Synthesis of Per(5-carboxy-5-dehydroxymethyl)-α- and β-Cyclodextrins – Self-Assembly of the Per(2,3-di-*O*-methyl)-Protected Homologues into Highly Stable Dimers, Driven by Multiple Hydrogen Bonds

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Keywords: Carboxylic acids / Cyclodextrins / Supramolecular chemistry / Self-assembly

Per(2,3-di-*O*-methyl)- and per(2,3-di-*O*-acetyl)- α- and β-cyclodextrins were smoothly converted into the corresponding per(5-carboxy-5-dehydroxymethyl) derivatives **2a**, **2b**, **4a** and **4b** by TEMPO-mediated oxidation. Alkaline hydrolysis of the per(2,3-di-*O*-acetyl)-substituted polycarboxylic acids affords the naked per(5-carboxy-5-dehydroxymethyl)cyclodextrins **5a** and **5b** in quantitative yields. Self-assembly, driven by hydrogen bonds, of the per(2,3-di-*O*-methyl)-protected homologues **2a** and **2b** affords highly stable dimers, as evidenced by vapour-pressure osmometry in 1,2-dichloroethane solution.

Introduction

Composed of α-1,4-linked D-(+)-glucopyranose units, cyclodextrins are cyclic oligosaccharides possessing the overall shape of a hollow truncated cone, with one (wider) rim being occupied by the secondary hydroxyl groups, the other (narrower) one by the primary hydroxyl groups. As a consequence of this unique geometry,[1] a great variety of applications, as well as chemical modifications, of cyclodextrins have emerged in the literature over the past decades. Selective permodification of the individual rims (faces) represents in this context a synthetic challenge of a particular interest. Various cyclodextrins[2] persubstituted at the primary rim, including perhalo, perazido, peramino, percyano and permercapto derivatives, have already been obtained.

Numerous attempts have also been directed towards selective conversion of the hydroxymethyl groups (at the primary rim) into carboxyl functions. So far, however, all such experiments, utilising a variety of oxidation agents (Pt/O_2, nitric oxides, TEMPO), have repeatedly failed to provide any pure materials.[3]

Having a vested interest in the application of polycarboxylic tectons in supramolecular self-assembly of chiral porous structures,[4] we have now revisited this old problem and report the synthesis of several chemically uniform α- and β-cyclodextrins persubstituted at the C_5 carbons of the primary rim by carboxylic groups. At the same time we report preliminary data concerning their self-assembly in solution.

Results and Discussion

Synthesis

Statistical prediction of overall yields of selective persubstitution of primary vs. secondary hydroxyls of cyclodextrins is a subject of continuing confusion. According to a recent review article,[5] an arbitrary persubstitution of primary hydroxyls of α-cyclodextrin proceeding with, say, 10:1 selectivity (91% per reaction) should give 57% overall yield ($0.91^6 = 0.57$). However, as was pointed out by Lehn[6] in a general analysis of the selectivity problem, the actual situation is more complex, and synthetic prospects much worse, since the varying number of the competing groups in the individual steps of the overall reaction has to be taken into account. The general formula for the percentage yield in the *i*th step of a given permodification where two groups of functions, with *n* members in the preferred group and *m* members in the alternative group, compete with a selectivity of *x*:*y* is given by Equation 1. The final overall yield for the selective permodification of all *n* groups is the product given by Equation 2. Neglecting other (presumably adverse[6]) effects, the maximum overall yield of 10:1 selective oxidation of α- and β-cyclodextrins cannot accordingly exceed 11% and 7%, respectively.

$$\%\ \text{yield-}i\text{-th reaction} = 100\left[\frac{x(n-i+1)}{my + x(n-i+1)}\right] \quad (1)$$

$$\%\ \text{overall yield} = 100\prod_{i=1}^{n}\frac{xi}{xi+my} \quad (2)$$

In order to obviate this statistical barrier, we have examined an alternative strategy based on a selective protection of the undesired (secondary) set of hydroxyl functions. It is known that amplification of the steric difference between the primary and secondary hydroxyl groups in cyclodextrins with an extremely bulky *tert*-butyldimethylsilyl reagent permits a selective persilylation of the primary rim.[7] A subsequent exhaustive alkylation (acylation) of the per-6-silylated derivatives followed by a desilylation opens access to a variety of cyclodextrins persubstituted at the secondary rim. We have chosen robust per(2,3-di-*O*-methyl) derivatives **1a** and **1b** as the model substrates.[7a,7b]

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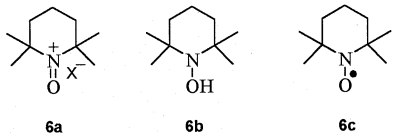
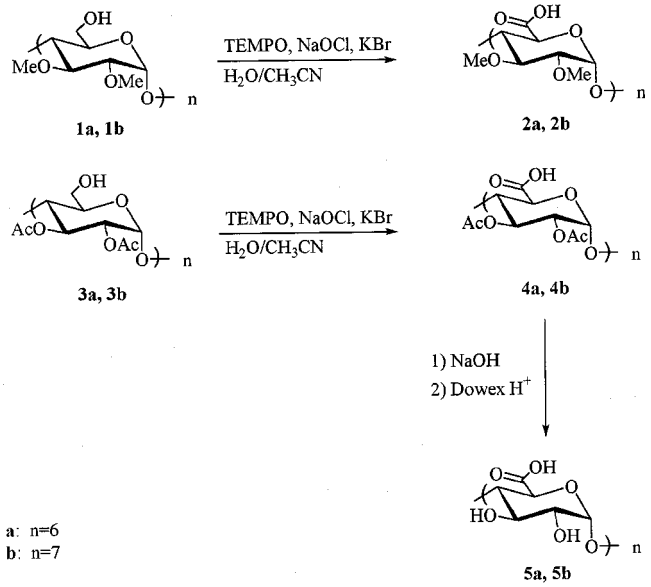
  1434–193X/00/0918–3133 $ 17.50+.50/0

Primary hydroxyl groups of carbohydrates are known to be oxidised only with difficulty with noble metal catalysts or nitrogen oxides,[8] and the TEMPO-mediated oxidation thus seemed to be the method of choice[8a,8c,9] for this conversion. The actual oxidant in the TEMPO process is the nitrosonium[9a] ion **6a**, which reduces to the hydroxylamine **6b** (Scheme 1). A rapid metathesis of **6a** and **6b** recovers the starting radical **6c**, which can be transformed back into the reactive ion **6a** by an appropriate auxiliary oxidant.



Scheme 1

Employing, at first, two-phase conditions[10] for the TEMPO oxidation (CH_2Cl_2/H_2O, NaClO/KBr, Aliquat 336, pH = 8.6) we could not achieve a complete conversion, owing probably to the increasing hydrophilicity of the carboxylic residues, driving the intermediates out of the reactive organic phase. Accordingly, a substantial improvement has been achieved under monophasic aqueous conditions. After some optimisation, a practically complete conversion of both per(2,3-di-*O*-methyl) cyclodextrin derivatives **1a** and **1b** (Scheme 2) into the corresponding carboxylic acids **2a** and **2b**, respectively, has been achieved, employing the known TEMPO−NaOCl-KBr system[11a] in a buffered (pH 10) acetonitrile-water solution. Significantly, no other oxidation products could be detected in ^1H and ^{13}C spectra of the products (Table 1) isolated in practically quantitative yields by successive quenching with methanol, extraction with ether (recovery of TEMPO), acidification and desalination on a reversed-phase chromatographic column.



Scheme 2

Encouraged by these results, we have sought an appropriate protecting group which would survive the alkaline conditions of the TEMPO oxidation, allowing at the same time a subsequent deprotection under reasonably mild conditions. Benzyl- and allyl-protected cyclodextrin derivatives[7a] failed to undergo the oxidation, presumably owing to their lipophilic character precluding application of the monophasic (aqueous) conditions. We have therefore focused our attention on more polar protecting groups. It has been found that acetyl groups in the (2,3-di-*O*-acetyl)persubstituted derivatives[7a,7b] **3a** and **3b** can survive the oxidation, provided that high concentration of all components of the TEMPO−NaOCl−KBr system ensures[11a] high rates of the conversion. Under such circumstances, yields of the protected polycarboxylic acids **4a** and **4b** higher than 60% have been obtained. Subsequent alkaline hydrolysis afforded the corresponding naked polyacids **5a** and **5b** in quantitative yields.

Table 1. ^1H and ^{13}C NMR data in [D_6]DMSO

	H-1 *J*(1,2)	H-2 *J*(2,3)	H-3 *J*(3,4)	H-4 *J*(4,5)	H-5	COOH	OAc		OCH_3	
2a	5.16 3.7	3.15 9.5	3.39 8.7	3.72 9.6	4.19	[a]			3.55	3.40
2b	5.11 3.3	3.14 9.6	3.48 8.4	3.73 9.3	4.10	12.90			3.48	3.41
4a	5.15 3.5	4.65 10.6	5.42 9.2	4.01 9.5	4.44	[a]	2.01	1.99		
4b	5.15 3.2	4.66 9.5	5.21 8.2	3.96 8.7	4.34	13.20	2.04	2.00		
5a	4.79 3.3	3.33 9.8	3.81 8.7	3.51 9.8	4.12	12.65				
5b	4.78 3.5	3.36 9.7	3.65 8.8	3.43 9.8	4.05	12.70				

	C-1	C-2	C-3	C-4	C-5	C-6	OAc		OCH_3	
2a	97.10	79.79	81.04	79.61	70.84	170.34			60.81	57.98
2b	97.27	80.87	80.50	79.47	71.72	170.15			60.39	58.08
4a	95.67	69.91	69.35	76.79	70.92	169.89 20.47	169.30 20.39	169.13		
4b	96.53	69.57	69.03	72.12	71.67	170.00 20.51	169.14 20.49	168.95		
5a	101.82	71.64	72.24	83.67	71.55	169.70				
5b	102.13	72.04	72.31	83.63	71.35	169.59				

[a] This signal was not observed

Once the pure polyacids **5a** and **5b** became available, the viability of the TEMPO-mediated direct oxidation[3d] of the native (unprotected) cyclodextrins to the target polyacids could be reexamined. In a series of parallel experiments, we used varying amount of the auxiliary oxidant (NaOCl) and TEMPO (catalytic as well as stoichiometric amounts) in the α-cyclodextrin oxidation. The crude product mixtures in the individual reaction runs were converted into the corresponding free acids and the composition was determined by FAB mass spectroscopy. It was found that, in the experiments performed with the theoretical amount and also with 20%, 50% and 100% excess of the oxidant, the corresponding tetra-, penta- and hexacarboxylic acids invariably remained present (Figure 1, A and B), indicating incompleteness of the target oxidation.[12] Moreover, in addition to the molecular peaks with the expected isotope distribution calculated for hexacarboxylic acid **5a**, prominent masses lower by 2, 4, 6 daltons etc. were found at the same time. Such satellite peaks, which are absent in the spectrum

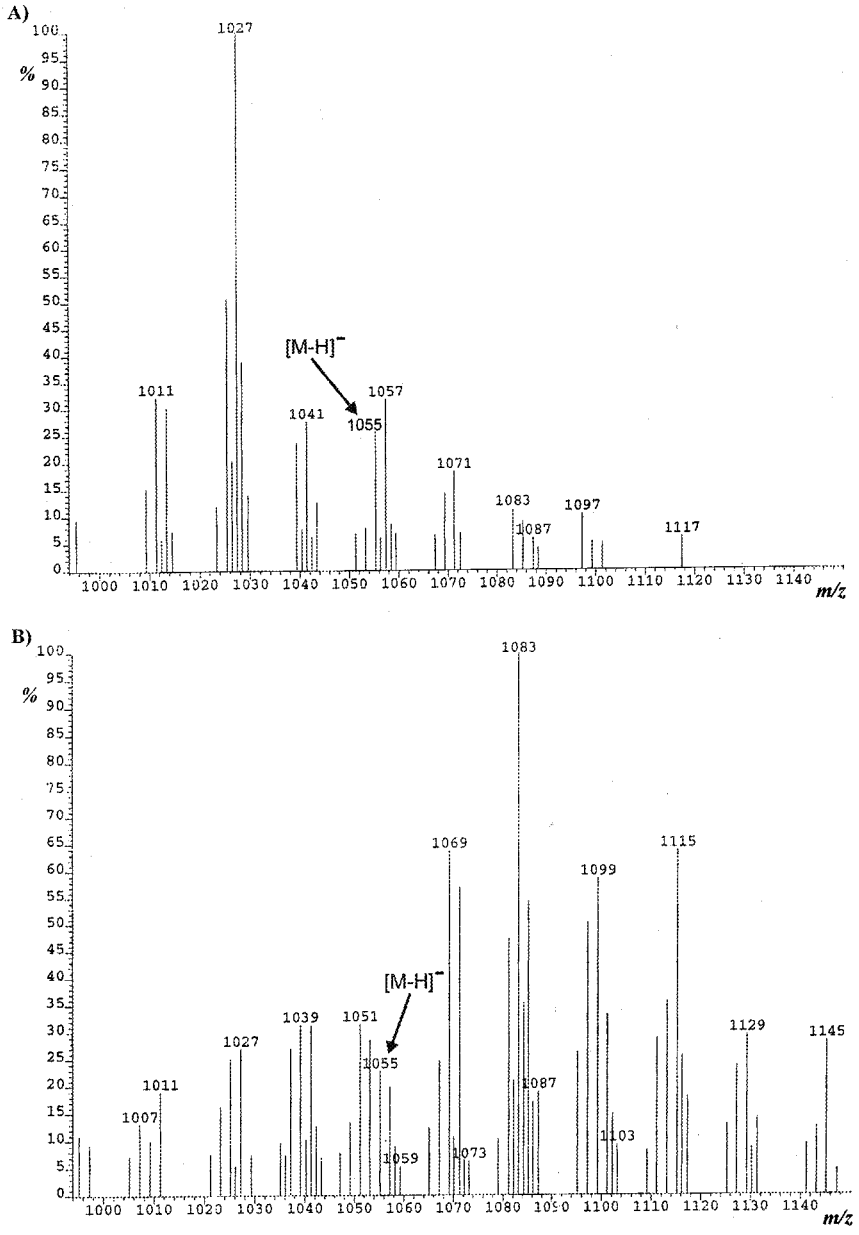


Figure 1. FAB MS of the product mixture composition of the TEMPO-promoted oxidation of α-cyclodextrin. A) 50% excess of NaClO (run 3). B) 100% excess of NaClO (run 4).

of the pure hexaacid **5a,** were attributed to competing oxidation of the secondary hydroxyls. Higher excesses of the oxidant promote a more complex overoxidation (Figure 1, B), demonstrating the practical inaccessibility of the pure hexacarboxylic acid **5a** by a direct oxidation of the unprotected α-cyclodextrin.

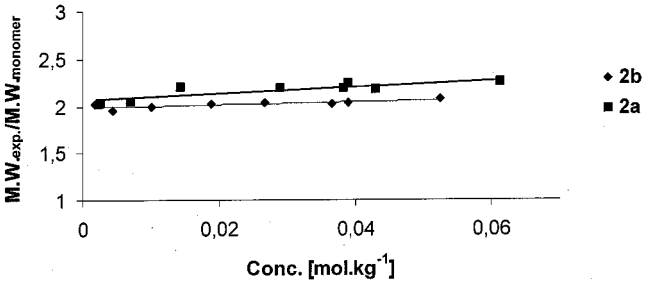


Figure 2. Degree of association of **2a** and **2b** ($MW_{exp}/MW_{theor.}$) determined by VPO in 1,2-dichloromethane solution at 40 °C.

Supramolecular Self-Assembly

The per(2,3-di-*O*-methyl)-substituted polycarboxylic acids **2a** and **2b** exhibit amphiphilic properties, being soluble in a broad spectrum of highly polar protic solvents, as well as in much less polar aprotic ones. This allowed us to examine their association properties in solution. Employing vapour-pressure osmometry, we have found that both of the two polyacids form very strong dimers in 1,2-dichloroethane and in chloroform, as evidenced by the near invariance of the apparent molecular masses ($MW_{exp.}/MW_{theor.} \approx 2$) over the full concentration range examined (Figure 2). It

strongly suggests self-assembly by multiple hydrogen bonding, directed towards supramolecular head-to-head dimer formation. More detailed information will be provided, we hope, by the forthcoming single crystal X-ray structural analysis.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were measured on a Varian UNITY-500 FT NMR spectrometer (^{1}H at 500 MHz, 20 °C; ^{13}C at 125.7 MHz, 40 °C) in [D$_6$]DMSO. Chemical shifts are referenced to the solvent signal [δ(^{1}H) 2.50 and δ(^{13}C) 39.7]. − 2D-COSY spectra were used for structural assignment of protons. Carbon signals were assigned using heteronuclear ^{1}H-^{13}C 2D-HMQC spectra. − FAB-MS spectra were recorded with a ZAB-EQ VG analytical instrument, using a glycerol-thioglycerol mixture matrix. − Optical rotations were measured with a Perkin−Elmer 241 polarimeter. − A precise pH meter (Radiometer TTT 85) with a combined electrode was used to adjust the pH of the solutions. − Vapour pressure osmometry (VPO) measurements were made in chloroform and 1,2-dichloroethane at 40° C, with a Knauer 1978 model equipped with gas-tight syringes. Each concentration was measured 5 times. − Preparative reversed-phase chromatography (RP) was carried out on a medium pressure column 2.5 × 65 cm, which contained 200 g of C-18 modified silica (Tessek, 30μm). Thin-layer (TLC) and reversed-phase thin-layer chromatography (RPTLC) were performed with precoated Silica Gel 60F and RP-18 F plates (E. Merck), respectively, which were developed by spraying with 5% H_2SO_4 in EtOH and heating. TEMPO and α- and β-cyclodextrins were purchased from Fluka; cyclodextrins were dried at 100 °C for 8 h over P_2O_5 in vacuo. Other chemicals used were commercially available. Solvents for VPO were purified by filtration through a column of basic alumina followed by distillation. Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin was used as a standard. Calculations based on accurate weights (molarity, molality, optical rotation, yields) of individual compounds **1a**, **1b** − **5a**, **5b** were corrected with respect to the water content as deduced from the carbon content found by elemental analysis.

Hexakis(5-carboxy-5-dehydroxymethyl-2,3-di-*O*-methyl)-α-cyclodextrin (2a): Compound **1a** (1.141 g, 1.0 mmol) was dissolved in water (25 mL), and potassium bromide solution (1 M, 6 mL, 6.0 mmol), TEMPO (0.938 g, 6.0 mmol) in acetonitrile (5 mL) and sodium hydrogencarbonate solution (0.5 M, 25 mL) were added successively. Sodium hypochlorite solution (0.67 M, 35.8 mL, 24.0 mmol) was cooled to 0 °C and added to the stirred reaction mixture (the temperature did not exceed 25 °C). The pH of the solution was immediately adjusted to 10.0 by addition of NaOH solution (0.5 M) and maintained for a further 60 min at room temp. Then methanol (1 mL) was added, and the colour of the solution turned rapidly from red to yellow. After 1 min, the pH was brought to about 7 by addition of 3 M HCl, and TEMPO was extracted with ether (5 × 30 mL). The colourless reaction mixture was acidified with 3 M HCl to pH 1.5 and loaded onto an RP column. Gradient elution using acetonitrile/water/trifluroacetic acid from 4.0:95.9:0.1 to 50.0:49.9:0.1 (v/v) gave **2a** after drying at 50 °C in vacuo over P_2O_5 for 10 h (1.186 g, 92%, calcd. for tetrahydrate) as a white powder, m.p. 207−215 °C. − $[\alpha]_D^{23}$ = +115 (*c* = 0.41, H_2O). − ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS; *m/z*: calcd. for $C_{48}H_{71}O_{36}$, [M − H]$^-$ 1223.3725; found 1223.3648 . − $C_{48}H_{72}O_{36}\cdot 4H_2O$: calcd. C 44.45, H 6.22; found C 44.41, H 5.99.

Heptakis(5-carboxy-5-dehydroxymethyl-2,3-di-*O*-methyl)-β-cyclodextrin (2b): Prepared from **1b** (1.331 g, 1.0 mmol) in an analogous manner to that described for **2a**. White powder (1.410 g, 93%, calcd. for pentahydrate) after drying at 50 °C in vacuo over P_2O_5 for 10 h, m.p. 205−208 °C. − $[\alpha]_D^{23}$ = +114 (*c* = 0.42, H_2O). ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS; *m/z*: calcd. for $C_{56}H_{83}O_{42}$, [M − H]$^-$ 1427.4358; found 1427.4254. − $C_{56}H_{84}O_{42}\cdot 5H_2O$: calcd. C 44.27, H 6.24; found C 44.42, H 5.83.

Hexakis(2,3-di-*O*-acetyl-5-carboxy-5-dehydroxymethyl)-α-cyclodextrin (4a): Compound **3a** (1.50 g, 1.0 mmol) was dissolved in acetonitrile (5 mL) and water (30 mL), and potassium bromide solution (1 M, 6.1 mL, 6.1 mmol) was added. TEMPO (0.953 g, 6.1 mmol) was dissolved in acetonitrile (5 mL) and added to the stirred reaction mixture, followed by sodium hydrogencarbonate solution (0.5 M, 30 mL). Immediately, sodium hypochlorite solution (0.67 M, 36.4 mL, 24.4 mmol), precooled to 0° C, was added (temperature did not exceed 25 °C), and the pH of the reaction mixture was adjusted to 10.0 by addition of 0.5 M NaOH and maintained for a further 40 min at room temp. Then methanol (1 mL) was added, and the colour of the solution turned rapidly from red to yellow. After 20 sec, the pH was brought to ≈ 7 by addition of 3 M HCl and TEMPO was extracted with ether (5 × 30 mL). The colourless reaction mixture was acidified to pH 1.5 with 3 M HCl, causing formation of a white precipitate which was dissolved upon addition of acetonitrile. RP chromatography with gradient elution using acetonitrile/water/trifluroacetic acid from 4.0:95.9:0.1 to 50.0:49.9:0.1 (v/v) afforded **4a** (1.010 g, 61% calcd. for tetrahydrate) as white powder after drying over P_2O_5 in vacuo, m.p. 220−225 °C (dec.). − $[\alpha]_D^{23}$ = +92 (*c* = 0.40, CH_3CN). − ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS; *m/z*: calcd. for $C_{60}H_{71}O_{48}$, [M − H]$^-$ 1559.3114; found 1559.2941. − $C_{60}H_{72}O_{48}\cdot 4H_2O$: calcd. C 44.12, H 4.94; found C 43.95, H 5.02.

Heptakis(2,3-di-*O*-acetyl-5-carboxy-5-dehydroxymethyl)-β-cyclodextrin (4b): Prepared from **3b** analogously to **4a** (1.090 g, 0.63 mmol). Compound **4b** was isolated as a white powder (0.820 g, 68%, calcd. for pentahydrate), m.p. 223−228 °C (dec.). − $[\alpha]_D^{23}$ = +103 (*c* = 0.40, CH_3CN). − ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS, *m/z*, calcd. for $C_{70}H_{83}O_{56}$, [M − H]$^-$ 1819.3647; found 1819.3537. − $C_{70}H_{84}O_{56}\cdot 5H_2O$: calcd. C 43.99, H 4.96; found C 43.82, H 4.70.

Hexakis(5-carboxy-5-dehydroxymethyl)-α-cyclodextrin (5a): Compound **4a** (0.470 g, 0.29 mmol) was dissolved in sodium hydroxide solution (0.5 M, 20.8 mL, 10.4 mmol) and allowed to react for 5 h at room temp. Then the reaction mixture was passed through a column of Dowex 50 W (40 mL) prepared in H^+ form. The eluate was lyophilised to give **5a** as a white solid (0.310 g, 99%, calcd. for dihydrate) after drying over P_2O_5 in vacuo at room temp. − $[\alpha]_D^{23}$ = +108 (*c* = 0.40, H_2O). − ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS; *m/z*: calcd. for $C_{36}H_{47}O_{36}$, [M − H]$^-$ 1055.1847; found 1055.1701. − $C_{36}H_{48}O_{36}\cdot 2H_2O$: calcd. C 39.57, H 4.80; found C 39.51, H 4.97.

Heptakis(5-carboxy-5-dehydroxymethyl)-β-cyclodextrin (5b): Prepared from **4b** (0.400 g, 0.21 mmol) analogously to **5a.** Compound **5b** was isolated as a white solid (0.260 g, 98%, calcd. for dihydrate.). − $[\alpha]_D^{23}$ = +122 (*c* = 0.41, H_2O). − ^{1}H and ^{13}C NMR spectra: see Table 1. − HR FAB-MS; *m/z*: calcd. for $C_{42}H_{55}O_{42}$, [M − H]$^-$ 1231.2167; found 1231.2094. − $C_{42}H_{56}O_{42}\cdot 2H_2O$: calcd. C 39.76, H 4.77; found C 39.51, H 4.68.

General Procedure for the Oxidation of Native α-Cyclodextrin: α-Cyclodextrin (97.3 mg, 0.1 mmol) was dissolved in sodium hydrogencarbonate solution (0.5 M, 1.2 mL). Potassium bromide solution

(1 M, 0.6 mL, 0.6 mmol) and TEMPO (93.8 mg, 0.6 mmol) were added successively and varying amounts (vide infra) of precooled 0.67 M sodium hypochlorite solution were added. Alkalinity was adjusted to pH 10.0 with 0.5 M NaOH and maintained for a further 10 min at room temp. During this period, the reaction mixture was tested for the presence of the oxidation reagents, using potassium iodide−starch impregnated indicator paper. Significantly,[13] the oxidation reagents were consumed in individual runs within 3−5 min of the addition of sodium hypochlorite. Methanol (0.1 mL) was added, the mixture was stirred for a further 1 min, and TEMPO was extracted with ether (5 × 3 mL). The solution was neutralised to pH ≈ 7 with 3 N HCl and passed through a column of Dowex 50 W (15 mL) prepared in Li^+ form. The eluate was evaporated to dryness and the residue was triturated with hot ethanol (3 × 30 mL) with simultaneous sonification to extract inorganic salts (LiCl, LiBr). The insoluble white material was separated by filtration and air-dried. Then it was dissolved in water (2 mL) and passed through a column of Dowex 50 W (10 mL) prepared in H^+ form. The eluate was lyophilised to give a white material which was subjected to FAB-MS (negative ion) analysis.

Run 1: NaOCl (1.80 mL, 1.2 mmol). Yield 85 mg. − FAB-MS; *m*/*z* (%): 997.2 (55), 999.2 (82), 1011.2 (43), 1013.2 (100), 1027.2 (15),

Run 2: NaOCl (2.15 mL, 1.44 mmol). Yield 92 mg. − FAB-MS; *m*/*z* (%): 997.4 (15), 1009.4 (7), 1011.4 (62), 1013.4 (100), 1025.4 (40), 1027.4 (94), 1039.4 (12), 1041.4 (22), 1053.4 (4), 1055.4 (11), 1057.4 (15).

Run 3: NaOCl (2.70 mL, 1.81 mmol). Yield 94 mg. − FAB-MS; *m*/*z* (%):1009.3 (16), 1011.3 (33), 1013.3 (30), 1025.3 (52), 1027.4 (100), 1039.4 (24), 1041.4 (28), 1053.4 (8), 1055.4 (26), 1057.4 (32), 1069.1 (14), 1071.1 (18), 1083.3 (12), 1097.3 (11), 1099.3 (5).

Run 4: NaOCl (3.60, 2.41 mmol). Yield 94 mg. − FAB-MS; *m*/*z* (%): 993.2 (18), 995.2 (13), 997.2 (12), 1007.2 (13), 1009.2 (10), 1011.2 (19), 1021.2 (7), 1023.2 (16), 1025.2 (25), 1027.2 (28), 1037.2 (28), 1039.2 (31), 1041.2 (31), 1049.2 (14), 1051.2 (32), 1053.2 (29), 1055.2 (23), 1057.2 (20), 1065.0 (13), 1067.0 (25), 1069.0 (64), 1071.0 (58), 1081.2 (47), 1083.2 (100), 1085.2 (55), 1095.2 (27), 1097.2 (52), 1099.2 (59), 1101.2 (34), 1111.2 (30), 1113.2 (36), 1115.2 (64), 1125.2 (15), 1127.2 (25), 1129.2 (31), 1131.2 (15), 1141.2 (10), 1143.2(13), 1145.2 (28), 1159.0 (13), 1189.2 (10).

Acknowledgments

This work was supported by the Grant Agency of the Czech Republic (grant No. 203/00/0138).

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[12] A similar situation has also been found for an electrochemical reoxidation of the TEMPO radical; cf. ref.[3e]

[13] In the course of the reaction of the protected homologues **1a**, **1b** and **3a**, **3b**, the oxidation reagents could be detected throughout the whole reaction time.

Received March 15, 2000
[O00129]