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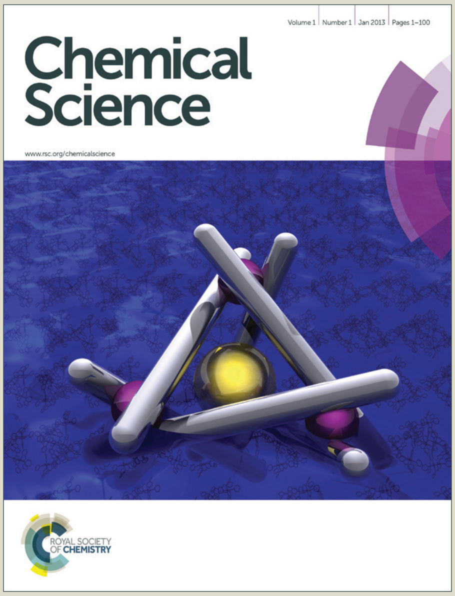

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Selective recognition of fluoride anion in water by a copper(II) center embedded in a hydrophobic cavity

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The ability of a water-soluble pentacationic calix[6]arene-based Cu^{II} complex to bind anions in water has been explored. Quite remarkably, the complex exhibits strong and selective fluoride binding in the [6-7] pH range. The binding constant at pH 5.9 was evaluated to be 85000, which is one of the highest values ever reported for a fluoride probe in water and at this pH. The complex also binds chloride ion, but it is bound 1000 times less efficiently. Combining the calix[6]arene hydrophobic cavity with the Cu^{II} complex, presenting its labile site in endo position, is cause for the selective recognition process. The single crystal X-ray structure of the organo-soluble parent complex revealed a strong interaction between the coordinated fluoride anion and a hosted $CHCl_3$ solvent molecule. Molecular modeling applying aqueous environment suggests that a water cluster, $[F\cdot H_2O\cdot H_2O]^-$, is the species recognized by the host, which provides an appropriate environment for the stabilization of such a hydrated fluoride guest/species.

Introduction

Anion recognition and complexation by hosting molecules is an active field of research in supramolecular chemistry, as witnessed by the intense activity of reviewing the subject in the last years.[1] Indeed, the design of anion receptors is particularly challenging: anions are larger than isoelectronic cations,[2] which leads to less effective electrostatic binding interactions; they may be sensitive to pH values, becoming protonated at low pH; hydroxylic solvents can strongly solvate anions through multiple hydrogen bonds. The major tools for building an anion receptor are charge-charge interactions, H-bonding, coordination bonds to metal ions and hydrophobic effect. Whereas anion recognition is relatively mastered in organic solvents, major difficulties arise in water, due to strong competition with the solvent. In particular, binding highly solvated anions such as fluoride and sulfate (the more hydrophilic anions of the Hofmeister series)[3] in water is a challenge *per se* as reflected by the small number of systems that have been reported in the literature. Fluoride recognition by synthetic hosts has been receiving a particular interest not only because of the scientific challenge, but also for societal reasons.[4] While a low concentration of fluoride in human diet has beneficial health effects, particularly in dental care, it seems to be toxic at high doses and it has been related to several human pathologies (osteosarcoma, neurological dysfunctions etc.). Hence, despite the interest in fluoride recognition in water, only few cases where the binding can be achieved in this medium have been reported in the literature. This recognition process was actually achieved either with polyprotonated azacryptands in acidic media[5a-e] or by coordinatively unsaturated rare earth[5g-j] or uranyl[5k] metal complexes, with one example employing a foldameric structure[5f] and only two examples employing copper center(s). [5a] Existence of few examples in the literature is probably due to the peculiar properties of this anionic species. Indeed, its high hydration energy ($\Delta_r G°_{hyd}$ = -429 kJ mol^{-1}),[6] makes its recognition process energetically highly demanding for a host, and as a hard base, it is difficult to distinguish from water.

Inspired by Nature, we have been developing a set of biomimetic systems associating a binding site for a metal ion to a hydrophobic cavity. Our recent efforts have aimed at synthesizing water-soluble "cavity-complexes". Our first example was obtained with calix[6]arenes functionalized at the small rim by three imidazole groups providing a tridentate coordination core, and at its large rim by hydrophilic substituents to insure water-solubilty. First studies showed that the calix[6]arene-based tris(imidazole) core was able to stabilize and protect a potentially reactive metal center (Cu^I), while maintaining a coordination site open to exogenous ligand binding. [7] We also described a Zn^{II} complex that can selectively host hydrophobic primary amines in water thanks to the embedment of the amino-guest inside the cone of the calixarene.[8] More recently, we succeeded in obtaining an open-shell copper complex that is stable in water in its both oxidation states, Cu^I and Cu^{II}. The latter complexes are based on a calix[6]arene core covalently capped at its small rim by a TMPA unit that allows strong binding of one isolated copper ion at the bottom of the conic hydrophobic cavity [see Fig. 1, calix-ligands **1** and **2**$(NO_3)_3$; TMPA: tris(2-pyridylmethyl)amine].[9] The water-solubility of the system is insured by the presence of three quaternary ammonium substituents implemented at the calix large rim.

These mononuclear copper complexes [Cu$^{II/I}$**2**]$^{5/4+}$ have an unsaturated coordination site available for exogenous ligand binding, and directed toward the cavity: the binding site is located in a protected microenvironment, shielded from the aqueous solvent by the calix[6]arene moiety. In this paper, we report the capacity of the Cu^{II} complex of **2**$(NO_3)_3$ to bind the highly hydrophilic fluoride anion in water, highlighting the importance of surrounding the binding site by a hydrophobic cavity in the recognition process.

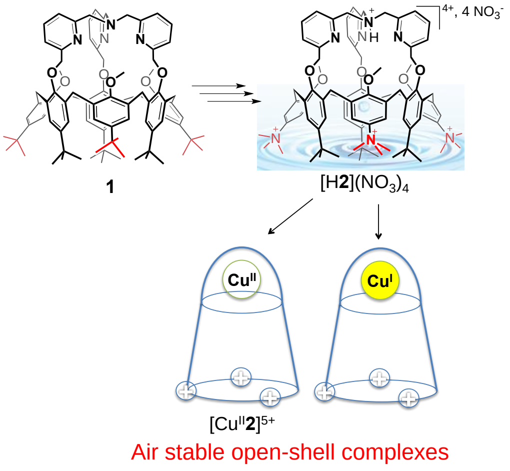


Fig. 1 Open-shell Cu^{I}/Cu^{II} funnel complexes of ligand [H**2**]$(NO_3)_4$, a water-soluble version of **1**.

Complexation of fluoride anion by complex [Cu^{II}2]$^{5+}$ in water

Compound [H**2**]$(NO_3)_4$ and complex [Cu^{II}**2**]$(NO_3)_5$[10] were prepared according to the procedure reported in the literature.[9] The interaction of [Cu^{II}**2**]$^{5+}$ with anions was investigated in buffered water by UV-Vis spectroscopy by measuring absorption bands due to *d-d* transitions. Previous studies on [Cu^{II}**2**]$^{5+}$ showed that the molecule of water coordinated to the copper center has a pK_a value of 6.7. Therefore, we conducted the studies in a slightly acidic medium (pH = 5.9), using a MES [2-(*N*-morpholino)ethanesulfonic acid]/KOH) buffer, in order to have the aqua species predominant in solution.[11] In a preliminary study, we noticed that the affinity of the aqua complex for the fluoride anion was very high. In order to measure the binding constant accurately, we evaluated this affinity through competition experiments with the chloro complex. Hence, we looked first at the coordination of chloride in water. To an aqueous buffered solution (pH = 5.9, [MES] = 30 mM) of [Cu^{II}**2**]$^{5+}$, progressive addition of NaCl up to 70 equivalents resulted in spectral changes of the *d-d* absorptions displayed in Fig. 2A. The resulting new species shows two absorption bands with maxima at 742 and 974 nm (ε = 107 and 120 M^{-1} cm^{-1}, respectively). These values are in agreement with the formation of complex [Cu^{II}(Cl)**2**]$^{4+}$, in which the chloride anion is coordinated to the metal center, since comparable values were obtained for [Cu^{II}(Cl)**1**]$^{+}$ in organic solvent.[12]

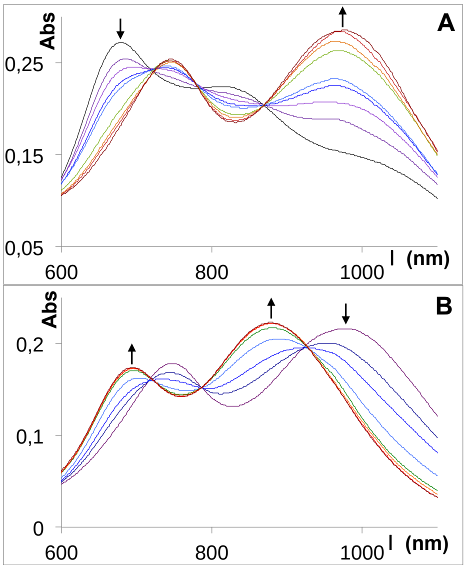


Fig. 2 UV-Vis spectra (298 K) in water (pH 5.9 buffered solution, [MES] = 30 mM) of: (A) [Cu^{II}**2**]$(NO_3)_5$ (2.4 mM) with stepwise addition of NaCl (from 0 to 70 eq.) and (B) [Cu^{II}**2**]$(NO_3)_5$ (1.7 mM) in the presence of NaCl (120 mM) with stepwise addition of NaF (from 0 to 1.3 eq.).

The presence of isobestic points clearly shows that the two cupric species involved in the equilibrium are linearly related by stoichiometry. Nonlinear least-squares treatment of the titration data, using a dedicated software,[13] indicated the formation of a [Cu(2)-Cl] complex with an association constant of 76 ± 4 M^{-1}..

In an analogous way, to an aqueous buffered solution (pH = 5.9, [MES] = 30 mM) of [Cu^{II}**2**]$^{5+}$ containing an excess of NaCl (70 eq.),[14] the progressive addition of NaF resulted in spectral changes of the *d-d* bands displayed in Fig. 2B. After the addition of 1.3 eq. of NaF (vs. [Cu^{II}(Cl)**2**]$^{4+}$), the two absorption bands characteristic of the [Cu^{II}(Cl)**2**]$^{4+}$ species completely vanished, being replaced by two new absorption bands with maxima at 696 and 872 nm (ε = 96 and 153 M^{-1} cm^{-1}, respectively). The presence of isobestic points again shows a simple ligand exchange at the metal center.

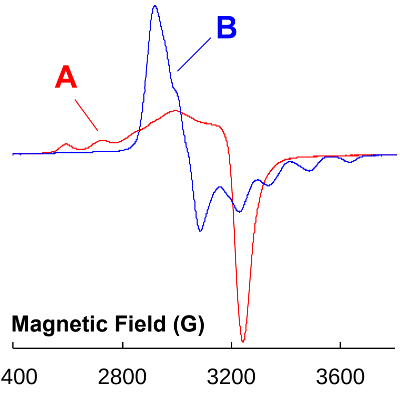
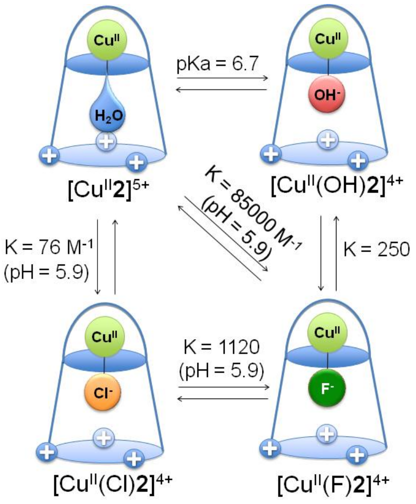


Fig. 3 EPR Spectra (100 K, H_2O) of: (A) $[Cu^{II}\mathbf{2}](NO_3)_5$ (15 mM); (B) $[Cu^{II}\mathbf{2}](NO_3)_5$ (11 mM) in the presence of NaF (24 mM), ($g_\perp = 2.21$, $g_\parallel = 1.96$, $A_\parallel = 146$ G).

This information, together with EPR (Fig. 3) and ESI-MS (Fig. S1) spectra, unambiguously attest to the substitution of the chloride anion by fluoride at the copper center. The affinity of complex $[Cu^{II}\mathbf{2}]^{5+}$ for fluoride anion was evaluated to be 85000 ± 4500 M^{-1},[13] which is more than three orders of magnitude higher than for chloride.

As expected, $[Cu^{II}(F)\mathbf{2}]^{4+}$ revealed to be pH-sensitive: increasing the pH of the solution induced spectral changes in the [6.9-11] pH window. At pH = 11, the spectroscopic features observed by UV-Vis absorption (maxima at 672, 830 and 1015 nm with $\varepsilon = 156$, 126 and 86 M^{-1} cm^{-1}, respectively) and EPR ($A_\parallel = 190$ G) spectroscopies indicate the exclusive formation of $[Cu^{II}(OH)\mathbf{2}]^{4+}$ (Fig. S2 and S3). The thermodynamic constant for substitution of fluoride by hydroxide is 250 (Scheme 1).[15]



Scheme 1 Anion binding by complex $[Cu^{II}\mathbf{2}]^{5+}$ in aqueous solution.

In order to evaluate the various contributions to fluoride binding by the metal center and the calix[6]arene cavity in $[Cu^{II}(F)\mathbf{2}]^{4+}$, titration experiments with NaF in water were conducted with $[H\mathbf{2}]^{4+}$ and $[Cu^{II}\mathbf{3}]^{2+}$ as possible hosts, under similar experimental conditions (Fig. 4). The addition of $[H\mathbf{2}](NO_3)_4$ to a D_2O solution of NaF did not affect the ^{19}F NMR spectrum, indicating that the two partners do not interact. Hence, the metal ion plays a crucial role in fluoride binding. The addition of up to 10 eq. of NaF to an aqueous buffered solution (pH = 5.9, [MES] = 30 mM) of $[Cu^{II}\mathbf{3}]^{2+}$ did not affect the UV-Vis absorption spectrum, suggesting that these two partners do not interact either. This demonstrates that the cavity also plays a crucial role in binding. Hence, as illustrated in Fig. 4, only the complexation of the cupric center within the calix[6]arene framework provides a receptor that efficiently recognizes fluoride in aqueous solution.

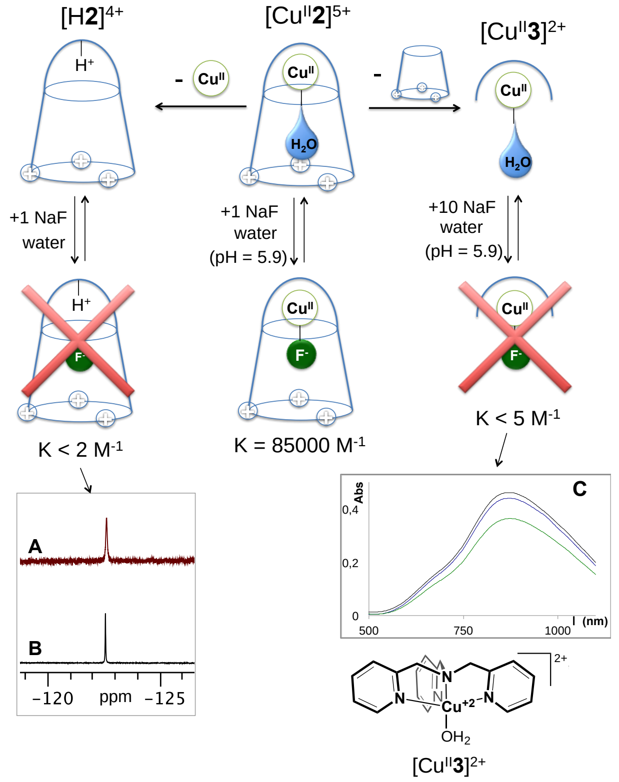


Fig. 4 Evidences for the synergistic contributions of the Cu^{II} complex and the calixarene cavity for fluoride binding in water by $[Cu^{II}\mathbf{2}]^{5+}$. ^{19}F NMR spectra (300 MHz, D_2O, 293 K) of: NaF 4.2 mM (**A**); NaF 4.0 mM and $[H\mathbf{2}](NO_3)_4$ 4.0 mM (**B**). UV-Visible spectra (298 K) in water (pH 5.9 buffered solution, [MES] = 30 mM) of $[Cu^{II}\mathbf{3}](OTf)_2$ (2.31 mM) in the presence of 0, 1 and 10 eq. of NaF (**C**).

Crystal structure of the organo-soluble version of the fluoride complex, $[Cu^{II}(F)\mathbf{1}]^+$

In order to rationalize the exceptional affinity of the calix-complex for fluoride, we first tried to get insights into the molecular structure of the complex. All our efforts to obtain single crystals of the water-soluble $[Cu^{II}(F)\mathbf{2}]^{4+}$ were unsuccessful, however, we succeeded in crystallizing the corresponding organo-soluble complex, $[Cu^{II}(F)\mathbf{1}](ClO_4)$.[#] This complex was obtained by reacting one equivalent of KF dissolved in water with the dicationic aqua complex $[Cu^{II}(OH_2)\mathbf{1}](ClO_4)_2$ dissolved in dichloromethane. Its spectroscopic data (EPR and UV-vis) were previously reported[12] and are very similar to those reported for the water-soluble complex herein. Single crystals of $[Cu^{II}(F)\mathbf{1}](ClO_4)$ were grown by slow diffusion of hexane into a chloroform solution of the complex at 4°C. Four different conformers of the host were observed within the crystal structure, out of which three are displayed in Fig. 5. The asymmetric unit contains three $[Cu^{II}(F)\mathbf{1}]^+$ moieties, each in a markedly different conformation A, B or C. While conformers A and B were modeled with full occupancy, C was modeled as disordered with occupancy 56.3(7) %, with the minor component B' (occupancy 43.7(7) %) exhibiting a conformation analogous to B (see SI).

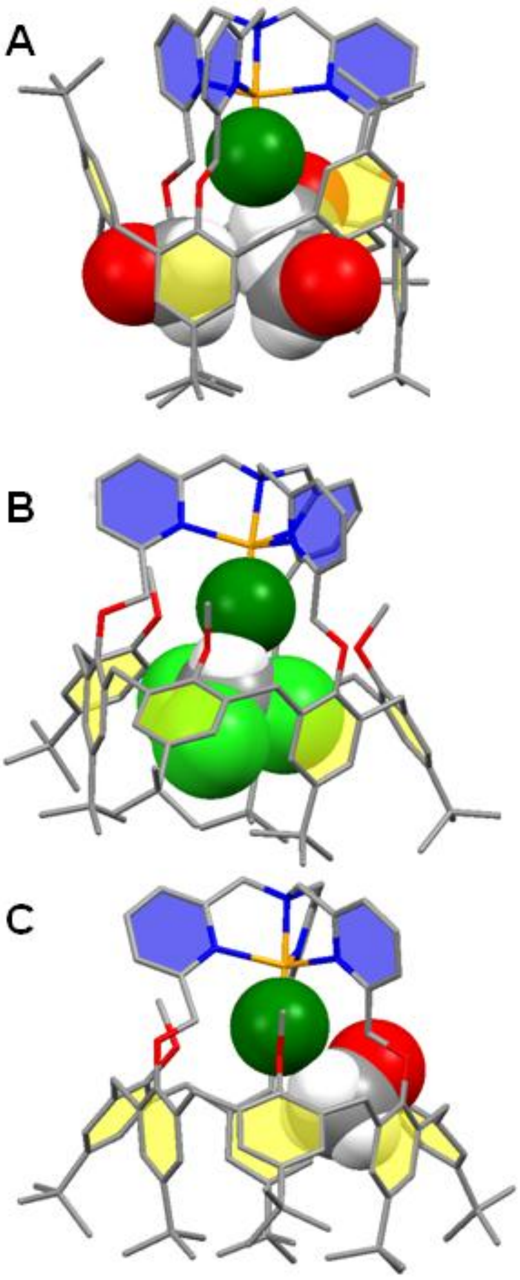


Fig. 5 Conformers of $[Cu^{II}(F)\mathbf{1}]^+$ as observed in the crystal structure. The groups inside the calixarene cavity are depicted in space filling model. The calixarene hydrogen atoms are excluded for clarity. Color code for the atoms: hydrogen in white, carbon in grey, oxygen in red, nitrogen in blue, copper in orange, fluorine in green and chlorine in light green.

Description of the host structures. The three conformers are all very different, each of them providing insights into the specific interactions of the fluoride anion and the surrounding host macrocycle. The conformer A presents a 1,3-alternate conformation where two anisole moieties are completely upside-down relative to the neighboring aromatic rings, while that in position 5 is nearly perpendicular to the neighboring rings. The conformers B and C are more symmetrical with the calixarene core in cone conformation. Structures B and B' (see SI) have an encapsulated $CHCl_3$ guest molecule in the calixarene cavity.

- *In structure A*, despite the differing orientations of the respective anisole moieties, all three methoxy groups are *endo*-oriented. They close the cavity opening, forming a closed hydrophobic pocket around the fluoride anion. One of the methoxy groups is hydrogen bonded to the fluoride anion with moderate strength [d(C···F) = 3.09 Å with C−H···F angle of 143.5°, Fig. 5.(A)]. No other H-bonds occur in this structure, the other H_3C···F distances being 4.05 and 4.47 Å.

- *In structure B*, a chloroform molecule occupies the center of the calix cavity completely. The $CHCl_3$ has a very snug fit into the cavity, the Cl···C contact distances to the methoxy-substituted benzene ring carbon atoms being only 3.22, 3.28 and 3.38 Å, somewhat shorter than the sum (3.45 Å) of the van der Walls radii of the chlorine (1.75 Å) and aromatic carbon (1.7 Å). The $CHCl_3$ is strongly hydrogen bonded to the fluoride anion (d(C···F) = 2.84 Å and C−H···F angle of 162.2°). The calixarene structure displays a flattened cone conformation with the aromatic units alternatively in *endo* and *exo* position relative to the center of the macrocycle. All methoxy groups point towards the outside, away from the CuF center.

- *In structure C*, and in contrast to structure A and B, one of the methoxy groups is oriented in *endo* position. This allows the methyl group to interact with the fluoride anion. The corresponding d(C···F) = 3.16 Å and C−H···F angle of 137.4° indicate hydrogen bonding, albeit weaker than in the case of the structure A.

These molecular structures are very informative about the possible stabilizing interactions between F^- and the calixarene host: Structures A and C for the self-inclusion of the methoxy groups through weak H-bond interactions without guest entrapment and the structure B for the solvent entrapment via strong H-bonding,

Molecular Modeling

In order to get some insight into the interaction energies, the relative stability of the structures and solvent interaction, molecular modeling studies were performed. With the focus of our efforts on the understanding of the strong affinity of the complex for fluoride in water,, all calculations reported below were performed with the fluoride complex based on **2**. Three different structures for the $[Cu^{II}\mathbf{2}(F)]^{4+}$ complex were geometrically optimized at the Density Functional Theory (DFT) level of theory modeling the solvent with a polarizable continuum: a C_3 cone conformation with an empty cavity and all methoxy groups in *exo* position; a cone conformation with one methoxy group in *endo* position interacting with F^- (analogous to structure C); and a cone conformation with a chloroform molecule sitting in the cavity (analogous to structure B). As expected, in each case, the cupric center in the complex adopts a trigonal bipyramidal geometry (Fig. S6). The Cu-F bond length is short for all structures (1.85 Å), suggesting a strong Cu-F bond in all three cases. The minimized structure obtained with a methoxy group hydrogen bonded to F^- is very similar to structure C obtained by XRD. However, this structure lies 7.5 kJ mol^{-1} above the one with all methoxy groups in *exo* position. This is indicative of a cost associated with the *exo* → *endo* re-orientation of the methoxy group, probably through structural tension of the macrocycle. The structure minimized with a chloroform guest resembles structure C. All these results validate the computational methodology. In view of this result, we further explored the putative role of solvent inclusion on the complex stabilization with water, in water.

Binding energies. We further estimated the Gibbs free energy of binding of different ligands (X^-) to the $[Cu^{II}\mathbf{3}]^{2+}$ complexes (ΔG_{bind}, Table 1). For this purpose, a key point is to define a theoretical method enabling a quantitative reproduction of the free energies of hydration of the halides. Our methodology (DFT CAM-B3LYP-D with implicit solvation model, see SI) leads to values of -424 and -308 kJ.mol^{-1} for $X^- = F^-$ or Cl^- ions, respectively, in excellent agreement with the experimental values reported by Tissandier *et al*. (-429 and -304 kJ.mol^{-1}).[6] Turning to the Gibbs free energy of binding ΔG_{bind}, they amount to −109 kJ mol^{-1} and −84 kJ mol^{-1} for $X^- = F^-$ or Cl^- ions, respectively, which indicates a stronger intrinsic coordination of fluoride ions to the cupric center within the first coordination sphere provided by the TMPA core. With the $[Cu^{II}\mathbf{2}(X)]^{4+}$ complex, the respective values are −110 kJ mol^{-1} and −52 kJ mol^{-1}, for X = F and Cl, respectively. This indicates that the second coordination sphere provided by the calixarene core slightly strengthens the Cu-F bond and significantly weakens the Cu-Cl bond, with, as a net result, an enhanced discrimination in the binding of these two halides. We attribute the origin of this increased affinity and selectivity in favor of fluoride to a delicate balance of electrostatic interactions at the small rim: attractive with the CH_2 arms linking the TMPA cap to the calixarene [$d(X\cdots C)$ = 3.00/3.17 Å for X = F/Cl)] and repulsive with the oxygen atoms of the anisole units [$d(X\cdots O)$ = 3.73/3.66 for X = F/Cl)]. However, we found that water molecule binds to the $[Cu^{II}\mathbf{3}]^{2+}$ and $[Cu^{II}\mathbf{2}]^{5+}$ complexes with ΔG_{bind} of −135 and −140 kJ mol^{-1}, respectively. As a consequence, the standard free energies associated to the displacement of a water molecule by either F^- or Cl^- (ΔG_{disp}) are thermodynamically unfavorable. The computational results are thus in line with the experiment performed on the the $[Cu^{II}\mathbf{3}]^+$ complex (Fig. 4). Knowing that the calix[6]arene cavity defines a space that can be occupied by two water molecules,[16] we explored the structures of hydrated complexes. We performed optimizations of $[Cu^{II}(F{\cdot}H_2O{\cdot}H_2O)\mathbf{2}]^{4+}$ starting from different initial geometries, in which from one to up to three water molecules interact directly with the halide anion. It turned out that all structures converged toward the same type of geometry, displayed in Fig. 6 for $[Cu^{II}(F{\cdot}H_2O{\cdot}H_2O)\mathbf{2}]^{4+}$. A single water molecule is hydrogen bonded to the F^- anion. This interaction is very strong in view of the hydrogen bond length [$d(F\cdots O)$ = 2.60 Å]. The water molecule also interacts with the aromatic unit through an OH-π interaction [the shortest $C(Ar)\cdots O(OH)$ distance equals 3.6 Å], and with a second water molecule through a hydrogen bond ($d(O\cdots O)$ = 2.73 Å). The second water molecule is located lower within the cavity and interacts through OH-π interactions [the shortest $C(Ar)\cdots O(OH)$ distance equals 3.4 Å]). A favorable value of −32 kJ mol^{-1} for ΔG_{disp} is found for replacing a water ligand by the hydrated $(F(H_2O)_2)^-$ fluoride ions within the $[Cu^{II}\mathbf{2}]^{5+}$ complex. Importantly, ΔG_{disp} remains positive with the $[Cu^{II}\mathbf{3}]^{2+}$ complex (5 kJ mol^{-1}), highlighting the capability of the calixarene core to stabilize the water cluster within the cavity.

	$[Cu^{II}\mathbf{2}]^{5+}$		$[Cu^{II}\mathbf{3}]^{2+}$	
	ΔG_{bind}	ΔG_{disp}	ΔG_{bind}	ΔG_{disp}
F^-	−110	39	−109	35
$(F(H_2O)_2)^-$	−182	−32	−139	5
Cl^-	−52	98	−84	60
H_2O	−140	-	−135	-

Table 1 Standard Gibbs free energies of binding (ΔG_{bind}) of various ligands to the $[Cu^{II}\mathbf{2}]^{5+}$ and $[Cu^{II}\mathbf{3}]^{2+}$ complexes and standard Gibbs free energies (ΔG_{disp}) of displacment of a water molecule by these ligands. ΔG_{disp} values are corrected to taken into account the fact that water is the solvent (see SI). Values are given in kJ mol^{-1}. All the calculations were performed at the CAM-B3LYP-D/6-311(+)G** level of theory in implicit aqueous solvent.[17]

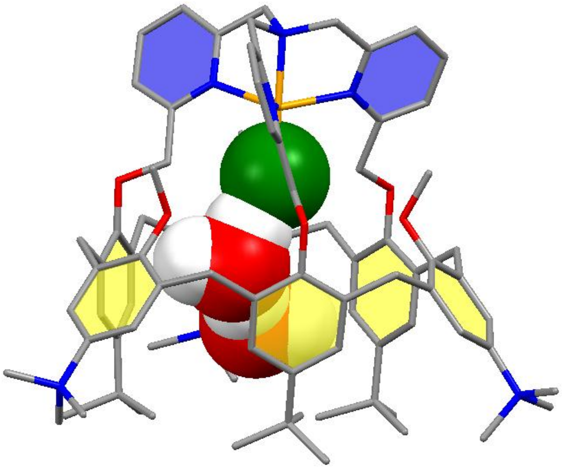


Fig. 6 DFT optimized structure of the $[Cu^{II}(F{\cdot}H_2O{\cdot}H_2O)\mathbf{2}]^{4+}$ complex. The calixarene hydrogen atoms are not shown for clarity. Color code: hydrogen in white, carbon in grey, oxygen in red, nitrogen in blue, copper in orange and fluorine in green.

A bis-aqua fluoride complex. It is well known that the calixarene macrocycle is flexible and can adopt many more conformations with fluctuating water content. In order to further investigate the dynamics of the water molecules within the flexible cavity, we have performed 120 ns of classical molecular dynamics simulations of the $[Cu^{II}(F{\cdot}H_2O{\cdot}H_2O)\mathbf{2}]^{4+}$ complex solvated in a box of water molecules. We observed two types of structures in the course of the MD simulations (Fig. 6). In the first type, the cavity is filled by two water molecules. The structure is very similar to that described above for the DFT optimized $[Cu^{II}(F{\cdot}H_2O{\cdot}H_2O)\mathbf{2}]^{4+}$ complex. In the second type of structure, the cavity of the fluoride complex is empty. The exchanges between the two types of structures, one filled with two water guests, the other empty, are easily seen by following the distances between the *t*Bu groups (Fig. 7).[18] When the cavity is empty, it is shrunk as seen by inter-*t*Bu distances fluctuating around 6.6 Å. When the cavity is filled, its volume is inflated and the distances increase by almost 1 Å. Note that the situations where three or four water molecules are present are rare. The cavity may eventually be filled by only one water molecule. Actually, we found that the content of the cavity is fluctuating with frequent exchanges of water molecules between the solvent and the cavity. These exchanges occur on the nanosecond time scale. The mechanism of exchange is dissociative with the departure of one water molecule from the cavity before another molecule enters. The situation where only one water molecule is present corresponds to these intermediate situations.

When the cavity is filled, the average interaction energy (AIE^{MM}) between the water cluster and the calixarene complex calculated at the MM level along the MD simulation amounts to -50 kJ mol^{-1}. This AIE^{MM} can be decomposed into contributions arising from the different molecular fragments of the complex. The main sources of stabilization of the water cluster are the fluoride ion and the cavity with only little contribution of the NMe_3^+ groups (Table S2). Hence, the MD simulations indicate that the complex can adopt either a packed conformation, in which the access of water molecules to the cavity is hindered by the *t*Bu groups, or an open conformation, that allows a water molecule to interact with the bound fluoride anion and the aromatic rings. When the cavity is open, the optimal number of water molecules inside the cavity is two. Quite remarkably, this shows that the macrocycle offers a well-defined cavity space suitable for stabilizing fluoride as a $[F{\cdot}H_2O{\cdot}H_2O]^-$ cluster. The presence of a couple of water molecules embedded in the calix[6]arene core was previously observed with a Zn^{II} funnel complex, in the solid state as well as in solution.[16]

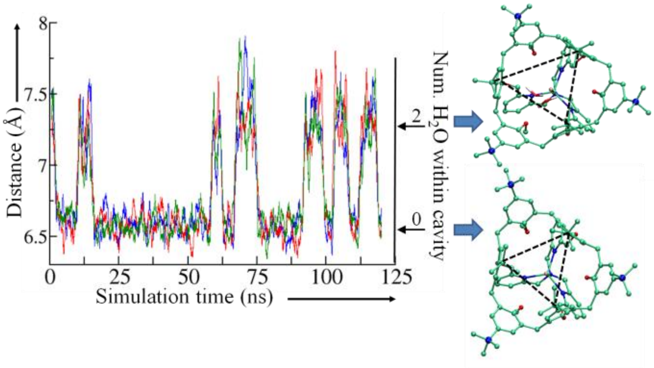


Fig. 7 Fluctuations**,** along the MD simulations of the three distances between the *t*Bu central carbon atoms of the fluoride Cu^{II} complex based on the tri-cationic ligand **2**. For clarity, we have plotted the running averages over time windows of 1.25 ns. Corresponding modeled structures (from top to bottom): two water molecules *in*; empty cavity. To count the water molecules inside the cavity, the edge of the cavity is identified as the plane defined by the three *t*Bu central carbon atoms.

Discussion

XRD analysis of the fluoride complex crystallized from chloroform led to the characterization of three different conformations for the calix-complex, which highlights the flexibility of the calix[6]arene macrocycle, in spite of the constraints imposed by the TMPA cap. In these structures, interaction of F^- with either a solvent molecule or a methoxy group belonging to the anisole units of the ligand is observed. Most interestingly, a very strong H-bond was evidenced between the embedded solvent molecule $CHCl_3$ and F^-, highlighting the well-known propensity of F^- for H-bonding. This suggests that in water too, the F^- anion can be stabilized through H-bonding to hosted solvent. Molecular modeling further supports this possibility with the synergistic binding of a cluster of two water solvents in the heart of the cone.

The possibility of binding partially hydrated F^- species has been highlighted by several solid-state investigations. Single crystal X-ray structures of fluoride-protein complexes (e.g.: pyruvate decarboxylase,[19] butyrylcholinesterase[20]) often show the anion interacting via hydrogen bonding with NH backbones and side chain residues (typically Ser, Thr, Asp…) and having a water molecule which completes its coordination sphere. In the case of synthetic receptors defining a protected and appropriate environment, hydrated fluoride species have been similarly observed for host-guest complexes in the solid state.[21] For these receptors, the number of water molecules directly coordinated to F^- depends on the host design (nature of coordinating groups, geometry, size etc.) and may reach quite high values in some cases. For example, a tetrahydrated cluster, $[F(H_2O)_4]^-$, encapsulated in a tricyclic organic molecular capsule has been reported.[21c] All these "biotic and abiotic" examples of hosts binding a cluster of fluoride and water as a guest, illustrate the high hydration energy of this anion. We calculated that the free energies of hydration of a "naked" fluoride and of a $[F(H_2O)_1]^-$ anion amount to -424 and -371 kJ.mol^{-1} respectively. Hence, it is reasonable to think that receptors able to recognize a partially hydrated $[F(H_2O)_n]^-$ species should be more efficient.

For compound $[Cu^{II}\mathbf{2}]^{5+}$, we noticed a good selectivity (ca. 10^3) for fluoride over chloride complexation, which is in agreement with a stronger Cu^{II}-F bond compared to a Cu^{II}-Cl bond. DFT calculations point to the enhancement of the binding selectivity by the calixarene cavity. The selectivity may also be related to the encapsulation of water molecules since the free energy of hydration for fluoride is higher than for chloride [$\Delta_r G°_{hyd}(F^-) = -429$ kJ mol^{-1}, $\Delta_r G°_{hyd}(Cl^-) = -304$ kJ mol^{-1}].[6] As suggested by molecular modeling studies of compound $[Cu^{II}(F)\mathbf{2}]^{4+}$, this result can be rationalized by taking in account $[F{\cdot}H_2O{\cdot}H_2O]^-$ as the guest species for host $[Cu^{II}\mathbf{2}]^{5+}$, in which water molecules facilitate the fluoride extraction from water in two ways: (Fig. 8): i) the dehydration cost is considerably lowered (by ca. 80 kJ mol^{-1} for the coordination of one remaining water; possibly more, due to the participation of water in the second sphere), and ii) water molecules present in the cavity interact with the aromatic walls of the macrocycle via OH-π interactions further stabilizing the host-guest complex.

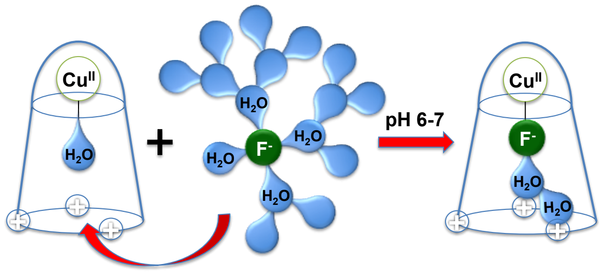


Fig. 8 Proposed mechanism for F^- binding in water by a calixarene Cu^{II} complex, according to molecular modeling.

Conclusion

In summary, complex $[Cu^{II}\mathbf{2}]^{5+}$ exhibits an exceptionally high affinity for fluoride anion in 100% water medium ($\log K = 4.93 \pm 0.02$). It is a rare example of a transition metal-based receptor, [5a] and as far as we know, it displays the highest association constant value among the monometallic systems described in the literature. [5a,g-j] In contrast to most azacryptand-based systems[5a-e] in which the recognition process is typically optimal at low pH values in order to obtain a polyprotonated host, complex $[Cu^{II}\mathbf{2}]^{5+}$ strongly binds F^- in the [6-7] pH window.[23]

Binding studies monitored with the Cu^{II} complex deprived of cavity and the calixarene ligand deprived of Cu^{II} have revealed that no complexation of fluoride takes places under the same experimental conditions. These observations bring to light the synergistic roles of Cu^{II} and the calixarene core in the binding process. XRD analysis of the organo-soluble fluoride complex based on ligand **1** highlights the possible embedment of one molecule of solvent ($CHCl_3$) inside the calix cavity with an associated strong hydrogen bond with F^-. Molecular modeling calculations have shown that the anionic guest F^- can strongly interact with two water molecules within the cavity. Hence, a possible explanation to rationalize the observed synergy between Cu^{II} coordination and cavity embedment for fluoride extraction from water may stem from the complexation of a partially hydrated species, likely $[F{\cdot}H_2O{\cdot}H_2O]^-$, which, compared to the complexation of a "naked" F^- ion, is energetically less demanding for the host.

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Notes and references

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CCDC 997677 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

& Electronic Supplementary Information (ESI) available: materials and methods, supporting data, DRX details. See DOI: 10.1039/b000000x/

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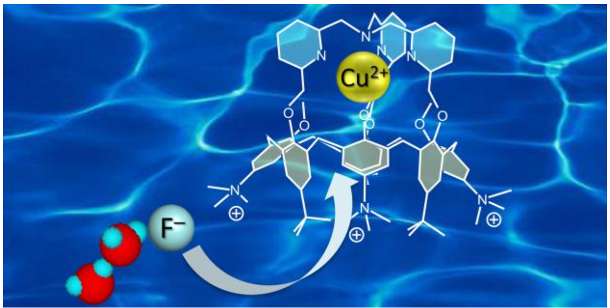
TOC



Cu^{II} coordination combined to hydrophobic pocket hosting allows strong and selective fluoride binding in water near neutral pH