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Synthesis of new polyoxapolycarboxylic ligands for lanthanide(III) ions complexation

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Abstract—The multidentate polyoxapolycarboxylic ligands **1** and **2** were obtained by a two-step synthesis from easily available chemicals. Preliminary data on their coordination properties are reported.

In the last decade great efforts have been devoted to the development of new multidentate ligands for transition metal and lanthanide ions. The purpose was to obtain complexes whose stability, physical properties and biodistribution would make them suitable as contrast agents for MRI (magnetic resonance imaging),[1] or as diagnostic–therapeutic radiopharmaceuticals[2] or as markers in fluorescence bioassays.[3] Most of these ligands were based on polyaminopolycarboxylic acids such as DTPA (diethylenetriaminopentaacetic acid), DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and many of their substituted or modified derivatives.[4] Recently interest has focused on polyoxapolycarboxylic ligands, mainly in consideration of their easy synthetic accessibility.[5] Most of them derive from the carboxyalkylation of diols or triols, generating tetradentate or hexadentate ligands.[6] However, the complexation of lanthanide ions for medical applications requires a higher ligand denticity to achieve a sufficient thermodynamic stability.[4]

In this paper we report the synthesis of two new polyoxapolycarboxylic ligands (**1** and **2**, Fig. 1), containing

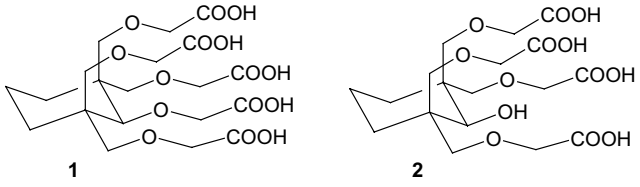

Figure 1.

10 and 9 oxygen donor atoms, respectively. A preliminary assessment of the complexing ability of **1** towards lanthanide(III) ions is reported, in view of the potential diagnostic use of the corresponding paramagnetic complexes as contrast agents for magnetic resonance imaging (MRI).

The synthesis of a high-denticity polyoxapolycarboxylic ligand was achieved by carboxylalkylation of the proper polyol substrate. The polyol chosen for this task was 2,2,6,6-tetrakis(hydroxymethyl)cyclohexanol **3**, readily obtained in high yield by the base-catalyzed tandem cross-condensation–Cannizzaro dismutation of cyclohexanone with excess formaldehyde.[7] The choice of pentol **3** relied on the number of OH groups prone to functionalization (five, to yield a total of 10 donor groups after derivatization) and their conformational arrangement, potentially favourable to metal chelation.

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Following a protocol employed for hydrophilic polyols,[6] pentol **3** was subjected at room temperature to phase-transfer-catalyzed alkylation with *t*-butyl bromoacetate in a biphasic system composed of 50% aqueous NaOH and toluene, with tetra *n*-butylammonium hydrogen sulfate as PTC catalyst (Scheme 1).

The functionalization of pentol **3** afforded a mixture of two products easily separated by silica gel column chromatography and identified by NMR and ESI-MS as the pentaalkylated pentol **4** and the symmetrically tetra-alkylated pentol **5**.[8] The reaction was repeated in a range of experimental conditions, mainly varying the reaction time and the ratios alkylating agent/polyol/catalyst. As expected, an excess of *t*-butyl bromoacetate tended to favour the formation of **4** instead of **5**, although complete conversion of **5** to **4** was never observed. Even after longer contact times complete pentaalkylation was prevented by the formation of large amounts of apolar byproducts from the self-condensation of *t*-butyl bromoacetate. Higher catalyst/**3** ratios sped up the reaction hardly affecting the ratio **4**/**5**. Attempts to direct the reaction towards exclusive formation of **5** by lowering the *t*-butyl bromoacetate/**3** or catalyst/**3** ratios, reducing the reaction time or operating at lower temperatures always yielded complex mixtures of alkylation products. Slow addition of *t*-butyl bromoacetate was found to have a beneficial effect on the overall yield, reducing the formation of the apolar byproducts and giving average yields of 52% and 31% for pentaester **4** and tetraester **5**, respectively.

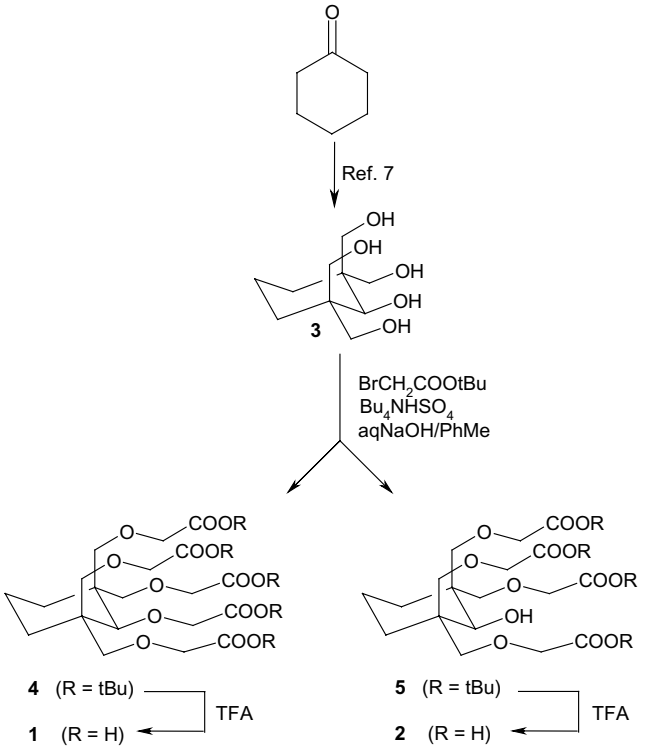
Although the higher denticity of **4** appeared more promising for the purpose of metal chelation, compound **5** could be seen as an octadentate ligand (denticity still adequate for stable chelation of lanthanides) possessing an extra OH group suitable for further functionalization, particularly for conjugation to biomolecules.

Deprotection of *t*-butyl esters **4** and **5** was accomplished by stirring overnight in neat TFA, to afford nearly quantitative yields of **1** and **2**, respectively.[9]

Next, we assessed the properties of the complexes of the ligands with Gd^{3+}, the paramagnetic ion of choice in the design of contrast agents for MRI. The complexes were prepared by adding a stoichiometric amount of $GdCl_3$ to a solution of the corresponding ligand while maintaining the pH at 7.0 by the addition of aq NaOH. The longitudinal relaxivity R_{1p} (defined as the increase of the longitudinal relaxation rate of water protons in the presence of 1.0 mmol/L of the paramagnetic species) of $[Gd(\mathbf{1})]^{2-}$ was found to be 11.4 $mM^{-1}\,s^{-1}$ in the freshly prepared solution. This value is strongly indicative of a pentacoordinated metal ion with a high hydration number (q). Further support to this suggestion was gained by measuring the variation of the transverse relaxation rate of water ^{17}O nuclei as a function of temperature. The fitting of data reported in Figure 2 yielded a value of 3 for q and a mean half-time of 87 ns for the residence of coordinated water molecules. These data were used for fitting the data obtained from the NMRD profile (proton longitudinal relaxivity plotted as a function of the Larmor frequency, Fig. 2), giving a rotational correlation time for the complex of 106 ps at ambient temperature.

Competitive titration of $[Gd(\mathbf{1})]^{2-}$ with several well-known ligands was carried out to make a preliminary assessment of its stability. As might be predicted for a five-coordinated chelate, competition with DTPA ($\log K_{[Gd(DTPA)]} = 22.46$), CDTA ($\log K_{[Gd(CDTA)]} = 19.47$), EDTA ($\log K_{[Gd(EDTA)]} = 17.35$) or HEDTA ($\log K_{[Gd(HEDTA)]} = 14.80$) resulted in nearly complete transmetalation, indicative of a lower stability.

$[Gd(\mathbf{2})]^{-}$ showed a longitudinal relaxivity R_{1p} of 15.0 $mM^{-1}\,s^{-1}$, suggestive of a higher hydration of the lanthanide ion in view of the decreased ligand denticity. The overall lanthanide-ion binding of **1** and **2** very likely



Scheme 1.

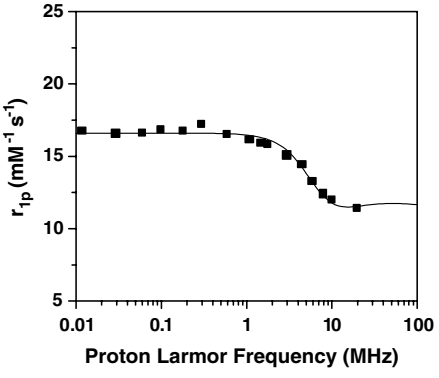


Figure 2.

reflects the overwhelming predominance of carboxylate oxygen donors in the putative O_{10}- and O_9-donor sets, respectively.

Extension of the work to other metal ions with **1** and **2** will be pursued. These molecules have not been optimized but manipulation of their structural framework aiming at enhancing denticity and reducing conformational mobility of the donor arms would eventually lead to ligands with improved stability.

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8. *Polyol alkylation*: Polyol **3** (4.5 mmol) was added to a biphasic mixture of toluene (20 mL) and 50% aq NaOH (20 mL). *t*-Butyl bromoacetate (30 mmol) is slowly added dropwise at room temperature. After 3 h the mixture is diluted with water (50 mL) and extracted with hexane (3×20 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated. The alkylation products are separated by flash chromatography (hexane–ethyl acetate 9:1). Selected data for compound **4**: ^{1}H NMR ($CDCl_3$) 4.29 ppm (s, 2H), 4.09 ppm (s, 1H), 3.94 ppm (s, 4H), 3.88 ppm (AB system, 4H, $J_{AB} = 16.0$ Hz), 3.71 ppm (d, 2H, $J = 9.6$ Hz), 3.68 ppm (d, 2H, $J = 9.6$ Hz), 3.48 ppm (d, 2H, $J = 9.6$ Hz), 3.37 ppm (d, 2H, $J = 9.6$ Hz), 1.89–1.42 ppm (m, 6H), 1.58 ppm (s, 9H), 1.44 ppm (s, 36H); ^{13}C NMR ($CDCl_3$) 170.5 ppm [C], 170.0 ppm [C], 169.9 ppm [C], 81.4 ppm [C], 81.3 ppm [C], 80.7 ppm [C], 79.9 ppm [CH], 74.7 ppm [CH_2], 72.0 ppm [CH_2], 71.4 ppm [CH_2], 69.5 ppm [CH_2], 69.4 ppm [CH_2], 45.3 ppm [C], 28.2 ppm $3 \times$[CH_3], 27.8 ppm [CH_2], 17.5 ppm [CH_2]. MS (ESI) 813 amu (MNa^+), 829 amu (MK^+) (Calcd for $C_{40}H_{70}O_{15}$: 790 amu). Anal. Calcd for $C_{40}H_{70}O_{15}$: C, 60.74; H, 8.92. Found: C, 60.57; H, 9.01. Compound **5**: ^{1}H NMR ($CDCl_3$) 3.98 ppm (d, 2H, $J = 18.1$ Hz), 3.94 ppm (d, 2H, $J = 18.1$ Hz), 3.91 ppm (s, 4H), 3.89 ppm (s, 1H), 3.72 ppm (d, 2H, $J = 9.2$ Hz), 3.64 ppm (d, 2H, $J = 8.8$ Hz), 3.63 ppm (d, 2H, $J = 9.2$ Hz), 3.50 ppm (d, 2H, $J = 8.8$ Hz), 1.77–1.21 ppm (m, 7H), 1.46 ppm (s, 18H), 1.45 ppm (s, 18H); ^{13}C NMR ($CDCl_3$) 170.0 ppm [C], 169.8 ppm [C], 81.4 ppm $2 \times$[C], 76.3 ppm [CH_2], 74.6 ppm [CH], 71.4 ppm [CH_2], 69.4 ppm [CH_2], 69.3 ppm [CH_2], 43.9 ppm [C], 28.3 ppm [CH_2], 28.3 ppm [CH_3], 28.2 ppm [CH_3], 17.4 ppm [CH_2]. MS (ESI) 699 amu (MNa^+), 715 amu (MK^+) (Calcd for $C_{34}H_{60}O_{13}$: 676 amu). Anal. Calcd for $C_{34}H_{60}O_{13}$: C, 60.34; H, 8.94. Found: C, 60.07; H, 9.09.
9. *Ester hydrolysis*: The *t*-butyl ester (1 mmol) is dissolved in trifluoroacetic acid (5 mL) and stirred overnight at room temperature. Volatiles are removed in vacuo, and the solid residue is triturated and washed thoroughly with diethyl ether. Selected data for compound **1**: ^{1}H NMR ($CDCl_3$) 4.33 ppm (s, 2H), 4.10 ppm (s, 4H), 4.07 ppm (s, 4H), 3.73 ppm (s, 1H), 3.63–3.54 ppm (m, 6H), 3.44 ppm (d, 2H, $J = 9.6$ Hz), 1.52–1.31 ppm (m, 6H); ^{13}C NMR ($CDCl_3$) 174.8 ppm [C], 174.6 ppm [C], 174.5 ppm [C], 81.5 ppm [CH], 74.2 ppm [CH_2], 72.7 ppm [CH_2], 71.1 ppm [CH_2], 68.3 ppm [CH_2], 68.1 ppm [CH_2], 44.4 ppm [C], 27.2 ppm [CH_2], 16.4 ppm [CH_2]. MS (ESI) 533 amu (MNa^+), 549 amu (MK^+) (Calcd for $C_{20}H_{30}O_{15}$: 510 amu). Anal. Calcd for $C_{20}H_{30}O_{15}$: C, 47.06; H, 5.92. Found: C, 46.87; H, 6.02. Compound **2**: ^{1}H NMR ($CDCl_3$) 4.14 ppm (s, 4H), 4.10 ppm (s, 4H), 3.91 ppm (s, 4H), 3.82–3.54 ppm (m, 9H), 1.60–1.35 ppm (m, 4H), 1.34–1.18 ppm (m, 2H); ^{13}C NMR ($CDCl_3$) 174.9 ppm [C], 174.7 ppm [C], 76.1 ppm [CH_2], 74.5 ppm [CH], 72.2 ppm [CH_2], 68.5 ppm [CH_2], 68.4 ppm [CH_2], 43.5 ppm [C], 28.1 ppm [CH_2], 16.5 ppm [CH_2]. MS (ESI) 475 amu (MNa^+), 491 amu (MK^+) (Calcd for $C_{18}H_{28}O_{13}$: 452 amu). Anal. Calcd for $C_{18}H_{28}O_{13}$: C, 47.79; H, 6.24. Found: C, 47.75; H, 6.37.