NOVEL AMPHIPHILIC CYCLODEXTRINS: PER[6-DEOXY-6-(4,5-DICARBOXY-1,2,3-TRIAZOL-1-YL)-2,3-DI-*O*-METHYL] DERIVATIVES

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Received February 10, 1998
Accepted March 20, 1998

Dedicated to the memory of Professor Vlado Prelog.

Per[6-deoxy-6-(4,5-dicarboxy-1,2,3-triazol-1-yl)-2,3-di-*O*-methyl] substituted α- and β-cyclodextrins **6a** and **6b** were prepared by 1,3-dipolar cycloaddition reaction of the corresponding per(6-azido-6-deoxy-2,3-di-*O*-methyl)cyclodextrins **4a** and **4b** with dimethyl acetylenedicarboxylate.
Key words: α-Cyclodextrin; β-Cyclodextrin; Per-carboxy cyclodextrins; 1,3-Dipolar cycloaddition; 1,2,3-Triazoles.

Cyclodetrins (CD) are a class of cyclic oligosaccharides composed of glucopyranose units. They possess a truncated cone geometry involving a hydrophobic cavity lined by two hydrophilic faces of primary (upper rim) and secondary (lower rim) hydroxyl groups (Fig. 1, **A**), which allows inclusion and/or transport of a variety of organic substrates in aqueous solution. This property[1–3] has led to a widespread application of cyclodextrins in separation processes as well as in food, cosmetic and pharmaceutical industries[2].

There has been a growing interest in a selective chemical modification of cyclodextrins aimed at transformation of the hydrophilic exterior into an amphiphilic one[4–6]. This should extend the applicability of cyclodextrins to non-aqueous solutions and allow, moreover, formation of a wide range of organized assemblies, either alone or in the presence of other amphiphilic or guest molecules, which might be useful in transport of biologically active compounds or in construction of biosensors.

We are interested in the self-assembly of amphiphilic cyclodextrins, organized by electrostatic interactions and/or ionic hydrogen bonds. As possible tectons for such

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self-assembly, we have chosen cyclodextrins persubstituted with carboxyl groups at the upper and with alkoxy groups at the lower rim, enhancing thus, simultaneously, the hydrophilicity of the former and lipophilicity of the latter face. Towards these ends, we have recently developed a novel synthetic procedure[7] allowing preparation of the hitherto inaccessible hexakis(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-α-cyclodextrin and heptakis(6-*O*-carboxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin (Fig. 1, **B**). In this communication we report another approach towards analogous amphiphilic compounds possessing, however, twice as many of carboxyl groups at the upper rim (Fig. 1, **C**).

RESULTS

Synthesis of the target amphiphilic cyclodetrins has been performed following Scheme 1. In the first two steps the parent cyclodextrins **1a**, **1b** were converted – *via* the corresponding 6-deoxy-6-iodo derivatives **2a**, **2b** – into per(6-azido-6-deoxy)cyclodetrins **3a**, **3b** by modification of known procedures[8]. In the next step the azides **3a**, **3b** were permethylated by treatment with sodium hydride and methyl iodide, giving rise to the pure crystalline per(6-azido-6-deoxy-2,3-di-*O*-methyl)cyclodextrins **4a**, **4b**. In the key step, the permethylated azides **4a**, **4b** were heated with an excess of dimethyl acetylenedicarboxylate. Dipolar cycloaddition[9] involving the acetylene and azide grouping yielded, after chromatography, pure per{6-deoxy-6-[4,5-bis(methoxycarbonyl)-1,2,3-triazol-1-yl]-2,3-di-*O*-methyl}cyclodetrins **5a**, **5b**. The methyl esters were quantitatively hydrolyzed with potassium hydroxide in aqueous methanol at ambient temperature, yielding, after ion exchange, the desired free acids **6a**, **6b**.

The structure of the novel compounds **5a**, **5b** and **6a**, **6b** was confirmed by ^{1}H NMR, ^{13}C NMR and FAB MS spectra. The NMR spectra showed a line broadening effect which was partly reduced at higher temperature (60 °C), 2D-COSY spectra were used

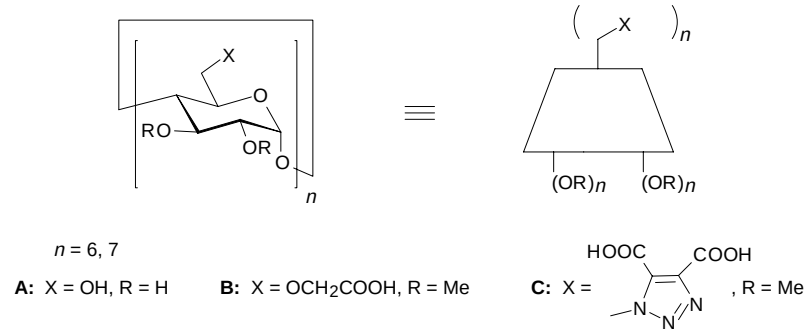
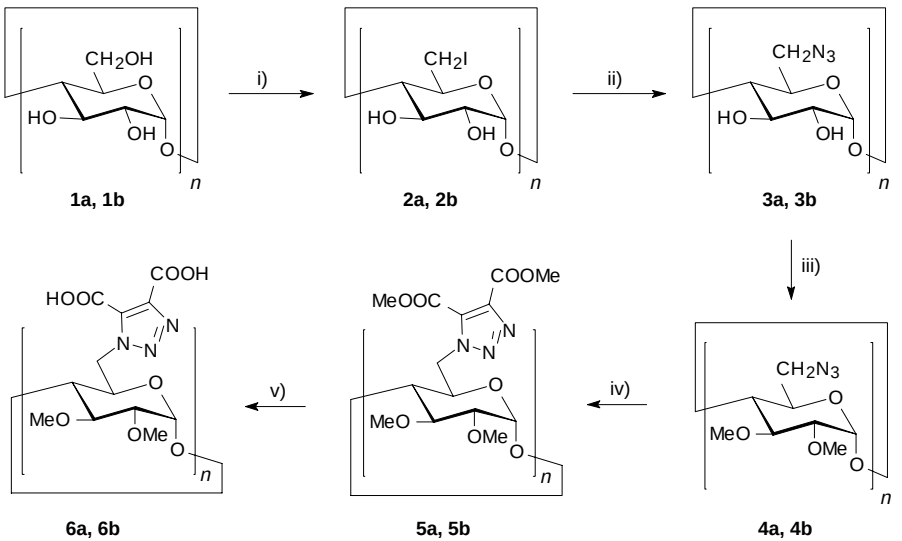


FIG. 1
Persubstituted cyclodextrins

for structural assignment of protons. Carbon signals were assigned using heteronuclear $^{1}H–^{13}C$ 2D-HMQC spectra (Table I).

In this way, an easy access to a new family of amphiphilic polycarboxycyclodetrins, which exhibit solubility in organic solvents (*e.g.* alcohols, acetone) as well as in water, has become available. It is assumed that the proposed synthesis will be applicable also for the homologues with longer (more lipophilic) alkoxy residues. On the other hand,



1a-6a: $n = 6$
1b-6b: $n = 7$

i) Ph_3P/I_2/DMF; ii) NaN_3/DMF; iii) MeI/NaH/DMF;
iv) MeOOC—≡—COOMe, toluene; v) 1. KOH/MeOH/H_2O, 2. Dowex 50X2, H^+

SCHEME 1

the cycloaddition methodology may also be employed for the preparation of "super-hydrophilic" cyclodextrin derivatives lacking the amphiphilic (lipophilic) properties. In the β-cyclodextrin series, a pertinent synthesis of the unalkylated analogue of **6b**, heptakis[6-deoxy-(4,5-dicarboxy-1,2,3-triazol-1-yl]-β-cyclodextrin has been concurrently reported[11].

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were measured on FT NMR spectrometer Varian UNITY-500 (^{1}H at 500 MHz; ^{13}C at 125.7 MHz) at +60 °C in hexadeuteriodimethyl sulfoxide. Chemical shifts are referenced to the signal of solvent (δ (^{1}H) 2.50 and δ (^{13}C) 39.7).

TABLE I

^{1}H NMR and ^{13}C NMR data of compounds **5a**, **5b** and **6a**, **6b** in hexadeuteriodimethyl sulfoxide at 60 °C

Compound	^{1}H NMR									
	H-1 *J*(1,2)	H-2 *J*(2,3)	H-3 *J*(3,4)	H-4 *J*(4,5)	H-5 *J*(5,6a)	H-6a *J*(5,6b)	H-6b *J*(6a,6b)	OCH_3	$COOCH_3$	
6a	5.28	2.83	3.46	3.46	4.34	5.14	4.88	3.37	–	
	3.4	9.7	[a]	9.5	4.0	2.5	14.4	3.52		
6b	5.45	2.93	3.46	3.35	4.21	5.05	4.78	3.39	–	
	3.6	9.8	8.5	9.7	4.0	3.7	14.4	3.52		
5a	5.27	2.93	3.48	3.41	4.22	4.75	4.75	3.38	3.80	
	3.4	9.8	8.5	9.5	~3.8	~3.8	[a]	3.52	3.82	
5b	5.39	3.04	3.45	3.36	4.14	4.80	4.68	3.40	3.80	
	3.7	9.5	8.3	9.6	3.6	4.5	14.5	3.51	3.82	
	^{13}C NMR									
	C-1	C-2	C-3	C-4	C-5	C-6	OCH_3	C=O	OCH_3	C=C
6a	98.66	81.09	80.30	82.35	68.95	48.24	60.90	161.77	–	139.53
							57.25	159.07		133.01
6b	97.41	80.76	80.98	80.12	68.86	48.74	60.57	161.60	–	139.11
							57.91	159.16		133.32
5a	98.50	80.66	80.29	81.50	69.28	49.01	60.80	159.76	53.12	138.64
							57.57	158.42	52.27	132.10
5b	97.54	80.22	80.82	79.60	69.04	49.08	60.49	159.80	53.11	138.63
							57.94	158.52	52.24	131.99

[a] The *J* value could not be obtained due to overlap of signals.

FAB MS spectra were recorded with a ZAB-EQ VG analytical intrument using a diethyl disulfide matrix. Specific optical rotations were measured on a Perkin–Elmer 241 polarimeter at 23 °C. Thin-layer chromatography (TLC) was performed with precoated Silica Gel 60F-254 plates (Merck) which were developed by spraying with 5% sulfuric acid in ethanol and heating. Compound **2b** was prepared using the procedure described by Stoddart *et al*.[6]. Cyclodetrins (Fluka) were dried at 100 °C for 20 h prior to use. Solvents were dried by common methods.

Hexakis(6-deoxy-6-iodo)-α-cyclodetrin (**2a**)

The reaction conditions for the preparation of **2a** are analogous to those described in literature[12]. Thus, triphenylphosphine (21 g, 80 mmol) was dissolved in dry DMF (80 ml) and iodine (20.25 g, 80 mmol) was slowly added. The mixture was stirred for 15 min and **1a** (5.8 g, 5.96 mmol) was added. The mixture was stirred for 18 h at 80 °C. The resulting dark brown solution was concentrated to about a half and cooled down to room temperature. Sodium methoxide (3 mol l^{-1}, 30 ml, 90 mmol) was added dropwise with stirring and efficient cooling, keeping the temperature below 10 °C. The mixture was further stirred for 30 min and poured into methanol (400 ml). The precipitate was washed with methanol, dried at room temperature, dissolved in DMF (100 ml) and reprecipitated by methanol (400 ml). This partially purified product was Soxhlet-extracted with methanol for 48 h to give 7.8 g (80.2%) of a fine powder, m.p. 249–250 °C (dec.), (ref.[12] 227 °C dec.). ^{13}C NMR spectrum was in accord with the reported one[12].

Hexakis(6-azido-6-deoxy)-α-cyclodextrin (**3a**)

To a solution of **2a** (1.3 g, 0.79 mmol) in DMF (25 ml), sodium azide (0.62 g, 9.6 mmol) was added. The mixture was stirred at 60 °C for 20 h and then poured into water (200 ml). The fine precipitate was decanted and resuspended in a new portion of warm water (200 ml). The suspension was stirred at 60 °C for 30 min, allowed to cool down to room temperature, partially decanted to reduce the total volume to about one half and filtered on fine sintered glass. Compound **3a** (0.85 g, 95.8%) was recovered as a white powder after drying over phosphorus pentoxide *in vacuo*. ^{1}H NMR and ^{13}C NMR spectra were in accord with the reported ones[13].

Heptakis(6-azido-6-deoxy)-β-cyclodextrin (**3b**)

This compound was prepared starting from **2b** (17 g, 8.93 mmol) and sodium azide (6.1 g, 93.8 mmol) using the same procedure as for **3a**. The product (11.5 g, 98%) was obtained as a white powder. ^{1}H NMR and ^{13}C NMR spectra were in accord with the reported ones[6].

Hexakis(6-azido-6-deoxy-2,3-di-*O*-methyl)-α-cyclodextrin (**4a**)

Compound **3a** (5.3 g, 4.72 mmol) was added to a stirred suspension of oil-free sodium hydride (2.58 g, 133 mmol) in dry DMF (200 ml). The mixture, which tended to solidify, was stirred vigorously for 15 min and methyl iodide (7.04 ml, 113.2 mmol) was added dropwise within 3 h under cooling, keeping the temperature of the reaction mixture below 20 °C. The mixture was stirred for 15 h at room temperature and the excess of sodium hydride was decomposed by dropwise addition of methanol (30 ml) under stirring and cooling. The solution was poured into an ice-water mixture, the resulting precipitate was collected, washed with water and dried *in vacuo*. The product was purified by column chromatography (silica gel, gradient elution chloroform–chloroform/methanol 98 : 2) followed by crystallization from heptane to give **4a** (5.55 g, 91%) after extensive drying *in vacuo*, m.p. (ref.[14]) 144–146 °C. ^{1}H NMR and ^{13}C NMR spectra were in accord with the reported ones[13].

Heptakis(6-azido-6-deoxy-2,3-*O*-methyl)-β-cyclodetrin (**4b**)

Compound **3b** (10.9 g, 8.32 mmol) was dissolved in dry DMF (300 ml) containing oil-free sodium hydride (5.59 g, 0.233 mol) and the solution was vigorously stirred for 30 min. Methyl iodide (14.5 ml, 233 mmol) was added portionwise during 3 h under intensive cooling. The mixture was further stirred for 15 h at room temperature and worked up as described for **4a**. Column chromatography followed by recrystallization from heptane afforded **4b** (11 g, 87.7%), m.p. (ref.[14]) 85–93 °C.

Hexakis{6-deoxy-6-[4,5-bis(methoxycarbonyl)-1,2,3-triazol-1-yl]-2,3-di-*O*-methyl}-α-cyclodextrin (**5a**)

Compound **4a** (0.516 g, 0.4 mmol) was dissolved in toluene (8 ml) and dimethyl acetylenedicarboxylate (0.590 ml, 4.8 mmol) was added. The solution was heated at 100 °C for 15 h, and the solvent was evaporated. Subsequent flash chromatography (silica gel, gradient elution chloroform–chloroform/methanol 25 : 1) gave **5a** (0.690 g, 80.4%) as a white foam; $[\alpha]_D$ +112.6° (*c* 0.13, $CHCl_3$). For ^{1}H NMR and ^{13}C NMR data see Table I. FAB MS, *m/z*: 2 145 $[M + H]^+$, 2 167 $[M + Na]^+$. For $C_{84}H_{114}N_{18}O_{48}$ (2 143.7) calculated: 47.04% C, 5.36% H, 11.76% N; found: 46.70% C, 5.28% H, 11.73% N.

Heptakis{6-deoxy-6-[4,5-bis(methoxycarbonyl)-1,2,3-triazol-1-yl]-2,3-di-*O*-methyl}-β-cyclodextrin (**5b**)

Prepared from **4a** (0.516 g, 0.343 mmol) and dimethyl acetylenedicarboxylate (0.590 ml, 4.8 mmol) in toluene (8 ml) as described for **5a**. The yield was 0.775 g (90.5%) of a white foam; $[\alpha]_D$ +100.9° (*c* 0.13, $CHCl_3$). For ^{1}H NMR and ^{13}C NMR data see Table I. FAB MS, *m/z*: 2 502 $[M + H]^+$. For $C_{98}H_{133}N_{21}O_{56}$ (2 501.2) calculated: 47.04% C, 5.36% H, 11.76% N; found: 46.65% C, 5.30% H, 11.48% N.

Hexakis[6-deoxy-6-(4,5-dicarboxy-1,2,3-triazol-1-yl)-2,3-di-*O*-methyl]-α-cyclodextrin (**6a**)

Compound **5a** (0.0858g, 0.04 mmol) was dissolved in MeOH (1.2 ml), potassium hydroxide (1.44 ml of 1 M aqueous solution, 1.44 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. The solvents were partially evaporated, water (2 ml) was added and the solution was applied onto a column of Dowex 50X8 H^+ (3 ml). The column was eluted with water to neutral reaction of the eluate. Evaporation of the eluate gave **3b** (0.08 g, 97%) as a white foam after drying over P_2O_5 in high vacuum; $[\alpha]_D$ +22.6° (*c* 0.13, H_2O). For ^{1}H NMR and ^{13}C NMR data see Table I. FAB MS, *m/z*: 1 976 $[M + H]^+$. For $C_{72}H_{90}N_{18}O_{48}$ (1 975.6) calculated: 43.77% C, 4.59% H, 12.76% N; found: 43.38% C, 4.79% H, 12.36% N.

Heptakis[6-deoxy-6-(4,5-dicarboxy-1,2,3-triazol-1-yl)-2,3-di-*O*-methyl]-β-cyclodextrin (**6b**)

Hydrolysis of **5b** (0.08 g, 0.032 mmol) under analogous conditions as described for preparation of **6a** gave **6b** (0.072 g, 97%); $[\alpha]_D$ +13.8° (*c* 0.12, H_2O). For ^{1}H NMR and ^{13}C NMR data see Table I. FAB MS, *m/z*: 2 306 $[M + H]^+$. For $C_{84}H_{105}N_{21}O_{56}$ (2 304.9) calculated: 43.77% C, 4.59% H, 12.76% N; found: 43.42% C, 4.71% H, 12.41% N.

We are grateful for the financial support from the Grant Agency of the Czech Republic (grant No. 203/97/0025).

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