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A new water-soluble ligand based on a calix[4]arene substituted by 2,2'-bipyridine chelating units

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Abstract—A new water-soluble calix[4]arene-based podand was prepared by tethering two 4,4'-dicarboxy-2,2'-bipyridine units on distal phenol rings. © 2001 Elsevier Science Ltd. All rights reserved.

Water-soluble calixarenes are mainly prepared by direct or indirect incorporation, at the lower and upper rims, of various types of polar functions such as, for example, carboxylate,^{1,2} sulfonate,³ phosphonate⁴ or alkylamino groups.^{2,5}

With the aim to translate into water complexation experiments previously developed with lipophilic calixarene-based bipyridine podands,⁶ we attempted to introduce a hydrophilic behaviour via carboxylate groups brought by the bipyridine units. This led to the new water-soluble ligand **5** described here (Scheme 1).

Reaction of 1 equiv. of *m*-CPBA on the 6,6'-dimethyl-4,4'-dicarbomethoxy-2,2'-bipyridine 1 gave the mono-*N*-oxyde **2**. Unstable on chromatographic supports, **2** was directly transformed via a Boeckelheide rearrangement in the non-isolated 6-trifluoroacetyl analogue, which, upon reaction with LiBr in a polar aprotic solvent, gave the desired monobromide **3** with a yield of



Scheme 1. (i) *m*-CPBA, CH₂Cl₂, 90%; (ii) (a) (CF₃CO)₂O; (b) LiBr, THF, DMF, 55%; (iii) calix[4]arene, MeCN, K₂CO₃, reflux, 83%; (iiii) NaOH, H₂O, EtOH, reflux, 80%.

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Figure 1. ¹H NMR spectrum of 5 (D_2O , 400 MHz, rt).



Figure 2. UV-visible titration of 5 by $Cu(MeCN)_4PF_6$. (a) 5, 1.71×10^{-5} M in H₂O; (k) 5+1 equiv. of Cu(I).

55% versus 2. Calix[4]arene-tetrol,⁷ 3 and K_2CO_3 reacted in refluxing MeCN⁸ to give the podand 4 which was finally saponified. Acidification to pH 3-4 (1 M HCl), followed by a controlled neutralisation with NaOH, afforded the tetra-carboxylate 5 with a yield of 80%. All compounds gave satisfactory C, H, N, IR, MS and NMR analyses. In particular, the elemental analysis of 5 was consistent with the presence of two molecules of NaCl and six molecules of H₂O. The ¹H NMR analysis of 5 in D₂O showed the presence of six bipyridyl and five calixarene signals, all perfectly well resolved, which confirmed the expected structure (Fig. 1). ¹³C NMR spectra showed that 5 was in the cone conformation,⁹ with Ar-CH₂-Ar signals at 30.79 ppm. The negative mode electrospray mass spectrum exhibited three signals at 240.04 $[5-4Na^+]^{4-/4}$, 327.87 [5 $3Na^+]^{3-/3}$ and 503.24 a.m.u. $[5-2Na^+]^{2-/2}]$. The mono-charged species was observed in the positive mode at 1075.98 a.m.u. $[5+Na^+]^+$.

To give a preliminary concrete form to this synthetic work, the complexation of Cu(I) by **5** was followed in water by UV–visible spectroscopy (Fig. 2). The metal-to-ligand charge transfer band which appeared at 470 nm, as expected with tetrahedral Cu(I)/diimine complexes, was completed on the addition of 1 equiv. of Cu(I), suggesting, as for parent hydrophobic ligands,^{6,8} the formation of a mononuclear complex involving coordination of both bipyridine units. Even after 24 or 48 h, or in the presence of BSA, this band remained unchanged, proving that **5** was able to stabilise Cu(I) in water and probably in biological media. This specific behavior and the complexation of various metal species by **5** are currently under investigation.

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