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Halide and Hydroxide Anions Binding in Water†

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The formation of halide and hydroxide anions complexes with the two ligands L1 (3,6-bis(morpholin-4-ylmethyl)-1,2,4,5-tetrazine) and L2 (3,6-bis(morpholin-4-ylethyl)-1,2,4,5-tetrazine) were studied in aqueous solution, by means of potentiometric and ITC procedures. In the solid state, HF_2^-, Cl^- and Br^- complexes of H_2L2^{2+} were analysed by single crystal XRD measurements. Further information on the latter were obtained with the use of density functional theory (DFT) calculations in combination with the polarization continuum model (PCM). The presence of two halide or bifluoride HF_2^- (F-H-F$^-$) anions forming anion-π interactions, respectively above and below the ligand tetrazine ring is the leitmotiv of the $[(H_2L2)X_2]$ (X = HF_2, Cl, Br, I) complexes in the solid state, while hydrogen bonding between anions and protonated morpholine ligand groups contribute to strengthen the anion-ligand interaction, in particular in the case of Cl^- and Br^-. In contrast to the solid state, only anion:ligand complexes of 1:1 stoichiometry were found in solution. The stability of these complexes displays the peculiar trend $I^- > F^- > Br^- > Cl^-$ which was rationalized in terms of electrostatic, hydrogen bond, anion-π interactions and solvent effects. DFT calculations performed on $[(H_2L2)X]^+$, X = F, Cl, Br, I) in PCM water suggested that the ligand assumes an U-shaped conformation to form one anion-π and two salt bridge interactions with the included anions and furnished structural information to interpret the solvation effects affecting complex formation. The formation of hydroxide anion complexes with neutral (not protonated) L1 and L2 molecules represents an unprecedented case in water. The stability of the $[L(OH)]^-$ (L = L1, L2) complexes is comparable to or higher than the stability of halide complexes with protonated ligand molecules, their formation being promoted by largely favourable enthalpic contributions that prevail over unfavourable entropic changes.

Introduction

Positively charged functions and hydrogen bond donor groups are the principal structural elements that have been included into synthetic receptors and made possible the achievement of efficient anion binding and recognition. Nevertheless, even if coulombic attractions and hydrogen bonds are relatively strong forces, anion binding remains a challenging task when the action of these receptors is required in solution of highly polar, protic solvents, like water.[1] But water is the most attractive medium, being related with all known living systems, and, accordingly, we observe a continuous shift of anion receptor chemistry toward applications under real-life conditions.[2]
Other weak forces can be used for anion binding. Among them, anion interactions with aromatic groups, referred to as anion-π interactions, have become rather popular[3,4] and are now taken into account for the construction of new functional materials,[5] anion receptors,[4a,6] carriers,[7] catalysts,[8] and sensors.[4a,9] Also the role of anion-π interactions in biological processes is increasingly appreciated.[4d-g] An electron-deficient π-system is the prime condition to make attractive the interaction between electron-rich species, like anions, and the π electron clouds of aromatic molecules. For instance, the *s*-tetrazine molecule (Figure 1) is characterized by a high and positive quadrupole moment (Q_{zz} = 10.7 B) and by a high molecular polarizability ($\alpha_{\|}$ = 58.7 a.u.), therefore, both electrostatic and ion-induced polarization terms contribute to make it a strong π-acid, that is a potentially good receptor for anions.[10]

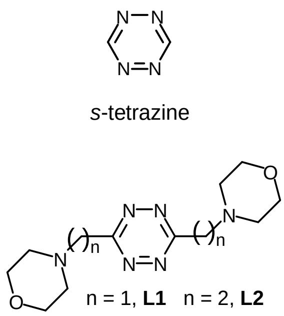

Fig. 1 *S*-tetrazine and its L1 and L2 derivatives.

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Unfortunately, the use of tetrazines for anion binding in water is hampered by their low solubility. Decoration of *s*-tetrazine with two morpholine pendants gave rise to L1 and L2 ligands (Figure 1) having sufficient solubility (especially L2) to be studied as anion receptors in water.[11] The positively charged species formed upon protonation of the morpholine groups (HL^+, H_2L^{2+}) and, in several cases, even the unprotonated (uncharged) molecules proved able to bind inorganic anions of different geometries, forming complexes of moderate, but significant, stability in water. All solution data acquired for these complex systems strongly suggested that, even in water, anion-π interactions are of prime importance to stabilize the anion complexes formed by both protonated and neutral forms of the ligands. In the solid state, the importance of anion-π interactions is evident for these systems, as revealed by the crystal structures of several anion complexes with diprotonated ligands (H_2L1^{2+}, H_2L2^{2+}), showing that the anions are invariably located over the positive electrostatic potential of the ligands' tetrazine ring, at short interaction distances, despite the presence of two ammonium groups in their structure, that only in some cases contribute to stabilize the anion complexes through salt-bridge interactions.[11]

The ability of s-tetrazines to act as acceptors of electron densities is further proved by the presence of lone pair-π interactions in the crystal structures of the free L1 and L2 molecules reported in this paper. Nevertheless, the main focus of the present work is the interaction of these ligands with halide anions F^-, Cl^-, Br^- and I^-. All four halides are present in biological systems, albeit at quite different levels, where they are involved in important roles and, accordingly, they are the most common targets for anion receptor chemistry.[1] Beyond biological aspects, halide anions are quite interesting because they are a group of mono-charged spherical anions whose physico-chemical properties vary rather uniformly with their size, thus making easier the correlation of complex stability with the contribution of binding forces. From F^- to I^-, the anion size increases while their charge density decreases, the anions lose basicity and acquire greater polarizability, their ability to form hydrogen bonds drops down and their hydration free energies as well. As shown later on, combination of these tendencies with the anion binding properties of L2 gives rise to a non-monotonous, V-shaped variation of the anion complex stability along the F^-–I^- series. Regrettably, in the case of L1, it was not possible to obtain equilibrium data for the whole series of halides (see experimental section).

Interestingly, during the treatment of equilibrium data, it came out that in alkaline solutions, from pH 10 on, even the OH^- ion interacts with the neutral L1 and L2 ligands. To the best of our knowledge, this is the first case of non-covalent binding of hydroxide anions in water with metal-free synthetic receptors.

Experimental procedures

Materials

All reagents and solvents were of reagent-grade purity or higher. They were purchased from commercial sources and used without further purification unless otherwise stated. The halide anions used for potentiometric measurements were obtained as high purity sodium salts from commercial sources and were used without further purification. L1 (3,6-bis(morpholin-4-ylmethyl)-1,2,4,5-tetrazine) and L2 (3,6-bis(morpholin-4-ylethyl)-1,2,4,5-tetrazine) were synthesized as previously described.[11c] Red crystals of L1 and L2 were obtained by slow evaporation at room temperature of solutions containing L1 and L2 in methanol. Red crystals of $H_2L2(HF_2)_2 \cdot HF \cdot H_2O$ suitable for X-ray diffraction analysis were obtained by the following procedure. A solution of HF in a methanol/water (9:1, v:v) mixture was layered over a butanol solution of L2 contained in a plastic vessel. The crystals appeared in a few days upon diffusion of the two solutions and slow evaporation at room temperature. Deep pink crystal of H_2L2Cl_2 were obtained by slow evaporation under anhydrous conditions of a methanolic solution of L2 acidified with gaseous HCl. Deep pink crystal of H_2L2Br_2 were prepared by slow evaporation of a methanolic solution of L2 containing a modest excess of HBr. Single crystals of L1 and L2 suitable for X-ray diffraction were grown from chloroform solutions.

Potentiometric Measurements

Potentiometric (pH-metric) titrations employed for the determination of equilibrium constants were carried out in degassed aqueous solutions at 298.1 ± 0.1 K, with a 0.1 M ionic strength, by using previously described equipment and procedures.[12] The determined ionic product of water was pK_w = 13.83(1) (298.1±0.1 K, 0.1 M Me_4NCl). Ligand concentration was about 5×10^{-4} M, while anion concentration was about 2.5×10^{-3} M. The ionic strength was adjusted to 0.10 M by the addition of Me_4NCl. In the case of Cl^-, the concentration was increased up to 0.11 M including Me_4NCl from the ionic medium. The studied pH range was 2.5-11. The computer program HYPERQUAD[13] was used to calculate equilibrium constants from potentiometric data deriving from three independent titration experiments for each system. Complications, denoted by a slight change of colour of the sample solution, were encounter for the system L1/Br^-. All attempts to treat the relevant potentiometric titration curves with the program HYPERQUAD were unfruitful. In the case of Cl^-, no interaction was found with both ligands.

Isothermal Titration Calorimetry

Anion complexation enthalpies were determined in 0.10 M Me_4NCl aqueous solutions at 298.1 K by using previously described equipment and procedures.[11c] Due to solubility problems or ligand (L1) instability in acidic solution, we only manage to study the interaction of neutral L1 and L2 with OH^-. In a typical experiment, a NMe_4OH solution (0.10 M, addition volumes 15 μl) was added to acidic solutions of the ligands (5×10^{-3} M, 1.5 cm^3). Corrections for the heats of dilution were applied. Data fitting and calculation of enthalpy changes were performed as previously described.[11c]

X-ray Structure Analyses

Red crystals of $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$ (a) and deep pink crystals of H_2L2Cl_2 (b), H_2L2Br_2 (c), L1 (d) and L2 (e) were used for X-ray diffraction analysis. A summary of the crystallographic data is reported in Table 1. The integrated intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied.[14] The structures were solved by direct methods (SIR-92).[15] Refinements were performed by means of full-matrix least-squares using SHELXL Version 2014/7.[16] All the non-hydrogen atoms were anisotropically refined. Hydrogen atoms were usually introduced in calculated position and their coordinates were refined according to the linked atoms, with the exception of the acidic protons of H_2L2Cl_2 (b) and H_2L2Br_2 (c), and of HF_2^- in $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$ (a). In (a), the disordered cocrystallized water molecule was refined with partial occupation factor (o.f. = 0.5). In case of L1 (d), due to very low intensity of reflections, data were collected only up to theta = 55.4° (0.94 Å resolution). CCDC 1584768-1584772 contain the crystallographic data for these structures.

Table 1. Crystal data and structure refinement for $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$ (a), H_2L2Cl_2 (b), H_2L2Br_2 (c), L1 (d) and L2 (e)

	(a)	(b)	(c)	(d)	(e)
Empirical formula	$C_{14}H_{31}F_5N_6O_3$	$C_{14}H_{26}Cl_2N_6O_2$	$C_{14}H_{26}Br_2N_6O_2$	$C_{12}H_{20}N_6O_2$	$C_{14}H_{24}N_6O_2$
Formula weight	426.4	381.31	470.23	280.34	308.39
Temperature (K)	293	293	150	150	100
space group	*C 2/c*	$P\,2_1/n$	$P\,2_1/c$	$P\,2_1/n$	$P\,2_1/c$
a (Å)	12.1360(5)	5.8409(2)	6.0275(6)	6.2753(4)	11.6821(6)
b (Å)	8.6567(4)	13.9837(7)	13.5630(9)	13.9813(8)	6.8313(2)
c (Å)	19.1395(7)	11.5093(5)	11.9342(9)	7.4837(4)	10.7321(6)
β (°)	92.145(4)	103.017(4)	104.374(8)	97.110(5)	117.200(7)
Volume ($Å^3$)	2009.3(1)	1418.74(16)	945.1(1)	651.55(7)	761.75(8)
Z	4	2	2	2	2
Independent reflections / R(int)	2418 / 0.0215	1741 / 0.0853	1770 / 0.0344	822/0.0303	1541/ 0.0169
μ (mm^{-1})	0.130/ (Mo-kα)	3.363 / (Cu-kα)	5.613/ (Cu-kα)	0.840/ (Cu-kα)	0.767/ (Cu-kα)
R indices [I>2σ(I)]*	R1 = 0.0501	R1 = 0.0484	R1 = 0.0321	R1 = 0.0549	R1 = 0.0355
	wR2 = 0.1242	wR2 = 0.0816	wR2 = 0.0804	wR2 = 0.1367	wR2 = 0.1002
R indices (all data)*	R1 = 0.0670	R1 = 0.0882	R1 = 0.0419	R1 = 0.0919	R1 = 0.0377
	wR2 = 0.1356	wR2 = 0.0964	wR2 = 0.0941	wR2 = 0.1958	wR2 = 0.1019
CCDC	1584768	1584769	1584770	1584771	1584772

* $R1 = \Sigma || Fo| - |Fc|| / \Sigma |Fo|$; $wR2 = [\Sigma w(Fo^2 - Fc^2)^2 / \Sigma wFo^4]^{1/2}$

Quantum Chemical Calculations

The density functional theory (DFT) calculations performed in this work employed the dispersion-corrected ωB97X-D functional of Chai and Head-Gordon[17] in combination with the 6-31+G(d,p) and LANL2DZ basis sets[18,19] (the latter for iodide ion). Implicit solvation (hydration) effects were included with the polarization continuum model (PCM) of Tomasi and coworkers[20] as implemented in the Gaussian 09 software package.[21]

Results and discussion

Crystal Structures of Anion Complexes

In the crystal structure of $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$ complex (Figure 2), the ligand is placed around an inversion centre, giving rise to anion-π interactions with two bifluoride anions placed, respectively, above and below its tetrazine ring (Figure 2a). The linear HF_2^- anion (H-F-H$^-$) forms an angle of 108.9(2)° with the tetrazine ring, one of its fluorine atoms pointing towards the ring centroid (anion-centroid/offset distances of 3.01/0.36 Å). The same fluorine atom is H-bonded to an adjacent ligand molecule, through the protonated morpholine nitrogen (N···F 2.595(3)Å), while the other fluorine atom gives a network of CH···F contacts with the nearby ligands (C···F distances in the range 3.3–3.4 Å) (Figure 2b). The disordered water molecule forms a H-bond bridge with the HF molecule (F···O distance 2.360(5) Å), which is kept in place by a network of CH···F interactions involving symmetry related ligands (C···F distances in the range 3.3–3.4 Å) (Figure 2b). It is noteworthy the remarkable structural similarity existing between this structure with that previously reported for $H_2L2I_2{\cdot}2H_2O$[11a] despite the considerable size and shape difference between HF_2^- and I^-. Also in $H_2L2I_2{\cdot}2H_2O$, the anion (I^-) is connected to three diprotonated ligand molecules via one anion-π contact and two H-bonds (N-H···I and CH···I). Even the conformations assumed by L2 in the HF_2^- and in the I^- complexes are very similar, being intermediate between the planar and the chair conformation of L2 found in previously reported complexes.[11c]

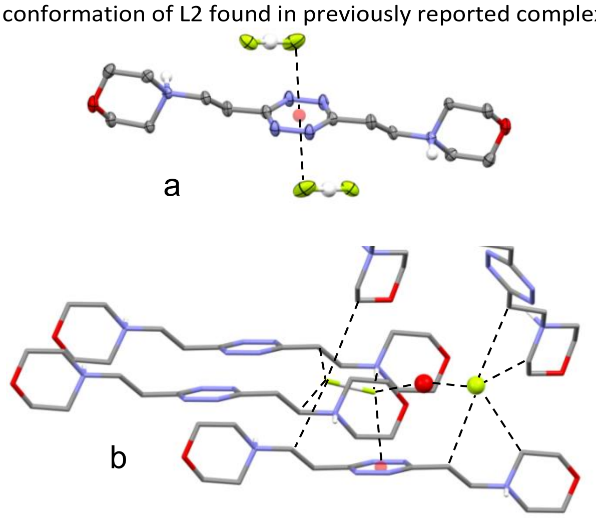

Fig. 2 Crystal structure of $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$. Details of the H_2L2F_2 complex (a) and of the crystal packing (b).

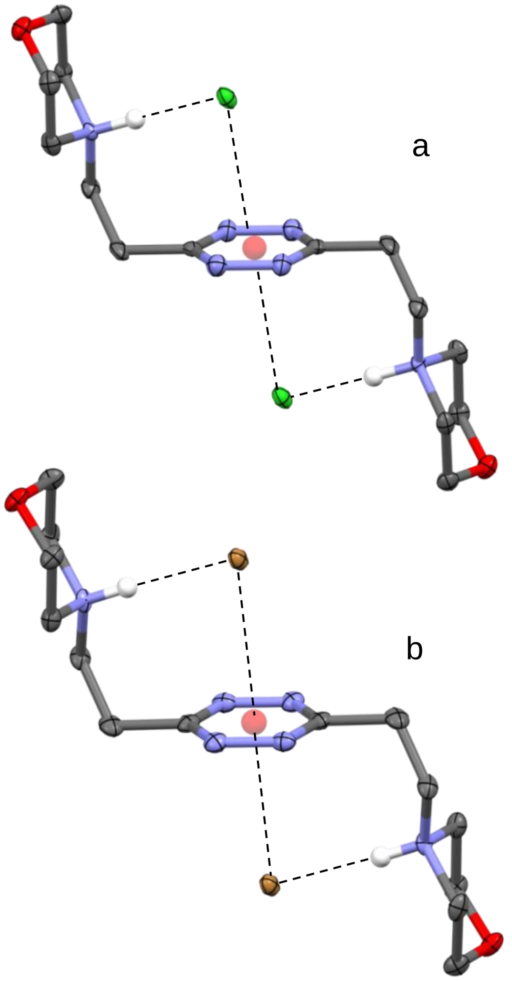

Fig. 3 Crystal structures of H_2L2Cl_2 (a) and H_2L2Br_2 (b).

Conversely, in H_2L2Cl_2 and H_2L2Br_2, the diprotonated ligand is placed around an inversion centre and assumes an overall symmetric chair conformation (Figures 3a,b). In both structures, the tetrazine ring forms anion-π interactions with two centrosymmetric anions that are involved in salt-bridge NH···X interactions (X = Cl 3.057(3) Å, X = Br 3.234(3) Å) with protonated morpholine groups. The Cl^- and Br^- anions lie, respectively, 3.31 and 3.41 Å from the tetrazine ring centroid, with offsets of 0.44 and 0.22 Å respectively, that can be compared with the anion-centroid/offset distances of 3.01/0.36 Å for bifluoride (the closest F atom of HF_2^-) and 3.7/0.3 Å for iodide complexes (Figure 4). Nevertheless, if the anion-centroid distances are corrected for the anion ionic radii, HF_2^- remains a little further from the tetrazine centroid (1.68 Å) than Cl^- (1.50 Å), I^- (1.5 Å) and Br^- (1.45 Å).

Crystal Structures of L1 and L2 free ligands

As in the structures of the anion complexes, in the crystal structures of the free ligands, L1 and L2 are centrosymmetric and the tetrazine ring gives rise to two lone pair-π contacts,

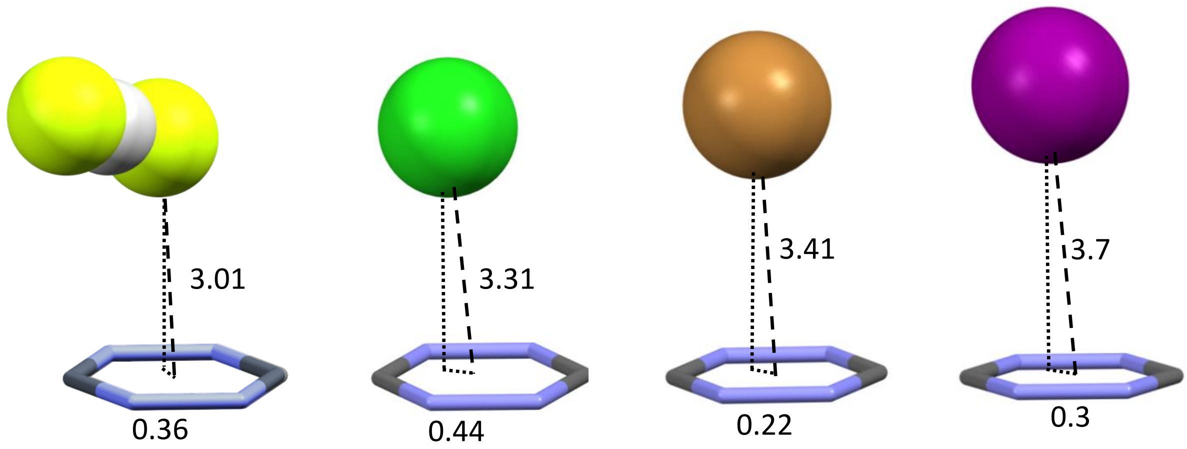

Fig. 4 Distances (Å) of anions from the tetrazine ring centroid and offsets in the crystal structures of $H_2L2(HF_2)_2{\cdot}HF{\cdot}H_2O$, H_2L2Cl_2, H_2L2Br_2 and $H_2L2I_2{\cdot}2H_2O$. Data for $H_2L2I_2{\cdot}2H_2O$ are form ref. 11a.

symmetric with respect to the aromatic ring and involving morpholine oxygen (L1) and nitrogen (L2) atoms of adjacent L1 and L2 molecules (Figure 5). The short lone pair-centroid/offset distances (2.96/0.17 Å for morpholine oxygen in L1, and 3.24/0.25 Å for morpholine nitrogen in L2) account for strong interactions. Actually, the distances from centroids are in the shorter range observed for all the studied systems, being 1.46 Å and 1.58 Å for oxygen (L1) and nitrogen (L2), respectively, when corrected for the proper VdW radii. Moreover, it is to be mentioned that while L2 assumes an almost planar conformation, like that found in the bifluoride and the iodide complexes,[11a] L1 shows a greater similarity to chloride and bromide structures, as it assumes a chair conformation allowing the morpholine oxygen atom to form a non-conventional H-bond with a morpholine C-H group (C···O 2.434(6) Å) in addition to the lone pair-π interaction (Figure 5a).

These crystal structures highlight the strong ability of the electron deficient tetrazine ring to attract species with available electron pairs, regardless whether they are negatively charged or not.

Anion Binding in Solution

Speciation of the L2/X^- (X = halide) systems and determination of the complex stability constants were performed by potentiometric (pH-metric) titrations in aqueous 0.10 M Me_4NCl solution at 298.1 K and successive analysis of the titration curves by means of the HYPERQUAD[13] program. The determined stability constants are listed in Table 2. As can be seen from this table, halide complexes are formed with mono- and diprotonated ligand forms. In the case of L1, only the stability constants of I^- complexes were determined for the reasons specified in the experimental section. In the L2/Br^- system, only H_2L2^{2+} appeared to interact appreciably with the anion, while in the case of Cl^- no evidence of complexation was found. Obviously, using 0.10 M Me_4NCl aqueous solution as ionic medium, all complexation equilibria involving anions are competitive with possible ligand-Cl^- interactions. Upon addition of further anions to this ionic medium, the titration curves change profile if further complexation equilibria are established or existing complexation equilibria are enhanced. This occurred with all anions studied in this and previous[11] works, with the exception of Cl^-. This means that Cl^- is the anion interacting less among those up to now studied, justifying its use as the anionic component of the ionic medium. According to these results, we can say that, relative to our experimental conditions, the stability constants of the Cl^- complexes is too small to be determined, at least by means of the employed potentiometric method.

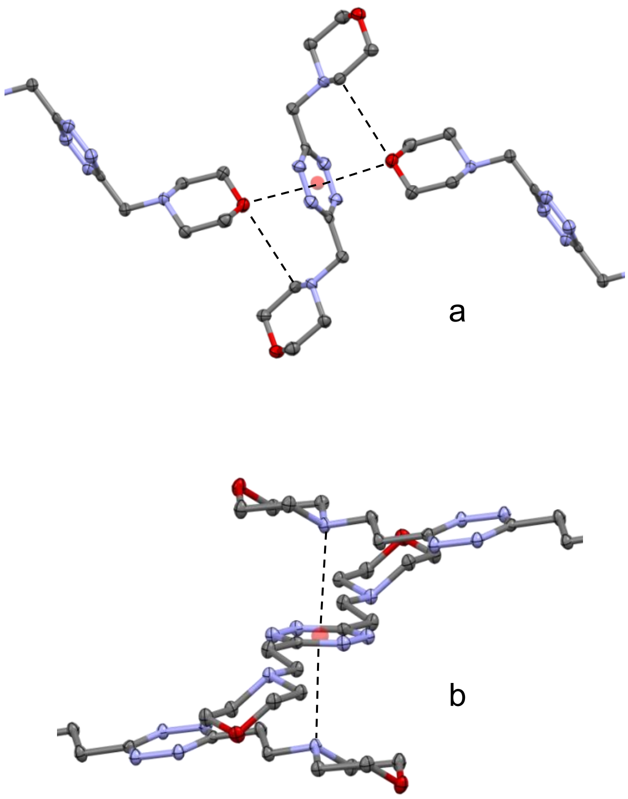

Fig. 5 Crystal structures of the free ligands L1 (a) and L2 (b) with details of the packing interaction.

Table 2. Equilibrium constants and relevant -ΔG° values for anion complex formation determined at 298.1±0.1 K in 0.1 M Me_4NCl aqueous solution. Values in parentheses are standard deviation on the last significant figure.

	log*K*	Δ*G*° kJ/mol	Δ*H*° kJ/mol	*T*Δ*S*° kJ/mol
$HL1^+ + I^- = (HL1)I$	1.5(1)	-8.6(6)		
$H_2L1^{2+} + I^- = [(H_2L1)I]^+$	2.01(6)	-11.5(3)		
$HL2^+ + F^- = (HL2)F$	1.58(8)[a]	-9.0(5)[a]		
$H_2L2^{2+} + F^- = [(H_2L2)F]^+$	1.97(3)[a]	-11.2(2)[a]		
$H_2L2^{2+} + Br^- = [(H_2L2)Br]^+$	1.3(1)	-7.6(6)		
$HL2^+ + I^- = (HL2)I$	2.03(7)[b]	-11.6(4)[b]		
$H_2L2^{2+} + I^- = [(H_2L2)I]^+$	2.35(4)[b]	-13.4(2)[b]		
$L1 + OH^- = [(L1)OH]^-$	2.60(7)	-14.8(4)	-25.1(4)	-10.3(8)
$L2 + OH^- = [(L2)OH]^-$	1.76(7)	-10.0(4)	-18.8(4)	-8.8(8)

a Taken from ref. 11c. b Taken from ref. 11a.

An inspection to data in Table 2 points out a few general trends. First of all, it is to be noted that the complex stability constants increase very little with ligand protonation. The free energy increment of 1.8-2.6 kJ/mol associated with the variation of a single positive charge of the ligand is remarkably smaller than the value 5±1 kJ/mol expected for the formation of a single salt bridge in water.[22] This is a common feature invariably observed with these tetrazine-based ligands,[11] indicating that forces other than charge-charge attraction are important for these system, i.e. the anion-π interaction, which dominates L2 complexes with halide anions in the solid state, and the effect of the solvent, which should be reckoned with in solution studies. Similar trends were previously observed for the formation of other anion complexes with other ligands that avail of anion-π interactions as prime binding forces.[4l,5d,23] Nevertheless, contributions from electrostatic attraction and hydrogen bonds, that are very significant for anion complexes with ammonium ligand,[24] cannot be neglected.

A special trend of complex stability is encountered moving along the halides series. As shown in Figure 6, the equilibrium constants (*K*) for the complexation equilibria $H_2L2^{2+} + X^- = [(H_2L2)X]^+$ (X = F, Cl, Br, I) give rise to a V-shaped profile with a minimum for Cl^-, that, as commented above, forms undetectable complexes ($K \approx$ zero) under the experimental conditions employed. On the basis of the crystallographic results, we would have expected that Cl^- and Br^- were the stronger interacting anions, as they form simultaneous anion-π and salt-bridge interactions with H_2L2^{2+}, while they actually interact little or nothing in solution. On the basis of the physico-chemical properties of the anions we would expect different and homogeneous trends. For instance, the charge density of the anions, as well as their ability to form H-bonds decrease from F^- to I^-, suggesting a steady weakening of both anion-π and salt-bridge contributions along the series. The same is expected for the polarization effect induced by the anions on the ligand π-electron system which should be modest and decrease with the anion charge density, while the opposite effect of anion polarization by the ligand is expected to be almost negligible. Also dispersion contributions to the total interaction energy are expected to be modest.[25] That is, according to these properties, the complex stability should decreases along the F^-–I^- series, in contrast with the experimental evidence.

Conversely, an opposite trend is to be expected if solvation effects are taken into account. As a matter of fact, the formation of anion complexes causes a release of solvent molecules from the interacting species. For a given ligand, the differences between the corresponding overall energetic effects are mostly determined by the hydration free energies ($\Delta G°_{hyd}$) of anions that may have quite different values. Indeed, for the halide anions, the $\Delta G°_{hyd}$ is -472 kJ/mol (F^-), -347 kJ/mol (Cl^-), -321 kJ/mol (Br^-) and -283 kJ/mol (I^-),[1a] the associated energetic cost for desolvation decreasing in the order $F^- > Cl^- > Br^- > I^-$, thus favouring complexation in the opposite direction.

Most likely, combination of these opposite trends generates the V-shaped profile of stability constants shown in Figure 6.

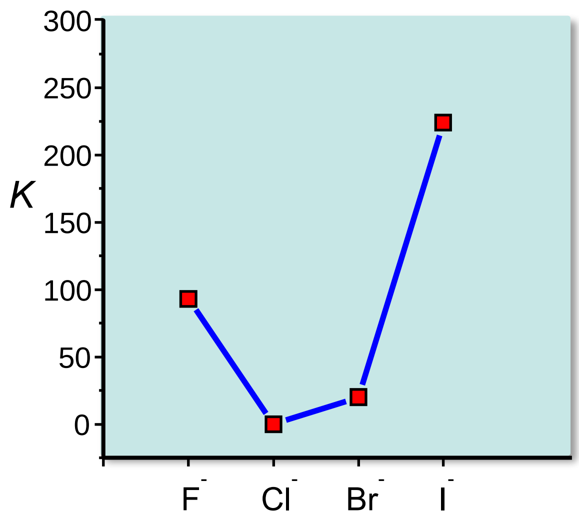

Fig. 6 Equilibrium constants (K) for the reactions H2L22+ + X- = [(H2L2)X]+ (X = halide). For Cl-, K was arbitrarily set equal to zero, as it is expected to be close to this value.

DFT optimized geometries for diprotonated complexes ($[(H_2L2)X]^+$, X = F, Cl, Br, I) in PCM water are shown in Figure 7. In these complexes, in contrast to the crystallographic results, the ligand assumes an U-shaped conformation and forms a pair of salt bridges with the included anions, while the morpholine pendants spread more and more as the guest anions becomes bigger and bigger. The selected structural parameters collected in Table 3 show that, in the minimized geometries, all halide anions are located along, or very close to, the perpendicular to the tetrazine passing through the ring centroid, and that the anion-centroid distances corrected for the anion ionic radii are short and similar. Conversely, the salt bridge contacts $NH^+\cdots X^-$ corrected for the anion ionic radii

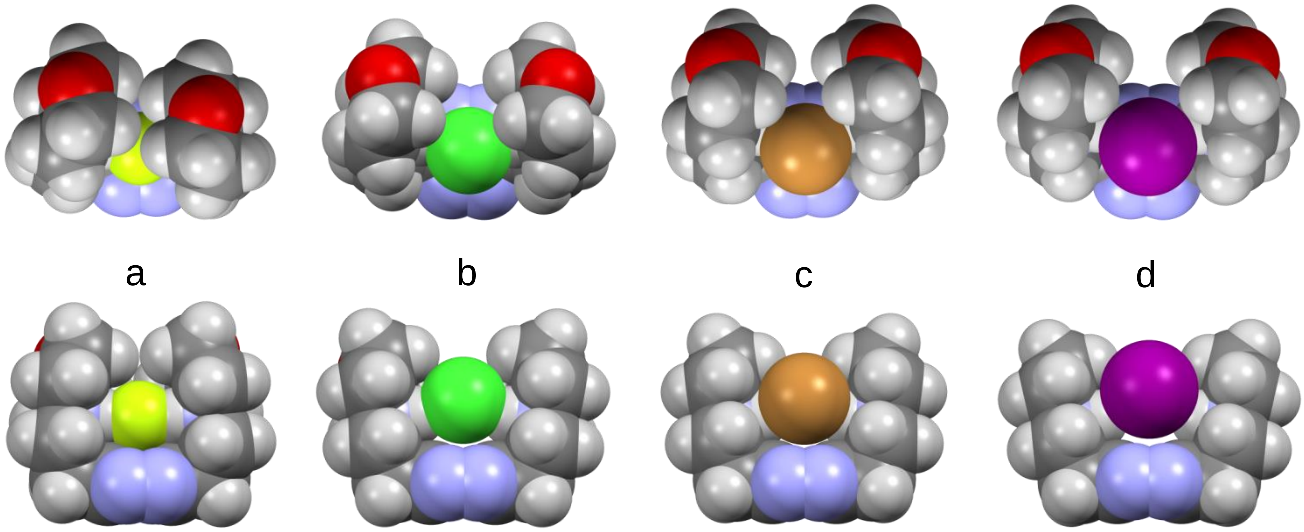

Fig. 7 DFT optimized geometries for fluoride (a), chloride (b), bromide (c) and iodide (d) complexes of H_2L2^{2+} in PCM water viewed along the directions normal (top) and parallel (bottom) to the tetrazine molecular plane.

account for a significant weakening of the interaction from F^- to I^-. While fluoride is totally engulfed by the ligand, forming quasi linear $H^+\cdots X^-\cdots {}^+H$ interactions (165.54°, Table 3) the bigger halide anions are more and more external (Figure 7), the $H^+\cdots X^-\cdots {}^+H$ angle becoming 106.93° in the iodide complex (Table 3). Accordingly, the halide anions become increasingly exposed to the solvent from F^- to I^-, thus being subject to a decreasing desolvation upon complexation. Therefore, the computational results are in line with the importance of the anion-π interaction and the interplay of opposite tendencies of salt bridge interactions and solvation phenomena that generate the V-shaped profile of complex stability shown in Figure 6.

Unfortunately, poor information is available for halide complexes with L1. With this ligand, we only managed to determine the stability constants of I^- complexes (see experimental section) that emerged to be relatively smaller than the constants determined for the analogous species with L2 (Table 2), as already observed for other anion complexes of the same ligands.[11c]

In contrast with complexes of the same ligands with other anions, the neutral (unprotonated) L1 and L2 molecules do not form halide complexes of sufficient stability to be detected by our potentiometric (pHmetric) method. Most likely, this is due to the general lower stability of halide complexes that is probably related to the monoatomic nature of these anions which makes more difficult the association of different binding forces in keeping together the interacting partners. Nevertheless, during the present study, we stumbled upon an unexpected result. We found that the neutral L1 and L2 ligands interact with hydroxide (OH^-) anions, in water, to form $[(L1)OH]^-$ and $[(L2)OH]^-$ complexes, a result that, at first, seemed rather surprising. Actually, as far as we know, these are the first reported cases of non-covalent binding of hydroxide anions in water with metal-free synthetic receptors, even if, examples of OH^- anions interacting with electron poor aromatic groups in the solid state can be found in published crystal structures.[26] In only few of them, the existence of anion-π interactions was noted.[26j,o]

Table 3. Interaction parameters for the minimized $[(H_2L2)X]^+$ (X = halide) complexes.

X	Centroid distance (Å)[a]	Corrected centroid distance (Å)[b]	Offset (Å)	$NH^+\cdots X^-$ distance (Å)[c]	Corrected $NH^+\cdots X^-$ distance (Å)[d]	H–X–H angle (°)[e]
F	2.73	1.45	0.00	1.46, 1.47	0.17, 0.18	165.54
Cl	3.31	1.50	0.00	2.07	0.26	134.05
Br	3.37	1.41	0.08	2.21, 2.22	0.25, 0.26	110.46
I	3.70	1.5	0.17	2.56	0.4	106.93

[a] Distance of the anion from the tetrazine ring centroid. [b] Centroid distance corrected for the anion ionic radius. [c] Hydrogen bond distance. [d] Hydrogen bond distance corrected for the anion ionic radius. [e] Angles formed by the anion and the ammonium protons involved in the formation of salt bridges.

In reality, there was no reason of surprise in this finding. OH^- is an anion, it can be involved in interactions of different natures with L1 and L2, its hydration free energy ($\Delta G°_{hyd}$ = -403 kJ/mol) is intermediate between those of F^- and Cl^- (see above), thus, OH^- has all the requisites to be bound by L1 and L2 like, or better than, other anions. The formation of these OH^- complexes was undetected in previous studies because their formation become appreciable only above pH 10, when the concentration of OH^- anions becomes significant, while all measurements previously used for the speciation of the complexes with other anions were conducted up to pH 9.[11] Accordingly, below pH 9 the OH^- anions are very scarce and unable to compete with the formation of other anions' complexes. For this reason, the stability constants previously reported for L1 and L2 anion complexes do not need to be corrected for OH^- binding.[27] As can be seen from Table 2, the stability of OH^- complexes with the neutral L1 and L2 is comparable with that of halide complexes of charged ligand forms, $[(L1)OH]^-$ being the most stable among all complexes in this work. Unlike halide anions, OH^- can act as hydrogen bond donor toward the unprotonated morpholine nitrogen atoms of the ligands (Figure 8), affording an important contribution to complex stability. Most likely, this is the reason why neutral L1 and L2 form complexes of appreciable stability with OH^-, while they do not bind halide anions. We believe that the marked exothermicity of the reactions of neutral L1 and L2 with OH^- ($\Delta H°$ = -25.1 and -18.8 kJ/mol, Table 2) reflects the contribution of hydrogen bonding in the formation of OH^- complexes, in contrast with the almost athermic binding of inorganic anions unable to donate hydrogen bonds ($L2/SO_4^{2-}$, $\Delta H°$ = -0.6 kJ/mol; $L2/PF_6^-$, $\Delta H°$ = -0.5 kJ/mol; $L2/ClO_4^-$, $\Delta H°$ = -2.3 kJ/mol).[11c] Consistently, the entropy changes for OH^- binding by the neutral ligands are negative ($T\Delta S°$ = -10.3 and -8.8 kJ/mol, Table 2), while in the case of SO_4^{2-}, PF_6^- and ClO_4^-, binding by L2 were positive ($T\Delta S°$ = 11.8, 17.0, 9.0 kJ/mol, respectively), as expected for the formation of an hydrogen bond anchorage ($OH^- \cdots N$), between OH^- and the nitrogen atom of the morpholine functionality, that reduces the freedom of this ligand arm.

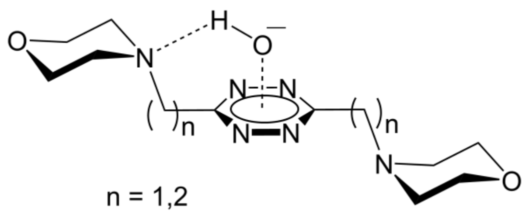

Fig. 8 Schematic representation of the hydrogen bond and anion-π interactions suggested for $[L1(OH)]^-$ (n = 1) and $[L2(OH)]^-$ (n = 2) complexes.

Conclusions

Protonated forms of the tetrazine-based ligand L2 display a significant ability to bind halide anion in water thanks to the interplay of electrostatic, hydrogen bond, anion-π interactions and solvent effects. Both crystallographic and theoretical analysis of the anion complexes show that the anions are invariably located over the tetrazine rings at close interacting anion-π distances. Combination of the above binding forces with solvation contributions gives rise to a particular stability pattern ($I^- > F^- > Br^- > Cl^-$), the I^- and F^- complexes being the most stable. Results obtained for the I^- complexes with L1, the only halide complexes that we managed to study for L1, are consistent with the behaviour of L2.

A remarkable feature of these ligands is their ability to bind OH^- in water when they are in the form of free (unprotonated) amines. At the best of our knowledge, this is an unprecedented observation for organic receptors in water. Dissection of the free energy changes for OH^- binding into their enthalpic and entropic contributions suggests that the formation of such complexes is granted by the ability of OH^- to act as hydrogen bond donor toward the nitrogen atoms of ligand morpholine residues, a property not available for halide anions.

In conclusion, all data confirm that anion-π interactions have a prominent position in the stabilization of anion complexes with L1 and L2 and are well suited for collaboration with other weak forces. Accordingly, the tetrazine ring appears to be a valuable element for the construction of anion receptors and, beyond them, for the construction of receptors for all kind of substrates carrying lone pairs of electrons.

Conflicts of interest

There are no conflicts to declare.

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27 The former potentiometric measurements used to study the formation of other L1 and L2 anion complexes in previous works[11] were reanalysed by using the program HYPERQUAD[13] –according to the procedure described in the experimental section– after the introduction of the stability constants obtained in this work for the formation of OH^- complexes (Table 2). The stability constants obtained by this procedure were equal, within experimental errors, to those previously determined neglecting the formation of OH^- complexes.