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Rendering a calixarene having dipyridyl pendants soluble in water results in different species with smaller binding constants

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Abstract—Sulfonato groups were introduced into the backbone of a dipyridyl-based calixarene to obtain a novel water-soluble compound able to complex Co(II) and Cu(II). Spectrophotometric titrations pointed out that the new ligand complexes Co(II) and Cu(II) in water, but with stoichiometries and stabilities that are different from the analogous water insoluble calixarene.

Calixarenes[1] have been used as scaffolds for the synthesis of multivalent ligands,[2] as well as attractive models for enzymes.[3] In the latter case, the receptors are functionalized with nitrogen ligands, which can coordinate transition metals.[4] Incorporation of these moieties into macrocyclic structures may allow the complexation features of nitrogen ligands to be combined with the hydrophobic cavity of calixarenes within the same ligand. This cavity is well adapted for the inclusion of small molecules or charged species and can promote the transformation of these substrates, owing to the close proximity to the metal center, giving rise to sophisticated metalloenzyme mimics. Earlier, we reported the synthesis[5] and metal complexation features[5,6] of dipyridyl-based calixarene **L1** (Chart 1) in acetonitrile. The tetrahedral arrangement of the $[Cu(\mathbf{L1})]^{2+}$ species accounts for the easy reversible reduction of this species and this electrochemically switchable complex, opportunely modified, forms SAMs on gold surfaces.[7] A comparison of the coordination features of ligands with the same coordinating groups, but soluble in water or in organic solvents (i.e., CH_3CN, CH_2Cl_2, etc.), has received a great deal of attention.[8] We have synthesized a new water-soluble dipyridyl-based calix[4]arene (**L2**) via the introduction of sulfonato groups into the calixarene backbone to obtain a water-soluble compound with the same coordinative core and similar electrochemical properties of compound **L1**.

L2 was synthesized from **L3**, obtained as previously described.[9] In **L3**, the propyl chains of **L1** have been replaced with ethylethylether pendants, that are stable to the sulfonation reaction.[10] Treatment of **L3** with H_2SO_4 at room temperature and then with NaOH[11] afforded the water-soluble compound **L2**, that was purified by RP column chromatography (yield 40%).[12] The ^1H NMR data of **L2** clearly show that all the protons in *para* to the phenolic rings have been substituted by the sulfonato groups, as indicated by the disappearance of their signals. Furthermore, the signals of the bridging methylene protons still reproduce a typical AB system, thus indicating that this calixarene is in the 1,3 alternate conformation, as found for compound **L3**.[9]

The complexation of **L2** with both Co^{2+} and Cu^{2+} was studied by UV–vis titrations. The spectrophotometric measurements were carried out at 25 °C and at an ionic strength of $0.1\ mol\ dm^{-3}$ ($NaClO_4$) (*Caution*! Perchlorates may be explosive and should be handled with caution) in unbuffered water, using a diode-array Agilent 8453 spectrophotometer. Usually an 8.0×10^{-4}–$1.5\times10^{-3}\ mol\ dm^{-3}$ solution of the metal ion (cobalt or copper perchlorate) was added to a solution of the host (7.0×10^{-5}–$8.0\times10^{-5}\ mol\ dm^{-3}$) and 60–70 points were recorded for each independent titration run. For more experimental details see Ref. 5.

In order to rule out pH variations that could be due to proton displacement, we measured for both Cu(II) and Co(II) the pH of a $7.4\times10^{-5}\ mol\ dm^{-3}$ solution of **L2** (ionic strength $0.1\ mol\ dm^{-3}$ ($NaClO_4$)), at the

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Keywords: Calixarenes; Cobalt(II); Copper(II); Stability constants.

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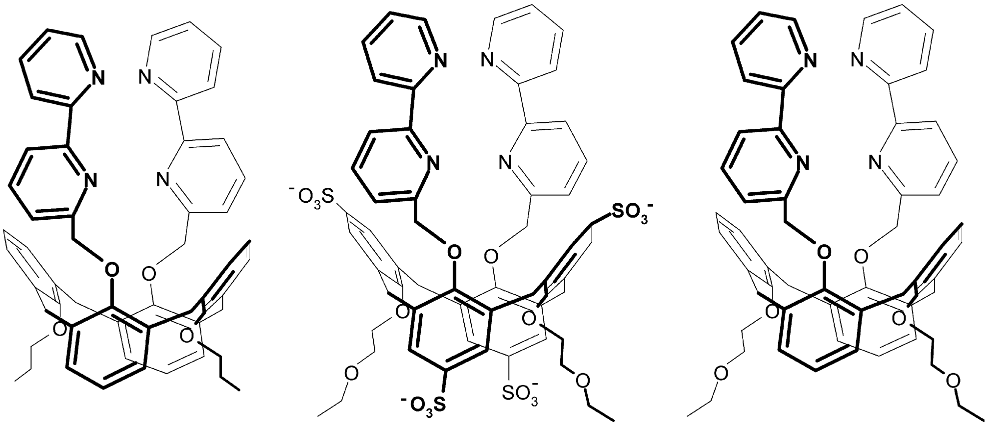

L1 **L2** **L3**

Chart 1.

beginning and at the end of titration, that is, before and after the addition of the metal ion solution. We also measured the pH of a solution containing only 0.1 mol dm^{-3} of $NaClO_4$ before and after the addition of $Cu(ClO_4)_2$ and $Co(ClO_4)_2$ solutions, respectively. The pH of the ligand solution, determined potentiometrically by a microelectrode, was 7.44. At this pH, the sulfonato groups, as well as the dipyridyl residues, are deprotonated and no proton displacement can result from the complexation with the metal ions. After the addition of the metal perchlorate solutions to **L2**, we measured a pH value of 6.00 for the sample with Cu^{2+} and of 6.86 for the sample with Co^{2+}, respectively. The lowering of the pH is exclusively due to the acidity of the metal perchlorate solutions, as revealed by the analogous pH titrations performed by adding the metal ion (Cu(II) or Co(II)) to the 0.1 mol dm^{-3} $NaClO_4$ solution; in both cases, the addition of the metal solution results in a decrease of about 1.5 and 0.5 pH units for copper and cobalt, respectively. The pH drop is also confirmed by calculations performed by using HYSS.[13]

A multiwavelength and multivariate treatment of spectral data was performed by means of two different software programs: Specfit[14] and Hyperquad.[15] Titration curves for Cu(II)–**L2** are shown in Figure 1.

The free ligand **L2** shows two absorption bands, at 202 and at 285 nm, due to the absorption of the phenyl and 2,2′-dipyridyl moieties, respectively. The addition of cobalt or copper solutions causes a bathochromic shift of the ligand absorption band centered at 285 nm; this band is shifted to 305 and 310 nm for Co^{2+} and Cu^{2+}, respectively, as displayed in the inset of Figure 1.

The stoichiometries of Co–**L2** and Cu–**L2** main species were initially determined by both the mole-ratio[16] and the Job plot[17] methods. Both methods indicated the presence of only one complex species (ML) for the Co–**L2**, as well as for the Cu–**L2** system. The multiwavelength and multivariate treatment of data confirms the existence of a 1:1 species only for the two systems, as previously reported for the cobalt system with the analogous non water-soluble dipyridyl-calix[4]arene **L1**.[5]

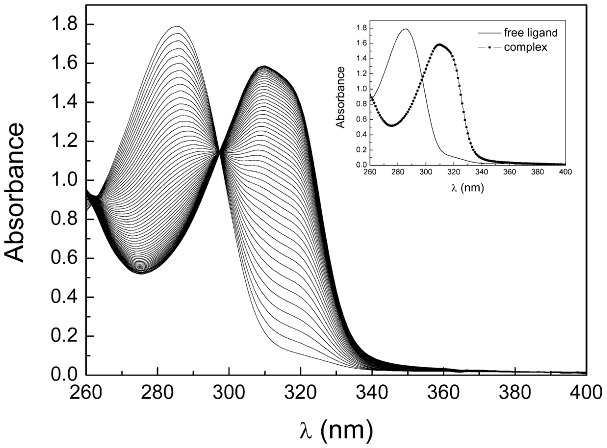

Figure 1. UV–vis titration curves for the Cu–**L2** system in water; the inset shows the ligand spectrum before (—) and after (–●–) the metal ion addition.

Surprisingly, no M_2L species were detected for the Cu–**L2** system, in contrast with that reported for **L1** that forms with copper(II) two complex species (i.e., ML and M_2L). As previously reported,[6] the mononuclear and the binuclear complex species have quite different spatial arrangements. In $[Cu(\mathbf{L1})]^{2+}$ species the ligand wraps around copper(II) in a tetrahedral arrangement, whereas $[Cu_2(\mathbf{L1})]^{4+}$ species adopts a 'both wings out structure' with the dipyridyl coordinating groups pointing outwards the cavity. This structure, that allows the ligand to accommodate two metal ions, is sterically hindered for compound **L2** owing to the presence of sulfonato groups.

The stability constant values obtained by the two different software packages virtually coincide within the standard deviations. The $\log\beta$ values reported in Table 1 show that Co^{2+} and Cu^{2+} form quite stable complexes with **L2**, but not as stable as the analogous species with **L1**. This trend is in line with the different dielectric constant (D) and thus with the different polarity of water and acetonitrile. In fact, metal ions are more or less extensively solvated in all solvents of high D, that is,

Table 1. log β values for the complex formation of Co^{2+} and Cu^{2+} with **L2**[a] (in water) and **L1**[b] (in CH_3CN) at 25 °C

Reaction	log β
$Co^{2+} + \mathbf{L2} \leftrightarrows [Co(\mathbf{L2})]^{2-}$	5.2 (2)
$Cu^{2+} + \mathbf{L2} \leftrightarrows [Cu(\mathbf{L2})]^{2-}$	5.4 (2)
$Co^{2+} + \mathbf{L1} \leftrightarrows [Co(\mathbf{L1})]^{2+}$	7.0
$Cu^{2+} + \mathbf{L1} \leftrightarrows [Cu(\mathbf{L1})]^{2+}$	7.3

[a] 2σ in parentheses.

[b] Ref. 5.

the solvent molecules act as ligands, competing with other ligands present in the solution;[18] the formation of metal complexes with analogous ligands turns out to be less favoured in water than in non-aqueous media. Hence, even though the two calixarenes have the same coordinative core, they display quite different coordination features both as concerns the stoichiometries of the complex species and their stability constants. The copper and cobalt complexes of both ligands provide useful model systems that can function as metalloreceptors for small molecules,[19] charged species[20] and can promote catalytic transformations[21] both in water and in non-aqueous environment.

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12. ^1H NMR (D_2O, 500 MHz): δ 8.67 (d, d, 2H, 6′-H), 8.04 (m, 6H, 3-H + 3′-H + 4-H), 7.70 (m, 6H, 4′-H + Ar-H *meta*), 7.56 (d, d, d, 2H, 5-H), 7.27 (s, 4H, Ar-H *meta*), 6.88 (t, 2H, 5′-H), 5.00 (s, 4H, CH_2-bipy), 4.06 and 3.72 (AB, 8H, Ar-CH_2-Ar), 3.76 (t, 4H, $OCH_2CH_2OCH_2CH_3$), 3.57 (q, 4H, $OCH_2CH_2OCH_2CH_3$), 3.24 (t, 4H, $OCH_2CH_2OCH_2CH_3$), 1.18 (t, 6H, $OCH_2CH_2OCH_2CH_3$). Anal. calcd for $C_{58}H_{52}N_4Na_4O_{18}S_4$: 53.04 C, 3.99 H, 21.93 O, 4.27 N, 9.77 S, 7.00 Na. Found: 52.66 C, 3.97 H, 4.30 N, 9.84 S, 6.96 Na. This compound was also characterized by ESI-MS (*m*/*z* 1335 ($M{+}Na^+$), 679 ($M{+}2Na^+$) and 668 ($M{+}H^+{+}Na^+$)) and UV–vis (λ_{max} (H_2O)/nm 285; ε/dm^3 mol^{-1} cm^{-1} 23,700).
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