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Bis antennae amphiphilic cyclodextrins: the first examples

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Abstract—Methylated 6A,6D-diamino 6A,6D-dideoxy β-cyclodextrin **4** was coupled with three cholesterol substituted glutaric or succinic acids **5**–**7** to give amphiphilic cyclodextrins **1**–**3** with good yields. The succinic acid derivative **1**, a typical member of this new family, has shown good compatibility with phosphatidyl choline monolayer and bilayer as confirmed by deuterium magnetic nuclear resonance (^{2}H NMR).
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1. Introduction

Cyclodextrins (CDs) are cyclic oligoglucosides, with a truncated cone shape. They present a large set of readily modified hydroxyl groups (21 for a beta CD).[1] Therefore, since Lehn's pioneering work,[2] they became valuable scaffolds for supramolecular chemistry and amphiphilic compound construction. Thus, amphiphilic cyclodextrins, formed by the association of a hydrophilic CD—eventually methylated—with a hydrophobic part (fatty acids or cholesterol derivative), are a glycolipid family of particular interest.[3] They can present original patterns and various organizations.[4] Their potential was however not fully exploited in the field of amphiphilic derivatives as only mono[4a,5] or per substituted[2,3] (or both[6]) amphiphilic cyclodextrins have been essentially prepared with fatty acids or with cholesterol. The main reason is that chemically pure and well-defined disubstituted cyclodextrins were not available in large quantities. A controlled disubstituted amphiphilic cyclodextrin will probably find applications in formulation, vectorisation or membrane protein stabilization.

We want to describe here the first members of a new family of neutral amphiphilic CD grafted with two cholesterol appendages in a trans annular way and disclose

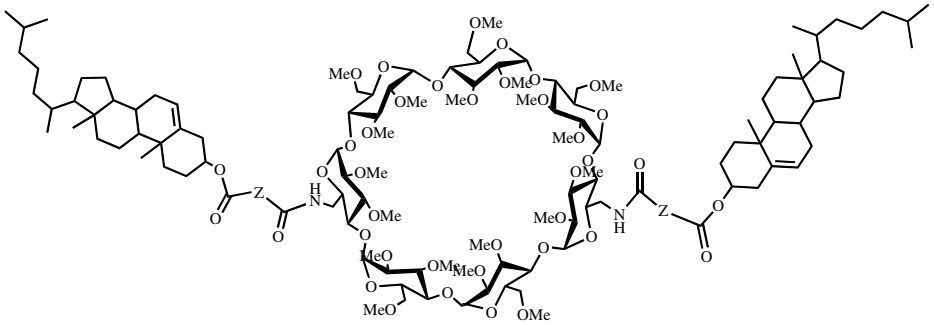

Figure 1. Amphiphilic CD (**1**–**3**): Compound **1**: Z = CH_2–CH_2. Compound **2**: Z = CH_2–$C(Me)_2$–CH_2. Compound **3**: Z = CH_2–O–CH_2.

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some preliminary results on their supramolecular behavior. Three different hinges of different flexibility have been selected (Fig. 1). These linkers are short enough to avoid auto inclusion of the rigid cholesterol.

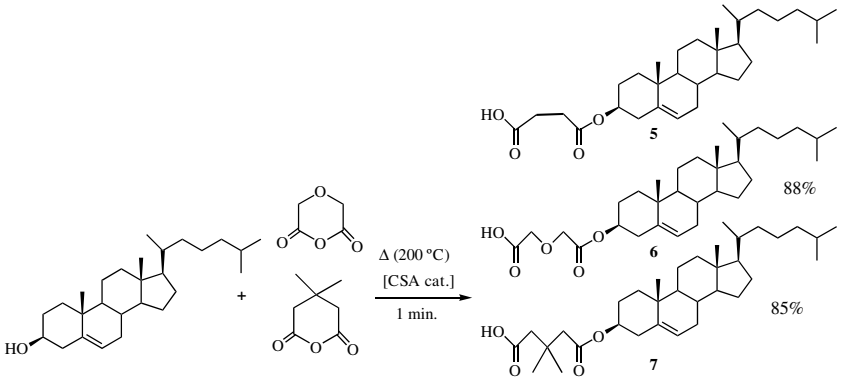
2. Synthesis

The amphiphilic cyclodextrins **1**–**3** were readily prepared from an acid derived from cholesterol **5**–**7** (Scheme 1) and a diamino cyclodextrin **4** (Scheme 2). We recently described a practical access to the 6A,6D diol of methylated β-CD.[7] This compound was converted in gram scale into a 6A,6D-diamino cyclodextrin **4**.[8] This versatile derivative is a very useful block for supramolecular chemistry[9] and is well suitable for the construction of an unprecedented yet still very simple amphiphilic neutral glycolipid. The acids used are depicted in Scheme 1. The succinic derivative **5** was commercially available, acids **6**[10] and **7**[11] were prepared by heating a solvent-free mixture of cholesterol with an excess of cyclic anhydride, in the presence of an acid catalyst (camphorsulfonic acid). This solvent-free procedure was more effective to those using pyridine or DMF as solvents, even in the presence of DMAP. This procedure gave reproducibly high yields (>85%). In the case of the most reactive (oxoglutaric anhydride), the use of a sulfonic acid as an acidic catalyst was not found critical.

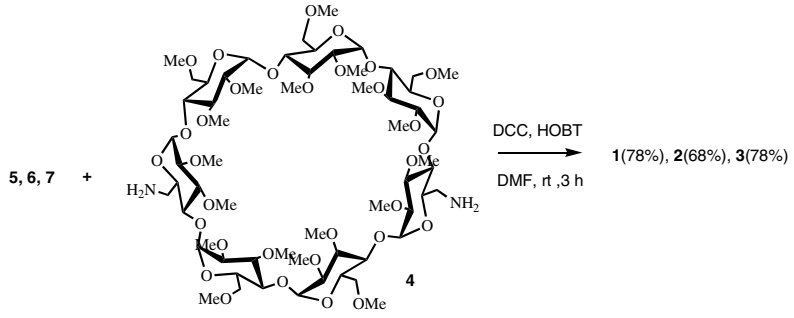
These acids have been then condensed uneventfully with diamine **4** using dicyclohexyl carbodiimide (DCC), hydroxybenzotriazole (HOBT) procedure in good yields to give **1** (78%), **2** (68%) and **3** (78%)[12] (Scheme 2). The use of a methylated compound at this stage is very convenient for isolation and purification procedures. It also ensures a good stability of the cholesteryl ester moiety against the known ester hydrolytic properties of the native cyclodextrins.[13]

3. Langmuir monolayers properties

We now describe the preliminary studies of compound **1**, as a typical member of this new family of amphiphilic cyclodextrins bearing the most commonly used succinate spacer. The length and nature of the link between the cholesteryl and the cyclodextrinyl parts should obviously play a key role as it was already described with analogous monosubstituted derivatives.[4a,c] This will be studied in the near future with compounds **2** and **3**. Here we explore the monolayer behavior of **1** in a pure form or mixed with dipalmitoyl phosphocholine (DPPC) as a synthetic model for biological membrane phospholipids. Indeed, slowly compressing the molecules spread at the air–water interface of a Langmuir trough filled with water and recording the Langmuir compression isotherm is the easiest and cheapest way to evaluate the amphiphilic behavior of a compound. As an example and as a reference (Fig. 2), the liquid expanded to gel phase transition of DPPC is evidenced by the compression plateau at ca. 10 mN/m induced by the rearrangement of the DPPC molecules required to



Scheme 1. Preparation of the acids.



Scheme 2. Final condensation steps.

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