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Anion Recognition in Water, Including Sulfate, by a *bicyclam* Bimetallic Receptor, a Process Governed by the Enthalpy/Entropy Compensatory Relationship

Massimo Boiocchi,[c] Marco Bonizzoni,*[a] Carlo Ciarrocchi,[b] Luigi Fabbrizzi,*[b] Michele Invernici,[b] and Maurizio Licchelli*[b]

Abstract: The dimetallic system $[Cu^{II}_2(L)]^{4+}$ contains two facing equivalent metallocyclam subunits and incorporates ambidentate anions, mono- (halides) and poly-atomic (sulfate), which bridge the two Cu^{II} centres. ITC experiments in water showed that log *K* of the inclusion equilibria for halides and sulfate vary over a restricted interval (3.6 ± 0.2) indicating lack of selectivity and that similarity of $\Delta G°$ values resulted from the unbalanced contribution of the $\Delta H°$ and $T\Delta S$ terms: the more favorable one contribution, the less favorable the other. In particular, a linear dependence between $\Delta H°$ and $T\Delta S°$ was observed (a typical enthalpy/entropy compensatory diagram), which assigned a major role to hydration terms: (i) the more hydrated the anion, the more endothermic the dehydration process; (ii) the larger the number of water molecules released to the solution, the more positive $T\Delta S°$. Limiting cases refer to the complexation (i) of the poorly hydrated iodide (highly exothermic process, entropically disfavored), and (ii) of the highly hydrated sulfate (moderately endothermic process, entropically very favored). Anion receptors operating in water belong to two main domains: 1) those exhibiting positive $\Delta H°$ and positive $T\Delta S°$ (+/+ signature); 2) those displaying the opposite behaviour: (-/-) signature). The receptor here investigated connects the two domains, along the $\Delta H°/T\Delta S°$ straight line, thanks to the hidden role of the versatile metal-anion interaction.

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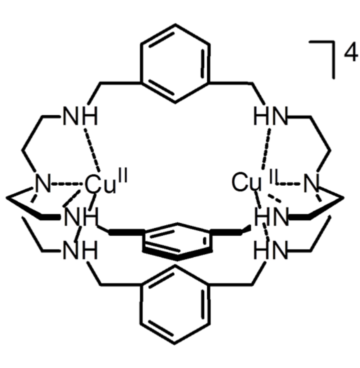
Supporting Information for this article is given via a link at the end of the document

CCDC 1814887-1814888 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre.

Introduction

Anion recognition chemistry originated from pioneering studies carried out in water involving cage shaped receptors, in whose cavities positive charges (from ammonium groups) had been strategically positioned. First receptors included: katapinands by Park and Simmons (containing two tertiary ammonium groups)[1] and bistren cryptands by Lehn (containing six secondary ammonium groups)[2]. A polycyclic and possibly rigid structure of the receptor was chosen in order to minimise the loss of conformational energy experienced by the receptor during anion complex formation. The nature of the interaction was electrostatic and hydrogen bonding (for receptors containing highly polarised and properly oriented N–H fragments). Apparently, such interactions were strong enough to overcome the energy spent for dehydrating the anion and the receptor's cavity.



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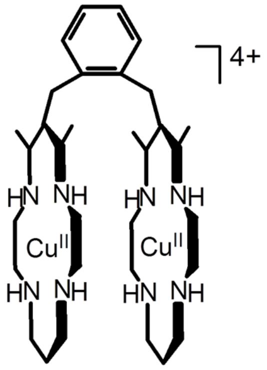

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Later, neutral receptors were considered (amides,[3-5] ureas,[6,7] thioureas,[8,9] pyrroles)[10] capable to donate H-bonds through polarised N–H fragments to the envisaged anion, from which a rich and lively anion coordination chemistry developed, however limited to aprotic solvents of varying polarity (CH_2Cl_2, MeCN, DMSO). A notable exception is represented by cyclopeptides and bis-cyclopeptides by Kubik,[11-13] which are able to bind in water highly hydrated anions such as sulfate, due their extremely preorganised concave arrangement of polarised peptide N–H fragments. More recently, receptors capable to recognize anions in water through the donation of halogen bonds were introduced.[14,15]

As a further possibility, positive charges inside the receptor's cavity can be generated through the inclusion of metal ions.[16] As an example, the bistren complex illustrated by formula **1** contains two coordinatively unsaturated copper(II) ions and it is prone to include an ambidentate polyatomic anion (e.g. N_3^-, HCO_3^-), which goes to bridge the two metal centres.[17,18] A sharp peak selectivity was observed, which was ascribed the more or less favorable matching of the anion bite length (the distance between two consecutive donor atoms) and the intermetallic distance. Noticeably, whereas polyammonium receptors operate at pH $\leq$ 3 in order to maintain all the secondary amine groups protonated, metal containing receptors of type **1** can work at a neutral pH or higher. In any case, metal-ligand interactions are typically more intense than electrostatic/H-bond interactions and afford the formation of more stable receptor/anion complexes.

Metallo-receptor **1** contains a substitutionally labile metal centre (Cu^{II}) and is therefore subject to demetallation in the presence of an excess of anion or under acidic conditions (due to the protonation of the nitrogen atoms). Such an inconvenience can be removed by using metallocyclam subunits: in particular, transition metal ions, when encircled by the 14-membered cyclic tetramine *cyclam*, achieve an extreme inertness towards demetallation even under severe conditions (due to the kinetic macrocyclic effect).[20] If two metallocyclam subunits are appended to an appropriate spacer, like in system **2**, they provide an opening for the inclusion of an ambidentate anion: matching of the anion bite and of the intermetallic distance may generate selectivity. In particular, the *bicyclam* ligand of complex **2** consists of two dimethylcyclam subunits bridged at the carbon centre with an *ortho*-xylyl group, thus providing a face-to-face arrangement of the two macrocycles. Dinickel(II) complexes of bicyclam were investigated in their unique magnetic properties by Ito and coworkers,[21,22] and later, very thoroughly, by Endicott and coworkers.[23] More recently, we have studied the behaviour of the $[Ni^{II}_2(bicyclam)]^{4+}$ complex as an anion receptor in DMSO, with a special reference to the effect of anion inclusion on the Ni^{II}-to-Ni^{III} oxidation processes taking place at the two metal centres.[24]

Here we report a complete thermodynamic investigation on the interaction of the $[Cu^{II}_2(bicyclam)]^{4+}$ receptor with anions *in pure water*. The $Cu^{II}(cyclam)^{2+}$ subunit exhibits a defined tendency to bind further ligands (e.g. anions) in order to achieve five-coordination,[25] a circumstance which should favor anion inclusion inside the intermetallic space of $[Cu^{II}_2(bicyclam)]^{4+}$. Anion binding equilibria have been investigated through Isothermal Titration Calorimetry (ITC), which allowed the determination of association constants (and $\Delta G°$), as well as of enthalpy, $\Delta H°$, and entropy contribution, $T\Delta S°$. It has been shown that the knowledge of these thermodynamic quantities may address the interpretation of the solution stability of the anion complexes in terms of inner effects (receptor-anion bonding, conformational rearrangement of the receptor's framework) and outer effects (release of water molecules to the solution due to anion and receptor dehydration).[26] X-ray diffraction studies on the crystalline complex salts $[Cu^{II}_2(bicyclam)(\mu\text{-}Br)_2]Br_2$ and $[Cu^{II}_2(bicyclam)(\mu_2\text{-}HSO_4)(HSO_4)_2]\cdot HSO_4\cdot EtOH\cdot H_2O$ provided a direct insight on the geometric nature of the receptor-anion adducts.

Results and Discussion

The structure of bromide and hydrogensulfate complexes: X-ray diffraction studies

Design and details on the synthesis of bicyclam and of the $[Cu^{II}_2(bicyclam)](ClO_4)_4$ complex salt are described in the Supporting Information (see Schemes S1 and S2).

The molecular structure of the $[Cu^{II}_2(bicyclam)(Br)_2]^{2+}$ cation present in the $[Cu^{II}_2(bicyclam)(\mu\text{-}Br)_2]Br_2$ crystalline complex salt in shown in Figure 1. A plot showing thermal ellipsoids is drawn in Figure S1 (see Supporting Information).

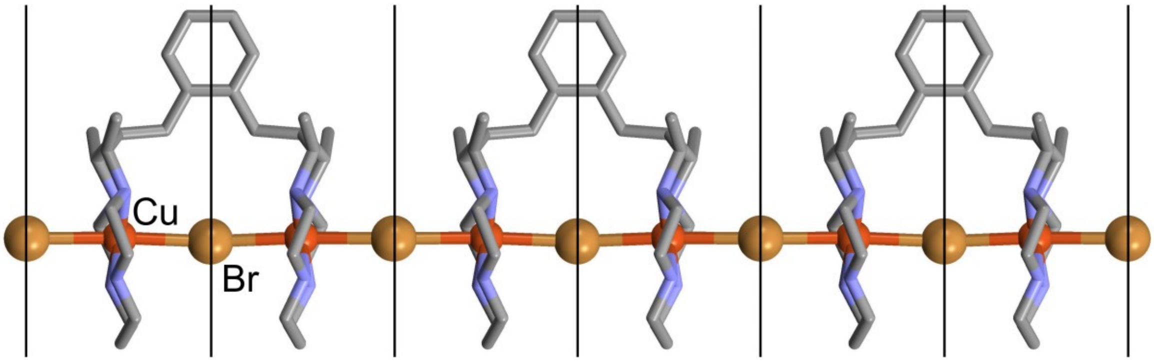

Figure 1. A simplified sketch of the $[Cu^{II}_2(bicyclam)(Br)_2]^{2+}$ molecular cations, which originate molecular chains held together by weak Cu^{II}–Br bond interactions (crystallographic mirror planes normal to the plane of projection of the figure are drawn with solid lines). The Cu^{II}–Br distances are 2.92(1) Å inside the dimer and 2.98(1) Å outside; the $Cu^{II}\cdots Cu^{II}$ distances are 5.83(1) Å inside the dimer and 5.94(1) Å outside.

The crystals of the bromide salt were obtained by slow evaporation of an aqueous solution of $Cu^{II}_2(bicyclam)(ClO_4)_4$ in the presence of an excess of NaBr. The face-to-face bimacrocycle exhibits a perfect C_s molecular symmetry, because a crystallographic mirror plane passes in the middle of the *ortho*-xylyl spacer. The two facing metallocyclam moieties are therefore symmetrically

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equivalent and are arranged in a *trans*-III (*RRSS*) configuration. The two copper(II) centres are slightly displaced from the best plane of the tetramine rings, being positioned at 0.06(1) Å from the equatorial N_4 plane and pointing inside the receptor's cavity. The observed mean Cu^{II}–N distance of 2.03(1) Å corresponds to that expected for a strain-free Cu–N bond in cyclam and cyclam-like macrocycles.[27] The Cu^{II} coordination of each metal centre is completed by two Br^- ions placed in the axial positions of a rather elongated octahedron. Since Cu^{II} ions are displaced towards the inside of the receptors, the two Cu^{II}–Br distances are slightly different: $Cu^{II}–N_{in}$ = 2.92(1) Å, $Cu^{II}–N_{out}$ = 2.98(1) Å. The $Cu^{II}\cdots Cu^{II}$ distance (5.83(1) Å) is comparable to the intermetallic distance observed in the analogous $[Ni^{II}_2(bicyclam)Br_3]^+$ complex, containing a high-spin Ni^{II} (bound to inner Br^-) and a low-spin Ni^{II} (not bound).[23]

In the crystal, both the bromide ions in the inner and outer positions are positioned on two crystallographic mirror planes and bridge the two Cu^{II} metal centres, with almost linear two-fold coordination. The $Cu^{II}–Br^-$ distance, the $Cu^{II}–Br–Cu^{II}$ angle and the $Cu^{II}\cdots Cu^{II}$ separation are 2.92(1) Å, 171.7(1)°, 5.83(1) inside the dimer and 2.98(1) Å, 170.9(1)°, 5.94(1) Å outside. These interactions originate infinite molecular chains of the dimetallic subunits extending along the direction of the **b** crystallographic axis (see Figure 1).

The structure of the $[Cu^{II}_2(bicyclam)(\mu_2\text{-}HSO_4)(HSO_4)_2]^+$ molecular cation present in the $[Cu^{II}_2(bicyclam)(\mu_2\text{-}HSO_4)(HSO_4)_2]HSO_4\cdot EtOH\cdot H_2O$ complex salt is shown in Figure 2. A plot showing thermal ellipsoids is drawn in Figure S2 (see Supporting Information).

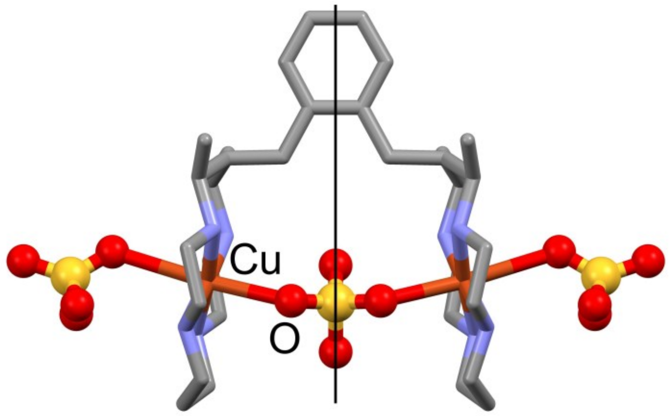


Figure 2. A simplified sketch of the $[Cu^{II}_2(bicyclam)(HSO_4)(HSO_4)_2]^+$ cation (the crystallographic mirror plane normal to the plane of projection of the figure is indicated by a solid line). The Cu^{II}–O distances are 2.38(1) Å inside the dimer and 2.74(1) Å outside; the $Cu^{II}\cdots Cu^{II}$ distance is 6.90(1) Å.

Crystals suitable for X-ray diffraction studies were obtained by slow diffusion of EtOH in an MeCN solution of $Cu^{II}_2(bicyclam)(ClO_4)_4$ containing an excess of $[Bu_4N]HSO_4$. Also in this case, a crystallographic mirror plane makes equivalent the two facing metallocyclam moieties, arranged in a *trans*-III (RRSS) configuration. However, the bimacrocycle assumes a more ordered C_{2v} molecular symmetry. Each metal centre remains slightly displaced from the best plane of the four coordinated amine nitrogen atoms (being placed at 0.08(1) Å over the N_4 plane and pointing inside the dimer), while the observed mean Cu^{II}–N distance of 2.02(1) Å does not significantly differ from the value observed in the bromide containing dicopper(II) complex. A HSO_4^- ion placed inside the cage bridges the two metal centres with two oxygen atoms, forming two equivalent Cu–O coordinate bonds of 2.38(1) Å. Two outer hydrogensulfate ions form longer Cu^{II}–O bonds, completing six-coordination of each Cu^{II} centre, according to an elongated octahedral geometry.

In contrast to what observed in the bromide complex, outer hydrogensulfate ions do not connect directly two metal centres. Connections between adjacent complexes are provided by hydrogen bonding –OH⋯O– interactions established between the –OH group of an HSO_4^- ion (H-donor) and the oxygen atom of an adjacent HSO_4^- ion or of an EtOH solvating molecule (H-acceptors). Further connections are provided by –NH⋯O– hydrogen bonding interactions involving the secondary amine groups of cyclam subunits (H-donor) and the oxygen atoms of adjacent HSO_4^- ions (H-acceptor). A possible H-bond motif, resulting from the assigned positions of hydrogen atoms belonging to hydrogensulfate ions and MeOH molecules, is shown in Figure S3 (see Supporting Information).

Structural data suggest that the $[Cu^{II}_2(\text{bicyclam})]^{4+}$ system is a versatile receptor capable to accomodate in its opening ambidentate anions of varying size and shape, either mono- or poly-atomic. Such a feature seems to be related to the capability of the system to properly orientate, at a low conformational cost, the two metallocyclam subunits. In the case of the bromide complex, the two facing metallocyclam moieties are kept close each other and the C···C interatomic distance between the xylene carbon atoms linked to cyclam (5.91(1) Å) results longer than the $Cu^{II}\cdots Cu^{II}$ intermetallic distance (5.83(1) Å). On the other hand, in presence of hydrogensulfate, the two metallocyclam moieties diverge substantially in the portion not linked by the xylene spacer: as a consequence, the cyclam carbon atoms linked to the *ortho*-xylene spacer remain at an interatomic distances of 5.91(1) Å, whereas the intermetallic $Cu^{II}\cdots Cu^{II}$ distance becomes 6.90(1) Å. Thus, it is the change of the reciprocal orientation of the two metallocyclam subunits that modulates the intermetallic distance and allows the inclusion of coordinating anions of varying bite length. Such a characteristic demonstrates the flexibility of the receptor's framework and is not expected to favour selectivity in anion recognition by $[Cu^{II}_2(\text{bicyclam})]^{4+}$ (bad news).

The nature of the $[Cu^{II}_2(\text{bicyclam})]^{4+}$ receptor in water

In order to elucidate the nature of the $[Cu^{II}_2(\text{bicyclam})]^{4+}$ receptor in water, a solution of $Cu_2(\text{bicyclam})(ClO_4)_4$ was brought to pH 2 by addition of strong acid, then it was titrated potentiometrically with standard NaOH. Titration data (emf of the cell vs. mL NaOH curve, see Figure S4 in Supporting Information) were processed with a non-linear least-squares program. Best fitting of the titration curve was obtained by assuming the occurrence of the two following hydrolytic equilibria (L = bicyclam):

$$[Cu^{II}_2(L)]^{4+} + H_2O \leftrightarrows [Cu^{II}_2(L)OH]^{3+} + H^+ \qquad (1) \qquad pK_{a1} = 9.41(1)$$

$$[Cu^{II}_2(L)OH]^{3+} + H_2O \leftrightarrows [Cu^{II}_2(L)(OH)_2]^{2+} + H^+ \qquad (2) \qquad pK_{a2} = 10.99(1)$$

It is suggested that water molecules undergoing hydrolysis lie in the receptor's cavity and are coordinated to a Cu^{II} centre, as sketched in Figure 3. Outer water molecules complete six-coordination of each metal ion according to an octahedrally distorted coordination geometry.

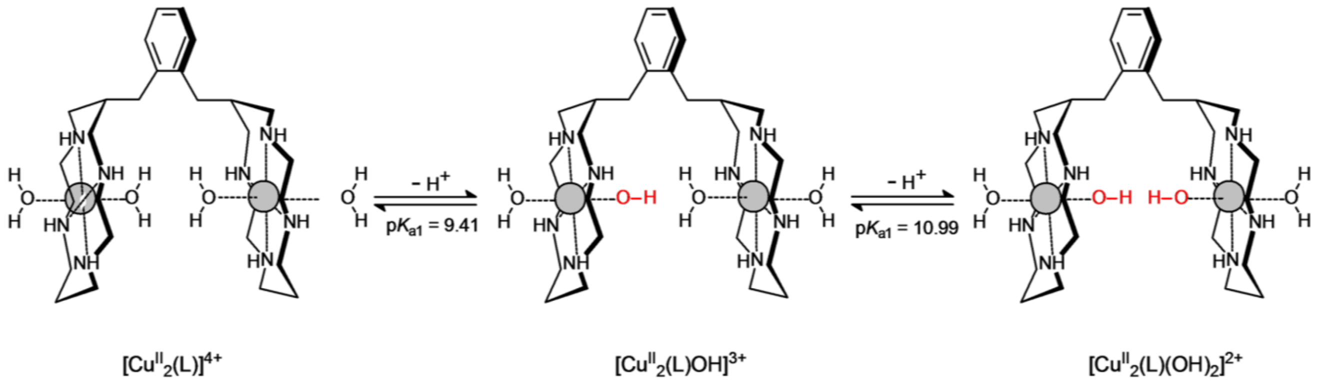


Figure 3. Hypothesised structures of the species $[Cu^{II}_2(L)]^{4+}$, $[Cu^{II}_2(L)OH]^{3+}$ and $[Cu^{II}_2(L)(OH)_2]^{2+}$ present in aqueous solution in the absence of any coordinating anion (L = bicyclam). It is suggested that on base addition protons are released from inner metal coordinated water molecules to give the corresponding mono- and di-hydroxo complexes.

It is assumed that in the di-aquo complex $[Cu^{II}_2(L)]^{4+}$ Cu^{II} ions are displaced from the cyclam plane, pointing towards the cavity, as observed in the bromide and hydrogensulfate inclusion complexes discussed in the previous Section. In these circumstances, a more intense $Cu^{II}–O$ bond is formed, which makes the inner water molecules more acidic, compared to the outer ones. From pK_{a1} and pK_{a2} values, the distribution diagram shown in Figure 4 was drawn.

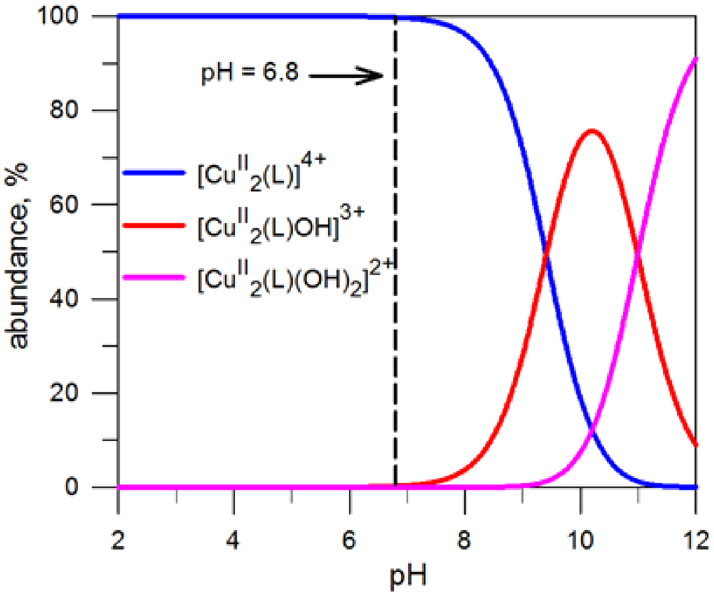


Figure 4. Distribution diagram of the species at the equilibrium for a solution 5 ×10^{-3} M in $[Cu^{II}_2(L)]^{4+}$ (L = bicyclam) over the 2–12 pH range. Species correspond to those illustrated in Figure 3.

It is observed that at neutral pH the complex $[Cu^{II}_2(bicyclam)]^{4+}$ predominates. In particular, 6.8 is the highest pH at which $[Cu^{II}_2(bicyclam)]^{4+}$ is present at 100%.

ITC studies on the $[Cu^{II}_2(bicyclam)]^{4+}$/anion association equilibria in water

The interaction of anions with $[Cu^{II}_2(bicyclam)]^{4+}$ was investigated by Isothermal Titration Calorimetry (ITC). In a typical experiment, a solution 5 ×10^{-3} M in $[Cu^{II}_2(bicyclam)]^{4+}$ and 5 ×10^{-2} M in the HEPES buffer (pH = 6.8, the highest pH at which complex $[Cu^{II}_2(bicyclam)]^{4+}$ is present at 100%) was titrated by a solution of the investigated anion, dissolved as a sodium salt (NaCl, NaBr, $[Bu_4N]I$I, NaN_3, NaNCO, NaNCS, Na_2SO_4). Thermograms and the ITC profiles of titration experiments are shown in Figures S5 and S6 (see Supporting Information). Best fitting of the titration data was obtained by assuming the occurrence of one equilibrium, corresponding to the formation of a 1:1 complex, e.g.

$$[Cu^{II}_2(bicyclam)]^{4+} + X^- \leftrightarrows [Cu^{II}_2(bicyclam)X]^{3+} \quad (3)$$

It is suggested that the X^- anion replaces the two inner water molecules, bridging the two metal centres, as observed in the solid complex salts. However, in aqueous solution anions cannot compete with water molecules, present in an overwhelming excess, for the two outer coordination site. Thus, the 1:1 receptor/anion complex should be correctly described by the formula $[Cu^{II}_2(bicyclam)(X_{in})(H_2O_{out})_2]^{3+}$, in which each Cu^{II} ion experiences an octahedrally distorted coordination geometry.

Table 1 reports the thermodynamic quantities (log K, $\Delta G°$, $\Delta H°$, $T\Delta S°$) at 25°C associated to equilibria of type (3) and obtained by fitting of pertinent titrations curves.

Table 1. Thermodynamic quantities for the equilibrium: $[Cu^{II}_2(bicyclam)]^{4+} + Cl^- \leftrightarrows [Cu^{II}_2(bicyclam)Cl]^{3+}$ in an aqueous solution buffered to pH = 6.8, 25 °C. Standard deviations in parentheses.

anion	log K	ΔG°, kcal mol^{-1}	ΔH°, kcal mol^{-1}	TΔS°, kcal mol^{-1}
Cl^-	3.15(2)	– 4.30(8)	– 0.79(1)	3.5(1)
Br^-	3.14(1)	– 4.28(4)	– 3.05(6)	1.8(1)
I^-	3.41(2)	– 4.65(4)	– 5.66(2)	–1.0 (1)
N_3^-	2.88(1)	– 3.93(4)	– 2.55(5)	1.9(1)
NCO^-	2.30(1)	– 3.14(4)	– 1.28(3)	1.8 (1)
NCS^-	2.33(9)	– 3.2(4)	– 0.62(9)	2.6(1)
SO_4^{2-}	3.10(1)	– 4.23(4)	1.53(9)	5.8(1)

For a visual understanding, ΔG°, ΔH° and TΔS° values of Table 1 are plotted in Figure 6a as a bar diagram.

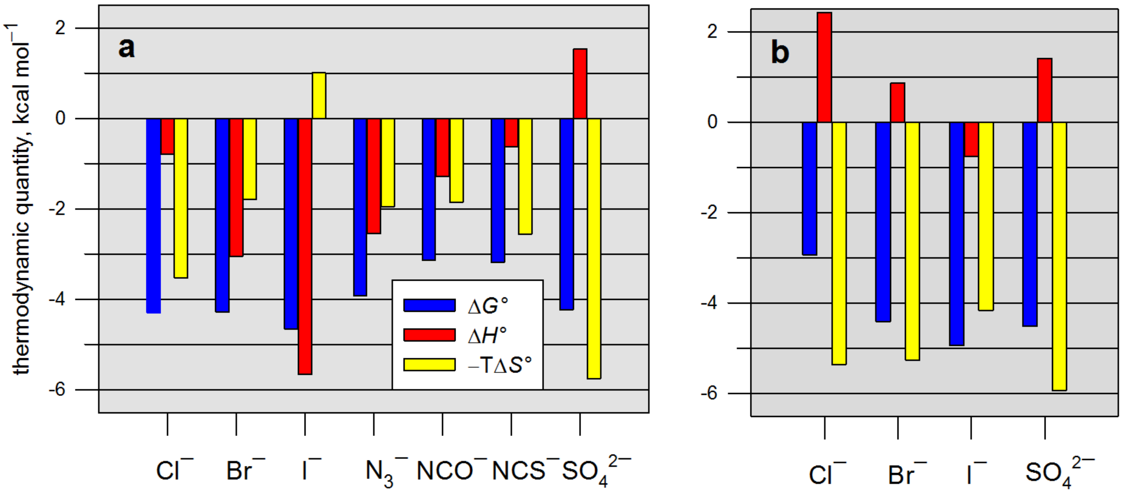


Figure 6. Bar diagram of the thermodynamic quantities referring to anion complex formation with: (a) receptor $[Cu^{II}_2(bicyclam)]^{4+}$ (data from Table 1); (b) bis(cyclopeptide) receptor **8** (data from ref. 42).

Inspection of thermodynamic quantities indicates that similarity of ΔG° values (= RTln K) results from the combination of very different and sometimes contrasting ΔH° and TΔS° contributions. For instance, complexation of iodide is highly exothermic (ΔH° = –5.7 kcal mol^{-1}) and entropically disfavored (TΔS° = –1.5 kcal mol^{-1}), whereas complexation of sulfate is moderately endothermic (ΔH° = 1.5 kcal mol^{-1}) and characterised by an extremely favorable entropy term (TΔS° = 5.8 kcal mol^{-1}). In the middle, progressive decrease of exothermicity and concomitant increase of TΔS° are observed. Moreover, on plotting TΔS° vs. ΔH° a straight line is obtained, with a positive slope (see Figure 7), an example of enthalpy/entropy compensation relationship.

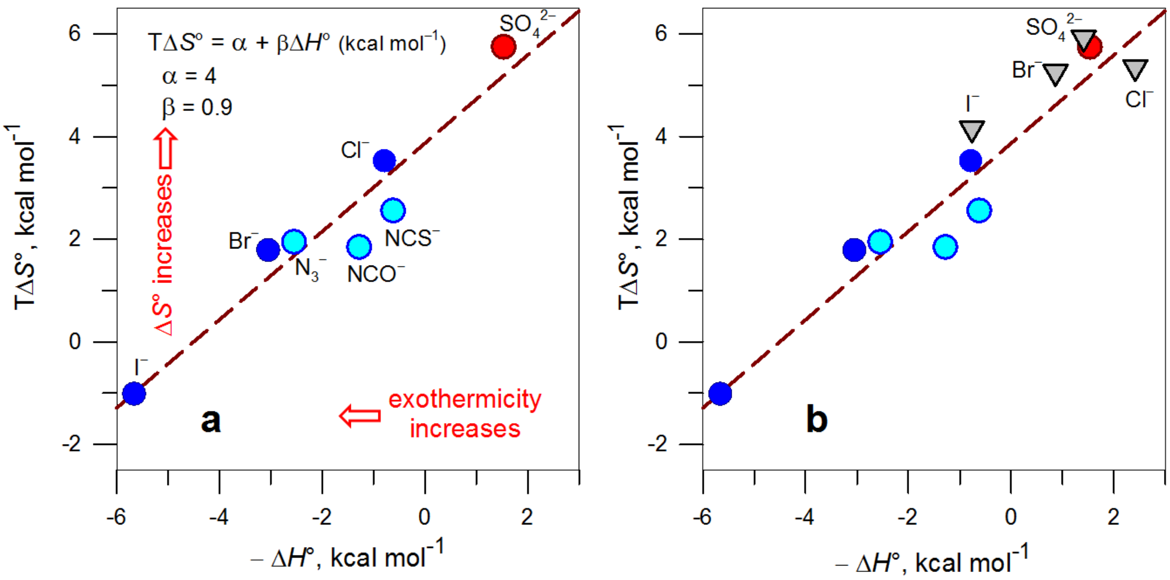


Figure 7. (a) Enthalpy /entropy compensation diagram for anion complexation by $[Cu^{II}_2(bicyclam)]^{4+}$ (colour symbols) and corresponding regression line (dashed); (b) the same diagram as in (a), with added symbols (grey triangles), which refer to halide and sulfate complexation by the bis(cyclopeptide) **3**.[28]

The compensatory enthalpy/entropy relationship has often been observed empirically for thermodynamic quantities determined for a large variety of equilibria, including recognition.[29,30] The slope β of the $T\Delta S$ vs. $\Delta H°$ plot indicates to what extent the enthalpic gain induced by complexation is canceled by the accompanying entropic loss. In other words, only a fraction (1 − β) of the enthalpic gain can contribute to the enhancement of complex stability.[29] According to the regression straight line for anion complexation by $[Cu^{II}_2(bicyclam)]^{4+}$ in Figure 7, such a fraction corresponds to (1.0 – 0.9) = 0.1 (10%). It should be noted at this stage that $\Delta H°$ is comprehensive of several hidden contributions, either endo- or exo-thermic. Endothermic contributions derive from the following processes: dehydration of the anion, dehydration of the receptor (associated to the removal of the two inner metal-bound water molecules), conformational rearrangement of the receptor's framework to adjust the intermetallic distance to the anion's bite length (achieved through a modification of the orientation of the two metallocyclam subunits). Exothermic contributions are related to the hydration of the complex (probably not relevant) and to the establishing of the coordinative interactions $Cu^{II}–X–Cu^{II}$. Major and contrasting contributions are the anion dehydration enthalpy and the coordinative bond enthalpy.

For halides the intensity of the metal ligand interactions, expressed for instance by Dq values of Crystal Field Theory, decreases along the series: $Cl^- > Br^- > I^-$. Noticeably, complexation exothermicity $\Delta H°$ follows the reverse direction: $I^- > Br^- > Cl^-$, which may suggest that the dehydration term prevails over coordinate bonding enthalpy. In particular, $\Delta H°$ values of anion complexation shown an *inverse* linear relationship with anion hydration enthalpies ($\Delta H°_{hydr\text{-}X^-}$),[31] i.e. the enthalpy changes associated to the process: $X^-_{(gas)} + \infty H_2O \rightarrow X^-_{(aq)}$ (see Figure 8, red symbols and red regression line).

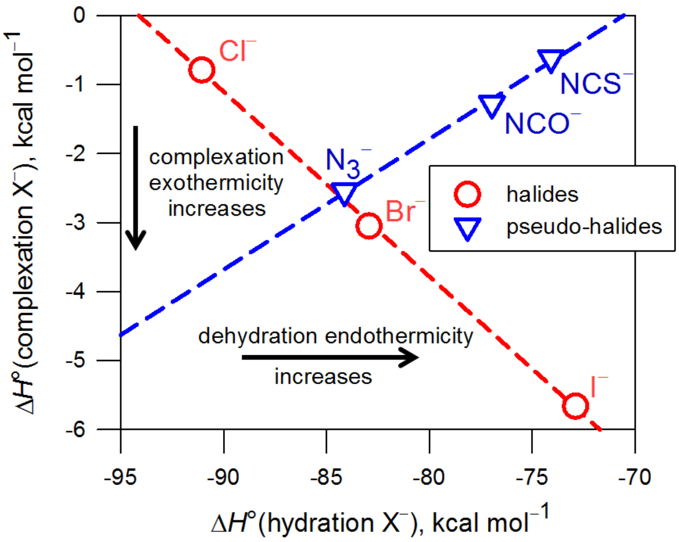


Figure 8. Plot of the complexation enthalpies ($\Delta H°$) in Table 1 vs. the anion hydration enthalpies ($\Delta H°_{hydr\text{-}X^-}$),41 i.e the enthalpy changes associated to the process: $X^-_{(gas)} + \infty H_2O \rightarrow X^-_{(aq)}$.

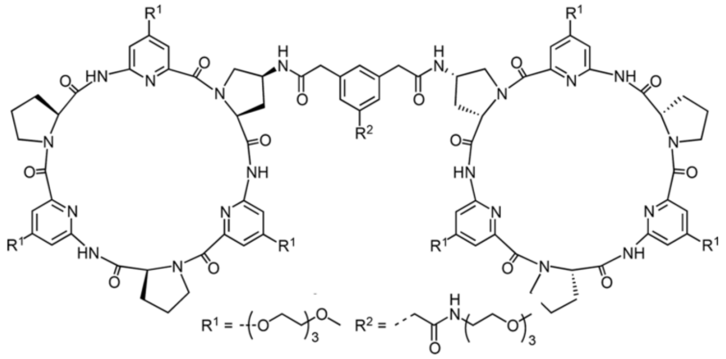
The less endothermic the anion dehydration, the less endothermic the anion complexation. In particular, iodide is enthalpically favored in complex formation because it is less hydrated than other halides and suffers to a lesser extent from dehydration. Thus, the enthalpy of formation of the Cu^{II}–I–Cu^{II} bonds prevails over the dehydration term and complexation is exothermic.

Pseudohalides display a completely different behaviour: first, the complexation exothermicity follows the spectrochemical series (N_3^- > NCO^- > NCS^-); second, $\Delta H°$ shows a *direct* linear dependence upon hydration enthalpy $\Delta H°_{hydr\text{-}X^-}$ (blue triangles and blue dashed line in Figure 8): the more endothermic the anion dehydration, the more exothermic the anion complexation. These two features suggest that the enthalpy change associated to the metal-anion interaction ($\Delta H°_{M\text{–}X}$) plays a prominent role with respect to the hydration term $\Delta H°_{hydr\text{-}X^-}$. This may be due to the fact that each pseudohalide anion offers two distinct donor atoms for coordination, thus allowing the formation of more intense coordinative interactions and reinforcing $\Delta H°_{M\text{–}X}$.

The compensatory effect illustrated in Figure 7 seems therefore essentially related to the anion solvational effects: the enthalpically disfavored anion dehydration is compensated by the increase in translational entropy associated to the release of water molecules to the solution. Indeed, receptor arrangement requires that the anion release all hydration molecules before to take refuge into the bicyclam's cavity and to bridge the two Cu^{II} centres. In any case, the more endothermic the anion dehydration, the more favorable the entropy contribution. Notice that the intercept α of the $T\Delta S°$ vs $\Delta H°$ regression line in Figure 7 corresponds to a complex process which is only entropically driven ($\Delta H° = 0$, $\Delta G° = -T\Delta S° = 4$ kcal mol^{-1}). Of the anions investigated here, only sulfate exhibits a $\Delta H° > 0$, which is more than compensated by an extremely favorable entropy contribution $T\Delta S°$ (5.8 kcal mol^{-1}). Sulfate, due to the double negative charge and to the symmetrical positions of its four oxygen atoms (each formally detaining ½ negative charge) is highly hydrated, from which an extremely large hydration enthalpy derives ($\Delta H°_{hydr\text{-}X^-} = -253$ kcal mol^{-1}), which can be hardly compensated by the $\Delta H°_{M\text{–}X}$ term. The X-ray structure previously described refers to the $[Cu^{II}_2(bicyclam)(HSO_4)]^{3+}$ complex, which contains a bridging hydrogensulfate. However, it seems reasonable to assume that SO_4^{2-} occupies, like HSO_4^-, the receptor'cavity and bridges with two oxygen atoms the two Cu^{II} centres. Inclusion between the two facing metallocyclam subunits completely undresses the anion from water molecules, to which a large increase of translational entropy corresponds. On the other hand, sulfate, like oxoanions in general, exerts relatively weak metal-ligand interactions, which cannot contrast the pronounced endothermicity of the H-bond breaking process of anion dehydration.

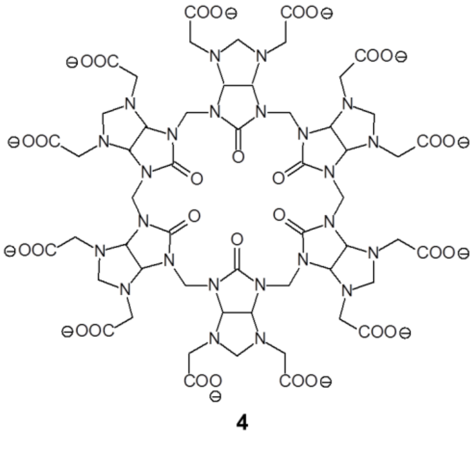
The enthalpy/entropy compensation relationship extended to varying anion receptors in water

Recognition of sulfate is attracting the attention of researchers in view of the dianion importance in biology,[32] and in the environment,[33] including treatment of nuclear waste.[34] One of the most stable aqueous sulfate complexes, whose formation has been thoroughly investigated from a thermodynamic point of view, involves the Kubik's bis(cyclopeptide) neutral receptor **3**.[28] Thermodynamic quantities for the inclusion of sulfate and halides by **3** in water are illustrated by the bar diagram in Figure 6b.



3

The sulfate complex of the bis(cyclopeptide) receptor is a bit more stable than the corresponding complex of $[\mathrm{Cu^{II}}_2(\mathrm{bicyclam})]^{4+}$ (log K = 3.30 and 3.15, respectively). For both systems, the relatively high solution stability results from a remarkably positive $T\Delta S°$ term, that overcomes a moderately unfavorable enthalpy term (endothermic processes). Moreover, bar diagram in Figure 6b shows that halide complexation by the bis(cyclopeptide) receptor **3** is in any case entropically very favored, whereas the enthalpy term is unfavorable (chloride and bromide) or moderately favorable (iodide). Noticeably, bis(cyclopeptide) complexes roughly obey the enthalpy/entropy compensatory relationship (see Figure 7b), even if they span a narrower range than $[\mathrm{Cu^{II}}_2(\mathrm{bicyclam})]^{4+}$ complexes. In any case, dehydration processes play a significant role. In particular, each cyclopeptide ring of the uncomplexed receptor **3** may contain an $(H_2O)_3$ trimer tightly bound to three N–H peptide fragments, for a total of six H-bonds (such an arrangement has been observed in the monocyclic derivative).[13] On anion inclusion, these six bonds are broken and replaced by the six bonds established on anion complexation, whose energy is expected to decrease with the H-bond acceptor properties of the anion decreasing along the series: Cl^- > Br^- > I^-. In any case, bonding exothermicity is overcome by the highly endothermic anion dehydration. Only the poorly hydrated iodide gives an exothermic complexation. The entropy term is in all cases favorable due to the large release of water molecules (from the anion and from the cyclopeptide rings).



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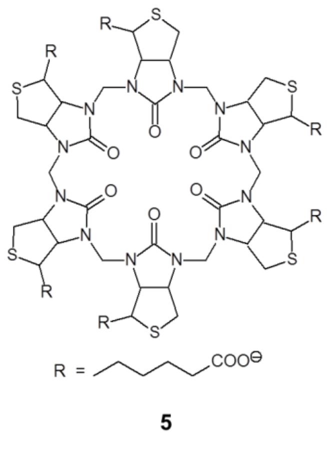

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At this stage, we wanted to briefly consider the behaviour of other families of aqueous anion receptors with respect to the enthalpy/entropy compensatory plot (see Figure 9). In particular, diagram includes ΔH° and $T\Delta S^\circ$ values for complexes of bambus[6]uril (**4**)[35] and biotin[6]uril (**5**)[36,37] with halides (comparison was limited to these anions for reasons of homogeneity). Halide complexation by the two macrocyclic receptors is characterised by a largely negative ΔH° (high exothermicity) and by a negative $T\Delta S^\circ$.

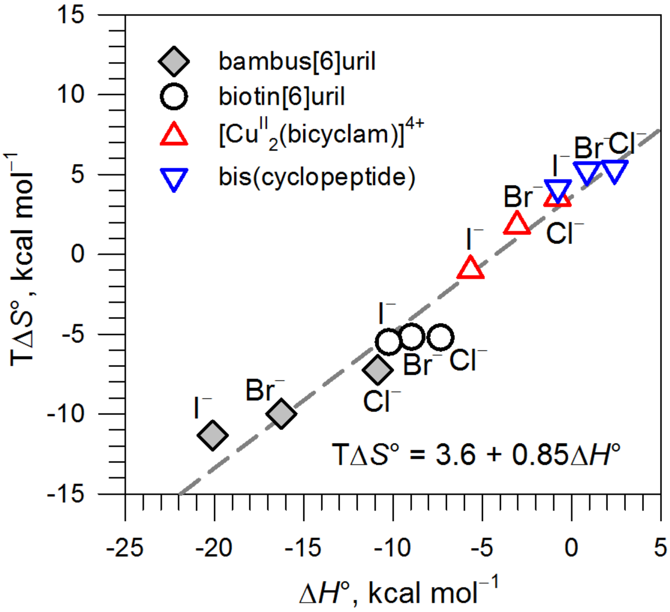

Figure 9. Enthalpy/entropy compensation diagram for halide complex formation in water with receptors: bambus[6]uril (**4**),[35] biotin[6]uril (**5**),[36] [Cu$^{II}_2$(bicyclam)]$^{4+}$ (**2**), bis(cyclopeptide (**3**).[28]

The two macrocycles bambus[6]uril and biotin[6]uril offer a shelter in which the anion receive twelve $C–H\cdots X^-$ hydrogen bonds from the polarised $–CH_2–$ groups linking the nitrogen atoms of two adjacent heterocycles, which accounts for complexation exothermicity. It may be surprising that dehydration of the included anion does not result in a strongly positive entropy term. However, it has been pointed out that, since the solution contains a 0.1 M phosphate buffer, it is possible that $H_2PO_4^-/HPO_4^{2-}$ occupies the receptor'cavity prior to X^- complexation:[35] thus, the release of water molecules by incoming X^- is compensated by the uptake of water molecules from the solution by the extruded phosphate. Quite surprisingly, if one considers the very different nature of the four receptors, all halide complexes satisfactorily obey the $\Delta H^\circ/T\Delta S^\circ$ relationship. While more data are needed before to draw sound conclusions and to formulate convincing interpretations, it seems quite reasonable to hypothesise that the common behaviour must be in some way related to solvational terms, a contribute especially relevant in water. In any case, the diagram in Figure 9 clearly defines the domains of the thermodynamic signatures of anion complex formation in water: (negative ΔH° and negativeΔS°: –/–) for bambus[6]uril and biotin[6]uril; (+/+) for bis(cyclopeptide), excepting iodide; a mixed combination, (–/+) and (+/–) for [Cu$^{II}_2$(bicyclam)]$^{4+}$.

Conclusions

Confident in the strength of the metal-ligand interactions, we looked to a metal containing receptor capable to recognise anions in water and we chose the water soluble dicopper(II) bicyclam complex **2**. We expected that selectivity could arise from a geometrical factor, i.e. from the matching of the distance between the interaction sites (the two metal centres) with the bite length of the included ambidentate anion, either mono- or poly-atomic. Discouraging news came from X-ray diffraction studies on single crystals of the two complex salts [Cu$^{II}_2$(bicyclam)(μ_2-Br)$_2$]Br$_2$ and [Cu$^{II}_2$(bicyclam)(μ_2-HSO$_4$)(HSO$_4$)$_2$]·HSO$_4$·EtOH·H$_2$O. In particular, it was observed that the cavity constituted by the two facing metallocyclam subunits was able to include both the monoatomic bromide and the polyatomic hydrogensulfate, and that the intermetallic distance could be

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modulated by adjusting the reciprocal orientations of the two metallocyclam subunits, probably with a moderate conformational energy cost.

Indeed, equilibrium studies in water showed lack of selectivity, as log *K* values for complexation of halides and sulfate in water varied over the 3.2 ± 0.2 range. Pseudohalides formed less stable complexes, again in the absence of a marked selectivity ($2.3 \leq \log K \leq 2.9$). However, examination of enthalpy and entropy terms showed that similarity of $\Delta G°$ values resulted from the rather unbalanced and sometimes contrasting contributions of the $\Delta H°$ term and the $T\Delta S°$ term. In particular, a linear dependence between $\Delta H°$ and $T\Delta S°$ was observed (a typical compensation diagram), which assigned a major role to hydration terms: the more hydrated the anion, the more endothermic the dehydration process (the more positive $\Delta H°$); the larger the number of water molecules released to the solution, the more positive $T\Delta S°$. Limiting cases refer to the complexation (i) of the poorly hydrated iodide (very exothermic process, entropically disfavored), and (ii) of the highly hydrated sulfate (endothermic process, entropically very favored).

Anion receptors operating in water are currently divided in two main domains, each showing its personal signature: 1) those whose complexation is endothermic, but characterised by a favorable entropy change (positive $\Delta H°$ and positive $T\Delta S°$, signature +/+); those displaying the opposite thermodynamic behaviour: (negative $\Delta H°$ and negative $T\Delta S°$, signature –/–). The dimetallic bicyclam receptor here investigated presents multiple signatures (–/–; –/+; +/–) and connects the two domains. Such a versatility may depend upon the particular nature of the coordinative bond, whose energy ($\Delta H°_{M-X}$) varies over a range of several tens of kcal mol^{-1}.

Experimental Section

Synthesis of bicyclam and of its dicopper(II) complex.

[Cu^{II}_2(bicyclam)]$(ClO_4)_4$ was prepared through 3 steps: (i) synthesis of the [Ni^{II}_2(bicyclam)]$(ClO_4)_4$ complex salt; (ii) demetalation with cyanide of [Ni^{II}_2(bicyclam)]$(ClO_4)_4$ to obtain the free ligand bicyclam; (iii) metalation of bicyclam with $Cu(ClO_4)_2 \cdot 6H_2O$ to give [Cu^{II}_2(bicyclam)]$(ClO_4)_4$. Details on the syntheses and characterization are reported in the Supporting Information.

Isothermal titration calorimetry (ITC) experiments.

ITC titrations were performed by using a Nano ITC Low Volume isothermal titration calorimeter (from TA Instruments). All titrations were performed at 25 °C, using solutions buffered to pH = 6.8 with HEPES 0.05 M. In particular, a solution of the sodium salt of the envisaged anion was added stepwise to a solution of [Cu^{II}_2(bicyclam)]$(ClO_4)_4$, placed in the sample cell. The thermodynamic quantities (*K*, $\Delta H°$, and $\Delta S°$), as well as the interaction stoichiometry, were determined by a fitting procedure using the software AFFINImeter.[38] Blank titrations were performed and subtracted from the corresponding titrations to remove the effect of dilution.

Potentiometric titrations

Potentiometric titrations were performed at 25° C by using a carbonate-free NaOH solution as a titrant, under a nitrogen atmosphere. In a typical experiment, a 5×10^{-4} M solution of [Cu^{II}_2(bicyclam)]$(ClO_4)_4$ (15mL), made acidic (pH = 2) with standard HNO_3, was titrated with standard NaOH. Titration was run by addition of 10 µL portions of a standard 0.1 M solution of NaOH and 165 points were collected. Prior to the potentiometric titration, the standard electrochemical potential (E^*) of the glass electrode was determined in pure water, by a titration experiment according to the Gran method.[39] On curve fitting of titration data (emf vs. mL of NaOH curve, see Figure S4 in Supporting Information) by using a non-linear least-squares procedure,[40] pK_{a1} and pK_{a2} values were determined.

X-ray Crystallographic Studies

Diffraction data for [Cu^{II}_2(bicyclam)(μ-Br)$_2$]Br_2 (violet, prismatic, 0.07 x 0.07 x 0.15 mm^3) and for [Cu^{II}_2(bicyclam)(μ-HSO_4)(HSO_4)$_2$]HSO_4 · EtOH · H_2O (pale red, lamellar, 0.02 x 0.32 x 0.50 mm^3) crystals have been collected by means of a Bruker-Axs CCD-based three circle diffractometer, working at ambient temperature with graphite-monochromatised Mo K*α* X-radiation (λ = 0.7107 Å). Crystal data are reported in Table S1 in Supporting Information. Data reductions were performed with the *SAINT* software,[41] and intensities were corrected for Lorentz and polarization effects. Absorption effects were empirically evaluated by the *SADABS* software,[42] and absorption corrections were applied to the data. Crystal structures were solved by direct methods (*SIR 97*)[43] and refined by full-matrix least-square procedures on F^2 using all reflections (*SHELXL 2014/7*).[44] Further details are reported in the Supporting Information.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anion recognition • receptors • macrocycles • enthalpy/entropy compensation • supramolecular chemistry

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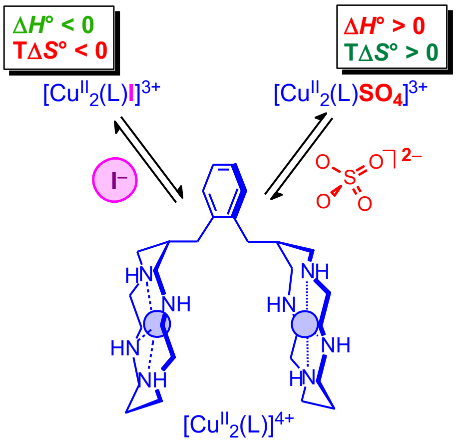
FULL PAPER

Selectivity is no longer a molecular property: the dicopper((II) bicyclam receptor $[Cu^{II}_2(L)]^{4+}$ includes in water ambidentate anions (halides, sulfate) with a poor selectivity, which derives from conflicting enthalpy and entropy contributions: the more favourable the one, the less favourable the other. This points toward the major role of solvational terms (mainly anion dehydration), which mitigate the contribution of the metal-anion coordinative interaction.



Massimo Boiocchi, Marco Bonizzoni,, Carlo Ciarrocchi, Luigi Fabbrizzi,*, Michele Invernici, and Maurizio Licchelli**

Anion Recognition in Water, Including Sulfate, by a *bicyclam* Bimetallic Receptor, a Process Governed by the Enthalpy/Entropy Compensatory Relationship