Anion complexes with tetrazine-based ligands: formation of strong anion-π interactions in solution and in the solid-state

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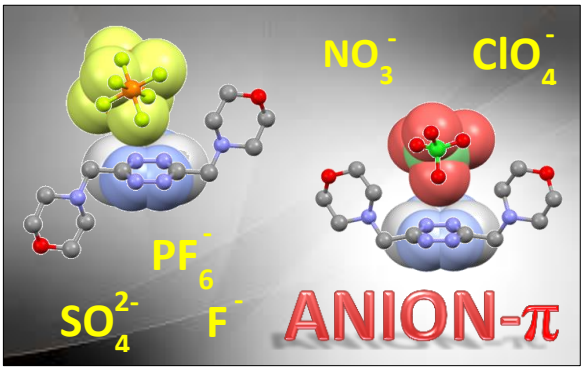
ABSTRACT: Ligands L1 and L2, consisting in a tetrazine ring decorated with two morpholine pendants of different lengths, show peculiar anion binding behaviours. In several cases, even the neutral ligands, in addition to their protonated HL^{+}, H_2L^{2+} (L = L1 , L2) forms, bind anions such as F^-, NO_3^-, PF_6^-, ClO_4^-, and SO_4^{2-} to form stable complexes in water. The crystal structures of $H_2L1(PF_6)_2{\cdot}2H_2O$, $H_2L1(ClO_4)_2{\cdot}2H_2O$, $H_2L2(NO_3)_2$, $H_2L2(PF_6)_2{\cdot}H_2O$ and $H_2L2(ClO_4)_2{\cdot}H_2O$, show that anion-π interactions are pivotal for the formation of these complexes, although other weak forces may contribute to their stability. Complex stability constants were determined by means of potentiometric titration in aqueous solution at 298.1 K, while dissection of the free energy change of association ($\Delta G°$) into its enthalpic ($\Delta H°$) and entropic ($T\Delta S°$) components was accomplished by means of ITC



measurements. Stability constants are poorly regulated by anion-ligand charge-charge attraction. Thermodynamic data show that the formation of complexes with neutral ligands, that are principally stabilized by anion-π interactions, is enthalpically favourable (-Δ*G*°, 11.1 to 17.5 kJ/mol; Δ*H*°, -2.3 to -0.5 kJ/mol; *T*Δ*S*°, 9.0 to 17.0 kJ/mol), while for charged ligands enthalpy changes are mostly unfavourable. Complexation reactions are invariably promoted by large and favourable entropic contributions. The importance of desolvation phenomena manifested by such thermodynamic data was confirmed by hydrodynamic results obtained by means of diffusion NMR spectroscopy. In the case of L2, the complexation equilibria were also studied in 80:20 (v:v) water:ethanol mixture. In the mixed solvent of lower dielectric constant than water, the stability of anion complexes decreases, relative to water. Solvation effects, mostly involving the ligand, are thought to be responsible for this peculiar behaviour.

INTRODUCTION

Anion coordination chemistry has sparked considerable interest in recent years due to the ubiquitous presence of anions in biological and environmental systems, the roles they play in various biochemical processes, and their involvement in many technological areas. Consequently, scientists from all areas of chemistry and beyond have joined forces to explore this relatively young field. However, the design of receptors for the binding of anions in solution, in particular in water, can be very challenging as the non-covalent interactions employed to anchor anions to the receptor are weak, they must prevail over the competing anion-solvent interactions, and structural features that provide them are often difficult to build into the receptor framework. Fortunately, while individual non-covalent interactions are weak, collectively they could be made sufficiently powerful to afford polyfunctional receptors capable of strong and selective anion binding.[1]

Anion-π interactions are among the most recently recognized non-covalent forces.[2-7] Their importance has long been underappreciated by the scientific community as it is counterintuitive to expect that an attraction may arise between a negatively charged species and common aromatic rings characterized by negative quadrupole moments. However, upon insertion of strongly electron-withdrawing substituents, these quadrupole moments can be inverted, turning parent aromatic systems into π-acids able to attract anions.[8] Indeed, reviews of archived crystallographic data showed that anion-π interactions in the solid phase are more frequent than

one might have expected,[3,9] evidencing that different geometries of the anion-arene interaction should be considered for a correct interpretation of the interaction itself (ref. 9c). Further structural studies were undertaken to characterize such interactions in the solid state,[8,10] while theoretical and experimental investigations were made to analyse their properties in the gas phase and in solution.[3,8,10f-j,11,12]

On account of the elusive character of anion-π interactions in solution, their functional relevance was demonstrated only very recently in a study on anion transport in bilayer membranes.[13] Further conclusive evidence of anion-π interactions at work appeared for transport[10f,12j,14] and catalytic[15] processes. Another intriguing matter concerns the thermodynamics of anion-π interactions in solution. Some attempts at the determination of stability constants[8,10j,12] and a few binding enthalpies[12d,e,16] for the association processes that involved anion-π interactions were reported, but the results obtained did not provide a clear-cut picture. All the same, they stimulated further attempts to determine energetic parameters that control such interactions in solution and to clarify their very definition. The measurement of thermodynamic parameters for a pure anion-π interaction in solution is a highly challenging task and, to date, not a single anion-receptor pair is known, which is surely kept together exclusively by this type of interaction. Commonly, the components are paired due to multiple contacts, and partitioning of the association free energy into its constituent contributions is not justified thermodynamically, except under severe restrictions and approximations.[17]

Theoretical studies have placed binding energies of the anion-π interactions in the gas phase in the range 17 to 71 kJ/mol,[18] though measured values as high as 125 kJ/mol have been reported.[12b] For the anion-π interaction in solution, a recent review of experimental results concluded that the binding free energy ($-\Delta G°$) for this attractive force in organic solvents is typically less than 4 kJ/mol per single phenyl ring-halide anion interaction, though larger values have also been reported.[8f] Such estimates of the anion-π contribution are often made by subtracting (with the aid of reference systems) from the combined effect of anion-π and H-bond interactions (sometimes multiple) the latter, under the implicit and, generally, arbitrary assumption that free energy changes are additive.[17] Furthermore, model structures and solvation effects may affect the magnitude of the measured term.[12h]

Recently, we have reported that protonated forms of the polyfunctional ligand NAP-T, assembled from the tripodal amine tren (T, tris(2-aminoethyl)amine) and a nitroso-amino-

pyrimidine (NAP), form complexes with a range of anions. Crystal structures of the complexes revealed the anions tightly anchored to the ligand both by salt bridges to T and very short anion-π interactions with NAP.[10o,12e] The neutral (unprotonated) NAP-T and variously protonated species of NAP-T formed complexes with anions in water. The fact that the neutral NAP-T, which is unable to form salt bridges, and the isolated NAP residue both form complexes of very similar stability with the studied anions (SO_4^{2-}, SeO_4^{2-}, $S_2O_3^{2-}$, $Co(CN)_6^{3-}$) corroborated the idea that the anion-π interaction is the major contribution to the anion-receptor binding energy in these complexes. Accordingly, the associated free energy changes (-Δ*G*° values were in the range 9 to 12 kJ/mol) were taken as good estimates of such anion-π interactions in water.[12e] Isothermal titration calorimetry (ITC) measurements revealed that these anion-π interactions were almost athermic (Δ*H*° values were in the range -2 to 3 kJ/mol), and were driven by large entropic contributions (*T*Δ*S*° terms were in the range 8 to 15 kJ/mol).[12e] Higher thermal effects were measured in acetonitrile for the complexes of mono-anions where multiple anion-π and hydrogen bond interactions were present.[12d,16] Majority of them were exothermic and the relevant complexation processes were accompanied by either negligible[12d] or favourable[16a] entropic contributions; in other cases,[16b] the coordination enthalpies were endothermic and the processes of complex formation were promoted by favourable entropy changes.

Taking into account that introduction of anion-π interactions into the make-up of anion receptors, anion carriers, catalysts, as well as new functional systems in general has become of great interest, we undertaken to advance understanding of these weak forces by developing a new type of anion receptors (Figure 1). These new receptors include a tetrazine ring decorated

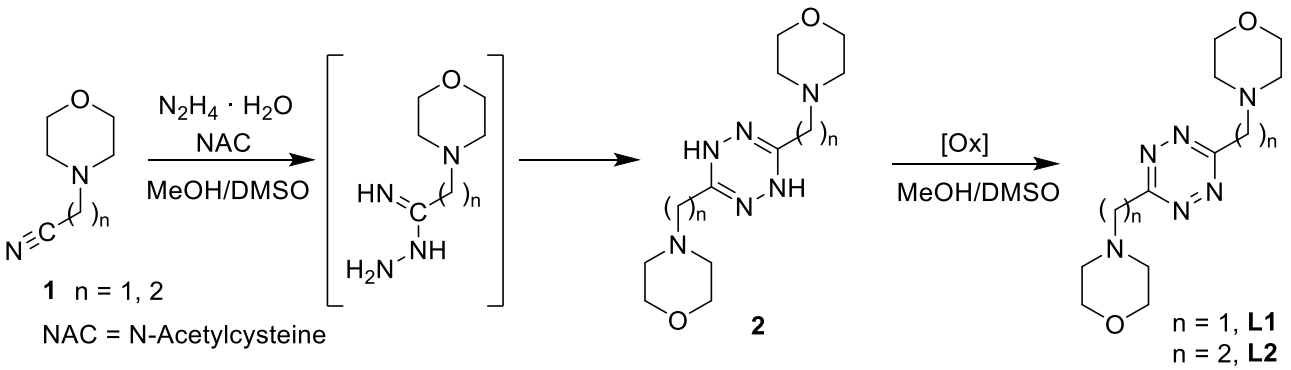


Figure 1. The tetrazine ligands L1 and L2.

with two morpholine pendants of variable length. We have characterized their ability to bind inorganic anions such as F^-, NO_3^-, PF_6^-, ClO_4^-, and SO_4^{2-} both in solution and in the solid-state. The latter included elucidation of the crystal structures of NO_3^-, PF_6^- and ClO_4^- complexes by single crystal X-ray diffraction analysis, while solution studies were concerned with the determination of the thermodynamic parameters ($\Delta G°$, $\Delta H°$ and $T\Delta S°$) for the formation such complexes in water. Furthermore, improved solubility of L2 made it possible to extend the solution studies to a mixed solvent (water:ethanol, 80:20 v:v) and to establish how the stability of these complexes is affected by solvent polarity.

Ligands L1 and L2 (Figure 1) were designed to deliver the tetrazine ring into aqueous medium without adding structural elements that might offer strong anchorage to anions in addition to the anion-π interaction. They were successfully prepared following a classical Pinner's synthesis from the corresponding morpholinyl-nitrile precursors. Tetrazines are strong π-acids and, thus, amenable to anion-π interactions, but usually they have low water solubility.[8c-e,l,10e,19a] Functionalization with two morpholine groups makes them sufficiently soluble in water to be studied by means of our thermodynamic techniques. In particular, both L1 and L2 are well soluble in acidic aqueous medium due to the protonation of morpholine nitrogen atoms. In general, the phenomenon of ligand protonation in the study of anion-π interactions is undesirable, as the protonated ligands may also form strong salt bridges with the anions. However, in this particular case our crystallographic studies revealed poor tendency of the protonated ligands to bind anions through the salt bridge interactions.

RESULTS AND DISCUSSION

Synthesis of L1 and L2. The preparation of ligands L1 and L2 (Figure1) was achieved following a two-step, classical Pinner's synthesis, consisting in a reaction of the morpholinyl-nitriles **1** with hydrazine hydrate to generate the corresponding dihydro-1,2,4,5-tetrazine intermediates **2**, which upon easy (though slowly) air oxidation yielded the fully aromatic *s*-tetrazines. Notably, the synthesis of L1 and L2 is one of the few non-metal catalysed Pinner synthesis of 3,6-dialkyl-*s*-tetrazine derivatives reported to date. Indeed, it is historically accepted that Pinner's procedures are of general applicability to the preparation of 3,6-diaryl-substituted *s*-tetrazines, but not to the synthesis of 3,6-dialkyl derivatives.[19] Only recently, a variant of the Pinner synthesis to prepare 3,6-dialkyl-*s*-tetrazines with a wide scope of application was

reported, but it was based on the use of anhydrous hydrazine and a metal Lewis acid catalyst,[20] with the drawback of needing intensive purification to remove metal traces in the case of products containing good transition metal binding moieties such as the morpholinyl groups in our molecules. On the other hand, in our preparations, the safer hydrazine hydrate is used together with N-acetylcysteine (NAC) as catalyst, with acceptable results in terms of isolated yields. Since the catalytic effect of NAC in the general preparation of amidines from primary amines and both alkyl and aryl nitriles is known,[21] we attribute the success of our preparations to the role of NAC as a catalyst in the reactions between the morpholinyl-nitriles, **1**, and hydrazine to give the corresponding amidrazone intermediates. The subsequent formation of dihydro-1,2,4,5-tetrazine derivatives by dimerization of amidrazones is a well-known process[22] that, in our case, leads to the isolable intermediates **2**.

Crystal Structure of $H_2L1(PF_6)_2{\cdot}2H_2O$. In this crystal structure, the diprotonated H_2L1^{2+} ligand lies on an inversion centre and assumes an overall symmetric chair conformation (Figure 2). The tetrazine ring forms two anion-π interactions with the centrosymmetric PF_6^- ions, one of the fluorine atom of these anions being only 2.94(9) Å apart from the ring centroid. Interestingly, the ammonium groups of the ligand are not involved in the binding of the PF_6^- anions but interact via hydrogen bonding with cocrystallized water molecules (N···OW 2.686(5) Å). As a consequence the anion is held in the crystal packing by the anion-π interaction with less relevant contributions from unconventional CH···F bonds (2.469(3) Å) and van der Waals interactions.

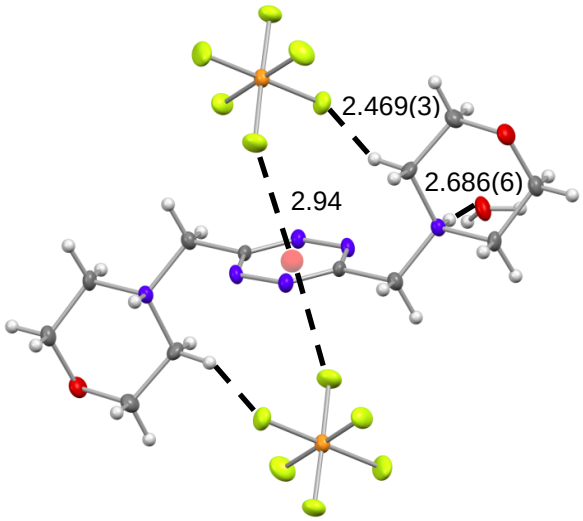


Figure 2. Crystal structure of $H_2L1(PF_6)_2{\cdot}2H_2O$. Distances in Å.

Crystal Structure of $H_2L1(ClO_4)_2·2H_2O$. In this complex, the ligand assumes a boat-like conformation, both morpholine pendants protruding from the same side of the tetrazine ring (Figure 3). The aromatic group forms anion-π interactions with the oxygen atoms of two symmetry related ClO_4^- anions. As in the previous structure, the anions are located almost above the centre of the tetrazine ring with O···centroid distances of 2.96(3) and 2.78(3) Å, respectively. Accordingly, this anion is sandwiched between tetrazine rings of two ligand molecules, while the other ClO_4^- anion, not shown in Figure 3, is H-bonded to water molecules interacting with ligand ammonium groups (NH···OW 1.88(3) Å, NH···OW 1.90(3) Å). It is noteworthy that, also in this complex, the sandwiched anion is held in place only by anion-π interactions and unconventional CH···O hydrogen bonds (Figure 3).

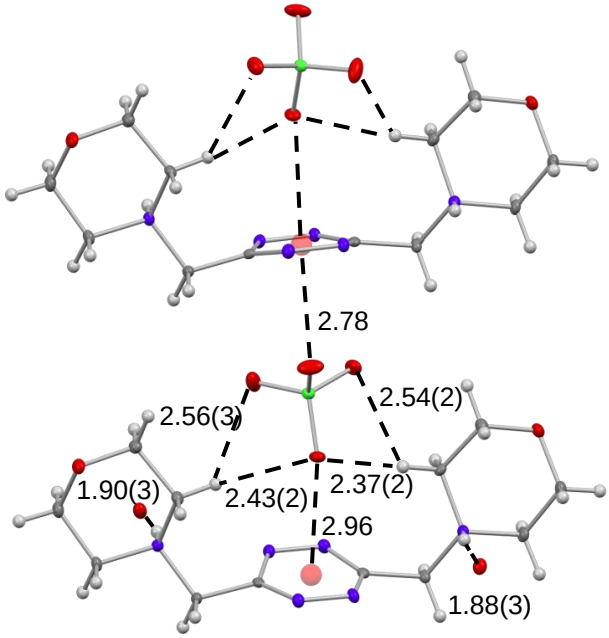


Figure 3. Crystal structure of $H_2L1(ClO_4)_2·2H_2O$. Distances in Å.

Crystal Structure of $H_2L2(PF_6)_2·H_2O$. The crystal structure of the PF_6^- complex with H_2L2^{2+} contains two centrosymmetric crystallographically independent ligand molecules (Figure 4). One of them assumes a chair conformation similar to that found in the structure of $H_2L1(PF_6)_2·2H_2O$, while the other one is almost planar. Also in $H_2L2(PF_6)_2·H_2O$ the tetrazine rings give rise to anion-π interactions with PF_6^-. Different kinds of interactions are established between the fluorine atoms of PF_6^- and the tetrazine groups. Actually, one of the fluorine atoms is located pretty well above the tetrazine ring centroid of the planar ligand (F···centroid 2.87(6) Å, Figure 4a), governed by the ion-dipole attraction, while three cofacial fluorine atoms face the other

tetrazine ring forming F···N, F···C and F···N-N contacts (3.110(5), 3.092(5) and 3.07 Å, respectively, Figure 4b). Due to the enhanced flexibility of the ethylenic chains connecting tetrazine and morpholine rings, the ligand in chair conformation is able to form a salt bridge with the anion (NH···F 2.10(5) Å), in contrast to the behaviour of L1 featuring shorter methylenic chains. It is to be underlined, however, that in this structure only one PF_6^- is in contact with

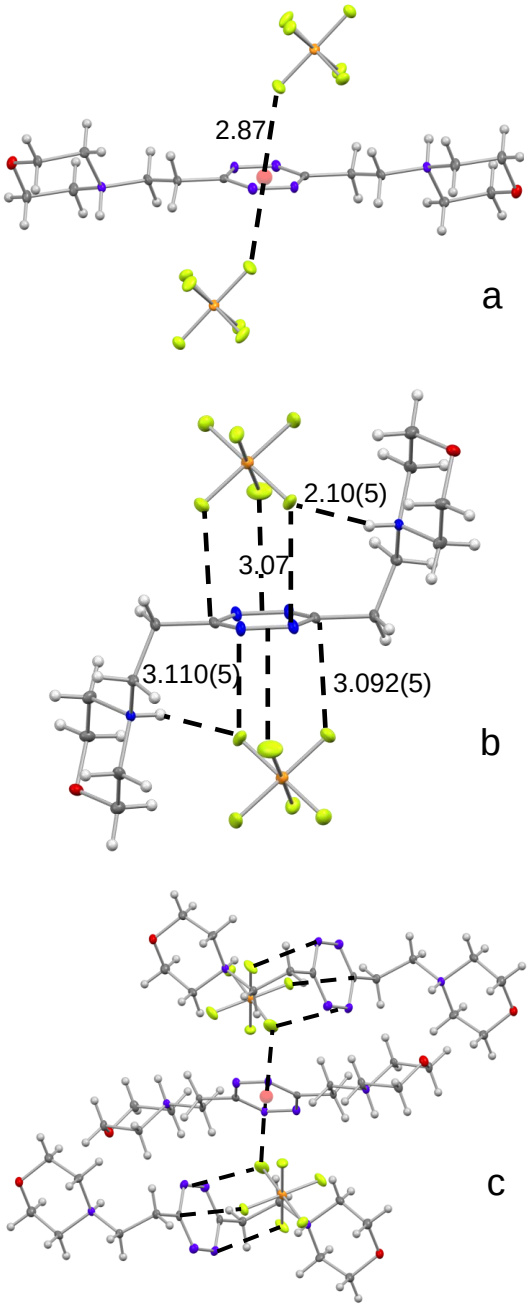


Figure 4. Crystal structure of $H_2L2(PF_6)_2 \cdot H_2O$. Distances in Å. Views of the ligand and of its anion···π contacts: (a) planar and (b) chair conformations, (c) portion of the crystal packing.

tetrazine rings, bridging the two ligands to form infinite zig-zag chains of anion-π contacts (Figure 4c). The second PF_6^- anion only interacts with a water molecule H-bonded to an ammonium group of the planar H_2L2^{2+} ligand form.

Crystal Structure of $H_2L2(ClO_4)_2 \cdot H_2O$. This crystal structure contains three crystallographically independent diprotonated ligand molecules H_2L2^{2+}. One of them assumes an almost planar arrangement (Figure 5a) while the other two, lying around a crystallographic center, adopt chair conformations (Figure 5b,c). Like in the crystal structure of $H_2L2(PF_6)_2 \cdot H_2O$, several types of anion···tetrazine interactions contribute to stabilize the crystal (O···centroid, O···C and O···N in Figure 5) and the overall crystal packing contains infinite zig-zag chains of alternating ligand and perchlorate units (Figure S29). In particular, in the adducts shown in Figures 5a,c one of the anion oxygen atom is located almost above the ring centroid. However, while in the case of the planar ligand no other relevant interactions are observed in addition to such O···centroid contact (Figure 5a), in the case of the complex in Figure 5c additional O···C interactions contribute to strengthen the anion-tetrazine binding.

As in the previous structure, each ligand molecule in chair conformation forms a salt bridge with ClO_4^- (NH···O 2.31(6), 2.46(5) Å, Figure 5b; NH···O 2.18(5) Å, Figure 5c). The crystal packing is further stabilized by additional hydrogen bonds involving the two remaining ClO_4^- and lattice water molecules.

Crystal Structure of $H_2L2(NO_3)_2$. Among the crystal structures obtained for anion complexes with L2, the NO_3^- complex is the one having more similarities with the structures seen for the shorter L1 ligand. Actually, the packing contains a single centrosymmetric ligand molecule in chair conformation, interacting with NO_3^- through the tetrazine ring (Figure 6). The planar anion is arranged almost parallel above the tetrazine group (dihedral angle 21.9(2)°), with an oxygen atom close to the ring centroid (O···ring centroid 2.850(2) Å). The same oxygen atom forms a salt bridge with a ligand ammonium group (NH···O 1.881(2) Å). Obviously, all groups and interactions are duplicated below the tetrazine ring by the inversion centre, but no chains based on repeated anion-π interactions are observed in this crystal.

Analysis of the anion-tetrazine ring interaction in the crystal structures. It was recently shown for the interaction of halides with electron-deficient arenes that, when the anion lies above the plane of the π system, both centred and off-centre interaction geometries are common.[9c] In

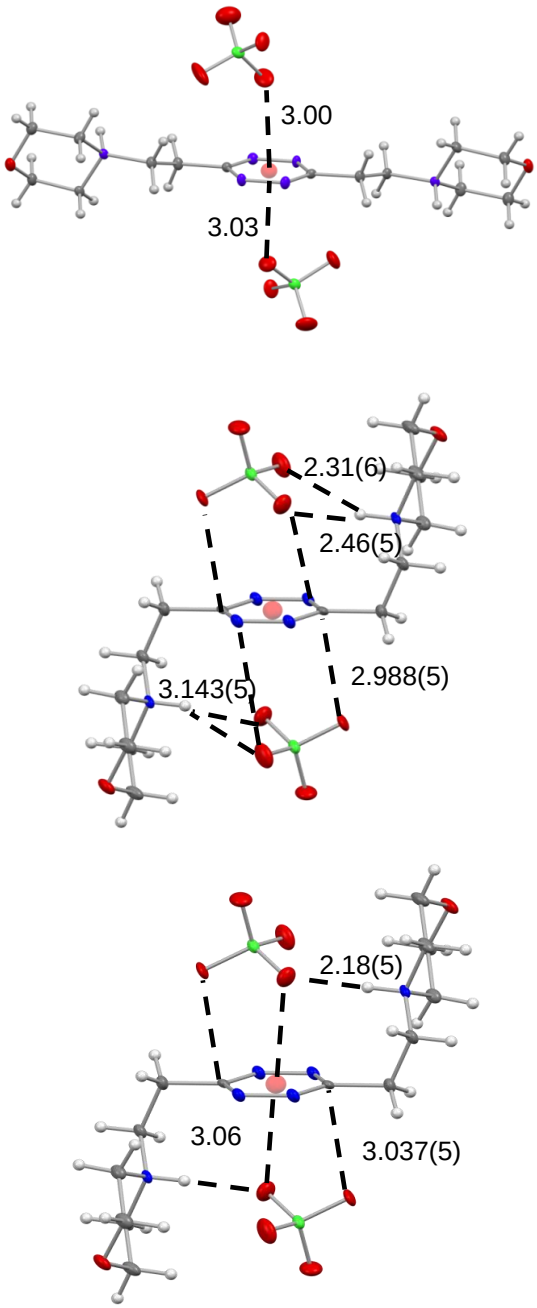


Figure 5. Crystal structure of $H_2L2(ClO_4)_2 \cdot H_2O$. Distances in Å. Views of the ligand and of its anion···π contacts: (a) planar and (b, c) chair conformations.

the latter case, the anion is positioned over the periphery of the ring and charge transfer (CT) complexes can be formed thanks to a certain covalent character of the interaction with ring atoms. Conversely, in the former case, the anion lies above the centroid of the ring where the CT contribution to the anion-π interaction is expected to be negligible. The geometric parameters d_{offset}, $d_{centroid}$ and d_{plane} (Figure 7a) were used to describe the location of the anion above the

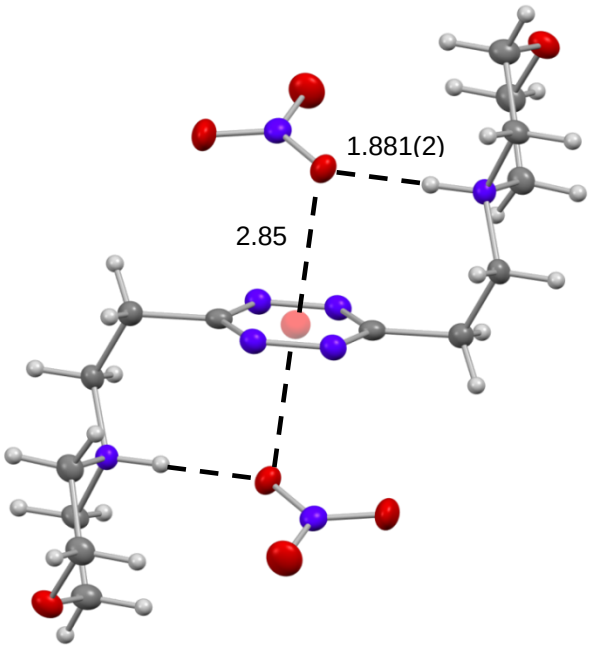


Figure 6. Crystal structure of $H_2L2(NO_3)_2$. Distances in Å.

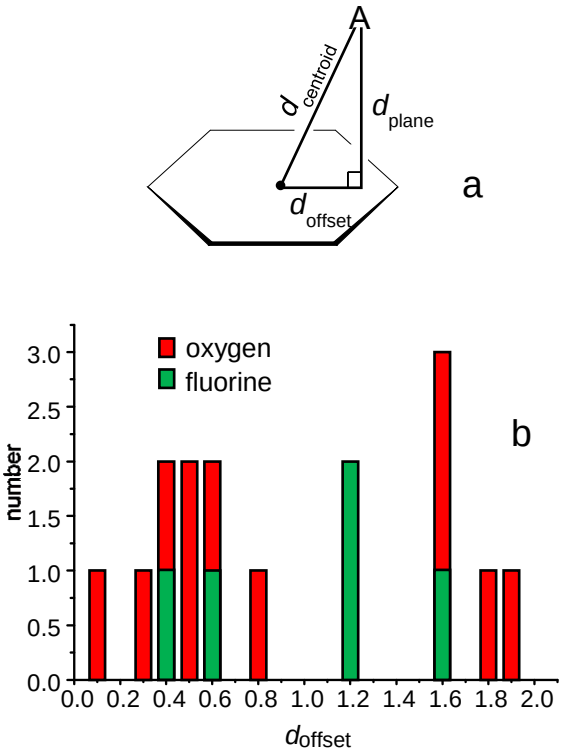


Figure 7. a) Displacement of an atom A from the center (centroid) of the tetrazine ring. b) Histogram of d_{offset} values (rounded to one decimal place) for the crystal structures here reported. Red and green bars refer, respectively, to oxygen and fluorine interactions with tetrazine rings.

ring.[9c] The d_{plane} parameter is the distance from the mean ring plane and defines d_{offset} which has a value of 0 Å for a perfectly centred anion-π complex and a value of 1.4 Å when the anion is exactly located above a ring atom.

A similar analysis of the crystal structures herewith reported, performed by considering oxygen and fluorine atoms within 4 Å from the tetrazine centroid, shows a preference of the studied polyatomic anions for centred interactions (in 50% of cases $d_{offset} \leq 0.6$ Å), although a significant number of off-centre interactions nearby the ring atoms (31% of cases are in the range 1.2 Å $\leq d_{offset} \leq$ 1.6 Å) are also present (Figure 7b).

PF_6^- and ClO_4^- complexes form only centred interactions with L1, while for L2 complexes a greater dispersion of d_{offset} values is observed (Table S2): oxygen atoms tend to form centred interactions while 3 out of the five ring-fluorine contacts are off-centre (Figure 7b).

Anion Binding in Solution. Protonated forms of L1 and L2 and, in some cases, even the neutral ligands give rise to detectable interactions with anions in water. Analysis, by means of the computer program HYPERQUAD,[23] of potentiometric (pH-metric) titrations performed for the various ligand/anion systems afforded the stability constants of the anion complexes reported in Table 1. As reported in the experimental procedures (supporting information), it was not possible to study the interaction of L1 with F^-, due to the low basicity of this ligand forming protonated species at enough low pH values to make F^- reactive toward the glass components of the measurement cell. Since these measurements were performed in the presence of 0.10 M Me_4NCl, we must assume that all the equilibria in this table are potentially affected by the competitive ligand interaction with Cl^-.

Although the crystal structures of the anion complexes previously described show the diprotonated ligand forms (H_2L^{2+}) interacting with pairs of anions, the 1:1 stoichiometry of the complexes in solution was unambiguously ascertained by the computer analysis of the titration curves. The stability of these complexes invariably increases with ligand protonation (increasing positive charge), even though the relevant association processes are poorly controlled by electrostatic forces. As a matter of fact, the mean increment of the complexation free energy change associated with the variation of a single positive charge of the ligand, 1.8 kJ/mol (0.4 kcal/mol), is considerably smaller than the value 5±1 kJ/mol expected for the formation of a single salt bridge in water.[24] Accordingly, other forces than salt bridges, are expected to furnish

Table 1. Equilibrium constants (log*K*) for ligand protonation and anion complex formation determined at 298.1±0.1 K in 0.1 M Me_4NCl aqueous solution or water/ethanol 80:20 (v:v) mixture.

	H_2O		H_2O/EtOH 80/20 (v/v)
	L1	L2	L2
$L + H^+ = HL^+$	4.45(3)	6.19(1)	6.04(2)
$HL^+ + H^+ = H_2L^{2+}$	3.45 (3)	5.37(1)	5.19(2)
$HL^+ + F^- = [HLF]$	n.d.	1.58(8)	1.16(7)
$H_2L^{2+} + F^- = [H_2LF]^+$	n.d.	1.97(3)	1.26(5)
$HL^+ + NO_3^- = [HL(NO_3)]$	1.43(5)	1.8(1)	1.72(7)
$H_2L^{2+} + NO_3^- = [H_2L(NO_3)]^+$	1.66(6)	2.32(4)	2.18(3)
$L + SO_4^{2-} = [L(SO_4)]^{2-}$		2.18(3)	
$HL^+ + SO_4^{-2-} = [HL(SO_4)]^-$	1.65(8)	2.31(3)	1.68(7)
$H_2L^{2+} + SO_4^{-2-} = [H_2L(SO_4)]$	2.08(3)	2.48(3)	2.29(3)
$L + ClO_4^- = [L(ClO_4)]^-$		1.98(5)	
$HL^+ + ClO_4^- = [HL(ClO_4)]$	2.07(9)	2.26(5)	1.55(8)
$H_2L^{2+} + ClO_4^- = [H_2L(ClO_4)]^+$	2.31(8)	2.51(4)	1.83(5)
$L + PF_6^- = [L(PF_6)]^-$	1.96(8)	3.07(8)	
$HL^+ + PF_6^- = [HL(PF_6)]$	2.67(7)	3.17(7)	1.67(9)
$H_2L^{2+} + PF_6^- = [H_2L(PF_6^-)]^+$	2.98(7)	3.39(8)	2.22(8)

the decisive contribution making favorable such association events. This is in agreement with the previously described crystal structures of anion complexes showing that, in the solid phase, the ligands can bind anions without resorting to salt bridges. The same crystal structures show that, both in the absence and in the presence (few cases) of salt bridges, the anions are firmly

anchored to the ligands through the formation of strong anion-π interactions. Actually, the most remarkable binding characteristics observed in the five crystal structures is that the anions invariably choose the tetrazine ring as preferential binding site, despite the presence of two ammonium groups. Indeed, DFT calculations showed that the lowest-unoccupied molecular orbital (LUMO) of the free ligands is localized on the tetrazine ring, which has the ability to accept the electronic charge of the interacting anion, while the highest-occupied molecular orbital (HOMO) is localized on the atoms of both morpholine rings, excluding the positively-charged NH groups (Figure S30).

We can reasonably expect that similar binding features are maintained in solution where the modest increment of complex stability with increasing ligand protonation is a clear evidence of the weak increment of electrostatic attraction exerted on the anion by ligand ammonium groups. Furthermore, anion contacts with aliphatic CH groups are not expected to furnish much stabilization since aliphatic CH groups are known to be very poor hydrogen bond donors[25] and the studied anions, except F^-, are not good hydrogen bond acceptors, since they are the conjugated bases of strong acids. Above all, these anions are not willing to replace hydrogen bonds to water molecules with hydrogen bonds to aliphatic CH groups. Accordingly, the main contribution to the stability of these complexes in solution should be provided by anion-π interactions that would become the most effective (almost unique) binding forces in the anion complexes of uncharged (not protonated) ligands. The free energy changes ($-\Delta G°$) for the formation of the latter are in the range 11.3-12.4 kJ/mol) for the complexes of L1 with PF_6^- and of L2 with ClO_4^- and SO_4^{2-}, while a somewhat greater value, $-\Delta G°$ = 17.5 kcal/mol, was determined for the PF_6^- complex with L2 (Table 1). These values well compare with the free energy changes ($-\Delta G°$ = 8.6-12 kJ/mol) previously determined for anion complexes, formed in water by SO_4^{2-}, SeO_4^{2-}, $S_2O_3^{2-}$ and $Co(CN)_6^{3-}$ with pyrimidine ligands, in which the anion-π interaction is thought to be the almost unique binding force.[12e] Of course, such free energy changes refer to association processes including solvent effects. DFT calculations performed on the complexes of these anions with protonated and neutral ligands in a continuum water environment showed that all complexes are stabilized by an interplay of different weak forces, among which, anion-π interactions are invariably present. In agreement with the above solution data, binding energies calculated for the formation of such anion complexes point out that even complexes with neutral ligands are significantly stable. Even the plain tetrazine ring, deprived of

morpholine residues, forms stable complexes with the anions, the anion-π interaction being the unique bonding interaction; for instance, the calculated binding energies for the interaction of ClO_4^- with 1,2,4,5-tetrazine and 3,6-dimethyl-1,2,4,5-tetrazine are 9.1 and 10.1 kJ/mol, respectively (Figure S31). However, the calculated binding energies increase faster with ligand charge (ligand protonation state) than the free energy changes determined in the real solutions, probably due to a theoretical underestimation of solvation effects. A comprehensive theoretical analysis of these binding processes will be the subject of a separate paper.

It is interesting to note that L2 forms complexes of greater stability than L1. Unfortunately the comparison between complexes of neutral ligands is only possible for PF_6^-, since neutral ligand complexes of L1 were not detected with the other anions. Most likely they are formed in very small amounts, not detectable with the potentiometric method.

Greater insight into the thermodynamic aspects governing the formation of these complexes was gained by dissecting the complexation free energy changes into their enthalpic and entropic contributions by means of isothermal titration calorimetry. The determined enthalpy changes are reported in Table 2 along with the derived entropy terms. Regrettably, only few calorimetric data were obtained for the anion complexes with L1 owing to insufficient solubility of ligand and complexes. Data in Table 2, however, clearly show that these anion binding equilibria are invariably promoted by large and favourable entropic contributions, while the relevant enthalpy changes are mostly unfavourable (endothermic). However, in the cases of anion binding by the neutral (not protonated) L2 ligand, in which anion-π interactions should make the major contribution, the complexation reactions are not hampered by thermal effects, since the measured enthalpy changes are favourable, although very small ($\Delta H°$ in the range -0.5 to -2.3 kJ/mol). A similar enthalpy and entropy dependence of binding equilibria is typical of association processes controlled by desolvation phenomena. Indeed, charge neutralization occurring upon interaction of charged specie causes an important release of solvent molecules, that is an endothermic process accompanied by a large entropy increase. When the anion binds an uncharged ligand, a smaller desolvation is expected to occur with respect to the association with a charged one and, accordingly, the reaction is expected to be less endothermic and less exoentropic, as actually found for our systems (Table 2).

Table 2. Thermodynamic parameters (kJ/mol) for ligand protonation and anion complex formation determined at 298.1±0.1 K in 0.1 M Me_4NCl aqueous solution.

	$\Delta G°$	$\Delta H°$	$T\Delta S°$
$L1 + H^+ = H\,L1^+$	-25.4(2)	-4.6(4)	20.8(4)
$H\,L1^+ + H^+ = H_2L1^{2+}$	-19.7(2)	4.6(4)	24.3(4)
$L2 + H^+ = H\,L2^+$	-35.32(6)	-26.8(4)	8.5(4)
$H\,L2^+ + H^+ = H_2L2^{2+}$	-30.64(6)	-18.4(4)	12.2(4)
$H_2L1^{2+} + ClO_4^- = [H_2L1(ClO_4)]^+$	-13.2(5)	-0.8(4)	12.4(6)
$L1 + PF_6^- = [L1(PF_6)]^-$	-11.1(5)	n. d.	n. d.
$HL1^+ + PF_6^- = [HL1(PF_6)]$	-15.2(4)	-5.9(4)	9.3(6)
$H_2L1^{2+} + PF_6^- = [H_2L1(PF_6^-)]^+$	-17.0(4)	0.8(4)	17.8(6)
$HL2^+ + NO_3^- = [HL2(NO_3)]$	-10.3(6)	9.1(3)	19.4(7)
$H_2L2^{2+} + NO_3^- = [H_2L2(NO_3)]^+$	-13.2(2)	6.4(3)	19.6(4)
$L2 + SO_4^{2-} = [L2(SO_4)]^{2-}$	-12.4(2)	-0.6(3)	11.8(4)
$HL2^+ + SO_4^{-2-} = [HL2(SO_4)]^-$	-13.2(2)	27.2(4)	40.4(4)
$H_2L2^{2+} + SO_4^{-2-} = [H_2L2(SO_4)]$	-14.12(2)	17.0(4)	31.1(4)
$L2 + ClO_4^- = [L2(ClO_4)]^-$	-11.3(3)	-2.3(2)	9.0(4)
$HL2^+ + ClO_4^- = [HL2(ClO_4)]$	-12.9(3)	9.6(4)	22.5(5)
$H_2L2^{2+} + ClO_4^- = [H_2L2(ClO_4)]^+$	-14.3(2)	6.7(4)	21.0(4)
$L2 + PF_6^- = [L2(PF_6)]^-$	-17.5(5)	-0.5(3)	17.0(6)
$HL2^+ + PF_6^- = [HL2(PF_6)]$	-18.1(4)	12.5(3)	30.6(5)
$H_2L2^{2+} + PF_6^- = [H_2L2(PF_6^-)]^+$	-19.3(5)	5.5(3)	24.8(6)

To get more information on solvent effects, the formation of anion complexes with the more soluble L2 ligand was also studied in the water/ethanol 80:20 v:v mixture, displaying a lower dielectric constant (ε = 69.05 at 25°C) with respect to pure water (ε = 78.56 at 25°C).[26] The stability constants of the complexes formed in the solvent mixture are listed in Table 1. These

data show that the addition of ethanol to water causes a general lowering of stability for complex with protonated ligand forms, while complexes of the unprotonated, uncharged ligand were not detected. At first glance, this results might be surprising, since one could reasonably expect that the association between charged species becomes stronger as the polarity of the solvent decreases. Nevertheless, when the association takes place between charged and neutral species, the stability of the assembly may increase with increasing solvent polarity. As a matter of fact, protonation constants of L2 are smaller in water/ethanol 80:20 v:v than in pure water, as it generally happens[27] for many other amines. Instructive examples, in this sense, are given by the protonation properties of molecules containing both neutral and negatively charged protonation sites, such as amino acids.[27,28] In these cases, as the solvent polarity decreases (upon addition of ethanol to water), protonation constants of carboxylate groups increase while protonation constants of amine groups decrease, as a consequence of the selective solvation occurring in the solvent mixture, water and ethanol molecules being preferentially attracted, respectively, by charged groups and by neutral functionalities. Accordingly, the lower stability of our anion complexes in the solvent mixture corroborates our previous conclusion that in pure water the anion complexation processes here studied are essentially controlled by other forces than charge-charge attractions.

Also anions can be subjected to selective solvation.[29] F^-, for instance, in water/ethanol 80:20 v:v. is selectively hydrated, with no ethanol molecules in its first solvation sphere. Upon increase of the anion size, also the involvement of ethanol molecules in anion solvation increases, and for ClO_4^- the composition of the first solvation sphere approaches the composition of the bulk solvents.[29b] Taking into account, however, that in the water/ethanol 80:20 v:v mixture there is one ethanol molecule every thirteen water molecules, even for ClO_4^- the participation of ethanol molecules in the solvation sphere is still modest. Then, anion desolvation occurring upon interaction with L2 is not expected to be at the origin of the difference of complex stability between water and the water/ethanol mixture and, accordingly, different ligand solvation should be responsible for the observed difference in the binding constants. Consistently with this general drop of stability, complexes of anions with the neutral L2 ligand are not formed or their formation is too scarce to be detected.

Unfortunately, our attempts to identify significant changes in the NMR spectra (^1H, ^{13}C, ^{15}N and also ^{19}F and ^{31}P for PF_6^-) of the species involved in the anion-π complexation equilibria were

unfruitful both in D_2O and acetonitrile-d_3. However, interesting information about the formation of such anion complexes in water was obtained by PGSE ^{19}F and ^{1}H NMR diffusion spectroscopy,[30] following the variation of the diffusion coefficients of PF_6^- and H_2L2^{2+} occurring upon complexation. Since the exchange between complexed and uncomplexed species in the anion-π complexation equilibrium is a fast process on the time scale of the (relatively slow) NMR measurements, the diffusion coefficient measured by PGSE NMR for a particular species is the weighted average of the diffusion coefficients of its uncomplexed and complexed forms. That is, for the equilibrium $H_2L2^{2+} + PF_6^- = [H_2L2(PF_6^-)]^+$ the observed diffusion coefficient for PF_6^-, $\bar{D}_{PF6}$, can be expressed as $\bar{D}_{PF6} = (1-\alpha)\cdot D_{PF6} + \alpha\cdot D_{L2PF6}$, where D_{PF6} and D_{L2PF6} represent the diffusion coefficients of the uncomplexed and complexed forms of PF_6^-, respectively, and α is the mole fraction of complexed PF_6^-. As shown in Figure 8a, addition of increasing amounts of H_2L2^{2+} to a solution of PF_6^- causes a significant decrease of the observed diffusion coefficient of the anion. According to the Stokes-Einstein equation $\bar{D} = k_B T/6\pi\eta r$, such variation of $\bar{D}$ can be ascribed to the increase of the hydrodynamic radius (r) of the measured species as PF_6^- is increasingly associated to H_2L2^{2+}. Furthermore, this figure also reveals a good agreement between the evolution of the observed diffusion coefficient $\bar{D}_{PF6}$ upon increasing concentrations of H_2L2^{2+} (black dots) and the evolution expected according to the value of the stability constant ($\log K = 3.39$, Table 1) measured by potentiometry for the $[H_2L2(PF_6^-)]^+$ complex, represented by the red line. This line was calculated by assuming D_{PF6} equal to the value of $\bar{D}_{PF6}$ measured for the sample containing pure PF_6^- (i.e. $\alpha = 0$), and D_{L2PF6} equal to the value of $\bar{D}_{PF6}$ obtained for a $[H_2L2^{2+}]/[PF_6^-]$ ratio greater than 1:1, at which $\bar{D}_{PF6}$ appears to become invariant (Figure 8a).

The evolution of the average diffusion coefficient of H_2L2^{2+}, $\bar{D}_{L2}$ (Figure 8b), gives rise to a less accurate fitting of the expected trend (red line calculated according to the procedure above described for $\bar{D}_{PF6}$), but it shows a noteworthy feature. When PF_6^- is gradually added to H_2L2^{2+}, the average diffusion coefficient of H_2L2^{2+} increases (Figure 8b), denoting that the complex has a smaller size than the free ligand, a phenomenon that can be only rationalized by considering that an extensive desolvation occurs upon interaction of the two oppositely charged species, the volume of lost water molecules being greater than the gained volume of the bound anion. This is a further evidence of the fact that solvation effects are of prime importance in such association processes. Furthermore, taking into account that both theoretical[31] and experimental[32] works coincide in that the interaction of PF_6^- with water molecules is extremely weak, the desolvation

phenomenon occurring upon the formation of the $[H_2L(PF_6^-)]^+$ complex should be mostly due to ligand desolvation. Interestingly these hydrodynamic results are in agreement with the important entropy increase, ascribed to desolvation effects, derived for anion binding from the above thermodynamic data.

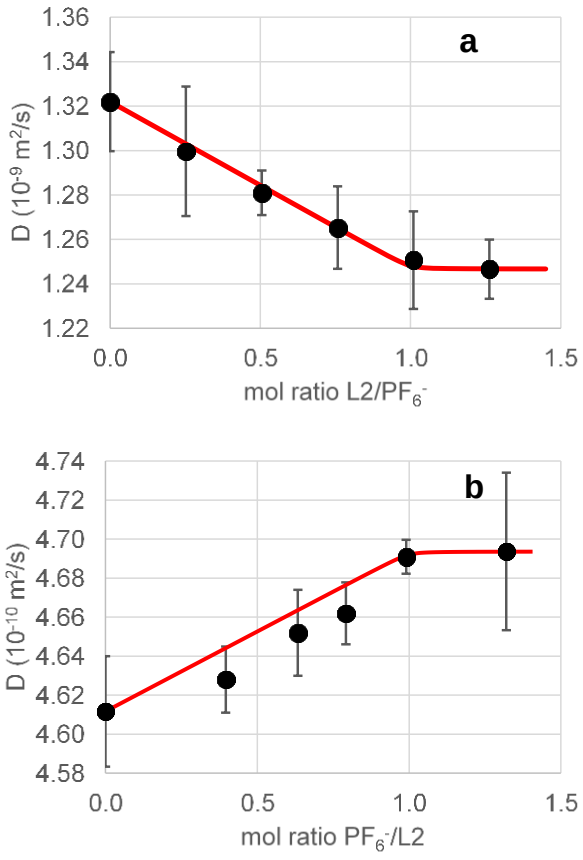


Figure 9. Average diffusion coefficients of a) PF_6^- in the presence of increasing concentration of H_2L2^{2+}, measured by means of ^{19}F NMR; b) H_2L2^{2+} in the presence of increasing concentration of PF_6^-, measured by means of ^1H NMR. Red lines represent the trends expected on the basis of the stability constant ($\log K$ = 3.39, Table 1) measured for the $[H_2L2(PF_6^-)]^+$ complex.

CONCLUSIONS

Crystallographic data obtained for five crystal structures of anion complexes formed by the diprotonated forms of L1 and L2 show that the anions invariably choose the tetrazine ring as preferential binding site, forming short anion-π contacts, despite the presence of two ammonium

groups. Nevertheless, weak anion contacts with aliphatic CH groups and, in few cases, salt bridge interactions with the ammonium groups also contribute to complex stability in the solid state. According to DFT calculations, the lowest-unoccupied molecular orbital (LUMO) of the free ligands is localized on the tetrazine ring, which is able to bind anions via anion-π interactions even in the absence of supplementary binding groups.

Equilibrium data reveal that anion binding takes place in aqueous solution with the ligands in different protonation states. In some cases, even the neutral (unprotonated) ligands form stable anion complexes. The main characteristic of these binding events is that the stability of the formed complexes is poorly related to the ligand charge, indicating that formation of these complexes is not governed by the dominating charge-charge attraction that is normally observed in the formation of anion complexes with positively charged ligands. The enthalpic ($\Delta H°$) and entropic ($T\Delta S°$) parameters for the binding equilibria, experimentally determined by dissecting the complexation free energy changes ($\Delta G°$) by means of ITC measurements, clearly show that these anion binding processes are invariably promoted by large and favourable entropic contributions, while the relevant enthalpy changes are mostly unfavourable (endothermic). A similar enthalpy and entropy dependence of binding equilibria is typical of association processes controlled by desolvation phenomena (desolvation is typically endothermic and exoentropic). The occurrence of a significant desolvation occurring upon the formation of these complexes is corroborated by diffusion NMR spectroscopy data that led to the unprecedented observation that the ligand undergoes a significant shrink in size (increase of diffusion coefficient) upon interaction with PF_6^-.

A somewhat different behaviour is observed for anion binding by the neutral ligand, in which anion-π interactions should make the major contribution. In this case, the complexation reactions ($-\Delta G°$ in the range 11.1 to 17.5 kJ/mol) are still favoured by dominant entropic contributions ($T\Delta S°$ in the range 9.0 to 17.0 kJ/mol) but are accompanied by favourable, although very small, enthalpy changes ($\Delta H°$ in the range -0.5 to -2.3 kJ/mol). Interestingly, these thermodynamic parameters are strongly consistent with previous values ($-\Delta G°$, 9 to 12 kJ/mol; $\Delta H°$, -2 to 3 kJ/mol; $T\Delta S°$, 8 to 15 kJ/mol)[12e] experimentally determined in water for the formation of various anion complexes with the two receptors based on nitroso-amino-pyrimidine NAP and NAP-T, cited above, which are thought to be almost exclusively stabilized by anion-π interactions.

Equilibrium data for the formation of anion complexes in a 80:20 (v:v) water:ethanol mixture, showed that a decrease of the dielectric constant of the medium (ε = 78.56 for pure water and ε = 69.05 for the mixture at 25°C)[25] causes a general lowering of stability for complex with protonated ligand forms, while complexes of the unprotonated ligand are no longer detectable. Taking into account that the presence of 20% of ethanol affect very little the solvation sphere of the anions,[28] the loss of stability observed in the aqueous-ethanolic solution, relative to pure water, can be reasonably ascribed to a stronger ligand solvation in the mixed solvent. Once again, solvation effects seem to play a fundamental role.

EXPERIMENTAL SECTION

Experimental details regarding synthesis and characterization of ligands, potentiometric, ITC and diffusion NMR measurements, X-ray structure analysis and DFT calculations are included in supporting information.

ASSOCIATED CONTENT

Supporting Information

Details of synthesis and characterization of ligands, potentiometric, ITC and diffusion NMR measurements, X-ray structure analysis and DFT calculations, crystallographic data (Tables S1) and geometric parameters (Table S2), ^{1}H and ^{13}C NMR spectra of ligands and synthetic intermediates (Figures S1−S12), ^{1}H-NMR, ^{1}H-DOSY, ^{19}F-NMR and ^{19}F-DOSY spectra of L2 and PF_6^- at pH 1.5 (Figures S13-S16), measured mean diffusion coefficients (Tables S3, S4), non-linear fittings of the signal decay in PGSE experiments (Figure S17-S28), a portion of the packing of the crystal structure of $H_2L2(ClO_4)_2 \cdot H_2O$ (Figure S29), calculated HOMO and LUMO orbitals of H_2L1^{2+} and H_2L2^{2+} (Figure S30), optimized geometries of the complexes between ClO_4^- and 2,3,5,6-tetrazine and 2,3,5,6-1,4dimethyl-tetrazine (Figure S31) (PDF)

Crystallographic data files (CIF)

This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) *Anion Coordination Chemistry*; Bowman-James, K.; Bianchi, A.; Garcia-España, E., Eds.; Wiley-VCH: New York, 2012. (b) Sessler, J. L.; Gale, P. A.; Cho, W. S. *Anion Receptor Chemistry (Monographs in Supramolecular Chemistry)*; RSC Publishing: Cambridge, 2006.

(2) Quiñonero, D.; Frontera, A.; Deyà, P. M. *Anion-π Interactions in Molecular Recognition*, in *Anion Coordination Chemistry*; Bowman-James, K., Bianchi, A., García-España, E., Eds.; Wiley-VCH: New York, 2012.

(3) Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3389–3392.

(4) Schneider, H.–J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3924–3977.

(5) Mascal, M.; Armstrong, A.; Bartberger, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 6274–6276.

(6) (a) Alkorta, I.; Blanco, F.; Deyà, P.; Elguero, J.; Estarellas, C.; Frontera, A.; Quiñonero, D. *Theor. Chem. Acc.* **2010**, *126*, 1–14. (b) Alkorta, I.; Rozas, I.; Elguero, J. *J. Am. Chem. Soc.* **2002**, *124*, 8593–8598.

(7) Hiraoka, K.; Mizuse, S.; Yamabe, S. *J. Phys. Chem.* **1987**, *91*, 5294–5297.

(8) (a) Giese, M.; Albrecht, M.; Rissanen, K. *Chem. Comm.* **2016**, ***52***, 1778–1795. (b) Giese, M.; Albrecht, M.; Rissanen, K. *Chem. Rev.* **2015**, *115*, 8867–8895. (c) Wheeler, S. E.; Bloom, J. W. G. *J. Phys. Chem. A* **2014**, *118*, 6133–6147. (d) Gamez, P. *Inorg. Chem. Front.* **2014**, *1*, 35–43. (e) Chifotides, H. T.; Dunbar, K. R. *Acc. Chem. Res.* **2013**, *46*, 894–906. (f) Ballester, P. *Acc. Chem. Res.* **2013**, *46*, 874–884. (g) Watt, M. M.; Collins, M. S.; Johnson, D. W. *Acc. Chem. Res.* **2013**, *46*, 955–966. (h) Schneider, H.–J. *Acc. Chem. Res.* **2013**, *46*, 1010–1019. (i) Wheeler, E. S. *Acc. Chem. Res.* **2013**, *46*, 1029–1038. (j) Frontera, A.; Gamez, P.; Mascal, M.; Mooibroek, T. J.; Reedijk, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9564–9583. (k) Salonen, L. M.; Ellermann, M.; Diederich, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4808–4842. (l) Berryman, O. B. Johnson, D. W. *Chem. Commun.* **2009**, 3143–3153. (m) Caltagirone, C.; Gale, P. A. *Chem. Soc. Rev.* **2009**, *38*, 520–563. (n) Schottel, B. L.; Chifotides, H. T.; Dunbar, K. R. *Chem. Soc. Rev.* **2008**, *37*, 68–83. (o) Hay, B. P.; Bryantsev, V. S. *Chem. Commun.* **2008**, 2417–2428.

(9) (a) Robertazzi, A.; Krull, F.; Knapp, E.-W.; Gamez, P. *CrystEngComm.* **2011**, *13*, 3293–3300. (b) Mooibroek, T. J.; Black, C. A.; Gamez, P.; Reedijk, J. *Cryst. Growth Des.* **2008**, *8*, 1082–1093. (c) Berryman, O. B.; Bryantsev, V. S.; Stay, D. P.; Johnson, D. W.; Hay, B. P. *J. Am. Chem. Soc.* **2007**, *1329*, 48–58. (d) Gamez, P.; Mooibroek, T. J.; Teat, S. J.; Reedijk, J. *Acc. Chem. Res.* **2007**, *40*, 435−444. (e) Ahuja, R.; Samuelson, A. G.; CrystEngComm 2003, 5 395

(10) For recent structural studies see: (a) Canellas, S.; Bauza, A.; Lancho, A.; Garcia-Raso, A.; Fiol, J. J.; Molins, E.; Ballester, P.; Frontera, A. *CrystEngComm* **2015**, *17*, 5987–5997. (b) Giese, M.; Albrecht, M.; Valkonen, A.; Rissanen, K. *Chem. Sci.* **2015**, *6*, 354–359. (c) Orvay, F.; Bauza, A.; Barcelo-Oliver, M.; Garcia-Raso, A.; Fiol, J. J.; Costa, A.; Molins, E.; Mata, I.; Frontera, A. *CrystEngComm* **2014**, *16*, 9043–9053. (c) Giese, M.; Albrecht, M.; Repenko, T.; Sackmann, J.; Valkonen, A.; Rissanen, K. *Eur. J. Org. Chem.* **2014**, *12*, 2435–2442. (d) Savastano, M; Arranz-Mascarós, P.; Bazzicalupi, C.; Bianchi, A.; Giorgi, C.; Godino-Salido, M. L.; Gutiérrez-Valero, M. D.; López-Garzón, R. *RSC Advances* **2014**, *4*, 58505–58513. (e) Chifotides H. T.; Giles, I. D.; Dunbar, K. R. *J. Am. Chem. Soc.* **2013**, *135*, 3039–3055. (f) Adriaenssens, L.; Estarellas, C.; Vargas Jentzsch, A.; Martinez Belmonte, M.; Matile, S.; Ballester, P. *J. Am. Chem. Soc.* **2013**, *135*, 8324–8330. (g) Wang D.-X.; Wang M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 892–897. (h) Giese, M.; Albrecht, M.; Krappitz, T.; Peter, M.; Gossen, V.; Raabe, G.; Valkonen, A.; Rissanen, K. *Chem. Commun.* **2012**, *48*, 9983–9985. (i) Canellas, P.; Bauza, A.; García-Raso, A.; Fiol, J. J.; Deyà, P. M.; Molins, E.; Mata, I.; Frontera, A. *Dalton*

Trans. **2012**, *41*, 11161–11169. (j) Li, S.; Fa, S.-X.; Wang, Q.-Q.; Wang, D.-X.; Wang, M.-X. *J. Org. Chem.* **2012**, *77*, 1860–1867. (k) Yong, G.-P.; Zhang, Y.-M.; She, W.-L. *CrystEngComm.* **2012**, *14*, 3923–3929. (l) Mooibroek, T. J.; Gomez, P. *CrystEngComm.* **2012**, *13*, 1027–1030. (m) Qin, L.; Yao, L.-Y.; Yu, S.-Y. *Inorg. Chem.* **2012**, *51*, 2443–2453. (n) Giles, I. D.; Chifotides, H. T.; Shatruk, M.; Dunbar, K. R. *Chem Commun.* **2011**, *47*, 12604–12606. (o) Arranz, P.; Bianchi, A.; Cuesta, R.; Giorgi, C.; Godino, M. L.; Gutiérrez, M. D.; López, R.; Santiago, A. *Inorg. Chem.* **2010**, *49*, 9321–9332; Inorg. Chem. 2012, 51, 4883−4883.

(11) For recent computational studies see: (a) Wang, K.; Lv, J.; Miao, J. *Theor. Chem. Acc.* **2015**, *134*, 1–6. (b) Mezei, P. D.; Csonka, G. I.; Ruzsinszky, A.; Sun, J. *J. Chem. Theory Comput.* **2015**, *11*, 360–371. (c) Wheeler, S. E.; Bloom, J. W. G. *J. Phys. Chem. A* **2014**, *118*, 6133–6147. (d) Bauza, A.; Quinonero, D.; Deya, P. M.; Frontera, A. Chem. Eur. J. **2014**, *20*, 6985–6990. (e) Wheeler, S. E.; Bloom, J. W. G. *Chem. Commun.* **2014**, *50*, 11118–11121. (f) Bretschneider, A.; Andrada, D. M.; Dechert, S.; Meyer, S.; Mata, R. A.; Meyer, F. *Chem. Eur. J.* **2013**, *19*, 16988–17000. (g) Bauzá, A.; Quiñonero, D.; Deyà, P. M.; Frontera, A. *Comp. Theor. Chem.* **2012**, *998*, 20–25. (h) Quiñonero, D.; Frontera, A.; Deyà, P. M. *Comp. Theor. Chem.* **2012**, *998*, 51–56. (i) Evans, J. D.; Courtney, C. A.; Hack, S.; Gentleman, A. S.; Hoffmann, P.; Buntine, M. A.; Sumby, C. J. *J. Phys. Chem A* **2012**, *116*, 8001–8007. (j) Estarellas, C.; Frontera, A.; Quiñonero, D.; Deyà, P. M. *ChemPhysChem* **2011**, *12*, 2742–2750. (k) Lao, K.–U.; Yu, C.–H. *J. Comput. Chem.* **2011**, *32*, 2716–2726. (l) Ali, Md. E.; Oppeneer, P. M. *J. Phys. Chem. Lett.* **2011**, *2*, 939–943. (m) Sánchez-Lozano, M.; Otero, N.; Hermida-Ramón, J. M.; Estévez, C. M.; Mandado, M. *J. Phys. Chem. A* **2011**, *115*, 2016–2025.

(12) (a) Hafezi, N.; Holcroft, J. M.; Hartlieb, K. J.; Dale, E. J.; Vermeulen, N. A.; Stern, C. L.; Sarjeant, A. A.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 456–461. (b) Zhang, J.; Zhou, B.; Sun, Z.-R.; Wang, X.-B. *Phys. Chem. Chem. Phys.* **2015**, *17*, 3131–3141. (c) Chang, K.-C.; Minami, T.; Koutnik, P.; Savechenkov, P. Y.; Liu, Y.; Anzenbacher, P. *J. Am. Chem. Soc.* **2014**, *136*, 1520–1525. (d) Adriaenssens, L.; Gil-Ramírez, G.; Frontera, A.; Quiñonero, D.; Escudero-Adán, E. C.; Ballester, P. *J. Am. Chem. Soc.* **2014**, *136*, 3208–3218. (e) Arranz-Mascarós, P.; Bazzicalupi, C.; Bianchi, A.; Giorgi, C.; Godino-Salido, M. L.; Gutierrez-Valero, M. D.; Lopez-Garzón, R; Savastano, M; *J. Am. Chem. Soc.* **2013**, *135*, 102–105. (f) Barceló-Oliver, M.; Bauzá, A.; Baquero, B. A.; García-Raso, A.; Terrón, A.; Molins, E.; Frontera, A. *Tetrahedron Lett.* **2013**, *54*, 5355−5360. (g) Watt, M. M.; Zakharov, L. N.; Haley, M. M.; Johnson, D. W. *Angew.*

Chem.,Int. Ed. **2013**, *52*, 10275−10280. (h) Baldridge, K. K.; Cozzi, F.; Siegel, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2903–2906. (i) Chudzinski, M. G.; McClary, C. A.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 10559–10567. (j) Vargas Jentzsch, A.; Emery, D.; Mareda, J.; Metrangolo, P.; Resnati, G.; Matile, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11675–11678. (k) Guha, S.; Goodson, F. S.; Roy, S.; Corson, L. J.; Gravenmier, C. A.; Saha, S. *J. Am. Chem. Soc.* **2011**, *133*, 15256–15259. (l) Sakai, N.; Mareda, J.; Vauthey, E.; Matile, S. *Chem. Commun.* **2010**, *46*, 4225–4237. (m) Chifotides, H. T.; Schottel, B. L.; Dunbar, K. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7202–7207. (n) Guha, S.; Saha, S. *J. Am. Chem. Soc.* **2010**, *132*, 17674–17677. (o) Wang, D.-X.; Wang, Q.-Q.; Han, Y.; Wang, Y.; Huang, Z.-T.; Wang, M.-X. *Chem. Eur. J.* **2010**, *16*, 13053–13057. (p) Mareda, J.; Matile, S. *Chem Eur. J.* **2009**, *15*, 28–37. (q) Gil-Ramírez, G.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Ballester, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4114–4118. (r) Berryman, O. B.; Sather, A. C.; Hay, B. P.; Meisner, J. S.; Johnson, D. W. *J. Am. Chem. Soc.* **2008**, *130*, 10895–10897. (s) Wang, D.-X.; Zheng, Q.-Y.; Wang, Q.-Q.; Wang, M.-X. *Angew. Chem., Int. Ed.* **2008**, *47*, 7485–7488. (t) Berryman, O. B.; Hof, F.; Hynes, M. J.; Johnson, D. W. *Chem. Commun.* **2006**, 506–508. (u) Maeda, H.; Morimoto, T.; Osuka, A.; Furuta, H. *Chem. Asian J.* **2006**, *1*, 832–844.

(13) Dawson, R. E.; Hennig, A.; Weimann, D. P.; Emery, D.; Ravikumar, V.; Montenegro, J.; Takeuchi, T.; Gabutti, S.; Mayor, M.; Mareda, J.; Schalley, C. A.; Matile, S. *Nat. Chem.* **2010**, *2*, 533−538.

(14) (a) Jentzsch A. V.; Matile S. *Top. Curr. Chem.* **2015**, *358*, 205–39. (b) Vargas Jentzsch, A.; Matile, S. *J. Am. Chem. Soc.* **2013**, *135*, 5302–5303. (c) Vargas Jentzsch, A.; Hennig, A.; Mareda, J.; Matile, S. *Acc. Chem. Res.* **2013**, *46*, 2791–2800. (d) Vargas Jentzsch, A.; Emery, D.; Mareda, J.; Nayak, S. K.; Metrangolo, P.; Resnati, G.; Sakai, N.; Matile, S. *Nat. Commun.* **2012**, *3*, 905. (e) Misek, J.; Vargas Jentzsch, A.; Sakurai, S.; Emery, D.; Mareda, J.; Matile, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 7680–7683.

(15) (a) Zhao, Y.; Benz, S.; Sakai, N.; Matile, S. *Chem. Sci.* **2015**, *6*, 6219–6223. (b) Zhao, Y.; Sakai, N.; Matile, S. *Nat. Commun.* **2014**, *5*, 3911. (c) Zhao, Y.; Beuchat, C.; Domoto, Y.; Gajewy, J.; Wilson, A.; Mareda, J.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2014**, *136*, 2101–2111. (d) Lu, T.; Wheeler, S. E. *Org. Lett.* **2014**, *16*, 3268–3271. (e) Phuengphai, P.; Youngme, S.; Mutikainen, I.; Reedijk, J. *Inorg. Chem. Commun.* **2012**, *24*, 129–133. (f) Estarellas, C.;

Frontera, A.; Quiñonero, D.; Deyà, P. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 415–418. (g) Rojas, C. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 5120–5121.

(16) (a) Dutta, R.; Ghosh, P. *Eur. J. Inorg. Chem.* **2012**, *21*, 3456–3462. (b) Xu, Z.; Singh, N. J.; Kim, S. K.; Spring, D. R.; Kim, K. S.; Yoon, J. *Chem. Eur. J.* **2011**, *17*, 1163–1170.

(17) (a) Bianchi, A.; Garcia-España, E. *Thermodynamic Aspects of Anion Coordination*, in *Anion Coordination Chemistry*; Bowman-James, K., Bianchi, A., Garcia-España, E., Eds.; Wiley-VCH: New York, 2012. (b) Schneider, H.-J.; Yatsimirsky, A. *Principle and Methods in Supramolecular Chemistry*, John Wiley & Sons: Chichester, 2000.

(18) (a) Frontera, A.; Saczewski, F.; Gdaniec, M.; Dziemidowicz-Borys, E.; Kurland, A., Deyà, P. M.; Quiñonero, D.; Garau, C. *Chem. Eur. J.* **2005**, *22*, 6560–6567. (b) Garau, C.; Frontera, A.; Quiñonero, D.; Ballester, P.; Costa, A.; Deyà, P. M. *Chem. Phys. Lett.* **2004**, *392*, 85–89. (c) Garau, C.; Frontera, A.; Quiñonero, D.; Ballester, P.; Costa, A.; Deyà, P. M. *J. Phys. Chem. A* **2004**, *108*, 9423–9427.

(19) (a) Clavier, G.; Audebert, P. *Chem. Rev.* **2010**, *110*, 3299–3314. (b) Tolshchina, S. G.; Rusinov, G. L.; Charushin, V. N. *Chem. Heterocyc. Compd.* **2013**, *49*, 66–91.

(20) Yang, J.; Karver, M. R.; Li, W.; Sahu, S.; Devaraj, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 5222–5225

(21) Lange, U. E. W.; Schäfer, B.; Baucke, D.; Buschmann, E.; Mack, H. *Tetrahedron Lett.* **1999**, *40*, 7067–7070.

(22) (a) Neunhoeffer, H. In *2.21 – Tetrazines and Pentazines;* Rees, A. R. K. W., Ed.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; pp 565. (b) Sagot, E.; Le Roux, A.; Soulivet, C.; Pasquinet, E.; Poullain, D.; Girard, E.; Palmas, P. *Tetrahedron* **2007**, *63*, 11189–11194.

(23) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739–1753.

(24) (a) Schneider, H.-J. *Chem. Soc. Rev.* **1994**, *22*, 227–234. (b) Schneider, H.-J.; Blatter, T.; Eliseev, A.; Rüdiger, V.; Raevsky, O. A. *Pure Appl. Chem.* **1993**, *65*, 2329–2334. (c) Schneider, H.-J.; Schiestel, T.; Zimmermann, P. *J. Am. Chem. Soc.* **1992**, *114*, 7698–7703. (d) Schneider, H.-J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417–1436. (e) Schneider, H.-J.; Theis, I. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 753–754.

(25) Gilli, G.; Gilli, P. *The Nature of the Hydrogen Bond*; Oxford University Press: New York, 2009.

(26) (a) Faraji, M.; Farajtabar, A.; Gharib, F. *J. Appl. Chem. Res.* **2009**, *9*, 7–12. (b) Åkerlöf, G. *J. Am. Chem. Soc.* **1932**, 54, 4125–4139.

(27) Petit, L. D., *IUPAC Stability Constants Data Base*, Academic Software: 1997.

(28) (a) Shamel, A.; Saghiri, A.; Jaberi, F.; Farajtabar, A.; Mofidi, F.; Khorrami, S. A.; Gharib, F. *J. Solution Chem.* **2012**, *41*, 1020–1032. (b) Doğan, A.; Kılıç, E.; Özel, A, D. *Amino Acids* **2009**, *36*, 373–379. (c) Canel, E.; Gültepe, A.; Doğan, A.; Kılıç, E. *J. Solution Chem.* **2006**, *35*, 5–19.

(29) (a) Marcus, Y. *Ion Solvation*, Wiley: New York, 1985. (b) Markus, Y. *J. Chem. Thermodynamics* **2007**, *39*, 1338–1345.

(30) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 520 – 554

(31) Wang, Y.; Li, H.; Han, S. *J. Phys. Chem. B* **2006**, *110*, 24646–24651.

(32) Dominguez-Vidal, A.; Kaun, N.; Ayora-Cañada, M.J.; Lendl, B. *J. Phys. Chem. B*, **2007**, *111*, 4446–4452.

Table of Contents Graphic and Synopsis

The tetrazine ligand shrinks in size upon interaction with the anion in solution. Peculiar solvation/desolvation effects act on the interacting partners that form anion complexes stabilized by pivotal anion-π interactions.