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Heptakis-6-(5-methylene-thioureido-5′-methyl-2,2′-bipyridyl)-β-cyclodextrin: synthesis and metal complexation study

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Abstract—A new heptapode heptakis-6-(5-methylene-thioureido-5′-methyl-2,2′-bipyridyl)-β-cyclodextrin was prepared and its complexation properties towards metal cations were investigated. Substituting the urea functions by the corresponding thioureas promoted the inversion of the metal coordination selectivity. Preliminary results showed the heptapode unable to complex lanthanides but authorise selective complexation of 'soft' and 'borderline' metal cations. © 2003 Elsevier Science Ltd. All rights reserved.

New attention has been focused on the organising properties of cyclodextrin core towards bi-heterocyclic coordinating or heterocyclic systems.[1] These new molecular devices were explored in the sense of a future contribution to nanotechnology developments.[2] Very recently, we described the particular versatility of such molecular scaffolds to undergo metallocyclodextrins which define selective intramolecular sites with respect to the nature of the complexed ion involved.[3] Allosterism, intramolecular translocation of cations (Fe^{II}/Fe^{III}) and (A-ET-E) light conversion process of the corresponding fluorescent lanthanide complexes have been described.

In order to pursue research on upper rim fully tethered CD (URFT-CD) family (Fig. 1), a new entity was designed by replacing the urea functions by the corresponding thioureas. Here, the expected effect should lie in a promoted metal complexation inversion of the selectivity between the two internal cavities arising from sulfur atoms which are known to prefer coordination with 'soft' HSAB classified metals.

The present work describes the convenient synthesis (Scheme 1) of the thioureido bipyridyl-β-cyclodextrin **5** using the 'one-pot' phosphine imide method[4] and some of its complexation properties towards metal cations. The 5-aminomethyl-5′-methyl-2,2′-bipyridine **3** was synthesised using a described synthesis[5] but include a modification of the azide **2** reduction step using the best efficient NH_4Cl/indium method of Iyengar.[6] The heptapode **5** was prepared by the 'one-pot' condensation process from the heptakis-[6-azido]-β-cyclodextrin **4**,[7] a slight excess of the amine **2** (8 equiv.), a 70-fold excess of triphenylphosphine and CS_2 in large excess (40 mL), over a period of 24 h at rt in dry DMF (10 mL). Crude **3** was isolated by precipitation from ether and then purified from residual triphenylphosphine by a soxhlet extraction with ether.

Analysis of **5** by FTIR, UV–vis, NMR, elemental analysis and ESI MS are in agreement with the proposed structure.[8] The positive mode ESI mass spectrum of **5**

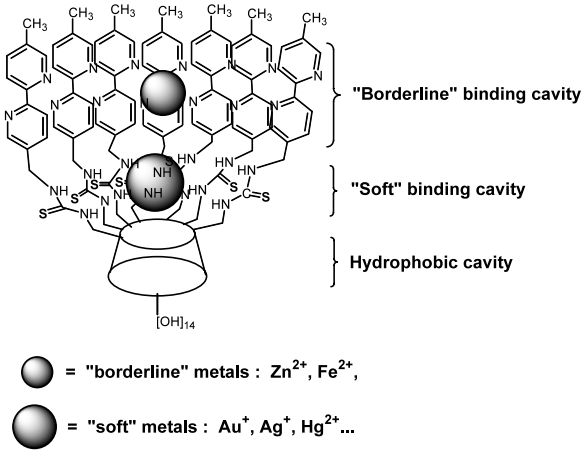

Figure 1. Schematic representation of an upper rim fully tethered CD binuclear complex with 'borderline' and 'soft' binding cavities.

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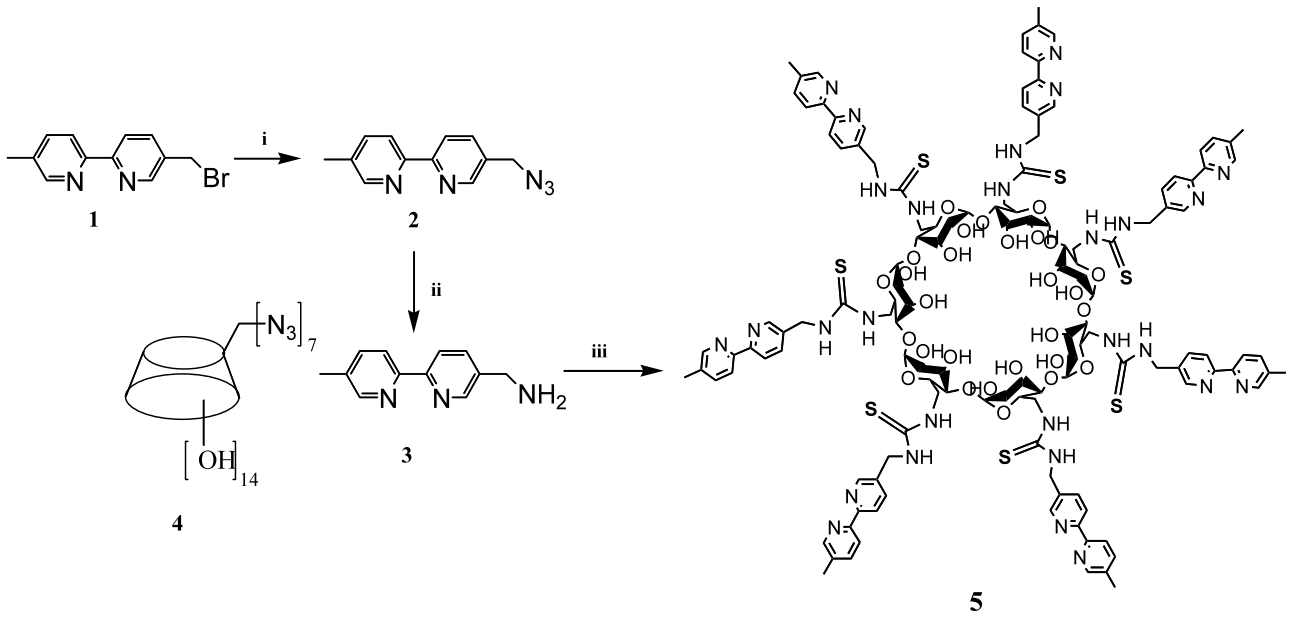

Scheme 1. (i) NaN_3, DMSO, 83%; (ii) In, NH_4Cl, EtOH, reflux 16 h, 86%; (iii) PPh_3, CS_2, DMF, rt, 24 h, Ar, 84%.

did not give the expected monocharged base peak but a complex pattern having characteristic monocharged and multicharged ion fragments as 1010.4 a.m.u. [M–(CH_3-bpy-CH_2-NH-CS-NH-)$_7$]$^+$ (20%), 930.3 a.m.u. [M+2K$^+$-(CH_3-bpy-CH_2-NH-CS-NH-)$_4$]/2 (40%), 763.2 a.m.u. [M+2H$^+$-(CH_3-bpy-CH_2-NH-CS-NH-)$_5$]/2 (58%), 738.5 a.m.u. [M+H$^+$+(3Na$^+$)]/4 (100%), indicating a rapid cleavage of the tethers (thioureido-bipyridyl) on the upper rim of **5**.

The electronic spectrum of **5** recorded in MeOH shows two distinct maxima at 269 nm (46400 mol^{-1} L cm^{-1}) and 288 nm (36600 mol^{-1} L cm^{-1}). The IR spectrum of **5** exhibited the characteristic frequency of the thiocarbonyl functions at 1083 cm^{-1}, the strong absorption of the thioamide frequency at 1438 cm^{-1} and the aromatic double bonds corresponding to the bipyridyl units between 1589 and 1553 cm^{-1}. Structural investigation of **5** was completed with the help of ^{13}C NMR. The spectrum exhibited the expected cyclodextrin and bipyridyl signals.

As illustrated in Figure 1, upper rim fully substituted bipyridinyl-thioureido-Cd **5** accommodated two potential metal complexation sites inside its structure (cyclodextrin core hydrophobic internal cavity is not taken into account). Titration of the ligand **5** with $Eu(Cl)_3$, $6H_2O$, $Tb(Cl)_3$, $6H_2O$ 'hard' HSAB classified lanthanide cation and Fe(SO4), ZnOTf, $Hg(CH_3COO)_2$, $AgPF_6$, Au[19] 'soft' or 'borderline' transition metals was monitored by UV–vis spectroscopy. In contrast to ureido-Cd compound metal complexation properties previously reported[3] and as expected the thioureido analog **5** was found unable to form any complex with lanthanides, e.g. Eu^{III} 'hard' cation. On the contrary, titration curves by 'soft' metals as Hg^{II}, Ag^{I}, Au^{I} or 'borderline' metals as Zn^{II} and Fe^{II} showed the formation of mononuclear and binuclear complexes of **5**. For example (Fig. 2) the titration by Hg^{II} determines an isobestic point at 304 nm along a slight red-shift of the 288 nm absorption band to 294 nm, appearance of an LMCT shoulder at 318 nm as a result of efficient metal coordination and according to conformational changes occurring in the ligand. The complex was found of [1:1] stoichiometry. Similar behaviour was obtained with Ag^{I} and Au^{I} complexes (not shown). In these complexes Hg^{II}, Ag^{I}, Au^{I} 'soft' cations are coordinated in the thiourea site of **5** probably by the thiocarbonyl sulfurs and/or thiourea nitrogens in accordance with their coordination preference. In contrast, titration of **5** by Zn^{II} and Fe^{II} exhibits different complexation patterns. Titration by zinc (Fig. 3) determines two

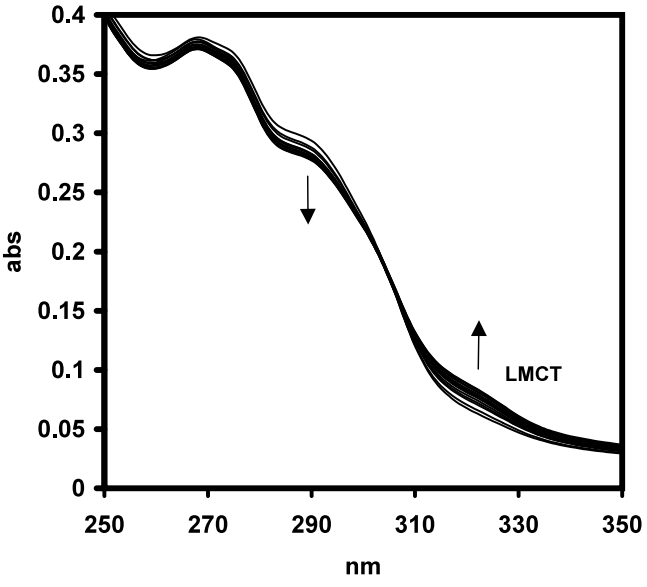

Figure 2. Absorption spectra of ligand **5** in MeOH; $C = 1.22 \times 10^{-5}$ mol L^{-1}. $Hg(CH_3COO)_2$ $C = 0.1$–1.2 equiv.

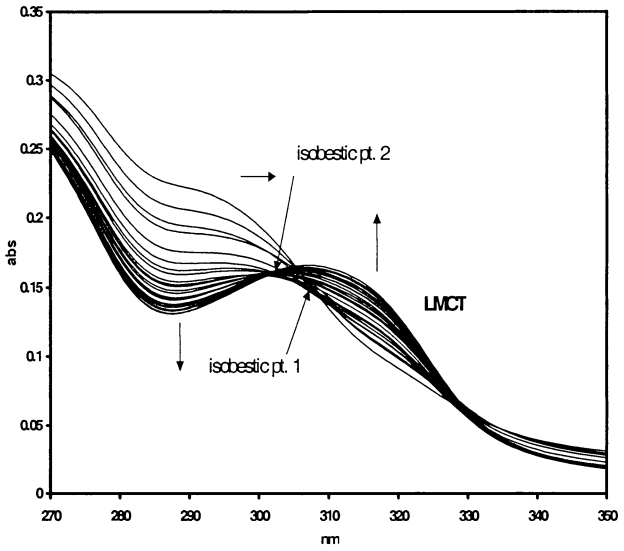

Figure 3. Absorption spectra of ligand **5** in MeOH; $C=1.0\times 10^{-5}$ mol L^{-1}. ZnOTf $C=0.1$–2.5 equiv.

distinct isobestic points, a first one with 1 equiv. of zinc added to the ligand and a second one with 2 equiv., indicating a further [2M:1L] binuclear complex formation. Looking at the absorbance evolution, the first isobestic point appears at 308 nm with an LMCT band (shoulder) at 316 nm, as observed with mercury, silver or gold, and suggests the formation of a first mononuclear Zn^{II} complex with thiourea functions in **5**. The second distinct isobestic point appears at 302 nm along with a strong red-shift of the 288 nm absorption band to 308 nm (Fig. 3) and suggests formation of a second mononuclear complex with the bipyridyl units. The titration of **5** by Fe^{II} determines (Fig. 4) only one isobestic point at 302 nm along a similar strong red-shift of the 288 nm absorption band to 306 nm. The complex was found to be of [1:1] stoichiometry. Appearance of an MLCT band at $\lambda_{max}=520$ nm was also observed along with appearance of the macroscopic characteristic purple colour of the [Fe^{II}-bipyridyl] complex in solution. This result confirms the previous one obtained with 'soft' metals and zinc indicating that the first equiv. of metal was complexed in the thiourea cavity and was followed by the selective formation of a second metal–bipyridyl complex.

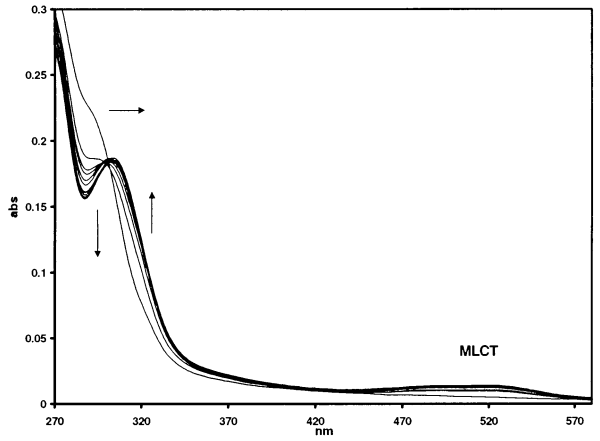

Figure 4. Absorption spectra of ligand **5** in MeOH; $C=1.22\times 10^{-5}$ mol L^{-1}. $FeSO_4$ $C=0.1$–1.5 equiv.

Finally, titration of the mononuclear zinc complex by Fe^{II} determines a second isobestic point, a strong red-shift and appearance of the characteristic MLCT at 520 nm as a result of the Fe^{II} coordination in the bipyridyl units. The resulting heterobinuclear complex was found of [1:1] stoichiometry for the second metal. The heterobinuclear complex absorption spectrum (Fig. 5) is a superimposition of the individual mononuclear complex absorption without appearance of any supplementary charge-transfer band. In contrast, titration of the mononuclear [Fe^{II}-bipyridyl] complex by $Zn(OTf)_2$ does not show further changes in the absorption spectrum. This feature was explained by the formation of the Fe^{II} complex with terminal bipyridines leading to a new pseudocryptand molecular architecture inhibiting the (zinc) cation access to the thiourea cavity. Such a negative allosteric control of cation recognition has been reported recently in the literature[3,10] in similar situations. Finally, a titration of a mononuclear [Fe^{II}-bipyridyl] complex water solution (conc. 10^{-5} mol L^{-1}) by bovine serum albumine (until 50 equiv.) did not show any modification of the UV–vis spectrum indicating a high stability of this complex even in a biological environment.

In conclusion, we have once more shown the versatility of the phosphine imide methodology to build readily and easily new CD ligands having highly selective cation complexation properties. As expected, replacing the urea functions by the corresponding thioureas promoted the inversion of the selectivity of metal complexation involving sulfur atoms in place of urea oxygens which are known to prefer coordination with 'hard' metals.[3] As one can imagine, this method may authorise the introduction of a wide range of functional

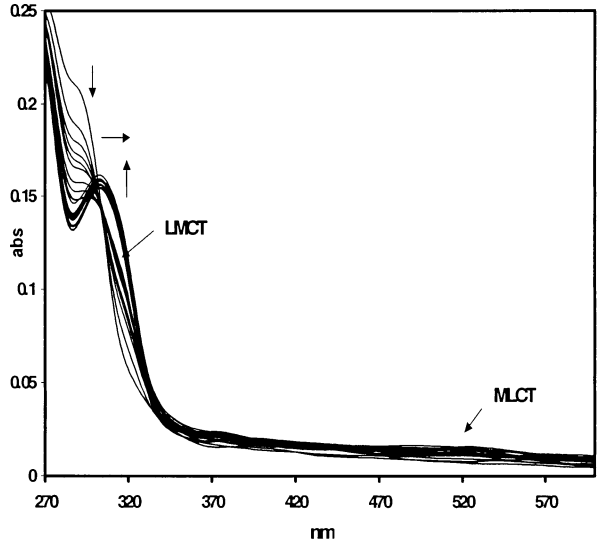

Figure 5. Absorption spectra of ligand **5** in MeOH, $C=8.25\times 10^{-6}$ mol L^{-1}. ZnOTf $C=0.1$–1 equiv. $FeSO_4$ $C=0.1$–1.2 equiv.

groups on the upper ring of the cyclodextrin and probably a fine tuning in control of cation recognition. Such ligands are of great interest because of the variety of potential binding modes and/or their potential pharmacological properties as e.g. gold complexes which have also been reported.[11] Among the new challenges that remain to be addressed, complexation studies of **5** with other cations of interest, with anions and complexation influence of small organic molecules on the cation recognition are in progress. Furthermore, chemical modifications are also planned in order to appreciate the scope and limitations of these properties.

Acknowledgements

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8. Structure 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 Plateform Micromass Platform spectrometer. Elemental analyses were obtained with a EuroEA-Vector analyser. The solvents were purified by standard methods.

Amine 3. 4.13 mmol of 5-azidomethyl-5′-methyl-2,2′-bipyridine ($m=930$ mg, MM = 225.25 g mol^{-1}), 4.54 mmol of indium (1.1 equiv. $m=521$ mg, MM = 114.82 g mol^{-1}), 4.54 mmol of ammonium chloride (1.1 equiv. $m=243$ mg, MM = 53.5 g mol^{-1}) are mixed in 50 mL of ethanol. The solution was stirred and refluxed under argon for 6 h. The mixture was then cooled to room temperature, diluted with 80 mL of ethyl acetate, stirred for 10 min then filtered through a celite pad, washed with 2×10 mL of ethyl acetate. The filtrate was then evaporated to dryness under reduced pressure. The product was obtained pure. Rdt%: 84 (690 mg, 3.46 mmol) TLC (Al_2O_3, CH_2Cl_2/MeOH 90/10): R_f: 0.52. ^{1}H NMR ($CDCl_3$, δ = ppm): 8.59 (s, 1H, H6-bpy); 8.49 (s, 1H, H6′-bpy); 8,32 (d, 1H, ^{3}J (H,H) = 8.20 Hz; H3-bpy); 8.26 (d, 1H, ^{3}J (H,H) = 8.20 Hz; H3′-bpy); 7.77 (d, 1H, ^{3}J (H,H) = 8.20 Hz; H4-bpy); 7,61 (d, 1H, ^{3}J (H,H) = 8.20 Hz; H4′-bpy); 3.94 (s, 2H, CH_2); 2.38 (s, 3H, CH_3); 1.62 (s, NH_2).

Heptakis-6-(5-methylene-thioureido-5′-methyl-2,2′-bipyridinyl)]-cyclomaltoheptaose 5. A mixture of 9.41×10^{-5} mol of heptakis-(6-deoxy-6-azido)-cyclomaltoheptaose ($m=123$ mg, MM = 1309 g mol^{-1}), 7.53×10^{-4} mol of 5′-aminomethyl-5-methyl-2,2′-bipyridine ($m=150$ mg, 199.25 g mol^{-1}, 8 equiv.) and 6.58×10^{-3} mole of triphenylphosphine ($m=1.73$ g, MM = 262.3 g mol^{-1}, 70 equiv.) in 10 mL of anhydrous DMF (freshly distilled and flushed with argon for 20 min) was added dropwise, under argon, to 40mL of CS_2 (excess, MM = 76.14 g mol^{-1}) in a tricol previously flushed with argon. The solution was stirred at room temperature under argon for 24 h then evaporated to dryness. The product was precipitated with diethylether, filtered over fritted and washed several times with diethylether then treated with a soxhlet in diethylether for 24 h. Rdt%: 84 (220 mg), IR (KBr): ν = 3394–2920 cm^{-1} (NH, OH), 1589–1553 (c=c aromatics), 1438 (NH–C=S), 1083 (C=S). UV–vis (MeOH): 269 nm (46400 mol^{-1} L cm^{-1}) and 288 nm (36600 mol^{-1} L cm^{-1}). ^{13}C NMR (DMSO-d_6): δ = 163.2 (C=S), 154.9 (C_2), 153.5 ($C_{2'}$), 150.5 (C_6), 149.2 ($C_{6'}$), 138.4 (C_4), 137.2 ($C_{4'}$), 133.6 (C_5), 120.7 (C_3), 120.5 ($C_{3'}$), 101.7 (C_1), 80.0 (C_4), 72.9 (C_2, C_3), 65.8 (C_5), 18.7 (CH_3). Anal. calcd for $C_{133}H_{154}N_{28}O_{28}S_7$ (2817.28): C, 56.70; H, 5.51; N, 13.92; S, 7.97; found: C, 56.61; H, 5.46; N, 14.73; S, 7.45.

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