

Interplay between salt bridge, hydrogen bond and anion- π interactions in thiocyanate binding[†]

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ABSTRACT

The L2 ligand (3,6-bis(morpholin-4-ylethyl)-1,2,4,5-tetrazine) is constituted by a tetrazine ring decorated with two morpholine pendants. The crystal structure of the $\text{H}_2\text{L2}(\text{SCN})_2$ anion complex shows the thiocyanate anion interacting with the ligand, protonated on the morpholine groups, through the formation of salt-bridge, anion- π and hydrogen bond interactions. The SCN^- anion lies over the tetrazine ring, with the nitrogen atom in proximity to the ring centroid, in a sort of π - π stacking binding mode. Density Functional Theory calculations performed on the interaction of SCN^- with the plain tetrazine ring showed that the anion- π attraction alone is sufficient to form the complex, even in a simulated implicit water environment. The arrangement of the interacting partners in the calculated most stable complex is very similar to the one actually assumed in the crystal structure. Potentiometric titrations performed in water (0.1 M Me_4NCl , 298.1 \pm 0.1 K) revealed that not only the protonated ligand forms, but even the neutral L2 molecule is able to bind SCN^- in solution. The stability of the complexes formed is almost insensitive to ligand charge, revealing that, even in water, anion- π interactions are of major importance in the interplay of weak forces contributing to the formation of similar anion complexes.

Keywords: Anion complexes; anion receptors; anion- π interaction; weak forces; tetrazine; thiocyanate.

1. Introduction

Anion coordination chemistry is a well-established area of supramolecular chemistry that is gathering a large deal of interest because of the importance and the specificity of the roles played by anions in abiotic and biological systems. In addition to strong electrostatic attractions with positively charged receptors, that fostered the birth of anion coordination chemistry, a plethora of weaker forces, including hydrogen bond, anion-dipole, halogen bond and anion- π interactions, as well as solvent effects, also proved to be efficient in promoting the formation of anion-receptor assemblies [1]. Anion- π interactions, exerting between anions and the π -system of electron-deficient arenes, have become rather popular, despite their relatively recent recognition [2, 3], and are now used as design tools for the construction of new functional materials [4], anion receptors [3a, 5], carriers [6], sensors [7] and catalysts [8], while we observed an increasing appreciation of their biological relevance [3a,b].

We have recently shown that protonated forms of the tetrazine-based molecules L1 and L2, decorated with two morpholine pendants of different lengths (Figure 1), bind several inorganic anions of different geometries, such as spherical F^- and I^- , trigonal NO_3^- , tetrahedral ClO_4^- and SO_4^{2-} , and octahedral PF_6^- , forming stable complexes in aqueous solution. Crystallographic information

obtained for some solid samples of these complexes showed that the anions are invariably involved in anion- π interactions with the tetrazine group, in agreement with the strong π -acid character of this ring [9]. Also the triiodide anion (I_3^-) forms complexes with H_2L2^{2+} in the solid state, where the linear anion assumes both end-on and side-on interaction modes with the tetrazine moieties. DFT calculations substantiated that the side-on arrangement corresponds to the most stable interaction mode among those computationally explored in the presence of simulated aqueous environment [9b]. Unfortunately, because of the very low solubility of compounds formed by I_3^- with protonated forms of L1 and L2, we could not manage to study the formation of I_3^- complexes in solution. For this reason, and with the aim of extending solution studies to complexes of similar ligands with linear anions, we investigated the interaction of L2 with thiocyanate (SNC^-) in aqueous solution.

In this paper, we report the result of this study along with a crystallographic analysis of the crystalline $H_2L2(SCN)_2$ complex in which SCN^- anions are bound to the ligand through salt-bridge and anion- π interactions. This is one of the very few cases of anion complexes including a receptor selected for involving anion- π interactions in the binding of SCN^- anions [10].

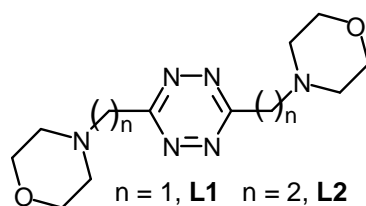


Figure 1. The tetrazine ligands L1 and L2.

2. Experimental procedure

2.1 Materials

L2 (3,6-bis(morpholin-4-ylethyl)-1,2,4,5-tetrazine) was synthesized as previously described [9a]. Pink crystals of $H_2L2(NCS)_2$ were obtained upon slow evaporation at room temperature of an aqueous solution containing the ligand and an excess of the anion at pH 3. High purity NaSCN (Merck) was used for all experimental procedures.

2.2 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 [11]. 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 8×10^{-4} M, while SCN^- concentration was about 2.4×10^{-3} M. The ionic strength was adjusted to 0.1 M by the addition of Me_4NCl . The studied pH range was 2.7-9.0. The computer program HYPERQUAD [12] was used to calculate equilibrium constants from potentiometric data deriving from three independent titration experiments. Ligand protonation constants used in calculation were previously determined [9a].

2.3 X-ray Structure Analyses

A suitable pink crystal of $\text{H}_2\text{L2}(\text{NCS})_2$ was 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 [13]. The structures were solved by direct methods (Olex2) [14]. Refinements were performed by means of full-matrix least-squares using SHELX Version 2014/7 program [15]. 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 cocrystallized water molecules.

Table 1. Refinement and crystallographic parameters for $\text{H}_2\text{L2}(\text{NCS})_2$

Empirical formula	$\text{C}_{16}\text{H}_{26}\text{N}_8\text{O}_2\text{S}_2$
Formula weight	426.57
Temperature (K)	293
space group	$P 2_1/c$
a (Å)	12.334(2)
b (Å)	6.816(1)
c (Å)	12.497(2)
β (°)	96.61(1)
Volume (Å ³)	1043.5(3)
Z	2
Independent reflections / R(int)	1834 / 0.0689
μ (mm ⁻¹)	2.566/ (Cu- $k\alpha$)
R indices [$I > 2\sigma(I)$]*	R1 = 0.0791
	wR2 = 0.2092
R indices (all data)*	R1 = 0.1215
	wR2 = 0.2731

2.4 Computational chemistry

DFT calculations were performed with the Gaussian 09 quantum chemistry package [16] using the dispersion-corrected ω B97X-D functional of Chai and Gordon [17] in combination with the 6-31+G(d) basis set of Pople and coworkers [18, 19]. Geometry optimizations were performed with the integral equation formalism – polarization continuum model (IEF-PCM) of Tomasi and coworkers [20] to simulate an implicit water environment surrounding the tetrazine-thiocyanate complexes. The binding energies (Be) computed for the tetrazine-thiocyanate complexes were corrected for the basis-set superposition error (BSSE) using the counterpoise method of Boys and Bernardi [21]. Atom charges were obtained from a natural population analysis [22] of the solvated complexes.

3. Results and discussion

The crystal structure of the $\text{H}_2\text{L2}(\text{SCN})_2$ compound contains centrosymmetric diprotonated ligand molecules interacting with two symmetry related thiocyanate anions (Figure 2). The ligand assumes a chair-type conformation, similar to that previously reported for its ClO_4^- , NO_3^- , PF_6^- complexes, in which the morpholine pendant arms are in trans position with respect to the tetrazine ring. The

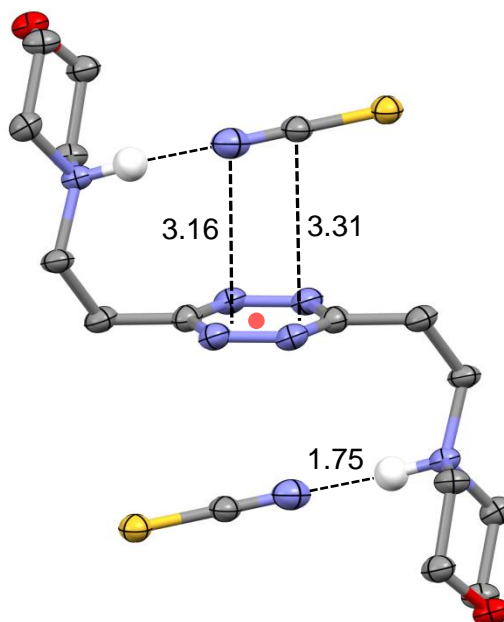


Figure 2. ORTEP drawing of $\text{H}_2\text{L2}(\text{NCS})_2$. Thermal ellipsoids plotted at 40% probability level. Distances are in Å. Colors code: grey, C; white, H; blue, N; red, O; yellow, S.

two SCN^- anions are localized in a side-on conformation just above and below the tetrazine ring, almost aligned along the C–C axis. The projection of the sulfur atom of each anion on the tetrazine plane lies completely outside the ring, while both nitrogen and carbon positions are representative of an anion- π interactions with the electron-poor aromatic group, the distance from the aromatic ring plane being 3.16 Å for N and 3.31 Å for C (distances from ring centroid/offset 3.19/0.46 Å for N and 3.35/0.72 Å for C). Furthermore, the thiocyanate nitrogen forms a strong H-bond ($\text{H}\cdots\text{N}$ distance 1.75(7) Å, $\text{N-H}\cdots\text{N}$ angle 174(6)°) with the morpholine protonated nitrogen. Interestingly, the $\text{H}\cdots\text{N-C}$ angle featuring the H-bond (161(2)°), as well the N-C intra-ion bond distance (1.187(8) Å), suggest the presence of a triple bond between nitrogen and carbon in the thiocyanate anion. This connectivity implies that some negative charge should be localized on the sulfur atom, which, as a matter of fact, is in contact with a hydrogen atoms of a CH_2 group linked to the tetrazine ring ($\text{H}\cdots\text{S}$ distance 2.861(1) Å).

Interesting comparisons can be done with some of the crystal structures previously reported for the $[(\text{H}_2\text{L}2)\text{X}]^+$ systems, with $\text{X} = \text{ClO}_4^-$, NO_3^- , PF_6^- and I_3^- . Figure 3, for instance, shows the SCN^- ion superimposed to the side-on (A) and to the end-on (B) $\text{H}_2\text{L}2\text{I}_3$ species found in the crystal of $\text{H}_2\text{L}2(\text{I}_3)_2\cdot 2\text{H}_2\text{O}$ [9b]. As in the case of the SCN^- anion, also the end-on I_3^- is approximately aligned along the C-C interatomic axis of the tetrazine, while the side-on one is displaced toward the N-N

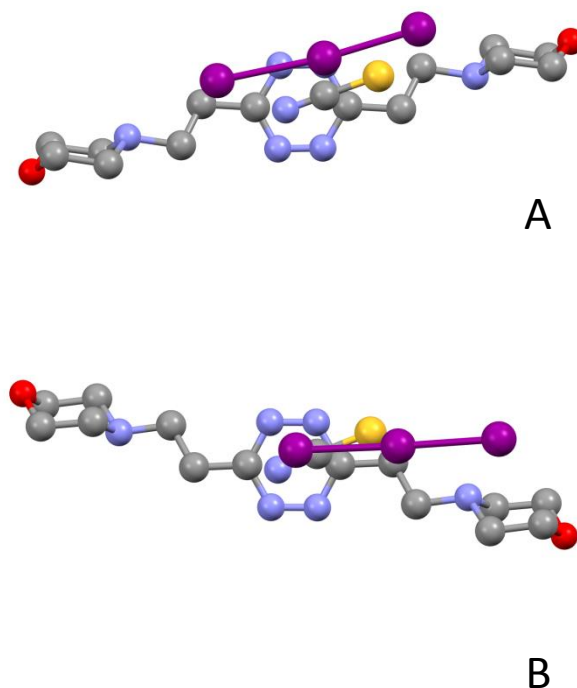


Figure 3. NCS^- ion superimposed to the side-on (A) and the end-on (B) $\text{H}_2\text{L}2\text{I}_3$ species found in the crystal of $\text{H}_2\text{L}2(\text{I}_3)_2\cdot 2\text{H}_2\text{O}$. Structures obtained overlapping the tetrazine rings.

side edge of the tetrazine ring. Notably, in the end-on $\text{H}_2\text{L}2\text{I}_3^+$ adduct, the main force taking triiodides in place is the anion- π interaction [9b], while in the case of the side-on $[\text{H}_2\text{L}2(\text{SCN})]^+$ an additional salt-bridge interaction, linking together the morpholine protonated nitrogen with the nitrogen atom of SCN^- , contributes to strengthen the assembly. Most likely, the stronger propensity to form H-bonds of nitrogen induces the $\text{H}_2\text{L}2^{2+}$ ligand to assume the chair conformation, which in the adduct with triiodide seems less favoured than the planar one. Nevertheless, such considerations do not take into account the effect of crystal packing forces, that could be important in determining the overall arrangement of these anion complexes.

Conversely, in $[(\text{H}_2\text{L}2)\text{X}]^+$ complexes with ClO_4^- , NO_3^- or PF_6^- , $\text{H}_2\text{L}2^{2+}$ assumes the chair conformation,^{9a} in analogy with the SCN^- complex. Figure 4 offers an overlaid vision of $\text{H}_2\text{L}2^{2+}$ molecules from SCN^- and PF_6^- complexes. The superposition has been calculated for all the non-hydrogen atoms, except the tetrazine rings. It is evident that the pendant arms in the two structures are almost equal, but the similarity is even greater for ClO_4^- , NO_3^- compounds. Actually the calculated Root Mean Square Deviation is 0.48 Å in the case of PF_6^- and at most 0.2 and 0.1 Å for NO_3^- and ClO_4^- , respectively. The tetrazine rings are never coplanar, dihedral angles ranging from 11.2° for NO_3^- to 21.4° for ClO_4^- . For all these adducts as well as for the SCN^- one, H-bonds involving the protonated morpholine nitrogen atoms and anion- π interactions are recognized.

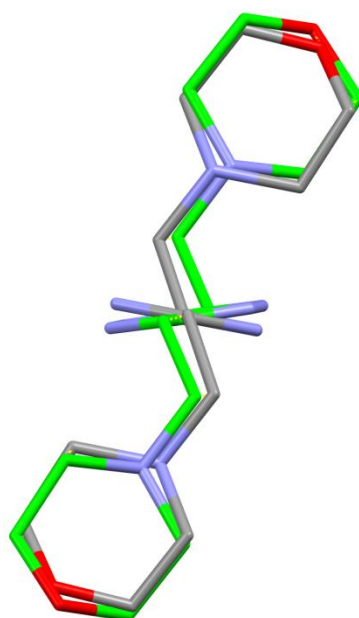


Figure 4. L2 from the SCN^- complex (gray carbons) overlaid on ligand L2 from the PF_6^- complex [9a] (green carbons). Superposition calculated for all the non-hydrogen atoms, except the tetrazine rings.

To our knowledge, no crystal structures of SCN^- complexes with tetrazine ligands have been reported so far, while only two papers containing crystallographic structures includes receptors expressly selected for involving anion- π interactions in the binding of SCN^- [10]. In these papers, both end-on [10a] and side-on [10b] binding modes were found for the thiocyanate anion. In particular, the end-on binding mode is established in the adduct between SCN^- and a V-shaped calix[2]arene[2]triazine molecule, where arene and triazine alternate in the calix ring. In this structure the anion is pinched between the two triazines, respectively interacting with nitrogen and sulfur on opposite sides [10a]. The side-on binding mode is instead found for the adducts formed with tetracyanopyrazine or trinitrobenzene rings. In the two adducts, the SCN^- anion shows different orientations, tetracyanopyrazine and trinitrobenzene interacting with thiocyanate nitrogen and sulfur atoms, respectively [10b]. The tetracyanopyrazine adduct is structurally very similar to our complex, having the projection of the sulfur atom completely outside the ring and the nitrogen in contact with the aromatic ring. Nevertheless, the $\text{N}\cdots$ centroid distances and related offsets seem to indicate weaker interactions than in our complex ($\text{N}\cdots$ centroid distances ranging from 3.3 to 3.5 Å, offsets ranging from 1.2 to 1.4 Å).

As noted above, no crystal structures of SCN^- complexes with tetrazine ligands have been reported, while only three structures are available for triazine complexes of this anion [10a, 22]. In all these structures, SCN^- is involved in concomitant end-on interaction of both N and S atoms with different aromatic rings.

Further information on the SCN^- -L2 interaction was obtained by performing a series of DFT calculations on complexes of SCN^- with the bare tetrazine ring, that is with L2 deprived of the morpholine residues. The calculations performed in a simulated implicit water environment showed that in the most stable adduct the anion forms an end-on anion- π interaction with the electron-deficient ring via the N atom (Figure 5a) characterized by a B_e of 10.04 kJ/mol (here a positive value of B_e indicates a stabilizing interaction). This complex, which also possesses the lowest energy, is characterized by a tetrazine centroid (X)-N atom distance of 3.168 Å; the SCN^- anion is almost parallel to the tetrazine ring as evinced by the X-N-C angle of 93.4° formed by the anion with the N-centroid line. When the SCN^- anion is oriented normal to the tetrazine molecular plane (X-N-C = 180°), the X-N distance (2.962 Å) is slightly shorter than the above value but B_e reduces to 7.11 kJ/mol (Figure 5c). This result indicates that the complex shown in Figure 5c lacks the extra-stabilization due to the π - π interaction that operates in the complex of Figure 5a.

The same trend is observed for the interaction of thiocyanate via the terminal S atom (Figures 5b,d). Interestingly, the parallel complex (Figure 5b) has only a slightly smaller B_e than the complex with the N-interacting anion (Figure 5a), while the X-S distances are always longer than

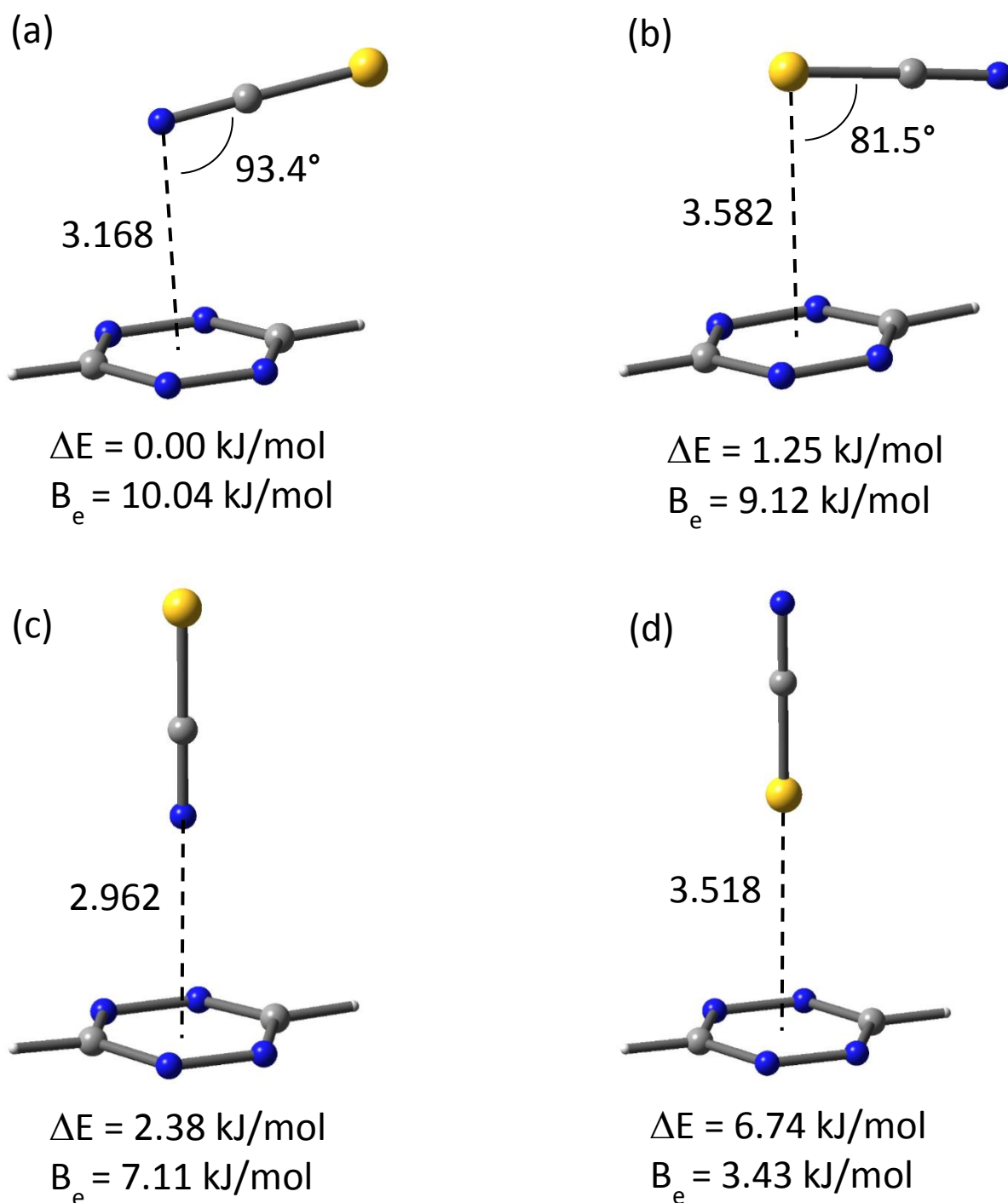


Figure 5. DFT-optimized geometries of four tetrazine-SCN⁻ complexes. Distances are in Å.

3.5 Å. This result appears to be in good agreement with our crystallographic findings, even in the absence of the additional salt-bridge and hydrogen bond contributions present in the crystal structure of H₂L2(SCN)₂. Interestingly, an analysis of the Cambridge Structural Database [23] evidenced that SCN⁻⋯π contacts established by S and N atoms are similarly recurrent, and distances from ring centroids and offsets have comparable mean values. Nevertheless, when the contact

implies nitrogen atoms, the end-on binding mode seems more frequent than the side-on one (Table 2).

Table 2. CSD search results for the thiocyanate $\cdots\pi$ contacts. (hits/obs = number of structure/number of measurements; Δ upper quantile = upper quantile for the difference between the distances from the ring plane of the contact and the carbon atoms; \langle dist \rangle = average contact atom-ring centroid distance; \langle offset \rangle = mean value for the calculated offset of the contact atom).

	N contact atom				S contact atom			
	hits/obs	Δ upper quantile	\langle dist \rangle	\langle offset \rangle	hits/obs	Δ upper quantile	\langle dist \rangle	\langle offset \rangle
Only C atoms in the ring	17/25	0.23	3.7(2)	1.2(7)	21/27	1.52	3.7(2)	1.2(4)
At least one N in the ring	44/57	0.47	3.6(2)	1.3(7)	40/58	1.43	3.7(2)	1.1(6)

Finally, the natural population analysis indicates that there is practically no charge transfer from the anion to the tetrazine ring, the natural charges of the three atoms of free SCN^- anion being almost same as those of the anion in the complexes shown in Figure 5. The negative charge within the (free) SCN^- anion, however, is localized mainly on the terminal atoms with $q(\text{N}) = -0.597e$ and $q(\text{S}) = -0.460e$. The larger magnitude of $q(\text{N})$ thus favours the end-on coordination of SCN^- via the nitrogen atom which results in the formation of a stronger monopole-quadrupole interaction with the tetrazine ring.

DFT and crystallographic results denote an important interplay of salt-bridge, hydrogen bond and anion- π interactions in stabilizing the thiocyanate complex. Nevertheless, salt-bridge interactions seem to have no effect when the complex is formed in aqueous solution. Equilibrium data determined for the formation of SCN^- complexes with neutral L2 and its protonated (charged) forms (HL2^+ , $\text{H}_2\text{L2}^{2+}$) in water furnished association free energies that are almost independent of ligand charge, being 9.5(5), 10.7(5) and 10.8(4) kJ/mol for the formation of $[(\text{L2})\text{SCN}]^-$, $[(\text{HL2})\text{SCN}]$ and $[(\text{H}_2\text{L2})\text{SCN}]^+$, respectively (Table 3). A similar behaviour, although not so marked, was previously observed for the binding of other anions by L2 and the analogous L1 molecule [9], and suggests that anion- π interactions afford a prominent contribution to the stability these complexes in a solvent, such as water, which has a high dielectric constant and is very competitive in the formation of hydrogen bonds. SCN^- ranks among the most hydrophobic anions of the Hofmeister series [1,24]

Table 3. Equilibrium constants and relevant $-\Delta G^\circ$ values for anion complex formation determined at 298.1 ± 0.1 K in 0.1 M Me_4NCl aqueous solution.

	log K	$-\Delta G^\circ$ kJ/mol
$\text{L2} + \text{SCN}^- = [(\text{L2})\text{SCN}]^-$	1.66(8) ^a	9.5(5)
$\text{HL2}^+ + \text{SCN}^- = [(\text{HL2})\text{SCN}]$	1.87(8)	10.7(5)
$\text{H}_2\text{L2}^{2+} + \text{SCN}^- = [(\text{H}_2\text{L2})\text{SCN}]^+$	1.90(7)	10.8 (4)

^a Values in parentheses are standard deviation on the last significant figure.

and, accordingly, its association with the aromatic ligand moiety, resembling a π - π stacking interaction, is not expected to be much hampered by the polar solvent. As a matter of fact, it was previously shown that lowering the dielectric constant of water by addition of ethanol results in a drop of stability of L2 complexes with several anions [9a].

4. Conclusions

Polyfunctional ligands are striking receptors of anions since they take advantage from multiple weak binding forces. In the crystal structure of $\text{H}_2\text{L2}(\text{SCN})_2$, the protonated ligand furnishes a firm anchorage to SCN^- anions via salt-bridge, anion- π and hydrogen bond interactions. The resulting binding mode of SCN^- , resembling a π - π stacking interaction with the tetrazine ring, is apparently determined by the interplay of these forces. Nevertheless, DFT calculations performed in a simulated implicit water environment showed that, even in the absence of other concurring binding forces, anion- π interactions afford enough stabilization for complex formation. In the most stable complex, the SCN^- anion and the tetrazine ring acquire a π - π stacking interaction mode with the N atom of the anion over the aromatic ring as in the crystal structure.

Moreover, thermodynamic data obtained for SCN^- binding with neutral L2 and its protonated forms (HL2^+ , $\text{H}_2\text{L2}^{2+}$) showed that the stability of the resulting complexes is poorly correlated with ligand charge, further suggesting that anion- π interactions give a prominent contribution to the stability of these complexes. This is a peculiarity of L2 (and L1), since salt-bridge and hydrogen bond interactions are known to be of utmost importance in promoting the formation of anion complexes with most of ammonium receptors [24].

Appendix A. Supplementary materials

CCDC 1533369 contains the crystallographic data of the structural analysis. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via the www.ccdc.cam.ac.uk/data_request/cif.

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Footnotes

† This paper is dedicated to Dr. Carlo Mealli.

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