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Preliminary communication / Communication

A,D-Oligomethylenic capping of α- and β-cyclodextrins

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Abstract

α- and β-cyclodextrins have easily been converted into basket molecules, the handle being an oligomethylenic chain bridging A and D positions on the primary rim. The size of the handle influences the complexing properties of these cyclodextrins. ***To cite this article: T. Lecourt et al., C. R. Chimie 6 (2003) 87–90.***

Résumé

Les α- et β-cyclodextrines ont été aisément transformées en molécules en forme de panier, l'anse étant constituée d'une chaîne oligométhylénique reliant les positions A et D du bord primaire. La taille de l'anse exerce une influence sur les propriétés de complexation de ces cyclodextrines. ***Pour citer cet article : T. Lecourt et al., C. R. Chimie 6 (2003) 87–90.***

Keywords: cyclodextrin; basket; metathesis; complexation

Mots clés : cyclodextrine ; panier ; métathèse ; complexation

We have recently described the efficient chemical synthesis of the 6A,6D-butylene-bridged α-cyclodextrin (CD) **3α**. As shown in Fig. 1 [1], this capped α-CD **3α** was easily derived from **1α**, a diol directly obtained in high yield through a diisobutylaluminium (DIBAL)-promoted regioselective de-*O*-benzylation of perbenzylated α-CD.

In this preliminary communication, we would like to report on the extension of this reaction to the synthesis of a new family of 6A,6D-capped cyclodextrins, together with a preliminary evaluation of their inclusion properties.

The corresponding 6A,6D-butylene-capped β-CD **3β** was first prepared in a similar manner (Fig. 2) from the known diol **1β** [1]. It is worth noting that **3β** has also been very recently synthesised using this procedure [2]. The per-*O*-methylated derivative was able to separate enantiomers of various molecules and shows high selectivity towards large and voluminous molecules. Selected data for **3β**: $[\alpha]_D^{20}$ = +129 (*c* = 0.2, MeOH); MS (MALDI-TOF): *m/z* (%): 1211.5 (100) [M + Na^+]; ^{13}C NMR (100 MHz, D_2O): 102.2, 102.1, 101.6,

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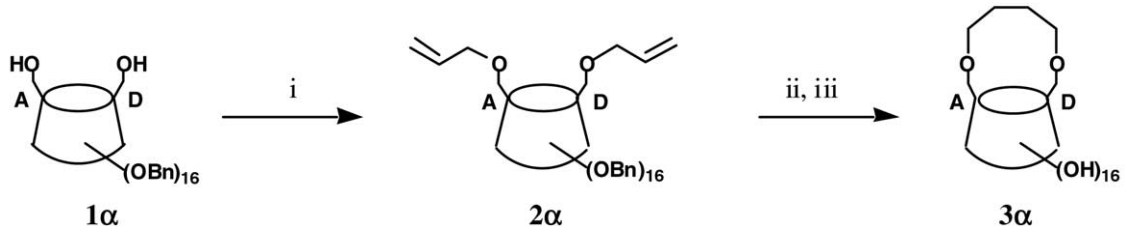
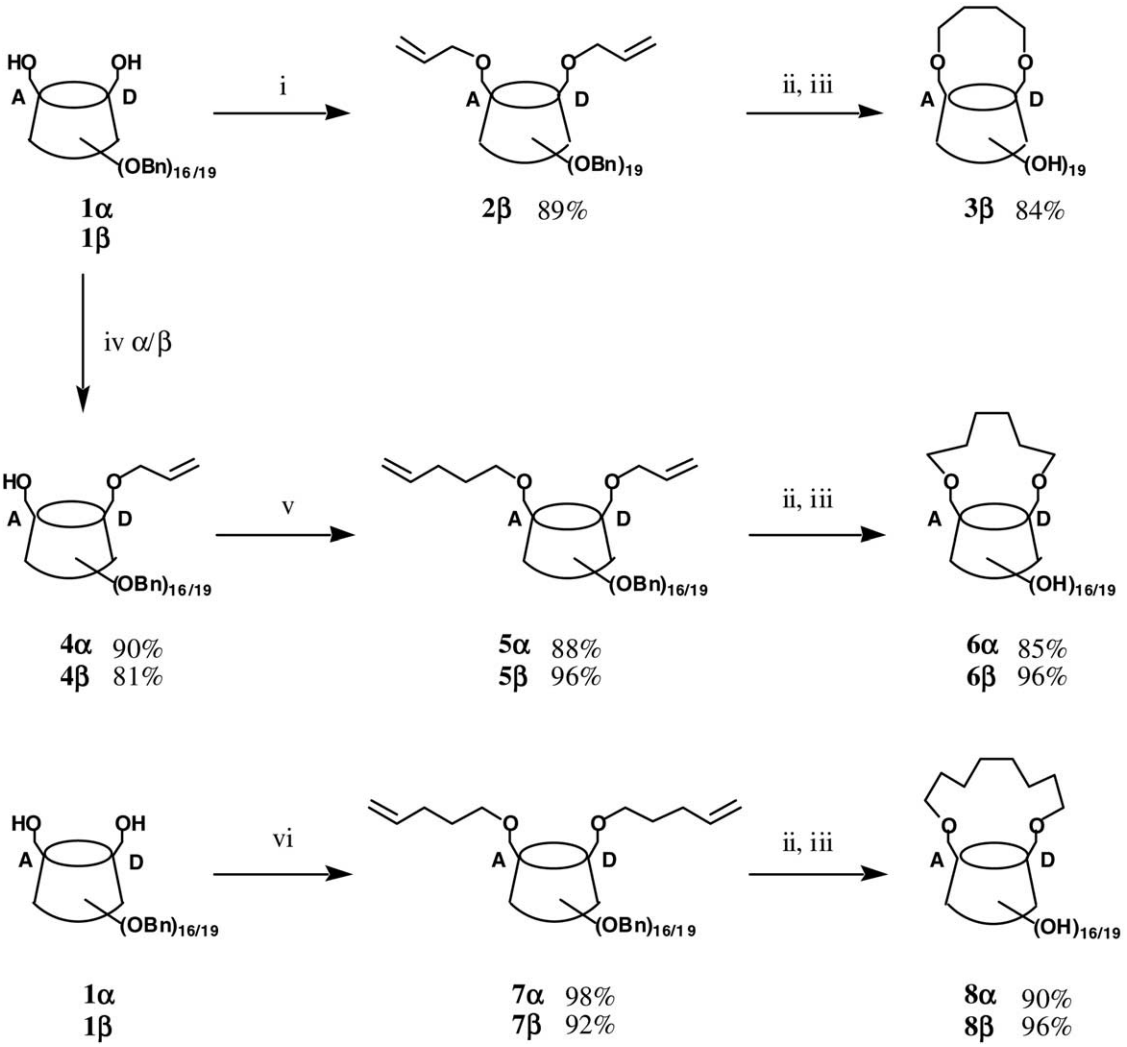


1α 2α 3α

Fig. 1. (*i*) NaH, AllylBr, DMF, rt (92%); (*ii*) Cl_2 $(PCy_3)_2$ Ru=CHPh (6 mol%), PhH, 60 °C; (*iii*) H_2, Pd/C 10%, Pd black, EtOAc/MeOH (1:1), 48 h, rt (87% over two steps).



1α **1β**

2β 89%

3β 84%

4α 90%
4β 81%

5α 88%
5β 96%

6α 85%
6β 96%

1α
1β

7α 98%
7β 92%

8α 90%
8β 96%

Fig. 2. (*i*) AllylBr (4 equiv), NaH (4 equiv), THF, $n$$Bu_4$ NI (0.1 equiv), rt, 6 h; (*ii*) Cl_2 $(PCy_3)_2$ Ru=CHPh (5 mol%), CH_2 Cl_2, reflux, 5 h then $Pb(OAc)_4$ [4], rt overnight; (*iii*) H_2, Pd/C 10%, Pd black, EtOAc/MeOH (1:1), 48 h, rt; (*iv*) for α-CD: AllylBr (1.1 equiv), NaH (2 equiv), THF, $n$$Bu_4$ NI (0.1 equiv), rt, 18 h; for β-CD: AllylBr (1.1 equiv), KH (1.1 equiv), THF, $n$$Bu_4$ NI (0.2 equiv), rt, 18 h (*v*) 5-bromo-pent-1-ene (4 equiv), tBuOK (4 equiv), $n$$Bu_4$ NI (0.1 equiv), THF, rt, 8 h; (*vi*) 5-bromo-pent-1-ene (8 equiv), tBuOK (8 equiv), $n$$Bu_4$ NI (0.1 equiv), THF, rt, 8 h.

101.4, 101.2, 100.4, 99.5 (7 × C_1), 26.2, 25.8 (2 × O–CH_2–$\underline{CH_2}$).

The synthesis of the 6A,6D-hexamethylene-bridged CDs **6α** and **6β** was next achieved as shown in Fig. 2. A key feature is the possibility to perform a high-yielding mono-*O*-allylation of either **1α** or **1β** to provide **4α** (90%) and **4β** (81%), respectively. This opens the door to the preparation of various oligomethylenic capped CDs with odd or even carbon atom numbers. As an example, pentenylation of the alcohol **4α**, followed by Ring Closing Metathesis (RCM), then hydrogenolysis, gave the capped CD **6α**. Selected data for **6α**: $[\alpha]_D^{20}$ = +121 (*c* = 0.2, MeOH); MS (MALDI-TOF): *m/z* (%): 1077.3 (100) [M + Na^+]; ^{13}C NMR (100 MHz, D_2O): 102.2, 101.8, 101.7 (3 × C_1), 29.2, 25.8 (O–CH_2–$\underline{CH_2}$–CH_2). A similar sequence provided **6β**. Selected data for **6β**: $[\alpha]_D^{20}$ = +123 (*c* = 0.2, MeOH); MS (MALDI–TOF): *m/z* (%): 1239.5 (100) [M + Na^+]; ^{13}C NMR (100 MHz, D_2O): 102.6, 102.4, 102.3, 102.2, 102.1, 102.0, 101.8 (7 × C_1), 29.5, 29.2, 25.7, 25.4 (2 × O–CH_2–$\underline{CH_2}$, 2 × O–CH_2–CH_2–$\underline{CH_2}$). This product has also been recently prepared by another route [3], then converted to the per-*O*-methylated derivative, which was also able to separate enantiomers of particularly large molecules, including pharmaceuticals of different structural types.

Selected data for **4α**: $[\alpha]_D^{20}$ = +34 (*c* = 1, $CHCl_3$); MS (FAB): *m/z* (%): 2477.0 (100) [M + Na^+]; ^{13}C NMR (100 MHz, $CDCl_3$): 134.5 (CH_2=$\underline{CH}$–CH_2–O), 116.9 ($\underline{CH_2}$=CH–CH_2–O), 98.7, 98.4, 98.1, 98.0, 97.9, 97.8 (6 × C_1), 61.2 (CH_2=CH–$\underline{CH_2}$–O).

Selected data for **4β** (obtained as an inseparable mixture of isomers): MS (FAB): *m/z* (%): 2910.2 (100) [M + Na^+]; ^{13}C NMR (100 MHz, $CDCl_3$): 134.64, 134.57 (CH_2=$\underline{CH}$–CH_2–O), 116.8 ($\underline{CH_2}$=CH–CH_2–O), 98.83 (1 × C_1), 98.73 (2 × C_1), 98.69 (2 × C_1), 98.64, 98.57, 98.45, 98.37, 98.31, 98.16, 98.10, 97.89, 97.70 (9 × C_1), 61.45, 61.38 (CH_2=CH–$\underline{CH_2}$–O).

Finally, the two 6A,6D-octamethylene bridged cyclodextrins **8α** and **8β** have been prepared as shown in Fig. 2. Selected data for **8α**: $[\alpha]_D^{20}$ = +120 (*c* = 0.15, MeOH); MS (MALDI–TOF): *m/z* (%): 1105.5 (100) [M + Na^+]; ^{13}C NMR (100 MHz, D_2O): 101.9, 101.5, 101.4 (3 × C_1), 29.2, 28.6, 25.4 (O–CH_2–$\underline{CH_2}$–$\underline{CH_2}$–$\underline{CH_2}$). Selected data for **8β**: $[\alpha]_D^{20}$ = +125 (*c* = 0.2, MeOH); MS (MALDI–TOF): *m/z* (%): 1267.2 (100) [M + Na^+]; ^{13}C NMR (100 MHz, D_2O): 102.7, 102.5, 102.4, 102.1, 102.0, 102.9, 101.7 (7 × C_1), 29.6, 29.3, 28.7, 28.3, 25.8, 25.5 (2 × O–CH_2–$\underline{CH_2}$, 2 × O–CH_2–CH_2–$\underline{CH_2}$, 2 × O–CH_2–CH_2–CH_2–$\underline{CH_2}$).

The capping of CDs had so far been achieved using tailor-made rigid aromatic disulfonylchlorides [4–16]. It is clear that the direct availability of diols **1α** and **1β**, combined with high regioselective mono-*O*-allylation and RCM methodology, provides a versatile entry to a family of oligomethylene-capped 6A,6D α- or β-cyclodextrins.

We have now studied the inclusion properties of *p*-nitro-phenolate (PNP) in **3**, **6** and **8α/β**. PNP derivatives are known to include with the nitro group close to the narrower rim [17], and to be very sensitive to the bulk of the guest [18]. The equilibrium constant is determined by UV–visible spectroscopy [19] in a phosphate buffer (pH = 11; *I* = 0.5). The concentration of PNP is 5×10^{-5} M and, even at the highest concentration of CD (5×10^{-3} M), all PNP is not bound. The values were therefore plotted according to the Hildebrand-Benesi [20] relation (equation (1)):

$$\frac{C_{PNP}}{\Delta A} = \frac{1}{C_{CD}\, K\, \Delta\varepsilon} + \frac{1}{\Delta\varepsilon}$$

with *K* the association constant of the CD–PNP complex, C_{PNP} is the concentration in PNP (5×10^{-5} M), C_{CD} is the concentration of CD (5×10^{-3} M; 2.5×10^{-3} M; 1.25×10^{-3} M; 5×10^{-4} M; 2.5×10^{-4} M), $\Delta A = A - A_0$, where A_0 is the absorption of the solution without CD, and *A* the absorption of the solution for a given concentration of CD, and $\Delta\varepsilon$ is the difference between the molar extinction coefficients for free and complexed PNP. The intercept of the linear plot $1/\Delta A = f(1/C_{CD})$ gives $1/\Delta\varepsilon$, and the slope gives $1/K\,\Delta\varepsilon$.

As reported in Table 1, the association constants for α- (log *K* = 3.24) and β-CD (log *K* = 2.80) are in agreement with the literature [21]. There is no inclusion of PNP with the shortly capped-CDs **3α/β**. The 6A,6D-hexamethylene capped-CDs **6α/β** show moderate association constants (log *K* = 2.83 and 2.66, respectively). Concerning the larger capped-CDs, **8α** shows an enhancement of its association constant (log *K* = 3.95).

It thus appears that AD-oligomethylenic capping is able to modulate the complexing properties of cyclodextrins.

Table 1
Association constants of PNP with AD-oligomethylene-capped-CDs **3,6** and **8α/β**. NB = no binding

	log *K*
α-**CD**	3.24
3α	NB
6α	2.83
8α	3.95
	log *K*
β-**CD**	2.80
3β	NB
6β	2.66
8β	2.33

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