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Ionic complexation properties of per(3,6-anhydro)cyclodextrin derivatives towards lanthanides☆

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Abstract—Using per(3,6-anhydro)cyclodextrin derivatives [per(3,6-anhydro)CD], it was possible to produce new lanthanide chelates by careful choice of the size and functional groups. Heptakis(3,6-anhydro-2-*O*-methyl)cyclomaltoheptaose fulfils the best criteria for complexation of lanthanide ions. Nuclear magnetic resonance was used to derive the association constants and the stoichiometries of these new complexes. Finally, a three-dimensional structure of these complexes consistent with the NMR data is proposed, to ascertain the position of lanthanide in the cavity of the per(3,6-anhydro)CD. For the present purposes, heptakis(2-*O*-acetyl-3,6-anhydro)cyclomaltoheptaose, octakis(2-*O*-acetyl-3,6-anhydro)cyclomaltooctaose, heptakis(3,6-anhydro-2-*O*-methyl)cyclomaltoheptaose and octakis(3,6-anhydro-2-*O*-methyl)cyclomaltooctaose have been synthesized and purified.

Keywords: Heptakis(2-*O*-acetyl-3,6-anhydro)cyclomaltoheptaose; Octakis(2-*O*-acetyl-3,6-anhydro)cyclomaltooctaose; Heptakis(3,6-anhydro-2-*O*-methyl)cyclomaltoheptaose; Octakis(3,6-anhydro-2-*O*-methyl)cyclomaltooctaose lanthanide shift reagents; Ionic complexation; $Pr(NO_3)_3$; Paramagnetic NMR complexes; Contrast agent

1. Introduction

It is well documented that the lanthanides, containing several unpaired electrons, enhance the relaxation rates, that is, shorten relaxation times, of water protons.[1,2] In this respect, magnetic resonance imaging (MRI) uses this property of lanthanide-chelates, in particular gadolinium-chelates.[1–4] Administrated intravenously, the Gd^{3+}-chelates increase the contrast between pathological and healthy organs and tissues and consequently improve the diagnostic value of MRI.[4] These gadolinium complexes include low molecular weight Gd^{3+}-chelates (Gd-DTPA, Gd-DOTA…)[4–9] as well as macromolecular Gd^{3+}-chelates (Gd-liposomes, polymeric conjugates…).[4,10–15]

The ligands act as carriers that provide the safe transport of Gd^{3+} towards the physiological site. However, these small complexes being extra-cellular lack specificity and consequently are poor contrast agents.[1,4]

The macromolecular Gd^{3+} complexes, so called blood pool agents, are more largely retained within the intravascular space mainly because of their molecular size.[1,4] These macromolecular conjugates display an increased lifetime in blood and allow better tumour imaging. However, none of these agents has as yet been found satisfactory enough to reach clinical trials.[4]

As early as in 1989, carbohydrates have been suggested as potential contrast agents.[16] Polysaccharides such as dextran bound covalently to DTPA or DOTA, have been investigated as blood pool MRI contrast agents[17] but they display rather weak relaxivity values.[4]

☆ Editor's note: No microanalytical nor polarimetric data supplied, but full NMR and ESIMS spectra are provided in Supplementary data.

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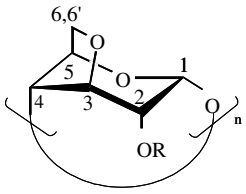

	R	n
1	H	6
2	H	7
3	H	8
4	Ac	6
5	Ac	7
6	Ac	8
7	CH_3	6
8	CH_3	7
9	CH_3	8

Chart 1. Structures of per(3,6-anhydro)CDs.

During recent years, the use of natural cyclodextrins (CDs) has led to new MRI contrast agents based on noncovalent adduct formation.[13] In those cases, the CD monomer[18,19] or polymer[13] forms an inclusion complex with the molecule chelating the paramagnetic cation. Consequently, in this ternary system (CD–metal ligand complexes), the CD does not directly scavenge the lanthanide.

In this respect, it was interesting to investigate the ionic complexation properties of the per(3,6-anhydro)cyclodextrins (Chart 1, compounds **1**–**9**), particularly towards their lanthanide derivatives.[20–24] It is well known that these compounds are capable of binding with cations[25–30] and of fulfilling the standard pharmaceutical requirements such as water solubility and biocompatibility. Furthermore, it has been demonstrated that chemical modification of per(3,6-anhydro)CDs can optimize their performances in terms of ionic complexation properties.[31]

In this study, we report on new per(3,6-anhydro)CDs (Chart 1) as supramolecular lanthanide-chelates and demonstrate that both the size of the CD and the nature of functional groups influence complexation. Nuclear magnetic resonance was used to derive association constants and stoichiometries of these new complexes. Finally, the NMR data are also used to generate a three-dimensional structure of the complexes. For this purpose, heptakis(2-*O*-acetyl-3,6-anhydro)cyclomaltoheptaose, octakis(2-*O*-acetyl-3,6-anhydro)cyclomaltooctaose, heptakis(3,6-anhydro-2-*O*-methyl)cyclomaltoheptaose and octakis(3,6-anhydro-2-*O*-methyl)cyclomaltooctaose (**5**, **6**, **8** and **9**) have been synthesized.

2. Results and discussion

2.1. Synthesis

In the present paper, βCD **5** and γCD **6** derivatives were obtained in one step from heptakis(3,6-anhydro)cyclomaltoheptaose **2** and octakis(3,6-anhydro)cyclomaltooctaose **3**, as previously described for the hexakis(3,6-anhydro)cyclomaltohexaose derivative **1**.[31] However, for **5** and **6**, a 7 h reaction time is sufficient compared to the 10 h reaction time required for hexakis(2-*O*-acetyl-3,6-anhydro)cyclomaltohexaose **4**.

The syntheses of **8** and **9** were achieved following the previously described procedure involving the nucleophilic reaction in dimethylformamide of methyl iodide with the alkoxides of **2** and **3**, respectively.[31]

2.2. Per(3,6-anhydro)CD/Pr complexes

Providing evidence of complexation of the guest in per(3,6-anhydro)CDs as potential lanthanide-chelate hosts requires a method such as NMR spectroscopy where the complexation of the metal is demonstrated unambiguously by comparing the proton spectra of the per(3,6-anhydro)CD with and without the lanthanide.

Praseodymium [III] nitrate was considered as the model lanthanide because it induces a weak broadening of NMR signals as compared to, for example, gadolinium.[2] The addition of $Pr(NO_3)_3$ to derivatives **1**–**7** (data not shown) led to no chemical shift variation in the ^1H NMR spectra, evidencing the absence of complexation in these cases. For derivatives **8** and **9**, the addition of $Pr(NO_3)_3$ induced chemical shift variations in the ^1H NMR spectra, indicative of a complexation process.

Figure 1 displays chemical shift variations of **8** upon addition of increasing amounts of $Pr(NO_3)_3$. Except for H-2 and H-3, located outside the cavity as depicted in Figure 2, all other signals are broadened and display

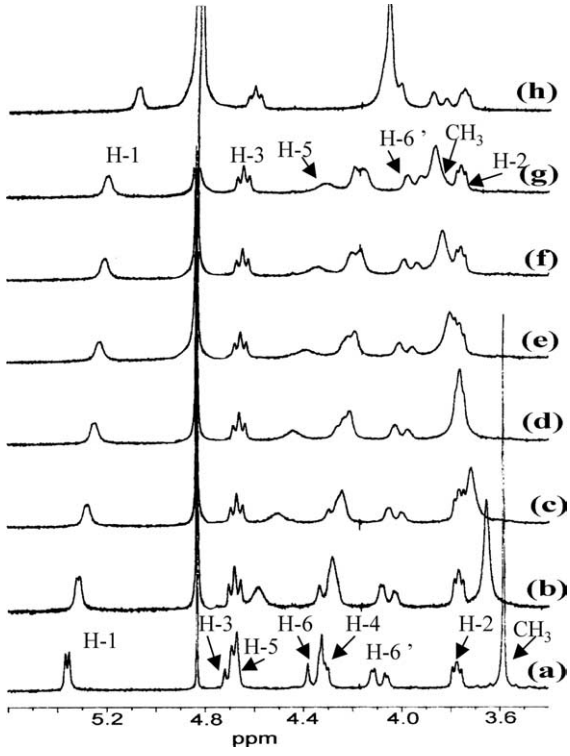

Figure 1. ^1H NMR spectra (200 MHz, 298 K, D_2O) of **8** (1.8 mM) in the absence (a) and in the presence of 0.2 (b), 0.4 (c), 0.6 (d), 0.8 (e), 1.0 (f), 1.3 (g) and 10 (h) equivalents of $Pr(NO_3)_3$.

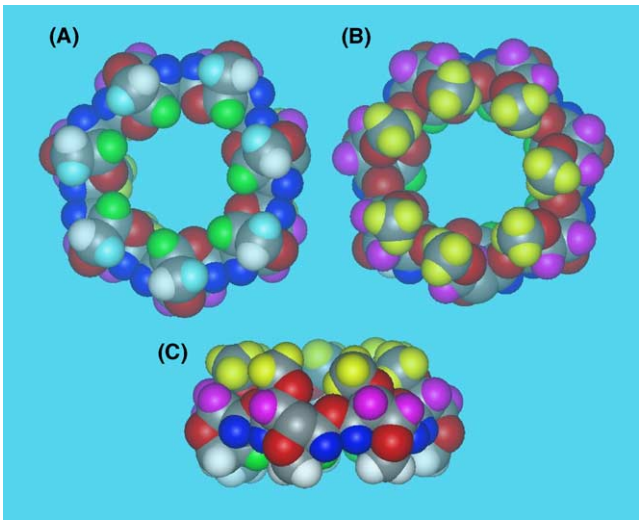

Figure 2. Molecular drawings of **8**: top views (A and B), side view (C) CH_3 group protons: yellow; H-5: green; H-3 and H-2: pink; H-1 and H-4: blue; H-6: white; H-6′: pale blue.

induced chemical shift variations. These effects are due to the paramagnetic effect of praseodymium, which is probably located close to the CD cavity.

Under the same conditions, addition of $Pr(NO_3)_3$ to **9** (data not shown) led to chemical shift variations for protons H-3, H-5, H-6 and methyl group protons. In this case, the shift variations are relatively small compared with those of **8**. Assuming the same basic complex structure, the complexation probably also occurs but without deformation of the cavity since the signals of H-1 and H-4 remain invariant. This observation conforms with the larger size of the cavity of the per(3,6-anhydro)γCD, therefore displaying fewer distortions than per(3,6-anhydro)βCDF upon complexation.

From this first set of results, it appears that the oxygen atom in position 2 of the per(3,6-anhydro)γCD plays a key role in the complexation of Pr, since only methylated derivatives appear able to complex the lanthanide. On the other hand, the size of the CD is also meaningful since the αCD derivative, conversely to βCD and γCD derivatives, is not sterically adapted to complex lanthanides. It can be concluded that the complexation occurs with per(3,6-anhydro)CDs provided that both the size of the per(3,6-anhydro)CD cavity and the functional group located at C-2 of the per(3,6-anhydro)CD have been properly selected.

From the ESI mass spectra performed for various host/guest ratios, the presence of main peaks at *m/z* 646 and 654 for **8** and at *m/z* 725 and 733 for **9** is observed. These values may be ascribed to species $[M + Pr(NO_3)^{2+}]/2$ and $[M + Pr(NO_2)^{2+}]/2$ confirming the affinity of Pr^{3+} for the CD cavity. For more than 3 equiv of $Pr(NO_3)_3$, a new peak was observed for both complexes at *m/z* 663 for **8** and *m/z* 742 for **9** corresponding to species $[M + Pr(NO_3)^{2+} + H_2O]/2$ for which one molecule of water fills the coordinate sphere of praseodymium.

2.3. Determination of stoichiometries and association constants (K_a) of per(3,6-anhydro)CD/Pr complexes

In order to obtain more information on the **8**/Pr and **9**/Pr complexes, their stoichiometries and their association constants (K_a) were determined using the continuous variation technique.[32]

Figure 3 displays the plots obtained using the Job's method[32] for the H-1, H-3 and the methyl group protons of the host molecule in the **8**/Pr complex. From the Job plot analysis, the 1:1 stoichiometry ($r = 0.5$) was ascertained. A numerical simulation was used to derive the corresponding association constant and provides a K_a value in the $8100\,M^{-1}$ range (Table 1). The data were processed with a home-made computer program and the curve fitting analysis is presented in Figure 4. The fitting curves were obtained with different K_a and different chemical shifts of host protons in the pure complex state. Although the percentage of bound ligand in the final experimental point reaches 85% of its initial

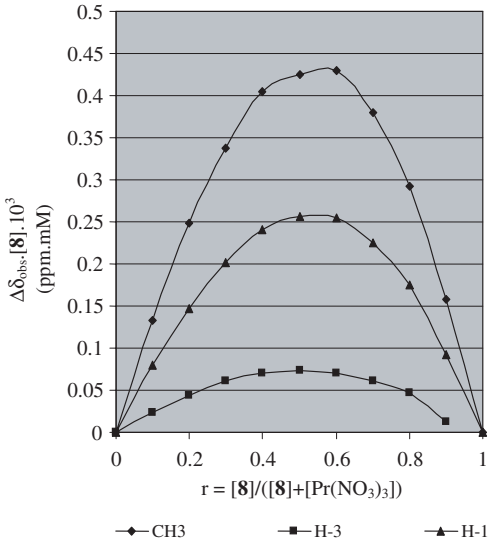

Figure 3. Continuous variation plot (Job plot) for protons H-1, H-3 and of methyl group CH_3 of **8**.

Table 1. Association constant values of **8**: Pr and **9**: Pr complexes and chemical shifts of the protons of **8** and **9** in pure complex states

	Compound **8**			Compound **9**		
Protons	H-1	H-6′	CH_3	H-3	H-5	H-6
δ_i (ppm)	5.53	4.23	3.89	4.736	4.684	4.355
$K_a \pm 100$ (M^{-1})	9600	5900	8800	3580	3700	2330
K_a mean (M^{-1})	8100 ± 2000			3200 ± 760		

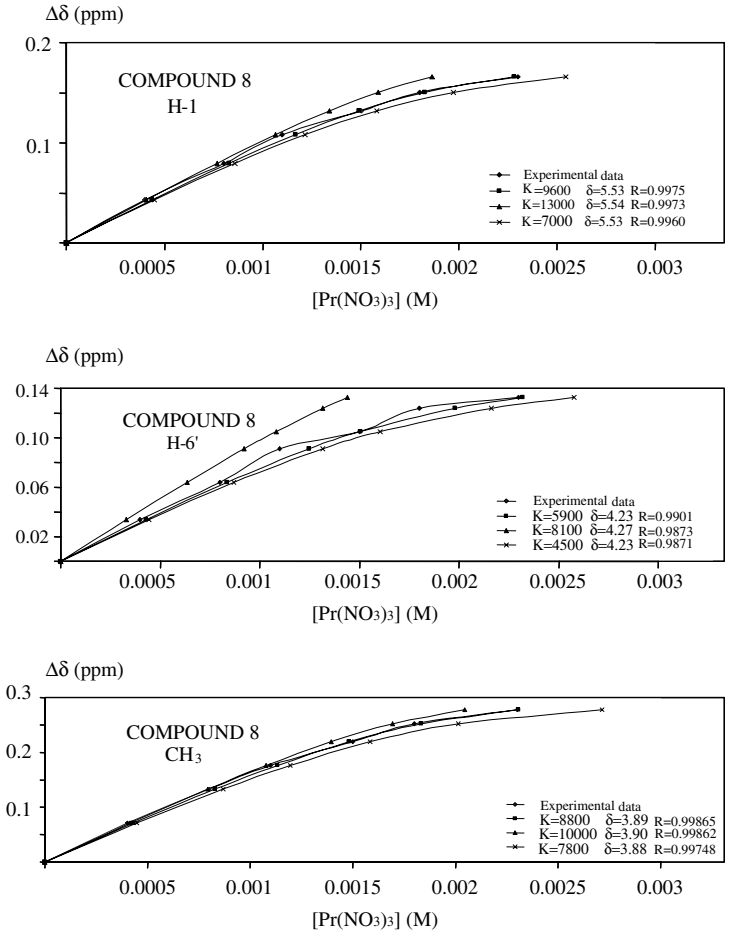

Figure 4. Fitting curves of calculated versus experimental $\Delta\delta_i$ chemical shift variations of H-1, H-6′ and CH_3 of **8** obtained with different K_a and δ_i of pure complex. [**8**] = 1.8 mM.

concentration, it can be considered that the K_a values are, nevertheless, significant on a qualitative basis.

When the same process was applied to the **9**/Pr complex, a 1:1 stoichiometry and a K_a value to $\sim 3200\,M^{-1}$ were calculated (Table 1). The same curve fitting has been performed with **9** and the results are displayed in Figure 5. As the geometries of both complexes are expected to be similar, the association constant seems to be higher for the βCD derivative.

2.4. Discussion on the structures of per(3,6-anhydro)CD/Pr complexes

It is well documented that in the paramagnetic lanthanide complexes the contact interactions are greatly diminished and the induced chemical shifts arise predominantly from the dipolar mechanism.[33,34] In that case, the dipolar shifts are ascribed to through space effects and if the complex is axially symmetric, the lanthanide-induced shifts (LIS) can be predicted by the simplified dipolar shift equation $LIS = K(3\cos^2\theta - 1)/R^3$. In this equation, R is the distance between the lanthanide ion and the nucleus of interest, θ the angle between the principal magnetic axis and the vector linking the lanthanide ion to the nucleus of interest and K the magnetic proportionality constant.

It seems reasonable to assume that for the per(3,6-anhydro)CD/Pr complexes, the above described conditions are fulfilled because of the *n*-fold axis of symmetry of per(3,6-anhydro)CDs. In this respect, more detailed indications concerning the geometry of the **8**/Pr and **9**/Pr complexes can be derived from Table 2, showing the induced chemical shift differences ($\Delta\delta_i$) observed for the protons of both **8** and **9** in the absence of and with up to 0.4 equiv of $Pr(NO_3)_3$.

For **8**, the methyl group protons shifted to high frequency whereas all other protons shifted to low frequency upon $Pr(NO_3)_3$ addition. This change in sign between H-2 and CH_3 determines the depth at which Pr^{3+} sits in the per(3,6-anhydro)CD cavity because the geometrical term $(3\cos^2\theta - 1)/R^3$ changes sign at a precisely defined angle. If the z axis is placed along the 7-fold axis of symmetry of per(3,6-anhydro)-βCD, the position of the lanthanide is such that the metal

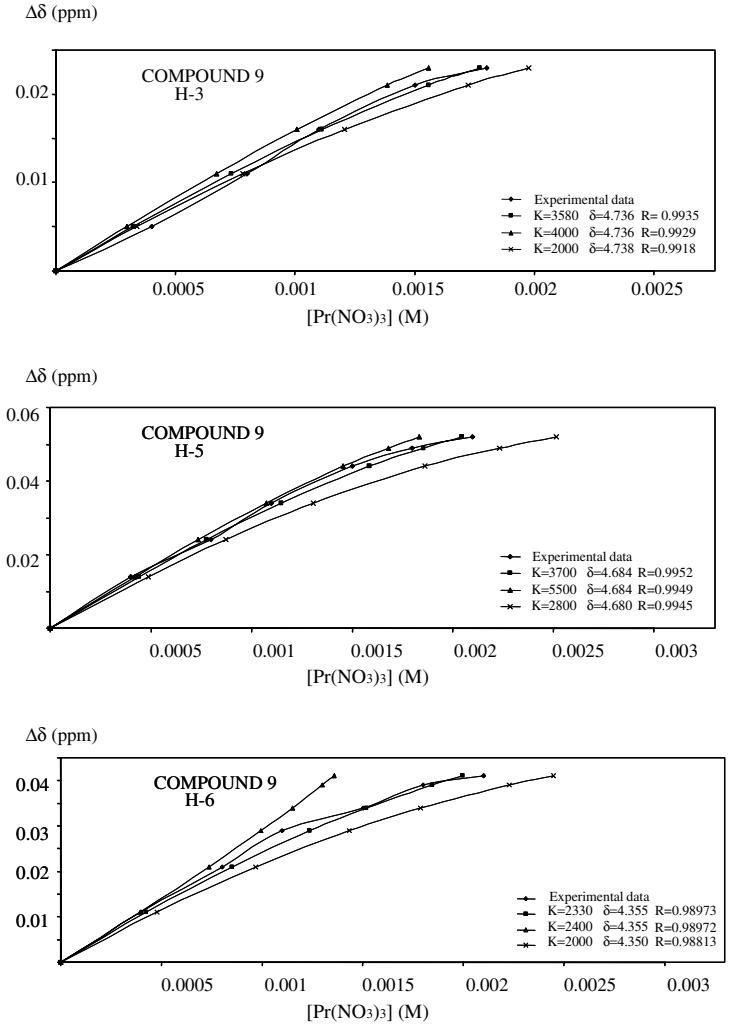

Figure 5. Fitting curves of calculated versus experimental $\Delta\delta_i$ chemical shift variations of H-3, H-5 and H-6 of **9** obtained with different K_a and δ_i of pure complex. [**9**] = 2 mM.

Table 2. $\Delta\delta_i$ or induced chemical shift differences observed for the protons of **8** and **9** in absence and in presence of 0.4 equiv of $Pr(NO_3)_3$([**8**] = [**9**] = 2 mM)

	$\Delta\delta_i$ (ppm)	
	8: Pr^{3+}	**9**: Pr^{3+}
H-5	−0.168	+0.020
H-1	−0.078	+0.001
H-4	−0.077	+0.004
H-6	−0.080	+0.021
H-6′	−0.601	+0.003
H-3	−0.031	+0.012
H-2	−0.011	+0.005
CH_3	+0.130	−0.012

ion is close to H-5. In that case, the angle θ for H-5 is such that θ>54.3°, which is consistent with an upfield chemical shift (Fig. 6). For methyl group protons located on the other side of the cavity (Fig. 2), a value of θ>125.3° can explain the downfield shift of these protons (Fig. 6). It should be noted that the $\Delta\delta_i$ of the other protons depend on the geometry of each proton relative to the paramagnetic centre. Therefore, H-2 and H-3 located outside the cavity and hence far from the cation display the weakest $\Delta\delta_i$ while H-1, H-4, H-6 and H-6′ located between H-2 and H-5, and for which the $(3\cos^2\theta-1)/R^3$ geometrical term is approximately equal, experience similar upfield $\Delta\delta_i$.

Table 2 shows that, under the same conditions, addition of $Pr(NO_3)_3$ to **9** leads to $\Delta\delta_i$ of opposite sign and one order of magnitude weaker than in the derivative **8**. Consequently, **9** cannot form a strong complex with Pr^{3+} since almost no detectable $\Delta\delta_i$ are experienced in the latter case. On the other hand, the larger size of the per(3,6-anhydro)-γCD cavity allows to assume that the protons of **9** are situated further from Pr^{3+} than are the protons of **8**. Such a situation could be depicted in Figure 7 where the lanthanide is positioned close to the methyl group protons. In that case, the θ angle of

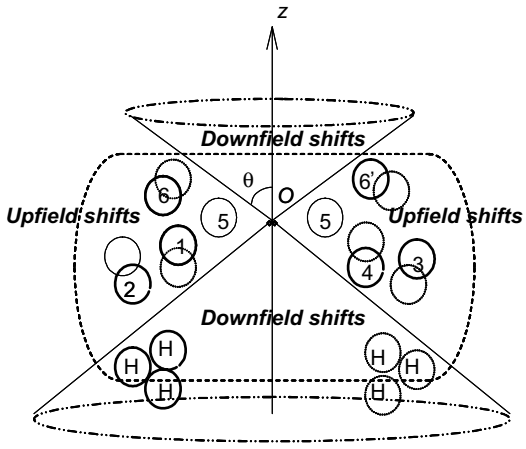

Figure 6. Schematic representation of the complex **8**: Pr^{3+} built from NMR data. The lanthanide is located on O_z axis at origin O and $\theta = 54.7°$. The numbers 1, 2, 3... correspond to H-1, H-2, H-3... protons, H represents the methyl group protons.

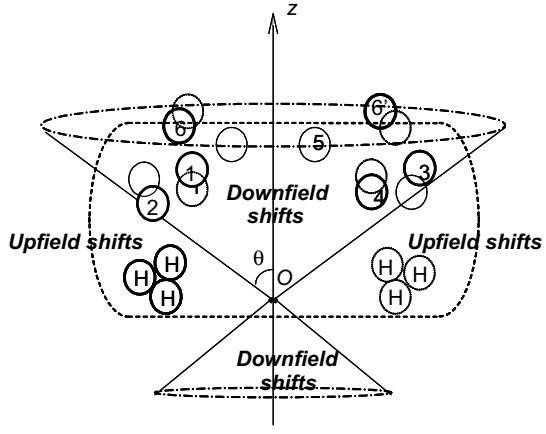

Figure 7. Schematic representation of the complex **9**: Pr^{3+} built from NMR data. The lanthanide is located on O_z axis at origin O and $\theta = 54.7°$. The numbers 1, 2, 3... correspond to H-1, H-2, H-3... protons, H represents the methyl group protons.

the methyl group protons is such that $\theta > 54.3°$, which is consistent with an upfield chemical shift of these protons and a downfield chemical shift of H-5. Finally, the cation positioned at this level probably does not induce conformational changes as reflected by the absence of chemical shift variation for H-1 and H-4.

In both kinds of complexes, the NMR data suggest that Pr^{3+} fits inside the cavity and that its position depends on the size of the cavity, the cation being more deeply included in **8** than in **9**. From these observations, it can be concluded that both complexes differ slightly in terms of geometry and that the differences observed between the proposed geometric models are consistent with a larger affinity of the βCD derivative for the Pr^{3+} ion as clearly reflected by the K_a value.

3. Experimental

3.1. Materials and methods

βCD (from Roquette, France) and αCD and γCD (from Waker-Chemie, France) were freeze-dried before use. $Pr(NO_3)_3$ was purchased from Aldrich and used as received.

TLC was performed on Silicagel 60 plates (E. Merck) followed by charring with 10% H_2SO_4. Semi-preparative HPLC was carried out with Delta Pack 3000 chromatograph (Water Associates) equipped with an Evaporative Light Scattering detector (ELSD).

Mass spectrometry experiments were performed in electrospray infusion mode (ESIMS) (Micromass, Quattro II (UK). NMR experiments were performed using Bruker AC200 (^{1}H at 200.13 MHz, ^{13}C at 50.32 MHz) and DRX500 (^{1}H at 500.13 MHz, ^{13}C at 125.77 MHz) spectrometers using standard Bruker NMR software. The measurements were performed at 298 K in D_2O with careful temperature regulation. One dimensional NMR spectra were collected using 16K data points. Chemical shifts were measured in δ (ppm) downfield from external tetramethylsilane (TMS). D_2O was obtained from Euriso-Top (France).

3.2. Heptakis(2-*O*-acetyl-3,6-anhydro)cyclomaltoheptaose, 5

It was synthesized in one step as described[31] except for the reaction time, which required only 7 h instead of 10 h. Semi-preparative HPLC using 1:1 MeOH–water as eluant at 10 mL min^{-1} on a μBondapak C_{18} column (Waters Associates) afforded chromatographically pure **5** (247 mg, 82 %). ^{1}H NMR (500.13 MHz): δ 5.42 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.95 (t, 1H, $J_{2,3}$ 4.0 Hz, H-2), 4.73 (t, 1H, $J_{5,4}$ 2,0 Hz, $J_{5,6}$ 0.0 Hz, $J_{5,6'}$ 3.0 Hz, H-5), 4.58 (t, 1H, $J_{3,4}$ 6.0 Hz, H-3), 4.35 (d, 1H, $J_{6,6'}$ −11.0 Hz, H-6), 4.28 (dd, 1H, H-4), 4.10 (dd, 1H, $J_{6',5}$ 3.0 Hz, H-6′), 2.26 (s, 3H, CH_3); ^{13}C NMR (125.77 MHz): δ 173.61 (C=O), 96.38 (C-1), 77.27 (C-4), 73.56 (C-5), 69.31 (C-3), 68.86 (C-6), 68.79 (C-2), 21.25 (CH_3); ESIMS: *m/z* 1325.3 $[M + Na]^+$.

3.3. Octakis(2-*O*-acetyl-3,6-anhydro)cyclomaltooctaose, 6

The synthesis was achieved following the previously described procedure.[31] Semi-preparative HPLC carried out using 1:1 MeOH–water as eluant at 10 mL min^{-1} on a μBondapak C_{18} column afforded chromatographically pure **6** (277 mg, 81%). ^{1}H NMR (500.13 MHz): δ 5.42 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.98 (t, 1H, $J_{2,3}$ 4.0 Hz, H-2), 4.72 (t, 1H, $J_{5,4}$ 2,0 Hz, $J_{5,6}$ 0.0 Hz, $J_{5,6'}$ 3.0 Hz, H-5), 4.61 (t, 1H, $J_{3,4}$ 5.5 Hz, H-3), 4.37 (d, 1 H $J_{6,6''}$ −11.0 Hz, H-6), 4.33 (dd, 1H, H-4), 4.13 (dd, 1H, $J_{6',5}$

3.0 Hz, H-6′), 2.17 (s, 3H, CH_3); ^{13}C NMR (125.77 MHz): δ 173.01 (C=O), 94.99 (C-1), 74.88 (C-4), 73.29 (C-5), 68.93 (C-3), 68.82 (C-6), 68.39 (C-2), 20.66 (CH_3); ESIMS: *m/z* 1511.3 $[M + Na]^+$.

3.4. Heptakis(3,6-anhydro-2-*O*-methyl)cyclomaltoheptaose, 8

The synthesis was carried out as described.[31] Semi-preparative HPLC using gradient elution from water (100%) to aq 30% MeCN at 10 mL min^{-1} on Y. M. C. PBMN polyamine column (AIT France) afforded chromatographically pure **8** (50 mg, 80%). ^1H NMR (500 MHz): δ 5.34 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.68 (t, 1H, $J_{3,4}$ 5.5 Hz, $J_{2,3}$ 4.0 Hz, H-3), 4.66 (t, 1H, $J_{5,4}$ 2.5 Hz, $J_{5,6}$ 0.0 Hz, $J_{5,6'}$ 2.5 Hz, H-5), 4.34 (d, 1H, $J_{6,6'}$ −11.5 Hz, H-6), 4.31 (dd, 1H, H-4), 4.07 (dd, 1H, H-6′), 3.76 (t, 1H, H-2), 3.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz): δ 97.88 (C-1), 76.63 (C-4), 76.24 (C-2), 73.55 (C-5), 69.73 (C-3), 68.38 (C-6), 59.29 (CH_3); ESIMS: *m/z* 1129.3 $[M + Na]^+$.

3.5. Octakis(3,6-anhydro-2-*O*-methyl)cyclomaltooctaose, 9

The synthesis was carried out as described.[31] Semi-preparative HPLC using gradient elution from water (100%) to aq 30% MeCN at 10 mL min^{-1} on Y. M. C. PBMN polyamine column afforded chromatographically pure **9** (60 mg, 84%). ^1H NMR (500 MHz): δ 5.35 (d, 1H, $J_{1,2}$ 3.0 Hz, H-1), 4.70 (t, 1H, $J_{3,4}$ 5.0 Hz, $J_{2,3}$ 4.5 Hz, H-3), 4.61 (t, 1H, $J_{5,4}$ 2.5 Hz, $J_{5,6}$ 0,0 Hz, $J_{5,6'}$ 3.0 Hz, H-5), 4.35 (dd, 1H, H-4), 4.29 (d, 1H, $J_{6,6'}$ −10.5 Hz, H-6), 4.04 (dd, 1H, H-6′), 3.71 (t, 1H, H-2), 3.56 (s, 3H, CH_3); ^{13}C NMR (125 MHz): δ 97.40 (C-1), 77.00 (C-2), 75.61 (C-4), 74.34 (C-5), 70.30 (C-3), 68.18 (C-6), 59.44 (CH_3); ESIMS: *m/z* 1287.1 $[M + Na]^+$.

3.6. Preparation of per(3,6-anhydro)CD/Pr complexes

The samples for NMR study were prepared using the following procedure: 50 μmol of $Pr(NO_3)_3$ was dissolved in 1 mL of D_2O and 5 μmol of the required per(3,6-anhydro)CD was freeze-dried and redissolved in 1 mL of D_2O. The per(3,6-anhydro)CD mother soln (0.4 mL) was poured into an NMR tube and the pertinent amount of the $Pr(NO_3)_3$ mother soln was added. ^1H NMR spectra were performed for $Pr(NO_3)_3$/per(3,6-anhydro)CD molar ratios ranging from 0.1 to 10.

The samples required for mass spectroscopy were prepared from a per(3,6-anhydro)CD mother soln 1 mM, to which a pertinent amount of $Pr(NO_3)_3$ soln 1 mM was added. The mass spectra were measured for $Pr(NO_3)_3$/per(3,6-anhydro)CD molar ratios from 1 to 8.

3.7. Molecular drawings

Molecular model of **8** was obtained using Chem3D and Weblab Viewer. For the sake of clarity, compound **8** was shown (Fig. 2) as spheres sized to the van der Waals radii. Distances between two atoms were calculated from the 'ball and stick' model.

4. Conclusion

In conclusion, all data show that it is possible to optimize the complexation criteria in controlling the design, that is, the function and the size, of the per(3,6-anhydro)CDs. In this respect, **8** best fulfils the complexation criteria. The association constant value of 8100 M^{-1} found for the complex **8**/Pr is higher than the mean value found in standard complexes of natural CDs.[19,35] These encouraging results open the way to the design of new potential carbohydrates as contrast agents in which the physical properties (relaxivity, metal content…) should be investigated. Chemical modifications of these carrier molecules are currently in progress in order to modify their structure, so as to increase the association constants of complexes. Moreover, grafting tissue-specific targeting moieties to the per(3,6-anhydro)CDs should allow the design of low-concentration receptors, despite the lack of specific vectors.[4]

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Supplementary data

NMR spectra (Figs. 1S–20S) and ESIMS spectra (Figs. 21S–28S) of compounds **5**, **6**, **8** and **9**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2004.10.011.

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