Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 281–284

Tetrahedron Letters

A new symmetrically modified α-cyclodextrin tripode: selective metal complexation and fluorescence properties

Romain Heck and Alain Marsura*

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

Received 30 September 2003; revised 18 October 2003; accepted 29 October 2003

Abstract—A new tripodal α-cyclodextrin having three ureido-bipyridyl tethers symmetrically distributed on its upper rim was prepared in one step by the polymer supported 'phosphine imide' reaction in a medium yield. As expected, the highly selective complexation properties towards 'hard' and 'soft' cations were maintained with regards to the URFT-Cd (upper rim fully tethered) family previously investigated. Its Eu^{III} and Tb^{III} lanthanide complex fluorescence behaviour clearly indicates that a limited number of tethers allow a better bis-heterocyclic antenna self-organisation around the cation leading to enhanced fluorescence properties.

One family of Cds: the metallocyclodextrins (metalloCds) are viewed as coordination compounds or metal complexes in which one or several modified Cds act as ligands and/or as 'distributors' of spatially preorganised substituents. However, the majority of metalloCds are formed from functionalised Cds, which incorporate one or more metal ion coordinating groups of varying degrees of complexity. Most of the studies on these systems concern the coordination of one or more metal ions to produce at least a binary metalloCd in which subsequently, a guest may be complexed in the Cd core and may also be coordinated by the metal to give a ternary metalloCd. Under these circumstances an opportunity arises to study the effects of the metal centre and Cd interactions on metalloCd stability and guest complexation.[1] In the past decade the metallocyclodextrins have been shown to be a valuable source of original supramolecular devices exhibiting a wide range of interesting properties such as enzyme mimicking,[2] catalysis,[3] chiral discrimination[4] and energy and electron transfer.[5] In recent years, a limited number of these mononuclear and/or polynuclear designed metallocyclodextrins in which energy and electron transfer processes have been observed, have appeared in current literature.[6] In particular, lanthanide complexes of modified cyclodextrins, which possess luminescent properties, make them interesting to build as molecular energy-conversion systems potentially able to act as miniature photomolecular devices in the development of nanotechnology.[7]

In the course of our investigations on the coordination properties of such systems we have recently reported a set of new URFT-Cds (upper rim fully tethered) with ureido-[8] or thioureido-bipyridyl[9] tethers affording powerful metal-chelating devices having three distinct superimposed selective intramolecular recognition sites.

The above-mentioned podands were able to discriminate between 'hard' and 'soft' metals, to afford distinct mononuclear or dinuclear metal complexes and to form inclusion complexes with the Cd hydrophobic cavity.[10] The aim of the present work is to propose an original synthesis of a new modified Cd having a limited number of ureido-bipyridyl tethers symmetrically distributed on the upper rim of an α-Cd (Fig. 1) and to explore the impact of these modifications on its complexation properties and fluorescence behaviour.

The synthesis of symmetrically substituted Cds of interest was directly conditioned by the accessibility of corresponding Cd intermediates, which could be obtained in bulk and if possible by an easy route with limited long chromatographic separations and/or tedious protection–deprotection steps. Recently, we

---

Keywords: Modified cyclodextrin; MetalloCds; Lanthanides; Luminescence; Complexation.

* Corresponding author. Tel.: +33-03-8368-2324; fax: +33-03-8368-2345; e-mail: alain.marsura@pharma.uhp-nancy.fr

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.172

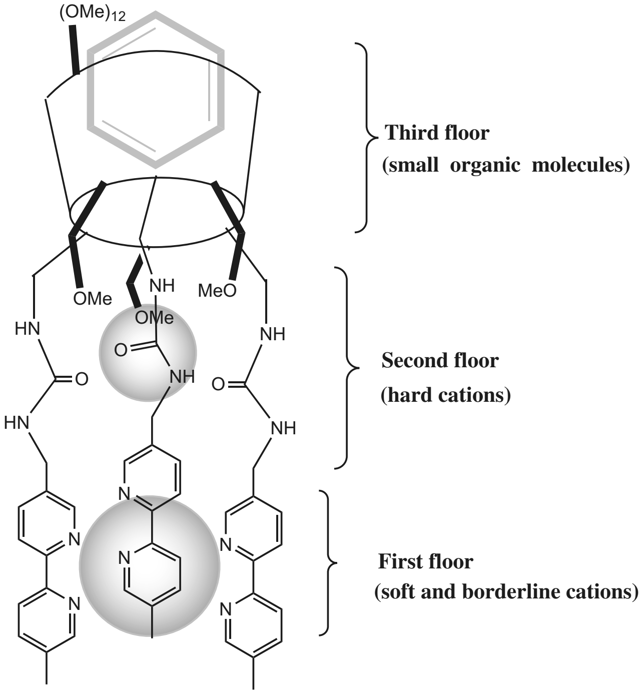


Figure 1. Schematic representation of the α-Cd tripode and its three selective sites of complexation.

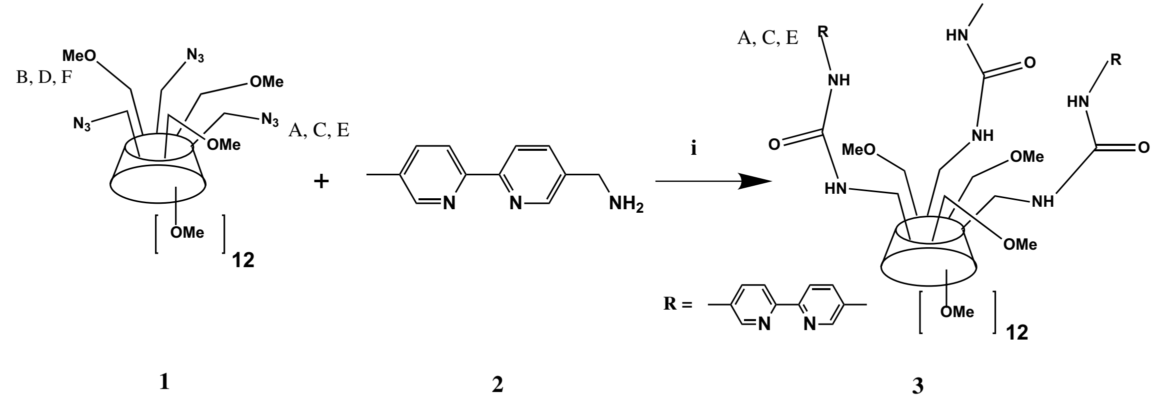
presented one example of such a preparation in the case of α-cyclodextrin.[11] This procedure allowed a direct efficient synthesis of the corresponding metallo-α-Cds in three steps from native α-Cd and in one step from the 6^A, 6^C, 6^E-triazido-6^A, 6^C, 6^E-trideoxy-6^B, 6^D, 6^F-tri-*O*-methyl-hexakis-(2,3-di-*O*-methyl)-cyclomaltohexaose **1** by the 'one pot' phosphine imide polymer-supported reaction[12] (Scheme 1). 5-aminomethyl-5′-methyl-2,2′-bipyridine **2** was obtained using a literature-modified method.[13,14] The tripode **3** was prepared by condensation of **1**, a slight excess of the amine **2** (4 equiv) and polystyrene-bound triphenylphosphine resin (2 g). The reaction was conducted for 24 h at rt in DMF, in a reactor for solid-phase peptide synthesis equipped with a CO_2 inlet. The product was precipitated from ether as a pure pink powder without any further purification (yield: 41%).

Analysis of **3** by FTIR, UV–vis, NMR and ESI-MS are in agreement with the proposed structure.[15] The positive mode ESI mass spectrum of **3** shows the expected monocharged base peak $[M+Na]^+$ at 1870.2 a.m.u. along characteristic fragment as $[M-(NH\text{–}CO\text{–}NH\text{–}Bpy)+Na]^+$ at 1635.2 u.m.a. indicating rapid cleavage of the tethers on the upper rim of **3**.

The electronic spectrum of **3** recorded in MeOH shows two distinct maxima at 244 nm (38,400 $mol^{-1}\,dm^3\,cm^{-1}$) and 286 nm (41,200 $mol^{-1}\,dm^3\,cm^{-1}$). The IR spectrum of **3** exhibits the characteristic frequency of the urea functionalities at 1660 cm^{-1}. In the lanthanide complexes this frequency was shifted to 1643 cm^{-1} indicating efficient coordination of the carbonyl with the lanthanide. The structural investigation of **3** was completed with the help of ^{13}C NMR.[15] The spectrum exhibited the expected cyclodextrin and bipyridyl signals.

As illustrated in Figure 1 the 6^A, 6^C, 6^E-trisubstituted-ureido-bipyridinyl-Cd **3** accommodated two potential metal complexation sites inside its structure. Titration of the ligand **3** with $EuCl_3{\cdot}6H_2O$, $TbCl_3{\cdot}6H_2O$, 'hard' HSAB classified lanthanide cations and $FeSO_4$, $CuSO_4$ 'borderline' transition metals was monitored by UV–vis spectroscopy.

As expected and observed previously in the case of URFT-β-Cds derivatives,[8] titration curves showed the formation of mononuclear complexes. For example (Fig. 2) the titration by Cu^{II} determined an isobestic point at 300 nm along a strong red shift of the 285 nm absorption band to 310 nm, as a result of efficient metal coordination of the copper cation at the bipyridyl functional groups. The complex was found to have [1:1] stoichiometry. The same stoichiometry and a similar set of curves with the addition of the characteristic MLCT band at 520 nm were found for Fe^{II}. The titration of **3** by Eu^{III} and Tb^{III} lanthanide trichlorides determined also an isobestic point but no red shift and give mononuclear complexes as found before with URFT-Cds analogues.[8] The stability constants $\log(\beta_{11})$ of all the metal complexes have been determined[16] and were 5.1 ± 0.6 and 5.6 ± 0.4 for the europium and terbium complexes, respectively, and 6.4 ± 0.2 for the copper and 6.7 ± 0.2



Scheme 1. Reagents and conditions: (i) Ⓟ—Ph-P-$(Ph)_2$/rt/DMF/CO_2/24 h, 41%.

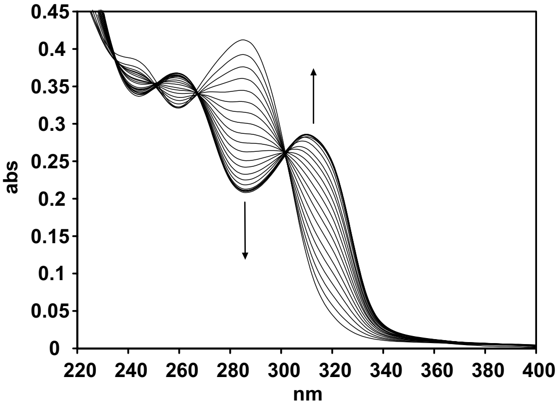


Figure 2. Spectrophotometric titration of ligand **3** with Cu^{2+}MeOH; $C = 1.0 \times 10^{-5}$ mol L^{-1}. $CuSO_4$ $C = 0.07$–1.47 equiv. $\varepsilon_{max} = 41{,}200$ M^{-1} cm^{-1}.

for the iron complexes. It is interesting to point out that the Fe^{II} complex was found to be soluble and very stable in water for several months. The corresponding Eu^{3+} or Tb^{3+} complexes of **3** are compounds, which also exhibit a strong luminescence arising from (A-ET-E) light conversion process (antenna effect). The luminescence excitation of the complexes at 289 nm caused standard emission of the Eu^{III} and Tb^{III} lanthanide ions, thus the transitions corresponding to $^5D_0$–^7F_j (Eu^{III}) and $^5D_4$–^7F_j (Tb^{III}); (Fig. 3) are normally observed. Lifetimes recorded in the time resolved mode for the two complexes from measurement of the decreasing emission intensity at 544 nm (terbium) and 615 nm (europium) gave $\tau_{(300\,K)} = 1.13$ and 0.7 ms, respectively. Quantum yields were also calculated using the relation of Haas and Stein[17] and gave $\Phi_f = 0.103 \pm 30\%$ and $0.015 \pm 30\%$ for the terbium and europium complexes, respectively. The sensitivity of the terbium complex of **3** to water also deserves to be mentioned. Addition of 3% v/v of water caused only 20% extinction of its fluorescence emission while 50% was observed in the case of its europium complex and URFT-β-Cds analogues. In a preliminary approach these results show that the fluorescence characteristics of terbium complex of **3** are better than those observed for the URFT-β-Cd terbium complex analogue ($\tau = 0.71$ ms).[8] Looking at these structures it is obvious that, very probably, only three ureido-bipyridyl tethers on the upper rim of the Cd should be sufficient to complete the coordination sphere of the lanthanide and transition cations. So, it is suggested that the supplementary noncoordinated heterocyclic units in the URFT-Cds preferentially brought a negative contribution on the bis-heterocyclic antenna self-organisation and led to a negative contribution to the fluorescence emission intensity.

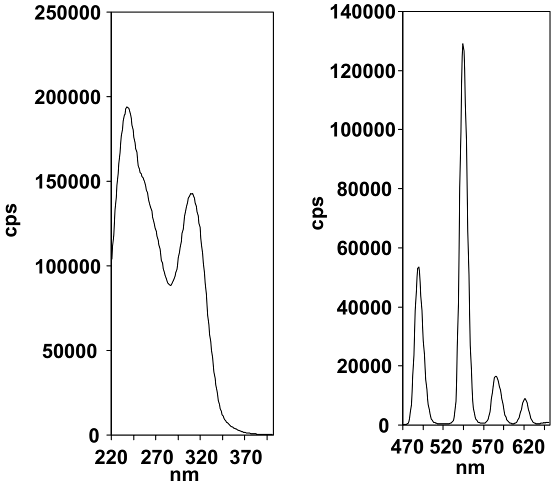


Figure 3. Excitation and emission spectra of the terbium complex of **3**; $C = 1 \times 10^{-5}$ mol L^{-1} in MeOH at 300 K.

In conclusion, it is interesting to note that the complexation properties of URFT-Cds were maintained in the new ligand **3** even with a limited number of tethers on the upper rim of the cyclodextrin. Moreover, the fluorescence properties of its lanthanide complexes were enhanced, probably by better organisation of the tethers around the lanthanide cation giving to it better protection from the solvent nonradiative deactivation. An extensive study of the steady-state photophysical properties of these systems is in progress and will be described in a forthcoming paper.

Acknowledgements

We are grateful to the MRES, to the CNRS, to the Région Lorraine for the financial support and to Cyclolab Ltd. (Hungary) for the generous gift of cyclodextrins. The authors wish to thank Mrs. N. Marshall for correcting the manuscript.

References and Notes

1. Easton, C. J.; Lincoln, S. F. *Modified Cyclodextrins*; ICP: London, 1999; pp 133–189.
2. Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997–2011.
3. Kim, D. H.; Lee, S. S. *Bioorg. Med. Chem.* **2000**, *8*, 647–652; Sallas, F.; Marsura, A.; Petot, V.; Pintér, I.; Kovacs, J.; Jicsinszky, L. *Helv. Chim. Acta* **1998**, *81*, 632–645; Barr, L.; Easton, C. J.; Lee, K.; Lincoln, S. F.; Simpson, J. S. *Tetrahedron Lett.* **2002**, *43*, 7797–7800.
4. Wenzel, T. J.; Bogyo, M. S.; Lebeau, E. L. *J. Am. Chem. Soc.* **1994**, *116*, 4858–4865.
5. Corradini, R.; Dossena, G.; Galaverna, R.; Marchelli, R.; Panagia, A.; Sartor, G. *J. Org. Chem.* **1997**, *62*, 6283–6289; Pikramenou, Z.; Nocera, D. G. *Inorg. Chem.* **1992**, *31*, 532–536; Haider, J. M.; Williams, R. M.; De Cola, L.; Pikramenou, Z. *Angew. Chem., Int. Ed.* **2003**, *42*, 1830–1833.
6. Pikramenou, Z.; Yu, J.; Lessard, R. B.; Ponce, A.; Wong, P. A.; Nocera, D. G. *Coord. Chem. Rev.* **1994**, *132*, 181–194; Charbonnier, F.; Humbert, T.; Marsura, A. *Tetrahedron Lett.* **1998**, *39*, 3481–3484.
7. Serroni, S.; Campagna, S.; Puntoriero, F.; Di Pietro, C.; McClenaghan, N. D.; Loiseau, F. *Chem. Soc. Rev.* **2001**, *30*, 367–375; Barboiu, M.; Lehn, J. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5201–5206.
8. Heck, R.; Dumarcay, F.; Marsura, A. *Chem. Eur. J.* **2002**, *8*, 2438–2445.

9. Heck, R.; Marsura, A. *Tetrahedron Lett.* **2003**, *44*, 1533–1536.
10. Peirera Silva, M.-J. J.; Haider J. M.; Chavarot, M.; Ashton, P. R.; Williams, R. M.; De Cola, L.; Heck, R.; Marsura, A.; Pikramenou, Z. *Supramol. Chem.* **2003**, *15*, 563–571.
11. Heck, R.; Jicsinszky, L.; Marsura, A. *Tetrahedron Lett.* **2003**, *44*, 5411–5413.
12. Porwanski, S.; Kryczka, B.; Marsura, A. *Tetrahedron Lett.* **2002**, *43*, 8441–8443.
13. Sasse, V. H. F.; Whittle, C. P. *J. Chem. Soc.* **1961**, 1347–1350.
14. Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937–3938.
15. Structures of all compounds were assigned by ^{1}H and ^{13}C NMR on a Bruker-DRX 400 spectrometer, FTIR spectra were recorded on a Bruker-Vector 22 spectrometer. Mass spectra were recorded on an ESI-MS Micromass Platform spectrometer. UV–vis on a Safas UVmc^2. Luminescence experiments were performed on a Spex/Jobin-Yvon Fluorolog II photon counting spectrofluorimeter equipped with a 450 W xenon continuous wave irradiation source or a 150 W pulsed xenon lamp. The solvents were purified by standard methods. Polymer-bounded triphenylphosphine ($\sim$3 mmol/g) is from FLUKA. 6^A, 6^C, 6^E-(5-methyleneureido-5′-methyl-2,2′-bipyridine)-6^A, 6^C, 6^E-trideoxy-6^B, 6^D, 6^F-tri-*O*-methyl-hexakis-(2,3-di-*O*-methyl)-cyclomaltohexaose 3. Polystyrene-bounded triphenylphosphine resin (2 g) was stirred for 20 min in 20 mL of anhydrous DMF (freshly distilled and flushed with argon for 20 min). 6^A, 6^C, 6^E-Triazido-6^A, 6^C, 6^E-trideoxy-6^B, 6^D, 6^F-tri-*O*-methyl-hexakis-(2,3-di-*O*-methyl)-cyclomaltohexaose (0.200 g, 0.16 mmol) and 5-aminomethyl-5′-methyl-2,2′-bipyridine (0.127 g, 0.64 mmol, 4 equiv) was then added. The mixture was stirred and flushed with CO_2 for 24 h at rt. The mixture was filtered over, the polymer was washed with 80 mL of DMF and dried. The filtrate was concentrated and the product was precipitated with ether, filtered, washed thoroughly with ether and finally dried under reduced pressure. A pure pink powder was obtained. Yield %: 41 (0.122 g, 6.57×10^{-5} mol). IR (KBr): $\nu = 3384\,\mathrm{cm^{-1}}$ (NH), $1660\,\mathrm{cm^{-1}}$ (*CO*-NH), 1600–$1557\,\mathrm{cm^{-1}}$ (C═C aromatics). UV/vis (MeOH): $\lambda_{\max}(\varepsilon) = 286$ ($41{,}200\,\mathrm{mol^{-1}\,dm^3\,cm^{-1}}$). ^{13}C NMR (DMSO-$d_6$,): $\delta = 163.2$ (*CO*NH), 155.8 (C_2, *bpy*), 153.7 ($C_{2'}$ *bpy*), 150.4 (C_6, *bpy*), 149.0 ($C_{6'}$, *bpy*), 138.4 (C_4, *bpy*), 132.3 ($C_{4'}$, *bpy*), 129.5(C_5, *bpy*), 128.9 (C_3, *bpy*), 126.4 ($C_{3'}$, *bpy*), 120.5 (NH–CH_2-bpy), 102.8 (C_1, *cyclodextrin*), 82.4, 82.0 (C_4, *cyclodextrin*), 73.9, 73.4, 72.9 (C_2, C_3, *cyclodextrin*), 65.8 (C_5, *cyclodextrin*), 61.8 (C_6, *cyclodextrin*), 60.8 ($C_{2,3}$–O–CH_3), 58.7 (C_6–O–CH_3), 21.6, 18.7, 16.0 (CH_3, *bpy*). ESIMS (*m/z*): 1870.15 [M+Na]$^+$, 1635.17 [M−NHCO-NHBpy+Na]$^+$.
16. $\log\beta$ values were calculated using SPECFIT® program v3.0, Ed. R. A. Binstead, Spectrum Software Associates, 1993–2001.
17. Haas, Y.; Stein, G. *J. Chem. Phys.* **1971**, *75*, 3668–3677.