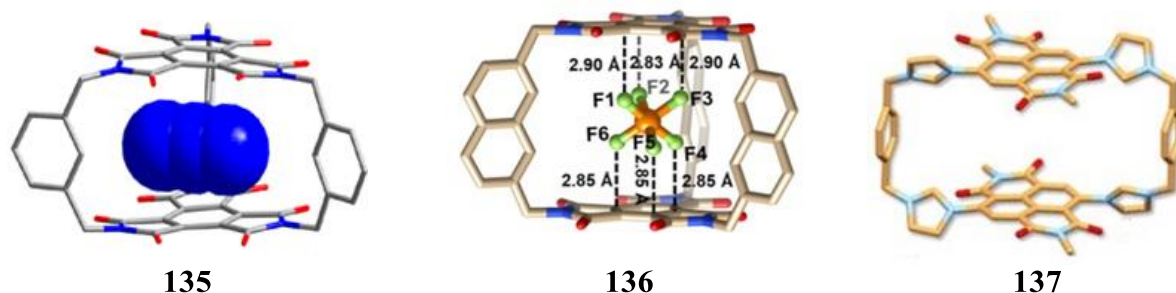


**Figure 21** Derived anion receptors proposed by Prim's group.<sup>[159]</sup>

### 3.7 Cooperativity between hydrogen bonds and anion- $\pi$ interactions : case of $\pi$ -slides/polyaromatic structures :

A first example of a structure combining a  $\pi$ -slide and a hydrogen-bond donor has been reported by Wang in 2019 (**135**, **Figure 22a**).<sup>[49,72,105]</sup> This design combines two benzene triamide groups linked together by three aromatic pendant arms. This design enables to set two highly cooperative anion- $\pi$  interactions ( $d_{\text{anion-plane}} = 2.7 \text{ \AA}$ ), inducing a charge transfer. Binding of bulky anions was observed ( $\text{N}_3^-$ ,  $\text{SCN}^-$ ,  $\text{I}^-$ ) with a marked selectivity for  $\text{N}_3^-$  anion ( $K_a = 11098 \pm 46 \text{ M}^{-1}$  in dichloromethane), with association constants 150- and 250-times higher than those observed for  $\text{SCN}^-$  and  $\text{I}^-$ , respectively. Formation of weak hydrogen bonds was also highlighted by NMR titration experiments. Recently, another example **136** was proposed where the benzene linker is replaced by a naphthalene linker.<sup>[161]</sup> This cage offers a huge cavity of  $\sim 7.6 \text{ \AA}$

able to bind polyhedral anions with exceptional affinities in DMA (for instance,  $K_{a,BF_4^-} = 31613 \text{ M}^{-1}$  and  $K_{a,H_2SO_4} = 84623 \text{ M}^{-1}$ ).<sup>[161]</sup>



**Figure 22** Benzene triimide-based anion receptor cages **135** and **136** and NDI-based anion receptor cage **137**.

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(This figure has been published in *CCS Chemistry* 2022; *Naphthalene-Pillared Benzene Triimide Cage: An Efficient Receptor for Polyhedral Anion and a General Tool for Probing Theoretically-Existing Anion- $\pi$  Binding Motifs* is available online at 10.31635/ccchem.021.202101366).

Another example was proposed by Mukhopadhyay *et al.*<sup>[160]</sup> In this structure **137**, two imidazolium groups are grafted next to the NDI electron-deficient group, amplifying the electron deficiency of the NDI. This results into stable complexes with multiple anions trapped within the cavity (2 hexafluorophosphate and up to 4 nitrate anions). Complexes formed with these two anion types, show both hydrogen bonding with triazolium units and anion- $\pi$  interaction with NDI.

## 4. Summary and Outlook

This review highlights the main theoretical and experimental studies of anion complexation based on the combination of hydrogen bonding and anion- $\pi$  interaction. For the latter, different families have been identified. The tetrazine core appears as a key-player alongside the more traditionally used fluorinated arenes for the development of anion receptors based on anion- $\pi$  interaction. Combining hydrogen bonding and anion- $\pi$  weak interactions led to develop both qualitative and quantitative models of the emerging concepts of cooperativity and anticooperativity involved during the complexation. Indeed, the grasp and the rationalization of these effects would help, in the long run, to maximize them in order to obtain even more powerful supramolecular systems. However, despite numerous sophisticated quantum chemistry tools to highlight complexation phenomena in such systems (interaction energy, NCIPLOT...), it remains often difficult to directly compare systems due to the diversity of molecular calculation methods used and the continuous improvement of molecular simulations nowadays, compared to ten or twenty years ago. However, today in solution, a large diversity of analytical tools is available for supramolecular chemists to understand complexation processes (NMR, fluorescence, UV spectroscopy, mass spectrometry, ITC, X-ray structure coupled or not with Hirschfeld surfaces...). Thus, applications are now foreseen for such supramolecular systems such as catalysis, colorimetric molecular recognition or transmembrane transport. To this issue, some futuristic functional systems introduced recently by the Stoddart group in particular, allow to oversee a bright future of diverse applications from such supramolecular systems.

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## Conflict of interest

There is no conflict of interest to declare.

**Keywords:** Anions – Anion- $\pi$  interaction – Cooperativity – Hydrogen bond – Molecular recognition –

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## Entry for the Table of Contents



Hydrogen Bonding and Anion- $\pi$  Interaction: two interactions of today's research in anion recognition supramolecular chemistry. Combining these two interactions give rise to interesting cooperativity effects that remains difficult to rationalize and quantify. In this review, concepts of cooperativity are illustrated on the example of the combination of hydrogen bonding and anion- $\pi$  interaction.

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