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A new water-soluble calix[4]arene podand incorporating *p*-phosphonate groups and 2,2′-bipyridine units

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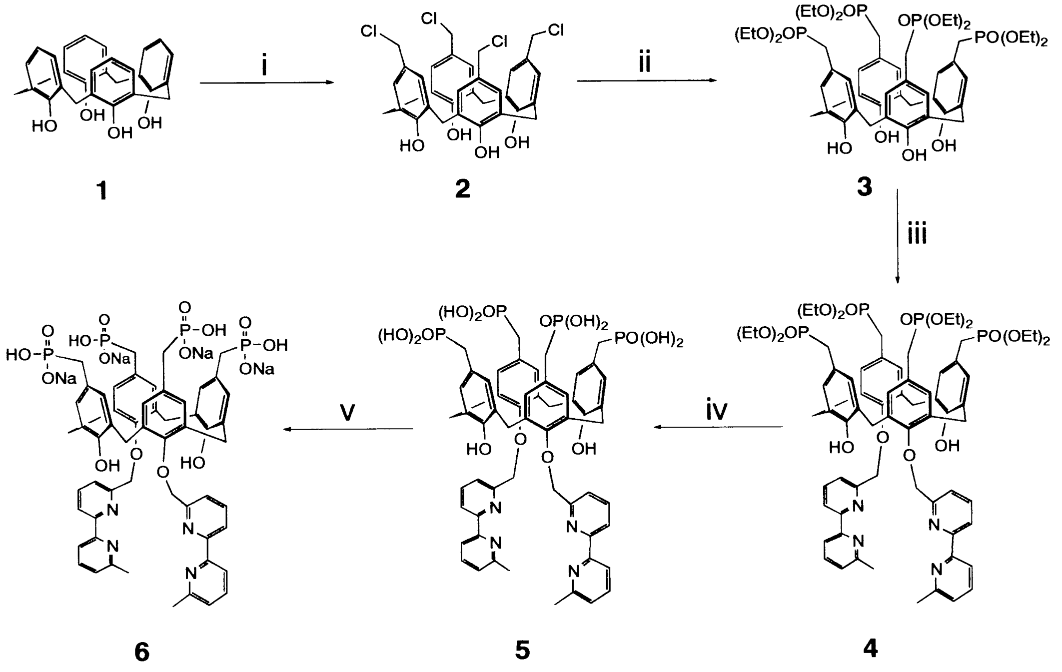
Abstract—A new water-soluble calix[4]arene-based bipyridyl podand was prepared by incorporation at the upper rim of four phosphonate groups; the association of its hydrophilic and chelating properties was positively evaluated in the complexation of copper(I) in water. © 2002 Elsevier Science Ltd. All rights reserved.

The introduction of hydrophilic groups on calixarene platforms allows the evaluation in aqueous media of their highly interesting spatial organising properties; in this sense, the main groups which have been employed for such studies are, for example, carboxylate,[1] phosphonate,[2] amino[3] or sulphonate groups.[4] A part of our studies is dedicated to the complexation of transition metal ions by calixarenes bearing heterocyclic chelating arms, in organic solvent,[5] and, more recently, in water. For this last purpose, we have described the introduction of water-solubility on the 1,3-bis-(2,2′-bipyridyl)-calix[4]arene podand by means of sulphonate functions at the upper rim of the calixarene,[6] or by carboxylate groups directly brought by the bipyridine units.[7] Both



Scheme 1. *Reagents and conditions*: (i) AcOH, H_2SO_4, HCHO, HCl_g, 94%; (ii) $POEt_3$, CH_2Cl_2, reflux, 98%; (iii) $BrCH_2bpy(Me)$, MeCN, K_2CO_3, reflux, 71%; (iv) (a) BTMS, rt, (b) HCl, 85%; (v) NaOH, H_2O, 100%.

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ligands displayed the expected water-solubility accompanied by a good ability to complex copper(I), even in the presence of natural complexing agents such as proteins.

In order to enlarge our library of such bipyridyl podands, we developed a third synthetic strategy which involves the introduction of methylene phosphonate salts at the upper rim of the calix[4]arene backbone. The choice of this functional group was monitored by its apparent easy access, in accordance with the initial work of Ungaro et al.[8] Among the various synthetic approaches leading to phospha-calixarenes, and as recently reviewed by Matt et al.,[9] we were surprised to find that this group has not been evaluated so far in calixarene chemistry.[10] Thus (Scheme 1), the *de*-*t*-butylated calix[4]arene **1** was chloromethylated at the *para*-positions of the phenol rings, following the inexpensive procedure of Huang et al.[11] The introduction of the diethyl phosphonate groups on the unstable chloromethyl functions of **2**[8,11] was performed via a modification of the Ungaro process,[8] consisting in refluxing **2** in a CH_2Cl_2 solution of a moderate excess (40 equiv.) of fresh triethyl phosphite. These conditions allowed us to render less drastic the conditions necessary to eliminate the excess of reagent. The tetra-(diethylphosphonate) **3** was thus isolated as a solid material after chromatography and lyophilisations from a cyclohexane suspension, this last operation resulting in a better but still non-exhaustive elimination of residual triethyl phosphite. At this stage, **3** was reacted with 6-bromomethyl-6-methyl-2,2′-bipyridine and K_2CO_3 in refluxing MeCN, to give the 1,3-bis-bipyridyl derivative **4** with a yield of 71%. Treatment of the latter by bromotrimethylsilane[8] at room temperature and under a dry atmosphere gave, after hydrolysis with 1 M HCl and a careful washing to remove the residual silyl compounds, the tetraphosphonic acid **5**. Finally, the controlled neutralisation–dissolution of **5** by 1 M NaOH afforded, after evaporation of water, the tetra sodio derivative **6** as a white solid. All compounds were fully characterised.

^{13}C NMR experiments confirmed that the cone conformation was conserved,[12] notably for compounds **3**, **4** and **6**, with Ar-CH_2-Ar resonance signals comprised between 31.00 and 32.00 ppm.

The tetrasodium salt **6** showed a good solubility in water at neutral pH. Its ^1H NMR analysis, performed in D_2O, showed the presence of the expected alkyl resonance signals, notably two doublets ($J_{PH}=20$ Hz) at 2.56 and 2.78 ppm, attributed to the phosphonomethylene protons, an AB system ($J_{AB}=13$ Hz) at 3.53,4.34 ppm corresponding to the Ar-CH_2-Ar groups, and two singlets at 2.45 and 5.05 ppm, attributed to the CH_3-bpy and OCH_2-bpy groups, respectively. Probably due to a poor solvation of the heterocyclic moieties, which could result in an aggregation process, the bipyridyl aromatic protons appear as relatively broad unresolved signals. Changing D_2O for CD_3OD resulted in the sharpening of these signals and confirmed the presence of the expected bipyridyl protons. The presence of the two expected kinds of phosphonate groups in compound **6** was confirmed by ^{31}P resonance signals at 17.64 and 18.61 ppm (D_2O, NaOD; H_3PO_4 as external standard; 161.97 MHz). Elemental analysis was consistent with the presence of 7.5 molecules of H_2O and one quarter sodium phosphate issued from similar amounts of residual triethylphosphite associated to compound **4**. Negative mode electrospray mass spec-

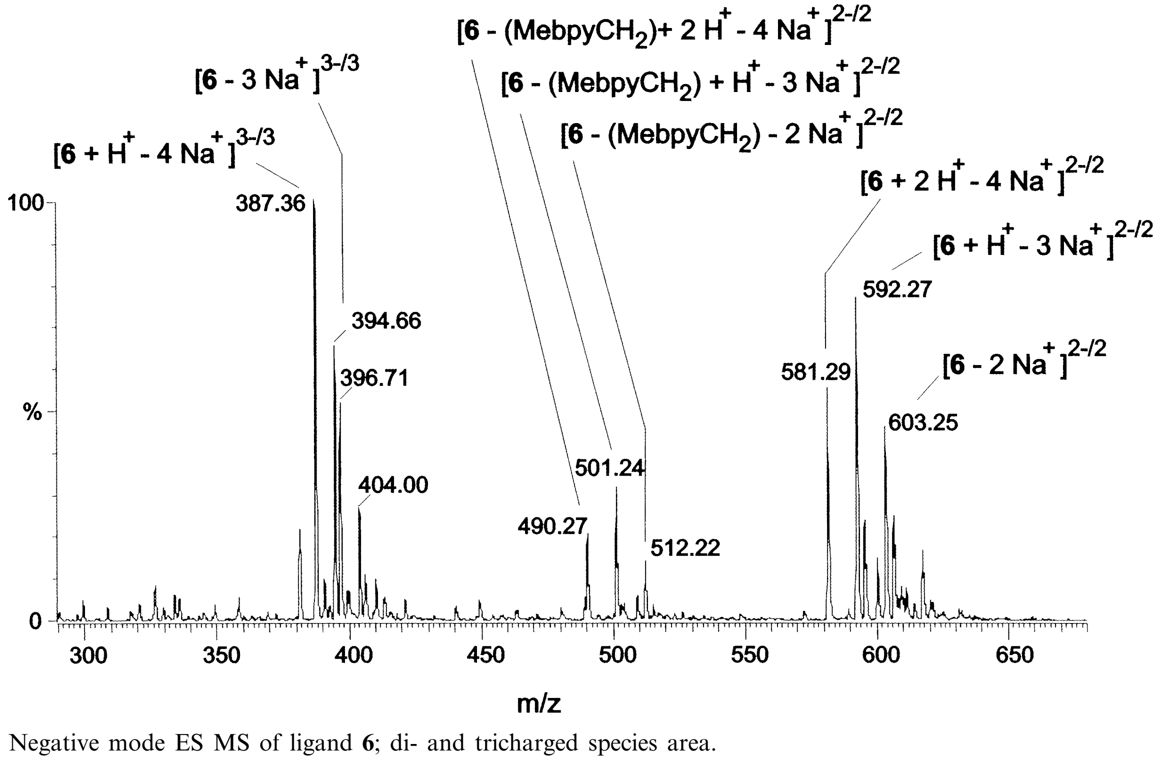

Figure 1. Negative mode ES MS of ligand **6**; di- and tricharged species area.

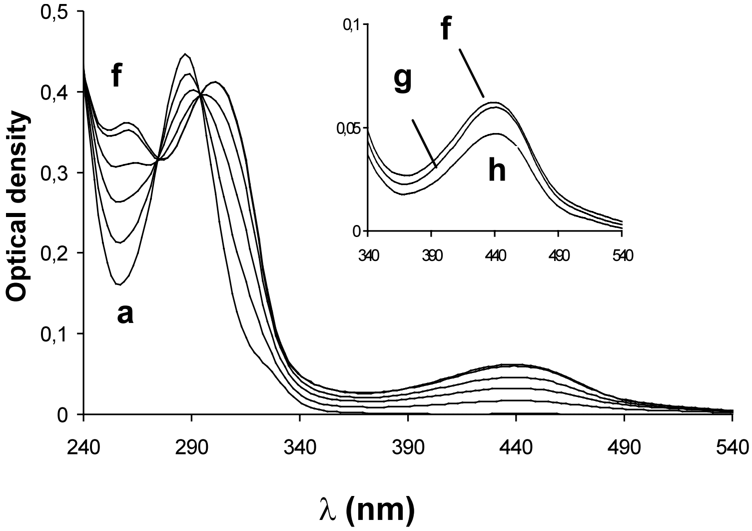

Figure 2. UV–vis titration of **6** by $Cu(MeCN)_4PF_6$. **6** 2.0×10^{-5} M in H_2O; (f) **6**+1 equiv. of Cu(I); (g) (f)+1 equiv. of BSA 10^{-3} M in H_2O (40 μL); (h) (f)+10 equiv. of BSA 10^{-3} M in H_2O (400 μL).

trometry showed, with a bad resolution, the presence of the monocharged species $[\mathbf{6}\text{-}Na^+]^-$; the better information obtained with di- and tricharged species (Fig. 1), confirmed the formation of **6**.

As in the previous reports,[6,7] the complexing ability of **6** towards Cu(I) salts was observed in water by UV–vis spectroscopy. The addition of $Cu(MeCN)_4PF_6$ in an aqueous solution of the ligand resulted in the formation of a 1:1 complex characterised by the specific metal-to-ligand charge transfer (MLCT) band at ca. 455 nm encountered in tetrahedral copper(I)/heterocycle complexes (Fig. 2).

A preliminary evaluation of the behaviour of this complex in biological media was performed by addition of BSA in the UV titration medium. The MLCT band remained unchanged in these conditions, suggesting, as for the two previous ligands,[6,7] an interesting role of cation carrier for biological applications. This point is under current investigation.

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