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Synthesis of hexakis(2-keto-3,6-anhydro)cyclomaltohexaose: structural studies and Pb^{2+} complexation evaluation

Thomas Berthelot [a,*], Julia Chamot-Rooke [b], Cécile Baudin [a,*]

[a] Laboratoire des Solides Irradiés, UMR7642, CEA, Ecole Polytechnique and CNRS, Route de Saclay, 91128 Palaiseau, France
[b] Laboratoire des Mécanismes Réactionnels, Département de Chimie, Ecole Polytechnique and CNRS, Route de Saclay, 91128 Palaiseau, France

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ABSTRACT

Molecules which scavenge heavy metals are of significant interest for medical applications such as toxic metal decontamination or medical imaging. We report the first synthesis of hexakis(2-keto-3,6-anhydro)cyclomaltohexaose in good yield using mild conditions (Swern oxidation). This potential synthon exhibits reactivity towards water which results in its total conversion into the per(*gem*-diol) derivative. The first computational study of Pb^{2+} complexation with per-3,6-anhydro-α-cyclodextrin in water is also reported.

Cyclodextrins (CDs)[1] are known especially for their ability to include organic guest molecules in their hydrophobic cavity and make the resulting inclusion complexes soluble in water. Therefore, most of the published papers concern inclusion complexes and offer a wide range of pharmaceutical and industrial applications.[2] Conversely, less work deals with cation inclusion complexes[3–5] because the hydrophobic character of the cavity is unsuitable for inorganic cation inclusion. Consequently, the ion complexation is most often achieved in an indirect way using an appended chelating group grafted onto a CD.[6–8] However, the drawback of this method lies in the number of steps necessary for the synthesis of functionalized CDs. A more direct pathway uses unmodified native CDs but requires working at strongly basic pH where the hydroxy groups can be deprotonated and act as nucleophiles that are able to form multinuclear sandwich-type complexes with cations.[9,10] In both the cases, the metal cation is located outside the cavity or near the receptor entrance.

In this respect, per(3,6-anhydro)CDs[11,12] appear to be the most versatile class of derivatives suitable for cation complexation[13–15] due to the hydrophilic character of their cavity. These derivatives are obtained from the dehydration of the 3- and 6-hydroxy groups of the D-glucopyranose residues of native CDs which transforms the $^4C_1$ chair conformation of the glucose unit into the $^1C_4$ conformation leaving all unmodified secondary hydroxy groups at position 2. This chemical modification drastically changes the nature of the cavity since per(3,6-anhydro)CDs are unable to complex organic molecules but can bind metal cations due to their reversed (inside-out) structure. per(3,6-Anhydro)CDs consisting of six, seven, and eight (3,6-anhydro)glucopyranose units are called per(3,6-anhydro)-α-, β-, and γ-CD, respectively. One of these, the per(3,6-anhydro)-α-CD is of interest due to its ability to bind heavy metals, Pb^{2+} in particular ($K = 2500\ M^{-1}$), with better selectivity than other CDs.[16] This observation has focused much attention on this derivative, and it was demonstrated that methylation of the per(3,6-anhydro)-α-CD strongly enhances the Pb^{2+} complexation ($K = 3.5 \times 10^6\ M^{-1}$).[17,18] Therefore, Pb^{2+} is a reference cation in complexation studies concerning the per(3,6-anhydro)-α-CD derivative.

Considering these attractive complexation properties, the potential use of these biocompatible agents in various fields such as medical imaging, for example, magnetic resonance imaging, biological decontamination of toxic or radioactive metals in human or in industrial liquid waste is anticipated.

Although these derivatives have not been studied extensively, it has been demonstrated that chemical modification of per(3,6-anhydro)CDs can orient or reverse the selectivity of these derivatives towards cations. It is well established that these properties are based on two parameters: (i) the cavity polarity, and (ii) the availability of the unshared electron pair of the oxygen atom at position 2 of the (3,6-anhydro)glucopyranose unit to form a coordinate bond with an inorganic cation. In this respect, chemical modification of the secondary hydroxy groups of per(3,6-anhydro)-α-CD represents a continuing challenge of particular interest resulting in the preparation of novel compounds with specific complexation properties. Among the potential reactions, oxidation of the secondary alcohol of per(3,6-anhydro)-α-CD appears to be a convenient way to obtain: (i) a new complexing derivative, and (ii) a potential synthon to provide new functionalized per(3,6-anhydro)-α-CD derivatives.

Oxidation of secondary alcohols usually requires acidic conditions and inorganic catalysts such as chromate or dichromate salts, permanganate, Cr(VI) reagents, pyridinium chlorochromate (PCC)

* Corresponding authors. Tel.: +33 169 334 542; fax: +33 169 334 554 (C.E.).
E-mail addresses: thomas.berthelot@polytechnique.edu (T. Berthelot), cecile.baudin@polytechnique.edu (C. Baudin).

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or dichromate (PDC), or ruthenium tetraoxide. These methods present drawbacks which are inconsistent with per(3,6-anhydro)-α-CD and its potential applications: (i) acidic conditions can open the α(1→4) rings, (ii) the molecules of interest can only be obtained as metal/per(3,6-anhydro)-α-CD complexes, and (iii) the toxicity of Cr(VI) reagents is incompatible with biological and environmental applications. Thus, we focused our approach on the Swern oxidation to obtain hexakis(2-keto-3,6-anhydro)-α-CD.[19,20]

Herein, we present improved experimental conditions for the synthesis of hexakis(2-keto-3,6-anhydro)-α-CD. The structure and stability of this new compound were studied by NMR and nano-electrospray ionization Fourier Transform Mass Spectrometry (nanoESI-FT-MS). A comparative study of the binding properties of per(3,6-anhydro)-α-CD **1** and the hydrated form **3** of hexakis(2-keto-3,6-anhydro)-α-CD **2** towards Pb^{2+} was undertaken. Molecular modeling was used for the first time with this type of compound, to confirm the experimental results.

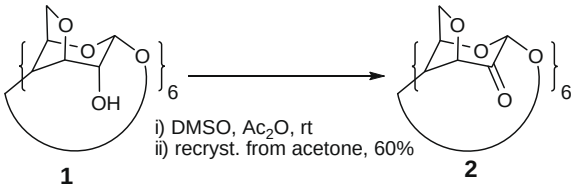
Hexakis(3,6-anhydro)cyclomaltohexaose **1** was synthesized following a modified Defaye's procedure[21] in which the native α-CD is perhalogenated with Br_2 in the presence of DMF and triphenylphosphine and isolated in 78% yield. The perhalogenated compound was treated with 3 M NaOH solution to afford **1** in 60% yield after desalination. Oxidation of hexakis(3,6-anhydro)-α-CD was carried out by treatment of **1** with a mixture of acetic anhydride and DMSO at room temperature to afford hexakis(2-keto-3,6-anhydro)-α-CD **2** in 60% yield after recrystallization from acetone (Scheme 1).

A comparison of the ^1H NMR spectra of **1** and **2** shows the lack of a proton at position 2 and no coupling due to the proton at position 1 of the keto form **2**. On the other hand, the triplet due to the proton at position 3 in compound **1** is converted into a doublet in the keto form **2**; the couplings of the other protons remained unmodified. The ^{13}C NMR spectrum of **2** exhibits a chemical shift at 198 ppm corresponding to a carbonyl group. COSY, HMQC, and ROESY experiments (see Supplementary data) confirm the structure of **2**. The infrared spectrum of **2** displayed a characteristic C=O stretch at 1759 cm^{-1}.

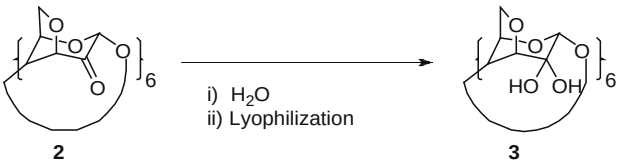
NMR investigation of the complexation properties of **2** requires spectra in D_2O.[16–18] Surprisingly, the ^{13}C NMR spectrum of **2** in D_2O exhibits an unexpected signal due to the carbon at position 2 compared to the ^{13}C NMR spectrum in DMSO-d_6. Analysis of the spectrum in D_2O revealed complete loss of the carbonyl signal at 198.0 ppm and the appearance of a new quaternary carbon at 93.8 ppm.[22] This can only be explained by conversion of **2**, in water, into a *gem*-diol derivative, hexakis(2,2-dihydroxy-3,6-anhydro)-α-CD **3** (Scheme 2). This rapid process can be ascribed to facile formation of the hydrate which relieves some of the internal strain of the ketone.

Analysis of **2** by mass spectrometry using H_2O/MeOH/formic acid (49.5:49.5:1) as the nanoelectrospray solvent revealed the presence of both compounds **2** [MH^+: *m/z* 853.1685] and **3** [MNa^+: *m/z* 983.2139] and [MK^+: *m/z* 999.1881] (Fig. 1). This result can be explained by the equilibrium between **2** and **3** under the experimental conditions used.

The transformation of compound **2** into a *gem*-diol in water prevents the investigation of complexation properties of this derivative contrary to compound **3** which remains stable in aqueous medium. In this respect, addition of 3 equiv of $Pb(NO_3)_2$ to **3** in D_2O resulted in no change in the ^1H NMR spectrum of **3**. Mass spectrometry confirmed these results since no complex formation with Pb^{2+} was observed for **3** whereas an intense signal corresponding to a Pb^{2+} complex of **1** was obtained.



Scheme 1. Experimental conditions for the synthesis of hexakis(2-keto-3,6-anhydro)-α-CD **2**.



Scheme 2. Experimental conditions for the synthesis of compound **3**.

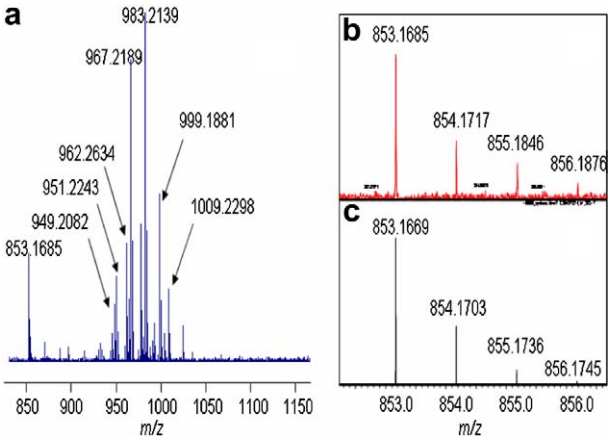


Figure 1. (a) nanoESI-FTMS spectrum of **2** in H_2O/MeOH/formic acid (49.5:49.5:1). (b) Experimental and (c) theoretical isotopic patterns for *m/z* 853.167 obtained for the nanoESI-FTMS analysis of **2** ($C_{36}H_{37}O_{24}^+$).

To probe the inclusion phenomenon, we investigated the formation of complexes of **1** and **3** with Pb^{2+} using molecular modeling.[23] Molecular modeling was performed with the MM^+ force-field using HYPERCHEM 7.5 software. The most stable complex of **1**/ Pb^{2+} is depicted in Figure 2a. In this system, Pb^{2+} is included completely in the per(3,6-anhydro)-α-CD with a binding energy of −19.73 kcal mol^{-1}. For **3**/Pb^{2+} (Fig. 2b), the calculated binding energy of 81.94 kcal mol^{-1} indicates that the complex is not stable. These theoretical results agree fully with the NMR and mass spectrometry data.

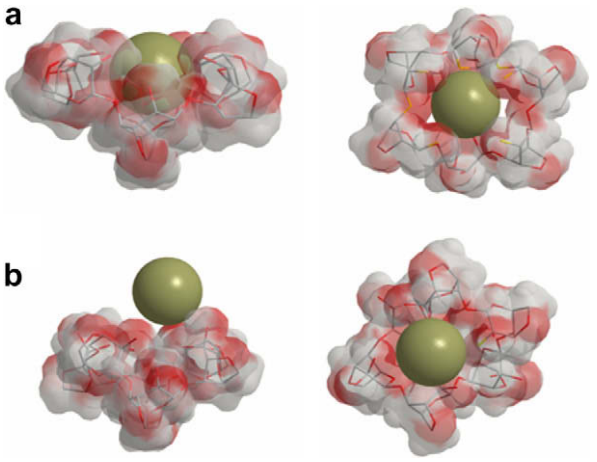


Figure 2. The most stable structures of (a) α-peranhydro cyclodextrin **1** with Pb^{2+} in water; (b) its hydrated form **3** with Pb^{2+} in water. These structures were obtained by molecular modeling using HYPERCHEM7.5 software

In summary, we have synthesized and characterized a new carbonyl derivative of per(3,6-anhydro)CD and provided evidence for its structure by NMR and mass spectrometry. The moderate yield of compound **2** shows that oxidation by acetic anhydride activated DMSO is a useful method for sterically hindered alcohols and that the axial position of the hydroxy group favors ketone formation and not alkylation of the alcohol by a methyl(methylene)sulfonium cation.

Water solubilization of compound **2** leads to the formation of a per(*gem*-diol) derivative which does not scavenge Pb^{2+} cation unlike the parent derivative **1**. Nevertheless, compound **2** remains a synthon of primary importance since it is expected to provide new complexing agents and to allow an a priori selection of the optimal host derivative for a given metal ion. Moreover, we have performed the first molecular modeling study of Pb^{2+} complexation with per(3,6-anhydro)CDs. The aim of this theoretical study was to shed light on inclusion complex structures. Work is in progress to synthesize new derivatives from **2** that will allow their use for medical and decontamination applications.

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Supplementary data

Supplementary data (computational, experimental details, NMR and nanoESI-FTMS experiments of all the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.019.

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