Pergamon

Tetrahedron Letters 43 (2002) 77–80

TETRAHEDRON LETTERS

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

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Received 5 November 2001; accepted 6 November 2001

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

Evaluating in aqueous media the excellent spatial organising properties of the calix[4]arene macrocycle may pass through the introduction of various polar functions at the lower or the upper rim, such as, for example, carboxylate,[1] phosphonate,[2] amino[3] or sulphonate groups.[4]

With the aim of translating in water some complexation experiments we have developed in the last years with lipophilic calixarene-based bipyridine podands,[5] we have preliminarily chosen a simple synthetic strategy involving the introduction of the hydrosolubility via the chelating units. Thus, a new water-soluble podand, including a calix[4]arene backbone bearing in alternate positions at the lower rim two 4,4′-dicarboxy-2,2′-bipyridyl chelating units, was prepared and showed interesting complexation properties of copper(I) in water.[6] In order to avoid modifications of the chelating properties of the 2,2′-bipyridine arms, we developed in parallel another synthetic strategy involving the introduction of water-solubility via the calixarene backbone.

The sulphonate function, previously employed with functional calixarenes to develop water-soluble receptors,[7] was chosen as the hydrosolubilising group. Attempts to prepare the title compound by alkylation of the sodium salt of the tetrasulphonyl calix[4]arene in accordance with the Shinkai's procedure failed,[4] giving mixtures of alkylated products we were unable to separate. We thus employed the chlorosulphonation pathway developed by Morzherin et al.,[7a] followed by hydrolysis in aqueous pyridine, and by salification by sodium hydroxide, in a similar way to that described by Nicod et al.[7c]

Expecting that the bipyridine units should not be reactive in these conditions, we attempted preliminary chlorosulphonations with the bis-bipyridyl calixarene **1**; this gave nevertheless other mixtures of compounds uneasy to purify. This problem, probably due to the presence of two phenol moieties in the calixarene backbone, necessitated the protection of the two residual hydroxyl groups.

Thus, the calixarene **1**[8] was treated by butyl bromide and NaH in dry DMF, affording the tetra-substituted analogue **2** with a yield of 86% (Scheme 1). ^{13}C NMR experiments confirmed that the cone conformation was conserved,[9] with Ar-CH_2-Ar resonance signal at 31.58 ppm. The reaction of **2** with chlorosulphonic acid in dry CH_2Cl_2 at rt afforded an acidic mixture which was suspected to contain the desired chlorosulphonated calixarene with, probably, salts of the bipyridine moieties. Attempts to isolate the corresponding basic analogue were unsuccessful. We thus proceeded to the direct hydrolysis of the chlorosulphonic group in a mixture of pyridine, acetone and water. The resulting material was purified by lixiviation with ethanol, affording the pyridinium salt **3** with a yield of ca. 90%. ^{13}C NMR confirmed that the cone conformation was preserved, with Ar-CH_2-Ar resonance signal at 31.92 ppm (D_2O). ^1H NMR analysis of **3** (Fig. 1) showed that two pyridines are associated to the calixarene structure, probably as hydropyridinium sulphonates.

pH-metric titration with NaOH evidenced the presence of six available acidities. This last result was in accor-

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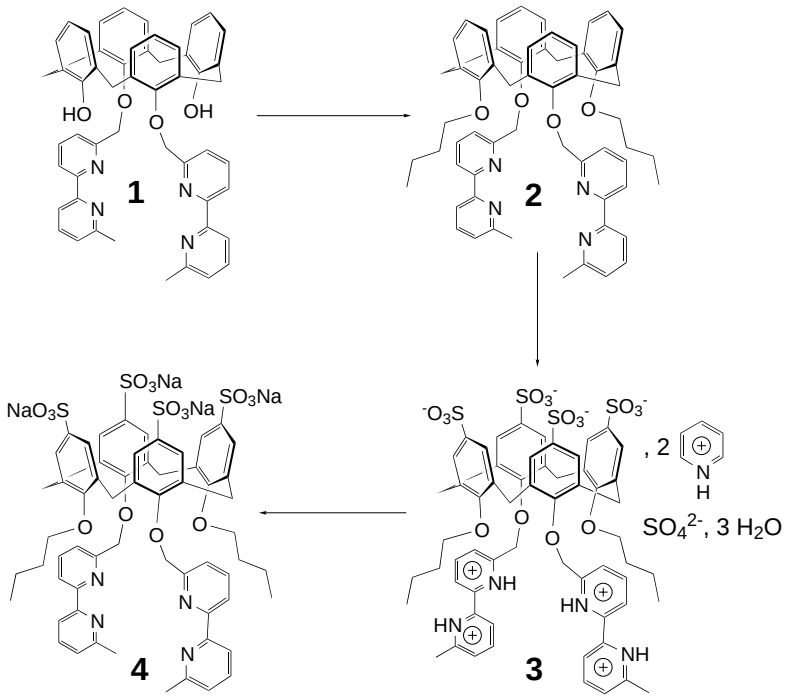
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02103-7



Scheme 1. *Reagents and conditions*: (i) BuBr, NaH, DMF, rt, 86%; (ii) (a) $ClSO_3H$, CH_2Cl_2, rt, (b) pyridine, Me_2CO, H_2O, reflux, 90%; (iii) NaOH, H_2O, 100%.

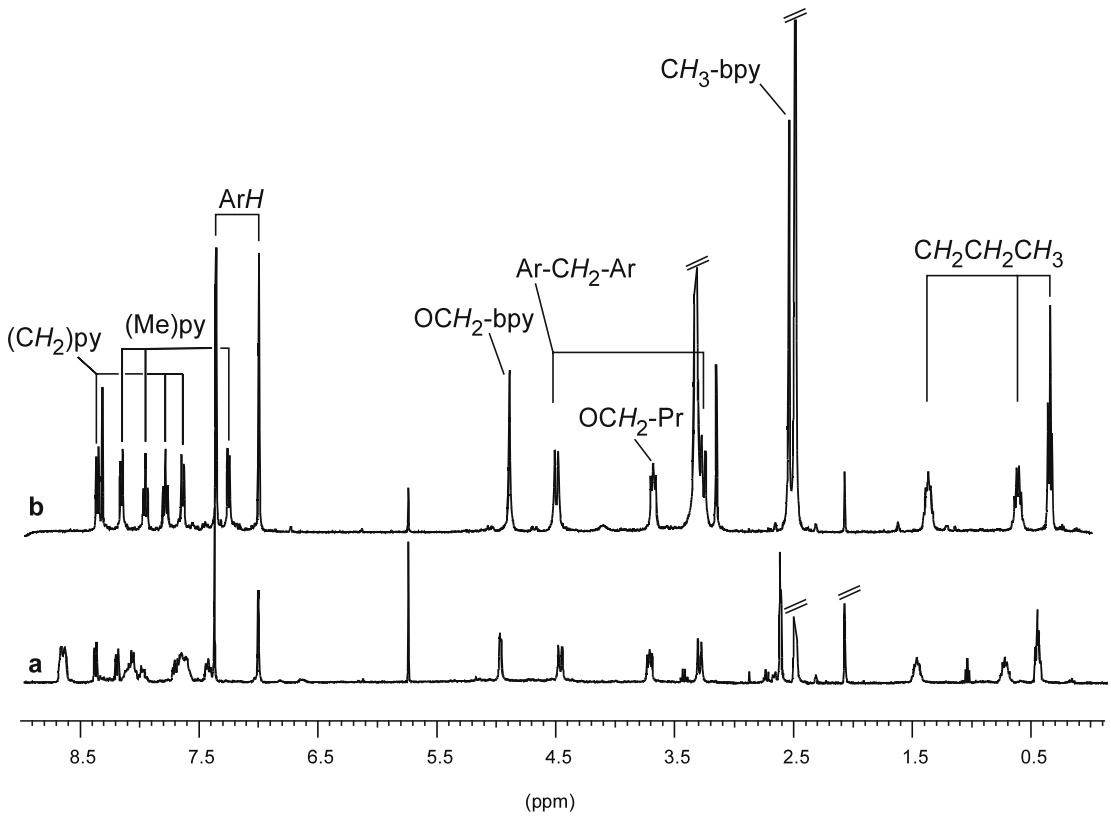


Figure 1. ^{1}H NMR of (**a**) ligand **3**; (**b**) ligand **4** (d_6-DMSO, rt, 400 MHz).

dance with the elemental analysis, consistent with the presence of the title calixarene sulphonic acid, a molecule of H_2SO_4, 3 molecules of H_2O and 2 molecules of pyridine. In this case, the six acidities mentioned above should be the two hydropyridinium ions (counter-anions: two sulphonate groups) and four

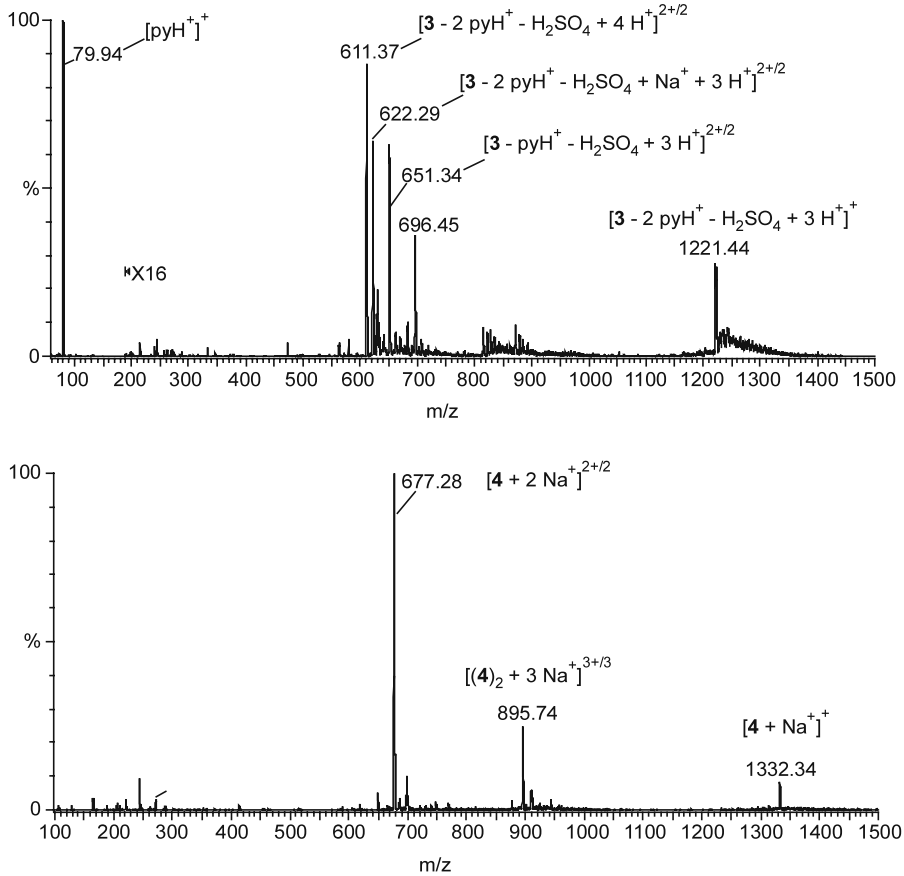


Figure 2. Positive-mode ES-MS of ligand **3** (top); ligand **4** (bottom).

bipyridyl hydropyridinium ions (counter-anions: two sulphonate groups and one sulphate).

Following these titration results, the addition of six equivalents of NaOH to **3** in water afforded the tensioactive sodium salt **4** which was obtained dry by a final lyophilisation process.

^{1}H and ^{13}C NMR (D_2O or d_6-DMSO) confirmed that the cone conformation was preserved. As shown in Fig. 1, **4** exhibited perfectly well-resolved signals in the relevant alkyl and aryl areas. All these signals were attributed by 2D COSY experiments. No residual pyridyl signals were observed, confirming the full exchange between hydropyridinium and sodium cations. Elemental analysis of **4** was consistent with the presence of one Na_2SO_4 and four H_2O.

Electrospray mass spectrometry confirmed the obtention of both species **3** and **4**, in the negative or positive mode. For the latter (Fig. 2), the compound **3** exhibited various mono- to dicharged species based on the tetrasulphonated calixarene skeleton, accompanied by the pyridinium ion at 79.9 a.m.u. A similar but simpler spectrum was obtained with **4**, which exhibited the mono-, di- and tricharged species.

As for the previously reported carboxylate analogue, **4** complexed Cu(I) in water with a ML stoichiometry, giving an orange–red species which remains stable against BSA, suggesting an interesting behaviour in biological media. This last point, as well as complexation studies with other metallic cations, is under current investigation.

Acknowledgements

We are grateful to the MRES and the CNRS for financial support, and to SAFAS (Monaco) for UV spectroscopy. The authors thank Mr. J.-M. Ziegler for mass measurements and Mrs. N. Marshall for correcting the manuscript.

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