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A Convenient One-Pot Synthesis of Cyclam-β-Cyclodextrins New Ligands

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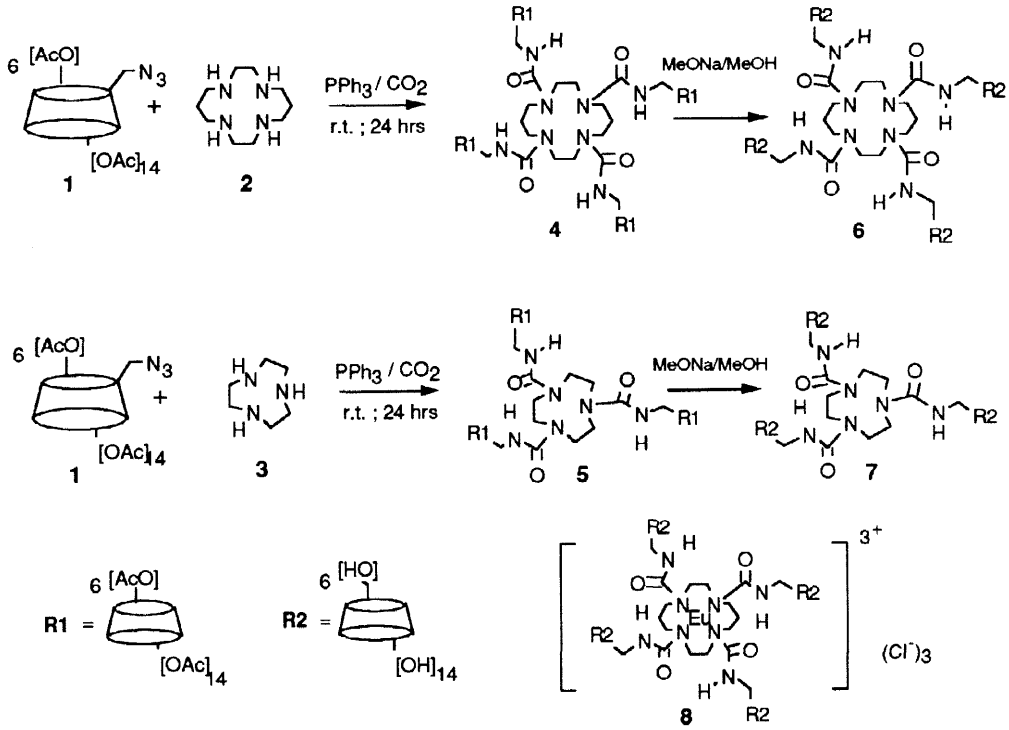
Abstract : The present work describes the one-pot synthesis of new polyazamacrocyclic compounds **4-7** having hydrophobic hosts cavities (β-cyclodextrins) attached to a metal chelating aza-macrocycle by ureido spacer arms. A coupling average of 30% was obtained, proving the efficiency of the "phosphinimine" method for a rapid access to new supramolecular devices. The subsequent complexation of **6** with $EuCl_3$ give the stable complex **8**. Preliminary results on fluorescence properties are reported.

Progressing in the research field of new direct and powerful synthetic approaches to oligosaccharidyl abiotic receptors builded on the basis of cyclodextrins (Cds) hosts cavities, we have recently reported a first scope for the "phosphinimine" approach leading to new supramolecular carbon-nitrogen linked Cds dimers from primary amines [1, 2]. Elsewere, among them, one bearing a bidendate ligand (e.g. phenantroline) have shown an interesting highly selective cation recognition and a strong catalytic esterase activity of it copper complex [3] at a competitive level regards to previously published thio-dimers [4].



Scheme

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Present work was performed to improve and extend this approach to cyclams. So we describe here a one-pot synthesis of new ligands **4-7** having three or four Cds hosts linked to a metal chelating aza-macrocycle moiety by an urea spacer (Scheme).

The condensation of peracetylated 6-monoazido-β-Cd[5] **1** with cyclic polyamines **2, 3** in presence of triphenyl phosphane in excess and anhydrous CO_2 continuous bubbling readily gives the expected, tri and tetra-Cds ligands **4** and **5** in a relative good overall yield (30%) after 24 hours of reaction and purification on a silicagel chromatography (CH_2Cl_2 98 / MeOH 2). The reaction occurs at room temperature in anhydrous DMF as solvent. The unprotected products **6** and **7** were obtained after a Zemplen deacetylation step (90%). It should be noted that the reaction could be also performed from the unprotected 6-monoazido-β-Cd as well as the acetylated one. Nevertheless, this method needing a more laborious purification workup (reverse phase HPLC chromatography) leads to significative lost of product and makes this approach less interesting. The structures of new compounds **4** to **7** were analyzed by IR, NMR and ESMS and the collected data are in agreement with the proposed structures [6]. IR spectra of new compounds show characteristic ν (*CO*-NH) carbonyl frequencies and amine ν (CO-*NH*) of urea functions formed. Compounds **4** to **7** show highly complex NMR spectra in the 3.4 to 5.6 ppm region (strong splitting and overlapping of the H_1 to H_6 glucosyl subunits and cyclam protons) and doesn't allow directly complete and safe attribution of each pattern. Still, HMQC experiments recorded on **4** and **5** allow assignment of most the protons.

More than the above ligands structure determination, our intention was also to study the complexation behavior toward lanthanides and transition metals: -to explore a potential biomimetic catalytic activity in comparison to, Cds dimers, macrocyclic tetraamides and other complexes near structures recently published [7] and : -to determine fluorescence properties of the lanthanides complexes. In this sense, we present preliminary results on the tetrakis-[ureido-Cd]-tetraazacyclotetradecane Eu (III) complex **8.** This complex was obtained by simple stirring 1.2 equiv of $EuCl_3$, $6H_2O$ with 1.0 equiv of **6** in MeOH / H_2O (4 / 1) solvent mixture, during 24 hours at room temperature.

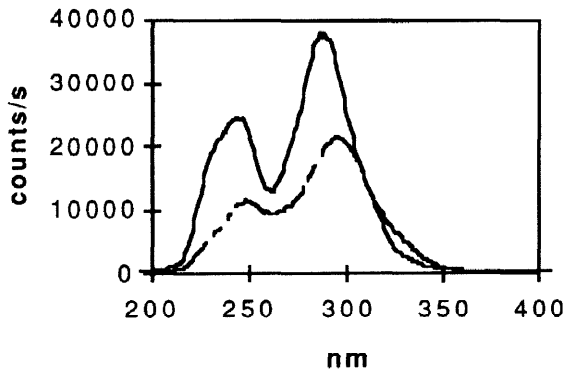
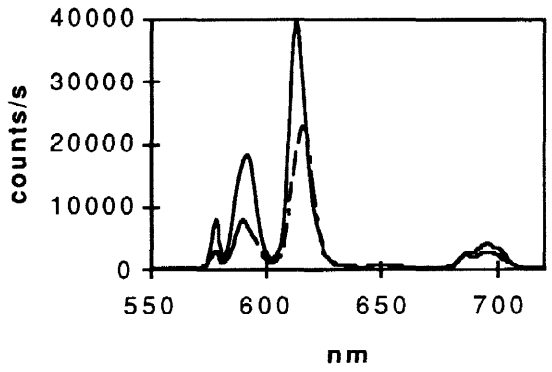


Fig 1. Luminescence excitation spectra of **8** (—) in D_2O; (- - - -) in MeOH; C = 1.0 X 10^{-5} mol.L^{-1}.



Luminescence emission spectra of **8** (—) in D_2O; (- - - -) in MeOH; C = 1.0 X 10^{-5} mol.L^{-1}.

Pink crystallized slides of pure **8** were obtained by crystallization in MeOH. The absorption spectra in H_2O and MeOH show same absorption maxima in the UV region at 248nm and 295 nm. Concerning the luminescence spectra of **8** (Fig. 1), excitation at 295 nm causes structured emission of the Eu^{3+} ion *via* the absorption -energy transfer-emission (A-ET-E) light conversion process. Thus the bands corresponding to the $^5D_0$ -> ^7F_J (J = 1, 2, 3, 4) transitions are observed either in MeOH or in D_2O, (Fig 1). The emission spectra

show the same pattern, indicating similar coordination features for Eu^{3+} in the two solvents. The lifetimes are found respectively of 0.66 ms (MeOH) and 3.03 ms (D_2O). Almost total extinction (90%) of the fluorescence was observed after dissolution of **8** in water indicating that the vibronic deactivation process is quite efficient along a probable complex unstability.

Reference to the above results we can conclude to interesting luminescent properties of **8** exhibiting medium luminescence and longer lifetimes than some found with early published lanthanide cryptates [9]. An interesting improvement of the "phosphinimine" approach for the synthesis of complex multi-cyclodextrin hosts has been obtained. The synthesis of new hosts and physicochemical studies on other lanthanides and transition metal complexes are actually in progress along their X-ray structures.

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3. Sallas, F.; Marsura, A.; Petot, V.; Pinter, I.; Kovacs, J.; Jicsinszky, L. *Helv. Chim. Acta* **1998**, (*in press*).
4. Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1994**, *116*, 7893-7894.
5. The 6-monoazido-6-monodeoxy-β-cyclodextrin **1** was prepared according to the literature [8].
6. Structure of all compounds were assigned by ^1H and ^{13}C NMR on a Bruker DRX-400 spectrometer, some of the chemical shifts assignements are based on HMQC experiments, H_a were designed as protons of the substituted Cd-glucosyl residue and H_b are those of the unsubstituted glucosyl units. FTIR spectra are recorded on a Perkin-Elmer-1600; Uv-Vis spectra on a Shimadzu UV-16. Luminescence experiments were performed in time resolved mode on a Spex Fluorolog II photon counting spectrofluorimeter equipped with a 150W pulsed xenon irradiation source. The luminescence decay was acquired using the Spex Fluorolog II and analyzed with a least-squares fitting program. Mass spectra were recorded in ESI positive mode on a Micromass *(UK)* VG-platform II. All new compounds gave satisfactory spectroscopic data.

   4 : Tetra-{ [hexakis-(2,3,6-tri-O-acetyl)]-2,3-di-O-acetyl-cyclomaltoheptaosyl-6-ureido}-1,4,8,11-tetraazacyclotetradecane. Obtained by condensation of **1** (1 mmol, 2 g, 5 equiv), **4** (0.2 mmol, 0.04g, 1 equiv) and triphenyl phosphane (8 mmol, 2.1g, 40 equiv). White powder (0.49 g, 30%); IR : 3459 (N-H); 1748 (C=O, acetate); 1654 (C=O, urea); ^1H NMR ($CDCl_3$, 25°) δ (ppm) : 5.32 (m, 28H, (H3)); 5.22 (d, 2H, (H_a1)); 5.08 (m, 24H, (H_b1)); 5.00 (d, 2H, ($H_a'1$)); 4.92 (t, 2H, (CH_2 , cyclam)); 4.87 (dd, 2H, (H_a2)); 4.80 (m, 24H, (H_b2)); 4.71(dd, 2H, (H_a2)); 4.65-4.50 (complex m, 52H, (H_b6 + CH_2 cyclam)); 4.29-4.22 (t, 4H (H_a5)); 4.12 (m, 24H, (H_b5)); 4.04 (m, 2H, (CH_2 , cyclam)), 3.80-3.65 (complex m, 28H, (H_b4, H_a4)); 3.58 (m, 8H, (H_a6)); 2.10-2.00 (several s, 240H, (80 CH_3CO)). ^{13}C NMR ($CDCl_3$, 25°) δ (ppm) : 170.5-169.4 (CH_3CO); 158.3 (N-*C*O-NH); 97.3-96.5 (C1); 77.2-76.5 (C4); 71.3-69.4 (C2,

C3, C5); 63-62.6 (C_b6 +CH_2-N cyclam); 42.7 (C_a6); 20.9 (*C*H3-CO). ESMS : 2073.8 [M+ Na^+] $^{4+}$; 2050.8 [M+2H^+] $^{4+}$.

5 : Tris-{ [hexakis-(2,3,6-tri-O-acetyl)]-2,3-di-O-acetyl-cyclomaltoheptaosyl-6-ureido}-1,4,7-triazacyclononane. Obtained by condensation of **1** (0.25 mmol, 0.5 g, 4 equiv), **3** (0.062 mmol, 0.08g, 1 equiv) and triphenyl phosphane (2.5 mmol, 0.66g, 40 equiv). White powder (0.15 g, 31%); IR : 3459 (N-H); 1748 (C=O, acetate); 1654 (C=O, urea); ^{1}H NMR ($CDCl_3$, 25°) δ (ppm) : 5.22 (m, 21H, (H3)); 5.10 (d, 2H, (H_a1)); 4.99 (d, 1H, (H_a'1)); 4.95 (m, 18H, (H_b1)); 4.76-4.60 (complex m, 21H, (H_a2+H_b2)); 4.22-4.12 (complex m, 3H, (H_a5)); 4.05 (m, 18H, (H_b5)); 3.70-3.55 (complex m, 21H, (H_b4+H_a4)); 3.50 (m, 8H, (H_a6)); 2.10-2.00 (several s, 180H, (60 *CH3*CO)). ^{13}C NMR ($CDCl_3$, 25°) δ (ppm) : 171.5-169.6 (CH_3*C*O); 158.4 (N-*C*O-NH); 97.3-96.2 (C1); 77.2-76.5 (C4); 72.1-69.2 (C2, C3, C5); 63.0-62.4 (Cb6 +CH_2-N cyclam); 41.9 (C_a6); 20.9 (*C*H3-CO). ESMS : 2067.7 [M+2H^++Na^+]$^{3+}$; 2045.6 [M+3H^+]$^{3+}$.

6 : Tetra-[cyclomaltoheptaosyl-6-ureido]-1,4,8,11-tetraazacyclotetradecane. White powder (0.075 g ; 90%); IR : 3708-3384 (N-H; O-H); 1651 (C=O, urea). ^{13}C NMR (D_2O /CD_3OD) δ (ppm) : 158.3 (N-*C*O-NH); 100.3-99.9 (C1); 79.-79.1 (C4); 71.5-69.1 (C2, C3, C5); 58.6 (C_b6); 58.1 (*C*H_2, cyclam); 47.4 (*C*H_2, cyclam), (40.1 (C_a6); 34.1 (*C*H_2, cyclam) ESMS : 1227.4 [M+Na^+]$^{4+}$; 1205 [M]$^{4+}$.

7 : Tris-[cyclomaltoheptaosyl-6-ureido]-1,4,7-triazacyclononane. White powder (0.047 g; 81%); IR : 3748-3384 (N-H, O-H); 1651 (C=O, urea). ^{13}C NMR (D_2O /CD_3OD) δ (ppm) : 158.4 (N-CO-NH); 102.9 (C1); 82.5 (C4); 73.7-72.7 (C2, C3, C5); 61.0 (C_b6); 42.1 (C_a6); 41.0 (*C*H_2, cyclam). ESMS : 1227.4 [M+2H^++Na^+]$^{3+}$; 1205.5 [M+3H^+]$^{3+}$.

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