Pergamon

Tetrahedron Letters 43 (2002) 8863–8866

TETRAHEDRON
LETTERS

A bifunctional calixarene designed for immobilisation on a natural polymer and for metal complexation

Philippe Engrand and Jean-Bernard Regnouf-de-Vains*

GEVSM, UMR 7565 CNRS-UHP, Faculté de Pharmacie, 5, rue Albert Lebrun, F-54001 Nancy Cedex, France

Received 18 September 2002; revised 2 October 2002; accepted 3 October 2002

Abstract—The present work describes the multi-step synthesis of a new bifunctional calix[4]arene designed for grafting on natural polymeric materials, such as water-soluble dextrans, and for metal complexation. The podand was then anchored to the polymer by means of a cyanuric linker. The resulting material showed an interesting ability to complex copper(I), giving stable yellowish light orange solids and aqueous solutions. © 2002 Elsevier Science Ltd. All rights reserved.

The dextrans are natural hydrosoluble carbohydrate polymers mainly composed of linear chains of glucose units with α-1,6 linkages. Their bioavailability and their potent biocompatibility can explain the interest taken in these structures by various industrial fields. They are mainly used in the formulation of cosmetics, pharmaceuticals, imaging agents and other domains in which they can act as carriers and/or protective agents for other compounds. The presence of secondary alcoholic functions confers to these materials a good ability for chemical transformation, allowing cross-linking such as in Sephadex, and the conjugation, via direct methods or via a pre-activation, of various types of active compounds.[1] The use of dextrans in the field of metal complexation has been essentially developed for the preparation of new image-enhancing agents, notably with lanthanides[2] and other paramagnetic ions via the grafting of amine–acetic acid derivatives (DTPA)[2] or of macrocyclic chelates.[3]

As calixarenes are known to be good candidates for complexing neutral or ionic organic guests in their cavities,[4] or, when modified by incorporation of chelating arms, of various metal species,[5] we were interested in the development of materials able to display these specific behaviours, but in a way that allows the recovery of the complexing agent and its intrinsic properties. This approach has been developed by immobilisation of various calixarenes on silica[6] and on synthetic polymers,[7] or by direct polymerisation of calixarenes monomers[8] but, except for chitosan[9] the use of natural polymers as supporting matrices has not been, as far as we know, investigated. We thus present here our preliminary results on the synthesis of a new metal-complexing dextran-supported calixarene. Thus, our first goal was to prepare a polyfunctional calixarene species bearing a complexing subunit and one anchoring substituent, both introduced at the lower rim for an easier synthetic accessibility. Using the base-strength driven regioselective functionalisation approach,[10] the introduction of the anchoring group was performed on the residual hydroxyl group of the previously described tris-bipyridyl calixarene podand **I**.[11] Among the various types of covalent linkages available in the chemistry of cellulose and parent polymers, we have chosen the cyanuryl chloride, employed notably in dying processes or covalent coating of bioactive amino compounds,[12] and which can be used as co-reactant in one-pot synthetic pathways.[13] Thus, the calixarene was activated by the introduction of an amino group separated from the macrocyclic platform by an alkylaromatic propyleneoxyphenyl linker, which was preferred to simple alkyl ones for analytical reasons, notably for NMR and UV spectroscopies.

The tris-bipyridyl calixarene **1** initially prepared in a low-yield two-step process from *p*-*tert*-butylcalix[4]arene and 6-bromomethyl-6′-methyl-2,2′-bipyridine was obtained here with a much better yield (ca. 90%) from the same reactants and the couple BaO:Ba$(OH)_2$ as base in DMF.[14] The *p*-nitrophenoxypropyl spacer was introduced at the residual calixarene hydroxyl group by reaction of its bromo analogue[15] with **1** in dry DMF and NaH as base, affording the nitro calixarene **2** with a yield of 93% (Scheme 1). The reaction of **2** with $SnCl_2$ in EtOH at

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* Corresponding author. Fax: (33)3 83 68 23 45; e-mail: jean-bernard.regnouf@pharma.u-nancy.fr

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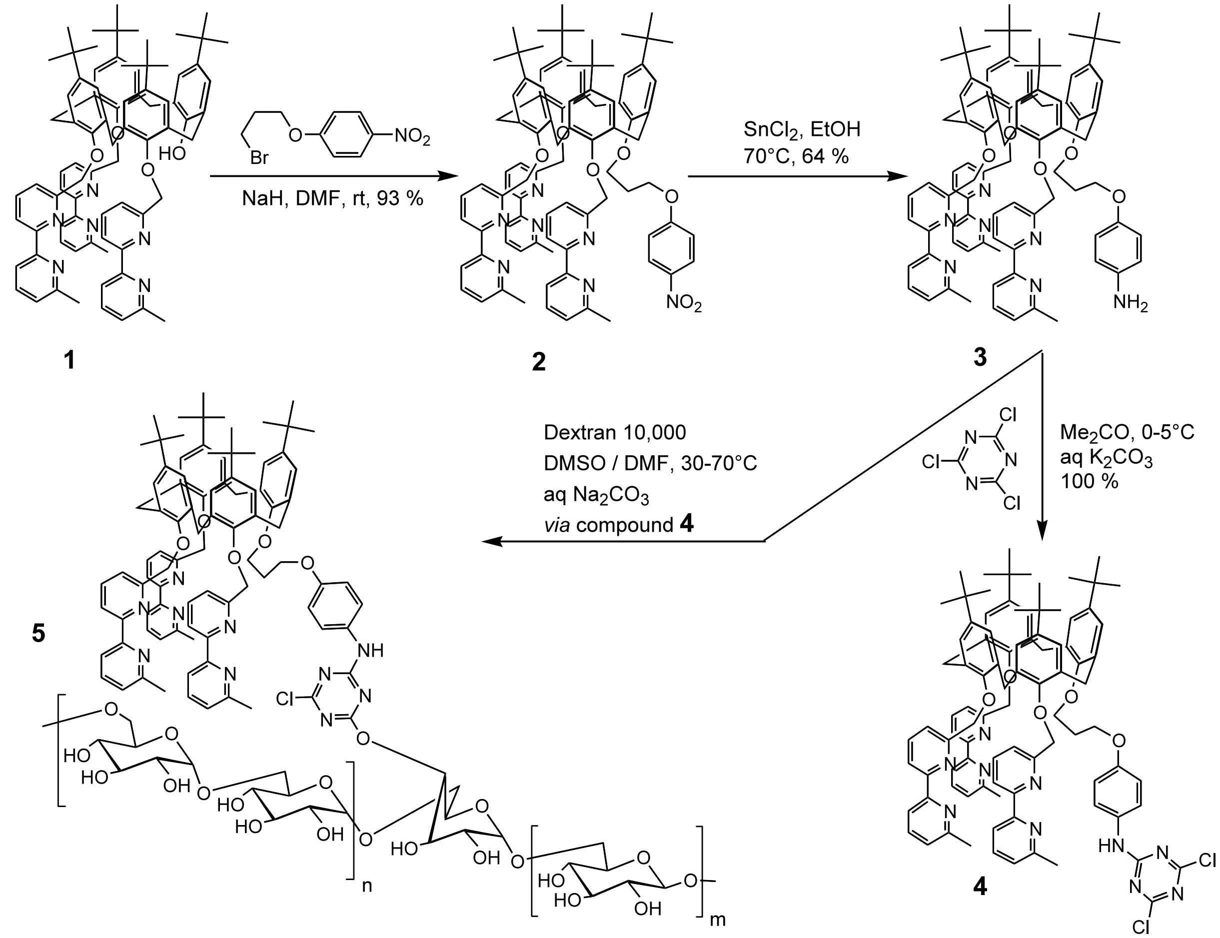
PII: S0040-4039(02)02203-7



Scheme 1. Synthetic pathway (**5**: proposition of structure).

70°C[16] gave the amino calixarene **3** with a yield of 64%. In order to understand the reaction mechanisms involved in the next grafting step, but also in order to try direct coupling reactions on dextran polymers, we synthesised the chlorocyanuryl derivative **4**, by reacting **3** with cyanuryl chloride and K_2CO_3 in acetone.[17] The calixarenes **1**–**4** gave satisfactory NMR, mass and elemental analyses. According to de Mendoza et al.,[18] ^{13}C NMR confirmed that the cone conformation was preserved, with Ar-*C*H$_2$-Ar resonance signals appearing between 31 and 32 ppm.

Various dextrans have been tested as supporting polymers, but the quasi-insolubility of high-molecular-weight species in standard organic solvent brought us, for analytical reasons, to give most of our attention to dextran 10,000, its good solubility in DMSO being useful for UV–vis and NMR spectroscopies. A one pot procedure involving the direct mixing of the amino compound **3**, cyanuryl chloride, polymer and base in the adapted solvent was chosen.[13] The preliminary evaluation of the grafting was monitored by the reaction of $Cu(MeCN)_4PF_6$ on the resulting material, that should give an orange-to-red colouring due to the formation of a tetrahedral bipyridine/Cu(I) complex. The main problem in this strategy was the choice of the solvent system: as water was prohibited due to the insolubility of the calixarene and to the risks of hydrolysis, we focused on polar aprotic organic solvents. Pure DMF, which is recommended for this synthetic approach,[13] does not solubilise dextran 10,000; the grafting reaction which must occur in this case at the surface of the polymeric material was not observed (based on the absence of an evident orange colouring after addition of Cu(I) salt). Pure DMSO, which is an excellent solvent for dextran 10,000, promised good operating conditions. Nevertheless, we found that this solvent did not favour the grafting: the compound **4**, which, on the base of TLC analyses, was formed in situ, remained unchanged and the resulting solid gave no reaction with Cu(I). We thus supposed that DMF was essential to the reaction, and found that the presence of 10% of DMSO in DMF was sufficient to solubilise dextran 10,000. Under these conditions, the grafting reaction occurred, giving, after treatment, solid materials which reacted, in the solid state or in aqueous solution with Cu(I); the resulting complexes remained stable over 2 weeks in ambient conditions (Fig. 1). Three different ratios of calixarene versus sugar units, 5, 10 and 30% (3, 6 and 18 calixarene units by dextran chain), were tested, giving the solid materials **5a**–**c**. Attempts to evaluate the amounts of grafted calixarenes involved ^{1}H NMR and UV–vis spectroscopies.

^{1}H NMR experiments, performed in DMSO-d_6, showed the apparition of aromatic signals between 5.5 and 8.5

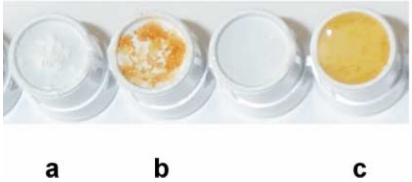


Figure 1. Visualisation of the complexation. (a) Solid **5c**; (b) solid **5c**+Cu(I) in MeCN; (c) aq. soln of **5c**+Cu(I) in MeCN.

ppm, and alkyl ones at ca. 0.9 and 1.2 ppm which were attributed to the calixarene moieties (Fig. 2). The integrations of calixarene and dextran parts were compared, resulting in an evaluation of grafting ratios (calixarene versus dextran chains) of 11, 59 and 48% for **5a**–**c**, respectively. At the same time, the amount of water associated to the polymers was evaluated to be 33, 16 and 27%, respectively. This allowed us to calculate the real mass of polymer involved in the following UV–vis experiments.

UV spectroscopy in H_2O confirmed the presence of chromophoric material with an absorption band at 285 nm attributed to the grafted bipyridyl calixarene. The controlled addition of $Cu(MeCN)_4PF_6$ resulted in the apparition of the expected MLCT (metal-to-ligand charge-transfer; orange-to-red colour) band at 455 nm. The ratios of grafting were thus evaluated, on the base of one Cu(I) ion for one calixarene unit,[11] to ca. 29, 54 and 58% for **5a**–**c**, respectively. Nevertheless, the irregular increase of absorbance at this wavelength suggested that mixing problems occurred and led us to operate in DMSO. In this solvent, the three species exhibited an absorption maximum at 279 nm. The absorbance values, directly correlated to the presence of the calixarene, were compared to **4** ($\varepsilon = 54{,}000$ mol^{-1} L cm^{-1}; DMSO). According to these measurements, the ratio of grafting was evaluated to 30, 57 and 55% for **5a**–**c**, respectively.

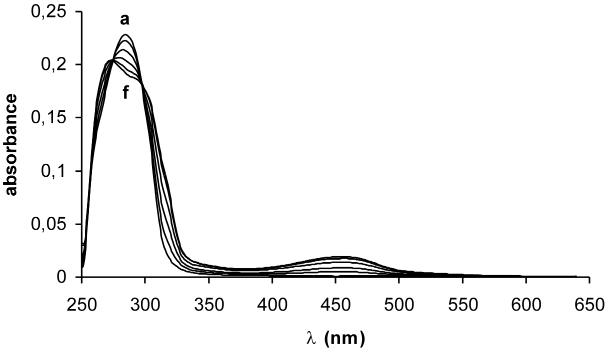


Figure 3. UV–vis titration of **5b** by $Cu(MeCN)_4PF_6$; DMSO. (a) free ligand; (f) free ligand+1 equiv. of Cu(I).

Titration with $Cu(MeCN)_4PF_6$, (Fig. 3), gave, on the base of the MLCT band which appeared at 455 nm, ratios of 12, 50 and 60%, for **5a**–**c**, respectively.

Attempts to directly graft the pre-activated calixarene **4** were unsuccessful in DMSO, and resulted in a rapid degradation process of **4** in DMF.

FT-IR analysis of **5** in KBr pellet showed that the 1800–1350 cm^{-1} region increased strongly, while the 1200–900 cm^{-1} region remained unchanged, with regards to pure dextran 10,000. Attempts to quantify the grafting process by this method were unsuccessful at this time.

We have prepared a bifunctional calixarene species dedicated to the complexation of transition metal cations and able to be fixed covalently on carbohydrate polymers. We have shown by spectroscopic methods and complexation experiments that the grafting was efficient, but in low yields. Improvement of the reaction conditions and development of new and more efficient synthetic strategies with soluble and insoluble polymers are under current investigations.

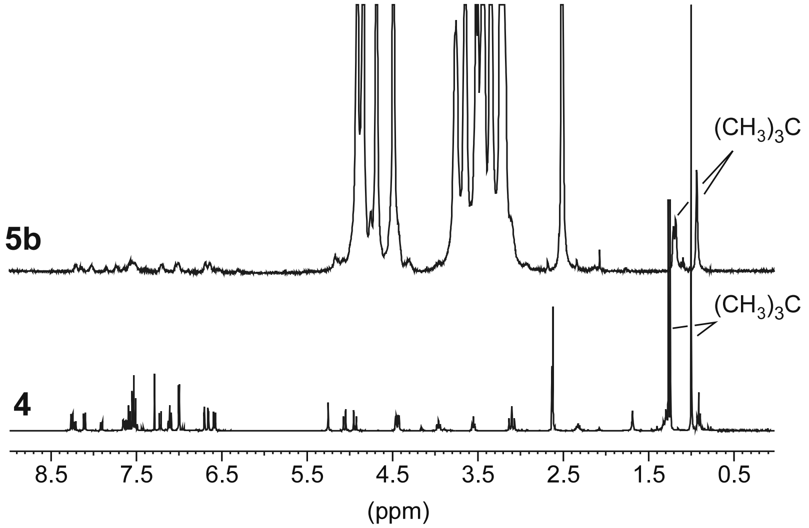


Figure 2. Comparison of ^1H NMR spectra of compounds **4** ($CDCl_3$) and **5b** (DMSO-d_6).

Acknowledgements

We are grateful to the CNRS for financial support and to SAFAS (Monaco) for UV spectroscopy. The authors thank Mrs. N. Marshall for correcting the manuscript.

References

1. For a recent review in the field of therapeutics, see: Mehvar, R. *J. Control. Release* **2000**, *69*, 1.
2. See, for example: Rongved, P.; Fritzell, T. H.; Strande, P.; Klaveness, J. *Carbohydr. Res.* **1996**, *287*, 77.
3. Kiefer, G. E.; Simon, J. (Dow Chemical Co., USA) WO 9,312,112, 1993.
4. (a) Gutsche, C. D. '*Calixarenes*', *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Series Ed.; Royal Society of Chemistry: Cambridge, 1989; (b) *Calixarenes. A Versatile Class of Macrocyclic Compounds*; Vicens, J.; Böhmer, V., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 1991; (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; (d) *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.
5. Wieser, C.; Dieleman, D. B.; Matt, D. *Coord. Chem. Rev.* **1997**, *165*, 93.
6. For example, see: (a) Glennon, J. D.; Horne, E.; Hall, K.; Cocker, D.; Kuhn, A.; Harris, S. J.; McKervey, M. A. *J. Chromatogr. A* **1996**, *731*, 47; (b) Nechifor, A. M.; Philipse, A. P.; de Jong, F.; van Duynhoven, J. P. M.; Ebgerink, R. J. M.; Reinhoudt, D. N. *Langmuir* **1996**, *12*, 3844; (c) Lee, Y. K.; Ryu, Y. K.; Ryu, J. W.; Kim, B. E.; Park, J. H. *Chromatographia* **1997**, *46*, 507.
7. For example, see: (a) Deligöz, H.; Tavasti, M.; Yilmaz, M. *J. Poly. Sci., A1, Polym. Chem.* **1994**, *32*, 2961; (b) Deligöz, H.; Yilmaz, M. *J. Poly. Sci., A1, Polym. Chem.* **1995**, *33*, 2851; (c) Deligöz, H.; Yilmaz, M. *React. Funct. Polym.* **1996**, *31*, 81; (d) Ohto, K.; Tanaka, Y.; Inoue, K. *Chem. Lett.* **1997**, 647.
8. For example, see: (a) Harris, S. J.; Barrett, G.; McKervey, M. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1224; (b) Dondoni, A.; Ghiglione, C.; Marra, A.; Scoponi, M. *J. Chem. Soc., Chem. Commun.* **1997**, 673; (c) Blanda, M. T.; Adou, E. *J. Chem. Soc., Chem. Commun.* **1998**, 139.
9. (a) Berthalon, S.; Thèse d'Université, Lyon, 1998; (b) Berthalon, S.; Regnouf-de-Vains, J.-B., in preparation.
10. (a) Bottino, F.; Giunta, L.; Pappalardo, S. *J. Org. Chem.* **1989**, *54*, 5407; (b) Pappalardo, S.; Giunta, L.; Foti, M.; Ferguson, G.; Gallagher, J.-F.; Kaitner, B. *J. Org. Chem.* **1992**, *57*, 2611.
11. Regnouf-de-Vains, J.-B.; Lamartine, R. *Helv. Chim. Acta* **1994**, *77*, 1817.
12. (a) Kay, G.; Crook, E. M. *Nature* **1967**, *216*, 514; (b) Crook, E. M.; Kay, G. US Pat. 742,978, 1971; (c) Fahmy, A. S.; Bagos, V. B.; Mohammed, T. M. *Biores. Technol.* **1998**, *64*, 121.
13. Pardal, A. C.; Ramos, S. S.; Santos, L.; Almeida, P. *Color. Technol.* **2001**, *117*, 43.
14. Pellet-Rostaing, S.; Regnouf-de-Vains, J.-B.; Lamartine, R. *Tetrahedron Lett.* **1996**, *37*, 5889.
15. Dodic, N.; Dumaitre, B.; Daugan, A.; Pianetti, P. *J. Med. Chem.* **1995**, *38*, 2418.
16. Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.
17. Thurston, J. T.; Dudley, J. R.; Kaiser, D. W.; Hechenbleikner, I.; Schaefer, F. C.; Holm-Hansen, D. *J. Am. Chem. Soc.* **1951**, *73*, 2981. Selected analytical data of **4**: ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.509 (C-NH cyanuryl), 170.388 (C-Cl), 171.644 (C-Cl); ES-MS (positive mode): 1493.74 $[\mathbf{4}+H]^+$, 1516.72 $[\mathbf{4}+Na]^+$. Anal. calcd for $C_{92}H_{96}Cl_2N_{10}O_5 \cdot HCl$ (1529.201): C, 72.26, H, 6.39, N, 9.16. Found: C, 72.25; H, 6.32; N, 9.26%.
18. (a) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372; (b) Magrans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, *62*, 4518.